German Guideline Program in Oncology (GGPO)

# Evidence-based Guideline Diagnosis, Treatment, and Follow-Up in Patients with Cervical Carcinoma

Version 2.2 - March 2022
AWMF-Registernummer: 032/033OL

Guideline (Long Version)

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
AWMF

# Important Updates

**Major changes introduced by the guideline update (Version 2.0, 2021).**

New items include:

- The new FIGO classification, published in 2018:

This takes into account long-standing criticisms, such as integration of imaging and surgical procedures for diagnosis and the classification of para-ortic lymph nodes as pN1 instead of pM1. However, due to the current lack of consistency between the (new) FIGO and the (old) TNM classification, the present revised version is still continuing to use the old version of the FIGO classification. Due to the new classification, which was first published in 2018, there are currently no data available from studies based on the new classification, so that the guideline group considered it justifiable to continue to use the old version.

- Surgical treatments:

Several studies have shown that open radical hysterectomy in patients with cervical carcinoma up to FIGO stage 1b1 is associated with better overall survival with abdominal methods rather than with minimally invasive methods. This aspect needed to be revised and a corresponding recommendation has been made here to inform patients about the of the current state of the data.

In addition, the concept of the sentinel lymph node has been included in tumors of up to 2 cm and in pT1a1 and L1. Methodologically, it is also evident here that blue and radioactive marking are equivalent to intraoperative indocyanine green (ICG), so that the technique here has changed and the associated statements and recommendations have been revised accordingly.

- Radio(chemo)therapy:

In radiotherapy, radiochemotherapy has been further defined as the standard. The data on intensity-modulated radiotherapy and individualized MRI-guided brachytherapy, or image-guided adaptive brachytherapy, have been reemphasized. This is an obligatory component of treatment for cervical carcinoma patients and should be performed in a setting with planning on a single site.

- Several studies have been carried out on imaging and drug therapy in the situation with recurrences and metastases:

PET-CT is reserved for the recurrence situation before planned therapy such as exenteration or radiochemotherapy. In other situations, it should be performed only if the findings are unclear, but not routinely.

In drug therapy, the addition of bevacizumab for first-line of primary recurrences and in metastatic therapy is now standard. In addition, cisplatin can be replaced equivalently by carboplatin in patients with prior platinum treatment. Cisplatin should continue to be prescribed in patients who have not previously received platinum.

With regard to second-line therapies, information is available on nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, and irinotecan. These can all be used

for second-line treatment, although the research studies on them have not included comparisons with best-supportive care.

Checkpoint inhibitors have been added as a new class of drugs. Pembrolizumab has been shown to be effective in PD-L1 positive carcinomas. If it is to be given, it should be administered in second-line treatment and not in the higher lines.

# Table of Contents


Important Updates ..... 2

1. Information about this Guideline ..... 12

1.1. Editors ..... 12

1.2. Leading Scientific Societies ..... 12

1.3. Funding of the Guideline ..... 12

1.4. Contact ..... 12

1.5. How to cite ..... 12

1.6. Previous Changes ..... 12

1.7. Special Comment ..... 13

1.8. Objectives of the German Guideline Program in Oncology ..... 13

1.9. Additional Documents relating to this Guideline ..... 14

1.10. Composition of the Guideline Group ..... 14

1.10.1. Guideline Coordination ..... 14

1.10.2. Involved Professional Societies and Organisations ..... 15

1.10.3. Patient Involvement ..... 18

1.10.4. Methodological Support ..... 18

1.11. Abbreviations Used ..... 18

2. Introduction ..... 26

2.1. Scope and Purpose ..... 26

2.1.1. Objective and Key Questions ..... 26

2.1.2. Target Audience ..... 28

2.1.3. Validity and Update Process ..... 28

2.2. Methodology ..... 29

2.2.1. Levels of Evidence (LoE) ..... 29

2.2.2. Grades of Recommendation (GoR) ..... 29

2.2.3. Statements ..... 31

2.2.4. Expert Consensus (EK) ..... 31

2.2.5. Independence and Management of Conflicts of Interest ..... 32

3. Epidemiology ..... 34

3.1. Incidence and mortality ..... 34
3.2. Regional differences ..... 36
3.3. Histological subtypes ..... 37
3.4. Risk factors and disease development ..... 38
3.4.1. HPV infection ..... 38
3.4.2. Hormonal contraception ..... 39
3.5. Protective factors ..... 39

**4. Prevention and early detection ..... 41**

4.1. Primary prevention – HPV vaccination ..... 41
4.2. Secondary prevention – early detection of cervical carcinoma ..... 42
4.2.1. Early detection of cervical carcinoma in Germany ..... 42
4.2.2. New program for early detection of cervical carcinoma starting in 2020 ..... 43

**5. Providing patient information ..... 45**

5.1. Patient information and education content ..... 45
5.1.1. Diagnostic message ..... 47
5.1.2. Providing information about treatment ..... 49

**6. Diagnosis ..... 55**

6.1. Definition of stages — terminology ..... 55
6.2. Diagnosis as the basis for choice of treatment ..... 63
6.2.1. Consensus-agreed diagrams from the guideline group for diagnosing and defining stages as the basis for treatment decision-making ..... 64
6.2.2. Recommendations on diagnostic procedures ..... 67
6.3. Transvaginal ultrasound (TVU) in the diagnosis of cervical carcinoma ..... 71

**7. Pathology ..... 73**

7.1. Classification of invasive cervical carcinomas ..... 74
7.1.1. Classifying tumor types ..... 74
7.1.2. Staging of cervical carcinoma ..... 74
7.1.3. Definition of TNM-relevant parameters ..... 75
7.2. Tissue processing ..... 78
7.2.1. Diagnostic biopsies ..... 78

7.2.2. Conizations ... 78
7.2.3. Cervicectomy ... 80
7.2.4. Specimen after radical hysterectomy ... 82
7.2.5. Lymphadenectomy specimens ... 85
7.2.6. Sentinel lymph nodes ... 86
7.3. Morphological prognostic factors ... 88

8. Foundations of treatment ... 97
8.1. Primary therapy ... 99
8.1.1. Surgery — hysterectomy and lymphadenectomy ... 99
8.1.2. Radio(chemo)therapy ... 105
8.2. Neoadjuvant drug therapy ... 106
8.3. Adjuvant therapy ... 107
8.3.1. Adjuvant therapy after primary surgery ... 107
8.3.2. Adjuvant therapy after primary radio(chemo)therapy ... 108
8.4. Treatment for locally limited cervical carcinoma ≤ FIGO stage IIA ... 108
8.5. Treatment for local recurrences, metastases, and in the palliative situation ... 108
8.5.1. Treatment for advanced cervical carcinoma ... 109
8.5.2. Treatment for locally advanced cervical carcinoma (FIGO stages IIB–IVA and IB2/IIA2 with several histological risk factors or pN1 and c/pM0) ... 109
8.5.3. Treatment for local recurrences (c/pM0) ... 110
8.5.4. Treatment in the metastatic situation (UICC stage IVB/pM1 or c/pM1) ... 110
8.6. Stage-dependent therapy ... 110
8.6.1. Treatment for preinvasive lesions ... 110
8.6.2. Standard therapy for invasive cervical carcinoma ... 110

9. Surgical treatment ... 121
9.1. Principles and techniques of treatment ... 121
9.2. Surgical procedure ... 122
9.3. Preoperative laboratory tests ... 125
9.4. Procedure following primary radio(chemo)therapy ... 126

10. Radiotherapy ... 128
10.1. Radio(chemo)therapy ... 128

10.1.1. Radiotherapy techniques (percutaneous radiotherapy) ..... 128
10.1.2. Brachytherapy technique in primary combined radio(chemo)therapy ..... 130
10.1.3. Simultaneous chemotherapy technique ..... 130
10.1.4. Indication for primary radiotherapy or radio(chemo)therapy ..... 131
10.1.5. Adjuvant radio(chemo)therapy ..... 133
10.1.6. Adjuvant (secondary) hysterectomy after complete radio(chemo)therapy ..... 134
10.1.7. Adjuvant chemotherapy after completed radio(chemo)therapy ..... 135
10.1.8. Neoadjuvant radio(chemo)therapy ..... 135
10.1.9. Ovary preservation and fertility ..... 136
10.1.10. Adjuvant brachytherapy ..... 136
10.1.11. Intraoperative radiotherapy ..... 137
10.1.12. Anemia during radio(chemo)therapy ..... 137
10.1.13. Hyperthermia in cervical carcinoma ..... 138

**11. Drug treatment ..... 140**

11.1. Primary treatment ..... 140

11.2. Local recurrence and metastasis ..... 143
11.2.1. Local recurrence ..... 143
11.2.2. Metastases ..... 143

**12. Supportive therapy ..... 145**

12.1. Antiemetic prophylaxis and treatment ..... 145
12.1.1. Tumor therapy-induced anemia ..... 145
12.1.2. Prophylaxis against tumor therapy-induced neutropenia with granulopoietic growth factors ..... 145
12.1.3. Tumor therapy-induced nausea and vomiting ..... 145
12.1.4. Tumor therapy-induced diarrhea ..... 145
12.1.5. Oral mucositis due to systemic tumor therapy ..... 146
12.1.6. Tumor therapy-induced skin toxicity ..... 146
12.1.7. Neurotoxicity — chemotherapy-induced peripheral neuropathy (CIPN) ..... 146
12.1.8. Osseous complications ..... 146
12.1.9. Extravasation ..... 146
12.1.10. Supportive measures in radio-oncology ..... 146

12.2. Locoregional side effects ..... 146
12.2.1. Radiogenic cystitis ..... 146
12.2.2. Lymphedema ..... 146
12.2.3. Vaginal dryness, vaginal stenosis, and vaginal fibrosis ..... 147
12.2.4. Radiogenic vulvovaginitis ..... 147

12.2.5. Disturbances of sexual function ..... 147

13. Psycho-oncology and quality of life ..... 148

13.1. Psycho-oncological assistance ..... 148

13.2. Measuring quality of life ..... 151

13.2.1. Importance of and data collection for quality of life ..... 151

14. Integrative medicine ..... 152

14.1. Introduction ..... 152

14.2. Definition of terms ..... 152

14.3. Spread of alternative and complementary medicine ..... 152

14.4. Counseling on the field of complementary and alternative medicine (CAM) ..... 153

14.5. Value of alternative medicine methods ..... 153

14.6. Value of complementary medicine methods ..... 153

14.6.1. Improvement in efficacy of treatment or prognosis ..... 154

14.6.2. Reduction of side effects ..... 154

14.6.3. Conclusions for practice ..... 157

15. Rehabilitation ..... 158

15.1. Before rehabilitation ..... 158

15.2. Goals of rehabilitation ..... 159

15.3. Overcoming physical, mental and social effects ..... 159

15.4. Occupational support ..... 159

15.5. State of research on rehabilitation in oncology patients ..... 160

15.6. Funding agencies and statutory basis ..... 160

15.7. Bio-psycho-social model ..... 161

15.8. International Classification of Functioning, Disability and Health (ICF) ..... 161

15.9. Physiotherapy during rehabilitation ..... 161

15.10. Treatment for lymphedema during rehabilitation ..... 162

15.11. Treatment of fatigue syndrome during rehabilitation ..... 163

15.12. Sexuality ..... 164

16. Follow-up care .....165
16.1. Follow-up with no suspected recurrence ..... 166
16.2. History, physical examination, and cytology ..... 169
16.3. Colposcopy, HPV, and ultrasound ..... 170
16.4. Tumor markers ..... 170
16.5. Imaging procedures ..... 171
16.6. Extended diagnostic procedures for suspected recurrence ..... 172
16.7. HPV vaccination after high-grade dysplasia or cervical carcinoma ..... 172
16.7.1. HPV vaccination after conization ..... 173
17. Local recurrence .....174
17.1. Epidemiology of local recurrences and metastases ..... 174
17.2. Diagnosis of local recurrence ..... 176
17.3. Treatment for local recurrence ..... 176
17.3.1. Treatment for a central tumor recurrence after primary surgical treatment ..... 177
17.3.2. Treatment for a central recurrence after primary or adjuvant radiotherapy or radio(chemo)therapy ..... 179
17.3.3. Treatment for pelvic wall recurrence after primary surgical therapy ..... 180
17.3.4. Treatment for pelvic wall recurrence after primary radiotherapy or adjuvant radiotherapy/radiochemotherapy ..... 180
17.3.5. Treatment for secondary para-aortic lymph-node metastases ..... 181
17.3.6. Systemic therapy in local/locoregional recurrences and distant metastases ..... 181
17.3.7. Palliative treatment for local recurrence when surgery with healthy margins is not possible ..... 182
17.3.8. Value of hyperthermia in cervical carcinoma ..... 183
17.3.9. Immunotherapy for recurrent/metastatic cervical carcinoma ..... 183
18. Distant metastases .....185
18.1. Epidemiology in metastases ..... 185
18.2. Imaging ..... 185
18.3. Treatment options in distant metastases ..... 186
18.3.1. Isolated distant metastases ..... 186
18.3.2. Regional metastases (pelvic/para-aortic) ..... 186
18.3.3. Osseous metastases ..... 186

18.3.4. Disseminated metastases ..... 187
18.3.5. Drug treatment in the metastatic situation ..... 188

19. Palliative medical care ..... 193

19.1. Patients' needs ..... 194
19.2. Relatives' needs ..... 195
19.3. Palliative and hospice care ..... 195
19.4. Treatment for specific symptoms ..... 196
19.4.1. Symptomatic treatment for malignant lymphedema ..... 196
19.4.2. Constipation ..... 197
19.4.3. Malignant intestinal obstruction (MIO) ..... 197
19.4.4. Management of colostomy / stoma ..... 197
19.4.5. Malignant wounds ..... 198
19.4.6. Tumor-related cloaca formation ..... 198
19.4.7. Pain ..... 198
19.4.8. Depression ..... 199
19.4.9. Fatigue ..... 199

20. Family planning ..... 200

21.1. Fertility protection methods (ovariopexy, cryopreservation of oocytes and ovarian tissue) .. 201

22. Cervical carcinoma during pregnancy ..... 204

22.1. Diagnosis of high-grade dysplasia and invasive cervical carcinoma during pregnancy ..... 204
22.2. Epidemiology of and treatment planning for cervical carcinoma in pregnancy ..... 205
22.2.1. Treatment options for cervical carcinoma in pregnancy relative to tumor stage and gestational age ..... 205
22.2.2. FIGO stages IIB, III, and IV ..... 208
22.3. Mode of delivery ..... 208
22.4. Cervical carcinoma during pregnancy — a solvable dilemma ..... 208

23. Incidental cervical carcinoma after simple hysterectomy ..... 210

24. Neuroendocrine cervical carcinoma ..... 211

25. Structures for the provision of medical care ..... 212

25.1. Preliminary remarks ..... 212

25.2. Treatment in oncological centers ..... 213

25.2.1. Interdisciplinary and cross-sectoral care ..... 213

25.2.2. Concept of the center — interdisciplinary tumor conference ..... 215

25.2.3. Interdisciplinary chain of care ..... 215

25.2.4. Longitudinal documentation of patient history ..... 217

25.2.5. Quality indicators for certification as statutory quality assurance measures ..... 218

25.2.6. Opportunities for further training ..... 219

**26. Quality indicators ..... 221**

**27. Research needs ..... 228**

**28. Appendices ..... 232**

**29. List of Figures ..... 238**

**30. List of Tables ..... 239**

**31. Bibliography ..... 240**

# 1. Information about this Guideline

## 1.1. Editors

German Guideline Program in Oncology (GGPO), organized by the Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF), German Cancer Society (*Deutsche Krebsgesellschaft*, DKG), and German Cancer Aid (*Deutsche Krebshilfe*, DKH).

## 1.2. Leading Scientific Societies

Arbeitsgemeinschaft Gynäkologische Onkologie der DGGG und DKG (AGO)

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG)

## 1.3. Funding of the Guideline

This guideline was sponsored by the German Cancer Aid within the framework of the German Guideline Program in Oncology.

## 1.4. Contact

Office Leitlinienprogramm Onkologie
c/o Deutsche Krebsgesellschaft e. V.
Kuno-Fischer-Straße 8
14057 Berlin

leitlinienprogramm@krebsgesellschaft.de
www.leitlinienprogramm-onkologie.de

## 1.5. How to cite

German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, AWMF): Diagnosis, Treatment, and Follow-Up in Patients with Cervical Carcinoma Long version 2.2, 2022, AWMF Registration Number: 032/033OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/; Accessed [dd.mm.yyyy]

## 1.6. Previous Changes

April 2021: Version 1.1: Correction of Figure 1 / Figure 3 (alteration of the stages in the footnotes) and Figure 5 (addition to the legend).

March 2022: Version 2.2: Addition of references to the definition of deep stromal infiltration (see 7.2.4) in recommendation 8.8 and Chapter 6.3.

## 1.7. Special Comment

The field of medicine is subject to a continuous process of further development, so that all details provided here, and in particular those on diagnostic and therapeutic procedures, can always only represent the state of knowledge at the time when the medical care guideline was printed. The greatest possible care has been taken with regard to the treatment recommendations given and to the choice and dosage of drugs. However, users are requested to check by referring to the patient package inserts and specialist information provided by the manufacturers, and in cases of doubt to consult a specialist. In the general interest of the guideline editors, readers are requested to draw attention to any questionable points or inconsistencies found.

**Users themselves remain responsible for all diagnostic and therapeutic applications, medications, and dosages.**

Registered trademarks (protected proprietary names) are not specially identified in this guideline. The absence of an indication of this type can therefore not be taken to suggest that such names are unregistered product names.



## 1.8. Objectives of the German Guideline Program in Oncology

The aim of the Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG), and the German Cancer Aid (Deutsche Krebshilfe) in implementing the German Guideline Program in Oncology is to jointly promote and support the development, updating, and use of scientifically based and practicable guidelines.

The program is based on medical and scientific findings established by the the scientific societies and the DKG, consensus among medical experts, users, and patients, as well as the AWMF's regulations for the guideline development. The program receives specialist support and financing from the German Cancer Aid. In order to reflect the current state of medical knowledge and to take into account medical progress, guidelines have to be regularly checked and updated. The use of the AWMF regulations is intended to provide a basis for developing high-quality oncological guidelines in this framework.

As guidelines represent an important instrument for quality assurance and quality management in oncology, they are intended to be used in a targeted and sustained way in everyday medical care. Active implementation measures and also evaluation programs are therefore important components of the support provided by the German Guideline Program in Oncology.

The aim of the program is to create professional preconditions, with secure medium-term financing, for the development and provision of high-quality guidelines in Germany. High-quality guidelines of this type not only serve for structured knowledge transfer, but can also be used in the design of the health-care structures. Relevant

aspects of this include evidence-based guidelines as a basis for establishing and updating disease management programs, and the use of quality indicators derived from guidelines in the context of certification procedures for organ tumour centres.

## 1.9. Additional Documents relating to this Guideline

In addition to the present long version of the Level 3 guideline on diagnosis, treatment, and follow-up in patients with cervical carcinoma, the following supplementary documents on the guideline are also available:

- Short version of the guideline
- Patient guideline
- Guideline report on the process of compiling guideline (including evidence)
- Short version – English/German

This guideline and all of the additional documents are available from the following web sites.

- German Guideline Program in Oncology (https://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/)
- AWMF (https://www.awmf.org/leitlinien/detail/ll/032-033OL.html)
- Guidelines International Network (www.g-i-n.net)

The guideline is also included in the Guideline Program Oncology app.

Further information is available at: https://www.leitlinienprogramm-onkologie.de/app/

## 1.10. Composition of the Guideline Group

### 1.10.1. Guideline Coordination

**Guideline coordinators**

Prof. Dr. Matthias W. Beckmann (Erlangen) DGGG/AGO/DKG
Prof. Dr. Tanja Fehm (Düsseldorf) DGGG

**Central guideline coordination – guidelines secretary**

Dr. Martin C. Koch (Erlangen)
Dr. Frederik A. Stübs (Erlangen)

**Project team**

Dr. Anna K. Dietl (Erlangen)
Anna Sevnina (Erlangen)
Dr. Franziska Mergel (Erlangen)
PD Dr. Laura Lotz (Erlangen)
PD Dr. Carolin C. Hack (Erlangen)
Dr. Anne Bartens (Düsseldorf)
Dr. Daniel Gantert (Düsseldorf)
Dr. Franca Martignoni (Düsseldorf)

## 1.10.2. Involved Professional Societies and Organisations

**Table 1: Involved Professional Societies and Organisations**

| Participating professional associations and organizations (alphabetical) | Representative(s) |
|---|---|
| Arbeitsgemeinschaft Bildgebung in der Onkologie der DKG (ABO) | Prof. Dr. med. Jan Menke |
| Arbeitsgemeinschaft Deutscher Tumorzentren e.V. (ADT) | Prof. Dr. Olaf Ortmann |
| Arbeitsgemeinschaft für gynäkologische Radiologie (AGR) | Michael Golatta (1) |
| Arbeitsgemeinschaft Gynäkologische Onkologie der DGGG und DKG (AGO) | Prof. Dr. Peter Mallmann<br>Prof. Dr. Tanja Fehm<br>Prof. Dominik Denschlag |
| Arbeitsgemeinschaft internistische Onkologie der Deutschen Krebsgesellschaft e. V. (AIO) | Dr. Anja Welt |
| Arbeitsgemeinschaft Internistische Onkologie in der DKG (AIO) | Dr. Volker Hagen |
| Arbeitsgemeinschaft Onkologische Rehabilitation und Sozialmedizin (AGORS) | Dr. Timm Dauelsberg (2)<br>Prof. Dr. Ingo J. Diel (3) |
| Arbeitsgemeinschaft Palliativmedizin der Deutschen Krebsgesellschaft e. V. (APM) | PD Dr. Jan Gärtner |
| Arbeitsgemeinschaft Palliativmedizin in der DKG (APM) | PD Dr. Carmen Stromberger<br>Prof. Dr. Karin Oechsle (Stellvertreterin) |
| Arbeitsgemeinschaft Prävention und integrative Onkologie der Deutschen Krebsgesellschaft e. V. (AG PriO) | Prof. Dr. Karsten Münstedt |
| Arbeitsgemeinschaft Psychoonkologie der Deutschen Krebsgesellschaft (PSO) | Dipl.-Psych. Beate Hornemann<br>Dr. Friederike Mumm |
| Arbeitsgemeinschaft Radiologische Onkologie der DKG e.V. (ARO) | Prof. Dr. Dirk Vordermark (4)<br>Prof. Dr. Katja Lindel (5) |
| Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie (AGSMO) | Prof. Dr. Ingo J. Diel |
| Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin (ASORS) | Prof. Dr. med. Karin Jordan<br>Dr. Christa Kerschgens |
| Arbeitsgemeinschaft Tumorklassifikation in der Onkologie der DKG (ATO) | Prof. Dr. Christian Wittekind |

| Participating professional associations and organizations (alphabetical) | Representative(s) |
|---|---|
| Arbeitsgemeinschaft Zervixpathologie und Kolposkopie (AG-CPC) | Volkmar Küppers (4) |
| Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der DGGG | Ralph Lelle (5) |
| Berufsverband der Frauenärzte (BVF) | Dr. Manfred Steiner<br>Dipl.-med. Ulrich Freitag |
| Berufsverband der Niedergelassenen Hämatologen und Onkologen e.V. (BNHO) | Alexander Schmittel |
| Berufsverband niedergelassener Gynäkologischer Onkologen in Deutschland (BNGO) | Dr. Hans-Joachim Hindenburg |
| Berufsverband zytologisch tätiger Ärzte in Deutschland (AZÄD) | Prof. Dr. med. Klaus Joachim Neis (7)<br>Prof. Dr. Henrik Griesser (6) |
| Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe (BLFG) | Prof. Dr. Alexander T. Teichmann<br>Prof. Dr. Michael Friedrich |
| Bundesverband der Frauenselbsthilfe Krebs e.V. (FSH) | Heidemarie Haase<br>Heidemarie Haase (4)<br>Marion Gebhardt (5) |
| Bundesverband Deutscher Pathologen e.V. (BDP) | Birgit Pöschel |
| Chirurgische Arbeitsgemeinschaft Onkologie - Viszeralchirurgie (CAO-V) | Prof. Dr. Christiane Bruns |
| Deutsche Gesellschaft für Endokrinologie (DGE) | Prof. Dr. Ludwig Kiesel |
| Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG) | Prof. Dr. Matthias W. Beckmann (8)<br>Prof. Dr. Christian Dannecker (2) |
| Deutsche Gesellschaft für Nuklearmedizin e.V. (DGN) | Prof. Dr. Michael J. Reinhardt (2)<br>Prof. Dr. Michael Kreißl (3) |
| Deutsche Gesellschaft für Palliativmedizin e.V. (DGP) | Dr. Marianne Kloke |
| Deutsche Gesellschaft für Pathologie e.V. (DGP) | Prof. Dr. Lars-Christian Horn |
| Deutsche Gesellschaft für Pflegewissenschaft e.V. (DGP) | Dr. Regina Wiedemann |
| Deutsche Gesellschaft für Radioonkologie e.V. (DEGRO) | Prof. Dr. Simone Marnitz-Schulze |

| Participating professional associations and organizations (alphabetical) | Representative(s) |
|---|---|
| Deutsche Gesellschaft für Ultraschall in der Medizin e.V. (DEGUM) | Prof. Eberhard Merz |
| Deutsche Gesellschaft für Urologie e.V. (DGU) | Isabella Zraik |
| Deutsche Gesellschaft für Zytologie (DGZ) | Bernhard Mangold (2)<br>Jochen Möckel (3) |
| Deutsche Röntgengesellschaft e.V. (DRG) | Dr. med. Celine Alt-Radtke |
| Deutsche Vereinigung für Soziale Arbeit im Gesundheitswesen e.V. (DVSG) | Prof. Dr. Claudia Schulz-Behrendt |
| European Society of Gynaecological Oncology (ESGO) | Pauline Wimberger |
| Komplementäre Leitlinie zur Früherkennung, Zertifizierungskommission gynäkologischer Krebszentren | Prof. Dr. Peter Hillemanns |
| Konferenz Onkologischer Kranken- und Kinderkrankenpflege (KOK) | Kerstin Paradies |
| Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO) | Prof. Dr. Alexander Mustea |
| Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG) | Prof. Christoph Grimm (4)<br>Prof. Alina Sturdza (5) |
| Österreichische Gesellschaft für Hämatologie und Onkologie (OeGHO) | Prof. Dr. Anne Letsch |
| Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG) | PD Dr. Edward Wight (4)<br>Dr. Kristina Lössl (5) |
| Ultraschalldiagnostik in Gynäkologie und Geburtshilfe (ARGUS) | Prof. Eberhard Merz |
| Zentralverband der Physiotherapeuten/ Krankengymnasten (ZVK) | Ulla Henscher<br>Ulla Henscher (2)<br>Reina Tholen (3) |

1: until 03/20, 2: mandate holder, 3: deputy, 4: mandate holder, 5: deputy, 6: since 01.09.2019, 7: until 31.08.2019, 8: guideline coordinator

Physicians from the Competence Center for Oncology of the National Association of Statutory Health Insurance Funds (*GKV-Spitzenverband*) and the MDK Association were involved in an advisory capacity in the development of this Level 3 guideline on individual aspects of sociomedical relevance. They did not participate in the voting on the individual recommendations and are not responsible for the content of this guideline.

### 1.10.3. Patient Involvement

The guideline was drawn up with direct involvement of Ms. Heidemarie Haase of the patient self-help group *Frauenselbsthilfe Krebs e.V.* (FSH). Her deputy was Ms. Marion Gebhardt. The patient representatives were involved in the preparation of chapters of the guideline, participated actively in the Patient Information Working Group, and were involved in the consensus conferences with their own voting rights.

### 1.10.4. Methodological Support

Provided by the German Guideline Program in Oncology (GGPO):

- Markus Follmann, MD, MPH, MSc (Office of the GGPO – German Cancer Society)
- Thomas Langer, Dipl.-Soz. Wiss. (Office of the GGPO – German Cancer Society)
- Monika Nothacker, MD, MPH (Deputy director of the AWMF Institute for Medical Science Management)

Through external contractors

- PD Dr. Simone Wesselmann, MBA (German Cancer Society –Certification, Quality indicators)
- Dipl. Biologe Gregor Wenzel (Berlin)

## 1.11. Abbreviations Used

**Table 2: Abbreviations Used**

| Abbreviation | Explanation |
|---|---|
| ABO | Arbeitsgemeinschaft Bildgebung in der Onkologie (DKG) |
| ACIS | Adenocarcinoma in situ |
| ADT | Arbeitsgemeinschaft Deutscher Tumorenzentren |
| AG CPC | Arbeitsgemeinschaft Zervixpathologie und Kolposkopie (DGGG) |
| AGO | Arbeitsgemeinschaft für Gynäkologie in der DKG |
| AGORS | Arbeitsgemeinschaft Onkologische Rehabilitation und Sozialmedizin |
| AGR | Arbeitsgemeinschaft für gynäkologische Radiologie (DGGG) |
| AGSMO | Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie |
| AIO | Arbeitsgemeinschaft Internistische Onkologie der DKG |
| AJCC | American Joint Committee on Cancer |
| APM | Arbeitsgemeinschaft für Palliativmedizin (DKG) |
| AQUA | Institut für angewandte Qualitätsförderung und Forschung im Gesundheits-wesen GmbH |

| Abbreviation | Explanation |
|---|---|
| ARO | Arbeitsgemeinschaft Radiologische Onkologie |
| ASCO | American Society of Clinical Oncology |
| ATO | Arbeitsgemeinschaft Tumorklassifikation in der Onkologie (DKG) |
| AUC | Area Under the Curve |
| AWMF | Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften |
| AZÄD | Arbeitsgemeinschaf zytologisch tätiger Ärzte in Deutschland |
| BDP | Bundesverband Deutscher Pathologen |
| BLFG | Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe e. V. |
| BMG | Bundesministerium für Gesundheit |
| BNGO | Berufsverband Niedergelassener Gynäkologischer Onkologen in Deutschland |
| BNHO | Berufsverband der Niedergelassenen Hämatologen und Onkologen in Deutschland e.V. |
| BQS | Bundesgeschäftsstelle Qualitätssicherung gGmbH |
| BVF | Berufsverband der Frauenärzte |
| c/o | care of (dt. wörtlich in der Obhut von, sinngemäß wohnhaft bei) |
| Ca-125 | Cancer-Antigen 125 |
| CAM | complementary and alternative medicine, Komplementär- und Alternativmedizin |
| CEA (eng) | Cardioembryonic Antigen |
| CEBM | Centre for Evidence-Based Medicine (Oxford, UK) |
| CIN | Cervical intraepithelial neoplasia |
| CME | Continuing Medical Education |
| CoI | Interessenkonflikt (Conflict of Interest) |
| CPD | Complex physical decongestive therapy |
| CT (eng) | Computer tomography |

| Abbreviation | Explanation |
|---|---|
| DEGRO | Deutsche Gesellschaft für Radioonkologie |
| DEGUM | Deutsche Gesellschaft für Ultraschall in der Medizin |
| DET | Datensparsame Einheitliche Tumordokumentation |
| DFS | krankheitsfreies Überleben (disease-free survival) |
| DGE | Deutsche Gesellschaft für Ernährung |
| DGGG | Deutsche Gesellschaft für Gynäkologie und Geburtshilfe |
| DGHO | Deutsche Gesellschaft für Hämatologie und Onkologie |
| DGN | Deutsche Gesellschaft für Nuklearmedizin |
| DGU | Deutsche Gesellschaft für Urologie e.V. |
| DGZ | Deutsche Gesellschaft für Zytologie |
| DKG | Deutsche Krebsgesellschaft e.V. |
| DKH | Stiftung Deutsche Krebshilfe |
| DRG | Deutsche Röntgengesellschaft |
| DRV | Deutsche Rentenversicherung |
| DWI | Diffusion-weightend imaging |
| EC (eng) | Expert Consensus |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ESGO | European Society of Gynaecological Oncology |
| FDG | Fluorodeoxyglucose |
| FFP | Freedom from First Progression |
| FIGO | Fédération Internationale de Gynécologie et d'Obstétrique |
| FSH (eng) | Follicle stimulating hormone |
| G-BA | Gemeinsamer Bundesausschuss |
| G-I-N | Guidelines International Network |
| GEKID | Gesellschaft der epidemiologischen Krebsregister in Deutschland |

| Abbreviation | Explanation |
|---|---|
| GKFP | Gesetzliches Krebsfrüherkennungsprogramm |
| GKV | Gesetzliche Krankenversicherung |
| GOG | Gynecologic Oncology Group |
| GoR | Grade of recommendation (Empfehlungsgrad) |
| GTV | makroskopisches Tumorvolumen (gross tumor volume) |
| HADS | Hospital Anxiety and Depression Scale |
| HBO | Hyperbaric oxygen therapy |
| HDR | high dose rate |
| HE | Hysterectomy |
| HE stain | Hematoxylin eosin stain |
| HPV | Human papilloma virus |
| HR | Hazard ratio |
| HR-HPV | High-risk genotypes of human papilloma virus |
| HRCTV | High risk clinical target volume |
| HSIL | High Grade Squamous Intraepithelial Lesion |
| i.v. | intravenously |
| ICCR | Internatioal Collaboration on Cancer Reporting |
| ICD-10 | International Statistical Classification of Diseases |
| ICD (eng) | International Classification of Diseases, internationale Klassifikation von Erkrankungen |
| ICF | International Classification of Functioning, Disability and Health |
| ICG | Indocyanine green |
| IECC | International Endocervical Adenocarcinoma Classification |
| IGABT | Image-guided adaptive brachytherapy |
| IGRT | Image-guided radiation therapie (bildgesteuerte Strahlentherapie) |
| IMRT (eng) | Intensity Modulated Radiation Therapy |

| Abbreviation | Explanation |
|---|---|
| IORT | Intraoperative radiotherapy |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| IRCTV | Intermediate risk clinical target volume |
| ITC (eng) | Isolated tumor cells |
| ITV | Internal Target Volume |
| IUD (eng) | intrauterine device |
| KFE | Krebsfrüherkennung |
| KFRG | Krebsfrüherkennungs- und –registergesetz |
| KOK | Konferenz onkologischer Kranken- und Kinderkrankenpflege, AG in der DKG |
| KoQk | Kooperationsverbund Qualitätssicherung durch klinische Krebsregister |
| KPE | komplexe Physikalische Erstauungstherapie |
| LEEP | Loop Electrical Excision Procedure |
| LEER | laterally extended endopelvic resection |
| LLETZ | Large Loop Excision of the Transformation Zone |
| LN | Lymph nodes |
| LNE (eng) | Lymphonodectomy |
| LoE | Level of Evidence |
| LSILL | Low Grade Squamous Intraepithelial Lesion |
| MDK | Medizinischer Dienst der Krankenkassen |
| MFS | metastasenfreies Überleben (metastasis-free survival) |
| MPH | Master of Public Health |
| MRI (eng) | magnetic resonance imaging |
| MSc | Master of Science |
| NACT | Neoadjuvant chemotherapy |
| NAKOS | Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen |

| Abbreviation | Explanation |
|---|---|
| NCCN | National Comprehensive Cancer Network |
| NECC | Neuroendokrines Zervixkarzinom (neuroendocrine cervical carcinoma) |
| NGC | National Guideline Clearinghouse (USA) |
| NICE | National Institute for Health and Care Excellence |
| Nll. | Nodi lymphatici |
| NOS | Nicht anderweitig spezifiziert (not otherwise specified) |
| NSE | Neuron-specific enolase |
| OEGGG | Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe |
| OP | Operation |
| OR | Quotenverhältnis (Odds-Ratio) |
| OS | Gesamtüberleben (Overall Survival) |
| Pap | Papanicolaou test |
| PCI | Percutaneous Coronary Intervention |
| PDR | Gepulste Dosisrate (pulsed-dose-rate) |
| PET | Positronen-Emissions-Tomographie |
| PFS | progressionsfreies Überleben (progression-free survival) |
| PICO | Population, Intervention, Comparison. Outcome |
| PrIO | Arbeitsgemeinschaft Prävention und integrative Onkologie |
| PSO | Arbeitsgemeinschaft für Psychoonkologie in der Deutschen Krebsgesellschaft |
| PTV | Planungszielvolumen (planning target volume) |
| QI (eng) | quality indicator |
| QLQ-CX | Quality of Life Questionaire Cervical Cancer Module |
| R(CH)T | Radio(chemo)therapy |
| RCT (eng) | Randomized Controlled Trial |
| RFA | Radiofrequency ablation |

| Abbreviation | Explanation |
|---|---|
| RKI | Robert-Koch-Institut |
| RT | radiotherapy = Radiotherapie |
| RTOG | Radiation Therapy Oncology Group |
| RVT | Radical vaginal trachelectomy |
| SCC | Squamous Cell cacinoma Antigen (Tumormarker) |
| SCC | squamous cell carcinoma |
| Scinti | Skeletal scintigraphy |
| SGB | Sozialgesetzbuch |
| SIB | Simultaneous integrated boost |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SMILE | Stratified mucin-producing lesion |
| SNLE/B | Sentinel lymph node excision/biopsy |
| SNP (eng) | Single Nucleotide Polymorphism, Einzel-Nukleotid-Polymorphismus |
| Sono | Sonography |
| SOP | Standard operating procedure |
| SPECT | Single-Photon-Emissionscomputertomographie |
| SR | Systematic research |
| STD | Sexually transmitted disease |
| STIKO | ständige Impfkommission des Robert-Koch-Institut |
| TILs | Tumor-infiltrating lymphocytes |
| TMMR | Total mesometrial resection |
| TNM (eng) | Tumor-Nodes-Metastases |
| UFK | Universitätsfrauenklinik |
| UICC | Union international contre le cancer |
| UMIT | Private Universität für Gesundheitswissenschaften, medizinische Informatik und Technik |

| Abbreviation | Explanation |
|---|---|
| VaIN | Vaginal intraepithelial neoplasia |
| VLP | virus-like-particles (dt: Virus-ähnliche Partikel) |
| WHO | World Health Organization (Welt-Gesundheitsorganisation) |
| ZVK | Deutscher Verband für Physiotherapie (ZVK) e.V. |

# 2. Introduction

## 2.1. Scope and Purpose

### 2.1.1. Objective and Key Questions

The incidence of cervical carcinoma has declined markedly during the last 30 years. This is mainly due to the early cancer detection program introduced in 1971. However, the reduction in the incidence, partly due to treatment of preinvasive lesions, has not led to a marked reduction in the mortality rate and, in particular, the morbidity rate among patients with cervical carcinoma during the last ten 10 years (see also Chapter 3). It has not yet been possible to change this situation, despite continuing technical progress and the introduction of innovative new treatment approaches. However, current surveys on quality assurance measures show that treatment for patients with cervical carcinoma continues to be extremely heterogeneous. Many different treatment variants, with combinations of different approaches, are being used for patients. When these combined approaches and the literature reports are put together, it can be seen that there are at present more than 20 different treatment options available in the adjuvant setting for a patient with cervical carcinoma. This shows that the treatment standards used, and consequently the quality of the treatment provided, are highly variable. This might indirectly be one reason for the lack of significant improvements in relation to patients' survival and treatment-related morbidity in recent years.

The problems of uncertain treatment, mortality and morbidity rates that have not declined during the last 15 years, and the current wide variations in treatment make an upgrading from the existing Level 2 consensus-based guideline to a Level 3 guideline necessary.

The aims of the Level 2 consensus-based guideline "Diagnostics and Treatment of Cervical Carcinoma" [327] were maintained, supplemented, and made more specific in 2014. Sections on prevention and early detection were placed in a separate Level 3 guideline on "Prevention of Cervical Carcinoma" (AWMF register no. 015/027OL). In general, the aim is to provide physicians working in private practice and in hospitals in the field of oncology with an accepted, – and as far as possible evidence-based – decision-making aid for selecting and carrying out appropriate measures in the diagnosis, treatment, and follow-up of patients with cervical carcinoma.

The recommendations are based either on an examination of the available evidence in accordance with the criteria of evidence-based medicine, adaptation of existing evidence-based national and international guidelines, or – in the absence of an evidential basis – on a consensus of participating specialists. All of the recommendations have been evaluated and voted on by a multidisciplinary group of specialists and representatives of patients' organizations.

In addition to the general goal of improving care for patients with cervical carcinoma by optimizing the diagnostic chain and carrying out stage-appropriate treatment when the patient first contracts the disease, and at recurrence and/or metastasis, the aims of this revised Level 3 guideline are as follows:

- Establishment of a "quality standard" as the basis for individually tailored, high-quality treatment;

- Improvement of the patients' quality of life and achieving a medium-term to long-term reduction in the mortality rate among these patients by implementing the guideline's recommendations;
- Ensuring universal implementation of multidisciplinary, quality-assured and inter-sector care for patients with cervical carcinoma, while at the same time making specific efforts to improve psychosocial care and rehabilitation in a need-oriented and quality-assured way;
- Providing support for physicians and patients in medical decision-making by providing recommendations that have received formal consensus;
- Supporting the involvement of the patients in treatment decision-making, taking their individual needs into account;
- Creating the basis for education, training, and further training measures with targeted contents for physicians, with the guideline recommendations being systematically taken into account in education, training, and further training and in quality management systems;
- Obtaining information about the status quo in medical care, with particular reference to quality indicator 6 on adjuvant radio(chemo)therapy, — as there are no data currently available on the way in which many patients receive stage-appropriate adjuvant therapy with combined cisplatin-containing radio(chemo)therapy. In the long term, the aim is to achieve a reduction in the numbers of adjuvant treatments in favour of primary chemoradiotherapy in the group of patients at risk, or unimodal therapy.

The goals set out in the guideline remain the same as in the first version. The guideline on "Diagnosis, Treatment, and Follow-Up in Patients with Cervical Carcinoma" is intended as an evidence-based and consensus-based instrument for the care of patients with cervical carcinoma. It serves to offer patients scientifically based, up-to-date, and economic procedures in diagnosis, treatment, follow-up, and rehabilitation that are appropriate to the relevant state of the disease. The present version of the guideline is intended to provide the basis for medical decision-making processes that are relevant to practical action. This is also against the background of the "shared -decision-making" approach. Shared "decision-making" is a model for a partnership-based doctor patient relationship, characterized by a common and equal decision-making process. The information provided in the guideline can enable physicians to help patients achieve their wish to participate in decisions about their health problem. On the basis of the information provided in the guideline, physicians and patients can communicate on a basis of partnership about the objective and subjective aspects of an upcoming decision.

The guideline is intended to contribute to ensuring appropriate health care in the diagnosis, treatment and follow-up of patients with cervical carcinoma and to provide the basis for individually stage-adapted, quality-assured therapy that respects the patient's wishes. Like its predecessor, this revised Level 3 guideline allows national implementation of interdisciplinary, quality-assured, inter-sector therapy. The aim of comprehensive distribution and implementation of the revised Level 3 guideline is to improve the diagnostic chain and stage-appropriate therapy both for the initial disease and also for recurrences and metastases.

## 2.1.2. Target Audience

**Group of patients**

This Level 3 guideline is aimed at all patients who have developed cervical carcinoma (cancer of the uterine cervix) (including microinvasive lesions / high-grade precursor lesions but excluding early stages / preinvasive lesions), as well as their relatives.

**Target group of users**

The recommendations given in the guideline are aimed at all physicians and members of professional groups who are concerned with outpatient and/or in-patient care for patients with cervical carcinoma — particularly gynecologists, gynecological oncologists, radiologists, pathologists, radio-oncologists, psycho-oncologists, and nursing staff.

The guideline also continues to provide information for family physicians and hemato-oncologists.

The intended audience also includes:

- Medical and scientific specialist societies and professional associations
- Groups representing the interests of women (women's organizations, patients' organizations, and self-help organizations)
- Quality assurance institutions and projects at the national and state level (e.g., AQUA, KoQK, ADT, IQWiG, GEKID, „gesundheitsziele.de", IQTIG)
- Health-policy institutions and decision-makers at the national and state level
- Certification institutes (e.g., DKG)
- Funding bodies

## 2.1.3. Validity and Update Process

The guideline is valid until the next updating, or at the latest until October 2025. Its need for updating is continuously monitored. The current literature is researched and methodically reviewed on an annual basis in a "living guideline" framework. The central guideline group decides on the need to update individual chapters.

When necessary – e.g. when studies providing relevant results or warnings become known – the updating procedure can be started earlier or a short-term amendment to the guideline may be made, depending on urgency.

Comments and suggested changes would be welcomed at the following address:

Prof. Dr. M. W. Beckmann
Dr. Frederik A. Stübs
Central Guideline Coordination (Level 3 Guideline on Cervical Carcinoma)
Universitätsfrauenklinik Erlangen
Universitätsstrasse 21 – 23
91054 Erlangen
Germany

fk-leitliniensekretariat@uk-erlangen.de
Tel: +49-9131 85-33553
Fax: +49-9131 85-33445

## 2.2. Methodology

The methodological basis for the compilation of the guideline is described in the Guideline Report, which is freely available, on the web site of the GGPO (https://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom) and on the AWMF's web site [386].

### 2.2.1. Levels of Evidence (LoE)

The system developed by the Scottish Intercollegiate Guidelines Network (SIGN), presented in Table 3, has been used in this guideline to classify the risk of distortion in the studies identified (see http://www.sign.ac.uk/pdf/sign50.pdf).

**Table 3: The SIGN evidence classification scheme**

| Grade | Description |
|---|---|
| 1++ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of systematic error (bias) |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of systematic error (bias) |
| 1- | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of systematic error (bias) |
| 2++ | High-quality systematic reviews of case control or cohort studies<br><br>or<br><br>High-quality case control or cohort studies with a very low risk of systematic distortion (confounding, bias, chance) and with a high probability of the association being causative |
| 2+ | Well-conducted case-control studies or cohort studies with a low risk of systematic distortion (confounding, bias, chance) and a moderate probability of the association being causative |
| 2- | Case-control studies or cohort studies with a high risk of systematic distortion (confounding, bias, chance) and a significant risk of the association not being causative |
| 3 | Nonanalytic studies, e.g., case reports, case series |
| 4 | Expert opinion |

### 2.2.2. Grades of Recommendation (GoR)

The Oncology Guidelines methodology involves the issuing of grades of recommendation by the authors of the guideline, in the framework of a formal consensus procedure. Accordingly, a complex nominal group process moderated by the AWMF was carried out.

In the guideline, all evidence-based statements (see Section 2.2.4) and recommendations are given an evidence level (in accordance with SIGN, see 2.2.1) for the studies they are based on, and, in the case of recommendations, the strength of the recommendation (grade of recommendation) is also given. With regard to the strength of the recommendation, this guideline distinguishes between three levels of recommendation (Table 4), which are also reflected in the way in which each recommendation is expressed.

**Table 4: The grade of recommendation scheme**

| Grade of recommendation | Description | Expression |
|---|---|---|
| A | Strong recommendation | shall |
| B | Recommendation | should |
| C | Open recommendation | can |

**Criteria for grading of recommendations**

In principle, the grade of recommendation is based on the strength of the available evidence — i.e., when there is a high level of evidence (e.g., meta-analyses/systematic reviews of RCTs, or several methodologically high-quality RCTs), a strong recommendation is given (recommendation grade A,“shall”).

In addition, however, the following criteria were taken into account, potentially leading to an upward or downward shift in the grade of recommendation:

- Consistency of the research results
- Example: The effect estimates for the study results point in different directions and do not show a consistent trend.
- Clinical relevance of the end points and strength of the effects
- Example: Although studies with results pointing in one direction are available, the importance of the selected end points and/or the strength of the effects are not considered to be relevant.
- Benefit-risk relationship
- Example: The demonstrated benefit of an intervention contrasts with a relevant element of potential harm, which argues against an unrestricted recommendation.
- Ethical obligations
- Examples: Downgrading for ethical reasons, an intervention with a demonstrated benefit cannot be offered without restrictions. Upgrading: strong recommendation on the basis of e.g. case-control studies, since an RCT cannot be carried out for ethical reasons.
- Patients' preferences
- Example: An intervention with demonstrated benefit is not strongly recommended, as it is regarded by patients as burdensome or impracticable.
- Applicability, practicality in health care
- Example: An intervention with demonstrated positive effects cannot be recommended, because it cannot be offered in the regional health-care system for structural reasons.

**Classification of strength of consensus**

To establish the strength of consensus, the percentage of specialists who were eligible to vote and the absolute number of votes in favor were calculated. If consensus was achieved, the reasons for this or differing positions expressed are presented in the corresponding background texts.

The classification of the strength of consensus is presented in Table 5 and is based on the AWMF regulations [386].

**Table 5: Classification of strength of consensus**

| Strength of consensus | Percentage agreement |
|---|---|
| Strong consensus | Agreement by > 95% of participants |
| Consensus | Agreement by 75 – 95% of participants |
| Majority agreement | Agreement by > 50 - 75% of participants |
| No consensus/dissent | Agreement by < 50% of the participants |

### 2.2.3. Statements

Presentations or explanations of specific matters or issues, without direct instructions for action, are described as "statements." They are decided on in the same way as for recommendations, in the framework of a formal consensus procedure, and may be based either on study results or expert opinions.

### 2.2.4. Expert Consensus (EK)

Statements/recommendations that have been decided on the basis of an expert consensus in the guideline group are marked as „expert consensus (EC)". No symbols have been used to grade these recommendations; the strength of the expert consensus is indicated by the form of expression used (shall, should, or can) in accordance with the gradation given in Table 4.

**Expert consensus (EC) after systematic research**

Systematic research was carried out on a few key questions, without any relevant literature related to them being identified. The following study designs were defined as inclusion criteria for all population, intervention, comparison, and outcome (PICO) questions:

- Randomized controlled studies (RCTs), including quasi-randomized controlled studies.
- Nonrandomized controlled studies (non-RCTs) — i.e., experimental prospective studies that only differ from RCTs in that the assignment of patients to the intervention groups was carried out without randomization, while the intervention groups were compared with each other.
- Prospective comparative observational studies.

- Systematic reviews on the above-mentioned study designs, with the following characteristics:
- The literature search was carried out in at least two electronic databases.
- The study question was formulated as a PICO question.
- The description of the study population, the results of the analysis of the risk of bias, and the results were presented in tabular form and comparably, in such a way that they can be clearly assigned to the individual studies.

As these questions were prioritized in advance for external processing, due to their high level of clinical relevance, the guideline group nevertheless formulated statements/recommendations on them. In the absence of data, these were thus ultimately based on an expert consensus in the guideline group. These statements/recommendations are marked as "expert consensus (EC) after systematic research" and linked to the corresponding key questions. The precise research strategy and research results are explained in the guideline report. Symbols are not used to grade these recommendations; the strength of the expert consensus is conveyed by the formulation used (must/should/can) in accordance with the gradation given in Table 4. The way in which the grade of recommendation was established, in view of the absence of an evidence base, is explained in each background text.

### 2.2.5. Independence and Management of Conflicts of Interest

German Cancer Aid (DKH) provided the funding for the preparation of the guideline, via the GGPO. These funds were used for staff costs, office materials, purchasing of literature, and for the consensus conferences (room hire, technical facilities, catering, chairpersons' fees, participants' travel costs). The guideline was prepared with editorial independence from the funding organisation. All members provided a written declaration concerning any conflicts of interest during the guideline preparation process. The disclosed conflicts of interest are listed in the guideline report for this guideline (https://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/).

In accordance with the requirements of the AWMF, all members of the guideline group were asked to disclose their conflicts of interest at the beginning of the guideline project. For this purpose, a standardized AWMF form was sent to all members. Submission of a completed conflict of interest (COI) form was mandatory for further participation in the guideline process. This applied not only to office-holders, but to everyone involved in the guideline. If the form was not available prior to the commencement of substantive work, it automatically resulted in disqualification from participation. The evaluation procedure for COIs was explained in detail to the guideline group at the first consensus conference. All COI forms were reviewed by the guideline coordinators and classified in accordance with formal criteria into the categories shown in Table 6. The guideline coordinators were not permitted to have any guideline-specific financial COIs (even of minor relevance). The results of this evaluation were presented at the first guideline group consensus conference.

**Table 6: Categories for evaluating conflicts of interest**

| Category | Classification |
|---|---|
| Low | Less than moderate |
| Moderate | Advisory work / industrial third-party funding or speaking fees > with an absolute value > 5000€/year, share ownership ≤ 5000€ |
| High | Share ownership < 5000€; patent ownership, third-party funding > € 50,000€ |

Guideline staff in supervisory positions (e.g., as members of steering committees / steering groups, working group leaders, persons primarily responsible for evidence preparation, chairpersons) were permitted to have a maximum of low COIs. Office-holders with a moderate or high COI were not permitted to vote on the topic-related statements/recommendations and had to abstain from voting. Unless their expertise could be dispensed with, they had the status of advisory, nonvoting experts.

The guideline group was composed of representatives from various specialist disciplines as well as members of the Oncology Guidelines Office, the AWMF, the DKG, and patient representatives. The study evidence was reviewed by external collaborators.

Before the second consensus conference and before voting on the statements and recommendations, all office-holders and participants in the guideline group were asked to update their COI statements. These were then presented again at the second consensus conference.

All statements and recommendations were approved with a strong or very strong consensus.

All COIs are published along with names in the guideline report (without stating the financial sums concerned).

**Topicality of recommendations and statements**

It has been noted in the headers of the recommendations and statements when they were created or updated and whether they have been modified or newly created. The following categories of marking are used:

- Checked 2021: the recommendation or statement was made at the time when the guideline was written (2014). The validity of the recommendation or statement was reviewed during the 2021 update process, and a decision was made to retain the content.
- Modified 2021: the recommendation or statement was modified in part or in its entirety during the 2021 update process.

# 3. Epidemiology

**Major changes in the chapter on epidemiology**

This chapter has hardly been changed. No recommendations are made in it. The data on the incidence and mortality rate for gynecological tumors have been updated on the basis of the current "Cancer in Germany, 2015/2016" report from the Robert Koch Institute, published in 2019.

In addition, new recommendations issued by Germany's Standing Committee on Vaccines (STIKO) on vaccination against human papillomavirus (HPV) and the initial results following the introduction of mandatory vaccination in Australia have been added.

*F.A. Stübs, M.C. Koch, F. Mergel, M.W. Beckmann*

## 3.1. Incidence and mortality

Cervical cancer is the fourth most common gynecological malignancy worldwide. A total of 528,000 women were newly diagnosed with cervical carcinoma in 2012, and 266,000 women died of the disease. In Germany, this tumor entity has become a less frequent tumor type in recent decades, partly due to early detection. Partly thanks to early detection, cervical carcinoma has become a less frequent type of tumor in Germany over the last few decades. This has led to a reduction in the incidence of invasive cervical carcinoma during the last 30 years — from being the most frequent type of carcinoma among women (in 1971) to the thirteenth most frequent, at 1.9% of the total incidence of all malignancies among women (in 2016) in Germany [4]. This decline in cervical carcinoma is explained, among other factors, by the introduction in 1971 of early detection examinations using a cytological smear, which have made it possible to detect precursors and early stages of cancer in a timely way and treat them successfully [1]. The development and introduction of human papillomavirus (HPV) vaccines does not explain the observed decline in the incidence, as these vaccines were only included in the recommendations of the Standing Committee on Vaccines (STIKO) in 2007 (GBA decision 2008). However, it is expected that the implementation of HPV vaccination will further reduce the incidence and mortality rates in the future. Since June 2018, the STIKO has also recommended vaccination for boys aged 9–14. This is expected to further reduce the incidence and mortality of cervical cancer provided that sufficient vaccination coverage is achieved, including through herd immunity [2].

IIn Australia, a vaccination program using the quadrivalent vaccine (HPV types 6, 11, 16, and 18) was introduced between 2007 and 2009 for girls aged 12–13. Between 2006 and 2009, a reduction in the incidence of HSIL lesions from 0.85% to 0.22% in females under 18 years of age was observed (P = 0.03). No reduction was seen in other groups of patients. The reduction in HSIL lesions was therefore only found in patients who received vaccination [5]. In a cluster-randomized trial of HPV-associated invasive carcinoma, including a total of 9,529 initially 14–17-year-old girls who received the bivalent or quadrivalent HPV vaccine and 17,838 initially 14–19-year-old females without HPV vaccination, eight cervical carcinomas were diagnosed in the unvaccinated women after 7 years and no cervical carcinomas were seen in the vaccinated women. However, the data were not available to the guideline group in the form of a full publication, which is expected in 2021 [6].

A meta-analysis of 20 studies from nine countries including 16,600 women vaccinated against HPV showed a 64% reduction in the incidence of infection with HPV 16 and 18 in women aged 13–19 years (RR 0.36; 95% CI, 0.25 to 0.53) [7].

The incidence of more advanced tumor stages (≥ FIGO stage IIB) and the numbers of deaths have declined since 1980, but have been stagnating over the last 10 years. Overall, approximately one in 340 women currently dies of cervical carcinoma in Germany; 30 years ago, the figure was more than twice that [4].

Data from the Robert Koch Institute and GEKID for 2019 report a total of 4380 new patients with cervical carcinoma in 2016, and 1562 deaths from the disease. The incidence in comparison with 2002 (n = 6500 to 4380) has thus clearly declined, and the number of deaths (n = 1700 to 1562) due to cervical carcinoma has fallen slightly [4] [3]. The relative 5-year survival rate for patients with cervical carcinoma was 67% in 2016, while the 10-year survival rate was 63%.

The age distribution shows a peak between 40 and 59 years of age. The mean age at first diagnosis of cervical carcinoma, currently 55, has declined by 15 years during the last 25 years [4]. The mean age at which the disease develops is 34 for preinvasive precursor stages — a mean of 20 years younger [4]. The 5-year prevalence was 17,400 women in 2014, slightly lower than the 2016 rate of 17,500. In 2013–2014, 44% of cervical carcinomas were in stage UICC stage I at first diagnosis, 13% in stage II, 23% in stage II, and 20% in stage IV [4].

**Table 7: Relative 5- and 10-year survival rates for cervical cancer in relation to UICC stage from the Bavarian Cancer Registry (n=14,606), 1998-2011.**

| UICC stage | 0 | I | II | III | IV |
|---|---|---|---|---|---|
| Relative 5-year survival rate | 100% | 95% | 75% | 58% | 21% |
| Relative 10-year survival rate | 100% | 93% | 71% | 51% | 16% |

UICC stages according to TNM classification: UICC 0 = Tis N0 M0; UICC I = T1 N0 M0; UICC II = T2 N0 M0; UICC III = T3 N0 M0 or T1-3 N1 M0; UICC IV = T4 N0 M0 or T4 N1 M0 or any T any N M1.

Source: Bavarian Cancer Registry, 2013.

**Table 8: Incidence and mortality rates for carcinomas specific to women, 2021**

| | Incidence<br><br>n = absolute | Age-standardized incidence in European population<br><br>per 100,000 | Total deaths<br><br>n = absolute | Age-standardized overall mortality rate in European population<br><br>per 100,000 |
|---|---|---|---|---|
| Women (total) | 340,590 | | 105,597 | |
| Gynecological carcinomas (total) | 95,100 | 153 | 29,155 | 36,7 |
| Breast carcinoma | 68,950 | 112,2 | 18,570 | 23,4 |
| Endometrial carcinoma | 11,090 | 16,5 | 2,600 | 3,0 |
| Ovarian carcinoma | 7,350 | 11,1 | 5,486 | 6,9 |
| Cervical carcinoma | 4,380 | 8,7 | 1,562 | 2,4 |
| Vulvar carcinoma | 3,330 | 4,5 | 937 | 1,0 |

The prognosis for those who develop the disease has improved markedly. The mortality rates have clearly declined since 1980. Table 7 shows the relative 5-year and 10-year survival rates relative to the UICC stage, from the Bavarian Cancer Registry for the period 1988–2011 (n = 14,606).

## 3.2. Regional differences

The incidence of cervical carcinoma varies worldwide between 3.6 (in Finland) and 45 (in Peru) per 100,000 women per year. In Germany, the incidence in 1971 was 45 per 100,000 (figures for the state of Saarland), while in 2014 it was 9.1 per 100,000 (figures from GEKID for Germany as a whole [11]). In a comparison with the EU countries, Germany's age-standardized rates for new cases and mortality were thus at place 13 out of 28 countries for incidence and 15 out of 28 for mortality. The Cytology Committee of the 17 Associations of Statutory Health Insurance Physicians reported to the Federal Association of Statutory Health Insurance Physicians that in 2016 there were 26,453 women with cervical intraepithelial neoplasia 3 and 637 women with adenocarcinoma in situ (AIS) [8]. Data from Austria show that the incidence of precancerous

cervical lesions in women in the 21–30-year-old age group increased significantly in 1985–1989 in comparison with 1980–1984, with a fourfold increase [9]. A similar trend has also been reported in individual studies on populations in Germany [10]. One possible explanation for this might be the higher rate of participation in early detection examinations for early cancer, as well as changes in lifestyle (e.g., nicotine abuse, combination oral contraceptives, earlier sexual activity).

## 3.3. Histological subtypes

Squamous cell or nonsquamous cell carcinoma, as well as adenocarcinoma and adenosquamous carcinoma, are the most frequent histological types. Squamous cell carcinoma is present in approximately 80% of cases. The proportion of adenocarcinomas has increased during the last 25 years from 10% to approximately 20% [23] [12] [13]. Other tumor entities such as mixed forms (adenosquamous), neuroendocrine (large cell or small cell) or clear cell or serous papillary carcinomas are rare.

Reasons for the increase in adenocarcinomas may include improved histopathological classification of cervical carcinoma and the increasing role played by cofactors in carcinogenesis; adenocarcinoma in situ (AIS) is diagnosed in an endocervical location during screening more rarely than preinvasive squamous cell lesions (cervical intraepithelial neoplasia, CIN) [14] [15] [16] [17] [18][19][19][20][21][22] [21]. Research is still continuing to determine whether HPV vaccination is leading to a shift in the histological subtypes. Reference may be made here to the relevant Level 3 guideline on “Prevention of Cervical Carcinoma” (AWMF registry no. 015/27OL) and to the Level 3 guideline on “Vaccine Prevention of HPV-Associated Neoplasia” (AWMF registry no. 082/002).

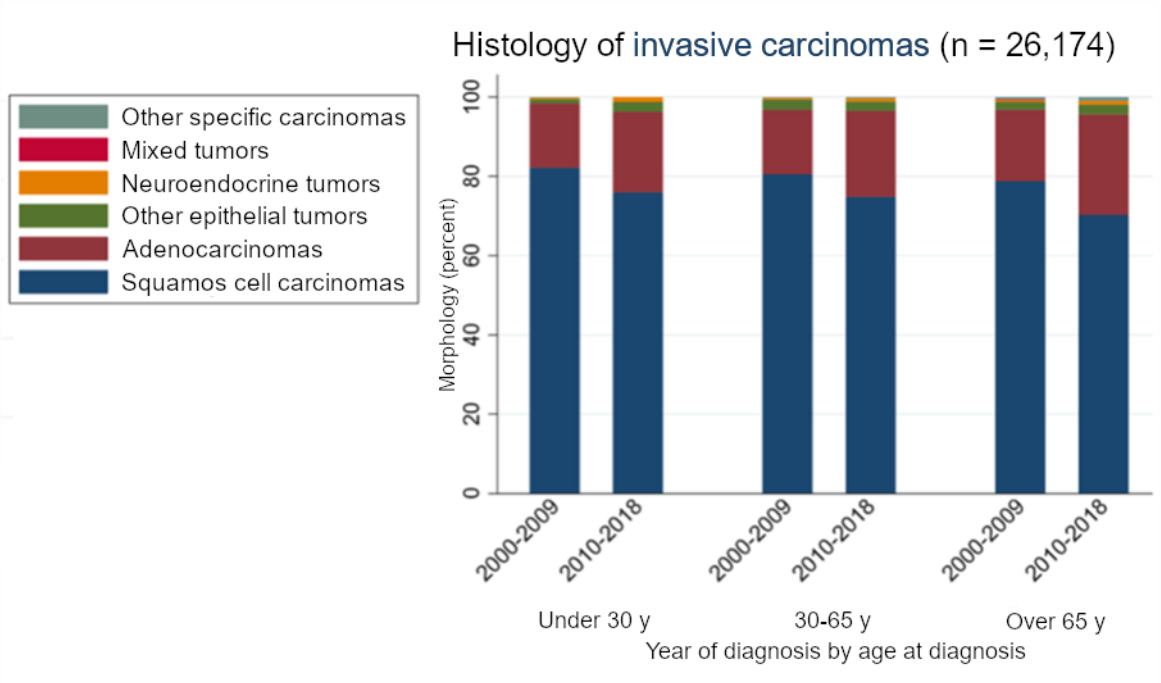



**Figure 1: Morphology of cervical carcinoma. Source: Arbeitsgemeinschaft Deutscher Tumorzentren, 2021 [24]**

## 3.4. Risk factors and disease development

The etiology and pathogenesis of cervical carcinoma have not yet been conclusively explained. The carcinogenetic process is multifactorial, with varying importance and interactions among the influencing factors. Different groups of risk factors for the development of invasive cervical carcinoma have been distinguished:

**Major risk factors**

- Infection with human papillomavirus (mainly HPV type 16+18; see section 3.4.1)
- Precancerous lesions/dysplasia — low-grade squamous intraepithelial lesion (LSIL); high-grade squamous intraepithelial lesion (HSIL), and adenocarcinoma in situ (AIS)

**Nongenetic risk factors / cofactors** [24] [25] [26] [27] [28]

- Smoking (> 15 cigarettes per day)
- Patients with immunosuppression (HIV, medications)
- Early start of sexual activity (< 14 years of age)
- Frequently changing sexual partners (more than four in 10 years)
- Other infections (e.g., genital herpes, chlamydiae, gonococci)
- Low socioeconomic status
- Poor sexual hygiene
- Long-term use of oral contraceptives, > 5 years (for possible confounding factors, see section 3.4.2)
- Large number of births

**Genetic risk factors / co-factors**

- Additional factors such as genetic variations (somatic) may influence the development of tumors. The extent to which these are of clinical relevance is as yet unclear. They have an odds ratio with just under a twofold increase [29][30]. By comparison, the OR for HPV high-risk positivity is 150, while with HPV 16 positivity it is as high as over 400 [31]. Nicotine abuse, with an OR of 2.17, also represents a higher risk [32]. Research is currently focusing on single nucleotide polymorphisms (SNPs) in the following genes, with no claim to completeness in the listing:
- HPV persistence: IRF 3, OAS3, SULF1, DUT, GTF2H4, FOXP3
- Progression to invasive cervical carcinoma: FANCA, IFNG, EVER1/EVER2, FAS
- Specific to cervical carcinoma: TP 53, CCND1
- Genes with a general disposition toward tumor development: ATM

### 3.4.1. HPV infection

An underlying infection with human papillomavirus (HPV) is almost always present with cervical carcinoma. Etiologically, the development of cancer is associated with infection with high-risk human papillomaviruses (mainly HPV types 16, 18, 45, 31, 33, 58, 52, 35, 59, 56, 6, 51, 68, 39, 82, 73, 66, and 70). However, the infection only persists in 5–10% of patients and only around 3% of women who are infected with papillomavirus actually develop cervical carcinoma [33].

This topic is discussed in detail in the Level 3 guidelines on “Vaccine Prevention of HPV-Associated Neoplasia” (AWMF registry no. 082/002) and “Prevention of Cervical Carci-

noma" (AWMF registry no. 015/027OL), and reference may be made to these. In particular, patients with known immunodeficiency or immunosuppressive therapy and HPV infection require particularly closely scheduled follow-up examinations in the framework of early cancer detection.

### 3.4.2. Hormonal contraception

There has been discussion regarding an increased risk of cervical carcinoma developing in patients with an existing HPV infection who are simultaneously taking oral contraceptives. The use of mainly combined oral contraceptives (with estrogen and gestagen components) for a longer period (five or more years) is associated with an increased risk for cervical carcinoma [25]. It was shown in an analysis of 24 epidemiological studies that more prolonged use of oral contraceptives is associated with a greater risk of disease [24]. On the other hand, a reduction in risk has been observed after cessation of oral contraceptive use, independently of the previous period of contraceptive use [24].

A report produced in 2002 by the International Agency for Research on Cancer, which is part of the WHO, examined data from eight studies dealing with the association between the use of oral contraceptives and the risk of cervical carcinoma in HPV-infected women. The analysis showed a threefold higher risk among women who had taken oral contraceptives for 5–9 years in comparison with women who had never taken oral contraceptives. In women who had used oral contraceptives for 10 years or longer, the risk of developing cervical carcinoma was four times higher [27]. These findings were confirmed by another cohort study in 2016. Oral contraceptive use was associated with an increased risk of both CIN 3/HSIL and also invasive carcinoma (HR 1.6 and 1.8, respectively, for > 15 years versus never taken). Placement of a hormonal coil appeared to have a protective effect on the development of CIN 3/HSIL or cervical carcinoma. However, this was not statistically significant (OR 0.7; 95% CI, 0.5 to 0.96). The authors of the study explain the protective effect with the chronic inflammatory reaction caused by the coil. This may reduce the persistence of the human papillomavirus [34].

Nearly all cervical carcinomas are caused by high-risk or oncogenic HPV subtypes, and the association with oral contraceptives is probably indirect (as a cofactor). The hormonal influence of oral contraceptives may make the mucosal cells of the cervix more receptive for viral infection, or may diminish local defenses against infection, or may influence the mutation leading to cancer developing in HPV-infected cells. It can be assumed that this indirect path mainly occurs in combination oral contraceptives with estrogen and gestagen components, increasing the risk of mutation. Drugs containing only gestagens (minipills) do not appear to increase the risk of cervical carcinoma developing [24] [26]. Research is currently still continuing on issues involving the development of disease in patients receiving oral contraceptives. It is also possible that long-term contraception may represent a confounding factor (with earlier start of sexual activity, more sexual partners) [26].

## 3.5. Protective factors

Nutritional factors (e.g., citrus fruit, diet high in vegetables, garlic, onions, vitamins C, E, and A1) may play a protective role to some extent. Stopping smoking and taking steps to avoid genital infections and sexually transmitted diseases are relatively easy ways of reducing risk. A meta-analysis of 17 studies including 7537 women and 4945 cases of cervical cancer showed that the use of an intrauterine device (IUD) reduced the risk of developing cervical cancer (OR 0.64; 95% CI, 0.53 to 0.77). The reduction in

incidence was observed in all 17 studies. However, the meta-analysis was to able to drawn any conclusions concerning the duration of IUD use or the type of IUD (e.g., copper vs. hormone) [35].

# 4. Prevention and early detection

**Major changes in the chapter on prevention and early detection**

This chapter has been considerably shortened. Detailed information is provided in the complementary Level 3 guideline on the prevention of cervical carcinoma (AWMF register no. 015/027OL).

*P. Hillemanns, B. Mangold, R. Lellé, M.C. Koch, M.W. Beckmann, M. Jentschke*

| 4.1 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | Recommendations on the prevention and early detection of cervical carcinoma are presented in the Level 3 guidelines (S3) "Vaccine Prevention of HPV-Associated Neoplasia" (AWMF register no. 082/002) and "Prevention of Cervical Carcinoma" (AWMF register no. 015/027OL). | |
| | Strong Consensus | |

## 4.1. Primary prevention - HPV vaccination

Recommendations on primary prevention of cervical carcinoma by vaccination against the high-risk genotypes of human papillomavirus (HR-HPV), HPV 16 and 18, are given in Germany in the Level 3 guideline on "Vaccine Prevention of HPV-Associated Neoplasia" (AMWF register no. 082/002), by the Paul Ehrlich Association for Chemotherapy (HPV Management Forum Working Group), the German STI Association, the German Dermatological Association, and in the recommendations of the Standing Vaccination Committee of the Robert Koch Institute (STIKO).

Infection of the cervical epithelium with high-risk types of human papillomavirus (HPV) is the main cause of the development of cervical carcinoma. More than 95% of cervical carcinomas are HPV-positive, with HPV type 16 being found in 50–60% and HPV type 18 in 10–20% of the carcinomas [38] [39]. In German studies, approximately 60% of all high-grade cervical intraepithelial neoplasias (CIN 2/3) have been found to be associated with HPV types 16 and 18. The risk of infection with HPV increases with the number of sexual partners. Consistent use of condoms reduces the risk of transmission, but does not provide absolute protection against infection [40]. HPV is a common sexually transmitted infection. The risk of infection with HPV increases with the number of sexual partners. Consistent condom use reduces the risk of transmission but is not absolute protection [41]. Cofactors that influence the risk of HPV-positive women developing invasive carcinoma include prolonged use of oral contraceptives, smoking, high parity, immunosuppression, HIV infection, and other genital infections such as chlamydia or herpes [37]. HPV infection is common, but not all patients develop manifest dysplasia or carcinoma, as the rate of spontaneous recovery is high.

TThe bivalent and nonavalent HPV vaccines that are currently approved contain noninfectious virus-like particles (VLPs) without any viral DNA and are directed against HPV 16/18 and in the nonavalent vaccines against HPV 6/11/31/33/45/52/58 in addition. These VLPs can stimulate the humoral and in some cases also the cellular immune system [42]. Many studies have confirmed that the vaccines are remarkably effective for prophylaxis in young women with no exposure to HPV, women aged 25–45, and also in HPV-naïve men and in children against vaccine type–specific anogenital diseases

[36]. The safety profile of these vaccines is very good — after two decades of their use. In several countries with high rates of vaccination coverage, a significant decline in genital warts (> 90%) and a reduction in the numbers of cases of intraepithelial neoplasia among young women have been recorded.

On the basis of theoretical vaccine efficacy, the nonavalent HPV vaccine introduced in 2016 will provide marked improvements of 90% against invasive cervical carcinomas, 75–85% against CIN 2/3, and 50–60% against CIN 1 [43] Studies have also confirmed very high effectiveness relative to the end points of vaccine type-specific intraepithelial neoplasia of the cervix, vulva, and vagina [44]. The current vaccination rate is 44.6% according to the RKI in 2018 and 57.9% after at least one vaccination dose. There is increasing evidence from national registry analyses — from Australia, for example — that a single vaccination provides adequate immunity.

The STIKO recommends general vaccination of all girls and boys aged 9–14. Vaccination with two vaccination doses at an interval of 6 months should be completed if possible before the first sexual intercourse [45]. A third vaccination dose is required above the age of 14. Repeat vaccination should be given by age 17. Since 2018, HPV vaccination is now also recommended by the STIKO for all boys aged 9–14. The background to this is the significant reduction in the disease burden of HPV-associated tumors in both sexes that can be expected with the current vaccination rates among girls as a result of the additional vaccination of boys [46].

## 4.2. Secondary prevention - early detection of cervical carcinoma

Recommendations for secondary prevention of cervical carcinoma are dealt with in the Level 3 guideline on “Prevention of Cervical Cancer,” register no. 015-027OL, under the auspices of the German Association for Gynecology and Obstetrics (DGGG) [47].

Primary screening and diagnosis are regulated in the guideline published by the Federal Joint Committee (G-BA) on November 22, 2018 on organized cancer screening programs and the program for the early detection of cervical carcinoma.

### 4.2.1. Early detection of cervical carcinoma in Germany

Early detection examinations for cancer were introduced in Germany on 23 June 1971, in accordance with the guidelines of the Federal Committee of Physicians and Health Insurance Funds. Through the Federal Joint Committee (G-BA), which was established in 2004, statutory reimbursement for early detection examinations for cancer has been further developed in guidelines in accordance with Section 92, paragraph 1, clause 2, no. 3 of the German Social Security Code (SGB) and Section 25, paragraph 2 of SGB V (Cancer Early Detection Guideline [KFE-RL], March 3, 2011). Entitlement to early detection examinations is established by statute in SGB V (Sections 25 and 26). With regard to cervical carcinoma, one genital examination per year is carried out starting from the age of 20. This consists of specific questioning, inspection of the cervix and uterine orifice, speculum examination of the vaginal portion of the cervix, taking a smear from the surface of the ectocervix and cervical canal and cytological examination of it (Pap smear), and gynecological palpation of the vagina. The examination also includes discussion of findings in the case of unusual cytological results. The costs are covered by the statutory health insurance funds.

The current average rates of participation in cancer screening examinations for cervical carcinoma are not reported by the Central Institute of Statutory Health-Insurance Physicians. Reasons for this include the widely differing participation rates among younger and older age groups, as well as the separate surveying conducted in the individual federal states. According to an analysis of data from the Statutory Health Insurance Fund (AOK) for Lower Saxony, the maximum average annual participation rate is around 45% [48]. Lower participation rates were observed in patients with lower professional qualifications. The highest rate was among 25–29-year-olds (annually approx. 60%; biennially approx. 77%). The biennial participation rate among women aged 30–39 was approx. 70%, while in the 50–59-year-old age group it was approx. 55%. Overall, there were no relevant differences between the 2-year (63.4–66.5%) and 3-year rates (64.4–67.6%). More than 30% of women did not participate in screening during a 3-year period.

As part of the quality assurance agreement (Section 8), physicians practicing cytology are required to submit their annual statistics to the relevant Associations of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen, KV). The cytology committees convened by the associations evaluate the submitted data, which are then sent in anonymized form to the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung). A total of 1898 squamous cell carcinomas, 679 adenocarcinomas, 26,453 CIN 3 lesions, 637 AIS, and 1795 extracervical malignancies, mostly endometrial carcinomas, were registered in the annual statistics for 2016. In all, 97.22% of the 15,839,847 women screened had unremarkable findings. A total of 441,027 screening participants had cytological findings requiring further examination. Histological analysis was performed for 51,195 women. This figure represents 0.32% of all the women screened [8].

The accuracy rate for lesions ≥ CIN2 was over 90% for Pap IVa-p. The accuracy rate for lesions ≥ CIN3 was over 97 % for Pap V-p [8].

The annual statistics indicate the frequency of pathological findings and the accuracy of group IV-p and V-p findings for carcinomas and precursor lesions. However, important information such as the corresponding histological correlate is lacking for the Pap groups II, III and IIID1/2, making it difficult to calculate the risk or draw conclusions about which diagnostic measures are preferable [8].

### 4.2.2. New program for early detection of cervical carcinoma starting in 2020

Recent findings from meta-analyses of randomized and controlled studies and cohort studies using testing for high-risk genital human papillomavirus (HPV) in comparison with cytology led to discussions concerning the further development of cervical cancer screening. The aims were to improve the sensitivity of the examination and to increase the participation rate. Following intensive discussions among the various groups of interested parties, the G-BA defined the design of the future screening program at a meeting held on September 15, 2018 and set it out in the a guideline [49] [50]. The guideline is largely based on the recommendations of the Level 3 guideline on prevention of cervical carcinoma [47], [49]. Organized screening in Germany started on January 1, 2020:

- For the first time, women are entitled to cervical cancer screening services starting from age 20: eligible women (Section 5) qualify to receive an invitation, information and explanations, cytology-based or combined primary screening with

a clinical examination, reporting of findings and counseling (Section 6), and further diagnosis (Section 7).

- Women aged 20–34 are eligible for annual cytology-based cervical cancer screening in accordance with Section 6, paragraph 3. If a negative HPV test is obtained, women aged 30–34 with Pap group II-p or II-g cytology results are eligible for repeat participation in primary screening.
- In the future, women aged 35 and over are to be offered a combination examination consisting of an HPV test and a cytological examination every 3 years instead of the annual cytological examination.
- Eligible women will be invited to participate when they reach the age of initial eligibility. Further invitations are to be issued in each case at the ages of 25, 30, 35, 40, 45, 50, 55, 60, and 65.
- No upper age limit has been set. However, women should be informed about the conditions in which stopping screening will only involve a low residual risk of cervical cancer.
- During a transitional phase of at least 6 years, data will be collected as part of the monitoring process to determine whether further changes in the screening strategy are needed.

# 5. Providing patient information

**Major changes in the chapter on patient information**

This chapter has hardly been changed. It has been revised in line with the existing current versions of the guidelines on breast carcinoma, ovarian carcinoma, and prostate carcinoma. The chapter has been expanded to include a recommendation based on the Level 3 guideline on breast cancer, and one statement has been revised.

*A. Sevnina, F.A. Stübs, H. Haase, R. Wiedemann, F. Mumm, M.W. Beckmann*

## 5.1. Patient information and education content

This section is closely adapted from the existing Level 3 guidelines on "Diagnosis, Treatment, and Follow-up in Breast Carcinoma" (AWMF register no. 032/045OL) and "Diagnosis, Treatment, and Follow-up for Malignant Ovarian Tumors" (AWMF register no. 031/035OL), as gynecological tumors in women, and on "Early Detection, Diagnosis, and Treatment for the Various Stages of Prostate Carcinoma" (AWMF register no. 043/033OL), as an additional lower abdominal tumor. The guideline group considered that the recommendations adopted in those guidelines at the expert consensus level are transferable [51], and they have been adapted where necessary to the specifics of the disease.

Duties connected with providing information to patients have been regulated since 2013 in the new "Law on Improving Patients' Rights" (PatRechte G; came into force on February 26, 2013). The German parliament approved the draft law on November 29, 2012. The law is concerned with the following aspects: duties to provide information between the physician and the patient, consent, duties to provide information, documentation of treatment, inspection of the patient's files, and burden of proof for liability in case of errors in treatment or in providing information. This legal regulation is associated with duties that have a legal character and go beyond the framework of guideline recommendations.

| 5.1 | **Consensus-based Recommendation** | **checked 2021** |
|---|---|---|
| **EC** | High-quality and pertinent information materials (using print or Internet media) ***shall*** be produced in accordance with defined quality criteria for health information and made available to patients, to support them in independent decision-making for or against medical measures by providing generally comprehensible risk information (e.g., with details of absolute risk reductions). | |
| | Consensus | |

The recommendations are based on an expert consensus and on the corresponding recommendations in the Level 3 guideline on breast carcinoma (version 4.2, 2019) [52].

Providing patients with comprehensible information and nuanced explanations is becoming increasingly important as a result of the use of new information technologies such as the Internet, as well as patients' increasing need for information and participation in the treatment of their disease. The importance of information and explanations for the physician–patient relationship, the course of the disease, and success in achieving the goal of treatment has been confirmed in numerous studies [53] [54] [55].

Providing patients with information, without prejudging the outcome, in combination with joint (participatory) decision-making, is what makes medical work possible in the first place.

Four ethical principles are at work in these interactions, according to the established Beauchamps & Childress model:

- Respect for patients' autonomy
- Avoidance of harm (non-maleficence)
- Beneficence
- Equality and justice [56]

Two ethical principles are at work in these interactions — the patient's self-determination (autonomy) and the physician's medical care [56]. The patient's autonomy is the highest value here. A decision made by the patient is always voluntary and places obligations on medical action. Patients may express preferences for or against medical measures in diagnosis and treatment, or may also decide in favor "not wanting to know." In order for patients to be able to make a decision that constitutes effective consent ("informed consent"), any information deficits they may have must be compensated for by the physician. Patients can approve or oppose medical measures in diagnosis and treatment, or may decide that they "do not want to know." To enable patients to take decisions in the sense of effective consent ("informed consent"), any information they may lack needs to be supplied by the physician. The personal discussion between the patient and the physician is particularly important as the basis for trusting and respectful understanding. Participatory decision-making is extremely important here ("shared decision-making") [52].

The discussion involves a process that follows specific rules and an intensive exchange of information between the physician and the patient and leads to a decision by the patient, supported by both parties, regarding the implementation of medical measures.

The prerequisite for participatory decision-making is a patient-centered discussion. The information provided by the physician must be comprehensive, true, complete with regard to the type of measure required and its purpose, benefits and risks, and in particular it must be comprehensible (including details of frequencies instead of relative percentages) [57] [58]. The patient's individual somatic, psychological, and social situation, age, and comorbidities should be taken into account during the discussion. Anxieties and worries, specific burdens, and in particular the patient's information needs, treatment expectations, and preferences, should be directly addressed by the physician [52] [58] [59] [60] [62]. The information provided by the physician for the patient should cover the following aspects: information about the disease, examination results that have been obtained, the course of treatment to date, diagnostic and therapeutic options including their expected side effects, and assessments of the associated prognoses and effects on the patient's life plans [52] [61] [63].

Preparing and providing access to written information is a further supportive and helpful measure for the patient's decision-making process [64]. The written information includes expert, factually competent, comprehensibly prepared, and quality-assured information materials [52] [61] [63].

### 5.1.1. Diagnostic message

| 5.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The patient ***shall*** be informed that their partner or a relative can be invited to be included in the discussion(s). | |
| | Strong Consensus | |

Providing patient information is an interdisciplinary task for all the professional groups involved in oncological care. Although providing the patient with medical information is primarily the physician's task, it should be supported by other professional groups such as nurses, psycho-oncologists, etc. for specific topics [65].

| 5.3 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | During the medical discussion, the patient's individual preferences, needs, worries, and anxieties ***shall*** be identified and taken into account. If a patient needs several discussions for the purpose, an offer of further discussions ***shall*** be available. | |
| | Strong Consensus | |

| 5.4 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| EC | Providing the patient with medical information is primarily a task for the attending physician, but for specific topics it ***should*** be provided by other professional groups such as nurses, psycho-oncologists, etc. | |
| | Strong Consensus | |

The Dartmouth-Hitchcock Medical Center in New Hampshire, USA, can be used as an example to illustrate the way in which patient information can be implemented as an interdisciplinary task. Since 1999, patients have been offered decision coaching in the Center for Shared Decision Making in order to clarify individual preferences and prepare for consultation with their physician. Decision-making aids are also provided during this process. The goal is to facilitate shared decision-making and informed decisions. The role of decision coaches is played in particular by nurses [70]. In Germany, corresponding curricula for qualification as a decision coach have already been developed for the areas of breast cancer [67] and multiple sclerosis [69]. These curricula are intended to enable nurses to provide decision coaching using evidence-based decision-making aids. Providing written information and offering access to it is supportive and helpful for the patient in reaching decisions [66] [68]. This includes specialist and factually authoritative information materials that are prepared in a comprehensible manner and are quality-assured [65].

Patients' rights legislation in Germany refers to the "person providing treatment" rather than to a "doctor" [71]. The guideline group therefore agreed on the compromise "attending physician." This is because the vast majority of medical information is provided by doctors.

| 5.5 | **Consensus-based Recommendation** | **modified 2021** |
|---|---|---|
| **EC** | Information ***shall*** be communicated and provided to the patient as early as possible on the basis of the following basic principles of patient-centered communication allowing participatory decision-making:<br>• Expressing empathy and active listening<br>• Direct, empathetic raising of difficult topics<br>• Avoiding specialist medical vocabulary, with specialist terms being explained if needed<br>• Using strategies for improving comprehension (repetition, summing up important information, using diagrams, etc.)<br>• Encouraging the patient to ask questions<br>• Permitting and encouraging expressions of emotion<br>• Offering further assistance | |
| | Consensus | |

| 5.6 | **Consensus-based Recommendation** | **checked 2021** |
|---|---|---|
| **EC** | The patient ***should*** be offered psychosocial and psycho-oncological support for psychological, sexual, and relationship problems. | |
| | Strong Consensus | |

| 5.7 | **Consensus-based Recommendation** | **checked 2021** |
|---|---|---|
| **EC** | The patient ***shall*** be informed about the option of contacting self-help groups. | |
| | Strong Consensus | |

As soon as a histopathological diagnosis of cervical carcinoma has been confirmed, the patient must receive information from the physician treating her in accordance with the criteria described above [52]. Basic patient information has usually already been provided by the private-practice physician or the physician who made the initial diagnosis or who has identified a recurrence or metastasis. As the period between and during the establishment of the diagnosis and the start of treatment is often very difficult for the patient, options for contacting self-help groups, making use of psycho-oncological care, and psychosocial cancer advice should already be mentioned at this early timepoint, depending on the situation (see also the Level 3 guideline on "Psycho-oncological Diagnosis, Consultation and Treatment in Cancer Patients" (AWMF register no. 032/051OL)). Contact details for local self-help groups are available from the National

Contact and Information Service for Promoting and Supporting Self-Help Groups (NAKOS):

Nationale Kontakt-und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen (NAKOS)

Otto-Suhr-Allee 115, 10585 Berlin

Tel.: 030 31018960 Fax: 030 31018970

E-mail: selbsthilfe@nakos.de

Internet: www.nakos.de

Contact details for advice services and places to go for patients with cervical carcinoma will also be available in the accompanying patient guideline.

The treatment that is ultimately recommended, alternatives to it, and the effects in each case are then discussed once again, possibly in a new discussion with the physician who will ultimately be administering the treatment (e.g., whether treatment should be carried out in the framework of research studies, whether surgery is possible, etc.) — as all of the information about the disease (with staging, etc.) is often not yet available at the first diagnosis. It is up to the patient whether her partner or a relative, or someone she trusts, should be included in the discussion or discussions. The discussion should take place in a form that is comprehensible and appropriate for the patient and in an appropriate framework [72]. The physician must inform the patient in accordance with the facts, without playing any matters down; despite this, hope for a cure or hope for alleviation, depending on the stage of the disease, should not be obstructed. The physician providing information should ensure that it corresponds to the current state of treatment [52]. It is not the patient's signature on the consent form that should be regarded as constituting patient information, but rather the start of the discussion about the disease and the documented treatment options. The signature represents the provisional END of the process of providing information.

### 5.1.2. Providing information about treatment

| 5.8 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In accordance with the "Law on Improving Patients' Rights," the patient ***shall*** be informed about all of the treatment options described in this guideline that are relevant to them and about their prospects of success and possible effects. In particular, effects on their physical appearance, sexual life, urinary and rectal continence, and aspects of female identity (self-image, fertility) should be mentioned. | |
| | Consensus | |

The physician providing information should explain the recommendations for a specific form of treatment, particularly if there is a case-related and consensus-based treatment recommendation from a multidisciplinary conference, and should present the principles of treatment and its benefits and risks. Evidence suggests that repeated recording of the patient's wishes (decision preferences) during the treatment process is necessary in order to adequately involve the patient in the decision-making process [65].

In addition to his or her duty to inform (Section 630c), the attending physician is obliged under Section 630d of the "Act on Improving Patients' Rights" (PatRechte G) to inform the patient orally, personally, and in a timely manner "of all circumstances essential to consent. This includes, in particular, the nature, scope, implementation, expected effects and risks of the measure, as well as its necessity, urgency, appropriateness, and prospects of success in relation to the diagnosis or therapy. The information must also refer to alternatives to the measure if several medically equally indicated and customary methods can lead to substantially different burdens, risks, or chances of recovery."

Specifically, this refers to information about treatment recommendations, particularly when they have been agreed by consensus in a case-related interdisciplinary conference. The principles of treatment and potentially expected benefits and risks must be presented. Alternative forms of treatment, which may be possible for the patient in the context of participation in a clinical study, for example, should be explained. Effects on the patient's lifestyle and quality of life should be mentioned in the discussion.

Particularly when providing information to premenopausal women, the effects of the treatment on fertility, as well as contraception issues, must be included. In addition, questions regarding the treatment of therapy-related ovarian insufficiency, its symptoms and treatment options should be discussed. Women should also be informed about options for fertility-preserving measures and referred to appropriate experts for advice if appropriate [73]. Due to the importance of tumor-associated fatigue as a sequela of adjuvant therapy, as well as the available evidence for preventive strategies such as physical exercise and educational measures, patients should be informed about options for prevention at an early stage [74]. The patient must be informed about measures for preventing lymphedema, the need for oncological follow-up, rehabilitation (see below), and social, financial, and psycho-oncological support [75]. For the above-mentioned areas (rehabilitation, social counseling, psycho-oncology), further specialist counseling should be recommended and initiated if needed. Every treatment requires the patient's collaboration. Aspects that lie in the area of personal responsibility should be addressed. This section has been taken from the new Level 3 guideline on breast cancer, version 4.3 [65].

Matters to be included in the information discussion can be taken from the following information box as an orientation guide, with no claim to completeness or inclusion of every specific situation or patient request. It is important to make a distinction here between the standard treatment procedure — i.e., the treatment that is currently best supported by evidence and universally available; and experimental treatment procedures — i.e., procedures that have only been evaluated by individual centers. A separate recommendation has been formulated for the special situation of an information discussion in the palliative situation. However, this can also make no claim to completeness in relation to matters possibly to be included in an information discussion. These suggestions should of course also be discussed with the patient in ways adapted to the relevant disease stage.

| 5.9 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | Principles, intended treatment goals, duration and implementation of the individual treatment measures<u>Surgical treatment measures:</u><br>• Conization; trachelectomy<br>• Surgical staging and associated additional measures<br>• Types of lymphadenectomy<br>• Types of radical hysterectomy<br>• Exenteration procedures<br>• Surgical options in case of recurrence<br><br>Radiotherapy:<br>• Primary radiotherapy / radio(chemo)therapy<br>• Secondary radiotherapy / radio(chemo)therapy<br><br>Systemic therapy:<br>• Neoadjuvant/adjuvant chemotherapy<br>• Combined radio(chemo)therapy<br>• Targeted therapy<br><br>Side effects of treatment and ways of treating themLate sequelae of the disease and therapy and ways of treating themComplementary therapy:<br>Mention of the availability of complementary medicine to reduce side effects<u>Participation in clinical studies:</u><br>• Principles and intended treatment goals<br>• Duration and implementation of therapy<br>• Effects and side effects currently known<br>• Special aspects (monitoring, additional measures, compliance, data storage and processing)<br><br>Other information:<br>• Psycho-oncological support and services provided by self-help groups<br>• Options for rehabilitation<br>• Necessity of follow-up care<br>• Aspects of patient's own responsibility and compliance (e.g., providing information about symptoms and problems, treatment compliance) | |
| | Strong Consensus | |

The above recommendation is based on expert opinion and is borrowed from the Level 3 guideline on breast carcinoma (version 4.3) [65].

Another important point is mentioning side effects and interactions between drugs and complementary medicine. These should be explicitly included in the patient information, as there is strong demand among patients for complementary medicine measures both in the primary setting and after recurrences or metastases (see GGPO-Guideline Complementary Medicine in the Treatment of Oncological Patients, AWMF registry no. 032/055OL) [77].

The patient must be informed about the necessity for oncological follow-up care (see Chapter 16), rehabilitation (see Chapter 15), and about social, financial, and psycho-

oncological support (see Chapter 13). Further specialist counseling should be recommended and initiated in these areas if needed (rehabilitation, social medicine, psycho-oncology). Every treatment requires the patient's collaboration. Aspects that lie within their own area of responsibility should be mentioned [76]. The patient can be motivated to take part in treatment and also in follow-up through regular follow-up appointments and by being spoken to personally when prescriptions for supportive measures are being issued.

| 5.10 | Consensus-based Recommendation |
|---|---|
| EC | The patient ***shall*** be informed about the patient guideline on diagnosis, treatment, and follow-up for patients with cervical carcinoma. |
| | Consensus |

This recommendation is based on an expert consensus and is borrowed from the corresponding recommendation in the Level 3 guideline on breast carcinoma (version 4.3) [65]. PThe physician should encourage patients to request more information and should support their desire for active participation, by providing direct and practical aids for achieving these goals [78] [79]. These include mention of written information that is available, particularly the patient guideline, as well as decision-making aids, addresses of self-help groups, cancer information services, Internet addresses, and the option of keeping their own patient diary/case history [52].

In collaboration with patients' representatives, an evidence-based patient guideline is being compiled on the basis of the content of the present guideline (http://leitlinienprogramm-onkologie.de/Patientenleitlinien.8.0.html) oriented to the contents of the present guideline will be developed. Another independent patient information web site, http://www.patienten-information.de is run by the Federal Medical Council and the Federal Association of Statutory Health Insurance Physicians and provides both an overview of numerous items of patient information on the subject and also a transparent quality evaluation of the information, so that the patient can reach her own conclusions about the seriousness and reliability of the information offered [51].

| 5.11 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | Cervical carcinoma is not an emergency case. The patient can and ***shall*** be given sufficient time for their own decision-making processes. | |
| | Consensus | |

This recommendation is based on expert opinion and is borrowed from the Level 3 guideline on ovarian carcinoma (version 4.0) [83].

The strength of the desire for information and inclusion in medical decisions varies widely among the affected patients (and also among their relatives), and may change over time [80] [81] [82]. When communicating information, the physician treating the patient should take this into consideration by leaving the patient sufficient time to process the information, and if needed offering several short discussions if possible

instead of a single discussion, leaving sufficient room for emotions and communicating emotional security through empathetic behavior (see recommendation 5.12). Following the principle of participatory decision-making, the amount of information being communicated should be adapted to the patient's needs according to the situation during the entire chain of diagnosis, treatment, and care.

#### 5.1.2.1. Contents of informed consent discussion with a patient with metastatic or recurrent cervical carcinoma

| 5.12 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The following points ***can*** be mentioned as forming the content of a discussion in the palliative situation:Aims of palliative medical therapy (alleviating suffering, treatment of pain — foremost goal: the patient's quality of life)<br>• Patient's anxieties and fears, with inclusion of her partner and relatives<br>• Radio(chemo)therapy — duration and intended effect<br>• Palliative drug treatment<br>• Palliative surgical treatment<br>• Individual treatment decisions, depending on the patient's personal life plans<br>• If the effectiveness of a treatment is limited, the result of the decision-making process may be to deliberately refrain from palliative tumor treatment<br>• Mention of different aspects of palliative care (rehabilitation, psychosocial medicine, psycho-oncology)<br>• Side effects and interactions of drugs and complementary medicine<br>• Involvement of local hospice group if appropriate<br>• Consultation with physicians and nursing services specializing in palliative medicine<br><br>Problem situations arising during the course of disease:<br>• Pain<br>• Ureteral stenosis leading to renal failure<br>• Fistulas<br>• Fetid discharge<br>• Bleeding<br>• Paralytic or mechanical ileus<br>• Thrombosis, pulmonary embolism<br><br>Symptomatic and supportive therapy:<br>• Treatment for lymphedema in the lower extremities<br>• Pain therapy<br>• Dysuria/bladder spasms<br>• Psychosocial and religious/spiritual assistance for the patient and her relatives<br>• Resources for assistance | |
| | Consensus | |

The above recommendation is based on a consensus among the participating experts. The guideline group would further refer the reader to the higher-level interdisciplinary

Level 3 cross-sectional guideline on “Palliative Medicine for Patients with Incurable Cancer” (AWMF register no. 128/001OL), the guideline on “Supportive Therapy in Oncological Patients” (AWMF register no. 031/054OL), and the guideline on “Psycho-oncological Diagnosis, Consultation and Treatment in Cancer Patients” (AWMF register no. 032/051OL), as well as the relevant sections of the present guideline. Here again, the physician should take into account the special discussion situation for the patient (and their relatives if appropriate) (see section Chapter 5.1.2).

# 6. Diagnosis

**Major changes in the chapter on diagnosis**

Some parts of the chapter on diagnosis have been significantly altered. The basis for diagnosis is still the existing TNM classification. In the current FIGO classification dating from 2018, staging on the basis of bimanual examination by the gynecologist has been abandoned and radiological sectional imaging has additionally been taken into account. FIGO regards this as providing benefits for communications within the multidisciplinary team and in improving care for patients with cervical cancer. Although the staging of cervical carcinoma is still clinical, the results of radiologic imaging and biopsies can be included in the assessment of all stages. In patients with cervical carcinoma from at least FIGO IB2 up to and including FIGO III in whom pelvic MRI is not possible for technical reasons, locoregional imaging should be carried out as part of the staging CT of the chest, abdomen, and pelvis. PET-CT is still not recommended in the diagnosis of primary cervical carcinoma, but it can be used in the setting of recurrences to exclude larger lymph-node metastases and distant metastases before planned local procedures.

*C.D. Alt, M.C. Koch, F.A. Stübs, E. Merz, J. Menke, M. Reinhardt, B. Zimmer*

## 6.1. Definition of stages — terminology

The 2014 WHO classification [84] is authoritative for characterizing tumors. The 2010 TNM classification [85] applies to the staging of the histological specimen, along with the FIGO 2018 classification optionally (see Table 9). In addition to these clearly defined tumor stages, the literature includes a number of neologisms and unclearly defined terms. These are listed here and an attempt is made to translate them into the authoritative 2010 TNM/UICC classification [85] (Table 9). The guideline group makes a distinction here between microinvasive and macroinvasive carcinomas, but it is clearly shown here that the histological risk factors also have to be stated in order to clearly define the stage, risk, and prognosis, and thus ultimately the treatment indication as well (see section 8.6). The guideline group also regards the distinction between regional and distant metastases as being adequately defined by the 2010 TNM/UICC classification [85]. Otherwise, the guideline group agreed that where possible the precise TNM and/or FIGO stages should be stated for tumor stages and that terms such as “advanced,” “locally (very) advanced,” and “early cervical carcinoma” should be avoided as far as possible, or at least given along with the stage that is meant. In contrast to the above classical definition, the guideline group prefers the view that advanced cervical carcinoma is a disease that cannot be treated unimodally, but requires multimodal therapy due to the histological tumor stage. Due to the tumor biology and extension that are present, this is associated with a poorer prognosis for the patient (mortality) or with more severe treatment side effects (morbidity).

Traditional definitions such as persistent, metastasized, and recurrent also continue to be used. However, a precise distinction must be made between isolated/disseminated metastasis (pM1) and local recurrence including regional metastases (pM0), and these terms must not be confused. The aim is to achieve as precise as possible a description of the tumor characteristics and its extension, in order to allow optimal therapy adapted to the disease stage. The guideline group rejects any distinction between “locally advanced” and “locally very advanced.” Otherwise, the definitions listed in Table 9 apply.

**Table 9: Definitions of the nomenclature for cervical carcinoma (checked 2021)**

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| **Preinvasive lesion** | | | | | | 2014 WHO classification [87] does not correspond to the 2010 TNM/UICC classification (7th edition) [89] | WHO 2014 [87]TNM/UICC 2010 [90] |
| CIN 1 | LSIL* | CIN 1/LSIL | - | - | - | - | WHO 2014 [87] |
| CIN 2 | HSIL* | CIN 2/HSIL | - | - | - | According to WHO [88], HSIL not mentioned in TNM since no pTis. | WHO 2014 [87] |
| CIN 3* | HSIL* | CIN 3/HSIL | Tis | FIGO does not have a stage 0 | 0 | Is evaluated as CIS | WHO 2014, TNM/UICC 2010 [89] |
| CIS* | HSIL* | CIS/HSIL | Tis | FIGO does not have a stage 0 | 0 | Is evaluated as CIN 3 | WHO 2014, TNM/UICC 2010 [89] |
| **Invasive carcinomas** | | | | | | The tumor entity is classified using the 2014 WHO classification [87].<br><br>Staging is carried out | TNM/UICC 2010 ,[89]<br><br>WHO classification 2014 [87] |

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| | | | | | | according to the 2010 UICC/TNM classification [89] | |
| Microinvasive carcinoma* | Early invasive carcinoma, early stromal invasion, microcarcinoma | Microinvasive disease<br><br>Early (minimal) stromal invasion, -<br><br>Early stage disease | T1a (T1a1 and T1a2) | IA (IA1 and IA2) | IA (IA1 and IA2) | All macroscopically visible lesions even with superficial invasion are evaluated as T1B/stage IB.<br><br>NCCN 2014: only IA1 without L1 [91]<br><br>SIGN Guideline 2008 [86]: „early stage disease" = IA1 and IA2) | **No published definition**<br><br>TNM/UICC 2010 distinguishes microscopically and macroscopically visible [89] |
| Macroinvasive carcinoma* | | Macroinvasive disease | ≥ Ib | ≥ IB | ≥ IB | | **No published definition**<br><br>TNM/UICC 2010 Differentiates microscopically and macroscopically visible [89] |

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| Early cervical carcinoma | Locally limited cervical carcinoma | Early cervical cancer | 1A, 1b1, IIa1 | IA, IB1, selected IIA1 | IA, IB1, selected IIA1 | Source: NCCN 2014 [91] | **No published definition** |
| Advanced cervical carcinoma | | Advanced (stage) disease | ≥ 2b<br><br>and/or pN1<br><br>and/or pM1 | ≥ IIB (up to IVB)<br><br>Or additionally IB2 and IIA2 with multiple histological risk factors or pN1 | ≥ IIB (up to IVB)<br><br>Or also additionally IB2 and IIA2 with multiple histological risk factors or pN1 | Locally advanced, recurrent, metastatic, and persistent are often combined as "advanced" in the literature<br><br>Source: NCCN 2014 [92]<br><br>For the guideline group definition of this guideline, see Chapter 8.5.1 | **No published definition** |
| Locally advanced cervical carcinoma | | Locally advanced disease | 2b to 4<br><br>and/or pN1<br><br>pM0 | IIB to IVA<br><br>Or additionally IB2 and IIA2 with multiple histological risk factors or | IIB to IVA<br><br>Or also additionally IB2 and IIA2 with multiple histological risk factors or | Source: NCCN 2014 [92] | **No published definition** |

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| | | | | pN1 and c/pM0 | pN1 and c/pM0 | | |
| Locally advanced cervical carcinoma. | | Disease confined to the pelvis, more advanced disease | 3 to 4<br>and/or pN1<br>pM0 | IIIA to IVA or pN1 and c/pM0 | IIIA to IVA or pN1 and c/pM0 | With infiltration of the bladder, vagina, or rectum, or extension to the pelvic wall (e.g., urinary stasis) with no distant metastases | **No published definition** |
| Incidental cervical carcinoma* | Accidentallly discovered cervical carcinoma | Incidental cervical cancer | - | - | - | Carcinoma detected by chance during a different operation | **No published definition** |
| Recurrence | | Recurrent disease, relapse | - | - | - | Reappearence of the disease (local or metastatic) after therapy | **No published definition** |
| Early recurrence | | | - | - | - | Instead, a distinction is made between symptomatic and asymptomatic | **No published definition** |

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| Late relapse | | | - | - | - | Instead, a distinction is made between symptomatic and asymptomatic | **No published definition** |
| Local recurrence* | Locoregional recurrence,<br><br>central recurrence, pelvic recurrence, vaginal recurrence,<br><br>isolated pelvic recurrence | Local recurrence, localized recurrence, locoregional recurrence<br><br>central pelvic recurrence,<br><br>-<br><br>isolated central pelvic recurrence | Any T, Any N, M0 | - | - | Recurrence in the area of the pelvis or vagina , with no distant metastases. | **No published definition** |
| Persistent primary disease* | Tumor persistence | Persistent disease | - | - | - | Continued presence of the disease (local or metastatic) after therapy | **No published definition** |
| Metastatic disease* | | Metastatic disease | Any T, Any N, M1 | IVB | IVB | The primary metastatic situation and recurrences with distant metastases | TNM/UICC 2010 [89] |

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| | | | | | | are combined. Para-aortic, inguinal, intraperitoneal, supraclavicular, mediastinal lymph-node metastases, and pulmonary, hepatic, bone, and cerebral metastases are regarded as M1. Metastases in the vagina, pelvic serosa, and adnexa are not included (M0) | |
| Regional metastases* | Locoregional metastases | Regional lymph node metastases | Any T, N1, M0 | IIIB, IVa | IIIB, IVA | Regional pelvic lymph-node metastases include: paracervical, parametrial, hypogastric (internal iliac artery, obturator artery region), common | TNM/UICC 2010 [89] |

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| | | | | | | iliac artery, external iliac artery, presacral, sacral | |
| Distant metastases* | | Distant metastasis | Any T, Any N, M1 | IVB | IVB | The primary metastatic situation and recurrences with distant metastases are combined.<br><br>Para-aortic, inguinal, intraperitoneal, supraclavicular, mediastinal lymph-node metastases, and pulmonary, hepatic, bone, and cerebral metastases are regarded as M1.<br><br>Metastases in the vagina, pelvic serosa, and | TNM/UICC 2010 [89] |

| Name | Synonyms | English | TNM | FIGO | UICC | Special characteristics | Definition in the literature |
|---|---|---|---|---|---|---|---|
| | | | | | | adnexa are not included (M0). | |
| Isolated distant metastases* | | Isolated distant metastases | Any T, Any N, M1 | IVB | IVB | Of questionable treatment relevance | **No published definition** |
| Disseminated distant metastases* | | Disseminated metastases, oligometastatic disease, | Any T, Any N, M1 | IVB | IVB | Of questionable treatment relevance | **No published definition** |

Legend: * = terms used by the guideline group.

CIN = cervical intraepithelial neoplasia; CIS = carcinoma in situ; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; UICC = Union internationale contre le cancer; NCCN = National Comprehensive Cancer Network; SIGN = Scottish Intercollegiate Guidelines Network; WHO = World Health Organization.

## 6.2. Diagnosis as the basis for choice of treatment

The new FIGO classification was introduced in 2018 after in-depth consultation. Previously, the FIGO classification of cervical carcinoma was a purely clinical staging classification and was based on the bimanual examination of the patient by the gynecologist. This was due to the fact that the vast majority of cervical carcinomas occur in non-industrialized countries, so that the women affected have limited access to radiological sectional imaging or histological confirmation. This approach has been abandoned in the new FIGO classification. In addition to improving resources in non-industrialized countries, FIGO regards this as providing benefits for communications within the multidisciplinary team and in improving care for patients with cervical cancer. Although the staging of cervical carcinoma is still clinical, the results of radiologic imaging and of biopsies can be included in the assessment of all stages. Unfortunately, however, there is still no recommendation regarding the methods to be used for diagnosis and staging [93]. This of course makes it difficult to compare registries. Some studies have demonstrated the benefits of complementary imaging techniques (e.g., MRI) [94], [95]. Anesthetic examination, cystoscopy, rectosigmoidoscopy, chest X-ray, intravenous pyelography and contrast colonoscopy are reserved for special questions. In particular, intravenous pyelography and contrast colonoscopy are no longer performed in Germany for diagnostic clarification of confirmed cervical carcinoma. The chest X-ray has also been largely replaced by staging CT of the chest and abdomen, which patients

receive starting from a localized tumor > 4 cm (FIGO IB2) in accordance with the guideline.

Some of the changes in the current FIGO classification (2018) have fundamental implications for staging and also for stage-based therapy. Since TNM and FIGO are currently not congruent, it is recommended to continue to use the previous TNM classification (see Chapter 7.1.2).

This makes the basis for the choice of treatment all the more difficult, since the relevant prospective and randomized studies that are cited in this guideline are in principle based on the imprecise digital FIGO classification system dating from 2009 and the current choice of therapeutic methods is usually not based on surgical or imaging procedures. This lack of clarity in the FIGO classification is also exacerbated by the definition of "macroscopically visible" lesions, and superficial invasion in particular. A cervical lesion that is classified as "microscopic" does not explicitly alter the classification in relation to an increase to stage Ib, but remains in stage IA even in the case of colposcopically visible lesions. The stage is only classified as Ib when there is a pathological T stage after excision or conization, with stromal invasion of more than 5 mm and a superficial size larger than 7 mm.

In addition to tumor-related criteria, additional patient-specific aspects also have to be taken into consideration:

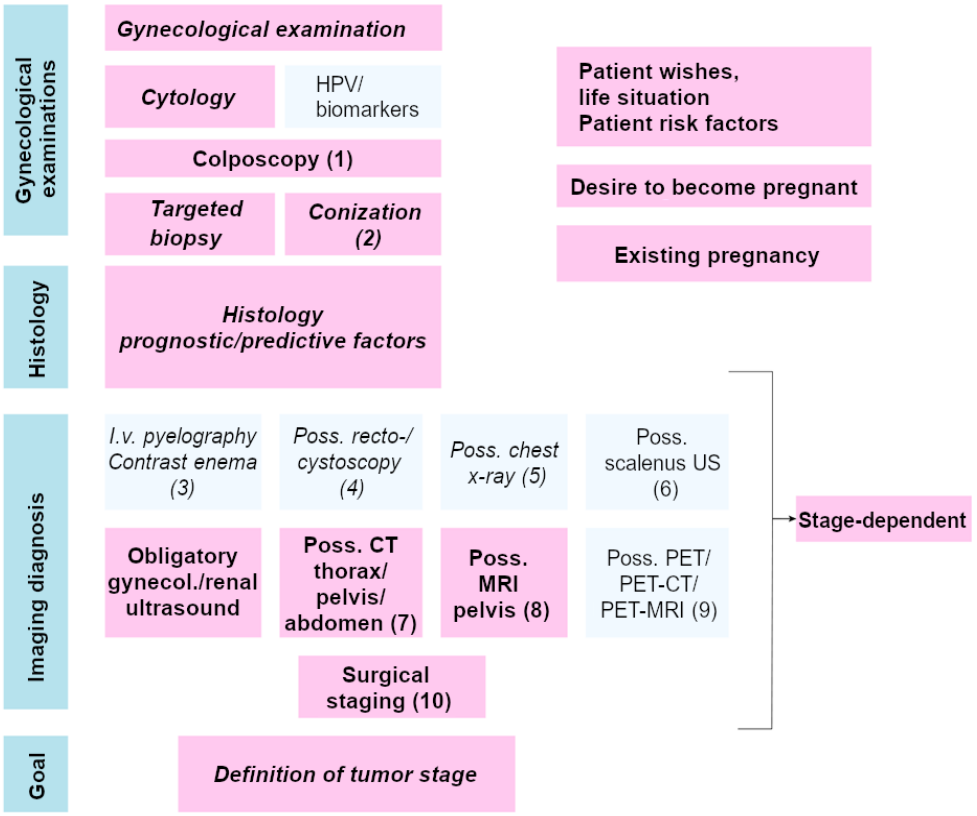
(1) In young patients, a possible wish to have children or an existing pregnancy at first diagnosis, depending on the gestational week, has to be included in the choice of diagnosis and therapy.

(2) In addition, the patient's menopausal status (pre-, peri-, or post-) is important for well-being and life expectancy in patients with cervical carcinoma, from the point of view of ovarian preservation to maintain intrinsic hormonal function.

Due to the structures for providing care described in this guideline, the diagnosis of cervical carcinoma in Germany is subject to different diagnostic algorithms from those proposed by FIGO.

### 6.2.1. Consensus-agreed diagrams from the guideline group for diagnosing and defining stages as the basis for treatment decision-making

Based on expert consensus, consensus diagnosis and stage definition as the basis for treatment decision-making ≤ FIGO stage IIB




Legend:

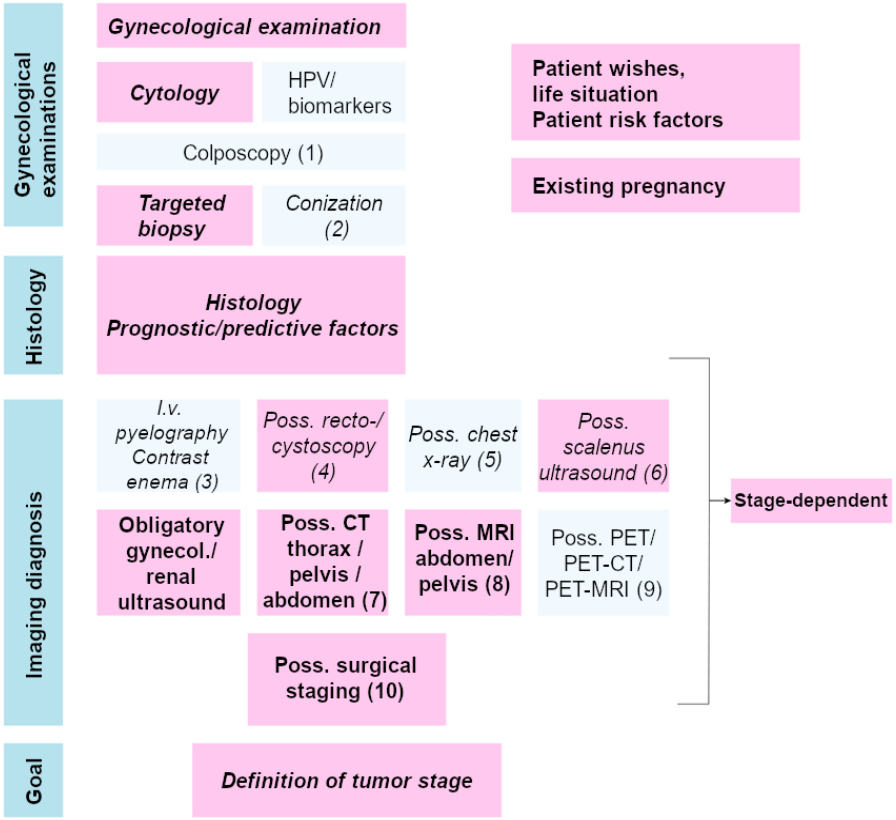
| | |
|---|---|
| **Bold** | = guideline recommendation |
| Italic | = FIGO recommendation |
| ***Bold and italics*** | = concordant FIGO and guideline recommendation |
| Normal font | = no recommendation; an option described in the literature |
| | = *Diagnostic modalities (higher-level terms)* |
| | = *Guideline recommendation* |
| | = *Possible diagnostic modalities outside guideline recommendation* |

Footnotes:

(1) Colposcopy only needed if tumor not yet macroscopically evaluable.
(2) Diagnostic conization only indicated up to a maximum of stage 1B1.
(3) Indicated only in exceptional cases.
(4) Only indicated in exceptional cases with advanced disease.
(5) If appropriate, in combination with an MRI for primary tumor assessment to carry out staging for pulmonary metastases. Not indicated if chest/abdomen CT has already been done.
(6) Starting from stage IB2.
(7) Pelvic CT if MRI is not possible for local assessment (stages IB2 to III). Chest/abdomen CT to diagnose extrapelvic spread (all patients from stage IB2).
(8) Stage IB2 to III.
(9) Only in exceptional cases with recurrence or a metastatic situation and in the setting of research studies.
(10) > Stage IA1 (without risk factors) to stage IIB; in certain conditions a sentinel procedure alone or in combination is also possible as an alternative (see section 8.1.1.2).

**Figure 2: Diagnosis and definition of stages as the basis for treatment decision-making ≤ FIGO stage IIB (2014/2021)**

### 6.2.1.1. Diagnosis and staging as the basis for treatment decisions > FIGO stage IIB




Legend:

| | |
|---|---|
| **Bold** | = guideline recommendation |
| *Italic* | = FIGO recommendation |
| ***Bold and italics*** | = concordant FIGO and guideline recommendation |
| Normal font | = no recommendation; an option described in the literature |
| | = *Diagnostic modalities (higher-level terms)* |
| | = *Guideline recommendation* |
| | = *Possible diagnostic modalities outside guideline recommendation* |

Footnotes:

(1) Colposcopy only needed if tumor not yet macroscopically evaluable.
(2) Diagnostic conization only indicated up to a maximum of stage 1B1.
(3) Indicated only in exceptional cases.
(4) Only indicated in exceptional cases with advanced disease.
(5) If appropriate, in combination with an MRI for primary tumor assessment to carry out staging for pulmonary metastases. Not indicated if chest/abdomen CT has already been done.
(6) Starting from stage IB2.
(7) Pelvic CT if MRI is not possible for local assessment (stages IB2 to III). Chest/abdomen CT to diagnose extrapelvic spread (all patients from stage IB2).
(8) Stage IB2 to III.
(9) Only in exceptional cases with recurrence or a metastatic situation and in the setting of research studies.
(10) > Stage IA1 (without risk factors) to stage IIB; in certain conditions a sentinel procedure alone or in combination is also possible as an alternative (see section 8.1.1.2).

**Figure 3: Diagnosis and definition of stages as the basis for treatment decision-making ≤ FIGO stage IIB**

### 6.2.2. Recommendations on diagnostic procedures

| 6.1 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| **EC** | Vaginal ultrasonography ***shall*** be used for clinical imaging to establish the extent of local tumor spread, and renal ultrasonography to exclude urinary transport disturbance. | |
| | Strong Consensus | |

| 6.2 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR **B** | Patients with histologically confirmed cervical carcinoma from FIGO stage IB2 to III inclusive ***should*** undergo pelvic MRI for assessment of locoregional tumor spread. Patients who are unable to undergo pelvic MRI for technical reasons ***should*** have a pelvic CT. | |
| LoE **1+** | [96]; [97]; [98] | |
| | Strong Consensus | |

| 6.3 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| **EC** | Starting from FIGO IB2 to III, patients in whom pelvic MRI cannot be carried out for technical reasons ***should*** undergo locoregional imaging of the pelvis for staging purposes during staging CT examinations of the chest, abdomen, and pelvis. | |
| | Strong Consensus | |

In this recommendation on imaging diagnosis in patients with cervical carcinoma, the guideline group has kept quite close to the recommendations given in the 2008 SIGN guideline [99]. This is based above all on consistent evidence that MRI is superior to CT and clinical staging for assessing the primary tumor and invasion of neighboring organs [100]. Data from a systematic review published in 2013 also confirm these data and again show that MRI (with a pooled sensitivity of 84%; 95% CI, 76–90%) is superior to the clinical examination (with a pooled sensitivity of 40%; 95% CI, 25–58%), particularly for detecting parametrial infiltration and cervical carcinomas > stage IIB (and thus potentially inoperable) [101]. For stages below IB2, the guideline group takes a critical view of the role of MRI/CT diagnosis in assessing the primary tumor. For stage IVA, the guideline group — in contrast to the SIGN guideline — also recommends a pelvic MRI for assessment of the primary tumor, due to the potential option of exenteration. For patients in whom MRI is not feasible for technical reasons — for example, due to a pacemaker — CT of the pelvis should no longer be carried out as an equivalent starting from FIGO stage IB2 onwards, but only staging by means of CT of the chest and abdomen, continuing up to and including the symphysis and thus including the pelvis (referred to as CT chest/abdomen/pelvis for precise identification). As early as 2007, the

German Medical Association stipulated in its guideline on quality assurance in computed tomography that the abdomen should be imaged in CT scans from the dome of the diaphragm to the pelvic floor in uninterrupted sections and in as similar a respiratory position as possible [102]. This reduces radiation exposure and contrast administration and is therefore less stressful for the patient.

| 6.4 | Consensus-based Recommendation | new 2021 |
|---|---|---|
| EC | Patients in FIGO stage IVA who are unable to undergo pelvic MRI for technical reasons ***should*** receive locoregional imaging staging of the pelvis as part of staging CT of the chest/abdomen/pelvis. | |
| | Strong Consensus | |

| 6.5 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| EC | Patients with histologically confirmed cervical carcinoma FIGO stage IB2 or above ***should*** undergo chest/abdominal/pelvic CT for assessment of tumor spread. | |
| | Strong Consensus | |

The current guideline recommendations are consistent with the 2008 SIGN guideline [99] with regard to the increased use of chest/abdominal CT for staging, and abandonment of hepatic ultrasonography and chest X-ray examinations. The guideline group also follows these recommendations. Despite this, in contrast to the 2008 SIGN guideline, a clear diagnostic emphasis is placed on surgical staging for the choice of treatment. This is above all because precise assessment of lymph-node status (pelvic and para-aortic) for treatment planning appears particularly important to the guideline group, especially in the setting of care in Germany (see also section Chapter 8.1.1).

| 6.6 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | If a tumor of the vaginal part of the cervix cannot be clearly assessed macroscopically, a differential colposcopy and targeted biopsy ***shall*** be carried out. | |
| | Strong Consensus | |

| 6.7 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The histologically confirmed tumor stage ***should*** be the basis for interdisciplinary treatment decision-making at the tumor conference. | |
| | Strong Consensus | |

In the framework of statutory early cancer detection guidelines, a gynecological examination and cytology are the initial components of the diagnostic process, along with HPV testing starting from age 35. In the case of higher-grade cytological abnormalities,

differential colposcopy with targeted biopsy sampling, or diagnostic/therapeutic conization or excision if the lesion is easily localized colposcopically, should be carried out.

These measures lead to the histological diagnosis, which by defining the FIGO stage after the digital examination points the way to the algorithm for further diagnostic procedures and treatment. The diagnostic measures listed by FIGO are reserved, if used at all, for carcinomas ≥ FIGO stage IIb or suspected distant metastases (e.g., inguinal, para-aortic lymph-node metastases, scalene lymph-node metastases). Data on the routine use of imaging procedures such as abdominal CT or MRI for classification and thus to provide the basis for treatment decisions are heterogeneous. While CT provides better information in the area of the lateral borders (osseous structures) to the pelvic wall, MRI provides better differentiation of the primary tumor size and infiltration relative to the parametria and the soft-tissue organs of the bladder and bowel, as well as in the lymph nodes [99] [94] [100] [106]. Using MRI with a field strength of at least 1.5 Tesla, diffusion imaging in combination with high-resolution T2 weighting and administration of Buscopan (hyoscine butylbromide) or glucagon to provide drug-produced intestinal atony significantly improves the detection of parametrial infiltration [95]. Studies on the use of vaginal ultrasound have shown that it has good validity, particularly for assessing the tumor size in the cervical region (kappa 0.81; 95% CI, 0.73 to 0.90) [109]. With regard to the parametrial infiltration depth, ultrasound examination underestimates the findings in up to one-third of patients [109] [105] [110]. Research to assess the value of PET or PET-CT continues to provide very heterogeneous results. Overall, in the view of the guideline group, PET-CT still does not have any value for routine diagnosis, due to its lack of differentiation between superinfection and infiltrating tumor in the cervical region and a lack of sensitivity and specificity for micrometastases and small metastases in the area of the lymph nodes [111] [107] [108]. On the basis of recent research data, however, pretherapeutic PET-CT may be advocated in individual cases — e.g., if histological clarification of the para-aortic lymph nodes is not possible, or to select patients for histological clarification of the para-aortic lymph nodes [112] [103]. With regard to lymph-node detection, a meta-analysis has shown that MRI with diffusion imaging had the best sensitivity at 88%, PET or PET-CT had the best specificity at 94%, and the AUC of DWI and PET-CT were both more than 90% in comparison with the histopathological results [104].

Due to the problems involved in the clinical FIGO classification, there are unclear aspects in the choice of treatment options, both with regard to surgical treatment and also radio(chemo)therapy. Particularly when there are unclear imaging findings in the area of the para-aortic lymph nodes, for example, or when the extent of the tumor is unclear during a digital examination, obtaining histological information from these areas is thus the best option for determining the histological tumor stage. Surgical staging makes it possible to assess the lymph nodes, the peritoneum, and local tumor spread. This leads to more precise staging. It allows more precise treatment planning and discrimination of the therapeutic options, with the goal of reducing the effects of the disease and treatment on morbidity and mortality as much as possible. Surgical staging has thus gained in importance in recent years. Surgical staging should allow precise classification. When there are bilateral negative sentinel lymph nodes, no further lymphadenectomy needs to be carried out for completeness. When there are positive para-aortic or pelvic lymph nodes, radical hysterectomy with subsequent radio(chemo)therapy needs to be critically considered as a treatment measure, and expansion of the radiation field is certainly necessary. If the lymph nodes are negative on quick-section diagnosis, radical hysterectomy is justified with lower tumor stages. The aim of surgical staging is therefore to achieve a precise definition of the tumor stage and thus in particular to provide the basis for the relevant stage-appropriate treatment

in the primary situation. In premenopausal women, simultaneous repositioning of the ovaries should be carried out to preserve hormonal production.

In the recurrent setting, when symptoms develop, or when there is a suspicion of metastases, imaging procedures are used — particularly vaginal ultrasound and pelvic MRI, and chest/abdomen/pelvis CT when there is a suspicion of metastases. If there are unclear findings, PET-CT has advantages for clear identification of lymph-node metastases and distant metastases, which is particularly relevant in case of planned exenteration or radio(chemo)therapy. Surgical measures using minimally invasive techniques can also influence the choice of therapy, particularly when there is evidence of peritoneal metastases or tumor spread extending into other organs.

| 6.8 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR **B** | PET-CT ***should not*** be used for treatment planning in primary cervical carcinoma. | |
| LoE **2+** | [113]; [114]; [111]; [115]; [116] | |
| | Strong Consensus | |

The 2008 SIGN guideline already recommends PET-CT in the primary situation (recommendation grade C) only as an option in patients who are not candidates for surgery and who due to their high tumor stage have a statistically high probability of lymph-node metastases. The negative predictive value in lower tumor stages is not sufficient, and micrometastases are often not detected [99]. A meta-analysis in 2010 showed that PET/PET-CT had a better diagnostic performance than CT or MRI, but only with very heterogeneous data. In addition, no distinctions were made between the various CT and MRI developmental stages [123]. Another 2010 meta-analysis investigated the diagnostic quality of PET-CT for diagnosing para-aortic lymph-node metastases in patients with cervical carcinoma. The authors concluded that PET-CT only detects para-aortic lymph-node metastases with sufficient certainty in patient groups in which there is a high probability of metastases [113]. Another study including 237 patients (stages IB2 to IVa) compared laparoscopic staging of the para-aortic lymph nodes with the results of PET-CT imaging. It was found that survival in patients with para-aortic lymph-node metastases > 5 mm was markedly poorer and that these metastases were not detected using PET-CT [124].

In more recent studies published in 2015 and 2018, some research groups advocate the use of PET in the primary therapeutic setting when suspicious pelvic lymph nodes are visible on CT, in order to reduce the likelihood of side effects due to extended combined radiochemotherapy [117] [118] [119]. Others have concluded that although PET-CT can be recommended to increase diagnostic accuracy, it is not justified due to its low sensitivity for abdominal lymph-node detection in locally advanced carcinoma [120]. Other studies have defined volume-based FDG-PET-CT parameters as prognostic factors for event-free survival and overall survival [121] aand recommend performing PET-CT pretherapeutically before planned radio(chemo)therapy and 3 weeks after the start of treatment for monitoring and adjusting therapy if necessary, as this improves the overall survival [122]. Overall, however, in the opinion of the guideline group, PET-

CT still has no value for routine diagnosis, also due to its well-known lack of differentiation between superinfection and infiltrating tumor in the cervical region and lack of sensitivity and specificity for micrometastases and small metastases in the area of the lymph nodes [111] [107] [108]. Data from a meta-analysis show that MRI with diffusion imaging had the best sensitivity for lymph-node detection, at 88%, while PET or PET-CT had the best specificity at 94%, and the AUC of DWI and PET-CT were both greater than 90% [104]. Martinez et al. reported that four of 78 patients (5.1%) had para-aortic lymph-node metastases in FDG-negative pelvic lymph-node sites [103]. De Cuypere et al. reported a high specificity with FDG-PET-CT, at 93.3%, with a low sensitivity of 23.5% [112]. Seven of nine false-positive findings were in region of the common iliac artery. Ultimately, the results of FDG-PET-CT in the primary setting are still too inconsistent for the guideline group to justify a general recommendation for PET-CT diagnosis in this setting.

| 6.9 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR **B** | When a local procedure (radiochemotherapy or exenteration) is being considered for treatment of a recurrence, PET-CT ***should*** be carried out to exclude lymph-node metastases and distant metastases. | |
| LoE **2+** | [125]; [126]; [127]; [96] | |
| | Strong Consensus | |

The 2008 SIGN guideline recommends whole-body PET-CT only for patients in whom a recurrence or persistent cervical carcinoma has been identified on MRI or CT, in whom a salvage operation is planned [99]. Several research groups also recommend FDG-PET-CT in patients with suspected recurrences and rising SCC-Ag levels but with negative or equivocal results on conventional imaging with CT or MRI. They report a sensitivity of 91% and a specificity of 92% [126] [127]. On the other hand, however, Meads et al. 2014 complained that although the recommendation of PET-CT in patients with recurrences before planned exenteration or even generally 9 months after completion of chemotherapy is anchored in the guidelines, but is not evidence-based [128] [129] [130] [131]. Particularly in patients who have local recurrences in whom exenteration or radio(chemo)therapy are options, distant metastases must be reliably ruled out. When there are unclear imaging findings on CT and MRI, the guideline group therefore advocates carrying out PET-CT before renewed therapy in order to reliably exclude metastases. For imaging when there are suspected recurrences or metastases, see also sections Chapter 16.5, Chapter 16.6, Chapter 17.2 and 18.2.

## 6.3. Transvaginal ultrasound (TVU) in the diagnosis of cervical carcinoma

In addition to gynecological palpation and speculum examination, transvaginal ultrasound (supplemented in selected cases with transrectal ultrasound) is part of the primary gynecological diagnostic approach in cervical carcinoma. In adenocarcinoma, cervical carcinoma tissue typically appears as a hyperechoic or isoechoic mass in contrast to the surrounding tissue. In squamous cell carcinoma, it is hypoechoic. The detection rate achievable for tumor extension > 4 cm is 78%, with a specificity of 99% [132]. In

cases of deep stromal infiltration (more than two-thirds of the wall thickness see Chapter 7.2.4), TVU has a sensitivity of 88–91% (specificity 93–97%), while for parametrial infiltration it has a sensitivity of 60–83% (specificity 89–100%). In specialized centers, diagnostic results achievable to those with MRI can be achieved [109] [132]. TVU has been reported to be advantageous in the search for residual tumor after conization. However, this observation does not appear to be transferable to the assessment of residual tumor size during or after neoadjuvant treatment [109], [133]. TVU is still suitable in connection with options for fertility-preserving surgery, since the distance between the tumor and the isthmus of the uterus and the expected length of the functional residual cervix can be accurately estimated due to the technique's high spatial resolution. Due to its limited depth of penetration, limited angle of view, and overlying bowel, TVU has limitations for assessing pelvic and/or para-aortic lymph-node metastases [134] [135].

Increased angiogenesis and neovascularization are risk factors and can be investigated using Doppler ultrasonography [132]. In addition to color Doppler ultrasound visualization of the vessels, attention should be paid to tumor vessels with low resistance indices (cut-off PI < 0.73). The state of the data on perfusion assessment using 3D (power) Doppler ultrasound is currently divergent. In a larger prospective study (PRICE), it was considered to be an insufficiently predictive response criterion in connection with neoadjuvant radiochemotherapy [136], [137]. However, newer techniques such as the inclusion of the glass-body mode, may significantly improve the assessment of the vascular architecture here. Additional prospects for extending the diagnostic value of ultrasound include tomographic 3D ultrasound and elastography, the value of which has yet to be evaluated in larger prospective a and controlled studies [138], [139].

# 7. Pathology

**Major changes in the chapter on pathology**

Major changes in the chapter on pathology due to the guideline update:

Pathological diagnosis and prognostic factors: the section on pathological diagnosis and prognostic factors has been extensively revised.

Current studies have shown that a histopathologically based definition of growth patterns, mainly based on tissue architecture criteria (known as Silva patterns), in adenocarcinoma of the uterine cervix has prognostic relevance. These patterns have so far been best studied in high-risk HPV-associated adenocarcinoma of the endocervical subtype (not otherwise specified, NOS). Whether the Silva pattern is also prognostically relevant in other histological subtypes of cervical adenocarcinoma cannot be conclusively assessed at present.

The International Endocervical Adenocarcinoma Classification (IECC) was developed in 2019. It classifies cervical adenocarcinoma in principle into HPV-associated and non-HPV-associated carcinomas and their respective subtypes. This classification also has prognostic significance.

Although the usefulness of these two new classifications (Silva pattern and IECC) still needs to be confirmed by prospective clinical studies and they do not have any therapeutic implications results at present, they are presented in the guideline.

The redefinition of the stages of cervical carcinoma proposed by FIGO in 2018 is presented and discussed in the guideline. However, it is not applied.

The definition of multifocality in microinvasive cervical carcinoma is new — see Recommendation 7.9 on multifocal microinvasive carcinoma.

Taking intratumoral heterogeneity into account, which can occur particularly in adenocarcinomas, there are now specific procedural instructions for the extent of work-up relative to tumor size — see Recommendation 7.13 on intratumoral heterogeneity.

A recommendation on the documentation of isolated tumor cells (ITCs) and micrometastases (pN1mic) in lymph nodes in accordance with the TNM system requirements has been newly included — see Recommendation 7.19 on isolated tumor cells and micrometastases.

The sentinel lymph-node approach is also becoming increasingly important in cervical carcinoma. For this purpose, a separate section on work-up and reporting, including any intraoperative quick-section examinations that may be needed, has been newly created — see Recommendations 7.21, 7.22, and 7.23.

The section on morphological prognostic factors has been completely revised.

See the section on pathological diagnosis and prognostic factors, including:

- Modified Recommendation 7.15, on reporting findings after radical hysterectomy
- New Recommendation 7.9, on multifocal microinvasive carcinoma
- New Recommendation 7.13, on intratumoral heterogeneity
- New Recommendation 7.19, on isolated tumor cells and micrometastases
- New recommendations 7.21, 7.22, and 7.23, on sentinel lymph nodes

*L.-C. Horn, B. Pöschel, D. Schmidt*

# 7.1. Classification of invasive cervical carcinomas

## 7.1.1. Classifying tumor types

Cervical carcinomas are classified typologically in accordance with the WHO classification of tumors of the female genitalia [140].

| 7.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Tumor classification ***shall*** be carried out on the basis of the currently valid edition of the WHO classification. | |
| | Strong Consensus | |

| 7.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In cervical carcinomas with neuroendocrine components, the latter ***shall*** be reported along with the percentage of the total tumor that they represent. | |
| | Strong Consensus | |

The majority of invasive cervical carcinomas are squamous cell carcinomas (≈ 80%) and adenocarcinomas (≈ 5–20%) [141]. Other tumor entities are rare.

Prognostically unfavorable tumor types include in particular neuroendocrine carcinomas (large-cell or small-cell) and non-HPV-associated adenocarcinomas, with the exception of clear cell adenocarcinomas. Serous carcinoma has been deleted from the current WHO classification. The WHO classification distinguishes between neuroendocrine tumors (low grade) and neuroendocrine carcinomas (high grade) [142]. One-quarter to one-third of all neuroendocrine carcinomas (high grade) have a non-neuroendocrine component [146] [143]. Due to the extremely poor prognosis [143] [147] [148] [144] [145] and possible modifications of treatment resulting when there is evidence of neuroendocrine differentiation, the latter should be explicitly stated in the pathology report, with details of the percentage of the neuroendocrine component as part of the overall tumor [146] [149] [150].

## 7.1.2. Staging of cervical carcinoma

| 7.3 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| EC | Staging ***shall*** be carried out in accordance with the current edition of the TNM classification. | |
| | Strong Consensus | |

Postoperative staging is carried out optionally in accordance with the TNM classification [85] (see also Table 21). In principle, a distinction is made between microinvasive and macroinvasive carcinomas.

| 7.4 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | A diagnosis of microinvasive cervical carcinoma ***shall*** be based on the definitions given in the current editions of both the WHO and TNM classifications. | |
| | Strong Consensus | |

Microinvasive cervical carcinoma is an exclusively histological diagnosis (see Table 9). Stage pT1a1 is defined as a tumor with stromal invasion ≤ 3 mm and a horizontal extension of ≤ 7 mm [84][85]. Stage pT1a2 consists of tumors with stromal invasion > 3 mm to ≤ 5 mm and a horizontal extension of ≤ 7 mm.

In 2018/2019, FIGO made the suggestion that microinvasive cervical carcinoma should be defined only by depth of invasion with the above thresholds, omitting horizontal tumor extension — but without citing studies to support this approach [151] [152]. However, this change would have had a fundamental impact on staging classifications and also on staging-based therapy [93]. In addition, a revision of the TNM classification by the American Joint Committee on Cancer (AJCC) and UICC is not expected until 2025, so that it is recommended that the current TNM classification should be retained (see Table 21). The guideline committee has therefore decided not to implement the new FIGO classification at present. For supplementary information, the classification proposed by FIGO can be included in a commentary on the histopathological findings report [93].

The new 2018 FIGO classification has been evaluated below and confirms the improved prognostic discrimination of stage IB/T1b and the less favorable prognosis for patients with para-aortic lymph-node metastases [153], [154]. These studies do not address the new definition of stage IA/T1a.

In microinvasive squamous cell carcinoma, stromal invasion is measured from the base of the underlying CIN 3 lesion — located either superficially or growing into endocervical glands [155]. In microinvasive adenocarcinoma, stromal invasion is measured from the base of the underlying gland of the adenocarcinoma in situ (ACIS).

### 7.1.3. Definition of TNM-relevant parameters

*Perineural sheath infiltration (Pn)* is defined as evidence of tumor cells in the perineural spaces, independently of the extent of the tumor cells within the spaces and independently of whether or not the nerve itself is infiltrated [174] [175].

*Lymphatic vessel infiltration* (L category) consists of evidence of individual tumor cells or groups of tumor cells located inside spaces that are clearly lined with (lymph) endothelia (L1) [176]. The TNM committee has stated that when there is evidence of tumor cells within spaces without a clear endothelial lining, the findings are to be classified as L0 (no lymphatic infiltration) [176], as this usually represents contraction-related fixation artifacts. However, routine use of immunohistochemistry to identify lymphatic endothelia (e.g., D2-40) is not indicated outside of research studies. Quantification of lymphatic infiltration, as described for example in endometrial carcinoma [156] [157]

is not recommended in cervical carcinoma due to the lack of a generally accepted definition as well as relevant studies.

With *Invasion in veins* (V category), a distinction is made between macroscopically visible (V2) and histologically confirmed venous infiltration (V1) [85]. Macroscopic venous infiltration is not relevant in cervical carcinoma. The microscopic V1 category is defined in the TNM system as evidence of tumor cells inside the lumen of the vein and/or evidence of tumor cells infiltrating the venous wall [176].

*Grading* is not relevant in the staging of cervical carcinoma, but should form an integral part of the documentation of findings (see below) and is also required, among other things, for tumor documentation in the setting of gynecological cancer centers. There is no grading system recommended by the WHO for squamous cell carcinoma or for the majority of adenocarcinomas of the cervix [88]. Despite recent studies on squamous cell carcinoma [158] [159] [160], there is also no accepted and standard grading system for squamous cell carcinoma as yet [161] [162]

For primary endometrioid adenocarcinoma of the cervix, grading analogous to the FIGO grading of endometrioid adenocarcinoma of the endometrium is recommended [88] [161]. However, findings in recent years suggest that the majority of endometrioid cervical carcinomas are a variant of the endocervical subtype adenocarcinoma (not otherwise specified, NOS) and that primary endometrioid adenocarcinoma of the cervix usually arising from endocervical endometriosis is extremely rare [163] [164] [165] [166]

The most frequent subtype, at 75%, is adenocarcinoma of the endocervical type (also known as “not otherwise specified,” NOS). A grading system based on the growth pattern has been developed in recent years for these lesions [167] [168] [169]. The pattern is also referred to as the Silva pattern, and the criteria for it are summarized in Table 10 [170] , [171].

The rarest type with pattern A has the fewest lymphatic vessel intrusions and the lowest number of pelvic lymph-node metastases, whereas pattern C has the most lymphatic vessel intrusions and consequently the highest number of lymph-node metastases and is prognostically the most unfavorable [168] [169]. It therefore seems useful to mention the growth pattern, mainly based on architectural tumor criteria, in the report on findings. In this context, it is important to note that this pattern-based system has mostly been studied in the endocervical subtype [168] [169], but may also be applicable to other HPV-associated subtypes of cervical adenocarcinoma [172].

The revised version of the NCCN guidelines recommends the use of the Silva pattern for the endocervical subtype [173].

**Table 10: Histological criteria for the different invasion patterns in endocervical adenocarcinoma (the Silva system [171], [172], [173])**

| Pattern classification according to the Silva system (new 2021) | |
|---|---|
| **Pattern A** | Sharply defined glandular proliferations with round outer contour<br><br>Often group-shaped storage of the glands<br><br>No single cell-growth<br><br>No destructive stromal invasion (no peritumoral desmoplasia)<br><br>No solid tumor parts<br><br>Complex intraglandular morphology possible (e.g., cribriform, papillary growth, etc.)<br><br>No lymphatic vessel invasion |
| **Pattern B** | Focal (initial) destructive tumor growth, originating from glands with pattern A morphology<br><br>Infiltration of small tumor cell groups or single cells adjacent to pattern A proliferates (often associated with peritumoral desmoplasia and/or peritumoral inflammation)<br><br>Lymphatic infiltration possible<br><br>No solid tumor components |
| **Pattern C** | Diffuse and destructive tumor growth (often in association with high-grade peritumoral desmoplasia)<br><br>Glandular proliferation with unclear borders and sometimes fragmentation of the glands<br><br>Confluent glands occupying a low-power field (approx. fourfold magnification; 5 mm²) with evidence of solid tumor components and/or papillary growth and/or mucinous deposits in the stroma<br><br>Polymorphic tumor cells<br><br>With or without lymphatic invasion |

# 7.2. Tissue processing

## 7.2.1. Diagnostic biopsies

| 7.5 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The biopsy sample that has been taken ***shall*** be processed in step sections. | |
| | Strong Consensus | |

| 7.6 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| EC | The report on the findings ***should*** mention the evidence and the grade of CIN, ACIS (and its variants in the form of stratified mucin-producing intraepithelial lesions [SMILE]), virus-associated changes, and possible invasion. | |
| | Strong Consensus | |

Tissue that is biopsied for histological confirmation of a precancerous lesions or invasive carcinoma must be processed in step sections [181] [182]. This applies in particular to biopsies that have no correlation with the cytological and/or colposcopic findings in the initial sections [181] [183]. Preparing step sections increases the diagnostic certainty in relation to the extent of CIN or ACIS, or of a stratified mucin-producing intraepithelial lesion (SMILE), which is a special variant of ACIS, as well as providing evidence of microinvasion. In addition, step sections allow better correlation between the cytological/colposcopic findings and the histological findings (for purposes of quality assurance). At least three step sections at intervals of approximately 200 µm are usually sufficient. The report on the findings should mention the evidence and grade of CIN or ACIS, as well as virus-associated changes that are found on the hematoxylin–eosin (HE) sections, and should note any possible invasion. Routine use of molecular-pathological and/or immunohistochemical methods for identifying HPV is not indicated outside of research studies. In addition, a distinction is made between low-grade squamous intraepithelial lesions (LSIL; = CIN 1) and high-grade squamous intraepithelial lesions (HSIL; = CIN 2 and CIN 3/CIS) [84].

When there is evidence of invasion, information about lymphatic, vascular, and perineural sheath invasion must also be given [177] [178] [179] [180].

## 7.2.2. Conizations

| 7.7 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The pathology report ***shall*** state the size and characteristics of the excised (conization) specimen. The conization specimen ***shall*** be completely processed and step sections must be prepared from each paraffin block. | |
| | Strong Consensus | |

| 7.8 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| EC | The histological report ***shall*** note the type of lesion (CIN, ACIS and its variants in the form of stratified mucin-producing intraepithelial lesions [SMILE]), its location (endocervical, ectocervical), and its extent, as well as the presence of invasive tumor. When there is evidence of invasion, details ***shall*** also be given of its extent and of lymphatic, vascular and perineural sheath invasion, as well as grading. The status of the resection margins ***shall*** also be noted. | |
| | Strong Consensus | |

Diagnostic or therapeutic resection of the transformation zone can be carried out using various techniques — e.g., laser conization, large loop excision of the transformation zone (LLETZ), loop excision, or scalpel conization. In accordance with the Rio nomenclature for colposcopy, the corresponding resection specimens are no longer described as conizations, but as excision types 1–3.

The classification of the excision specimen and the size of the specimen is given in accordance with the 2011 Rio classification (http://www.ifcpc.org/images/docs/nomenclature711.pdf) [184] (see Table 11) and should be carried out by clinicians. Details of the three-dimensional size of the resection specimen are given by the pathologist.

The prerequisite for standardized morphological processing of these excision specimens is the sending of a specimen that is intact and marked (usually with a thread marking at the 12-o'clock position [177] [185] [189] [190]. The report on the pathological findings must provide information about the quality of the excision specimen [177] [178] [180] [189][190]. The size of the specimen should be stated with three-dimensional measurements [186]. The entire excision specimen must be completely processed [177] [178] [180], and the segmental processing technique is preferred [177]. Step sections of each paraffin block must be made [177]. At least three step sections, at intervals of approximately 200 µm, are usually sufficient. Precancerous lesions of the cervix usually arise in the area of the transition from the endocervix to the ectocervix, known as the transformation zone. The report on the findings should therefore mention whether that zone is contained in the excision specimen, or whether and where it is missing [177] [185]. The same applies to evidence of iatrogenic changes (such as thermal damage, for example) of the type that occur during conizations obtained with laser or diathermy techniques [187] [188]. Thermal damage can impair the diagnostic certainty of the histological examination.

The report on the histological findings should note the type of lesion (CIN, ACIS, SMILE), its location (endocervical, ectocervical), and its extent (with details given clockwise — e.g., from the 2-o'clock to 6-o'clock positions). For practical purposes, details of the extent of a precancerous lesion can be given in millimeters [186]. When there is evidence of invasion, details of its size must be given along with information about lymphatic, vascular, and perineural sheath invasion [177] [178] [179] [180].

Microinvasive carcinomas may be multifocal [191] [192] [193]. On the basis of previous studies, albeit with limited case numbers [192] [193], multifocal growth is defined by the International Collaboration on Cancer Reporting (ICCR) as evidence of invasive foci that are histologically clearly separate from each other at a minimum distance of 0.2 cm [162]. The ESGO guideline on cervical carcinoma states that the size of each invasive tumor should be reported separately, with the largest single lesion being relevant for

staging [189] [190]. To exclude a confluence of various separate invasive foci, it is useful to make (additional) step sections.

| 7.9 | Consensus-based Recommendation | new 2021 |
|---|---|---|
| EC | A multifocal microinvasive carcinoma is defined as evidence of invasive foci that are histologically clearly separate from each other at a minimum distance of 0.2 cm.The size of each invasive tumor focus ***shall*** be reported separately, with the largest single lesion being relevant for staging. | |
| | Strong Consensus | |

Precise details on the status of the resection margins (free, involved [200], [194], [195], [196], [197], [189], [190], are obligatory, and firm details should be given on the vaginal (ectocervical), endocervical, and lateral margins (soft-tissue resection margin of the cervical stroma), preferably with information about the measured distance from the resection margin.

When each resection margin is being checked and HPV-induced, non-precancerous changes are being distinguished, p16 immunohistochemistry can be recommended in cases of doubt, and with glandular lesions Ki-67 immunohistochemistry as well [200], [198], [199].

**Table 11: Rio classification (2011), addendum 1**

| Addendum (checked 2021) | |
|---|---|
| **Excision types** | Type 1 – flat; type 2 – medium; type 3 – steep<br>[Editors' note: by analogy with the nomenclature for the transformation zone] |
| **Dimensions of conization specimens** | Height (length): distance from the cervical to the vaginal resection border<br>Width (thickness): distance from the stromal resection border to **the** epithelial surface<br>Circumference (optional): perimeter of the opened cone specimen |

### 7.2.3. Cervicectomy

| 7.10 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Morphological processing ***shall*** take place in such a way that all therapeutically and prognostically relevant parameters can be assessed. The report ***shall*** be produced on the basis of the currently valid WHO classification for tumor type and the current TNM classification for staging, as well as the R classification (UICC). | |
| | Consensus | |

| 7.11 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| **EC** | The tracheclectomy report ***shall*** include the following details:<br>• Histological type (WHO)<br>• Grading<br>• Presence/absence of lymphatic or venous invasion (L and V status)<br>• Presence/absence of perineural sheath infiltration (Pn status)<br>• Staging (TNM),<br>• Depth of invasion and extent in millimeters in pT1a1 and pT1a2<br>• Three-dimensional tumor size in centimeters (from pT1b1)<br>• Minimum distance from the resection margins (endocervical stroma in pT1b tumors)<br>• R classification (UICC). | |
| | Consensus | |

The prerequisite for standardized morphological processing is the sending of a specimen that is intact and marked (usually with a thread marking at the 12-o'clock position [194], [201]). The report on the pathological findings must provide information about the size and quality of the excision specimen (cervix component, parametria, vaginal cuff if appropriate) [195], [197], [189], [190]. The ESGO guideline recommends that changes following a previous conization should be described (e.g., erosions, ulcerations) [189], [190]. The specimen should be completely processed [195], [197], this applies in particular to the proximal and vaginal resection margins [189], [190]. The processing should be carried out in such a way that all the details required as listed in the section on radical hysterectomy can be collected [195], [196], [197], [202]. The ESGO guideline recommends complete embedding/processing of the resected parametrial tissue [189], [190]. The ICCR does not comment on this [162].

The report on the findings must be based on the WHO classification of tumor types [88] and the current pTNM classification for staging [85] and the R classification must be based on the current UICC classification for (see also Table 21), which is an obligatory component of the pTNM classification. For the definition and staging of multifocal (microinvasive) carcinomas, see section Chapter 7.2.

If the transformation zone has previously been excised (known as conization) and in the presence of findings, the tumor size from the conization specimen and from the cervicectomy specimen should be combined to calculate the final tumor size. It is useful to note here that the additively measured tumor size is a calculated tumor size, which may also combine findings from different pathologies [162], [189], [190]. If conization and cervicectomy have been assessed in different pathologies, the measurement of the calculated tumor size is the responsibility of the gynecologists who last handled the case.

If there is evidence of adenocarcinoma, then it is currently recommended as an option that details on the growth pattern (known as the Silva pattern [167], [169], [173]; (see Table 4 and section Chapter 7.1.3) and the IECC classification [172]; see section Chapter 7.3 and Table 12) should be given [162].

### 7.2.4. Specimen after radical hysterectomy

| 7.12 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Morphological processing ***shall*** take place in such a way that all therapeutically and prognostically relevant parameters can be assessed. The report ***shall*** be produced on the basis of the currently valid WHO classification for tumor type and the current TNM classification for staging, as well as the R classification (UICC). | |
| | Strong Consensus | |

If a conization was performed prior to (radical) hysterectomy, it is useful to include the relevant macroscopically visible changes in the macroscopic description (e.g., erosions, ulcerations) [189], [190].

Morphological processing should be carried out in such a way that all of the details given in the following list can be obtained [162], [194], [195], [196], [197], [189], [190], [202], [203]. The report on the findings must be based on the WHO classification for tumor type [77] and on the current TNM classification for staging [207], as well as the current UICC classification for the R classification, which is an obligatory component of the pTNM classification.

The ESGO guideline here recommends, among other things, complete embedding/processing of the resected parametrial tissue, as well as of the distal vaginal resection margin [189], [190], [203].

In order to record the intratumoral heterogeneity that has been reported in particular with adenocarcinomas [204], [205], [206] and also neuroendocrine carcinomas [146], [143], the ESGO recommends complete processing of macroscopically visible tumors < 2 cm and embedding of at least one block per centimeter at the greatest tumor extension in tumors larger than 2 cm [189], [190]. Adequate embedding of tumor tissue also appears to be important in relation to the precise assignment of the invasion pattern in the endocervical subtype of adenocarcinoma [169].

| 7.13 | Consensus-based Recommendation | new 2021 |
|---|---|---|
| EC | To document intratumoral heterogeneity, macroscopically visible tumors ≤ 2 cm in size ***should*** be completely processed and at least one block per centimeter at the greatest tumor extension ***should*** be embedded from tumors larger than 2 cm. | |
| | Strong Consensus | |

The report on findings is to be based on the WHO classification for tumor typing [87] and the current pTNM classification for staging [89], as well as the current UICC classification for R classification (see Table 21), which is an obligatory component of the pTNM classification. For the definition and staging of multifocal (microinvasive) carcinomas, see section 7.2.2 on conizations.

After previous excision of the transformation zone (known as conization) and presentation of the findings, the tumor sizes from the previous conization specimen and/or from the previous cervicectomy specimen should be combined in order to calculate the final tumor size. It is useful to note here that the additively measured tumor size is a

calculated tumor size that may combine findings from different pathologies [162], [189], [190]. If conization and trachelectomy have been assessed in different pathologies, the assessment of the calculated tumor size is the responsibility of the gynecologists who last handled the case.

Standard factors required for the report on histological findings in hysterectomy specimens are [162], [173], [195], [208], [189], [190], [203], [209]:

- WHO histological type
- Grading
- Presence/absence of lymphatic or venous invasion (L and V status)
- Presence/absence of perineural sheath infiltration (Pn status)
- Staging (TNM and FIGO)
- Depth of invasion and extent in millimeters in pT1a1 and pT1a2
- Three-dimensional tumor size in centimeters (from pT1b1)
- Minimum distance from the nearest resection margin of the endocervical stroma in pT1b tumors
- Minimum distance from the vaginal margin in pT2a tumors
- Distance from the lateral (parametrial) margin in pT2b
- R classification (UICC)

Measurement of the distance from each resection margin is carried out at the point of deepest tumor infiltration to the surgical resection margin, either after marking with a ruler on the microscopic slide or using an ocular micrometer for small distances.

Studies in recent years have shown in adenocarcinoma that the growth pattern (known as the Silva pattern; see Table 10 and section 7.1.3) correlates with tumor stage, evidence of lymphatic invasion, and lymph-node metastases, and that it is relevant for the prognosis [167], [168], [169], [170]. In accordance with the ICCR recommendation [162] and the 2020 revised version of the NCNN guidelines [173], it is recommended that the growth pattern should be mentioned in the histological findings.

Mention of the IECC classification of an adenocarcinoma [165]; (see section 7.3 and Table 12) is optional, but recommended.

| 7.14 | **Consensus-based Statement** | **checked 2021** |
|---|---|---|
| **EC** | Deep stromal infiltration is defined as invasion by the cervical carcinoma into the outer third of the cervical stroma (> 66%). | |
| | Strong Consensus | |

In the majority of studies, deep stromal infiltration is defined — due to its prognostic importance — as invasion of the cervical carcinoma into the outer third of the cervical stroma (> 66% [105], [210]). The ICCR classifies depth of infiltration as a “required data item” [162], and it should therefore be reported in the findings. Measurement of the depth of infiltration is carried out, by analogy with measurement of endometrial carcinoma, from the level of the cervical mucosa to the deepest point of tumor infiltration. This value is expressed as a proportion of the total thickness of the cervix, obtained from a measurement from the level of the cervical mucosa to the transition between the cervical stroma and the parametrium.

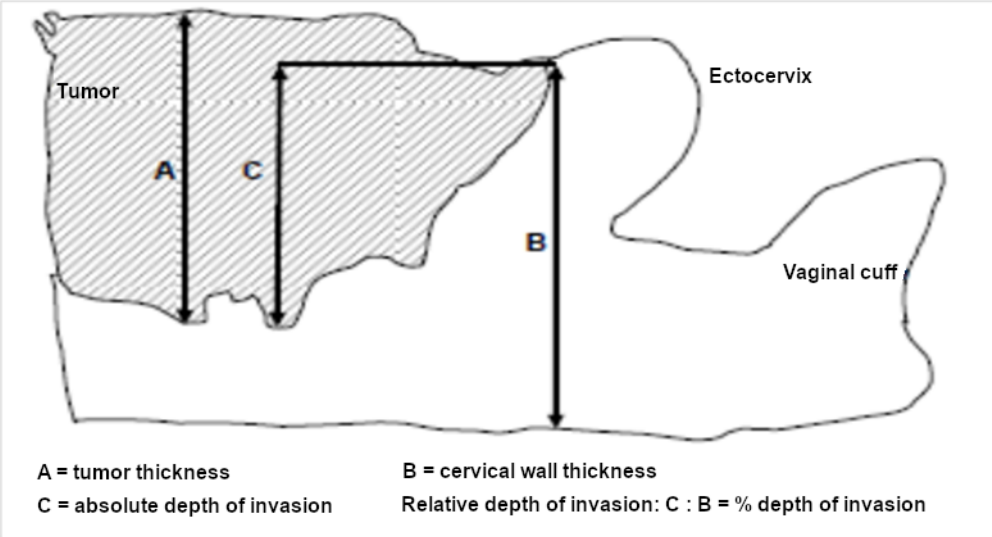



**Figure 4: Assessing stromal infiltration**

The relative stromal infiltration is the ratio of the measured deepest point of tumor infiltration relative to the total thickness of the cervical wall [211] [203].

| 7.15 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| EC | The radical hysterectomy report ***shall*** include the following details:<br>• WHO histological type<br>• Grading<br>• Presence/absence of lymphatic or venous invasion (L and V status)<br>• Presence/absence of perineural sheath infiltration (Pn status)<br>• Staging (TNM), taking the conization findings into account in patients who have undergone conization<br>• Depth of invasion and extension in millimeters in pT1a1 and pT1a2<br>• Depth of invasion relative to the cervical wall thickness (measurement or percentage figure)<br>• Three-dimensional tumor size in centimeters (from pT1b1)<br>• Minimum distance from the resection margins (endocervical stroma in pT1b tumors, vagina in pT2a tumors, and parametrium in pT2b tumors)<br><br>R classification (UICC) | |
| | Strong Consensus | |

If the transformation zone has previously been excised (known as conization) and in the presence of findings, the tumor size from the conization specimen and from the hysterectomy specimen should be combined to calculate the final tumor size.

### 7.2.5. Lymphadenectomy specimens

| 7.16 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Micrometastases are defined as histological evidence of tumor cells in lymph nodes measuring ≥ 0.2 mm, but no larger than 0.2 cm. | |
| | Strong Consensus | |

| 7.17 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In lymphadenectomy specimens obtained during surgical treatment for cervical carcinoma, all removed lymph nodes ***shall*** be histologically examined. | |
| | Strong Consensus | |

| 7.18 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Lymph nodes up to approx. 0.3 cm in size ***should*** be completely paraffin-embedded, and larger lymph nodes ***should*** be halved along the long axis and also completely paraffin-embedded. | |
| | Strong Consensus | |

With lymphadenectomy specimens obtained during surgery for cervical carcinoma, all removed lymph nodes must be histologically examined. Lymph nodes up to approximately 0.3 cm in size should be completely paraffin-embedded, and larger lymph nodes should be halved along their long axis and also completely paraffin-embedded [178] [179] [180] [211]. Preparing step sections increases the chances of detecting small metastases or micrometastases [212].

In accordance with the UICC and TNM classifications, micrometastases are defined as histological evidence of tumor cells in lymph nodes ≥ 0.2 mm, but no larger than 0.2 cm [213] [176]. Tumor cells with an overall size of < 0.2 mm are defined as isolated tumor cells in the lymph node [213] [176].

The prognostic and therapeutic significance of isolated tumor cells is as yet unclear, as is molecular-biological evidence of HPV DNA in pelvic or para-aortic lymph nodes. The same also applies to isolated evidence of lymphatic invasion in perinodal adipose tissue or in the lymph-node capsule without the simultaneous presence of lymph-node metastases. Isolated evidence of lymphatic invasion in perinodal adipose tissue or in the lymph-node capsule without the simultaneous presence of lymph-node metastases should be mentioned in the findings report and should classified as L1 [203].

In a revision of the FIGO classification of cervical carcinoma, FIGO has proposed that evidence of isolated tumor cells should not be mentioned in the report [151]. This suggestion by FIGO contradicts the general TNM staging recommendations [176]. As there are insufficient data, the prognostic significance of isolated tumor cells in cervical

carcinoma is unclear [214], [215]. However, evidence of isolated tumor cells should still be stated in the findings report [93], [189], [190], [203].

| 7.19 | Consensus-based Recommendation | new 2021 |
|---|---|---|
| EC | Evidence of isolated tumor cells or micrometastases ***should*** be mentioned in the histological report and included in the TNM classification. | |
| | Strong Consensus | |

| 7.20 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The report on lymph nodes ***shall*** include the following details: number of affected lymph nodes relative to the number of lymph nodes removed, correlated with the location of removal (pelvic/para-aortic). | |
| | Consensus | |

Standard factors required for the report on histological findings in lymphadenectomy specimens are [178] [179] [180] [211]:

- Details of the number of removed/examined lymph nodes, correlated with the removal site
- Details of the number of affected lymph nodes relative to the number of lymph nodes removed/examined, correlated with the removal site (e.g., 4/12 left communicating lymph nodes)
- Details of largest extension of the largest lymph-node metastasis, in mm/cm
- Details of the presence/absence of capsule penetration by the lymph-node metastasis

## 7.2.6. Sentinel lymph nodes

| 7.21 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Sentinel lymph nodes in cervical carcinoma ***shall*** be completely paraffin-embedded and examined in step sections. | |
| | Strong Consensus | |

A standardized protocol for the histopathological examination of sentinel lymph nodes in cervical carcinoma is not currently available [162], [190], [215], [216], [219]. On the basis of the results of larger studies [216], [217], [218], [220], [221] and the ESGO guideline, the following procedure is recommended for the processing of sentinel lymph nodes [189], [190], [219]:

- Lamellation of the adipose tissue that has been received, with identification of all sentinel lymph nodes
- Complete embedding of all lymph nodes,
- Halving of all lymph nodes ≤ 0,3 cm in size

- Lamellation of all lymph nodes > 0, 3 cm into 0,2 cm thick lamellae
- Preparation of step sections (see below),
- Immunohistochemical ultrastaging (see below).
- With sentinel lymph nodes that cannot be identified macroscopically, complete embedding of the adipose tissue

| 7.22 | **Consensus-based Recommendation** | **new 2021** |
|---|---|---|
| **EC** | Sentinel lymph nodes in cervical carcinoma should be processed as follows:<br>• Lamellation of the adipose tissue that has been received, with identification of all sentinel lymph nodes<br>• Complete removal of all lymph nodes<br>• Halving of all lymph nodes ≤ 0.3 cm in size,<br>• Lamellation of all lymph nodes > 0.3 cm into 0.2 cm thick lamellae<br>• Preparation of step sections<br>• Immunohistochemical ultrastaging<br>• With sentinel lymph nodes that cannot be identified macroscopically, complete embedding of the adipose tissue | |
| | Strong Consensus | |

There are no generally valid recommendations for the preparation of step sections [162], [190], [202], [219]. In analogy with other AWMF guidelines and previous recommendations [202], [203], at least three step sections should be made from the paraffin blocks, each at a maximum distance of 200 µm, and HE-stained.

If no tumor cells can be detected in the HE-stained section specimens, immunohistochemical examination with one (or more) pancytokeratin antibodies (known as "ultrastaging") is useful [215], [216], [219], [217], [218]. In addition, an antibody against p16 can be used. It should be noted that not all histological tumor types are p16-positive, particularly in adenocarcinoma [165], [222], [223].

There are no generally valid guidelines for *intraoperative quick-section examination* of sentinel lymph nodes in cervical carcinoma [162], [215], [224] The ESGO guideline on cervical carcinoma recommends [189]:

- Macroscopic work-up, as described above
- Examination of ALL sentinel lymph nodes in quick section
- If there is a macroscopically visible tumor, intraoperative examination of a sample of the involved lymph node is sufficient
- Macroscopically unremarkable lymph nodes must be examined completely intraoperatively
- Step sections (three) should be made from the frozen blocks (see below)
- The histological frozen-section examination can be supplemented with intraoperative imprint cytology

| 7.23 | Consensus-based Recommendation | new 2021 |
|---|---|---|
| EC | Intraoperative rapid frozen-section examination (when clinically indicated) of sentinel lymph nodes in cervical carcinoma should be performed as follows:<br>• Standard work-up of the sentinel lymph nodes<br>• Examination of ALL sentinel lymph nodes in quick section<br>• If there is a macroscopically visible tumor, intraoperative examination of a sample of the involved lymph node is sufficient<br>• Macroscopically unremarkable lymph nodes must be examined completely intraoperatively<br>• Step sections (three) should be made from the frozen blocks<br><br>The histological frozen-section examination can be supplemented with intraoperative imprint cytology | |
| | Strong Consensus | |

The ESGO guideline does not comment on the number of step sections in the context of quick-section examinations [190]. In analogy with the recommendations in other AWMF guidelines (e.g., vulvar and vaginal carcinoma, endometrial carcinoma) and with the above-mentioned recommendations on the work-up of sentinel lymph nodes in the paraffin block, preparation of three step sections from the frozen block appears useful.

With lymph nodes that are free of tumor in the quick section, the work-up and ultrastaging should be carried out as described above.

## 7.3. Morphological prognostic factors

Established prognostic factors in cervical carcinoma include the *tumor stage* and evidence of pelvic or para-aortic l*ymph-node metastases* [230], [231], [232], [233], [234], [235], [229].

The prognostic relevance of a positive *resection margin* after radical hysterectomy is a comparatively rarely studied parameter. The majority of studies have reported unfavorable recurrence-free and overall survival rates [230], [236] [148], [237], [238], [239]. However, this unfavorable prognostic significance can be positively influenced by adjuvant radiotherapy or radiochemotherapy [233].

*Tumor size* is an established prognostic factor, independently of the tumor type [235], [225], [226], [240], and it is relevant for staging in FIGO stage IB/T1b (FIGO IB1/T1b1 versus FIGO IB2/T1b2 [234] or, in accordance with a proposal made by FIGO: FIGO IB1/T1b1 versus FIGO IB2/T1b2 versus FIGO IB3/T1b3 [151], [152]. It has been shown in recent years that FIGO IB1/T1b1 tumors ≤ 2 cm are associated with a better prognosis than tumors 2–4 cm in size [240], [241] so that a more limited radical surgical approach may be possible [242]. FIGO has therefore proposed further subdividing IB/T1b tumors on the basis of the tumor size [151], [152]: FIGO IB1/T1b1 macroinvasive tumors ≤ 2 cm in size, FIGO IB2/T1b2 tumors 2–4 cm in size, and FIGO IB3/T1b3 tumors > 4 cm in size.

In FIGO stage II/T2, tumor size is prognostically relevant with surgical therapy (cut-off 4 cm [240], [241]), and also with primary radiotherapy (cut-off 6 cm [240]).

All other risk factors or prognostic factors have no predictive, prognostic, or therapeutic relevance as individual factors. It is only with a combination of at least two additional factors that they have any influence on treatment decision-making. pT1a1 tumors with lymphatic vessel invasion are an exception to this. In these cases, sentinel-node biopsy is recommended (see recommendation 8.11.).

With regard to the ***histological tumor type***, it is important that neuroendocrine carcinomas are associated with a poor prognosis [143], [147], [148], [243] With regard to the prognostic distinction between squamous cell carcinoma and adenocarcinoma, there are contradictory findings [233], [228]. In relation to current therapeutic modalities, the distinction between adenocarcinoma and squamous cell carcinoma is apparently of only secondary prognostic relevance [161], [228], [227], [244], [245], [246], [247]. To what extent this will be confirmed when HPV status and specific histological subtypes are taken into account, as well as the IECC classification in adenocarcinoma (see below), is currently unclear. Independently of the HPV status, adenocarcinomas continue to show a less favorable response to radiotherapy alone [244].

The International Endocervical Adenocarcinoma Criteria and Classification (IECC) has been developed on the basis of the HPV status and thus the pathogenetic background [166], [248] (see Table 12). Non-HPV-associated adenocarcinomas here show a significant association with higher age at onset, larger tumors, a larger number of lymphatic vessel invasions or (pelvic) lymph-node metastases, a higher tumor stage, and Silva pattern C [170], [248] — and thus also a less favorable prognosis.

**Table 12: International Endocervical Adenocarcinoma Criteria and Classification (IECC) for adenocarcinoma of the cervix uteri [248], [248]**

| **IECC classification (new 2021)** | |
|---|---|
| **1) HPV-associated adenocarcinomas** | a. Endocervical subtype (synonym: usual type, not otherwise specified (NOS)<br>i. Villo-glandular growth<br>ii. Micropapillary growth<br>iii. Endometrioid phenotype (corresponds to secretion-poor variant of endocervical subtype; see text)<br>b. Mucinous subtype<br>i. Intestinal<br>ii. Withsignet-ring cells<br>iii. Stratified mucin-producing intraepithelial lesions (SMILE)<br>c. Unclassified |
| **1) HPV-negative adenocarcinomas** | a. Gastric subtype<br>b. Clear cell subtype<br>c. Mesonephric carcinoma<br>d. Endometrioid subtype<br>e. Unclassified<br>f. (Serous) |

Independently of HPV association and the IECC classification, studies in recent years have shown that adenocarcinoma with gastric [273] and micropapillary morphology [204], as well as invasive stratified mucin-producing carcinoma [166], [206] are associated with an unfavorable prognosis, with atypical (distant) metastases (particularly in the lung) [274].

Lymphatic infiltration in microinvasive cervical carcinoma was long under debate as having prognostic relevance [253], [254], [255], [256], but the available case numbers were considered too low. A recent study indicates that in both stage pT1a1 and pT1a2, when there is evidence of lymphatic invasion the number of pelvic lymph-node metastases is twice as high, leading to a less favorable prognosis [275]. In *macroinvasive* squamous cell carcinoma, there is a strong correlation between evidence of lymphatic infiltration and tumor stage, tumor size, depth of invasion into the cervical stroma, and lymph-node metastases [257]. There is a lack of multivariate analyses with Cox regression analysis and studies with larger case numbers of node-negative patients within a defined tumor stage [227], so that lymphatic status in macroinvasive squamous cell

carcinoma cannot so far be regarded as a confirmed prognostic factor so far [258]. The evidence for the significance of quantifying lymphatic infiltration in squamous cell carcinoma is considered to be too slight [276]. Quantification of lymphatic infiltration — as described, for example, in endometrial carcinoma [156], [157] — is not recommended in cervical carcinoma, due to the lack of a generally accepted definition and of relevant studies.

In adenocarcinoma of the cervix uteri, lymphatic vessel infiltration correlates with tumor size and depth of invasion [225], as well as with the growth pattern (pattern C) [165], [168], [204]. Quantification of lymphatic infiltration appears to be prognostically relevant in the pattern C growth pattern [166], [204], [277] although there is as yet no generally accepted definition of quantification.

The WHO classification [88], does not have a standardized grading for all of the histological subtypes of cervical carcinoma. For squamous cell carcinoma, what is known as conventional grading, based on the extent of keratinization, is mentioned in the WHO classification [88]. Due to a lack of detailed stage-by-stage and multivariate analyses, very different results have been published for this [105], [249], [259]. A binary grading model based on conventional grading (low-grade versus high-grade cases) may possibly allow better prognostic discrimination [160], [278]. The same applies to a grading system based on the degree of tumor cell dissociation and adapted from colorectal adenocarcinoma, distinguishing between various so-called “budding” types [158]. In summary, however, none of the grading systems so far developed for squamous cell carcinoma currently has sufficient prognostic evidence [162], [227]. In adenocarcinoma, grading analogous to FIGO grading of endometrioid endometrial carcinoma is recommended for the endometrioid subtype [88], [161]. However, there are increasing doubts as to whether primary endometrioid cervical carcinoma is a distinct entity, or rather a variant of the endocervical subtype [165], [166]). The extent to which the growth pattern (known as the pattern system or Silva system [168], [169]; see 7.1.3 above) can be used as a surrogate for grading in the endocervical subtype (not otherwise specified, NOS) or in HPV-associated adenocarcinoma of the cervix uteri, independently of the histological subtype [172], is currently an open question. A grading system based on the degree of tumor cell dissociation and adapted from colorectal adenocarcinoma, distinguishing between different “budding” types with prognostic relevance, has also been reported in one study [279]. This budding-based system shows some overlapping with the above-mentioned Silva patterns. It is currently unclear whether or not certain histological subtypes of cervical adenocarcinoma, such as the HPV-negative gastric subtype [273] and HPV-positive micro-papillary subtype [204] as well as the mostly HPV 18-associated invasive SMILE [166], [206] in analogy with serous endometrial carcinoma, should be classified per se as “high-grade” (G3) due to their unfavorable prognosis.

Assessment of the prognostic relevance of *venous infiltration* is problematic, as it is too rare, at up to 11% of cases [260] and only few studies have analyzed this parameter [261]. Venous infiltration is not explicitly evaluated in many studies, or infiltration into small veins/venules is subsumed into “vascular invasion” or involvement of the lymphovascular space.

*Perineural sheath infiltration* is a parameter that has so far only been examined in a few studies in relation to cervical carcinoma [262]. However, a meta-analysis classed it as prognostically relevant [280] although with limited evidence due to the small numbers of cases so far investigated.

The *depth of infiltration* of cervical carcinoma into the cervical stroma is a parameter that has been investigated in numerous studies [105], [210], [225], [263], [251], [252] It usually has some prognostic significance, but it is often associated with the tumor size and pelvic lymph-node metastases. The definition of deep stromal infiltration is not standardized and varies between > 50% to > 75% in various studies [105], [210], [225], [263], [251], [252], [264]. On the basis of existing research results and to allow standardization of the procedure for future studies as well, infiltration by the carcinoma into the cervical stroma of up to or more than two-thirds (≥ 66%) is defined as deep stromal infiltration. In addition to the relative depth of infiltration, the absolute depth of infiltration is often also examined, but without any definition of standardized threshold values and without multivariate analyses of each cohort. Overall, there is insufficient evidence for deep stromal infiltration as an independent prognostic factor. The ICCR classifies depth of infiltration as a "required data item" [162].

The extent to which the distinction between micrometastases and macrometastases into the pelvic lymph nodes may be of prognostic significance cannot currently be assessed due to the small number of available studies [229], [265], [266], [267]. In addition, evidence of isolated tumor cells and of micrometastases is not infrequently combined into "minimal nodal disease" [151] , [152], [272]. Nevertheless, it appears that patients with conventional lymphadenectomy and evidence of micrometastases have a less favorable prognosis than those without lymph-node involvement [229], [265], [272]. The extent to which this is applicable to patients with sentinel lymph nodes remains to be seen [220]. In addition, evidence of micrometastases is usually an indication for adjuvant radiotherapy, which also applies to a limited extent to isolated tumor cells [214]. Even fewer data area available in relation to evidence of isolated tumor cells or the differentiation between micrometastases and macrometastases in para-aortic lymph nodes [250], [268], [269].

*Immunohistochemical ultrastaging* of pelvic and para-aortic lymph nodes (outside of the work-up for sentinel lymph nodes) may increase the detection rate for (micro)metastases [250], [268], [269]. Due to the small number of cases, the prognostic significance of this kind of ultrastaging is still insufficiently clear [250], [268], [269].

In recent years, *HPV status* in cervical carcinoma has been the subject of numerous studies. The rate of HPV-negative *squamous cell carcinomas,* at < 10 %, is in all probability not prognostically relevant [222], [281]. In contrast, HPV-negative adenocarcinomas represent a group with an unfavorable prognosis [166], [223], [281], [282] HPV-negative adenocarcinomas, in comparison with HPV-positive adenocarcinomas, are associated with significantly older age, greater horizontal tumor extension, greater depth of invasion, more lymphatic invasion, higher tumor stage, and increased destructive tumor growth (Silva pattern C [166], [248]). HPV-negative tumors are mostly gastric or clear cell or mesonephric, and more rarely genuine primary endometrioid adenocarcinomas [166], [248]. For the IECC classification of endocervical adenocarcinoma, which is based on HPV status in addition to morphological criteria [165], reference may be made to the section on histologic tumor types and Table 12. HE staining is usually sufficient to classify adenocarcinoma in the IECC classification, and it can be supplemented by p16 immunohistochemistry if appropriate. HPV assessment and typing are only necessary in individual cases.

The prognostic evidence is limited due to the association between HPV-negative adenocarcinomas and the above-mentioned unfavorable prognostic factors [166], as well as the above (rare) histologic subtypes, and, again, by the lack of stage-by-stage and

multivariate analyses. However, histopathological evidence of gastric clear cell or mesonephric adenocarcinoma should be taken into account in decision-making on adjuvant therapy and in the prognostic assessment at the multidisciplinary tumor conference.

Only limited data are currently available on the relevance of *molecular marker* and of the *TCGA classification* (based on molecular investigations in the Cancer Genome Atlas project (low-keratin versus high-keratin squamous cell carcinomas) [234], [283], [284]. Probably the most common mutation in cervical cancer is the PIK3CA mutation, accounting for about 33%. There are no differences between squamous cell carcinomas and adenocarcinomas in terms of mutation frequency, but mutant tumors are associated with a significantly shorter survival [285]. KRAS mutation appears to be exclusive to adenocarcinomas [285], although it may be characteristic of mesonephric carcinomas [286]. TCGA analysis has also revealed amplification of immunomodulatory genes [284]. In this context, it is worth mentioning that assessment of intratumoral microsatellite instability [287], as well as the *tumor mutational burden* (TMB), as well as pathological-anatomical evaluation of PD-L1 expression [288], [289] is also possible a posteriori using archived tumor tissue (FFPE material). Testing *PD-L1 expression* as a prerequisite for immunomodulatory therapy in locally advanced or recurrent cervical carcinoma has been reported [289], [290], [291]. Pembrolizimab has been approved by the FDA in the United States (FDA 2018), but not currently by the European Medicines Agency (EMA). In the FDA approval, the combined positive score (CPS) with the antibody PD-L1 IHC 22C3 pharmDx kit is on file [173]. In the revised version of the NCCN guidelines, the use of pembrolizumab in second-line therapy is classified as category 2A in terms of its evidence [160], but this requires testing of the tumor tissue with a PD-L1 antibody or an assessment of microsatellite status. In the same setting, the use of neurotrophic tyrosine receptor kinase (NTRK) inhibitors is classified with an evidence level of category 2B after prior testing.

Due to the currently limited state of the data, molecular markers and the TCGA classification do not yet play any role in the prognostic assessment of cervical carcinoma, or as possible therapeutic targets [234], [247], [270], [271], [292], [293], [294], [295].

**Table 13: Summary of standard factors, risk factors, and prognostic factors and their therapeutic relevance in microinvasive carcinoma (stage T1a in the TNM classification) (modified 2021)**

| Name | Standard factor[1] | Risk/Prognostic factor | Treatment relevance[2] |
|---|---|---|---|
| Tumor stage | Yes | Yes | Yes |
| Tumor type | Yes | Yes (only neuroendocrine) | Unclear |
| Perineural sheath infiltration (Pn status) | Yes | Unclear | no |
| Lymphatic vessel infiltration (L-status) | Yes | Unclear (possibly sentinel in pT1a1) | Yes[3] |
| Venous invasion (V status) | Yes | Unclear | Yes[3] |
| Location<br><br>(endocervical/ectocervical) | Yes | No | No |
| Resection margins<br><br>(R classification) | Yes | Yes | Yes |
| Grading | Yes | Unclear[4] | No |
| p16 | No (only CIN) | No (only CIN) | No |
| Ki-67 | No (only CIN) | No (only CIN) | No |
| Depth of invasion and extent in mm | Yes | Yes | Yes[5] |
| Pelvic lymph node metastases | Yes | Yes | Yes[6] |
| Micro/macrometastases | Yes | Unclear | Yes (pN0 vs. pN1) |
| Immunohistochemical ultrastaging of lymph nodes (apart from sentinel nodes) | No | Unclear | No |

[1] Standard factors are regarded as factors for tumor classification that are regularly recorded in routine practice and are described in the corresponding sections on specimen processing.
[2] Treatment relevance refers to the guideline statements. In unclear factors, decisions were taken at expert level.
[3] Only in combination with other risk factors, not as an individual factor.
[4] In addition, G3 is hardly seen in microinvasive carcinoma.
[5] Depending on the tumor stage.
[6] Para-aortic lymph nodes are almost excluded in microinvasive carcinoma.

**Table 14: Summary of standard factors, risk factors, and prognostic factors and their therapeutic relevance in macroinvasive carcinoma (stage > T1a in the TNM classification) (modified 2021)**

| Name | Standard-factor[1] | Risk/Prognostic Factor | Therapy relevance[2] |
|---|---|---|---|
| Tumor stage | Yes | Yes | Yes |
| Tumor type | Yes | Yes (only neuroendocrine) | Yes (only neuroendocrine) |
| Growth pattern in adenocarcinoma | Yes/no[3] | Yes (probably only endocervical subtype) | Unclear |
| Perineural sheath infiltration (Pn status) | Yes | Unclear | No |
| Lymphatic infiltration (L status) | Yes | Unclear | Unclear |
| Venous invasion (V status) | Yes | Unclear | Unclear |
| Location (endocervical/ectocervical) | No | Unclear | No |
| Resection margins (R classification) | Yes | Yes | Yes |
| Deep stromal invasion | Yes | Unclear[4] | Yes[4] |
| Grading | Yes | Yes | Yes[5] |
| p16 | No (only CIN) | No (only CIN) | No |
| Ki-67 | No (only CIN) | No (only CIN) | No |
| Depth of invasion and extent in mm | Yes | Unclear | No |
| Three-dimensional tumor size in cm | Yes | Yes[6] | Yes |

| Name | Standard-factor[1] | Risk/Prognostic Factor | Therapy relevance[2] |
|---|---|---|---|
| Pelvic lymph node metastases (N-status) | Yes | Yes | Yes |
| Para-aortic lymph node metastases (M-status) | Yes | Yes | Yes |
| Micro-/macrometastases | Yes | Unclear | Yes (pN0 versus pN1) |
| Isolated tumor cells in lymph nodes | Yes | Unclear | Unclear |
| Immunohistochemical ultrastaging of lymph nodes (apart from sentiel lymph nodes) | No | Unclear | No |
| HPV status in adenocarcinoma | No | Unclear[7] | No |
| PD1/PDL1 testing | No | Unclear | Unclear (poss. in advanced carcinoma) |

[1] Standard factors are regarded as factors for tumor classification that are regularly recorded in routine practice and are described in the corresponding sections on specimen processing.

[2] Treatment relevance refers to the guideline statements. In unclear factors, decisions were taken at expert level.

[3] Giving details of what is known as the growth pattern (or Silva pattern) is recommended in particular in the endocervical subtype of cervical adenocarcinoma, where it is evidently of prognostic relevance. Insufficient data are currently available regarding its prognostic relevance in other histological subtypes.

[4] Various studies, with different definitions.

[5] Only in combination with two other risk factors, not as an individual factor.

[6] In FIGO IB/T1b tumors, the cut-off point for maximum tumor extent 2 cm or 4 cm (see text); in FIGO IIA/T2a tumors, the cut-off point is 4 cm.

[7] HPV-negative adenocarcinomas probably have a more unfavorable prognosis; on this point, see also the IECC classification and WHO 2020.

# 8. Foundations of treatment

**Major changes in the chapter on foundations of treatment**

This chapter has been little revised. The new changes in the sentinel concept have been incorporated. Women with cervical carcinoma FIGO IA1 and L1 and with cervical carcinoma up to 2 cm without risk factors should be offered sentinel-node biopsy. At the time of the guideline preparation, the new FIGO classification was already available to the guideline group. The data are based on the previous classification. All of the tumor stages therefore refer to the old FIGO classification.

*D. Denschlag, M.W. Beckmann, F.A. Stübs, M.C. Koch, C. Dannecker*

| 8.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The aim of treatment for primary cervical carcinoma ***should*** be individualized therapy.The choice of treatment ***should*** take the following factors into account:<br>• Patient's general condition (with high levels of comorbidity)<br>• Patient's life situation<br>• Clinically/histologically defined stage of the disease<br>• Menopausal status<br>• Potential wish to have children<br>• Short-term and long-term sequelae of the various treatment options<br>• Any risk factors<br>• Overtreatment and undertreatment should be avoided. | |
| | Strong Consensus | |

This chapter presents the higher-level structure that sums up the detailed diagnostic methods and treatment modalities, and the indications for them, in the corresponding chapters (Chapter 6; Chapter 9; Chapter 10; Chapter 11; Chapter 17; Chapter 18; Chapter 22; Chapter 23; Chapter 24). It also describes the standard procedure. The standard is defined as the currently best possible treatment that is based on scientific findings and is universally available.

The decision regarding which treatment modality is appropriate must be taken on an interdisciplinary basis, including the fields of gynecological oncology, radiotherapy, pathology, radiology, and anesthesiology, as well as nuclear medicine where appropriate.

Decision-making criteria here consist of factors such as the short-term and long-term effects of the various treatment options; the patient's general condition, risk factors, and life situation; the stage of the disease; menopausal status; and family planning considerations. The treatment decision is taken on an individual and participatory basis together with the patient.

The aim in treatment for women with primary cervical carcinoma should be to avoid overtreatment and undertreatment. Due to the increased comorbidity with combinations of several therapies, only one primary treatment procedure should be used when possible.

The classification of cervical carcinoma in accordance with the previously valid 2009 FIGO system was based on a bimanual clinical examination by the gynecologist. This is mainly justified by the fact that over 85% of cervical carcinomas are diagnosed in countries with limited access to radiological tomography [296]. This approach has been abandoned in the current 2018 classification, and some aspects that are very useful clinically have been included, which have in fact already found their way into routine care (Table 21). The aim is to offer the patient the treatment that is regarded as the current standard. This treatment must have a positive risk–benefit pattern, and data on the technique, benefits, and risks must be available for evaluation that have a sufficiently secure basis. Previously, the aim was to avoid combination therapies in the treatment of women with cervical carcinoma. This has been abandoned in first-line therapy for recurrent or metastatic cervical carcinoma. In line with the results of the GOG-240 study, the antibody bevacizumab has been added to the combination treatment with cisplatin/paclitaxel.

**Consensus-agreed diagrams from the guideline group on treatment types and combinations of them in patients with cervical carcinoma**

Based on expert consensus, consensus

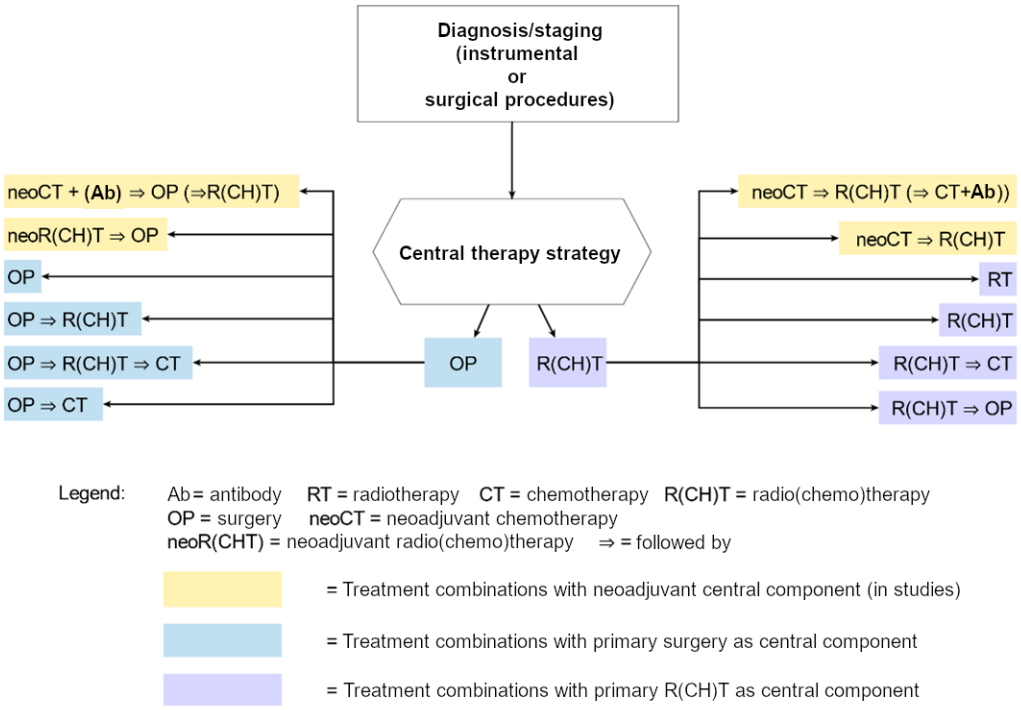



**Figure 5: Types of treatment and combinations of them for women with primary cervical carcinoma (not all are standard procedures, and not all have been investigated in larger prospective and randomized studies) (2021)**

Figure 5 shows possible treatments and combinations of them. A distinction is initially made between the central treatment options of primary radio(chemo)therapy (right) and primary surgery (left). The possible combinations are then presented in a structured way relative to each time course of treatment (without hierarchical evaluation of possible treatment options). The illustration is intended as an overview of options that are possible and/or described in the literature. However, not all of them are standard,

nor are they to be regarded as equivalent treatment options. Which form of therapy is indicated or should be rejected in which situation is described in the relevant individual sections here.

There are a large number of chemotherapy regimens (Chapter 11), radiotherapeutic options (Chapter 10), and surgical treatments (Chapter 9). These various options make it difficult, using the criteria mentioned above, to define the standard in the treatment of a patient with cervical carcinoma. Only a new classification system in which the stage is defined on the basis of pathology will be capable of creating the prerequisites for a correct stage-adapted treatment standard. This affects not only the various radio(chemo)therapy and chemotherapy protocols, but also the large number of surgical options. With the declining incidence of cervical carcinoma, the question arises of which form of treatment can still be described as "standard" and how structured training and further education in the techniques involved will be possible in the future. This group of topics is discussed in Chapter 25.

## 8.1. Primary therapy

Primary therapy consists either of surgery or radio(chemo)therapy. The fact that the unimodal approach is becoming increasingly established in Germany is now reflected in the quality indicators (QIs) for the gynecological cancer centers (Chapter 26). In comparison with the English-speaking world and the international sphere, more surgical procedures are carried out in Germany in the treatment of cervical carcinoma. Surgical procedures are mainly carried out in Germany in the early stages (IA to IIA) and with locally limited cervical carcinoma (Chapter 9 and section 8.6) [297]. This differs from the international and above all English-language literature, in which primary radio(chemo)therapy is used starting from stage IB2 [298]. In the present guideline, in contrast to earlier guidelines, primary R(CH)T is preferred after surgical staging in stage IIB. Radio(chemo)therapy is also recommended in the presence of several preoperatively confirmed risk factors — i.e., lymphangiosis (L1), R1, G3 (of questionable significance and only in combination with two additional risk factors), neuroendocrine carcinoma, tumor > 4 cm (stage), or intraoperative findings of pN1 or histologically positive lymph-node metastases (see Table 13 and Table 14). An intraoperative decision may be taken to carry out radical hysterectomy or to stop the operation and administer radio(chemo)therapy. Primary radio(chemo)therapy is mainly used in the extended stages (starting from stage IIB), and when there is lymph-node involvement and inoperability. The choice of treatment in stage IV should be made on an individual basis. In general, no distinctions between the histological tumor entities (e.g., adenocarcinoma or squamous cell carcinoma) are made here in the choice of treatment.

In stages IB and II, surgery and simultaneous radio(chemo)therapy lead to long-term results that are equivalent despite different pretherapeutic indications, although with different recurrence patterns and side effect profiles for the treatments.

### 8.1.1. Surgery — hysterectomy and lymphadenectomy

The surgical treatment options (primary, adjuvant) have become quite varied as a result of new technical developments.

#### 8.1.1.1. Uterine surgery

The 1974 Piver–Rutledge classification is used as the standard for classifying radical hysterectomy [299]. The classification is incomplete in some respects. Suggestions for ways of optimizing it (e.g., TNM-Leiden 2009, Querleu/Morrow 2008, EORTC/GCG

2008) [300][301][302] were subsequently made, but none has prevailed. The present guideline is therefore based on the Piver–Rutledge classification [299], which is the one that is or has been mainly used in the published literature and in most research studies.

#### 8.1.1.1.1. Consensus-based diagram on treatment techniques and principles (2014)

Based on expert consensus, consensus

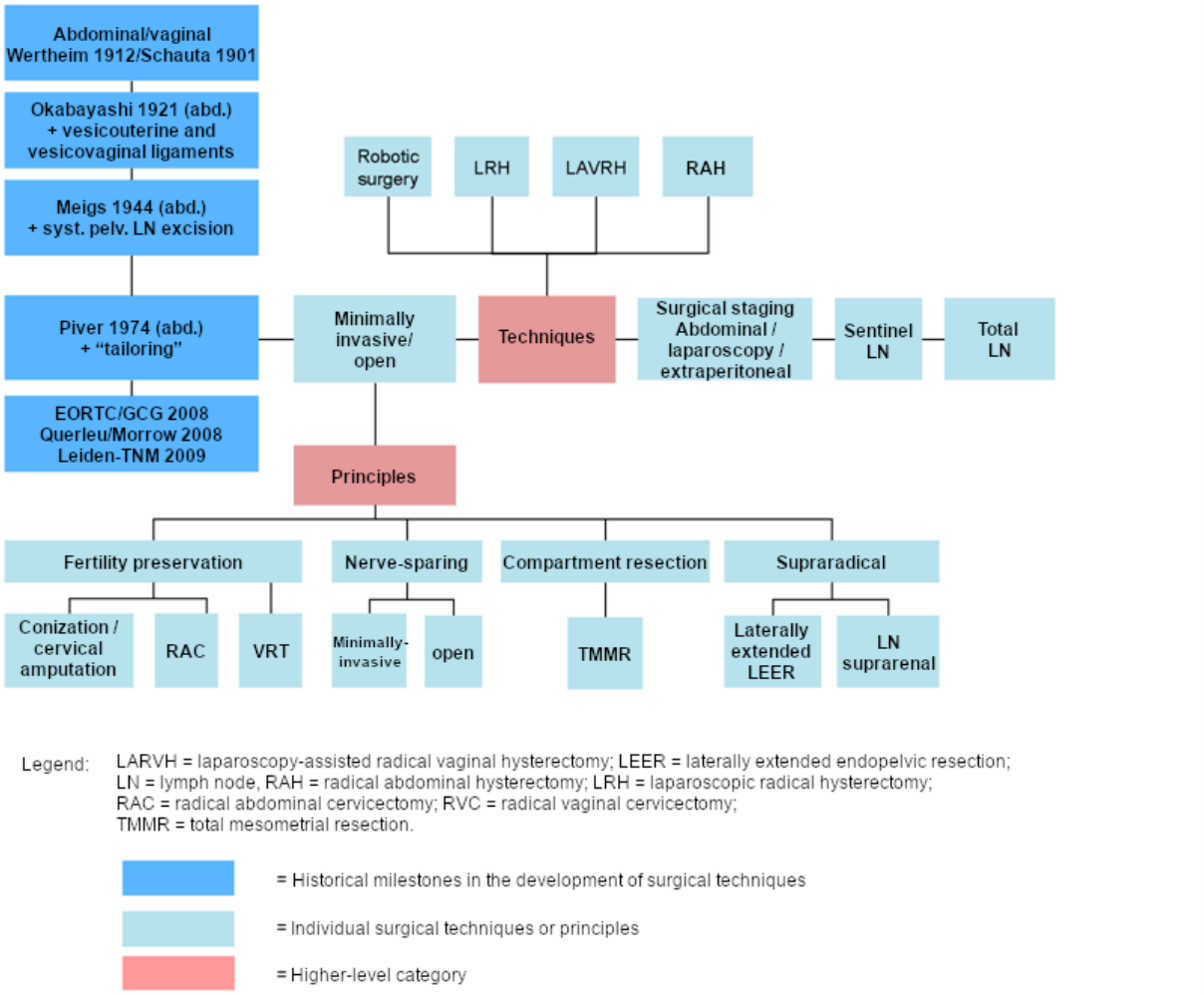



**Figure 6: Surgical techniques and principles (2014, 2021)**

### 8.1.1.2. Lymphadenectomy and sentinel lymph nodes for defining the tumor stage

| 8.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Treatment must be administered relative to the histological tumor stage, verified using surgical staging or interventional diagnosis. | |
| | Consensus | |

Treatments relative to the intraoperative lymph-node status (with quick-section examinations) are included here under the relevant stages. The central component of treatment decision-making is the establishment of the histological tumor stage, including the lymph-node status. Alternatively, methods of interventional diagnosis such as CT-guided, MRI-guided, or ultrasound-guided punch biopsies, or fine-needle cytology, can be used for pretherapeutic diagnosis in order to histologically clarify lesions that are suspicious for metastases.

| 8.3 | Consensus-based Statement | modified 2021 |
|---|---|---|
| EC | Sentinel lymphadenectomy alone ***should*** be used:<br>• For preoperative imaging (patent blue and radioactive)<br>• Or intraoperative imaging (indocyanine green)<br>• When sentinel lymph nodes are imaged or detected bilaterally<br>• In primary tumors in stage T IA 1 L1 and/or FIGO IA 2<br>• In primary tumors in stage T IB1 (≤ 2 cm)<br>• Removal of all imaged or detected sentinel lymph nodes | |
| | Strong Consensus | |

| 8.4 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR<br>A | If the sentinel lymphadenectomy method alone is being carried out, the following staining methods ***shall*** be used:<br>• Staining demonstration or detection using patent blue and radioactive tracer<br><br>or<br>• Staining demonstration or detection using indocyanine green<br>• Primary tumor < 2 cm in size, with no risk factors<br>• Removal of all sentinel lymph nodes identified using imaging | |
| LoE<br>2++ | [303]; [304]; [305] | |
| | Strong Consensus | |

The imaging procedures CT, MRI, and FDG-PET-CT are not sufficiently sensitive and specific for certain detection of lymph-node metastases [306], [307], [308], [309]. As an example, mention may be made of a meta-analysis including 72 studies and 5042 patients, which compared the sentinel method in cervical carcinoma with the various imaging methods (CT, MRI, PET-CT) in relation to the detection of a lymph-node metastases [309]. The study reported a sensitivity of 91.4% in comparison with 74.7% (for PET-CT), 55.5% (for MRI), and 57.5% (for CT) and a specificity of 100% in comparison with 97.6% (for PET-CT), 93.2 % (for MRI), and 92.3 % (for CT). This indicates the superiority of the sentinel method over the imaging techniques.

Small metastases in particular often remain undetected on conventional imaging (see Chapter 6). On the other hand, systematic lymphadenectomy is associated with a substantial rate of intraoperative and postoperative complications (paresthesias, lymphoceles, lymphedema, etc.). The approach using sentinel lymph-node detection in specific conditions in primary cervical carcinoma therefore appears reasonable and recommendable in specific conditions (see recommendation 8.3.). However, the SENTICOL I study showed that after 6 months at the latest, no differences in lymphedema symptoms were detectable between the groups compared (radical lymphadenectomy vs. sentinel-node lymphadenectomy) [311].

In this context, with cervical carcinoma as a “midline tumor,” the sentinel method appears to have sufficient safety only in the case of a primary tumor < 2 cm in size, with combined imaging using patent blue and radioactive tracer, and bilateral imaging of sentinel lymph nodes [308]. However, the more recent Senticol studies include patients with tumors up to 4 cm. Full publications with the results have not yet appeared, however [311]. In the meantime, intraoperative imaging of sentinel lymph nodes using ICG is at least equivalent to combined imaging using radioactive tracer and patent blue [303].

The sentinel-node approach in women with cervical carcinoma has now been under evaluation for more than 15 years. However, the great majority of the available publications only report single-center and retrospective experience, so that their validity is limited. In the largest prospective, multicenter study to date (AGO Uterus 3), including a total of 590 patients, the rate of detection was 94% when technetium and patent blue were used in combination for marking. In addition, subsequent stratification between tumors > 2 cm and < 2 cm showed that the decisive negative predictive value only reached acceptable values (< 99%) with small tumors [307].

The superiority of the combined use of technetium and patent blue in relation to detection rates (94–97%; cf. Tax et al. 2015 and Wang et al. 2014) has in the meantime been confirmed by various meta-analyses and systematic reviews.

The same applies to dependence on tumor size. As an example, a 2014 meta-analysis by Kadkhodayan et al. may be mentioned here. In the study, the pooled analysis showed a detection rate of 94% and a sensitivity of 95% for tumors  2 cm, for which the detection rate was only 74% and the sensitivity 82%.

The need for bilateral imaging was described by Cibula et al. in a publication including 645 patients. In this study, the authors detected a significantly higher rate of lymph-node metastases in comparison with unilateral detection alone [310].

The certainty provided by bilateral detection is also confirmed by data from the prospective SENTICOL I study [311], in which not a single false-negative sentinel lymph node finding was noted in 104 patients in whom bilateral imaging was successful.

Previously, lymph-node marking using patent blue and a radioactive tracer was regarded as the standard sentinel method for cervical carcinoma [312], [313]. The combination of the two methods provided the highest rates of detected lymph nodes and highest sensitivity levels for positive lymph nodes (sensitivity 91.3%; 95% CI, 87.5 to 94.2) [314].

In recent years, the use of indocyanine green (ICG), visualized with "near-infrared" fluorescence filters, has increasingly become established as a valid alternative (however, this use is off-label). The advantage is that radioactive substances and patent blue (with an allergenic potential in pregnancy) can be completely avoided [304].

A systematic review including 538 patients showed that ICG achieves equivalent detection rates in comparison with the combination of technetium and patent blue (OR 0.96; 95%: CI, 0.45 to 2.02; P = 0.91). For detection of bilateral lymph nodes, ICG tended to be superior to the combination of patent blue and radioactive tracer, but without reaching statistical significance (OR 0.37; 95% CI, 0.07 to 2.12; P = 0.27) [303].

With regard to histological processing of the tissue, what is known as ultra-staging should be used in analogy with breast carcinoma in order to achieve a sufficiently high rate of detection of any metastases that are present. This technique is discussed in detail in Chapter 7.

Sentinel lymphadenectomy alone is therefore still not a standard procedure for all stages. The great majority of studies to date only refer to the sentinel technique in conjunction with systematic lymphadenectomy and do not have any data regarding survival. Only limited conclusions can therefore be drawn regarding the safety of sentinel lymphadenectomy alone. In addition, the maximum tumor size of 2 cm [307] for achieving adequate safety with the method is based on retrospective analyses.

The primary goals in the planned prospective randomized phase III study (Senticol III; ClinicalTrials.gov identifier: NCT03386734) are the 3-year disease-free survival rate and quality of life in patients with early cervical carcinoma. For this purpose, patients are to be randomized 1 : 1 into the following two groups: sentinel lymph-node extirpation vs. pelvic systematic lymphadenectomy. A total of 950 patients are to be included. The study will hopefully provide a conclusive answer to the question of the safety of this technique, with the highest level of evidence. The study also includes higher-stage tumors (FIGO IA1 to IIa1) [311].

The publication of a comparable prospective and randomized study by the AGO/ARO, including 1200 patients, for evaluation of the sentinel approach is also pending at the time of the revision of the guideline (NCT01157962). However, the authors of the guideline consider that the data are sufficient for the method to be recommended in the conditions mentioned, particularly in view of the low rate of lymph-node metastases in early stages (TIA1 + L1, IA2, IB1 < 2 cm).

#### 8.1.1.3. Definition of terms in lymphadenectomy

In the context a lymphadenectomy for cervical carcinoma, a distinction is made on the one hand between the different anatomical lymph drainage areas (pelvic and para-aortic) that drain the uterus.

Different terms are also used in the literature in relation to the radicality of a lymphadenectomy. These are explained below to allow better understanding of the recommendations.

In general, assessment of the parametrial, vesicouterine, and peritoneal spread is possible or useful in the context of a histological lymph-node evaluation.

**Radical lymphonodectomy**

The aim in radical systematic lymphadenectomy is to remove all lymph nodes along the lymphatic tracts in the corresponding lymphatic drainage area. It is used for diagnosis (supplemented by quick-section examinations) and treatment. Validated data on the number of lymph nodes that need to be removed per lymphatic drainage area in order to achieve sufficient safety are not available to the guideline group. At least 15–20 pelvic lymph nodes and 8–10 para-aortic lymph nodes can be used as an indication.

Systematic pelvic lymphadenectomy includes the removal of all lymph nodes and adipose tissue in the area of the pelvic vessels. The lymphatic vessels and lymph nodes medial and lateral to the external and internal iliac artery, around the common iliac artery, and in the area of the obturator artery and vein are removed as far as the pelvic floor.

If there is pelvic lymph-node involvement, para-aortic lymphadenectomy is carried out along the aorta and vena cava as far as the end of the renal vessels.

**Selective lymph node staging**

Selective lymph-node staging is used for histological diagnosis. An attempt is made to remove a representative number of lymph nodes from the corresponding lymphatic drainage areas in order to define the stage.

In principle, this procedure is not recommended by the guideline group, as no valid data are available regarding the benefit of the technique.

**Lymph node debulking**

Lymph-node debulking is an attempt in the advanced setting (≥ FIGO stage IIB) to remove at least the macroscopically affected lymph nodes in order to reduce the tumor size before primary radio(chemo)therapy.

**Therapeutic lymphonodectomy**

Therapeutic lymphadenectomy is a term that can only be viewed in connection with total mesometrial resection (TMMR). In this procedure, systematic radical lymphadenectomy is carried out along the anatomic and embryonic developmental borders in order to avoid adjuvant radio(chemo)therapy despite lymph-node involvement. As only single-center data are available, this approach cannot currently be regarded as a standard procedure [316], [317].

**Sentinel lymphonodectomy**

Sentinel lymphadenectomy is carried out similarly to the already established procedure in breast carcinoma. The aim is to achieve sufficient diagnostic/oncological certainty with maximum tissue-sparing. The sentinel lymph nodes are initially detected bilaterally and then removed. The sentinel procedure is also used in parallel with radical lymphadenectomy. In addition to its low morbidity, this technique can potentially detect unusual lymphatic drainage pathways [11] or increase the detection rate of micrometastases through the use of histologic ultrastaging [7] [12]. The role of detection of intrauterine nodes (Lucas-Championnière lymph nodes) and/or parametrial lymph

nodes is unclear. These lymph nodes are difficult to detect with the sentinel technique using technetium, due to their proximity to the primary tumor [315].

#### 8.1.1.4. Drain placement after lymphadenectomy

| 8.5 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **B** | Following pelvic lymphadenectomy, placement of a retroperitoneal drain in the surgical area ***should*** be avoided, in order to prevent lymphoceles. | |
| LoE **1+** | [318] | |
| | Strong Consensus | |

Pelvic lymphadenectomy is an essential component of the surgical procedure for many gynecological malignancies, and particularly with cervical carcinoma. Complications may occur in connection with the operation, particularly lymphoceles. These in turn are associated with symptoms such as swelling of the legs, ureteral stenosis, deep venous thrombosis in the legs, constipation, and infections. Although there was no clear basis of evidence for it, placement of passive or even active suction drains became established traditionally as a method of preventing these complications. A Cochrane analysis in 2010 [319] investigated the effects of retroperitoneal drains in relation to the prevention of lymphoceles and related symptoms (symptomatic lymphoceles) after pelvic lymphadenectomy in the context of surgery for gynecological malignancies. A total of four RCTs with 571 patients were included. The patients mainly had cervical or endometrial carcinoma, and one study included patients with ovarian carcinoma. With a low risk of distortion in the studies, it was found that placing drains with a closed peritoneum conferred no benefits in the prevention of lymphoceles in comparison with leaving the peritoneum open. Placement of drains instead showed a trend toward an increase in both the short-term and long-term risk for symptomatic lymphoceles. The authors therefore advise against placement of pelvic drains following pelvic lymphadenectomy.

### 8.1.2. Radio(chemo)therapy

Radio(chemo)therapy can be administered on a neoadjuvant basis, as primary therapy, and as an adjuvant treatment. Following the unimodal treatment principle, it is desirable to use R(CH)T mainly as a sole primary therapy when the indication is appropriate. It is usually carried out with cisplatin as the radiosensitizer. A distinction is made between percutaneous radiotherapy and brachytherapy. The irradiation fields (pelvic/para-aortic) are adapted to the histologically confirmed lymph-node involvement, not to areas based on imaging suspicion alone. The standard form of radio(chemo)therapy starting from stage IIB or lower stages in patients with histologically confirmed risk factors is primary, initially percutaneous, irradiation of the primary tumor and the pelvic lymph nodes, in combination with cisplatin-containing chemotherapy, followed by brachytherapy.

## 8.2. Neoadjuvant drug therapy

| 8.6 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **0** | Neoadjuvant drug therapy ***can*** be carried out in selected patients who are at high-risk. | |
| LoE **1-** | [320]; [321] | |
| | Strong Consensus | |

The treatment options and indications for neoadjuvant drug therapy, and the data available on the topic, are discussed in Chapter 11. This treatment option is not currently standard. There is a higher rate of operable findings after neoadjuvant therapy [322]. This may also be taken into consideration in specific situations if the patient is wishing to have children.

In a systematic review including 88 pregnant patients with cervical carcinoma (FIGO I–IV) who received platinum-containing neoadjuvant chemotherapy, all of the children were healthy after a median follow-up period of 17 months [323]. No improvement in the progression-free survival or overall survival was observed with the use of neoadjuvant chemotherapy. One meta-analysis included 739 patients from randomized RCTs of patients with cervical carcinoma (FIGO IB1–III), reporting the overall survival rate (OR 1.17; 95% CI, 0.85 to 1.61; P = 0.35) and disease-free survival rate (OR 1.09; 95% CI, 0.77 to 1.56; P = 0.62) [324]. A significant reduction in lymph-node metastases (OR 0.45; 95% CI, 0.29 to 0.7; P = 0.0005) and parametrial infiltration (OR 0.48; 95% CI, 0.25 to 0.92; P = 0.03) was demonstrated, although with no effect on the overall survival. A detailed description of at-risk patients and of potential risks is given in section 11.1, Primary treatment.

| 8.7 | Consensus-based Statement | checked 2021 |
|---|---|---|
| **EC** | The significance of tumor-affected lymph nodes for further treatment planning after neoadjuvant chemotherapy is unclear. | |
| | Consensus | |

Despite a systematic search, it was not possible to identify any publications in the literature that would allow any conclusions to be drawn on the significance of affected lymph nodes after neoadjuvant treatment. The question of the extent of treatment and of adjuvant therapy thus remains unresolved both for the standard surgical procedures and also for the TMMR approach (after neoadjuvant chemotherapy).

# 8.3. Adjuvant therapy

## 8.3.1. Adjuvant therapy after primary surgery

Adjuvant treatment after primary surgical therapy depends on the postoperative findings and the resulting histological tumor stage.

| 8.8 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | Adjuvant therapy following primary surgical therapy should be administered on the basis of the postoperative histological tumor stage as follows:<br><br>Negative lymph nodes; R0; no risk factors.<br>• Follow-up<br><br>Negative lymph nodes; R0; one or two risk factors (L1, V1, deep stromal invasion (see Chapter 7.2.4), tumor size > 4 cm)<br>• Individualized decision<br><br>Histologically confirmed lymph-node metastases, pelvic (pN1) or R1 or several (≥ 3) simultaneous risk factors (L1, V1, deep stromal invasion, tumor size > 4 cm, as well as grade G3 if two additional risk factors are present)<br>• Adjuvant radio(chemo)therapy including lymphatic drainage areas in the histologically identified area (pelvic)<br><br>EC after systematic research (see Guideline Report) for pN1Histologically confirmed para-aortic lymph-node metastases (pM1)<br>• Extended adjuvant radio(chemo)therapy including lymphatic drainage areas in the histologically identified area (pelvic and para-aortic fields)<br><br>EC according to systematic search (see guideline report) for pM1Distant metastases, M1 (organ metastases, peritoneal carcinosis, ovarian metastases)<br>• Systemic chemotherapy; radiotherapy only indicated in case of bleeding problems | |
| | Consensus | |

Despite a systematic search, it was not possible to identify any publications in the literature that would allow any conclusions to be drawn on whether additional pelvic radiotherapy or radiochemotherapy in stage pN1 pelvic (including a single micrometastasis) or stage pM1 para-aortic (including a single micrometastasis) after therapeutic lymphadenectomy has any influence on improvement in rates of local recurrence, disease-free survival (DFS), metastasis-free survival (MFS), or overall survival (OS). These questions thus remain open. However, a study that was actually investigating the accuracy of detection of para-aortic lymph nodes using staging laparoscopy in comparison with PET-CT and their influence on the prognosis concluded that due to the poor prognosis for patients with lymph-node metastases, the irradiation area should be extended to the anatomically affected regions [124]. The guideline group is in agreement with this assessment.

The state of the data on adjuvant radio(chemo)therapy in patients with more than two risk factors, pN1, or an R1 situation is presented in sections 10.1.5, 11.2, and 11.2.2. The risk factors are also listed in detail in section 7.3.

The state of the data on the procedure in patients with distant metastases and the precise procedure are presented in detail in sections 11.2 and Chapter 18. If three or more risk factors are already known preoperatively (e.g., L1, V1, G3), then primary R(CH)T after surgical staging is indicated in order to allow unimodal therapy as in the above recommendation.

In patients with one to a maximum of two risk factors and an R0 situation, as well as in those with negative lymph nodes (exception: in pT1a1 with up to one risk factor and therefore an unknown histological lymph-node status: adjuvant therapy is not indicated), an individual approach is advisable in the view of the guideline group, and it should be based on the patient's preferences (desire to have children, organ preservation, reduction of treatment side effects, desire for maximum safety).

### 8.3.2. Adjuvant therapy after primary radio(chemo)therapy

After primary radio(chemo)therapy, a secondary hysterectomy in specific circumstances (Chapter 9) or extended chemotherapy (Chapter 11) may be considered.

## 8.4. Treatment for locally limited cervical carcinoma ≤ FIGO stage IIA

| 8.9 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| **EC** | In stages ≤ FIGO stage IIA, primary surgical therapy should be carried out if adjuvant therapy is not expected (no preoperative risk factors). | |
| | Consensus | |

Despite a systematic search, it was not possible to identify any publications in the literature that would allow any conclusions to be drawn on whether surgical therapy and radiochemotherapy are oncologically equivalent in stages IB and II. This question thus remains open.

In stages ≤ FIGO stage IIA (cM0 and suspected pN0), surgery is recommended [325] [326] (on this point, see section 8.6). The guideline group is in agreement with this recommendation at the level of an expert consensus. Since pelvic radio(chemo)therapy, which may potentially be indicated postoperatively, inevitably leads to ovarian insufficiency in premenopausal patients, ovariopexy should be considered here to protect intrinsic ovarian function [99].

## 8.5. Treatment for local recurrences, metastases, and in the palliative situation

Advanced disease is often already present at first diagnosis in patients with cervical carcinoma. By definition, para-aortic lymph-node involvement is an M1 situation, so that all patients with FIGO stage III, IV, or lower tumor stages and less locoregional spread, but with para-aortic lymph-node metastases, must be regarded as primarily

having metastases (UICC stage IVB). This aspect is an important element of the information discussion with the patient regarding the prognosis and choice of treatment strategies. The aim is to avoid unnecessary morbidity if treatment is not effective.

### 8.5.1. Treatment for advanced cervical carcinoma

The term “advanced cervical carcinoma” is not clearly defined. Three groups are usually distinguished in the literature:

- Locally advanced cervical carcinoma (FIGO stages IIB to IVA and IB2/IIA2 with several histological risk factors, or pN1 and c/pM0)
- Local recurrence (c/pM0)
- The metastatic situation (UICC stage IVB or c/pM1)

Otherwise, the guideline group was in agreement that where possible, the precise TNM and/or FIGO stages should be given for tumor stages, avoiding unclearly defined terms as much as possible or at least stating the stages intended.

In contrast to the above classical definition, the guideline group prefers the view that advanced cervical carcinoma is a disease that cannot be treated unimodally and due to the histological tumor stage requires multimodal therapy. Due to the biology and extent of the tumor present, this is associated with a poorer prognosis for the patient, with more severe side effects.

### 8.5.2. Treatment for locally advanced cervical carcinoma (FIGO stages IIB–IVA and IB2/IIA2 with several histological risk factors or pN1 and c/pM0)

Locally advanced cervical carcinoma is considered to consist of cervical carcinoma stages IIB to IVa. Locally advanced cervical carcinoma is now also considered to start already at stages IB2 and IIA2 with several histologically confirmed risk factors (tumor characteristics or pelvic lymph-node involvement) [325]. In patients with locally advanced cervical carcinoma, in whom several successive treatment modalities may potentially need to be used, cisplatin-containing radio(chemo)therapy with brachytherapy is indicated. If appropriate, extended-field radiotherapy may be necessary if there are histologically confirmed para-aortic lymph nodes (pM1). This already represents a metastatic situation (UICC stage IVB) (see section 8.5.4). In the new 2018 FIGO classification, para-aortic lymph-node metastases are regarded as regional lymph-node metastases, rather than distant metastases as previously. In dependently of that, it is decisive for the target volume in radiotherapy to define whether pelvic and/or para-aortic lymph-node involvement is present. In Germany, (laparoscopic) surgical staging is carried out for this purpose, in order to detect lymph-node metastases (including micrometastases) histologically and to diagnose the extent of pelvic spread (e.g., peritoneal carcinosis, etc.). Imaging procedures in the abdominal area do not offer adequate diagnostic certainty. MRI can be used to assess the locoregional spread of the central tumor, or CT can be used to assess lymph nodes and the pelvic walls. PET is not currently of any importance for treatment planning in primary cervical carcinoma and should be reserved for specific questions in the recurrent situation. When a tumor is suspected, histological confirmation is required before treatment planning.

### 8.5.3. Treatment for local recurrences (c/pM0)

For the definition of local recurrence, see Chapter 17. Histological evidence and (imaging or surgical) diagnostic assessment of spread are the basis for treatment of local recurrences. See Chapter 6.

### 8.5.4. Treatment in the metastatic situation (UICC stage IVB/pM1 or c/pM1)

For the definition of the metastatic situation, see Chapter 18. Histological evidence and (imaging or surgical) diagnostic assessment of spread are the basis for treatment of metastases. See Chapter 6.

## 8.6. Stage-dependent therapy

### 8.6.1. Treatment for preinvasive lesions

The diagnosis and treatment of preinvasive lesions (up to CIN 3) is dealt with in the Level 3 Guideline "Prevention of Cervical Carcinoma" (AWMF register no. 015/027OL).

### 8.6.2. Standard therapy for invasive cervical carcinoma

The recommendations given in this section are mainly based at the expert level in the guideline group. The state of the data is insufficient for an evidence-based recommendation on too many of the subtopics. On the basis of its expertise, and in conformity with international guidelines, the guideline group has developed as precise as possible a treatment corridor for stage-dependent therapy for cervical carcinoma, which should be regarded as the standard for care in Germany. The data are presented in the relevant sections.

The stage-dependent risk factors as the basis for treatment are presented in section 7.3, Table 13 and Table 14.

In the present guideline, R(CH)T refers to simultaneous radiochemotherapy with cisplatin as a radiosensitizer. This differs from other regimens of sequential and consecutive radiochemotherapy that have been used in various study designs but do not represent a standard procedure. Starting from stage III, it is the therapeutic gold standard (and it is also already indicated for preferred use starting from stage IIb). Contraindications against combined simultaneous cisplatin-containing radiochemotherapy include for example renal insufficiency. Only radiotherapy alone is possible in such cases.

The FIGO stages listed in the following recommendations refer to the 2009 FIGO classification. At the time when the present guideline was compiled, the authors already had the current 2018 FIGO classification available. However, the studies that form the basis of evidence for this guideline were still conducted under the old FIGO classification. The recommendations in this guideline therefore refer to the old FIGO classification.

#### 8.6.2.1. FIGO stage IA

Histologically confirmed invasive carcinoma, stage IA (synonymous with: early stromal invasion, microcarcinoma, microinvasive carcinoma).

| 8.10 | Consensus-based Recommendation | modified 2020 |
|---|---|---|
| **EC** | In *stage IA1* without any risk factors, treatment ***shall*** be administered as follows:<br>Surgery:<br>• Lymph node removal is not indicated<br>• If family planning has been completed, or if the patient wishes greater certainty:<br>• Simple hysterectomy.<br>• If the patient wishes to have children:<br>• Conization (within healthy margins) with cervical curettage.<br>• If there are positive margins in the conization specimen (R1):<br>• Repeat conization, or<br>• Trachelectomy (within healthy margins, with prophylactic permanent cerclage).<br>• Following successful pregnancy:<br>• Secondary hysterectomy is possible, particularly if there is persistent HPV, abnormal Pap findings, if the patient wishes maximum safety, or if the cervix is difficult or impossible to assess.<br><br>Radio(chemo)therapy: Not indicated. | |
| | Consensus | |

| 8.11 | Consensus-based Recommendation | new 2021 |
|---|---|---|
| **EC** | In stage *IA1* with lymphatic infiltration (L1), treatment ***shall*** be administered as follows:<br>Surgery:<br>• Sentinel lymphadenectomy is indicated.<br>• If family planning has been completed, or if the patient wishes greater certainty:<br>• Simple hysterectomy.<br>• If the patient wishes to have children:<br>• Conization (within healthy margins) with cervical curettage.<br>• If there are positive margins in the conization specimen (R1):<br>• Repeat conization, or<br>• Trachelectomy (within healthy margins, with prophylactic permanent cerclage).<br>• Following successful pregnancy:<br>• Secondary hysterectomy is possible, particularly if there is persistent HPV, abnormal Pap findings, if the patient wishes maximum safety, or if the cervix is difficult or impossible to assess.<br><br>Radio(chemo)therapy: Not indicated. | |
| | Consensus | |

Stage pT1a1 is associated with lymphatic infiltration (L1) in approximately 4.4% of cases (invasion depth < 1 mm) to 16.4% of cases (invasion depth 1–3 mm). In the absence of this risk factor, positive lymph nodes are found in fewer than 1% of the patients; in L1, the rate rises to more than 8% [328]. Lymphadenectomy is therefore not indicated in stage pT1a1 with the presence of up to one risk factor [334]. In patients with pT1A1 cervical carcinoma and lymphatic infiltration (L1), the guideline group recommends bilateral sentinel lymphadenectomy (SNB) (see recommendation 8.11.).

With the surgical procedures, the patient must have the advantages and disadvantages of the various treatment procedures explained (e.g., conization vs. cervicectomy vs. simple hysterectomy). Data on conization are mainly available for preinvasive lesions. The guideline group accepts the argument by analogy here for microinvasive cervical carcinoma. Conization is preferably carried out in the form of high-frequency loop excision (loop electrosurgical excision procedure, LEEP / large loop excision of the transformation zone, LLETZ), or as laser conization. The two procedures are oncologically comparable and can be used depending on the local circumstances and the operator's level of experience [329][330][331][332]. Earlier guidelines already rejected scalpel conization and in particular the Sturmdorf suture [327]. The Sturmdorf suture is rejected because of the markedly altered postoperative anatomy, which makes adequate follow-up care difficult or almost impossible [330][332]. The recurrence rate is also low after conization alone (with negative resection margins) [333].

In simple hysterectomy in patients who are not wishing to have children, the various access routes (vaginal, abdominal, laparoscopic) can be regarded as equivalent. The choice can be based on the patient's preferences and general surgical principles.

The stage-dependent risk factors as the basis for treatment are presented in section 7.3, (Table 13) and (Table 148).

| 8.12 | **Consensus-based Recommendation** | **modified 2021** |
|---|---|---|
| **EC** | In *stage IA1* with at least two risk factors, and *stage IA2* with up to one risk factor, treatment ***should*** be administered as follows:<br>Surgery:<br>• If the patient does not wish to have children and if she wants to be particularly safe and has histologically negative lymph nodes (pelvic) after surgical staging with SNB:<br>• Hysterectomy (with bilateral adnexectomy if appropriate), without resection of the parametria (Piver I)<br>• If the patient wishes to have children and has negative lymph nodes after surgical staging with SNB:<br>• Conization with cervical curettage or<br>• Radical trachelectomy with prophylactic permanent cerclage.<br>• If there are sentinel lymph nodes affected by tumor, or there are pelvic lymph-node metastases:<br>• Para-aortic lymphadenectomy (surgical staging).<br>• In premenopausal patients:<br>• Ovariopexy to maintain intrinsic ovarian function.<br>• If there are macroscopically tumor-affected pelvic and/or para-aortic lymph nodes:<br>• Surgical removal before radio(chemo)therapy.<br>• After successful pregnancy: | |

| 8.12 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| | • Secondary hysterectomy, particularly when there is persistent HPV infection, Pap abnormalities, if the patient wants greater safety, and if the cervix can only be assessed to a limited extent or not at all.<br><br>Radio(chemo)therapy:<br>• If there is histological evidence of pelvic and/or para-aortic lymph-node metastases or there are several risk factors:<br>• R(CH)T in the histologically confirmed area of spread. | |
| | Strong Consensus | |

If there are histologically negative sentinel lymph nodes bilaterally, the sentinel methods alone can be carried out in patients with microinvasive tumors (IA1–IA2) and a maximum of two risk factors (see Chapter 8.1.1.2).

The stage-dependent risk factors as the basis for treatment are presented in section 7.3, Table 13 (microinvasive carcinoma) and Table 14 (macroinvasive carcinoma).

In the present guideline, R(CH)T means simultaneous radiochemotherapy with cisplatin as a radiosensitizer (for details, see section 8.6.2.4).

| 8.13 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| **EC** | In stage IA2 with at least two risk factors, treatment ***should*** be administered as follows:<br>Surgery (preserving fertility is not possible) with SNB:<br>• With negative lymph nodes (pelvic) after surgical staging:<br>• Radical hysterectomy (with bilateral adnexectomy if appropriate), with resection of the parametria (Piver II)<br>• If there are sentinel lymph nodes affected by tumor or if there are pelvic lymph-node metastases:<br>• Additional para-aortic lymphadenectomy (surgical staging).<br>• In premenopausal patients:<br>• Ovariopexy to maintain intrinsic ovarian function.<br>• If there are macroscopically tumor-affected pelvic and/or para-aortic lymph nodes:<br>• Surgical removal of these before radio(chemo)therapy.<br><br>Radio(chemo)therapy:<br>• If there is histological evidence of pelvic and/or para-aortic lymph-node metastases or there are several risk factors:<br>• R(CH)T in the histologically confirmed area of spread. | |
| | Strong Consensus | |

In stage pT1a2 (depth of invasion 3.1–5.0 mm), affected lymph nodes are already found in 8.3% of cases even without infiltration of the lymphatic vessels, so that pelvic lymphadenectomy or pelvic lymph-node staging (bilateral sentinel lymphadenectomy) should be carried out [328]. It is unclear whether radical cervicectomy offers greater safety in comparison with conization (with free resection margins) in stage pT1a2 without infiltration of the lymphatics. Parametrial involvement is unlikely at this stage, so that the benefit of radical cervicectomy in comparison with conization (or simple cervicectomy) in these early stages cannot be clearly assessed. Radical cervicectomy is associated with a higher morbidity rate [335] [336] [337] [338].

In all of the published retrospective studies, an organ-preserving procedure is equivalent to other procedures when there is an infiltration depth of < 5 mm and despite the additional presence of individual risk factors (L1, V1 G3 ?) [339] [340]. Even when the patient is not wishing to preserve her fertility, there is no indication from the oncological point of view for carrying out a hysterectomy [339] [340]. If the patient wishes maximum safety, a simple hysterectomy can be discussed with them.

Patients in stage pT1a1/pT1a2 with several risk factors and organ preservation must be informed preoperatively that adjuvant postoperative radio(chemo)therapy is recommended if there are three or more risk factors postoperatively. This is not compatible with fertility preservation, however.

The stage-dependent risk factors as the basis for treatment are presented in section 7.3, Table 13 (microinvasive carcinoma) and Table 14 (macroinvasive carcinoma).

In the present guideline, R(CH)T means simultaneous radiochemotherapy with cisplatin as a radiosensitizer (for details, see section 8.6.2.4).

### 8.6.2.2. FIGO Stadium IB1 and IIA1

Histologically confirmed cervical carcinoma, stages IB1 and IIA1.

| 8.14 | Consensus-based Recommendation | modified 2021 |
|---|---|---|
| **EC** | In stages *IB1* and *IIA*, treatment ***should*** be administered as follows:<br>Surgery:<br>• If there are negative lymph nodes (pelvic) after surgical staging:<br>• Radical hysterectomy with resection of the medial (near the uterus) half of the parametria, with an adequate safety margin and resection within healthy margins (Piver II).<br>• With a tumor-free resection margin at the vaginal cuff (IIA1).<br>• If the tumor is < 2 cm, with no risk factors:<br>• Surgical staging with SNB and<br>• Radical hysterectomy with resection of the medial (near the uterus) half of the parametria, with an adequate safety margin and resection within healthy margins (Piver II).<br>• With a tumor-free resection margin at the vaginal cuff (IIA1).<br>• If the patient is wishing to have children and the tumor is < 2 cm without risk factors:<br>• Surgical staging with SNB and<br>• Radical trachelctomy with prophylactic permanent cerclage.<br>• If family planning has been completed:<br>• Secondary hysterectomy.<br>• If there are pelvic lymph-node metastases:<br>• Additional para-aortic lymphadenectomy (surgical staging).<br>• In postmenopausal patients:<br>• Bilateral adnexectomy.<br>• In premenopausal patients:<br>• Ovariopexy to maintain intrinsic ovarian function.<br>• If there are pelvic and/or para-aortic lymph nodes macroscopically affected by tumor:<br>• Surgical removal of the nodes, or radio(chemo)therapy.<br><br>Radio(chemo)therapy:<br>• When there is histological evidence of pelvic and/or para-aortic lymph-node metastases, or several confirmed risk factors: R(CH)T.<br>• If the patient is inoperable or requests it: R(CH)T.<br>• The radiation volume should be based on the anatomy and histologically confirmed lymph-node involvement. | |
| | Consensus | |

Patients with cervical carcinoma up to FIGO IB1 should be offered open radical hysterectomy (see recommendation 8.14.). This recommendation is based on a randomized and controlled study by Ramirez et al. A total of 631 patients with FIGO IA1–IB1 cervical carcinoma were randomly assigned to undergo either laparoscopic radical hysterectomy (including robotic surgery) or abdominal open radical hysterectomy. The study

does not allow conclusions to be drawn about stages IIA1 and IIA2. The exact data are presented in Chapter 9.

The stage-dependent risk factors as the basis for treatment are presented in section 7.3, Table 13 (microinvasive carcinoma) and Table 14 (macroinvasive carcinoma).

In the present guideline, R(CH)T means simultaneous radiochemotherapy with cisplatin as a radiosensitizer (for details, see section 8.6.2.4).

### 8.6.2.3. FIGO stages IB2, IIA2, and IIB

Histologically confirmed invasive cervical carcinoma, *stages IB2, IIA2*, and *IIB*.

| 8.15 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| **EC** | In stages *IB2, IIA2*, and *IIB* with a maximum of two risk factors, treatment ***should*** be administered as follows:<br>Surgery:<br>• With negative lymph nodes (pelvic) after surgical staging:<br>• Radical hysterectomy (with bilateral adnexectomy if appropriate), Piver type III.<br>• With tumor-free resection margin at the vaginal cuff.<br>• When there are pelvic lymph-node metastases:<br>• Additional para-aortic lymphadenectomy (surgical staging).<br>• When there are pelvic and/or para-aortic lymph-nodes with macroscopic tumor involvement:<br>• Surgical removal of these before radio(chemo)therapy.<br>• When there is vaginal involvement:<br>• (Partial) radical colpectomy, with a tumor-free resection margin.<br>• In postmenopausal patients:<br>• Bilateral adnexectomy.<br>• In premenopausal patients with adenocarcinoma:<br>• Bilateral adnexectomy.<br>• In premenopausal patients with squamous cell carcinoma:<br>• Pre-treatment ovariopexy to preserve intrinsic ovarian function, both before planned R(CH)T and also during surgery with necessary adjuvant therapy.<br><br>Radio(chemo)therapy:<br>• With histologically confirmed pelvic and/or para-aortic lymph-node metastases, or with several risk factors: R(CH)T.<br>• When the patient is inoperable or requests it: R(CH)T.<br>• Stage IIB: Preferably R(CH)T.<br>• The radiation volume should be based on the anatomy and histologically confirmed lymph-node involvement. | |
| | Strong Consensus | |

The guideline group's recommendation is based at the expert level. The underlying data are presented in Chapters 9 and 10, section 8.3, and Chapters 11 and 18.

The stage-dependent risk factors as the basis for treatment are presented in section 7.3, Table 13 (microinvasive carcinoma) and Table 14 (macroinvasive carcinoma).

In the present guideline, R(CH)T means simultaneous radiochemotherapy with cisplatin as a radiosensitizer (for details, see section 8.6.2.4).

| 8.16 | Consensus-based Statement | modified 2021 |
|---|---|---|
| EC | Radical hysterectomy before planned radio(chemo)therapy offers no benefits for the patient in relation to disease-free survival or overall survival. | |
| | Strong Consensus | |

Despite a systematic search (see the Guideline Report), it was not possible to identify any studies that would allow a clear answer to the question of whether radical hysterectomy offers any benefits for the patient with pelvic and/or para-aortic lymph-node metastases, in relation to disease-free survival or overall survival. In view of the increased morbidity due to the combination of procedures (see also Chapter 9), the guideline group is of the opinion that no benefit for the patient can therefore be assumed. The patient should in any case be informed about the increased morbidity resulting from the standard operation and radio(chemo)therapy.

#### 8.6.2.4. FIGO stage III

Histologically confirmed invasive cervical carcinoma, stage III.

| 8.17 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In *stage III*, the following treatment ***should*** be administered:<br>Surgery:<br>• Histological verification of spread<br>• Surgical staging or interventional clarification.<br>• When there are pelvic and/or para-aortic lymph nodes with macroscopic tumor involvement:<br>• Surgical removal before radio(chemo)therapy.<br><br>Radio(chemo)therapy: R(CH)T after surgical staging. | |
| | Strong Consensus | |

In the present guideline, R(CH)T refers to simultaneous radiochemotherapy with cisplatin as a radiosensitizer. This differs from other regimens of sequential and consecutive radiochemotherapy that have been used in various study designs but do not represent a standard procedure. Starting from stage III, it is the therapeutic gold standard (and it is also already indicated for preferred use starting from stage IIb). Contraindications against combined simultaneous cisplatin-containing radiochemotherapy include for example renal insufficiency. Only radiotherapy alone is possible in such cases. The underlying data and the rationale for this recommendation are presented in the relevant subsections of Chapter 10.

#### 8.6.2.5. FIGO stage IV

Histologically confirmed invasive cervical carcinoma, stages IVA and IVB.

| 8.18 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In stage *IVA*, treatment ***should*** be administered as follows:<br>Surgery:<br>• In selected cases:<br>• Primary exenteration<br><br>Radio(chemo)therapy: R(CH)T is treatment of choice. | |
| | Strong Consensus | |

The data on which this recommendation is based are presented Chapter 17, Local recurrence. The specific situations in which exenteration is possible are also presented there. Overall, the state of the data is very limited here as well. A recent Cochrane review in 2014, for example, which examined the efficacy and safety of exenterative procedures in gynecological malignancies (not including ovarian carcinoma) in comparison with other treatment options was not able to identify any RCTs meeting the inclusion criteria [341].

In the present guideline, R(CH)T means simultaneous radiochemotherapy with cisplatin as a radiosensitizer (for details, see section 8.6.2.4).

| 8.19 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In stage *IVB*, treatment ***should*** be administered as follows:<br>Surgery:<br>• Symptom-oriented therapy.<br><br>Radiotherapy or radio(chemo)therapy:<br>• Symptom-oriented therapy.<br><br>Drug therapy:<br>• Palliative systemic therapy is the treatment of choice.<br><br>Additional measures:<br>• Best supportive care.<br><br>Palliative medicine:<br>• Early palliative medicine intervention. | |
| | Strong Consensus | |

In this Level 3 guideline, the term “palliative therapy” includes the complete treatment of patients with incurable disease. This is the case, for example, in the metastatic or locally advanced situation (≥ FIGO stage IIB). “Palliative therapy” thus means not exclusively the specialized palliative medicine administered after the completion of oncological therapy. Palliative therapy takes place with various stage-dependent and situation-

dependent aims: (1) improving quality of life, (2) symptomatic control, and (3) prolonging life. The interdisciplinary conference is a good opportunity for establishing which of these goals is the priority for the patient in each situation. A treatment recommendation such as “further therapy with palliative considerations” is too unspecific in this context.

# 9. Surgical treatment

**Major changes in the chapter on surgical treatment**

The chapter has been substantially changed. On the basis of new evidence from the LACC trial, the recommendation on the surgical procedure for radical hysterectomy in patients with cervical carcinoma has been altered. The open procedure must be clearly preferred to laparoscopic procedures. The corresponding recommendation has been revised. The guideline group evaluates prophylactic salpingectomy as positive when hysterectomy is planned.

*D. Denschlag, C. Dannecker, M.W. Beckmann, F.A. Stübs, M.C. Koch*

## 9.1. Principles and techniques of treatment

A wide variety of principles and techniques in surgical treatment have developed during the last 20 years alongside the therapeutic standard for the treatment of patients with cervical carcinoma (Fig. 6). These are presented in Chapter 8. Unfortunately, therefore, there are wide variations in treatment in Germany, with results that are not comparable, and without the individual treatment procedures being confirmed by larger randomized controlled studies. This is ultimately to the detriment of patients, for whom universal access to standardized, stage-dependent and thus comparable therapy of proven efficacy should be available — therapy that can be expected to benefit them.

The aim is therefore to define the stage-dependent standard treatment. Deviations from it and modifications of it must be explained to the patient, and the advantages and disadvantages (e.g., morbidity, the physician's own experience and training) must be discussed with her critically.

Various principles and combinations of them are available (preserving fertility, nerve-sparing treatment, compartment resection/total mesometrial resection [TMMR], supra-radical surgery). There are also various distinct surgical techniques, such as conization (scalpel conization, laser conization, high-frequency loop electrosurgical excision procedure [LEEP]), cervical amputation (simple cervicectomy), radical cervicectomy, simple total hysterectomy, radical hysterectomy, and various extended techniques (e.g., laterally extended endopelvic resection [LEER], exenteration).

The aim in surgical treatment for early cervical carcinoma is to avoid multimodal therapies — i.e., to avoid adjuvant radiochemotherapy or adjuvant surgery and to keep morbidity low. This goal is particularly served by the nerve-sparing therapeutic approach of total mesometrial resection (TMMR). Very promising survival data have been reported in a prospective single-center study including more than 500 patients [316], [317]. An open multicenter observational study will clarify whether the excellent survival data can be confirmed on a multicenter basis.

The access route for these techniques also has to be decided on (abdominal, vaginal, laparoscopic, robot-assisted), as well as the lymphadenectomy technique (diagnostic sentinel technique, diagnostic surgical staging, therapeutic pelvic and para-aortic lymphadenectomy). These principles and techniques overlap in several areas (see Fig. 6).

The phase III study published in 2018, which randomly assigned 631 patients with FIGO IA1–IB1 cervical cancer either to one arm with laparoscopic radical hysterectomy (including robotic surgery) or another with abdominal open radical hysterectomy, provided the guideline group with the first randomized controlled trial concerned with the

surgical approach for these tumor stages. The study did not identify any non-inferiority of microsurgery vs. open surgery in relation to the disease-free survival could be shown: 96.5% vs. 860 % (95% CI, −16.4 to −4.7; P = 0.87 for non-inferiority). In relation to overall survival after 3 years, open hysterectomy was also significantly superior to laparoscopic hysterectomy: 99.0% vs. 93.8% (hazard ratio [HR]: 6.00; 95% CI, 1.77 to 20.30).

This is in contrast to the current figures from the Eighth Oncology Quality Conference in 2020, for which tumor center data for 43,091 patients from 11 federal states in Germany were retrospectively evaluated for the period 2000–2018. One of the items evaluated was surgical treatment: minimally invasive vs. open surgery. Minimally invasive operations increased over time regardless of age and stage. Vaginal hysterectomy was the main access route used, accounting for almost 60% of cases. In contrast to internationally published prospective data, this evaluation demonstrated the superiority of minimally invasive surgical techniques in relation to overall survival, independently of the disease stage (HR 1.494; 95% CI, 1.334 to 1.673; P < 0.0001) [22]. In view of the much stronger significance level, the guideline group has followed the RCT.

## 9.2. Surgical procedure

The classic surgical technique is radical hysterectomy, which is carried out in a stage-dependent manner on the basis of the 1974 classification by Piver et al. [299], in accordance with the recommendations by Wertheim, Meigs, Latzko, Okabayashi and others (see Fig. 6 and the classification of radical hysterectomy).

The basic principles of the radical abdominal operation involve the following steps. The procedure in laparoscopic or robot-supported methods is analogous.

- Opening of the abdominal cavity, systematic inspection.
- In premenopausal women, the ovaries may be retained.
- Opening of the paravesical fossa. If there is a suspicion of involvement of the ureterovesical junction, a quick-section examination is carried out. If there is tumor involvement, the operation is stopped. Additional options include partial bladder resection or exenteration.
- Incision into the Douglas peritoneum and opening of the pararectal fossa; removal of connective and adipose tissue with the lymphatic vessels and nodes (see section 8.1.1.3).
- Demonstration and removal of the parametria in a stage-dependent manner, with a sufficient safety margin to the tumor (see the classification of radical hysterectomy).
- Mobilization of the rectum and removal of the sacrouterine ligaments.
- Complete dissection of the ureter from the parametria.
- Mobilization of the ureter after dissection of the bladder pillar.
- Removal of the paracolpium and vagina, depending on the size of the primary tumor and extent of vaginal involvement; the aim is to achieve an adequate vaginal safety margin.
- Closure of the abdominal wall.

The Piver classification distinguishes between five degrees of radicality in the hysterectomy [299]:

**Table 15: Classification of radical hysterectomy (checked 2021)**

| Classification of radical hysterectomy (checked 2021) | |
|---|---|
| **Piver I:** | Extrafascial hysterectomy (with no appreciable mobilization of the ureters). |
| **Piver II:** | (Modified radical hysterectomy.) Ligation of the uterine artery at the point where it crosses the ureter. Removal of the uterosacral and cardinal ligaments at half the distance to the sacrum or pelvic wall. Resection of the upper third of the vagina. Dissection of the ureters without separating them from the pubovesical ligament. This is basically an extrafascial hysterectomy with resection of the parametria medial to the ureters. |
| **Piver III:** | ("Classical" radical hysterectomy.) Ligation of the uterine artery at its origin (internal iliac artery or superior vesical artery). Removal of the uterosacral and cardinal ligaments near their origins (sacrum, pelvic wall). Resection of the upper third of the vagina (up to half of the vagina). Dissection of the ureters as far as their junction with the bladder, sparing a small lateral part of the pubovesical ligament. |
| **Piver IV:** | (Extended radical hysterectomy.) As in Piver III, but with complete separation of the ureters from the pubovesical ligament, resection of the superior vesical artery, and resection of up to three-quarters of the vagina. |
| **Piver V:** | Resection of parts of the bladder and distal ureter, with ureteral reimplantation. |

| 9.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| **EC** | In postmenopausal patients with macroinvasive carcinoma, bilateral adnexectomy ***should*** be carried out during hysterectomy. | |
| | Strong Consensus | |

Removal of the uterine tubes does not have any negative effects on ovarian function [344], [345], but may reduce the risk of an ovarian or tubal carcinoma developing [342] [346]. Estimates show that the rate of high-grade serous ovarian carcinomas could be reduced by 40% over the next 20 years if both fallopian tubes were removed during hysterectomy [346]. This procedure also does not appear to be associated with increased morbidity for the patient [347]. This additional measure and its potential benefits should therefore be discussed with the patient on an individual basis.

In the largest study dealing with squamous cell cervical carcinoma (n = 3471), the incidence of ovarian metastases relative to stage was 0.22% (Ib), 0.75% (IIa), and 2.2% (IIb). For adenocarcinoma, the rates were 3.72% (Ib), 5.26% (IIa), and 9.85% (IIb). Overall, ovarian metastases are found much more often with adenocarcinoma in comparison with squamous cell carcinoma: 5.31% vs. 0.79% [343]. The guideline group therefore recommends adnexectomy for all postmenopausal patients starting from stage IB1 and

in premenopausal patients with adenocarcinoma in stages IB2, IIA2, and IIB (see recommendations 8.14 and 8.15).

| 9.2 | Evidence-based Recommendation | new 2021 |
|---|---|---|
| GoR **B** | Open radical hysterectomy ***should*** be offered to patients up to FIGO stage IB1. | |
| LoE **1+** | [348] | |
| | Strong Consensus | |

In a large multicenter phase III trial published in 2018, 631 patients with FIGO IA1–IB1 cervical cancer were randomly assigned to either laparoscopic radical hysterectomy (including robotic surgery) or abdominal open radical hysterectomy. The primary outcome measure was disease-free survival after 4.5 years and non-inferiority of the minimally invasive group. Secondary outcome measures were the recurrence rate and overall survival after 3 years. No non-inferiority of microsurgery vs. open surgery was found in relation to disease-free survival: 96.5 % vs. 86.0% (95% CI, −16.4 to −4.7; P = 0.87 for non-inferiority). In relation to overall survival after 3 years, open hysterectomy was also significantly superior to laparoscopic hysterectomy: 99.0% vs. 93.8% (HR 6.00; 95% CI, 1.77 to 20.30). The rate of intraoperative and postoperative complications was the same in both arms. For the subgroups of low-risk tumors < 2 cm, without lymphatic invasion, with a depth of invasion of < 10 mm, or negative lymph nodes, no conclusions could be drawn [348]. The Uterus Committee of the Working Group on Gynecologic Oncology (AGO) and the Working Group on Gynecologic Endoscopy (AGE) of the German Society for Gynecology and Obstetrics (DGGG) have stated that patients with FIGO IA1 cervical carcinoma with lymphatic invasion, IA2, or IB1 should be informed about the results of this study before a decision is taken on the planned access route for radical hysterectomy when it is indicated [349].

In a cohort study from the USA, also published in 2018, 1225 patients (FIGO IA2–IB1) who had undergone laparoscopic surgery were compared with 1236 patients who had undergone abdominal incision surgery. After a median follow-up period of 45 months, the 4-year mortality rate was 9.1% after laparoscopic hysterectomy and only 5.3% after open hysterectomy (HR 1.65; 95% CI, 1.22 to 2.22; P = 0.002 in log-rank test). A longitudinal analysis showed that the 4-year survival rate had decreased by 0.8% (95% CI, 0.3–1.4) per year (P = 0.01) since the introduction of laparoscopic hysterectomy in 2006 [350].

Similar results were obtained in another cohort study including 958 patients (475 with open abdominal surgery and 483 with minimally invasive procedures — 90% laparoscopic and 10% robotic) [351]. After adjustment, the use of a minimally invasive procedure resulted in a significantly higher risk of death (HR 2.20; 95% CI, 1.15 to 4.19) or recurrence (HR 1.97; 95% CI, 1.10 to 3.50) in comparison with an open abdominal approach for tumor stage FIGO IB — but not in tumor stage FIGO IA (n = 244; death HR 0.73; 95% CI, 0.13 to 4.01; recurrence HR 0.34; 95% CI, 0.10 to 1.10).

This difference in the outcome relative to tumor size is also confirmed by another cohort study, although it is only available as an abstract [352]. The study included a total of 721 patients with FIGO IB1 cervical carcinoma, and the different access routes (open vs. minimally invasive) or techniques (with or without uterine manipulator) were compared retrospectively. It was shown that it was only for tumors > 2 cm that the open approach was significantly superior to the minimally invasive approach in relation to disease-free survival. In addition, this advantage was not demonstrable in comparison with the subgroup who underwent surgery without a uterine manipulator.

With regard to this specific question — whether radical hysterectomy should be performed as an open abdominal or minimally invasive laparoscopic or robot-assisted procedure — three meta-analyses have also been published [353], [354], [355].

In the publication by Jin et al. (2018), 229 patients undergoing robotic radical hysterectomy were compared with 913 patients receiving laparoscopic or 948 receiving open hysterectomies. Only reduced blood loss, fewer postoperative complications, and shorter hospital stays were reported when a minimally invasive procedure was used. Data on overall survival or disease-free survival were not provided in the paper [353].

The Park et al. research group already published similar results in 2016, although they included significantly more patients with robotic radical hysterectomy in the analysis (n = 821) [354].

Finally, a pure comparison between laparoscopy and open surgery was reported in a meta-analysis by Wang et al. published in 2015. This study also confirms the benefit of the minimally invasive approach in terms of less blood loss, fewer postoperative complications, and shorter hospital stays, but with significantly longer operating times [355].

In a cohort study in Germany, a total of 389 patients were included in accordance with the LACC study criteria. In contrast to the laparoscopic/robotic technique used in the LACC study, the patients underwent surgery with a combined transvaginal-laparoscopic approach without a uterine manipulator [356]. After a median follow-up period of 99 months (range 1–288 months), the 3-year, 4.5-year, and 10-year disease-free survival rates were 96.8%, 95.8%, and 93.1%, respectively, and the overall survival rates were 98.5%, 97.8%, and 95.8%, respectively. This very good oncologic outcome, based on retrospective data, supports the hypothesis that surgical tumor hygiene is necessary, and it should be validated in further randomized trials.

The value of purely robotic surgery in relation to the oncological outcome is unclear. There is a lack of large randomized studies to assess the value of this minimally invasive procedure. However, the general use of minimally invasive techniques does not appear to be recommendable, against the background of the phase III study published by Ramirez et al. The guideline group therefore recommends that patients with < FIGO IIB cervical carcinoma should be informed about the data and that an open abdominal radical procedure should be recommended up to FIGO stage IIA.

Lymphadenectomy is a diagnostic procedure. The optimal approach for lymphadenectomy cannot be deduced from the currently available data. However, staged female patients were found to have a better prognosis.

## 9.3. Preoperative laboratory tests

The preoperative laboratory tests that are necessary are:

- Blood count
- Electrolyte status
- Coagulation status
- Creatinine
- Creatinine clearance in the presence of hydronephrosis when planned chemotherapy is planned
- Transaminases, alkaline phosphatase, gamma-glutamyltransferase (GGT)
- Urinary status

## 9.4. Procedure following primary radio(chemo)therapy

| 9.3 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | The value of secondary hysterectomy after primary radio(chemo)therapy is unclear in relation to the rate of local recurrence, disease-free survival, metastasis-free survival, and overall survival. | |
| | Strong Consensus | |

| 9.4 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | Hysterectomy after primary radio(chemo)therapy in patients with complete remission on clinical and imaging findings is associated with a higher morbidity rate in comparison with primary radio(chemo)therapy alone. | |
| | Strong Consensus | |

| 9.5 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | It is unclear whether secondary hysterectomy should be carried out in the form of simple or radical hysterectomy after primary R(CH)T. | |
| | Strong Consensus | |

Few data are available regarding the effect of secondary simple hysterectomy following primary radio(chemo)therapy. The guideline group commissioned systematic research on this issue (see the Guideline Report). Only one randomized study — which was small and was prematurely stopped (n = 61) — is available that investigated radio(chemo)therapy alone in comparison with R(CH)T followed by simple hysterectomy. For stages IB2/II in the combined group — with R(CH)T plus surgery — there was a trend toward a poorer result in comparison with radio(chemo)therapy alone (event-free survival after 3 years 72% [standard deviation 9%] vs. 89% [SD 6%]; and overall survival after 3 years 86% [SD 6%] vs. 97% [SD 3%]; not significant) [357]. The few other studies available also showed no survival benefit with secondary hysterectomy after radio(chemo)therapy [358][359]. Hysterectomy after primary radio(chemo)therapy in patients with complete remission on clinical and imaging findings is associated with a higher morbidity rate in comparison with primary radio(chemo)therapy alone

[357][360][361][362]. Retrospective analyses showed mainly symptomatic lymphoceles, bleeding, bladder and ureteral injuries, as well as fistula formation and bladder and pelvic inflammations. In addition, lymphoceles, abscesses, chylous ascites, incontinence, and wound healing disturbances (e.g., including dehiscence of the vaginal stump) have been reported. Intestinal injuries, also with fistula formation, and pulmonary embolisms occur less frequently [357][360][361][362]. Despite this, simple hysterectomy may be considered for larger tumors (> 4 cm) after primary R(CH)T, particularly if a primarily curative effect of R(CH)T alone is considered not to have been achieved [361]. The current state of the data does not allow any recommendation to be made with regard to the appropriate degree of surgical radicality (simple versus radical hysterectomy). It is unclear whether hysterectomy after primary radio(chemo)therapy without complete clinical remission, with histological evidence of tumor, has any advantages in relation to the disease-free survival or overall survival (EC after systematic research). In this case, however, the aim of any supplementary surgery that is carried out must in most cases be to achieve complete removal of any residual tumor that is still present.

# 10. Radiotherapy

**Major changes in the chapter on radiotherapy**

The recommendations for primary radiochemotherapy — consisting of the elements external radiotherapy, simultaneous cisplatin-containing chemotherapy, and brachytherapy — were confirmed after review. The level of recommendation for the use of intensity-modulated radiotherapy techniques and MRI-supported planning of brachytherapy in the context of primary radiochemotherapy for cervical carcinoma has been raised, as there are now new data for a clinical benefit with these techniques.

*D. Vordermark, S. Marnitz, K. Lössl, A. Sturdza, C. D. Alt*

## 10.1. Radio(chemo)therapy

*S. Marnitz*

This section presents first the techniques and then the indications for them.

### 10.1.1. Radiotherapy techniques (percutaneous radiotherapy)

| 10.1 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR **B** | Intensity-modulated techniques should be used to achieve optimal sparing of the surrounding tissue during primary radiochemotherapy for cervical carcinoma. | |
| LoE **1+** | [363] | |
| | Strong Consensus | |

The use of modern techniques in radio-oncology, particularly intensity-modulated radiotherapy (IMRT) and related methods such as spiral tomotherapy and volumetric arc techniques, help protect at-risk organs such as the bladder, rectum, small intestine, ovaries, etc., and make it possible both to reduce treatment-related acute and delayed reactions and also to safely administer selective dose escalation or simultaneous integrated boost (SIB) plans. Which of these techniques should be used here is unclear from the available literature [369], [370], [371], [372]; comparisons between different techniques depend on many planning variables [364], [365], [366], [367]. A large randomized trial reported a very favorable toxicity profile and treatment adherence when predominantly modern IMRT techniques were used [373]. Although the data on toxicity reduction using IMRT are mainly based on studies of definitive radiochemotherapy studies [363], it can be assumed that reducing the dosage in at-risk organs also has a favorable effect on the side effect profile in the postoperative situation.

Fractionation is conventional, with single doses of 1.8–2.0 Gy and five fractions per week. In the area of the pelvic and para-aortic lymphatic drainage routes, standard treatment consists of administering individual doses of 1.8 or 2 Gy in a total dosage of 45–50.4 Gy or 50 Gy. The size of lymph-node metastases correlates with the prognosis [374]. For macroscopically enlarged lymph nodes, a local dosage increase (boost) can

be considered if surgical staging was not possible. There is a clear dose–outcome relationship. The rate of in-field recurrences was significantly lower for pelvic and para-aortic lymph-node metastases < 10 mm than for lymph-node sizes > 10 mm [375]. In individual cases, this justifies the administration of what are called sequential or simultaneous boosts in regions with a higher risk of recurrence.

When there is an indication for para-aortic irradiation of para-aortic lymph-node metastases that have been confirmed histologically or on imaging morphology, it should be carried out at the same time as pelvic irradiation. Prophylactic para-aortic irradiation is not justified. It increases therapy-related toxicity without any evidence of prognostic improvement [376], [377], [378]. Patients with histologically confirmed para-aortic metastases should be treated using an extended-field plan and simultaneous chemotherapy with curative intent [379], [380], [381], [382], [383].

The target volumes include the internal, external, interiliac and common iliac lymph-node regions and also the presacral group up to the S2/S3 vertebrae (RTOG consensus guideline) [368]. In the primary situation, the uterus, cervix, parametria, and — depending on the depth of involvement of the vagina — also tumor-infiltrated areas are included in the target volume, along with a safety margin [368]. With small tumors, simultaneous treatment of the entire uterus is currently under discussion. However, there are as yet no prospective data to justify a departure from the previous usual practice of simultaneous treatment of the entire uterus. There is currently controversy over what constitutes an adequate safety margin for organ movement and positional inaccuracy, as well as patient movement, and no general recommendation can currently be given [368]. RTOG recommendations are available for defining the target volume in postoperative percutaneous radiotherapy [368], [355]. The selection of the safety margin (known as the planning target volume, PTV) depends on the mobility of the individual structures (mobile uterus versus less mobile lymph-node areas) as well as the technique and frequency of so-called on-board imaging. For daily IGRT and structures with little mobility, PTVs can usually be reduced to 5–8 mm. For mobile structures, it is advisable to consider using an internal target volume (ITV). Against this background, regular checks of reproducible bladder and bowel filling should be carried out during treatment — e.g., using cone-beam CT. With regard to optimal local control, it is recommended to keep the total duration of percutaneous therapy and brachytherapy as short as possible and to avoid treatment interruptions. Older recommendations assume a loss of local control if therapy is prolonged for > 56 days [367]. More recent data from the era of combined radiochemotherapy only note a deterioration in the outcome beyond the eleventh week of treatment [384]. Occasionally unavoidable delays in therapy can be compensated for by a dosage increase [385].

### 10.1.2. Brachytherapy technique in primary combined radio(chemo)therapy

| 10.2 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **B** | Brachytherapy ***should*** be a component of the curative treatment approach in primary treatment for cervical carcinoma that includes radio(chemo)therapy. | |
| LoE **4** | [99] | |
| | Strong Consensus | |

| 10.3 | Consensus-based Statement | modified 2021 |
|---|---|---|
| **EC** | MRI-planned brachytherapy should be used in primary radiochemotherapy for cervical carcinoma, to reduce the rate and severity of gastrointestinal and urogenital toxicities. | |
| | Strong Consensus | |

Brachytherapy in the area of the macroscopic tumor is an obligatory component of radiochemotherapy in primary therapy for cervical carcinoma [387]. Brachytherapy should preferably be administered in the form of image-guided adaptive brachytherapy (IGABT). This is based on performing an MRI of the pelvic region before initiating radiochemotherapy and at least one MRI at the start of afterloading. Recommendations have been published for the technical performance of the MRIs, which should be conducted consistently [388]. Repetitively performed MRI examinations allow adaptive radiation planning. In this process, a 40–50 Gy equivalent dose (EQD2, alpha/beta 10 Gy) is administered in three to five fractions after MRI-guided planning in the high dose rate (HDR) or pulse dose rate (PDR) procedures. The EQD2 in the tumor area from percutaneous irradiation and brachytherapy should reach at least 85 Gy [385]. The target volumes include the residual tumor after or during ongoing percutaneous radiotherapy as the gross tumor volume (GTV), the entire cervix including the presumed microscopic involvement, in what is termed a high-risk clinical target volume (HR-CTV). The GTV is part of the HRCTV. An intermediate-risk clinical target volume (IR-CTV) is defined as the initial extent before the start of percutaneous therapy. Graded dosage recommendations are defined in the GEC-ESTRO recommendations and ICRU Report 89 [389], [390]. Dose prescription in 4D brachytherapy corresponds to target volumes and dose-effect curves [6][7][11]. The total treatment duration including teletherapy and brachytherapy should not exceed 45–50 calendar days [5], as each additional day reduces the overall survival after 5 years by 1% [386].

### 10.1.3. Simultaneous chemotherapy technique

Three systematic reviews have shown that primary combined radio(chemo)therapy offers a highly significant advantage in the overall survival and progression-free survival in comparison with radiotherapy alone [391], [392], [393] (see also section 10.1.4). Another meta-analysis of three randomized studies also showed, in the adjuvant setting

in early cervical carcinoma, that additional platinum-containing chemotherapy along with radiotherapy consistently reduced the risk of death in all of the studies and significantly increased the progression-free interval, as well as achieving an increase in local control [394] (see also section 10.1.5, Adjuvant radio(chemo)therapy).

Simultaneous chemotherapy during irradiation is administered with cisplatin monotherapy. At least five doses of 40 mg/m² body surface area (BSA) on days 1, 8, 15, 22, and 29 of the radiotherapy are usually administered. An alternative dosage scheme with the identical dose density is administration of 20 mg/m² BSA on days 1–5 in the first and fifth weeks of radiotherapy [395]. In the rare case of contraindications against cisplatin, the use of carboplatin, for example, is an option. Combination therapies do not show any significant difference between the treatments, although with an increase in the range of side effects.

In the case of poor renal function due to hydronephrosis, decongestion using appropriate measures is indicated before the start of therapy.

### 10.1.4. Indication for primary radiotherapy or radio(chemo)therapy

| 10.4 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **A** | In patients with cervical carcinoma in whom there is an indication for primary radiotherapy from stage IB2 onwards, the radiotherapy ***shall*** be combined with cisplatin-based chemotherapy. | |
| LoE **1++** | [396]; [397] | |
| | Consensus | |

This recommendation is based on the recommendation given in the 2008 SIGN guideline, which also recommends platinum-based radiochemotherapy when primary radio(chemo)therapy is indicated and the patient is in a sufficiently good state of health [99].

Since the publication of the prospective randomized studies on radiotherapy versus radio(chemo)therapy in patients with cervical carcinoma, simultaneous radio(chemo)therapy has replaced the use of radiotherapy alone [400] [401] [402] [403] [404]. A total of 44,926 patients from 1987 to 2006 were included in the studies. Various chemotherapy regimens were used (cisplatin alone in three studies, cisplatin in combination in eight studies, and other agents [5-fluorouracil, mitomycin C, etc.] in three other studies). Three systematic reviews [396] [397] [399] confirmed the significant improvement in overall survival, progression-free survival, and local control achieved with radio(chemo)therapy in comparison with radiotherapy alone. According to a Cochrane analysis in 2005 (with 24 RCTs included, n = 4921), the HR of 0.69 pooled over all the studies (95% CI, 0.61 to 0.77; P < 0.00001) corresponds to a 31% reduction in the risk of death, or an absolute survival improvement of 10% (95% CI, 7 to 13%), from 60% to 70% [396]. Combined platinum-based radio(chemo)therapy, with an absolute survival improvement of 13% [396] is better in this respect (although not significantly) than non-platinum-based treatment [396] [399]. The main side effects of

simultaneous chemotherapy are an increase in the acute hematological and gastrointestinal toxicity, with low urogenital toxicity [396] [397]: risk for grade I/II hematological toxicity (OR 4.57; 95% CI, 3.08 to 6.79; P < 0.00001) and grade III/IV hematological toxicity (OR 8.97; 95% CI, 6.11 to 13.15; P < 0.00001); risk for grade I/II leukopenia (OR 2.40; 95% CI, 1.91 to 3.00; P < 0.00001) and grade III/IV leukopenia (OR 6.32; 95% CI, 4.39 to 9.07; P < 0.00001); risk for grade III/IV gastrointestinal toxicity (OR 2.77; 95% CI, 1.90 to 4.02; P < 0.00001) and grade I/II neurological toxicity (OR 6.04; 95% CI, 2.35 to 15.55; P = 0.0002) [391].

As more than 70% of the above studies included patients in FIGO stages ≥ II and III, combined radio(chemo)therapy for tumors (≥ FIGO stage IIB) is the therapeutic standard. In patients in stage IIA without risk factors, primary surgery or primary radio(chemo)therapy are options. A randomized study from the period in which radiotherapy alone was used showed equivalent oncological results for radical HE and for radiotherapy in FIGO stages IB–IIA, although with different side effect profiles. In the period of combined radio(chemo)therapy, a prospective and randomized comparison of radical HE with lymphadenectomy and combined radio(chemo)therapy with or without a para-aortic field has not been published for any of the FIGO stages [398]. For patients with FIGO stage III, radio(chemo)therapy is regarded as the standard therapy (see section 8.6.2.4). For patients in FIGO stage IVA, an individual decision should be taken after interdisciplinary consultation with the patient (see section 8.6.2.5). Radiotherapy in stage IVA is associated with a high risk of fistula development [405].

If indicated, radio(chemo)therapy should be carried out in the primary situation and also in the adjuvant situation (see recommendation 10.4).

For patients with locally advanced cervical carcinoma, neoadjuvant chemotherapy followed by radical hysterectomy does not improve oncological outcomes in comparison with primary radiochemotherapy. Two randomized studies have not only shown negative results, but have also reported a serious increase in hematologic toxicity to the disadvantage of neoadjuvant chemotherapy [406], [407]. The dose density of the chemotherapy administered is a matter of debate in this context, and is regarded as problematic in the studies mentioned. The use of neoadjuvant chemotherapy can therefore not be recommended as an oncologically safe alternative to primary combined radiochemotherapy outside clinical trials [408], [409]. The advantage of neoadjuvant chemotherapy over simultaneous radiochemotherapy has not been established, and it is therefore not recommended. Early results from a randomized trial including only 80 patients show comparable response rates in both arms (radiochemotherapy plus/minus neoadjuvant chemotherapy), but the oncological end points are still awaited [410].

### 10.1.5. Adjuvant radio(chemo)therapy

| 10.5 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **B** | Adjuvant cisplatin-containing radiochemotherapy ***should*** be used in patients with histologically confirmed postoperative risk factors. | |
| LoE **1-** | [29]; [411] | |
| | Consensus | |

Adjuvant radiochemotherapy is used in patients who have risk factors after histopathological processing of the radical operation. The indications for this defined by the guideline group are presented in recommendation 10.5. The background to these indications is discussed in more detail below. The prescribed dose is independent of the indication concerned. The standard dose for adjuvant treatment corresponds to the elective dosage in primary radiotherapy of 45–50 Gy (ED 1.8) (NCCN etc.). The irradiation volume (PTV) is also similar to the volume of the lymphatic drainage routes and of the primary tumor bed, of the upper vaginal dome described above. As described above, the complete lymphatic drainage area (obturator lymph nodes and internal, external, and common iliac lymph nodes, as well as the para-aortic region if affected) should also be treated in the adjuvant situation, as recommended by the 2008 RTOG guidelines on contouring for intensity-modulated radiation volumes [368]. Since there may be altered lymphatic drainage pathways after surgery, reduced treatment volumes as specified by the earlier irradiation boundaries of the former four-field box or "shortened four-field box" (up to the level of the promontory), may lead to marginal recurrences and should be avoided [378]. In order to keep long-term toxicities low, the use of more recent radiation techniques to protect at-risk organs (see above) is also required here, as in primary radiochemotherapy.

Following the GOG-92 and GOG-109 studies on the adjuvant situation in cervical carcinoma, there is an international consensus exists that the indication should be assessed in accordance with the "Sedlis" criteria [412]. In these, the risk factors are divided into "high-risk" and "intermediate-risk" categories. The "high-risk" factors include lymph-node metastases, parametrial infiltration, and positive surgical margins. One high-risk factor is sufficient to establish an indication for postoperative radiochemotherapy. Although in the 1990s the indication for radiotherapy if there was only one affected lymph node was a matter of debate, following the GOG-109 study and its follow-up publications, the locoregional and overall survival benefit has also been confirmed in this situation [414]. It has been shown that the prognosis depends on the number of affected lymph nodes, and in particular on the use of simultaneous chemotherapy in case of multiple lymph-node metastases. The situation with micrometastases is still less clear. Only a few retrospective data are available on the topic. However, since the prerequisite for micrometastasis is lymphovascular invasion, micrometastasis should also be regarded as representing a clear indication for adjuvant radiotherapy [267] as an "intermediate-risk" indication (see below).

For the "intermediate-risk" factors, which include lymphovascular invasion, deep cervical stromal invasion (see Chapter 7), and tumor size, a combination of at least two risk

factors should be present in order to establish an indication for adjuvant radiochemotherapy. The 12-year follow-up data from the GOG-92 trial (FIGO IB, after surgery and lymphadenectomy, without lymph-node metastases but with "intermediate" risk factors) are continuing to show improved progression-free survival after adjuvant therapy in high-risk patients in comparison with surgery alone. With regard to overall survival, there is a clear trend towards a better outcome with additional radiotherapy. This is confirmed by a meta-analysis from China published in 2016. Although the study reported a benefit in terms of overall survival only for the "high-risk" patients as a result of the additional chemotherapy , this was not observed for the intermediate factors [415]. If necessary, additional factors can be taken into account here, such as young age, vascular invasion, grading, or the presence of an adenocarcinoma. More information may be provided here by the results of GOG-0263, which are expected at the end of 2020 (a randomized trial in postoperative cervical carcinoma patients in FIGO stages I–IIA, with intermediate risk factors, radiochemotherapy versus radiotherapy alone).

In rarer histologies such as adenocarcinoma or adenosquamous carcinoma, which account for approximately 5–20 % of all cervical carcinoma histologies, the focus is primarily on systemic metastases, which is why the use of radiotherapy is justified here and, if necessary, additional adjuvant chemotherapy can be considered.

An even rarer finding (approx. 2% of all histologies) is neuroendocrine cervical carcinoma, which has a very poor prognosis, according to the literature. It is one of the small cell tumors and should be treated analogously to these, primarily with intensified radiochemotherapy or even trimodal therapy [416], [417].

Independently of discussions on the need for adjuvant radiotherapy after surgery for cervical carcinoma, there are few randomized data available on either the postoperative situation or the treatment choice between surgery and definitive radiochemotherapy. The only randomized trial on the issue of surgery versus radiotherapy, dating from 1997 [413], discussed above in section 10.1.4, published its 20-year follow-up data in 2017 [413]. The patients were properly randomized between surgery and radiotherapy in then FIGO stages IB2 and IIA1, but the overall survival was found to be the same. However, approximately 50% of the patients who underwent surgery also received adjuvant radiotherapy. A significantly increased rate of late toxicities was observed in this group of patients who received surgery and radiotherapy.

Trimodal therapy (surgery + radio(chemo)therapy) thus doubles the rate of severe long-term toxicities without improving the oncological results, and it should be reduced to a minimum by using appropriate patient selection measures (see section 8.1.1.2) to assign them either to surgery alone OR to primary radio(chemo)therapy.

### 10.1.6. Adjuvant (secondary) hysterectomy after complete radio(chemo)therapy

When combined simultaneous radio(chemo)therapy has been carried out correctly, secondary ("adjuvant") hysterectomy does not provide any survival benefit for patients [419], [420], [421]. TRetrospective data are available here suggesting a potential benefit for patients with confirmed residual tumor [422] and for a subgroup of patients with adenocarcinoma [423]. Surgery may increase the risk of complications. For salvage hysterectomy, simple hysterectomy rather than a radical procedure is therefore recommended [424]. The benefits of the procedure and its risks should therefore be discussed with the patient in a nuanced way. The presence of residual tumor is a surrogate

parameter for a greater probability of progression. The majority of patients who undergo secondary hysterectomy develop distant metastases during the later course [418], [425], [426], [427] (see section Chapter 9.4).

### 10.1.7. Adjuvant chemotherapy after completed radio(chemo)therapy

| 10.6 | Evidence-based Statement | checked 2021 |
|---|---|---|
| LoE<br>1- | The value of consolidating chemotherapy after the completion of radio(chemo)therapy has not been confirmed. | |
| | [428]; [429] | |
| | Strong Consensus | |

Due to the high rate of distant metastases in patients with advanced tumors (≥ FIGO stage IIB), several studies included adjuvant ("consolidation") chemotherapy after the completion of radio(chemo)therapy in their treatment protocols [430] [431]. Another recent randomized study (n = 515) [429] administered adjuvant chemotherapy with cisplatin 50 mg/m² d1 and gemcitabine 1000 mg/m² d1, d8 q21d in the test group. The 3-year progression-free survival and also to a slight extent the overall survival were significantly improved in comparison with the control group without adjuvant chemotherapy, but at the cost of doubling the grade III/IV treatment-related acute side effects (PFS 3 years: 74.4% vs 65.0%, P = 0,029; PFS overall: log-rank, P = 0.0227; HR: 0.68, 95% CI, 0.49 to 0.95; OS, log-rank P = 0.0224; HR: 0.68, 95% CI, 0.49 to 0.95; time to progression: log-rank P = 0.0012; HR: 0.54, 95% CI, 0.37 to 0.79; grade III/IV toxicity: 86.5% vs. 46.3%, P = 0.001, including two deaths potentially causally connected with the toxicity) [429]. A Cochrane review in 2010 in which the effects of adjuvant radio(chemo)therapy vs. radiotherapy in cervical carcinoma were investigated showed a potential additional benefit for the 5-year overall survival (HR 0.46; 95% CI, 0.32 to 0.66; P = 0.000021, absolute improvement of 19% in 5 years) as a result of consolidating chemotherapy after adjuvant radio(chemo)therapy, although with a high risk of distortion due to the study by Duenaz-Gonzales [395]. Another randomized study comparing four arms investigated radiotherapy alone with and without adjuvant chemotherapy and simultaneous radiochemotherapy with and without adjuvant chemotherapy. It failed to demonstrate any oncologic benefit for either radiotherapy alone or radiochemotherapy with the addition of adjuvant chemotherapy [432]. On the basis of the currently published literature, no recommendation can therefore be made for additional chemotherapy outside of the framework of research studies. It is possible that the adjuvant use of immunotherapies may change the state of the data for this specific clinical situation.

### 10.1.8. Neoadjuvant radio(chemo)therapy

| 10.7 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Neoadjuvant radio(chemo)therapy ***should not*** be administered outside of research studies.. | |

| 10.7 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| | Strong Consensus | |

Therapeutic approaches for neoadjuvant radio(chemo)therapy include various groups of patients with widely varying tumor stages, treatment approaches, radiotherapy techniques and dosages, and with different forms of chemotherapy. Although promising response rates have been observed, none of the studies has shown any clear advantage with regard to the overall or disease-free survival in comparison with standard radio(chemo)therapy or primary radical surgery [433] [434] [435] [436] [437]. Two meta-analyses published in 2012 and 2013 reflect the unclear state of the data [320] [321] ((see section 11.1). A wide range of different surgical approaches make comparability even more difficult. Due to the approximately 10% rate of severe postoperative complications, with no proven benefit, this treatment approach should therefore not be used outside of clinical research studies [433] [434] [435] [436] [437] (see section 11.1).

## 10.1.9. Ovary preservation and fertility

| 10.8 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Young patients ***should*** be offered ovariopexy and high-conformal radiotherapy techniques to preserve ovarian hormone function. | |
| | Strong Consensus | |

Together with modern techniques, ovariopexy in young premenopausal patients before the start of radio(chemo)therapy can achieve a marked reduction in the dosage to the ovaries [438], [440]. The prerequisite for this is adequate ovariopexy well above the pelvic irradiation field [439] (see section 8.6). The risks and benefits must be discussed with the patient. The presence of adenocarcinomas, poorly differentiated tumors, and evidence of lymphovascular invasion should be regarded as risk factors [441]. The risk of ovarian metastases is 1% for squamous cell carcinoma and 6% for adenocarcinoma [442].

On questions of hormone replacement therapy after squamous cell carcinoma or adenocarcinoma and after bilateral adnexectomy, or after radiotherapy with loss of ovarian function, reference may be made to the guideline currently in preparation on “Hormonal Therapy (HT) in the Perimenopause and Postmenopause” (AWMF register no. 015/062).

## 10.1.10. Adjuvant brachytherapy

In contrast to endometrial carcinoma, no research results were available to the guideline group on the use of vaginal brachytherapy for purposes of vaginal stump prophylaxis in cervical carcinoma. On the basis of individualized treatment approaches, consideration may be given to brachytherapy of the vaginal stump after hysterectomy with R1 or narrow R0 resection in the area of the vaginal stump, large tumors, initial vaginal involvement, or marked lymphovascular invasion in combination with teletherapy [443].

### 10.1.11. Intraoperative radiotherapy

Intraoperative radiotherapy (IORT) is a procedure for local dosage-boosting in high-risk areas defined during surgical resection — e.g., areas with expected or confirmed residual tumor and clinically or histologically confirmed involvement of lymph nodes. It is typically used with high single doses of 10–20 Gy with electrons, low-energy photons (100–250 kV), or as brachytherapy using moulages adapted to the tumor bed. In case series and nonrandomized studies, IORT has been incorporated both into approaches for recurrence treatment and also into the primary treatment [444] [445] [446] [447] [448]. A positive effect has been demonstrated in individual cases, although these are also influenced by additional risk factors. This is a procedure that does not currently have any place outside of research studies.

### 10.1.12. Anemia during radio(chemo)therapy

*D. Vordermark*

| 10.9 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR **B** | During radiotherapy or radio(chemo)therapy for cervical carcinoma, the patient's hemoglobin values ***should*** be monitored and corrected via transfusion at values below 10 g/dL (6.2 mmol/L). | |
| LoE **2++** | [99] | |
| | Strong Consensus | |

Anemia before or during primary radio(chemo)therapy in patients with cervical carcinoma is associated with clinical factors (tumor size, stage) and is an independent prognostic factor for overall survival [449], [450]. In clinical series of patients in whom systematic transfusion was not carried out, low hemoglobin (Hb) values during the course of treatment were associated with unfavorable survival [450]. In a pooled analysis of 494 patients in two studies by the Gynecologic Oncology Group (GOG) on radio(chemo)therapy, the Hb value in particular, adjusted to the tumor stage during therapy ("mean weekly lowest value"), was prognostic [449].

The positive effects of transfusion on survival after radiotherapy for cervical carcinoma that were reported in an older randomized study have been questioned in more recent publications on the basis of methodological errors [451]. In a more recent analysis of 2454 patients from the treatment period 1980–2011, the development of a hemoglobin nadir of < 10 ng/mL during therapy was prognostic for disease-free survival in the multivariate analysis in both the overall group and the group of patients treated with concurrent radiochemotherapy [456]. The authors recommend transfusion in patients with pretherapeutic levels

In four randomized trials, the use of erythropoiesis-stimulating factors to prevent or treat anemia during radio(chemo)therapy in patients with cervical carcinoma did not yield any positive results. Increased rates of thromboembolic events were seen without any improvement in tumor control, overall survival, or recurrence-free survival [452], [453], [454], [455].

## 10.1.13. Hyperthermia in cervical carcinoma

| 10.10 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **0** | Locoregional hyperthermia ***can*** be used in combination with percutaneous radiotherapy to treat locoregional recurrence or primary cervical carcinoma ≥ FIGO stage IIB. | |
| LoE **1-** | [457] | |
| | Strong Consensus | |

| 10.11 | Evidence-based Statement | modified 2021 |
|---|---|---|
| LoE **1-** | No advantage in relation to overall survival or disease-free survival has so far been confirmed in randomized trials, with the addition of locoregional hyperthermia to primary radiochemotherapy for cervical carcinoma. | |
| | [458] | |
| | Strong Consensus | |

| 10.12 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| **EC** | Locoregional hyperthermia ***shall*** be administered in a quality-assured and standardized fashion, preferably in the framework of scientific studies. | |
| | Strong Consensus | |

The purpose of hyperthermia in malignant diseases to use the treatment's own independent cytotoxic effects along with the supportive influence of the temperature increase on simultaneously administered radiotherapy or chemotherapy (radiosensitizing, chemosensitizing) [459]. Local/locoregional hyperthermia is distinguished from whole-body hyperthermia. Since the studies published to date on the use of hyperthermia in cervical carcinoma only refer to the local/regional use of hyperthermia, with one exception [460], the following statements apply exclusively to the local/regional hyperthermia treatment of cervical carcinoma. The practical implementation of local/regional deep hyperthermia must follow the relevant guidelines [462].

A Cochrane meta-analysis published in 2012 compared various studies on primary therapy (radiotherapy +/– hyperthermia) in patients with locally advanced cervical carcinoma (tumor stage FIGO IIB–IVA, 74% of which were FIGO IIIB) [457]. Although some of the individual studies presented contradictory data, the meta-analysis showed a statistically significant improvement in response rates, a reduction in the local recurrence rate, and an improvement in overall survival by combining radiotherapy with hyperthermia, with no differences in the treatment-related side effects in the two groups [457].

Since radiochemotherapy is now regarded as the standard treatment in primary therapy for locally advanced cervical cancer, it was important to determine whether the combination of hyperthermia plus radiochemotherapy would also lead to an improvement in treatment success. Harima et al. (2016) showed in a small, randomized, multicenter study including 101 patients (FIGO stage IB–IVA) that neither the disease-free survival nor the overall survival were significantly improved by the combination of radiochemotherapy with hyperthermia [458] [461].

# 11. Drug treatment

**Major changes in the chapter on drug treatment**

Few changes have been made in this chapter. The most recent studies and data on neoadjuvant chemotherapy for cervical cancer have been added. Neoadjuvant chemotherapy is still an experimental therapeutic approach and should not be used outside of research studies. Data from the GOG-240 study on the use of bevacizumab in women with recurrent or metastatic cervical cancer have also been added. Another treatment option is the checkpoint inhibitor pembrolizumab. It has been approved in the United States for use in women with PD-L1-positive cervical cancer in the metastatic setting.

*F.A. Stübs, M.W. Beckmann, M.C. Koch, P. Mallmann*

Systemic drug treatment for patients with cervical carcinoma is administered in various situations (neoadjuvant, adjuvant, recurrence, and in the palliative setting), either on its own as drug therapy (chemotherapy, targeted therapy) or in combination with radiotherapy (see Chapters Chapter 8; Chapter 9; Chapter 10; Chapter 17; Chapter 18). The tumor types that are specific for cervical carcinoma (squamous cell carcinoma and adenocarcinoma) basically respond to drug therapy less well than other types of genital carcinoma (e.g., ovarian carcinoma). The strongest effects of drug therapy on recurrence-free survival and overall survival are seen in patients with cervical carcinoma both in the primary and in the adjuvant situations with a simultaneous combination of cisplatin and radiotherapy (see sections 10.1.4, Indication for primary radiotherapy or radio(chemo)therapy and 10.1.5, Adjuvant radio(chemo)therapy).

## 11.1. Primary treatment

The standard in the treatment of patients with cervical carcinoma in stages ≤ FIGO stage II is either surgery or radio(chemo)therapy (see Chapter 8). Randomized controlled studies comparing radiotherapy with or without simultaneous chemotherapy were carried out in the mid-1990s (see section 10.1.4, Indication for primary radiotherapy or radio(chemo)therapy).

The agent used for drug treatment was usually cisplatin monotherapy. Combination drug therapies did not show any significant improvement in the progression-free or overall survival, although they had increased toxicity [391], [392], [393], [463], [464], [465], [466], [467], [468] (see section 10.1.4). In the primary and adjuvant situations, none of the studies showed any benefit from using additional targeted therapy alongside chemotherapy. The standard treatment protocols in the primary situation are therefore currently protocols without targeted therapy.

Systemic chemotherapy, as an integral component of combined radio(chemo)therapy, is one of the standards in the primary treatment of patients with cervical carcinoma [391], [392], [393], [468]. Targeted therapies have a potential benefit only on the basis of the data from the GOG-240 study in the primary metastatic, persistent, or recurrent situation, with an increased range of side effects (see section 18.3.5.1, Targeted therapy). The individual treatment goals must be discussed with the patient here (see recommendation 8.6).

The same principle also applies to adjuvant radio(chemo)therapy, in which research studies have also shown an advantage for radio(chemo)therapy in comparison with radiotherapy alone [105], [252], [394], [469] (see also section 10.1.5, Adjuvant radio(chemo)therapy). Due to the increased morbidity resulting from the combination of

several procedures, the unimodal principle applies: surgery alone or radio(chemo)therapy alone after histological definition of the irradiation field [470] (see Chapter 8).

Two option in primary treatment are currently the subjects of critical debate: neoadjuvant chemotherapy and extended adjuvant chemotherapy after the completion of surgical treatment or radio(chemo)therapy.

Administration of neoadjuvant chemotherapy (NACT) has been shown to have advantages in relation to several organ cancers, particularly with regard to local operability (e.g., Level 3 guideline on "Diagnosis, Treatment, and Follow-up of Breast Cancer," AWMF register no. 032/045OL, version 4.3) [473]). This treatment principle has therefore also been included in studies on patients with cervical carcinoma. A 2012 Cochrane analysis showed that neoadjuvant chemotherapy — planned before subsequent surgery — at a dosage of cisplatin > 25 mg/m² per week and with an interval for total administration of less than 14 days leads to a longer progression-free survival (HR 0.75; 95% CI, 0.61 to 0.93; P = 0.008) and overall survival (HR 0.75; 95% CI, 0.62 to 0.96; P = 0.02) [322] When the random effect model was used, the effect was no longer significant (OR 0.60; 95% CI, 0.32 to 1.12; P = 0.11). Due to the small numbers of patients in the six studies on which the analysis was based (n = 1078), the authors continue to recommend that this should not be used outside of research studies.

A 2016 meta-analysis did not show any improvement in the progression-free survival, overall survival (overall survival: OR 1.17; 95% CI, 0.85 to 1.61; P = 0.35) or disease-free survival (OR 1.09; 95% CI, 0.77 to 1.56; P = 0.62) with neoadjuvant chemotherapy [324]. This meta-analysis included 739 patients from five RCTs. A significant reduction in lymph-node metastases (OR 0.45; 95% CI, 0.29 to 0.7; P = 0.0005) and parametrial infiltration (OR 0.48; 95% CI, 0.25 to 0.92; P = 0.03) was observed, but with no effect on the overall or disease-free survival. In a phase III study, patients with cervical carcinoma FIGO IB2–IIB were randomly assigned to receive either NACT (bleomycin 7 mg on days 1–5, vincristine 0.7 mg/m2 on day 5, mitomycin 7 mg/m² on day 5, cisplatin 14 mg/m² on days 1–5) along with radical hysterectomy, or radical hysterectomy directly. A total of 134 patients were randomized equally to the two arms. The study was terminated early after the first interim analysis 4 years after study entry due to inferiority of patients in the NACT arm (HR 2.11; 99% CI, 0.34 to 13.2). The rate of adjuvant radiotherapy was significantly reduced in the NACT arm (58% vs. 80%) [474]. chemotherapy. The recurrence rate was significantly higher in the intervention arm than in the control arm (10 vs. six recurrences) [475]. In a meta-analysis of 1302 patients with cervical cancer (FIGO IB–IIB), no significant differences in the overall survival were observed between patients who received neoadjuvant chemotherapy and those who received direct surgery (OR 1.07; 95% CI, 0.48 to 2.41; P = 0.86). However, the rate of positive lymph-node metastases was significantly reduced by neoadjuvant chemotherapy in this meta-analysis (OR 0.57; 95% CI, 0.41 to 0.79; P = 0.0008) [476].

Neoadjuvant chemotherapy followed by surgery versus primary radiochemotherapy was compared in an RCT including 633 patients. Patients with cervical carcinoma FIGO IB2–IIB were included. Three cycles of carboplatin AUC5 or AUC6 d1, q21d and paclitaxel 175 mg d1, q21d were administered. The primary end point was disease-free survival. Primary radiochemotherapy was superior to the combination of neoadjuvant chemotherapy and radical hysterectomy in relation to disease-free survival (HR 1.38; 95% CI, 1.02 to 1.87; P = 0.038). A clinically nonsignificant advantage in terms of overall survival was observed for neoadjuvant chemotherapy in combination with radi-

cal hysterectomy (75.4% vs. 74.7%; HR 1.025; 95% CI, 0.752 to 1.398; P = 0.87). Hematologic side effects markedly predominated in the group of patients receiving neoadjuvant chemotherapy [406].

The decisive aspect for the effectiveness of neoadjuvant chemotherapy is the response rate during therapy. Several meta-analyses have shown an improvement in overall survival, progression-free survival, and disease-free survival between responders and non-responders [477], [478], [479], [480]. In a meta-analysis including 4727 patients with cervical cancer (FIGO IB2–IVa), Zhu et al. noted an improvement in overall survival among clinical responders (HR 3.36; 95% CI, 2.41 to 4.69). The hazard ratio was even higher in patients who had a pathological response (HR 5.45; 95% CI, 3.42 to 8.70). Effects were also evident for disease-free survival [477]. In another meta-analysis, the odds ratio for 5-year survival was 5.785 (95% CI, 4.124 to 8.115) [478].

A major, although experimental, indication for neoadjuvant chemotherapy in cervical cancer is the desire to preserve fertility in women of childbearing age. The guideline group had two systematic reviews on this topic available to it. Laios et al. included a total of seven trials including 86 patients with cervical carcinoma who were of childbearing age. Most of the chemotherapy protocols were cisplatin-based. After neoadjuvant chemotherapy and fertility-preserving surgery, five of ten women became pregnant (0.49; 95% CI, 0.32 to 0.66) and four of ten women had live births (0.42; 95% CI, 0.32 to 0.53) [481]. In another meta-analysis including 88 pregnant women who received neoadjuvant chemotherapy for cervical cancer, 80.7% of the infants were healthy at birth. After a median follow-up period of 17 months, all of the infants were healthy. The mean weight of the neonates was 2163.2 g. Long-term data were available for 81 women. Among them, 16 (19.8%) had recurrences and 11 (90%) died of cervical cancer [323].

Neoadjuvant drug treatment may be offered to patients if risk factors have already been found during the preoperative diagnostic work-up that establish a need for postoperative radiochemotherapy (see recommendation 8.6). This is the case in the following clinical situations:

- Bulky disease, with a tumor size of more than 4 cm documented on imaging
- Imaging suspicion of positive lymph nodes
- Presence of several histopathologically defined risk factors such as G3, L1, V1

When the indication for carrying out neoadjuvant chemotherapy is being established, the benefits and risks need to be weighed up against each other. According to the available literature, the intention in neoadjuvant drug therapy is to improve operability, as it reduces the incidence of positive lymph nodes and parametrial infiltration [472], [322]. Neoadjuvant drug chemotherapy also reduces the need for adjuvant radiochemotherapy (OR 0.57; 95% CI, 0.33 to 0.98) [472]. These potential benefits have to be compared with the risks and side effects of dose-intensified platinum-containing chemotherapy (e.g., nephrotoxicity, ototoxicity, and hematological side effects).

Successful treatment with neoadjuvant chemotherapy can be documented using vaginal ultrasonography or magnetic resonance imaging of the pelvis. The decisive aspect here is that the same procedure should always be chosen that was used as the primary diagnostic procedure (see Chapter 6, Diagnosis). If surgery is carried out after neoadjuvant chemotherapy, it is currently unclear what effect tumor-involved lymph nodes after neoadjuvant chemotherapy have on the further treatment. It is also unclear what the surgical resection margins should be. Adequate assessment of the previous tumor

spread is not possible intraoperatively. Surgery should therefore be carried out in the form that was previously planned.

With regard to adjuvant chemotherapy alone after surgery or after radiotherapy or radio(chemo)therapy, no conclusions can be reached due to the considerable heterogeneity of the studies and sometimes small numbers of patients. An indication for adjuvant chemotherapy has been established in high-risk patients with several risk factors — L1, V1, deep stromal infiltration, R1 resection or advanced tumors (≥ FIGO stage IIB). According to the published studies, consolidating chemotherapy after surgery or after the completion of radio(chemo)therapy does not lead to any certain improvement in overall survival, but involves increased toxicity [471] (see also section 10.1.7, Adjuvant chemotherapy after completed radio(chemo)therapy).

## 11.2. Local recurrence and metastasis

Advanced disease is often present at first diagnosis in patients with cervical carcinoma. As in the current 2019 FIGO classification, patients with para-aortic lymph nodes are not considered to have distant metastatic disease. However, these patients continue to have a poor prognosis. This aspect is an important component of the information discussion with the patient regarding the prognosis and choice of treatment strategy, in order to avoid unnecessary morbidity with ineffective long-term treatment.

### 11.2.1. Local recurrence

The indication for drug treatment for local recurrences is dependent on the imaging diagnosis, with prior exclusion of distant metastases. If there are no distant metastases, a treatment decision on local tumor recurrence can be taken depending on the patient's general condition, the location and extent of the local recurrence, and the type of primary therapy (see Chapter 17). Treatment for local recurrence depends on the prior treatment and the primary stage, and includes the entire range, from exenterative surgical procedures to radio(chemo)therapy or radiotherapy, depending on prior radiation treatment or drug treatment. The chemotherapeutic agent of choice is cisplatin for the combination with radiotherapy (see Chapter 10). For drug therapy alone, various combinations of cisplatin with paclitaxel (135 mg/m²), vinorelbine (30 mg/m², days 1 + 8), gemcitabine (1000 mg/m², days 1 + 8), and topotecan (0.75 mg/m², days 1, 2, and 3) have been tested [482]. The effectiveness of the combination therapies does not differ widely [483], but to date only the combination of cisplatin with topotecan has been shown to offer a survival benefit in comparison with cisplatin monotherapy [484]. However, this may be due among other things to the fact that the other studies were stopped when the primary goal — i.e., differences in the disease-free survival — was not reached. The state of the data relative to achieving the final study goal of overall survival was therefore not further pursued. In comparison with the combination of cisplatin with gemcitabine or vinorelbine, the combination of cisplatin with paclitaxel shows a higher response rate with a lower range of side effects [482], [483]. The treatments that are most often used are the combinations of cisplatin with paclitaxel and cisplatin with topotecan.

### 11.2.2. Metastases

With regard to metastases, the first question that needs to be answered is whether there is an isolated metastasis or extensive organ metastases or locoregional metastases in the para-aortic lymph-node region. With isolated metastases, it can be discussed with the patient whether a surgical procedure or locoregional radiotherapy is an option.

If appropriate, this can also be combined with subsequent chemotherapy. The combination of cisplatin plus paclitaxel, or cisplatin plus topotecan, at the standard dosages (see above) is again the option of choice here.

Since 2015, bevacizumab has been approved in Germany for patients with recurrent or metastatic cervical carcinoma as a first-line treatment in combination with cisplatin/topotecan or cisplatin/paclitaxel. The GOG-240 study demonstrated a survival benefit of 3.5 months with both treatments (13.3 months vs. 16.8 months; HR 0.77; 95% CI, 0.062 to 0.95; P = 0.007), along with an improved progression-free interval (8.2 months vs. 6 months; HR 0.68; 95% CI, 0.56 to 0.84; P = 0.0002) and higher response rates (49% vs. 36%; P = 0.003) [485]. In the meantime, the combination of cisplatin/paclitaxel and bevacizumab has come to be regarded as the standard of care in first-line treatment for persistent, recurrent, or metastatic cervical carcinoma. As in the data from the JCOG-0505 study, cisplatin can be replaced with carboplatin. This leads to lower rates of neutropenia and renal failure, with the same degree of efficacy [486]. A recently published network meta-analysis has confirmed this approach on the basis of the expected equivalent effectiveness [487]. In platinum-naive patients, a survival benefit for cisplatin vs carboplatin was reported in the same study (overall survival 13.0 months vs. 23.2 months; HR 1.571; 95% CI, 1.06 to 2.32) [486].

Monotherapy is usually recommended for patients with progression after the first line of therapy. There are no data providing evidence of any improvement in the overall survival in comparison with “best supportive care.” Possible treatment options if therapy is desired are described in section 18.3.5.2.

Another option for second-line or higher-line therapy is the checkpoint inhibitor pembrolizumab (200 mg q3w) in patients with PD-L1-positive cervical cancer (combined positive score [CPS] ≥ 1). In the single-arm Keynote-028 study (phase 1b), the overall response rate with pembrolizumab (10 mg/kg q2w) in the cohort of heavily pretreated cervical carcinoma patients with PD-L1 expression was 17% (95% CI, 5% to 37%), with a median duration of response of 5.4 months (4.1–7.5 months) (see section 18.3.5.2) [461].

The probability of survival for a patient with metastases is much lower with cervical carcinoma than with other carcinomas, as the rate of response to chemotherapeutic agents is much lower than with the other entities.

Providing information about this is a component of the overall care concept for the patient, in which the option of “best supportive care” in the metastatic situation should also be discussed (see section 8.6.2.5 and recommendation 8.19).

# 12. Supportive therapy

**Major changes in the chapter on supportive therapy**

This chapter has been considerably shortened and refers essentially to the higher-level interdisciplinary Level 3 guideline, "Supportive Therapy in Oncology Patients," long version 1.3, February 2020 (AWMF register number 032/054OL).

*K. Jordan, T. Dauelsberg*

Supportive therapy is an integral component of the treatment approach. Side effects may occur in the form of acute changes during or immediately after treatment, or as late sequelae.

| 12.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Supportive therapy for prophylaxis against and minimization of treatment-related or tumor-related symptoms must be administered in accordance with guidelines. | |
| | Strong Consensus | |

## 12.1. Antiemetic prophylaxis and treatment

We would refer the reader here to the Level 3 guideline, "Supportive Therapy in Oncology Patients," long version 1.3, February 2020 (AWMF register number 032/054OL) [442].

This cross-sectional guideline discusses the following areas in detail.

### 12.1.1. Tumor therapy–induced anemia

Please refer to Chapter 3 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.2. Prophylaxis against tumor therapy–induced neutropenia with granulopoietic growth factors

Please refer to Chapter 4 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.3. Tumor therapy–induced nausea and vomiting

Please refer to Chapter 5 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.4. Tumor therapy–induced diarrhea

Please refer to Chapter 6 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.5. Oral mucositis due to systemic tumor therapy

Please refer to Chapter 7 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.6. Tumor therapy–induced skin toxicity

Please refer to Chapter 8 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.7. Neurotoxicity — chemotherapy-induced peripheral neuropathy (CIPN)

Please refer to Chapter 9 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.8. Osseous complications

Please refer to Chapter 10 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.9. Extravasation

Please refer to Chapter 11 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

### 12.1.10. Supportive measures in radio-oncology

Please refer to Chapter 12 of the Level 3 guideline on "Supportive Therapy in Oncology Patients."

## 12.2. Locoregional side effects

### 12.2.1. Radiogenic cystitis

Acute radiotherapy-induced cystitis leads to symptoms such as dysuria, increasing urination frequency, and nocturia. The focus is on symptomatic treatment with analgesia and spasmolysis (metamizole [dipyrone], centrally acting analgetics, butylscopolamine, oxybutynin). Alkalization of the urine and iron substitution, or even transfusions in cases of recurrent micro- and macrohematuria, can supplement the therapy. Bacterial superinfections require the appropriate antibiotic therapy. According to the ASCO guideline (2008 Clinical Practice Guideline Update: Use of Chemotherapy and Radiation Therapy Protectants), preventive administration of amifostine (an aminothiol compound) may be considered in order to reduce radiotherapy-induced toxicity. Ethyol® (amifostine) is not approved for this indication in Germany. Critical weighing up of the side effects and benefits of amifostine for this off-label indication is necessary [488].

### 12.2.2. Lymphedema

The standard treatment for lymphedema is complex physical decongestive (CPD) therapy. This consists of the following coordinated components:

- Skin care and, if necessary, skin sanitization
- Manual lymphatic drainage, if necessary supplemented with additive manual techniques

- Compression therapy with special multilayer, compressive alternating bandages and/or lymphological compression stockings
- Sports/movement therapy to promote decongestion
- Education and training for individual self-treatment

The goals of treatment are to return the disease to an edema-free state or to a lower lymphedema stage and thus to enable sustainable stability of the findings, an improved quality of life, and participation in social and occupational life, and to prevent complications. The combination of CPD with self-management and information can ensure long-term therapeutic success [489].

### 12.2.3. Vaginal dryness, vaginal stenosis, and vaginal fibrosis

Radiogenic and/or chemotherapy-induced vaginal dryness can be reduced in patients with cervical carcinoma by administering inert lubricant gels. In individual cases when there is severe pain, local estrogen treatment can be administered after careful consideration of the risk and provision of the appropriate information to the patient. Approximately 4–6 weeks after the end of radiotherapy that has included the vaginal region, mechanical dilation (with vaginal dilators, dexpanthenol [Bepanthen] tampons) is a possible method for prophylaxis against vaginal stenosis [490].

### 12.2.4. Radiogenic vulvovaginitis

Acute radiogenic vulvovaginitis can occur up to 90 days after the start of radiotherapy and is often reversible. Agents available for the treatment of vulvovaginitis include dexpanthenol, sitz baths with chamomile, and sitz baths with synthetic tannins such as phenol-formaldehyde-urea polycondensate. To restore the physiological pH value in the vagina, as a prerequisite for restoring the physiological vaginal flora, suppositories with freeze-dried cultures of Lactobacillus acidophilus and topical vaginal estrogens can be used if there are no absolute contraindications (estrogen-containing creams or gels, ovula, inserts, or vaginal tablets), or benzydamine-containing creams.

### 12.2.5. Disturbances of sexual function

Providing the patient with sufficient information about the effects of the treatment on her sexual life and about the options for prophylactic and therapeutic measures (e.g., vaginal dilation) is an essential component of therapy for patients with cervical carcinoma [490] (see also chapter 15.5 Chapter 15.5).

# 13. Psycho-oncology and quality of life

**Major changes in the chapter on psycho-oncology and quality of life**

Few changes have been made in this chapter. There are no new statements or significant changes in section 12.1, Psycho-oncology aids. Section 13.2, Measuring quality of life, has been considerably shortened.

*B. Hornemann, J. Weis, H. Haase, F. Mumm*

## 13.1. Psycho-oncological assistance

Patients with cervical carcinoma have a number of psychosocial burdens [491][492][493][494][495]. In addition to impairment of their psychological state, disturbances of sexual function are of immediate importance that have effects on their sense of self-esteem, body image and perceived sexual attractiveness, and consequently on their quality of life. The patient's sexuality is particularly impaired in cervical carcinoma if comprehensive surgery or radio(chemo)therapy has to be carried out and adhesions develop in the treatment area or the vagina is shortened. In addition, treatment-related nerve injuries can disturb lubrication. Radio(chemo)therapy can lead to radiation fibrosis or fistula formation and can make the vaginal tissue more susceptible to infections. All of these treatments can make sexual intercourse very difficult — partly due to pain — or even impossible [496][497].

| 13.1 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | Psycho-oncological care for patients with cervical carcinoma is an integral component of oncological diagnosis, treatment, and follow-up and represents an interdisciplinary task. | |
| | Strong Consensus | |

Psychosocial counseling and psycho-oncological care for patients with cervical carcinoma are integral components of oncological diagnosis, treatment, and follow-up and represent an interdisciplinary task [498][499][500][501][502]. Psycho-oncological care for patients is based on an interdisciplinary approach involving all of the professional groups taking part in the treatment. Psycho-oncological measures should be incorporated into an overall approach to oncological care.

The physician treating the patient should therefore have basic psycho-oncological skills. In addition, a specialist in psycho-oncology should be a member of the treatment team in order to provide psycho-oncological counseling and treatment.

| 13.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Psycho-oncological advice and support ***shall*** be offered to all patients and their relatives in a manner appropriate to their needs. | |
| | Strong Consensus | |

Psychosocial assistance (counseling and psycho-oncological treatment) includes patient-appropriate information and counseling, competent psychosocial diagnosis, and targeted psychosocial support. This includes ways of coping with the disease, treatment, and side effects and sequelae that occur, as well as dealing with continuing functional disturbances and other disease-related or treatment-related limitations such as financial difficulties and issues involved in returning to working life. Specifically, these measures can thus be carried out through psychological/psycho-oncological interventions, counseling by social workers, oncological rehabilitation measures, or other professional institutions. These forms of assistance are aimed at the patients and relatives in their milieu and apply to the entire disease phase ranging from diagnosis, information provision, treatment, supportive therapy, rehabilitation, to follow-up and palliative medical care where appropriate.

| 13.3 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Individual needs and the corresponding advice and treatment ***shall*** be ascertained using a standardized screening procedure, in accordance with the Level 3 guideline "Psycho-oncological Diagnosis, Advice, and Treatment in Cancer Patients" (AWMF register no. 032/051OL`; version 1, January 1, 2014). | |
| | Strong Consensus | |

Diagnostic clarification and establishment of the indication for psycho-oncological interventions should be carried out in accordance with the Level 3 guideline on "Psycho-oncological Diagnosis, Advice, and Treatment in Cancer Patients" (AWMF register no. 032/051OL, version 1, January 1, 2014; update expected in 2021) [502]. This means that the patient should be informed about facilities for psycho-oncological assistance at an early point after establishment of the diagnosis or during the course of treatment. The aim should be to achieve close coordination with everyone involved in the patient's treatment (e.g., the gynecological oncologist, family physician, gynecologist, radio-oncologist, outpatient nursing service) and a continuous flow of information should be ensured [494].

Standardized and validated screening procedures should be used to establish the psychosocial burden and need for psycho-oncological treatment [503]. A psycho-oncological screening instrument should be used as early as possible and repeated at appropriate intervals if clinically indicated, or when there are changes in the patient's disease status (e.g., recurrence or progression of the disease). In accordance with the requirements given in the Level 3 guideline on "Psycho-oncological Diagnosis, Advice, and Treatment in Cancer Patients" (AWMF register no. 032/051OL), the Distress Thermometer or Hospital Anxiety and Depression Scale (HADS) are particularly recommended [504]. If the screening process shows positive results, a diagnostic discussion should take place for further diagnostic clarification.

| 13.4 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The subject of sexuality ***should*** be actively explored in order to ascertain what further assistance may be needed and initiate the corresponding support measures. | |
| | Strong Consensus | |

Sexual problems should always be actively mentioned by those treating the patient, since due to the embarrassment and taboos associated with of the topic of sexuality patients rarely mention the subject on their own initiative.

| 13.5 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Psychosocial assistance ***should*** be offered with a low threshold to all patients and their relatives in every phase of the disease. | |
| | Strong Consensus | |

In accordance with the Level 3 guideline on "Psycho-oncological Diagnosis, Advice, and Treatment in Cancer Patients" (AWMF register no. 032/051OL, version 1, January 1, 2014), psycho-oncological interventions are defined as nonpharmacological interventions in which psychological methods such as psychoeducation, stress management training, psychotherapy, and relaxation procedures are carried out on their own or in combination by a professional therapist in a personal interaction with cancer patients in order to reduce their psychological and social burden and improve their quality of life. Psycho-oncological interventions include:

- Relaxation methods
- Psychoeducation
- Psychotherapy (individual, group, couple)
- Psychosocial counseling
- Art therapy

These psycho-oncological interventions are indicated in cases of severe psychological burdens, relationship conflicts, and psychological disturbances — particularly depressive disturbances and anxiety disturbances [505], [506]. Psycho-oncological interventions should be adapted to the patient's individual needs [507] and should follow the algorithm given in the Level 3 guideline on "Psycho-oncological Diagnosis, Advice, and Treatment in Cancer Patients" (AWMF register no. 032/051OL, version 1, January 1, 2014). The wishes of the patient and her partner and relatives should also be integrated into the patient's psychosocial counseling and treatment.

Patients with cervical carcinoma have a number of psychosocial burdens [508][509][510][498][494]. In addition to impairment of their psychological state, disturbances of sexual function are of immediate importance that have effects on their sense of self-esteem, body image and perceived sexual attractiveness, and consequently on their quality of life. The patient's sexuality is particularly impaired in cervical carcinoma if comprehensive surgery or radio(chemo)therapy has to be carried out and adhesions develop in the treatment area or the vagina is shortened. In addition, treatment-related nerve injuries can disturb lubrication. Radio(chemo)therapy can lead to radiation fibrosis or fistula formation and can make the vaginal tissue more susceptible to infections. All of these treatments can make sexual intercourse very difficult — partly due to pain — or even impossible [511][512].

## 13.2. Measuring quality of life

*B. Hornemann, O. Damm, W. Greiner, H. Haase, F. Mumm*

| 13.6 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Research on the quality of life in patients with cervical carcinoma ***shall*** be carried out both in clinical studies and also in nursing-care research. | |
| | Strong Consensus | |

### 13.2.1. Importance of and data collection for quality of life

Including quality of life as a patient-relevant parameter for results is becoming increasingly important in medical and health-care research [513]. Quality of life is now a well-established criterion for evaluating the success of treatment, in which the focus is on the patient's point of view. Particularly in the field of oncology, improving or maintaining quality of life can be described as an important treatment goal alongside reducing morbidity and mortality. The patient's quality of life becomes more important particularly when higher response rates with new drugs or combinations of them are associated with increased toxicity and an exacerbated range of side effects. The explicit mention of quality of life in the German Social Security Code V (*Sozialgesetzbuch*, SGB) further underlines the relevance of this topic in the field of health policy in Germany.

Health-related quality of life must be regarded as a multidimensional construct that combines physical, psychological, and social aspects of health and places the patient's subjective perceptions in the foreground [513]. In addition to physical status, the focus in quality of life research is thus also on the patient's psychological state and social relationships.

There are now a large number of standardized and validated instruments with which the complex construct of quality of life can be measured.

For assessing quality of life, the EORTC recommends a complementary survey of quality of life [513]: generic (EORTC QLQ-C30; FACT-G) [513], entity-specific (EORTC QLQ-CX24; FACT-Cx) [513], and also supplementary individual items if necessary (e.g., from the EORTC item library) for symptomatic areas that are not yet reflected [513].

# 14. Integrative medicine

**Major changes in the chapter on integrative medicine**

The definition of integrative medicine has been adapted. The chapter has been expanded to include the use of probiotics and coffee in integrative medicine.

*C.C. Hack, M.W. Beckmann*

## 14.1. Introduction

The aim in complementary and alternative medicine, which is often summed up in the term "integrative medicine," is to improve the patient's general well-being and/or quality of life and in this way make a distinct contribution to overcoming the disease. More and more healthy and ill individuals are making use of these options, known as "complementary and alternative." Examples include homeopathy, acupuncture, yoga, hypnosis, mediation, phytotherapy, dietary approaches, nutritional supplements, and exercise. These forms of medicine are becoming increasingly popular both among patients and among physicians, and many people already regard them as components of current medical practice [478]. Women in particular appear to be very receptive to these methods. It is often difficult to obtain information about the safety of the treatments offered, due to a scarcity or absence of data. In view of the prevalence of these methods, conventional medicine needs to engage with the treatment approaches involved in order to identify their potential benefits and also to prevent harm to patients.

## 14.2. Definition of terms

Integrative medicine is an umbrella term that refers to the interplay of scientific evidence-based medicine ("conventional medicine") and complementary experience-based medicine ("complementary medicine"). Complementary methods that are intended to contribute to holistic care are included in this approach as a supplement to current medical concepts [479], [480]. The term "complementary and alternative medicine" (CAM)) is not clearly defined.

## 14.3. Spread of alternative and complementary medicine

With regard to usage, a Canadian study has shown that patients with cervical carcinoma generally use methods from the field of complementary and alternative medicine (CAM) less often in comparison with patients with other gynecological tumor entities [481]. According to a study conducted in Connecticut, 87% of patients with cervical carcinoma used methods supplementary to conventional cancer therapy — mainly vitamins (80.3%) and prayer (69.7%), followed by massage (38.5%), herbal infusions/teas (36.1%), and visualization/meditation (31.3%) [482]. Whether and to what extent these data are applicable to Germany or Europe is questionable. In general, some 40% of all tumor patients use methods from complementary and alternative medicine, although the prevalence varies in relation to tumor entity and country [514]. The relevant prioritization in relation to usage and choice of methods is based on intercultural differences in the area of lay etiology.

## 14.4. Counseling on the field of complementary and alternative medicine (CAM)

| 14.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Advice on complementary and alternative medicine (CAM) should be given to patients. If patients make use of such methods, it should be documented. | |
| | Strong Consensus | |

In view of the widespread use of the above methods and their potential interactions with radiotherapy and/or chemotherapy, it is important from a medical point of view to inform patients about the potential for interactions. In addition, patients wish to have objective information about the methods [484]. Medical necessity, on the one hand, and the patient's wishes on the other, need to be taken into account (see the Level 3 "Guideline Complementary Medicine in the Treatment of Oncology Patients" [75]).

## 14.5. Value of alternative medicine methods

| 14.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Alternative medicine treatment options — i.e., measures that attempt to treat women who have cervical carcinoma while avoiding the methods of conventional medicine — shall be rejected. | |
| | Strong Consensus | |

There are no reliable data on the efficacy of alternative treatment methods in cervical carcinoma, only two case reports in which the course of the disease was progressive. With the use of nonspecific homeopathic therapy, vitamin C and mistletoe lectins (subcutaneous) [485], one patient who initially had Pap IVa findings developed a cervical carcinoma. All conventional measures were declined, and subsequent treatment with locoregional hyperthermia, Horvi-Reintoxin enzyme therapy, and a combination therapy with Carnivora, mistletoe and the drug ukrain led in the end to a dramatic course and death at the age of 42 [482]. The second case also had a fatal course [486]. The Federal Institute for Drugs and Medical Products (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) has classified ukrain as a suspect substance. This classification means that ukrain may neither be circulated as a medication in Germany nor administered in patients. The BfArM has in particular informed members of the healing professions that the importation of ukrain is illegal [515], [516].

Studies on alternative medicine in other tumor entities have without exception shown less favorable survival figures when alternative methods are used [488], [489], [490], [508], [509], [510]. These methods should therefore be rejected.

## 14.6. Value of complementary medicine methods

Among the complementary medicine methods, a distinction is made between measures that improve the efficacy of the treatment or improve the prognosis and those that are

intended to reduce the side effects of treatments. The majority of the methods are excluded under Section 135 of the German Social Security Code V *(Sozialgesetzbuch,* SGB) and are therefore not panel-physician services that can be charged to statutory health insurance.

## 14.6.1. Improvement in efficacy of treatment or prognosis

### 14.6.1.1. Hyperbaric oxygen (HBO) therapy

Various methods have been promoted in the past in which increased oxygen saturation in tissue is intended to enhance the efficacy of conventional treatment measures. However, as long ago as the 1970s, it was shown in a small randomized study including 82 cervical carcinoma patients who were receiving radiotherapy that additional hyperbaric oxygen therapy did not offer any treatment benefits in relation to local control, survival, or side effects, and according to the authors it was of no clinical value [517].

## 14.6.2. Reduction of side effects

### 14.6.2.1. Mistletoe therapy

The only study on mistletoe therapy in cervical carcinoma concludes that it is advantageous in relation to overall survival. However, the study has substantial methodological deficiencies; for example, the way in which patients were selected for the matched-pair analysis is not reported [498]. A survival advantage has not so far been demonstrated in relation to other tumor entities [511]. Mistletoe therapy is said to have benefits in relation to quality of life, but high-quality research studies are still awaited [511].

### 14.6.2.2. Enzyme therapy

In a prospective, randomized study including 120 Indian patients, additional enzyme therapy with papain, trypsin, and chymotrypsin alongside radiotherapy was tested in cervical carcinoma. The analysis of the findings showed significant differences in favor of the group receiving enzyme treatment with regard to radiotherapy-related skin reactions and gastrointestinal and urogenital symptoms [512]. On the basis of these data, further research would be useful, but a general recommendation for enzyme therapy cannot at present be made.

### 14.6.2.3. Vitamins, antioxidants, selenium

Few data are available on the use of antioxidants and vitamins during active conventional treatment for cervical carcinoma. There are at present two contradictory hypotheses:

- The high-dose vitamin therapy variant is said to increase the effectiveness of radiotherapy on malignant cells and to reduce the toxicity for healthy cells. A similar finding has been demonstrated for vitamin E in cervical cell lines [518], [502].
- Antioxidants intercept the free radicals that are generated during radiotherapy and in vitro thus protect the cancer cells from the radiotherapy.

Both of these theories are based on experimental in vitro studies [502]. Little research has so far been conducted on this topic and on the transferability of the findings to the in vivo situation, and there is insufficient research in connection with cervical carci-

noma. A study in which a group of women undergoing radiotherapy for cervical carcinoma received a combination of vitamin C (60 mg), vitamin E (10 mg), vitamin A (1000 IU), and selenium (50 mg) showed evidence of reduced apoptosis in the study group in comparison with the control group who did not receive this type of supplementation [499]. Patient-relevant end points such as overall survival and disease-free survival were not investigated. Relevant data are also not available for any other tumor entities [519]. According to the data reported by Halperin et al., topically administered vitamin C did not relieve radiation dermatitis [520].

A multicenter, randomized phase 3 study has been published on uterine carcinoma (endometrial and cervical carcinoma) that investigated the effects of supplementation with sodium selenite on the adverse effects of radiotherapy. The study only included 81 patients with uterine carcinomas (11 of whom had cervical carcinomas) and confirmed selenium deficiency. It was found that diarrhea occurred significantly less often (20.5% versus 44.5%) with selenium supplementation. There was no evidence of a less favorable recurrence-free survival or overall survival. A recent Cochrane analysis in 2011 did not find any evidence of a cancer-preventive effect of selenium supplementation [521].

Several studies have investigated vitamin A in connection with cervical carcinoma. In a small randomized study (n = 42), an improved immune reaction and a trend towards a lower rate of recurrence was noted with vitamin A administration [522], [513]. An uncontrolled study observed a stronger response to radiotherapy with a combination of retinoids and interferons [523]. There is some evidence that vitamin A may be of value in cervical carcinomas [524].

The above research evidence is not sufficient for a recommendation in favor of prophylactic administration of vitamin preparations, antioxidants, and/or selenium to prevent adverse side effects in the treatment of patients with cervical carcinoma.

#### 14.6.2.4. Healing touch

"Healing touch" is an energy treatment that is intended to support the balance of physical, mental, emotional, and spiritual well-being and to stimulate self-healing forces. The method is popular both in the USA and also increasingly in Germany. A randomized, three-armed study on it, including 51 patients with cervical carcinoma, has been published that tested changes in the adverse effects of radio(chemo)therapy relative to healing touch and to a form of relaxation therapy, in comparison with the standard treatment [525]. The analysis of the data showed that with healing touch there was a significantly lower decline in natural killer cells in comparison with patients who underwent relaxation exercises during the treatment and those who received only conventional therapy. There were also benefits with healing touch with regard to depression [525]. No negative effects were observed, and potential long-term effects were not reported.

Reliable larger studies investigating the efficacy of healing touch in the treatment of cervical carcinoma patients in relation to patient-relevant clinical parameters are not yet available, so that the use of the method must be classed as experimental.

#### 14.6.2.5. Phytotherapy

A large number of prescription and nonprescription drugs, as well as nutritional supplements and foodstuffs, are summed up under the umbrella term "phytotherapy." It is

often not possible for any conclusions to be drawn regarding the safety of nonprescription drugs and nutritional supplements and they therefore have to be checked on a case-by-case basis.

A systematic review with a meta-analysis on cervical carcinoma is available in relation to phytotherapy. The review concludes that complementary phytotherapy can both improve the efficacy of conventional therapy and also alleviate its side effects, but that methodologically high-quality studies with better validity are required before it can be recommended [527]. The herbs most often used were astragalus root, ginseng root, Chinese angelica root, poria fungus (Wolfiporia extensa (Peck) Ginns), licorice root, turmeric root, and the rhizome of Pinellia. The review refers exclusively to Chinese studies whose transferability to Germany is limited. In vitro studies show that these agents have a similar profile of effects in cervical carcinoma cells [528], [524], [529], [526], [530]. It has been shown in in-vitro studies that genistein in combination with radiotherapy also inhibits cell growth and triggers apoptosis [531].

A clinical study on the effect of an extract of Agaricus blazei in 100 patients with cervical, ovarian, or endometrial carcinoma (39 with active treatment, 61 in the placebo group) during carboplatin-containing chemotherapy showed significantly increased activity of NK cells (P [276832 et al. 2011].

In preclinical studies, a drug from Indian Siddha medicine (Rasagenthi Mezhugu) showed evidence of efficacy in relation to DNA damage and increased apoptosis [533].

The validity of these studies and in vitro investigations is insufficient for a qualitative evaluation of the clinical application of phytotherapies alongside recognized oncological treatments for cervical carcinoma.

#### 14.6.2.6. Probiotics

Radiotherapy-induced diarrhoea is one of the most common side effects of radiotherapy for cervical cancer. A randomized controlled trial of 57 cervical carcinoma patients demonstrated a significant effect on the incidence and severity of radiotherapy-induced diarrhea [534]. The incidence of diarrhea was lower in the group treated with probiotics (Lactobacillus acidophilus LA-5 plus Bifidobacterium animalis subsp. lactis BB-12) than in the placebo group (53.8% vs. 82.1%, P [Han, E. et al. 2011]. The use of loperamide was lower in the probiotic group than in the placebo group (P [Han, E. et al. 2011]. Supplementation of a probiotic consisting of Lactobacillus and Bifidobacterium strains may therefore reduce chemotherapy-induced and radiation-induced diarrhea in patients with cervical carcinoma. However, a general recommendation for probiotic therapy cannot be made due to the paucity of data.

#### 14.6.2.7. Coffee

A randomized controlled trial was conducted, including 114 patients with endometrial, ovarian, cervical, or tubal carcinoma after complete stage-appropriate surgery to determine whether consumption of coffee postoperatively accelerated the recovery of bowel function [535]. The time to onset of bloating, defecation, and ability to tolerate food was significantly reduced in comparison with the control group (P [Bagenal, F. S. et al. 1990].

Larger, better-powered studies examining the efficacy of postoperative coffee consumption on bowel function are not yet available, and its use should therefore be regarded as experimental.

### 14.6.3. Conclusions for practice

Scientifically based complementary medical treatment of cervical carcinoma is hardly possible at the present time. For most of the methods, the studies that are available are too few and too poor in quality. The methods mentioned (and also others) can therefore not be recommended. Further well-planned research studies with a clear focus on individual agents or methods and on the specific characteristics of patients with cervical carcinoma appear to be useful and necessary.

# 15. Rehabilitation

**Major changes in the chapter on rehabilitation**

The statements are unchanged. The background text on rehabilitation has been rewritten; application procedures, objectives and implementation are described, as well as the legal framework and theoretical background. A new feature is the listing of evidence regarding treatments that are carried out in rehabilitation clinics. The section on lymphedema has been completely revised and aligned with the Level 2 consensus-based guideline on the subject. The background text for the section on fatigue has been expanded.

*T. Dauelsberg, M.C. Koch, U. Henscher, R. Tholen, L. Kiesel, R. Wiedemann*

| 15.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The purpose of medical oncological rehabilitation is to provide specific treatment for the sequelae of the disease and of its treatment. All patients shall receive information and advice about the statutory options available for applying for and using rehabilitation measures. | |
| | Strong Consensus | |

| 15.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Treatment-related disturbances shall be inquired after and treated during rehabilitation. | |
| | Strong Consensus | |

## 15.1. Before rehabilitation

All patients must be informed and advised in detail about the statutory availability of options for follow-up rehabilitation, nonmedical treatment, and outpatient rehabilitation services. The attending physician and social worker involved must collaborate for the purpose. The patient's capacity for rehabilitation results from positive motivation and the physical and psychological ability to make use of the rehabilitation programs offered in a goal-oriented way.

The extent of the patient's need for rehabilitation in the somatic and psychosocial areas emerges from the establishment of disease-related and treatment-related sequelae based on the principles set out in the World Health Organization's International Classification of Functioning, Disability and Health (ICF) (2001). These can be differentiated in greater detail into functional disturbances, disabling conditions, impairments, and context and risk factors, and can also be recorded in coded form.

Accordingly, the assessment of the need for rehabilitation (e.g., in the context of application procedures) requires consideration of bio-psycho-social impairments in addition to biomedical health problems.

Rehabilitation is carried out on an in-patient or outpatient basis, or if necessary as a mixed form, but always in an interdisciplinary and multimodal fashion.

## 15.2. Goals of rehabilitation

Oncological rehabilitation is the next therapeutic step for patients with cervical carcinoma after completion of primary therapy, to enable them to return to normal everyday family, social, and professional life.

The overall goal of oncological rehabilitation is the recovery of physical, mental, and social well-being. In the case of chronic disease sequelae, support and care should be provided to help patients accept or compensate for unavoidable disabilities and symptoms and lead their own lives again to their own satisfaction and on their own initiative.

Oncological rehabilitation aims to significantly improve or restore any substantially endangered or already reduced ability to work, or at least to prevent deterioration.

The aim of oncological rehabilitation is to avoid the need for long-term care or postpone the time point at which long-term care becomes needed.

## 15.3. Overcoming physical, mental and social effects

Oncological rehabilitation takes place in a multidisciplinary setting based on the ICF and the bio-psycho-social model:

- Diagnosis of the sequelae of the cancer and its treatment
- Preparation of an individual rehabilitation plan
- Multidisciplinary treatment of specific sequelae — e.g., local sequelae due to surgery or radiotherapy, or due to estrogen deficiency, dyspareunia, lower urinary tract or bowel disorders, lymphedema, or chronic tumor-associated fatigue syndrome
- Exercise and a physiotherapeutic training program to increase the patient's strength and condition and overcome or compensate for specific secondary disorders
- Physical therapy, provision of aids
- Ergotherapy
- Psycho-oncological services, including individual and group services, relaxation procedures, creative therapies
- Social counseling on the professional, domestic, family or social situation
- Provision of information on the disease and healthy lifestyles
- Motivation and training to ensure a healthy lifestyle and enable the patient to cope with the disease and health on her own responsibility

## 15.4. Occupational support

The sequelae of cervical carcinoma and cancer treatments that have been carried out may involve impairment of the ability to work. After a cancer illness, there is a greater risk of unemployment, change of job, reduced working hours, and lower remuneration.

An important task for oncological rehabilitation is to compensate for these disadvantages and risks:

- Is the rehabilitant's ability to work sufficient for the demands of the workplace in the medium term?

- Can the rehabilitant continue to do her job to the same extent as before?
- Does the rehabilitant need equipment for the workplace that is suitable for her condition?
- Is it necessary for her to change jobs within the company she is working for?
- Does the rehabilitant need services to promote participation (e.g., further vocational training)?
- Has the rehabilitant lost the ability to work?

Oncological rehabilitation is suitable for provide patients with competent support on their way back to working life. In the process, it satisfies the requirement in Germany's Basic Law that "No one may be disadvantaged because of his or her disability" (article 3, paragraph 3, clause 2 of the Basic Law ) and the "right to participation" set out in Chapter IX of the Social Security Code V *(Sozialgesetzbuch,* SGB)

In the medical discharge report provided by the rehabilitation clinic, a sociomedical performance assessment is drawn up for patients who are of working age, which, in addition to assessing the patient's previous activity profile, also refers to her capacity to take part in the general employment market.

## 15.5. State of research on rehabilitation in oncology patients

Many therapeutic measures in oncological rehabilitation are provided on the basis of scientifically proven effectiveness. For methodological reasons, the relevant research is mostly conducted in relation to the frequent diagnoses of breast cancer, prostate cancer, and colorectal cancer. Evidence has been reported for the effects described below, and we consider that analogous measures are appropriate in patients with cervical carcinoma:

- Exercise therapy: reducing fatigue symptoms, increasing exercise capacity and physical functionality, improving body image, reducing depression, improving quality of life [537], [538], [539], [540], [541], [542], [543]
- Health education: reducing uncertainty, improving quality of life, improving sense of well-being [544], [545], [546], [547]
- Patient training: reducing physical symptoms, improving quality of life, improving mood [544], [548], [549], [550], [551]
- Practical nutritional training: achieving intentional weight loss through practical interventions [552]
- Relaxation training: pain reduction, improving quality of life, reducing anxiety and depression [553], [554], [555]
- Psychological counseling and therapy: improving quality of life, reducing fatigue and stress, reducing anxiety and depression [536], [556], [557], [558], [559], [560], [561], [562], [563], [564], [565], [566], [567], [499], [568]

## 15.6. Funding agencies and statutory basis

Rehabilitation services are services for participation that may be charged to a rehabilitation provider (e.g., the German pension insurance system, statutory health insurance companies, statutory accident insurance companies). In the field of oncological rehabilitation, the pension insurance funds are the funding agencies most frequently responsible. In accordance with German social legislation, disabled people or people at

risk of disability receive rehabilitation benefits in order to promote their self-determination and equal participation in life in society, and to avoid or counteract disadvantages. The benefits are provided by the relevant rehabilitation provider in accordance with Book 9 of the Social Security Code (SGB) and the benefits legislation applicable to the rehabilitation provider concerned — e.g., SGB V in the case of statutory health insurance (GKV) or SGB VI in the case of pension insurance (DRV).

## 15.7. Bio-psycho-social model

The bio-psycho-social conception of illness is a prerequisite in medical and vocational rehabilitation in order to initiate rehabilitation (including the application process for it and the report on findings) and to establish the (therapeutic) content of rehabilitation procedures and planning of the individual rehabilitation goals. The rehabilitation providers implement the WHO recommendation to apply the International Classification of Functioning, Disability and Health (ICF) in the field of health care.

## 15.8. International Classification of Functioning, Disability and Health (ICF)

The ICF supplements the International Statistical Classification of Diseases and Related Health Problems (ICD) in areas in which the focus is not on the diseases (diagnosis and findings) themselves, but rather on the associated impairments, including impaired earning capacity, mobility, communication, self-care, home life and participation in social life.

## 15.9. Physiotherapy during rehabilitation

| 15.3 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **B** | In case of stress urinary incontinence and/or fecal incontinence, patients with cervical carcinoma should be offered pelvic floor training. | |
| LoE **1++** | [569]; [570]; [571]; [572]; [573]; [574]; [575] | |
| | Consensus | |

The physiotherapeutic part of follow-up treatment focuses on therapy for various side effects of cancer treatment (surgery, radiotherapy, or chemotherapy). This includes treatment for incontinence, lymphedema, and interventions to relieve fatigue syndrome.

Functional disturbances in the pelvis may occur during treatment of gynecological tumors using surgery or radiotherapy. These disturbances include symptoms of urinary incontinence (urge incontinence, stress incontinence, and mixed incontinence) and fecal incontinence, pain, dyspareunia (e.g., due to a shortened or scarred vagina), circulatory changes, or inadequate elasticity in scar tissue.

These disturbances can be reduced using various passive physiotherapy techniques (scar mobilization, stretching of vaginal tissue, positioning, complex physical decongestive therapy, etc.), as well as active techniques (instructions on low-pain everyday behavior, exercises to promote the circulation, decongestive exercises, therapeutic exercise measures and training forms).

Pelvic floor training is still the treatment of choice in relation to urinary incontinence [570], [572], [576]. Specific data on patients with cervical carcinoma are not available, and this is the reason for the grade B recommendation. Pelvic floor training is particularly effective with stress incontinence and mixed incontinence, and also particularly in women under the age of 60 [569]. In addition, there is evidence that supervised training is more successful than training that is carried out independently by the patient [576]. If supportive forms of treatment — such as machine-aided biofeedback or electrostimulation — are used in addition to pelvic floor treatment in accordance with the relevant diagnosis, they can enhance the pelvic floor training [577], [578].

In the treatment of urge incontinence, combined therapy with bladder training, pelvic floor training, and educational measures has shown the best results and is quite comparable with drug treatment [579]. Another possible option in the treatment of urge incontinence may be treatment with functional electrostimulation [580], [581].

In the treatment of fecal incontinence, there is strong evidence for anal sphincter muscle training and pelvic floor training [571], [573]. It is not clear whether additional use of biofeedback and electrostimulation shows better results than pelvic floor training alone [571], [573].

## 15.10. Treatment for lymphedema during rehabilitation

| 15.4 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In case of manifest lymphedema, combined therapy with skin care, manual lymph drainage, therapeutic exercises, and compression should be offered. | |
| | Strong Consensus | |

The standard therapy for lymphedema is complex physical decongestive (CPD) therapy. This consists of the following coordinated components:

- Skin care and, if necessary, skin cleansing
- Manual lymphatic drainage, supplemented with additive manual techniques if needed
- Compression therapy with special multilayer, compressive temporary bandages and/or lymphological compression stockings
- Exercise/movement therapy to promote decongestion
- Information and training for individual self-therapy

The goals of treatment are to return the disease to an edema-free state or to a lower lymphedema stage and thus allow continuing stability of the findings, improvement of the patient's quality of life and participation in social and occupational areas of life, and to prevent complications. The combination of CPD with self-management and the provision of information ensures long-term therapeutic success (analogous to the Level

2 consensus-based guideline "Diagnosis and Treatment of Lymphedema," AWMF register no. 058-001, May 2017) [582].

## 15.11. Treatment of fatigue syndrome during rehabilitation

| 15.5 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **B** | In case of fatigue, patients should be offered forms of active training (strength training and/or stamina training). | |
| LoE **1++** | [583]; [584]; [585] | |
| | Consensus | |

Cancer-related fatigue has been reported in 53% of women treated for gynecological cancers, with a higher proportion in the cervical cancer group, followed by ovarian cancer. Younger participants were more likely to report fatigue than older participants. With adjustment for age, the type of cancer a woman experienced was found to have little effect on her risk of experiencing fatigue. Participants with fatigue reported higher levels of anxiety and depression than participants without fatigue. There was an association between fatigue and quality of life as measured by the SF-36 domains in health questionnaires.

Fatigue in cancer patients refers to unusually persistent tiredness that occurs during or after the treatment. In addition to physical limitations such as pain, nausea, and fatigue, psychological aspects such as depression or anxiety are very important here. Other causes of weakness or exhaustion symptoms, such as anemia, metabolic disturbances, and other differential diagnoses should always be checked as a matter of principle beforehand.

A systematic literature search identified four systematic reviews and in addition 16 randomized studies on exercise interventions in cancer patients and patients receiving treatment for fatigue. No studies on exercise interventions in cervical carcinoma patients were identified. The available studies mainly included breast cancer patients, as well as prostate carcinoma patients and mixed groups. The guideline group regards these data as being in principle transferable to the situation for cervical carcinoma patients. Due to the indirect evidence of the efficacy of exercise interventions in cervical carcinoma patients, the recommendation grade was reduced to B (recommendation).

The studies included (for a detailed presentation, see the evidence report accompanying this guideline) show that exercise therapy measures can lead to improvement in cancer-related fatigue [583], [584], [585]. This applies both to patients during primary therapy and also to "cancer survivors." Forms of exercise such as stamina training, strength training, or a combination of the two appear particularly suitable. The question of the frequency of training cannot be clearly answered; on average, treatment frequencies of two to three times per week for 8–12 weeks were examined [588], [589], [590], [591], [592], [593], [594], [595], [596], [597], [598], [599], [600], [601]. An important factor behind a lack of improvement in fatigue syndrome is a lack of compliance on the part of the patients in relation to exercise interventions. Additional cognitive

interventions did not show any clear improvement in the results [593], [598], [599], [602].

The general approach to the management of cancer-related fatigue (CRF) includes providing information, counseling, and other strategies. Nonpharmacologic interventions include psychosocial interventions, exercise, yoga, physically based therapy, nutritional management, and sleep therapy [603]. The first approach to any fatigue treatment is to provide information and counseling for the patient and family. Information, establishment of an individualized treatment plan, self-confidence, and stress management can be important and crucial factors that influence the treatment of patients' CRF. In addition, an individualized treatment plan should essentially include diet, exercise, sleep, and stress management tactics to help the patient gain confidence in the treatment plan. Nonpharmacological treatments have shown promising results in the areas of exercise, sleep therapy, and cognitive-behavioral interventions [586].

Although a gold standard treatment for fatigue is not currently available, a variety of intervention approaches have shown positive effects in randomized controlled trials, including physical activity, psychosocial, physical-mental, and pharmacological treatments [587].

## 15.12. Sexuality

Malignant tumors of the genital tract, and cervical carcinoma and its treatment in particular, have enormous effects on the patients' sexuality. In addition to reduced libido, the patients report vaginal dryness and dyspareunia as being particularly troublesome subjectively [605], [606]. In addition, the disease and its treatment have serious effects on emotional integrity, associated with the change in sexual anatomy [604]. Identity crises are not rare [604], [418], [419].

There is good epidemiological evidence for the effects of the disease on sexual health, but the literature on ways of treating this is limited [607]. However, a positive effect of psychoeducational measures on quality of life has been demonstrated for patients who received treatment with curative intent [608]. These patients benefit from receiving information about alternative hormone therapies, vaginal suppositories, and vaginal dilators [609], [610]. From the point of view of functional, emotional, and partnership considerations, sexual activity should be resumed soon after the completion of therapy, depending on the patient's wishes and anxieties. The patient's anxieties should be relieved through discussion and the provision of information about support. After the completion of each treatment, an interval of approximately 3–6 weeks after surgery and radio(chemo)therapy has become established as an interval that can usually be recommended.

Due to the integral nature of the complex of symptoms, multi-professional and interdisciplinary care for these patients, including psychological and psycho-oncological expertise, is recommended.

# 16. Follow-up care

**Major changes in the chapter on follow-up care**

The chapter has been completely revised editorially and new literature references on the subject have been added. Overall, the value of PET-CT in symptomatic patients during follow-up has been emphasized in special situations for treatment planning. No new recommendations or statements have been added.

*M.C. Koch, P. Hillemanns, F.A. Stübs, V. Küppers, M.W. Beckmann*

Follow-up in patients with cervical carcinoma starts when the primary treatment has been completed. It consists of a patient history, physical examination, medical counseling, nursing care, and support. When there are abnormal findings during the follow-up, or if there is any clinical suspicion, imaging diagnosis should be carried out on a symptom-oriented basis in order to detect any locoregional or distant recurrences [611], [612], [621], [613], [614], [615], [616].

In a systematic literature review on follow-up strategies in patients with cervical carcinoma, including 17 retrospective studies, Elit et al. found that a follow-up interval of 3–4 months for the first 2–3 years, followed by a 6-monthly interval for a further 2 years, can be regarded as an international standard [617]. After that, check-ups were annual. The mean interval to recurrence is 7–36 months after completion of the primary therapy. The recurrence rates were 8–26%, with 14–57% of these being local pelvic recurrences and 15–61% distant metastases. Among the 8–26% of the patients who suffered a recurrence, the recurrence mainly (89–99%) developed within 5 years. The mean survival after recurrent disease was 7–17 months [617].

Asymptomatic recurrences were detected in 29–71% of cases through the clinical bimanual examination, with a chest X-ray in 20–47% of cases, with CT in 0–34% of cases, and with cytology in 0–17% of cases [617].

A study published in 2017 including 358 patients, 64 of whom (17.8%) had had recurrences, reported that 34 (53.1%) were symptomatic and 30 (46.9%) were asymptomatic. In most patients, the recurrence was detected by gynecological examination, both in symptomatic patients (50%) and asymptomatic ones (66.7%; P = 0.27). Cytological examination was able to detect only one recurrence in each of the two groups. This represents 2.9% in the symptomatic patients and 3.3 % in the asymptomatic ones (P = 0.99). Imaging techniques confirmed 10 recurrences (29.4%) in the symptomatic patients and eight recurrences in the asymptomatic ones (P = 0.77). There were no statistically significant differences between the two groups or between the different methods of detecting recurrences. Even after adjustment for potential confounders such as age or type of primary treatment, no association was detected [618]. The authors concluded that the gynecological examination was able to detect most recurrences in both symptomatic and asymptomatic patients and that all other examinations were able to detect recurrences effectively. In the authors' view, therefore, prospective studies are needed particularly for the follow-up, analyzing the follow-up intervals and follow-up examinations in relation to survival improvement, quality of life, and costs.

During the follow-up, the patient requires intensive interdisciplinary and interprofessional care and support. Depending on need, specialist physicians with oncological expertise and also other professional groups — e.g., psycho-oncologists, physiotherapists, and specialist oncology nurses — should be included. Depending on individual

need, the patient should be given information about options for further treatment and care [619], [620].

| 16.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The following points should be mentioned in discussions with the patient during the follow-up:<br>• Temporary and long-term effects of the disease and treatment<br>• Assistance available (self-help groups, psychosocial cancer advice services)<br>• Psycho-oncological / psychotherapeutic treatment options<br>• Sexuality and partnership<br>• Quality of life | |
| | Strong Consensus | |

The present section of this guideline is intended as a consensus section on the best possible ways of providing counseling, care, and support. The authors and the guideline group are aware that the state of the evidence on the benefits of follow-up is very meagre and must be regarded extremely critically. The 2013 Cochrane analysis on follow-up in cervical carcinoma was unable to identify any RCTs for inclusion. The aim was to evaluate potential benefits, potential impairments, and the costs of follow-up, as well as the best possible follow-up protocol. The authors concluded that no evidence is available [622].

Imaging in particular should be used with due consideration, since according to the current data earlier detection of a recurrence is not associated with improved survival, but is associated with a deterioration in quality of life [619]. Cytological diagnosis [623] also only has very limited validity.

In addition, follow-up is used to ensure the quality of the primary therapy. It should be noted here as well, from the point of view of health policy, that the 5-year prevalence of patients with cervical carcinoma is approximately 17,400 women (representing the number of patients in follow-up). By comparison, the 5-year prevalence of patients with breast carcinoma is 313,500 [624].

The 2017 European Society for Medical Oncology (ESMO) guideline states that there is no universally applicable follow-up regimen for patients with cervical cancer. The minimum should be a medical history and a gynecological examination (including rectal examination) carried out by a physician with experience in the follow-up of gynecological malignancies. In addition, the guideline refers to potential improvement in the early detection of recurrences with the addition of a cytological examination. Routine imaging or tumor markers in asymptomatic patients are not recommended, as the state of research is insufficient here. CT or PET-CT should only be carried out if clinically indicated. Check-ups every 3–6 months in the first 2 years and every 6–12 months in years 3–5 are recommended as a reasonable follow-up interval. After that, a return to annual screening with a gynecologic examination should be possible [625], [626].

## 16.1. Follow-up with no suspected recurrence

The following scheme for follow-up examinations was developed by the guideline group for the first 5 years after diagnosis and treatment, both for patients who have

received organ-preserving therapy (independent of tumor stage) and also for those who have undergone hysterectomy.

| 16.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Obligatory examinations should be carried out every 3 months for 3 years, and then every 6 months for a further 2 years. These include patient history, rectovaginal examination, speculum examination, and cytology. | |
| | Consensus | |

| 16.3 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Optional examinations can be carried out if there are clinically unremarkable findings (in asymptomatic patients). These include colposcopy, HPV testing, vaginal ultrasonography of the lesser pelvis, and ultrasonography of the urinary tract. | |
| | Strong Consensus | |

Follow-up is carried out in the chain of care. With higher tumor stages, in fertility-preserving surgery with a higher risk profile, and with unclear findings or results, the established practice is that follow-up is carried out alternately between the physician who carried out the primary treatment and the specialist in charge of the patient's care. A follow-up card or tumor-specific documentation is issued by the primary physician and optimally kept up to date by all of the physicians participating in follow-up care (the gynecologist, radiotherapist, and family physician) in order to ensure case-related communication.

The following three tables present details of the examinations and indications on which the recommendations are based. Further data collection or altered appointment intervals and additional examinations should be noted for patients who are taking part in research studies.

Obsolete measures include regular imaging procedures (CT, MRI, PET-CT) in asymptomatic patients and short-term tumor marker check-ups.

For explanations of the recommendations, see also sections Chapter 16.2, Chapter 16.3, Chapter 16.4, and Chapter 16.5.

From the sixth year onward, the regulations for regular check-ups in the framework of the Statutory Cancer Early Recognition Program (GKFP) apply.

**Table 16: Obligatory locoregional follow-up examinations and intervals (checked 2021)**

| Examination | Years 1-3 | Years 4 and 5 |
|---|---|---|
| Patient history[1] | 3-monthly check-ups | 6-monthly check-ups |
| Clinical examination[2] | 3-monthly check-ups | 6-monthly check-ups |
| Speculum examination and cytology (Pap)[3] | 3-monthly check-ups | 6-monthly check-ups |

[1] **History:** general (prior and ancillary diagnoses, drug intake) and tumor-specific and treatment-specific history. In particular: itching, bleeding, pain, urination problems (incontinence, urinary retention), defecation problems (incontinence, constipation), respiratory symptoms, weight loss, unilateral or bilateral leg edema, lymphedema, vaginal dryness, dyspareunia, symptoms of hormonal failure, sensory disturbances, documentation of Eastern Cooperative Oncology Group (ECOG) status and the Karnofsky index.

[2] **Clinical examination:** bimanual rectovaginal examination, precise inspection, bilateral examination of the inguinal and cervical lymph nodes (including scalene).

[3] **smears:** speculum examination and removal of a vaginal cytology sample (Pap); cervix (P+C) only in patients who have had primary radiotherapy or organ-preserving therapy. Surgical demonstration of the vaginal part of the cervix (in case of synechiae, e.g., after radio(chemo)therapy) to make assessment easier should only be carried out in individual cases after individualized consideration.

| | |
|---|---|
| **EC** | Strong consensus |

**Table 17: Optional locoregional follow-up examinations and intervals (checked 2021)**

| Investigation | Years 1-3 | Years 4 and 5 |
|---|---|---|
| HPV[4] | In special situations | In special situations |
| Colposcopy/Vaginoscopy[5] | 3-monthly check-ups | 6-monthly check-ups |

[4] **HPV testing:** for specific issues (e.g., status post cervicectomy, suspected dysplasia with "level change," status post primary R(CH)T, as Pap is difficult to assess).

[5] **Colposcopy (reflective light microscopy of the vaginal part of the cervix and vagina):** recommended at expert consensus level; carried out without staining and after acetic acid and iodine testing with a biopsy of the suspicious area. Particularly indicated if there is any suspicion of pathological findings and for early recognition of preinvasive and central invasive lesions, also after primary radio(chemo)therapy and status post organ-preserving therapy.

| | |
|---|---|
| **EC** | Strong consensus |

**Table 18: Optional extended follow-up examinations and intervals (checked 2021)**

| Investigation | Years 1-3 | Years 4 and 5 |
|---|---|---|
| Vaginal and renal ultrasound[6] | 6-monthly | 6-monthly |
| Ultrasound of the liver[7] | On clinical suspicion | On clinical suspicion |
| Port rinsing[8] | 6-monthly | 6-monthly |
| Breast diagnosis[9] | At baseline, then GKFP | At baseline, then GKFP |
| Tumor markers[10] | Not routinely | Not routinely |
| Other imaging procedures[11] | On clinical suspicion | On clinical suspicion |

[6] **Vaginal and renal ultrasound:** possible at intervals of approx. 6 months for early recognition of ureteral obstructions (status post radio(chemo)therapy, pelvic wall recurrence).

[7] **Ultrasound (upper abdomen, scalene):** only in case of clinical suspicion.

[8] **Port:** inspection of the port if present and rinsing of it at 6-monthly intervals (also if follow-up interval is > 6 months).

[9] **Breast diagnosis:** mammography, breast ultrasonography at baseline, then in accordance with GKFP guidelines.

[10] **Tumor markers:** SCC in serum in patients with squamous cell carcinoma, CEA and CA-125 in patients with adenocarcinoma only if levels were raised at the primary diagnosis, not in routine practice.

[11] **Other imaging examinations:** CT of the chest/abdomen, MRI of the pelvis, cystoscopy and rectoscopy only in case of clinical suspicion and/or in symptomatic patients. For PET examinations and PET-CT/MRI, there are no data showing a positive effect on locoregional control or overall survival.

| | |
|---|---|
| **EC** | Strong consensus |

## 16.2. History, physical examination, and cytology

Taking a detailed history makes it possible to identify sequelae of the disease or treatment in patients with cervical carcinoma. Information can then be provided about specific assistance and treatment services (see Chapters Chapter 15, Rehabilitation and Chapter 12, Supportive therapy). The genital examination not only allows rapid and easy diagnosis of atrophic phenomena (status post radio(chemo)therapy, hormonal failure), ulcerations, and recurrences, but also of lymphedema in the legs. The physical examination with palpation allows assessment of the pelvic wall and lymph-node stations (scalene, inguinal). Inflammations can be diagnosed using a pH examination and an unstained specimen and can be treated. Another important point in the patient history is sexuality (see section Chapter 15.12, Sexuality).

In contrast to the diagnosis of primary CIN and primary cervical carcinoma, it must be remembered that a benefit from cytology can only be expected in recurrent cervical carcinoma if the recurrence is central and the vaginal mucosa is infiltrated. In addition, technical analysis of the Pap smear following radio(chemo)therapy is difficult due to marked atrophic and radiogenic changes, and it often provides only little diagnostic information.

In 2011, Rimel et al. showed, in a retrospective multicenter study including 929 patients and 4167 cytological examinations, that abnormal Pap findings occur during the follow-up (particularly after radiotherapy) in one-third of patients who have had cervical carcinoma [623]. There were 147 recurrences, only 12 of which (8.1%) were detected using cytology. Cytology is a possible diagnostic method during the follow-up. However, in the absence of a further symptom-oriented clinical examination, it is by no means sufficient [627].

## 16.3. Colposcopy, HPV, and ultrasound

Similarly, it must also be borne in mind that a benefit of colposcopy can only be expected in cases of central recurrence with vaginal infiltration or in residual tumors following primary radio(chemo)therapy. For preinvasive recurrent lesions (CIN, VAIN), earlier recognition may be possible in some cases using colposcopy. There are no published data on this. Colposcopic findings are documented in accordance with the 2011 Rio Classification (http://www.ifcpc.org/images/docs/nomenclature7-11.pdf) [630].

In meta-analyses on follow-up in women who had undergone conization due to CIN 2/3, a significantly better pooled sensitivity of 93% (95% CI, 85–97%) was observed in the HPV test in comparison with cytology at 72% (95% CI, 66–78%), with similar specificity [628]. For preinvasive recurrent lesions after invasive cervical carcinoma, it can be assumed that earlier detection is possible with the HPV test, but there are no published data on this. Pap smears following cervicectomy are of limited diagnostic value [629]. Depending on the patient's HPV high-risk status, continuing check-ups at 6-monthly intervals may be considered even after the 5-year follow-up if there have been positive findings.

An ultrasound examination (vaginal, renal ultrasound) makes it possible to diagnose urinary disturbances, new ureteral stenoses, or increasing tissue in the lesser pelvis, as well as newly appearing free fluid in the pouch of Douglas.

## 16.4. Tumor markers

| 16.4 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Routine controls of tumor markers to diagnose recurrences shall not be carried out. | |
| | Strong Consensus | |

The SCC level after primary therapy shows a strong correlation with the clinical course of disease in women with squamous cell carcinoma. There is no evidence to date that an earlier diagnosis of recurrences or metastases improves the overall survival in patients with cervical carcinoma [631], [632]. Regular checking of the SCC level is therefore not recommended [632]. The guideline group also had no data available regarding the value of regular check-ups on the markers carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125) in adenocarcinomas, or neuron-specific enolase (NSE) in neuroendocrine carcinomas.

## 16.5. Imaging procedures

Imaging procedures are of no value in asymptomatic patients. Curative approaches are possible with central recurrences, which are usually diagnosed at the vaginal examination, or on vaginal ultrasound or cytology. In symptomatic patients, diagnostic procedures with which those treating the patient have the greatest personal experience should be carried out in such a way as to allow the appropriate treatment planning and monitoring of therapies. The standard procedures are CT or MRI, both with contrast administration. Cervical carcinoma is not included in the assessment of the value of PET-CT in oncology conducted by the Institute for Quality and Cost-Effectiveness in the Health-Care System (IQWiG).

No clear statements can be made regarding the value and benefit of PET-CT during the follow-up after cervical carcinoma, due to limited data (few studies, poor methodology). There are some indications that PET-CT may have a certain value in the recurrent situation, especially before exenterative treatment options or radio(chemo)therapy, and that it can influence treatment planning (see Chapter 6, Diagnosis).

An FDG-PET study including 42 patients showed a sensitivity of 82%, a specificity of 97%, and an accuracy of 92% for local recurrence of cervical carcinoma. For distant recurrences, the sensitivity was 100%, the specificity 90%, and the accuracy 94% in comparison with the final histological findings [633].

A meta-analysis published in 2018 including 707 patients from 17 studies investigated the clinical value of PET and PET-CT in patients with suspected cervical cancer recurrences. The diagnostic quality was evaluated both in relation to individuals and in relation to regions. The pooled sensitivity for PET and PET-CT was 0.97 (0.95–0.99). If the tumor marker SCC was elevated, the pooled sensitivity was 0.99 (0.93–1.00). Comparably high values were seen here in the lung, mediastinum, liver, spleen, inguinal, paraaortic and supraclavicular lymph nodes. In addition, it was shown that there was a change in treatment plan in 57% of cases. The authors concluded that PET-CT is a reliable diagnostic tool in suspected cervical cancer recurrence and can influence the subsequent treatment management [637].

A Brazilian meta-analysis published in 2019 examined the use of PET and PET-CT for staging and re-staging in patients with cervical cancer in comparison with the use of CT or MRI. It included six studies with 233 patients that investigated the detection rate for local recurrence. FDG-PET showed significantly better results (AUC 0.9882 PET vs. AUC 0.606 control; P [Mohandas, H. et al. 2017].

Another 2018 publication sums up the literature on the use of PET and PET-CT in cervical cancer. It also concludes that PET-CT is routinely used internationally in the primary setting, for evaluation of treatment response, and also during the follow-up [639].

The 2020 NCCN guideline clearly recommends PET-CT as the primary diagnostic imaging modality for patients with suspected cervical cancer recurrence — with the known methodological weaknesses of this clinical guideline [634].

In women with a clinical or imaging suspicion of recurrence, PET-CT may support the search for distant metastases [635]. However, it can only be helpful in cases in which there is a manageable disease situation in the pelvis or in the locoregional lymph nodes, and the clinical benefit of PET-CT in this situation is unclear [636].

## 16.6. Extended diagnostic procedures for suspected recurrence

| 16.5 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | If a locoregional recurrence is suspected, histological confirmation shall be obtained. | |
| | Consensus | |

Imaging diagnosis in symptomatic patients with suspected locoregional recurrences or metastases is discussed in sections Chapter 17.2, Diagnosis of local recurrence, and Chapter 18.2, Imaging. If a locoregional recurrence is suspected, then histological confirmation must be obtained in addition to the exclusion of distant metastases; prior treatments that have already been carried out must be ascertained; and the feasibility of locoregional treatment must be checked. The necessary diagnostic procedures correspond to the preliminary preoperative investigations (see also recommendations Chapter 17.1 and Chapter 17.2).

For assessment of the local findings, a gynecological examination (vaginal and rectal palpation and speculum examination), vaginal ultrasonography, renal ultrasonography, and pelvic MRI (to assess the tumor's relationship to other organs) are appropriate, as well as cystoscopy and rectoscopy if there is suspected extension of the tumor into neighboring organs. Biopsy confirmation of the recurrence should also be obtained.

To exclude distant metastases, CT of the chest and abdomen and PET-CT in special situations (for organ metastases and lymph-node metastases) and scalene ultrasound (for lymph-node metastases) can be carried out additionally, but this is increasingly being abandoned in initial re-staging in favor of whole-body imaging.

## 16.7. HPV vaccination after high-grade dysplasia or cervical carcinoma

Vaccination of girls aged 12–17 years before first sexual intercourse is currently recommended by the STIKO, and the costs are met by the statutory health insurance companies [640]. Two vaccines starting from age 9 are approved throughout Europe for both sexes, with no upper age limit. Many health insurance companies continue to reimburse HPV vaccinations on an individual case basis even beyond the interval set by the STIKO. There is evidence that HPV vaccination can still be useful even after age 18 [641], [642], [643], [490] and after a previous HPV infection in order to reduce the reinfection rate [644], [645], [646], [647], [648], [649]. The limitations of the existing data need to be taken into account and are mentioned in the studies cited. The Level 3 guideline on "Vaccine Prevention of HPV-associated Neoplasias" (AWMF register no. 082/002) and the Level 3 guideline "Prevention of Cervical Carcinoma" (AWMF register no. 015/027OL) include statements on vaccination outside of the age group recommended by the STIKO, or after prior HPV infection.

### 16.7.1. HPV vaccination after conization

| 16.6 | Consensus-based Statement | checked 2021 |
|---|---|---|
| EC | The significance of prophylactic HPV vaccination after the completion of treatment for cervical carcinoma is unclear. | |
| | Strong Consensus | |

No data are available to the guideline group regarding vaccination following invasive cervical carcinoma. Positive data have in the meantime become available on the benefit of HPV vaccination after conization with dysplasias (CIN 2+) to reduce the likelihood of recurrence.

Analyses of study populations from the phase III approval studies for both HPV vaccines show that there is protection against recurrent disease in women who were vaccinated during their HPV infection but before the development of CIN. There is no effect on the course of the active infection, but after treatment (conization), there was a 46% reduction in the rate of recurrent genital dysplasia/condylomas and a 64.9% lower rate of CIN 2+ [649]. One reason for this might be the patients' lack of immunocompetence. Following surgical treatment for dysplasia, there is a 5% risk of recurrence. However, this risk can be reduced by more than 50% through vaccine-induced immunity [649]. Similar results were seen when the HPV vaccination was administered 1 week after conization, with a reduction in the risk of recurrence from 7.2% (with the placebo) to 2.5% (in the vaccination group) [650]. All patients with recurrent CIN had positive HR-HPV findings after conization [650].

Against this background, vaccination following dysplasia or after treatment for dysplasia appears to be a possible option, although it has markedly lower success rates [641], [642], [649], [650], [651], [652], [654], [653].

# 17. Local recurrence

**Major changes in the chapter on local recurrence**

The chapter on local recurrence has been substantially changed. The recommendations have remained the same. A section on "Immunotherapy for recurrent/metastatic cervical carcinoma" has been added. The topic of hyperthermia has been moved to chapter 10, Radiotherapy. New literature references have been added to the background texts in the other sections.

*E. Wight, K. Loessl, M.C. Koch, M.W. Beckmann*

## 17.1. Epidemiology of local recurrences and metastases

In just under 50% of cases, cervical carcinoma is limited to the cervix at the time of first diagnosis. Regional lymph-node metastases (pelvic) are present in around one-third of cases, and the disease is primarily metastatic (to the para-aortic lymph nodes or with organ metastases) in 12% of cases [655]. Progression of the tumor following primary therapy for invasive cervical carcinoma may be localized, on the one hand, and persistent tumor or recurrence in the lesser pelvis after complete remission of the primary tumor can be assumed. On the other hand, pelvic lymphogenic metastases may occur (if there was no primary lymph-node extirpation or only incomplete extirpation; = locoregional recurrence), and/or para-aortic lymphogenic metastases, or there may be organ metastases. With local recurrence in the pelvis, a distinction is made between central recurrence and pelvic wall recurrence.

The recurrence rate for cervical carcinoma across all tumor stages and all forms of treatment is between 22% and 31% [662]. [663]. Risk factors for local/locoregional recurrence were found to be FIGO stage (tumor diameter, parametrial tumor invasion, metastatic involvement of pelvic lymph nodes), younger age ([Marth, C. et al. 2018], [656], [657], [86], [658]. Perez et al. in 1991 reported local recurrence rates after primary therapy with radiotherapy and after a follow-up period of at least 3 years in 1211 patients of 10% in stage Ib, 19% in stage IIa, 23% in stage IIb, 41% in stage III, and 75% in stage IVa [658]. Analysis of the recurrence rates relative to histological subtype showed that 20.6% of the recurrences were in squamous cell carcinoma, 28.6% in adenosquamous carcinoma, 33.6% in adenocarcinoma, and 42.8% in undifferentiated carcinoma [663], [657].

In 526 patients with cervical carcinoma (all stages), tumor recurred in 20% of cases within 6 months to 12 years after therapy, with 58% of the recurrences arising within the first year and 76–82% within the first 2 years after primary therapy (surgery or radiotherapy) [662], [656]. Only 6% of patients with recurrences survived for 3 years or more [662].

Risk factors for distant metastases were assessed by Fagundes et al. (1992) in the same patient population that had been available to Perez et al. (1991). In a retrospective analysis, after radiotherapy alone for invasive cervical carcinoma, distant metastases occurred in 3% after stage Ia, 16% after stage Ib, 31% after stage IIa, 26% after stage IIb, 39% after stage III, and 75% after stage IVa over the course of 10 years, depending on the primary tumor stage [659]. In addition to the FIGO stage (ingrowth of the cervical carcinoma into the uterine cavity was of particular importance), an elevated level of the SCC antigen tumor marker before the start of treatment was associated with an in-

creased probability of metastasis during the course of the disease [656]. Initial manifestations of distant metastases involved the para-aortic, supraclavicular, and inguinal lymph nodes in 11%, 7%, and 3%, respectively. Organ metastases occurred in the lung in 21%, liver in 4%, abdominal cavity in 7%, gastrointestinal tract in 4%, and bone (mainly in the spine) in 7% [659]. Distant metastases occurred in 77% of cases within 3 years and in 88% within 5 years after completion of radiotherapy [659]. In a retrospective survey of 177 patients (FIGO stages IB–II) after radical hysterectomy and pelvic lymphadenectomy, Wang et al. (1999) found that the prognosis was unfavorable if recurrences arose, with a 5-year survival of 10.1% [660]. Lymph-node involvement during primary therapy and the presence of adenocarcinoma or adenosquamous carcinoma were found to be unfavorable prognostic factors. Hong et al. (2004) confirmed the poor prognosis for patients with local recurrence and distant metastasis (with 10% and 11% 5-year survival rates, respectively), but were able to identify subgroups of patients who had a significantly better prognosis and even a chance of cure. These were patients with central local recurrence after radiotherapy of squamous cell carcinoma of the uterine cervix that could be surgically extirpated (5-year survival: 29%). The extent of the local recurrence was of considerable importance for the prognosis: the 5-year survival if the local recurrence was confined to the cervix was 22%; if the tumor had spread to the parametria, uterus, and/or vagina it was 9%; and if the pelvic wall was reached, it was 4%. Subgroup analysis of patients with distant metastases showed a 5-year survival rate of 27% with metastases to the para-aortic lymph nodes, whereas patients with supraclavicular lymph-node metastases or with organ metastases had died by that time point. The authors concluded that in the presence of para-aortic lymph-node metastases, curative treatment options (radiotherapy, radiochemotherapy) were still available, whereas if the metastases were beyond that point, a palliative situation was present [656]. If the time interval between the completion of primary treatment (radiochemotherapy) for gynecological carcinomas (two-thirds of which were cervical carcinomas) and recurrence treatment by exenteration was less than 2 years, the study by McLean et al. (2001) showed a significantly shorter survival period (8 vs. 33 months) than if the recurrences arose later (> 2 years)[661]. Nicotine abuse also had a significant impact on survival [661]. The treatment approach should be decided on an individual basis for each patient with local recurrence, in the setting of an interdisciplinary tumor conference.

Tumor follow-up appointments after primary therapy for cervical carcinoma should be closely scheduled (every 3 months) during the first 3 years, since three-quarters of all recurrences arise within the first 2 years [664]. After that 6-monthly check-ups are indicated for a further 2 years before moving on to annual check-ups 5 years after the primary treatment.

The symptomatic triad of weight loss, leg edema, and pelvic pain, especially if accompanied by an aqueous and bloody vaginal discharge, is highly suspicious for the presence of local recurrence and should prompt appropriate diagnostic measures. The development of ureteral obstruction during tumor follow-up is rarely a sequela of postradiogenic fibrosis, and is usually due to tumor recurrence. A repeated positive HPV test (in the cytological smear) during follow-up after radiotherapy for cervical carcinoma is associated with an increased risk of local recurrence [665].

## 17.2. Diagnosis of local recurrence

| 17.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | If a local recurrence develops, the appropriate imaging diagnostic procedures shall be carried out to exclude distant metastases and for treatment planning. | |
| | Strong Consensus | |

If there is a suspicion of recurrent tumor or tumor persistence in the lesser pelvis following primary treatment for cervical carcinoma, histological confirmation must be obtained and the extent and location of any metastases that are present must be clarified (see recommendations 17.5 and 18.2) — since, depending on the FIGO stage of the primary tumor, the probability of distant metastases is increased by a factor of 4–17 in case of local recurrence [667].

Depending on the location, the diagnosis can be made using vaginal ultrasound, CT, or MRI [91], [666]. The data on PET-CT in the recurrent situation are unclear [668].

## 17.3. Treatment for local recurrence

| 17.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | With local recurrences, treatment decisions should be based on the following points:<br>• Patient's general condition (comorbidities)<br>• Location and extent of the local recurrence<br>• Presence of distant metastases<br>• Extent of metastasis development<br>• Type of primary therapy/prior therapies<br>• Patient's request | |
| | Strong Consensus | |

The generally unfavorable prognosis for patients in the recurrent situation, in which individually adjusted treatment modalities are often used, makes it difficult to set up research studies, and this is reflected in the small numbers of randomized controlled studies available. The present section is again a consensus-based section that is not based on systematic research and evaluation of research studies.

Treatment decisions on recurrent tumors should be based on the location and extent of the local recurrence, the presence of distant metastases, the extent of any metastases, and the type of primary therapy that has been administered, as well as the patient's general condition (comorbidities) and her wishes. In addition, risk factors (e.g., age under 45, HPV persistence after primary therapy, HIV status) should also be taken into consideration [656], [665], [669]. The treatment approach should be established on an individual basis in the setting of an interdisciplinary tumor conference. Treatment should take place in a specialized (tumor) center. Table 18 provides an introductory overview of the possible treatment options in various situations.

**Table 19: Treatment options in recurrent cervical carcinoma (modified 2021)**

| Prio treament | local recurrence/locoregional recurrence | |
|---|---|---|
| | **Central** | **Lateral** |
| Cervicectomy | Radical HE<br>Exenteration<br>R(CH)T[/RT] ± BT | R(CH)T ± BT<br>[poss. LEER] |
| Radical HE | R(CH)T[/RT] ± BT<br>Exenteration | R(CH)T(/RT) ± BT<br>[LEER] |
| Radical HE + RT/R(CH)T | Exenteration± IORT | CT ± bevacizumab<br>[LEER ± IORT] |
| RT/R(CH)T | Exenteration± IORT<br>[radical HE± IORT] | CT ± bevacizumab<br>[LEER ± IORT] |

Legend: BT, brachytherapy; CT, chemotherapy; HE, hysterectomy; IORT, intraoperative radiotherapy; LEER, laterally extended endopelvic resection; RT, radiotherapy; R(CH)T, radio(chemo)therapy; [...], experimental.

| | |
|---|---|
| **EC** | Consensus (92.3% [12/13]) |

### 17.3.1. Treatment for a central tumor recurrence after primary surgical treatment

| 17.3 | Consensus-based Statement | checked 2021 |
|---|---|---|
| **EC** | In case of a central recurrence in a patient who has not previously undergone radiotherapy, exenteration or radiochemotherapy are possible. | |
| | Strong Consensus | |

| 17.4 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| **EC** | Due to its lower morbidity, radiochemotherapy should be carried out in patients with no previous radiotherapy who develop a recurrence. | |
| | Strong Consensus | |

Some 30–45% of all cervical carcinoma recurrences after radical hysterectomy develop at the vaginal stump, located centrally in the lesser pelvis [646]. The treatment of choice is radiotherapy [195] by analogy with studies on the primary treatment of cervical carcinoma [377], [380], [381], [672], with response rates of up to 74% [673], with both monochemotherapies and combined chemotherapy schemes being used in addition to percutaneous radiochemotherapy ± brachytherapy. There are no randomized controlled studies comparing radio(chemo)therapy with radiotherapy alone in this situation [671]. Retrospective studies argue in favor of a therapeutic advantage for combination treatment with regard to tumor regression, progression-free survival, and overall survival [671], [673]. In comparison with exenteration, radiotherapy is associated with lower morbidity, and for this reason it is usually the preferred treatment option. The success of treatment depends on the one hand on the size of the recurrence. Ito et al. (1997) reported a 10-year overall survival rate of 72% with nonpalpable tumors, 48% with a tumor diameter  3 cm [674]. On the other hand, the success of treatment is also influenced by the location of the recurrence. Jain et al. (2007) described a 5-year overall survival rate of 55% when the vaginal stump alone was affected. With pelvic lymph-node involvement, the 5-year overall survival fell to 12.5% [675]. If the recurrent tumor reached the pelvic wall, the 5-year overall survival in a study by Ijaz et al. (1998) declined from 69% to 18% [474]. In the group of patients included, it was also found that the histology of the recurrence had a significant influence on the 5-year survival: 51% with squamous cell carcinoma, 14% with adenocarcinoma [676]. In a retrospective study, new radiotherapy techniques (intensity-modulated radiotherapy, IMRT; three-dimensional radiotherapy) held out the promise of better 5-year survival (35% vs. 21%) in comparison with conventional radiotherapy in the treatment of locoregional tumor recurrences, and a meta-analysis [670] reported fewer side effects (gastrointestinal, urogenital) due to the ability to focus on the target volumes, together with reduced radiation injury to the surrounding area. Prospective data on patient-relevant end points (progression-free survival and overall survival) are at present still awaited. A corresponding study ("The re-irradiation of recurrent cervical cancer by IMRT," NTC03170570) is recruiting patients.

| 17.5 | **Consensus-based Recommendation** | **checked 2021** |
|---|---|---|
| **EC** | Exenteration must only be carried out in cases of recurrence if resection with healthy margins appears possible and there are no distant metastases. | |
| | Strong Consensus | |

Exenteration is the method of second choice with central tumor recurrences after radical hysterectomy. In view of the morbidity associated with exenteration, this procedure should be carried out with curative intent. Exceptions to this rule may be present with existing or immediately imminent fistula formation (e.g., with tumor involvement of the bladder or bowel), in which case exenteration can also be carried out with palliative intent (see section Chapter 17.3.7, Palliative treatment for local recurrence when surgery with healthy margins is not possible). The scope of the exenteration must be based on the extent of the recurrent tumor, as tumor-free resection margins must be achieved. An R1 resection is associated with a marked deterioration in the prognosis. Berek et al. (2005) reported an overall survival rate after 5 years of 61% when local recurrences were excised with healthy margins; when there was tumor involvement of the resection margins, none of the patients was still alive after 3 years [678]. A distinc-

tion is made between anterior, posterior, and total exenteration, as well as supralevatory and infralevatory exenteration and exenteration with vulvectomy [682]. If it is feared even in advance of a planned exenteration operation that tumor removal with healthy margins may not be possible, then the indication for this burdensome procedure must be questioned [679]. If the recurrence is in a central or purely vaginal location, a radical colpectomy procedure with or without the creation of a neovagina (e.g., sigmoid) is an option [680]. Pretherapeutic (neoadjuvant) chemotherapy [681], intraoperative radiotherapy [422], or extension of the operation in the form of laterally extended endopelvic resection (LEER) may be considered if the recurrent tumor is growing towards the pelvic wall [677].

### 17.3.2. Treatment for a central recurrence after primary or adjuvant radiotherapy or radio(chemo)therapy

The frequency of recurrent or persistent tumors after primary radiotherapy or radio(chemo)therapy for squamous cell carcinoma of the uterine cervix is reported to be 32% [689]. Forty-three percent of the recurrences are in the lesser pelvis and the remaining 57% are either in the para-aortic and supraclavicular lymph nodes or are distant metastases, located mainly in the lung, bone, or liver. Risk factors reported for local recurrence include young age ([Arbyn, M. et al. 2012].

The treatment of choice with a central tumor recurrence after primary or adjuvant radiotherapy or radio(chemo)therapy is exenteration. According to the review by Peiretti et al. (2012), including nearly 3000 women treated from the years 1957 to 2010, the 5-year overall survival rate is 33.8% [671]. Higher rates of cure, with a 56–61% 5-year overall survival rate, are possible in a selected group (age under 70, no histological evidence of resection margin involvement, no involvement of the pelvic wall or rectum) [678], [683]. In view of the high level of morbidity associated with exenteration surgery after prior radiotherapy or radio(chemo)therapy — with an overall complication rate of 44% (mainly with early complications consisting of wound infection and late complications involving fistulas) — the selection process must be restrictive [678], [683]. Distant metastases should be excluded before the operation. The time interval between primary therapy and the diagnosis of recurrence correlates significantly with survival after exenteration. Marnitz et al. (2006), for example, reported a 5-year overall survival rate of only 17% when the recurrence developed within the first 2 years after the first diagnosis; if the interval was 2–5 years or more than 5 years, the 5-year survival rates increased to 28% and 83%, respectively [684]. Para-aortic and possibly also pelvic lymphogenic metastases (the details in the literature are controversial here) [685], [686] aggravate the prognosis after exenteration. Exenteration is not useful if — despite preoperative negative diagnosis — the intraoperative situation shows peritoneal tumor seeding, para-aortic lymph nodes affected by metastases, or tumor involvement of the pelvic wall (described as occurring in around one-third of cases by Estape et al. 1999) [687]. Possible alternative treatment measures in this situation include LEER or IORT [195], [677], although both of these options must be regarded as experimental.

A small tumor recurrence limited to the uterine cervix or persistent tumor after primary radiotherapy/radiochemotherapy can be treated with an extended hysterectomy instead of exenteration [688]. However, the postoperative complication rate was high, at 42% (mainly vesicovaginal and rectovaginal fistulas, ureteral injuries, postoperative bladder dysfunction). The 5-year overall survival rate in this group was 72%.

### 17.3.3. Treatment for pelvic wall recurrence after primary surgical therapy

Radiotherapy or radiochemotherapy can be administered with curative intent not only with central recurrences, but also with pelvic wall recurrences. However, the success rate of the treatment is lower (5-year overall survival with central recurrences 55–69%, with pelvic wall recurrences 13–28% [675], [676], [693]). The relevant factors (time interval between primary therapy and recurrence, tumor size, etc.) also have to be established in advance of salvage radiotherapy/radiochemotherapy in order to estimate the prognosis, and organ metastases in particular have to be excluded. Initial studies have been published on optimizing radiotherapy/radiochemotherapy in the recurrent setting by using alternative radiotherapy techniques (IORT, 3D radiotherapy, intensity-modulated whole-pelvis radiotherapy, stereotactic body RT, imaging-guided interstitial brachytherapy, 3D conformal brachytherapy, interstitial brachytherapy), also affecting combinations with systemic therapies and/or with locoregional hyperthermia [692], [673], [125], [690], [694]. There is a notable rate of late complications in 15% of cases, in the form of rectovaginal fistulas, strictures (rectum, ureter) and chronic pain [425], [695]. One treatment alternative with pelvic wall recurrences involves laterally extended endopelvic resection (LEER), possibly after neoadjuvant chemotherapy and in combination with IORT. The indication for IORT is justified by the assumption that in the case of narrow or involved resection margins, local control might be improved by IORT. However, practical experience with these methods is very limited. Prospective randomized studies are lacking so far [681], [677], [696], [691].

### 17.3.4. Treatment for pelvic wall recurrence after primary radiotherapy or adjuvant radiotherapy/radiochemotherapy

| 17.6 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| **EC** | Repeat radiotherapy at a curative dosage must not be administered in the previously irradiated volume. | |
| | Strong Consensus | |

In a review article, Jurado et al. (2010) reported, on radical surgery (exenteration) in patients with pelvic wall recurrences after primary RT, that resection with healthy margins (R0) was possible in 29% of cases. In contrast, R0 resection for central recurrences was successful in 65% of patients [679]. Tumor-specific survival was significantly associated with tumor-free resection margins and local tumor control and was 14.9% for patients with pelvic wall recurrences and 27% for those with central recurrences, after a median observation period of 115 months. The treatment-related morbidity associated with radical pelvic wall surgery was extremely high, at 73% [679]. Publications by Höckel et al. (2003, 2008, 2012) presented LEER, a treatment approach aiming at attempted cure in patients with pelvic wall recurrences after radio/radiochemotherapy for a selected population [677], [698], [699]. The following criteria for performing LEER were defined: curative goal/prolongation of life; realistic prospect of local tumor control (tumor-free resection margins, no involvement of the sciatic foramen, no peritoneal tumor seeding); no distant metastases detectable; size of the recurrent tumor less than 5 cm; no multifocality in the recurrence; time interval between primary therapy and recurrence diagnosis more than 5 months; no pelvic, para-aortic, or inguinal lymph-node metastases; age under 70; no significant comorbidity). The approach included

surgery of embryonic developmental structures with complete resection of lateral tissue structures (muscle, vessels, nerves) as far as the pelvic bone. In a nonrandomized, single-center study, It a 5-year overall survival rate of 61% was achieved, although the recurrent tumor was attached to the pelvic wall in three-quarters of the patients, sometimes with development of a hydronephrosis [698]. LEER is a very complex surgical procedure, with a 70% rate of severe complications (wound dehiscence, anastomotic insufficiency, necrosis of the advancement flap, abscess formation, thromboembolism) [697]. Concomitant use of IORT is limited due to prior primary therapy. Chemotherapy is significantly less effective with recurrences arising within the radiation field [453].

### 17.3.5. Treatment for secondary para-aortic lymph-node metastases

The incidence of isolated para-aortic lymph-node recurrences after primary therapy (surgery or radio(chemo)therapy) for cervical carcinoma is reported to be 2–12% [662], [656], [659]. The prognosis is regarded as very unfavorable, as other distant metastases are frequently present at the same time. With para-aortic lymph-node recurrences, the time interval between the primary treatment and the development of the recurrence has prognostic significance. The data presented by Chou et al. (2001) show that a 5-year overall survival rate of 51% can be achieved when radiochemotherapy is administered (unless the recurrence is located in the original irradiation field for primary radiotherapy/radiochemotherapy) [700]. Singh et al. (2005) found that if the para-aortic lymph-node metastases are clinically symptomatic (leg edema, sciatic pain, hydronephrosis) after radiochemotherapy (none of the patients received the full dosage), the prognosis is poor (all seven patients died within 1.5 years); whereas asymptomatic patients had good chances of cure following complete salvage radiochemotherapy (45–50 Gy, cisplatin 40 mg/m2, q7d; 5-year overall survival 100%, again in seven patients) [701]. A retrospective study including 50 patients with isolated lymph-node recurrences reported an overall 3-year survival rate of 47% and an overall 5-year survival of 36.2% for the whole group [702]. The 3-year overall survival was strongly dependent on the treatment administered: after radiochemotherapy, 85.7%; after surgery, 66.7%; after chemotherapy, 48.8%; after radiotherapy, 41.3%; after best supportive care, 0%. Prognostically significant factors for treatment failure were found to be the age of the patients (> 57), a raised value for the tumor marker SCC-Ag at the time of recurrence diagnosis, and more than three lymph-node metastases being found. Although the conclusions of these studies regarding treatment success are concordant, reservations are appropriate in view of the small numbers of cases.

### 17.3.6. Systemic therapy in local/locoregional recurrences and distant metastases

Patients with locoregional tumor recurrences and/or metastases should have their cases discussed at an interdisciplinary tumor board and treated by a specialized team before systemic therapy is started. Systemic therapy may be with curative intent (neoadjuvant, adjuvant) or palliative. Maintaining or promoting the patient's quality of life is of central importance when establishing the indication for palliative systemic therapy. Organ metastases are usually only suitable for palliative chemotherapy, with low response rates. In rare individual cases, mainly isolated pulmonary or hepatic metastases, metastasis surgery or radiofrequency ablation are also available as options.

Systemic treatment for metastatic cervical carcinoma is discussed in section Chapter 18.3.5, "Drug treatment in the metastatic situation."

### 17.3.7. Palliative treatment for local recurrence when surgery with healthy margins is not possible

| 17.7 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | A surgical intervention can be carried out with palliative intent for a local recurrence, to relieve tumor-specific symptoms. | |
| | Strong Consensus | |

When there are simultaneous distant metastases or when the local recurrence has extended to the pelvic bones or abdominal cavity, the situation is a palliative one. Exenteration surgery is only indicated in exceptional cases, as the extent of the procedure, the associated morbidity, and the long recovery period of 3–6 months are only justified if the patient can also expect a longer survival period and/or an improved quality of life after the operation. This is usually only the case with an R0 resection. However, exenteration may be justified in specific situations. These include tumor-related or treatment-related symptoms that are severely impairing the patient's quality of life (fistula formation, radiation-related hemorrhagic cystitis/proctitis, painful conditions) [705], or an effort to achieve local control of the tumor process despite systemic disease. Various studies have reported 5-year survival rates of 17–19% after palliative exenteration surgery [704], [703].

| 17.8 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | A radiotherapeutic intervention can be carried out with palliative intent for a local recurrence that is not operable with healthy margins, to relieve tumor-specific symptoms. | |
| | Strong Consensus | |

Pain and vaginal bleeding are typical indications for palliative radiotherapy of recurrent cervical carcinoma. The treatment scheme and dosage must be based on the patient's individual condition. Tumor-related bleeding can be well treated with hemostyptic radiation [707], but embolization is preferable if there is acutely life-threatening bleeding. Bone metastases occur in 1–4% of cases in patients with cervical carcinoma, and are most often (36%) located in the lumbar spine. Evidence of bone metastases is associated with a poor prognosis (median overall survival 23 months) [708], [709]. Bone metastases must be differentiated from radio-osteonecroses in the radiation field. As a result of pain symptoms, or if there is a risk of fracture, the metastases often require therapy, and for this reason palliative radiotherapy may be indicated, taking into account the possible radiation fields from the primary treatment. In addition, systemic bisphosphonates or anti-RANKL antibody (denosumab) are available in accordance with the indications for other tumors [709]. In the case of brain metastases, in addition to steroid therapy to reduce peritumoral edema, whole-brain radiotherapy is occasionally used in combination with stereotactic radiosurgery (gamma knife) [706].

The palliative treatment options with recurrent tumor or metastatic disease must be discussed on an interdisciplinary basis and individually with the patient, taking into account her preferences, and implemented in a symptom-oriented way. Embolization,

decompression procedures for intestinal obstruction (stenting, colostomy, PEG tube), pain treatment, and in general psycho-oncological care, may be administered in addition to chemotherapy and radiotherapy in this situation.

## 17.3.8. Value of hyperthermia in cervical carcinoma

This section discusses the current state of the data for women with recurrent or metastatic cervical carcinoma. Hyperthermia in the primary situation is dealt with in Chapter 10, Radiotherapy. The results for the use of radiochemotherapy in combination with local/regional hyperthermia in recurrent or metastatic cervical carcinoma have been summarized in a review by Burchardt et al. (2018) [702]. The effect of hyperthermia treatment for recurrent tumor or after metastasis was evaluated differently in two papers by the same research group. In a more recent retrospective study including 38 patients [709] with local recurrence of cervical carcinoma after primary radiotherapy, the combination of chemotherapy with hyperthermia significantly increased the response rate in comparison with chemotherapy alone (72% vs. 40%).

The study results on the value of hyperthermia in the treatment of cervical carcinoma can be summed up as follows:

- The value of combining hyperthermia with radiotherapy, chemotherapy, or radiochemotherapy in recurrent or metastatic cervical carcinoma is unclear. Further clinical studies are needed in order to answer this question.

## 17.3.9. Immunotherapy for recurrent/metastatic cervical carcinoma

Various options for immunotherapy in cervical carcinoma are currently being evaluated [710]. The evidence available to date is based entirely on small studies and case reports.

*Therapeutic vaccines*

Prophylactic vaccines against HPV infection induce antiviral antibodies using the L1 antigen of the viral capsid. The vaccines used for treatment have a cytotoxic effect on tumor cells via activation and proliferation of T cells, mediated by the tumor antigens E6 and E7 that are expressed. A therapeutic vaccine using live but attenuated bacteria as the vector (Listeria monocytogenes) achieved a response rate of 11% (response duration 9.5 months) in patients with relapsed or progressive cervical carcinoma, with no improvement in the effect when combined with cisplatin. Typical side effects of therapeutic vaccines are flu-like symptoms with chills, fever, vomiting, and fatigue [710].

*Checkpoint inhibitors*

Checkpoint inhibitors block inhibitory receptors of the immune system and can therefore lead to the activation of cytotoxic cells, increasing their antitumor effect. Increased expression of PD-L1 (programmed death ligand-1) on tumor-infiltrating lymphocytes (TIL) may indicate that blocking PD-1/PD-L1 might be a treatment option in cervical carcinoma. In phase I and II trials, pembrolizumab — the antibody targeted against PD-1 — was associated with a 17% response rate in patients with inoperable or metastatic cervical cancer after unsuccessful prior systemic therapy. The treatment-related toxicity was high, in 70–75% of the patients, particularly since severe adverse events occurred in 39% of them (fever, edema, rash, musculoskeletal pain, anemia, colitis, Guillain–Barré syndrome) [711]. On the basis of these data, pembrolizumab was approved by the U.S. Food and Drug Administration (FDA) in June 2018 for the treatment of recurrent and metastatic cervical cancer (see section Chapter 18.3.5.2).

*Adoptive cell transfer*

Adoptive cell transfer involves autologous return transfer of tumor-infiltrating T cells (TIL) directed against tumor antigens (E6, E7) in patients with cervical carcinoma after the cells have been amplified in vitro (with or without genetic modification). A report including nine patients with metastatic cervical carcinoma, previously treated with chemoradiotherapy, described a response rate of 3/9, with two patients showing persistent remission 22 and 15 months, respectively, after the treatment [712].

With the exception of pembrolizumab, the approaches described above are experimental studies. Market approval is currently pending.

# 18. Distant metastases

**Major changes in the chapter on distant metastases**

This chapter has been revised. The following statements have been amended or expanded: 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, and 18.9.

*T. Fehm, P. Mallmann, M.C. Koch, M.W. Beckmann, A. Sturdza, C. Grimm, A. Letsch, V. Hagen*

## 18.1. Epidemiology in metastases

In the new 2018 FIGO classification, the para-aortic lymph nodes are designated as N1 — i.e., regional disease — and no longer as M1 metastases. FIGO has thus standardized the individual classifications, since para-aortic lymph nodes are also classed as regional lymph nodes in endometrial and ovarian cancer [144], [713].

A distinction is thus made between regional lymph-node metastases and distant metastases. In addition, extensive peritoneal spread into the pelvic serosa or primary infiltration of neighboring organs is often referred to as a locally advanced stage (see Table 9). Since the rate of treatment failure here is high — i.e., the rate of early recurrences and the trend toward persistent tumor and also secondary early organ metastases — patients with locally advanced tumor stages (≥ FIGO stage IIB) and those with metastases are often combined in many studies (see Chapter 17 and Table 9). This, and the small number of patients in absolute terms who have isolated organ metastases without simultaneous local recurrence, means that conclusions regarding the choice of treatment and its effectiveness can only be drawn to a limited extent.

## 18.2. Imaging

In patients with local recurrences of or metastases from cervical carcinoma, regional imaging diagnosis is carried out with pelvic MRI or vaginal ultrasonography to assess the extent of pelvic tumor spread. Extrapelvic spread also has to be diagnosed using CT of the abdomen and chest. PET-CT is mainly used to differentiate between benign findings and recurrence/metastasis. This applies in particular to the assessment of enlarged/suspicious lymph nodes (see Chapter 6).

If pulmonary findings suspicious for malignancy are identified during the metastatic work-up, it should be borne in mind that in addition to a recurrence of the cervical carcinoma, the patient may also have a primary lung carcinoma as a differential diagnosis. Lim et al. (2010) noted this in 29% of cases examined, particularly when a history of nicotine abuse was known [714]. Histological confirmation is therefore desirable if possible.

# 18.3. Treatment options in distant metastases

## 18.3.1. Isolated distant metastases

| 18.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | With an isolated metastasis, the option of local therapy in the form of surgery, local irradiation, or locally destructive treatment procedures should be considered on an interdisciplinary basis at the tumor conference. | |
| | Strong Consensus | |

Despite systematic research (see the guideline report), no RCTs, nonrandomized controlled prospective studies, or prospective comparative observational studies were identified on this issue (see section 2.2.6). The recommendation is based on the 2008 SIGN guideline and must be regarded as an expert consensus. If multiple metastases have been excluded with the relevant imaging diagnostic methods, then it may be considered whether surgical resection of the metastasis is possible on the basis of the imaging findings [715].

There is evidence from a retrospective single-center analysis that with an isolated distant metastasis in strictly selected patients, complete surgical resection of the metastasis or locally destructive procedures such as radiofrequency ablation can lead to an increase in the progression-free survival and overall survival [717]. No prospective randomized and controlled studies or matched-pair controlled studies are available on this topic. In patients with a metastasis in whom surgery is not possible and who have not previously received any radiotherapy or radio(chemo)therapy, or in whom the metastasis is located outside of the previous irradiation field, the indication for radiotherapy, with radio(chemo)therapy if appropriate, should be examined. Radio(chemo)therapy of metastases is carried out in the same way as primary therapy, in the form of monotherapy with cisplatin [716].

## 18.3.2. Regional metastases (pelvic/para-aortic)

With the primary presence of regional lymph-node metastases, the irradiation field is based on the histologically identified pattern of spread.

With isolated secondary para-aortic metastases, the option of surgical resection should be examined using imaging, with laparoscopy or exploratory laparotomy if appropriate. If surgical resection is not possible, there is an option here for isolated para-aortic radio(chemo)therapy (see also section Chapter 17.3.5).

## 18.3.3. Osseous metastases

In contrast to regional metastases, systemic metastases (pulmonary, hepatic, osseous) usually only present the option of systemic drug therapy (see Chapter 11, Drug treatment). In the case of (isolated) osseous metastasis, the possibility of local radiotherapy and/or osteo-oncological therapy (bisphosphonate therapy, denosumab) should be examined, especially if there is a risk of fracture. If the lesion is located in a previously irradiated area, osseous radionecrosis should be excluded.

### 18.3.4. Disseminated metastases

| 18.2 | Evidence-based Statement | checked 2021 |
|---|---|---|
| LoE<br>1+ | With disseminated metastases or metastases that are not accessible for local therapy, there is an indication for administering palliative drug therapy. | |
| | [453]; [718]; [708] | |
| | Strong Consensus | |

| 18.3 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR<br>B | Palliative drug therapy should be administered in the form of platinum-containing combination chemotherapy. | |
| LoE<br>1+ | [453]; [456]; [718]; [708] | |
| | Strong Consensus | |

With metastases that are not isolated and are not suitable for local treatment in the form of surgery or radiotherapy, palliative drug treatment is an option. This is capable of achieving a response and reducing the progression of the disease [453]. It can lead to a longer overall survival with the combination therapy (cisplatin plus topotecan) in comparison with cisplatin monotherapy [719]. In a phase III study including 253 patients, carboplatin/paclitaxel was found to have a comparable effect to cisplatin/paclitaxel, with better tolerability. There were no significant differences in the overall survival (HR 0.99; 90% CI, 0.79 to 1.25) or overall response rate (63% versus 59%) [456]. No comparisons with “best supportive care” are available [453]. With metastases in a previously irradiated area, chemotherapy should be avoided due to the significantly lower response, or it can be discussed with the patient on an individual basis [453]. Two other older meta-analyses support the view that, with a generally small absolute prolongation of the overall survival, cisplatin-containing combination therapies appear to be the most promising option with metastases [718], [708].

## 18.3.5. Drug treatment in the metastatic situation

| 18.4 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR<br>**0** | Following radio(chemo)therapy with cisplatin as a "radiosensitizer," cisplatin administration can be repeated.In recurrences/metastases after prior chemotherapy with cisplatin, repeat administration of cisplatin can be carried out in combination with topotecan, paclitaxel, gemcitabine, or vinorelbine, or carboplatin can be administered with paclitaxel. | |
| LoE<br>**1+** | [453]; [456]; [720] | |
| | Strong Consensus | |

| 18.5 | Evidence-based Statement | checked 2021 |
|---|---|---|
| LoE<br>**1+** | Combination therapies are associated with higher rates of morbidity and toxicity than the monotherapy.Combination therapies have a better response rate.In relation to overall survival, a slight absolute survival benefit has so far only been demonstrated for the combination of cisplatin with topotecan. | |
| | [453]; [718]; [719] | |
| | Strong Consensus | |

According to the 2012 Cochrane analysis, systemic drug therapy for metastases should optimally include administration of cisplatin [453]. Following radio(chemo)therapy with cisplatin as "radiosensitizer," cisplatin administration can be repeated at 50 mg/m2. An increase in the dosage to 100 mg/m2 every 21 days, or 20 mg/m2 on days 1–5 every 21 days, increased the response rate, but not the survival. Combination chemotherapies with cisplatin significantly improved the response rate and progression-free survival in comparison with monotherapy. It was only with a combination of cisplatin plus topotecan that a slight improvement in the overall survival was achieved [454]. When all of the combination therapies were compared with monotherapy, no improvement in the overall survival was observed in this meta-analysis [453].

In comparison with cisplatin-containing monotherapy, combination therapy with cisplatin as expected increases the risk of side effects. The Cochrane review calculated the following toxicity rates (based on the 2006 Common Terminology Criteria for Adverse Events, CTCAE) for combination therapy with cisplatin in comparison with monotherapy:

- Neutropenia, grade 3/4 (four studies, n = 1073): risk ratio 0.04; 95% CI, 0.02 to 0.12 (1.4% vs. 36.7%)
- Thrombocytopenia, grade 3/4 (four studies, n = 1104): risk ratio 0.16; 95% CI, 0.05 to 0.48 (2.1% vs. 18.3%)
- Infections, grade 3/4 (two studies, n = 552): risk ratio 0.42; 95% CI, 0.22 to 0.81 (4% vs. 9.8%)

- Renal dysfunction, grade 3/4 (three studies, n = 980): risk ratio 0.81; 95% CI, 0.46 to 1.41 (5% vs. 5.5%, n.s.)
- Neuropathy, grade 3/4 (two studies, n = 552): risk ratio 1.39; 95% CI, 0.45 to 4.33 (2.5% vs. 1.8%, n.s.)

Data on quality of life were only reported in three of 26 studies. Despite the increased toxicity data, the available data showed no significant differences between cisplatin-containing monotherapy and combination therapy with cisplatin [453].

Despite the increased toxicity with the combination therapies, patients who respond to palliative chemotherapy have hardly any reduction in their quality of life [453].

According to the comparative studies available, combination therapy with cisplatin and paclitaxel is superior to the other chemotherapy regimens with regard to response rates and progression-free survival [721], [722]. In the absence of superiority for any of the four drug combinations, leading to the research studies being stopped, the end point of survival was not pursued. It was extrapolated that the combinations of cisplatin with topotecan and cisplatin with paclitaxel are equipotent. The recommended dosages are: cisplatin 50 mg/m2, paclitaxel 135 mg/m2 every 3 weeks. Administration of cisplatin in combination with gemcitabine is an alternative [718].

Long et al. (2005) observed a slightly but significantly longer overall survival (6.5 vs. 9.4 months; HR 0.76) with combination therapy with cisplatin/topotecan in comparison with cisplatin monotherapy [719]. The study was also included in the 2012 Cochrane analysis. However, due to the incomplete and inadequate presentation of overall survival data in the other studies (e.g., often with the response rate as the primary end point), it was not possible to carry out a pooled analysis. The results of the individual studies were therefore presented descriptively in the Cochrane analysis [453].

| 18.6 | Evidence-based Recommendation | new 2021 |
|---|---|---|
| GoR **0** | As an alternative to cisplatin, carboplatin can also be used in monotherapy and combination therapy. | |
| LoE **1+** | [456]; [720] | |
| | Strong Consensus | |

| 18.7 | Evidence-based Recommendation | new 2021 |
|---|---|---|
| GoR **B** | Cisplatin should be preferred in patients who have not previously received it. | |
| LoE **1-** | [456] | |
| | Strong Consensus | |

Cisplatin can be replaced with carboplatin. This applies in particular to patients with impaired renal function and patients who have already received cisplatin as part of radiochemotherapy. In the JCOG-0505 study, patients received either six cycles of cisplatin (50 mg/m2) d2 / paclitaxel (135 mg/m2) d1 or carboplatin AUC5 d1 / paclitaxel (175 mg/m2) d1 every 3 weeks [456]. Among the patients, 43% or 50% had already received radiochemotherapy with cisplatin or carboplatin, respectively (only two patients). There were no significant differences in the overall survival (HR 0.99; 90% CI, 0.79 to 1.25) or in the overall response rate (63% versus 59%). Significantly less neutropenia and rates of renal failure, nausea, and vomiting were seen in the carboplatin arm. However, rates of thrombocytopenia and sensory neuropathy were higher. A retrospective analysis showed that previous administration of cisplatin affected the treatment response to carboplatin. There were no differences in survival in the cisplatin-pretreated group. By contrast, patients with no previous chemotherapy who received carboplatin tended to have a shorter survival (median survival 13 months versus 23 months; HR 1.57; 95% CI, 1.06 to 2.23). A systematic review including a total of 17 studies with over 1181 patients confirmed the JCOG-0505 results. Although there was a significant difference between cisplatin/Taxol and carboplatin/Taxol in relation to the PFS (6.9 months versus 5 months; P = 0.03), there were no differences in relation to OS (12.87 months versus 10 months; P = 0.17)) or RR (48.5% versus 49.3%) [720].

For patients who have already received cisplatin in primary or adjuvant radio(chemo)therapy, carboplatin is thus also available in palliative chemotherapy as an alternative to repeat treatment with cisplatin [723].

### 18.3.5.1. Targeted therapy

| 18.8 | Evidence-based Recommendation | modified 2021 |
|---|---|---|
| GoR **B** | Patients with metastatic or recurrent/persistent cervical cancer should receive concurrent bevacizumab — independently of prior treatment with radio(chemo)therapy — for first-line palliative chemotherapy with cisplatin/paclitaxel or topotecan/paclitaxel. | |
| LoE **1+** | [724] | |
| | Consensus | |

The value of adding bevacizumab administration (15 mg/kg, q3w) to platinum-containing (cisplatin/paclitaxel) or platinum-free combination therapy (topotecan/paclitaxel) was investigated in the four-arm randomized GOG study 240 (phase III). In the final analysis, it showed that the addition of bevacizumab (a VEGF inhibitor) to palliative chemotherapy (cisplatin/paclitaxel or topotecan/paclitaxel) resulted in a combined survival benefit for both therapies of 3.5 months (13.3 months vs. 16.8 months; HR 0.77; 95% CI, 0.062 to 0.95; P = 0.007) and an improved progression-free interval (8.2 months vs. 6 months; HR 0.68; 95% CI, 0.56 to 0.84; P = 0.0002), as well as higher response rates (49% vs. 36%; P = 0.003). A negative rebound effect (shorter survival after bevacizumab) was excluded, as there were no significant differences in survival after progression ("postprogression survival"; 8.4 months vs. 7.1 months; HR 0.83; 95% CI, 0.66 to 1.05; P = 0.06) [724]. On the basis of these data, bevacizumab received approval in Germany in 2015 for this indication with the corresponding chemotherapy regimens. In everyday clinical practice, however, cisplatin is often replaced with carboplatin due to the comparable efficacy (JCOG-0505 study) and its lower rates of neutropenia and renal insufficiency. A recently published network meta-analysis has confirmed this approach on the basis of the presumed equivalent effectiveness [457].

Both chemotherapy regimens (cisplatin/paclitaxel with or without bevacizumab vs. topotecan/paclitaxel with or without bevacizumab) were found to have similar overall survival, but a significantly shorter progression-free survival was observed in the topotecan/paclitaxel group [23]. No direct comparison is available of the administration of cisplatin/paclitaxel/bevacizumab versus the only combination therapy approved in Germany — cisplatin/topotecan — in this situation. The chemotherapy partners for bevacizumab in the GOG-240 study [23] were selected on the basis of the data published by Monk et al. [3], which were also mentioned in the 2012 Cochrane meta-analysis [23].

The additional administration of bevacizumab leads to increased side effects, which include high blood pressure (CTCAE grade II or higher: 25% vs. 2%), thromboembolic events (CTCAE grade III or higher: 8% vs. 1%), neutropenia (CTCAE grade IV or higher: 36% vs. 26%) and gastrointestinal fistulas (grade III or higher: 3% vs. [He, D. et al. 2015]. Febrile neutropenia (CTCAE grade III or higher), gastrointestinal bleeding (CTCAE grade III or higher), and pain (CTCAE grade II or higher) occurred in both groups, without any significant differences [229]. The patients' quality of life was assessed in this study using a combination of individual questions from various instruments ((FACT-Cx-TOI, BPI, FACT/GOG-NTX). No significant differences between the study arms were observed with regard to quality of life up to 9 months after the first cycle [229].

### 18.3.5.2. Second-line therapies in cervical carcinoma

For patients who have progression after first-line therapy, monotherapy is usually recommended if treatment is desired. There are currently no treatment studies available showing an overall survival benefit in this setting in comparison with best supportive care. Possible treatment options include: Nab-paclitaxel (125 mg/m2 d1, 8, 15 q3w) [727], vinorelbine (30 mg/m2, d1, 8, q3w) [728], ifosfamide (1.2 mg/m2, d1–5, q4w) [729], topotecan (1.5 mg/m2 d1–5, q3w) [730], pemetrexed (500 mg/m2 q3w) [726], or irinotecan (125 mg/m2 q1w) [725].

| 18.9 | Consensus-based Statement | new 2021 |
|---|---|---|
| EC | In patients with PD-L1-positive metastatic cervical carcinoma, checkpoint inhibitors are another therapeutic option. | |
| | Consensus | |

Another option for the second-line or a higher line of therapy is the checkpoint inhibitor pembrolizumab (200 mg q3w) for patients with PD-L1-positive cervical cancer (CPS score ≥ 1) (see section 7.3) [711]. In the single-arm Keynote 028 trial (phase Ib), the overall response rate with pembrolizumab (10 mg/kg q2w) in the cohort of multiply pretreated cervical carcinoma patients with PD-L1 expression was 17% (95% CI, 5% to 37%) with a median duration of response of 5.4 months (4.1–7.5 months). With regard to treatment-related side effects, rash (21%) and pyrexia (17%) were the most common. Testing for a PD-L1 should be carried out during the first line of therapy, if possible. Currently, testing for PD-L1 can take several days. It is therefore advisable to perform testing at the onset of metastasis, in order to avoid a time delay in the second line.

The results of the single-arm Keynote 158 study (phase II) were published in 2019 and led to the approval of pembrolizumab in the USA [458]. This was a basket trial that included 77 cervical cancer patients with positive PD-L1 expression and progression during or after first-line therapy. The patients received pembrolizumab for a period of 2 years, or until progression. The overall response rate was 14.6% (95% CI, 7.8% to 24.2%), with two complete responders in the PD-L1-positive cohort after first-line treatment failure. The estimated 6-month PFS rate was 25%, with a median overall survival of 11 months (95% CI, 9.1 to 14.1 months) in the PD-L1-positive overall cohort (9.4 months in the overall group; 95% CI, 7.7 to 13.1). The main side effects noted were hypothyroidism (10.2%) and loss of appetite (9.2%), as well as fatigue (9.2%) and diarrhea (8.2%). Grade 3/4 toxicities occurred in 12.2% of the patients. The main immune-mediated toxicities were hypothyroidism (11.2%) and hyperthyroidism (9.2%). In June 2018, the FDA approved pembrolizumab for the treatment of recurrent or metastatic PD-L1-positive cervical cancer after failure of first-line treatment, based on the results of Keynote study 158 in this subgroup. In Germany, the health-insurance companies require applications to be made for cost coverage if the treatment is indicated and the patient has a positive PD-L1 status.

# 19. Palliative medical care

**Major changes in the chapter on palliative medical care**

This chapter has been altered. It has been revised and shortened with reference to the cross-sectional guideline (Level 3 guideline on "Palliative Care for Patients with Incurable Cancer," AWMF register no. 128/001OL, version 2.1, January 2020). The topics "Management of colostomy/stoma" and " Pain" have been added.

*C. Stromberger, M. Kloke, A. Letsch*

More detailed discussions on this topic are available in the Level 3 guideline "Palliative Care for Patients with Incurable Cancer" (AWMF register no. 128/001OL, version 2.1, January 2020). The following recommendations and statements are borrowed from that guideline.

| 19.1 | Evidence-based Recommendation |
|---|---|
| GoR<br>**A** | **Evidence-based recommendation from S3 guideline Palliative Medicine (AWMF Reg. No. 128/001OL, Version 2.1 - January 2020)**<br>Following a diagnosis of incurable cancer, all patients ***shall*** be offered palliative care, regardless of whether tumor-specific therapy is being provided. |
| LoE<br>**1-** | [731]; [732]; [733]; [734]; [735]; [736]; [737]; [738] |
| | Strong Consensus |

| 19.2 | Consensus-based Recommendation |
|---|---|
| **EC** | **Consensus-based recommendation from S3 guideline Palliative Medicine (AWMF Reg. No. 128/001OL, Version 2.1 - January 2020)**<br>In the case of incurable cancer, the physical, psychological, social, and spiritual needs, as well as burdens and information requirements, of patients and their relatives ***shall*** be assessed repeatedly and reassessed again if the clinical situation changes. |
| | Strong Consensus |

| 19.3 | Evidence-based Recommendation |
|---|---|
| GoR<br>**A** | **Evidence-based recommendation from S3 guideline Palliative Medicine (AWMF Reg. No. 128/001OL, Version 2.1 - January 2020)**<br>Patients with incurable cancer and a highly complex situation ***shall*** receive specialized palliative care. |
| LoE<br>**1-** | [735]; [736]; [738] |
| | Strong Consensus |

Palliative medicine (synonymous with palliative care) is defined as an approach aimed at improving the quality of life of patients and their families who are facing the problems associated with a life-threatening disease [744], [745], [746], [747], [748], [739], [740], [741], [483], [742], [743], [742], [471], [484], [484]. This is achieved by preventing and alleviating suffering, through early recognition and careful assessment and treatment of pain and of other problems of a physical, psychosocial and spiritual nature [744], [745], [746], [747], [748], [739], [740], [741], [483], [742], [743], [742], [471], [484], [484].

The WHO definition of palliative care implies a holistic approach, taking into account all four dimensions of the human being. This also justifies the inclusion of the family in treatment efforts, which do not end with the patient's death but include the mourning phase. Palliative care requires a multiprofessional and interdisciplinary team approach. Early integration (based on the principle of involving palliative care specialists as systematically as possible in parallel with tumor-modifying treatment) has proven to be relevant for quality of life and, in individual cases, survival time, and it is now considered the standard of care. Palliative care affirms life and recognizes dying as a normal process, so that its goal is neither to delay nor to accelerate death.

Patients with advanced cervical carcinoma in whom curative treatment is not possible (with surgery, radiochemotherapy, or surgery with adjuvant radiochemotherapy) or with distant metastases (M1) can usually be assumed to have progressive disease leading to death.

## 19.1. Patients' needs

The foremost goal in palliative medical treatment — individual quality of life — can only be evaluated and defined by the patient herself [749], [751]. Burdens for the patient may be of a physical, psychosocial, spiritual, and existential nature [746], [747], [748], [739], [740], [741], [483], [742], [471], [742], [743], [484], [484]. The need for support should be regularly assessed together with the patient using suitable validated and multidimensional instruments (see also the Level 3 guideline on palliative medicine).

A high regard for the patient's autonomy and involvement is a prerequisite for the treatment of these patients and is one of the essential components of palliative medicine. In addition to the routine recording of the patient's own assessment of her quality of life and symptomatic burden, this also includes supportive monitoring of treatment decisions in compliance with the medical ethical principles of beneficence, nonmaleficence and appropriateness (justice). Information about palliative medical options

should be provided in the context of promoting and supportively monitoring treatment decisions. Relatives or other persons whom the patient trusts should be included in the discussions. To enable the patient to have her person of trust express her presumed will to the best extent possible even if disturbances of consciousness occur during the course of the disease, counseling and support are offered for establishing treatment wishes and goals, and if appropriate for drawing up an advance health-care directive ("living will") and precautionary power of attorney. These should be expressed as specifically as possible and should include plans for probable or possible emergency situations during the course of the disease.

With regard to other palliative medicine considerations, independent of the underlying diagnosis, reference may be made to the GGPO guideline on "Palliative Medicine" (AWMF register no. 128/001OL, version 2.1, January 2020) [750]. This provides a detailed discussion covering multiple organs regarding symptomatic control, palliative care, psychosocial support, and available care structures.

## 19.2. Relatives' needs

The inclusion of the patient's relatives is a central aspect of palliative care. The patient has the option to have relatives or other persons of trust included in discussions in accordance with her own wishes. However, the wishes and anxieties of the relatives themselves, as well as their needs for information, for example, also play an important role. With regard to other aspects of palliative medicine involving looking after relatives, reference may be made to the GGPO guideline on "Palliative Medicine" (AWMF register no. 128/001OL, version 2.1, January 2020) [750].

## 19.3. Palliative and hospice care

Palliative medical care covers medical control of symptoms, palliative nursing, and psychosocial support form the onset of incurable cancer up to death [746], [747], [748], [739], [740], [741], [759], [742], [471], [742], [471], [484], [484], [752]. In the palliative situation, all of the steps required are oriented towards the patient's individual treatment and life goals [746], [484]. The availability of palliative treatment services in accordance with need is the result of a consent process lasting many years [746]. Staged palliative care is the necessary prerequisite for varying the intensity of treatment according to the symptomatic burden, while at the same time ensuring the continuity of palliative support [753], [754].

Symptomatic control, palliative nursing, and psychosocial and spiritual support represent four dimensions of palliative treatment here, which must be included in every high-quality palliative care service, independently of the level of specialization at which the service is located [747]. To ensure timely integration of support services, palliative care is also provided simultaneously with tumor-specific therapies — ideally at the same time as (i) disease-modifying treatments with the primary therapeutic goal of prolonging life or achieving sustained symptomatic relief (*palliative therapy*); (ii), for prophylaxis against or treatment of side effects of the disease or therapies for it (*supportive therapy*) [744], [745], [739], [484], [755], [756], [757], [758]; and (iii) for psychosocial and psycho-oncological care tailored to need.

In patients who continue to have a severe physical, psychosocial, or spiritual burden despite palliative medicine measures, specialized palliative medical care is useful. This is provided by a specialist palliative care team (*Spezialisierte ambulante Palliativversorgung*, SAPV) in the outpatient field and for inpatients by the hospital's palliative

care service, supplemented by the outpatient hospice service (Level 3 guideline on "Palliative Medicine in Incurable Cancer," AWMF register no. 128/001OL, version 2.1, January 2020) [746], [484].

## 19.4. Treatment for specific symptoms

Patients with cervical carcinoma often have a severe symptomatic burden even in the locally advanced stage. Complex pain syndromes, malignant lymphedema, gastrointestinal symptoms (from constipation to malignant intestinal obstruction), malignant wounds, depression, and fatigue are common. The general and specific principles of treatment for these symptoms are presented in detail in the expanded GGPO guideline on "Palliative Medicine in Incurable Cancer" (AWMF register no. 128/001OL, version 2.1, January 2020) [750].

In the following, malignant lymphedema is discussed specifically in patients with cervical carcinoma and, for frequently occurring symptoms or symptom complexes, reference may be made to the relevant chapters in the expanded GGPO guideline on "Palliative Medicine in Incurable Cancer" (AWMF register no. 128/001OL, version 2.1, January 2020) [750].

### 19.4.1. Symptomatic treatment for malignant lymphedema

Secondary lymphedema in the context of cancer is mostly of multifactorial origin: surgical interventions, particularly lymphadenectomy, status post radiotherapy/radiochemotherapy, obstruction of the lymphatic drainage pathways by tumor, and post/infectious [760]. No data are available on the prevalence of lymphedema in the lower extremities.

Malignant lymphedema significantly limits the quality of life for the affected patients. It leads to immobility, causes pain, and prevents the wearing of clothing. It can lead to significant volume shifts with electrolyte imbalance and protein loss, as well as erysipelas. In extreme cases, it causes compartment syndrome, with a risk of losing the limb.

#### 19.4.1.1. Detection and evaluation

The pillars of basic diagnosis are taking a medical history, inspection, and palpation, and they should be performed in this order. In the presence of comorbidities relevant for differential diagnosis, such as previous cardiac diseases, leg vein thrombosis, post-thrombotic syndrome, or hypo-/dysproteinemia, and/or inconclusive results of the clinical examination, appropriate additional procedures should be performed in order to confirm the diagnosis, depending on the patient's general condition and her resilience.

#### 19.4.1.2. Treatment

Malignant lymphedema (MLE) is a chronic clinical picture that requires treatment. Treatment for MLE differs from therapy for primary and secondary lymphedema of nonmalignant origin in several respects [760]. The basic treatment consists of skin care and if necessary skin cleansing. In reversible MLE, manual lymphatic drainage followed by compression therapy may be used. Complex decongestive therapy is always contraindicated if the return flow of the mobilized fluid will lead to new problems, such as an increase in the volume of the interstitial space (ascites, pleural effusion, pericardial effusion), deterioration of organ function (cardiac insufficiency), reduction in arterial blood flow (e.g., peripheral arterial occlusive disease, PAOD), risk of thrombus spread, and hematoma formation in the presence of cellular or humoral coagulation disorders.

Particularly in the palliative situation, the patient's burden of therapy should be in acceptable proportion to the potential gain. This issue must be considered together with the patient. It has been shown that patients' self-answered questions on quality-of-life impairment correlate with objective functional impairment and assessments of extent [761].

Surgical intervention in the lymphatic drainage system is not indicated in MLE.

If lymphatic fluid leaks spontaneously, the patient's quality of life is severely impaired and infection is highly probable. This condition can be prevented by targeted percutaneous lymphatic drainage. For this purpose, after local anesthesia (optional), small needle puncture incisions with a depth of 0.3–0.5 mm are usually made at four to eight sites on the extremity. These are then treated using a bag system such as that commonly used for neonatal stomas. In addition, a special form of manual lymphatic drainage can be used, in which the MLE is mobilized in the direction of the puncture channels. Mild compression therapy with anti-thrombosis stockings (with holes at points of the pouch tips for drainage) may be used as a supportive measure. This procedure, which is also highly effective in relation to patient mobility and pain relief, very rarely results in infections. Compartment syndromes can also almost always be prevented in this way. In extreme cases, several liters of fluid per day can be drained from the legs under high tissue pressure. This procedure was first described in 2009 and has undergone minor technical modifications by users over the years. Since then, it has undergone numerous modifications, although the principle of drainage of interstitial fluid via stab incisions in the skin has remained the same [762].

### 19.4.2. Constipation

For the definition, detection, assessment and therapeutic principles in constipation, reference may be made to Chapter 13 of the expanded GGPO guideline on "Palliative Medicine in Incurable Cancer" (AWMF register no. 128/001OL, version 2.1, January 2020).

### 19.4.3. Malignant intestinal obstruction (MIO)

For the definition, cause, diagnosis and treatment options in MIO, reference may be made to chapter 14 of the expanded GGPO guideline on "Palliative Medicine in Incurable Cancer" (AWMF register no. 128/001OL, version 2.1, January 2020).

### 19.4.4. Management of colostomy / stoma

Patients who receive an ostomy experience sometimes drastic changes, with a significant reduction in their quality of life. There appears to be a clear correlation between stoma-related complications and a deterioration in the patient's quality of life [763]. Comprehensive stoma care has preoperative and postoperative roles. For example, the future site of the stoma can be marked preoperatively with a trial plate to allow good intraoperative positioning. Postoperative provision of the patient with the relevant information should be offered by stoma therapists as early as possible and should allow safe self-care. If this is still difficult to start with or is limited by other factors, the aim should be to achieve an individually adapted care approach in the outpatient setting.

Stoma-related complications are particularly distressing. These include secondary bleeding, hematoma formation, stoma edema, skin irritation, ulceration, and stoma necrosis. During the later course, stress may occur due to stoma prolapse, stoma retraction, stoma stenosis, and parastomal hernias. These complications may be due to

patient factors such as obesity and increased intra-abdominal pressure, as well as surgical and technical reasons. In addition, the risk of electrolyte disturbances, dehydration, and renal failure must also be considered in the palliative situation.

### 19.4.5. Malignant wounds

For the definition, detection, assessment, and treatment principles in malignant wounds, reference may be made to Chapter 15 of the GGPO guideline on "Palliative Medicine in Incurable Cancer" (AWMF register no. 128/001OL, version 2.1, January 2020).

### 19.4.6. Tumor-related cloaca formation

In the advanced local or metastatic situation, tumor-related infiltration of the bladder or rectum may lead to fistula formation and subsequent cloaca formation. Depending on the overall situation, exenteration with palliative intent for symptomatic control may be useful in such situations. The usefulness and feasibility of such a measure should be carefully discussed and weighed up in consensus with the patient, especially in the palliative situation. In individual cases, such operations can even lead to a prolongation of life and provide a better initial situation for other palliative treatment options. During the discussion, the patient's level of suffering is the decisive factor, and an individual assessment of the balance between the risk of surgical mortality and the massive burden of cloaca formation is necessary.

If surgical resection or exenteration does not appear possible or reasonable, an alternative urinary and fecal diversion via a suprapubic catheter or colostomy should be evaluated as an effective method of symptom control. Even in the presence of distant metastases, these measures are often capable of alleviating the distressing effects of cloaca formation and achieving significant short-term improvement in the patient's quality of life.

### 19.4.7. Pain

For the definition, detection, assessment, and treatment principles in tumor pain, reference may be made to Chapter 9 of the GGPO guideline on "Palliative Medicine in Incurable Cancer" (AWMF register no. 128/001OL, version 2.1, January 2020).

Special mention should be made here of the special situation of tumor-related nerve infiltration in the lesser pelvis. Tumors in the pelvis can lead to damage to the sacral plexus, lumbar plexus, or entire leg plexus. In some cases, this can even be an initial symptom of advanced tumor disease.

As a rule, plexus lesions are caused by direct tumor spread, but they can also be caused by adjacent bone or lymph-node metastases. Symptoms are often intensifying and usually severe pain, along with progressive sensorimotor deficits in the supply area of the leg plexus. In addition, the affected leg may become dry and overheated if the sympathetic nerve trunk is affected. Incontinence may be an indication of bilateral involvement. The diagnostic work-up includes rectal, gynecological, and, if necessary, urological examinations, abdominal ultrasound, and CT/MRI of the pelvis.

Treatment, also with palliative intent, can include surgical measures, radiotherapy, and chemotherapy. Adequate pain therapy is obligatory in all cases. In view of the neuropathic pain component that is often present, this may be complex and should include a multimodal pain approach (see the chapter on tumor pain in the Level 3 guideline on palliative medicine; AWMF register no. 128/001OL, version 2.1, January 2020).

### 19.4.8. Depression

For the definition, detection, assessment, and treatment principles in depression, reference may be made to Chapter 17 of the GGPO guideline on “Palliative Medicine in Incurable Cancer” (AWMF register no. 128/001OL, version 2.1, January 2020).

### 19.4.9. Fatigue

For the definition, detection, assessment, and treatment principles in depression, reference may be made to Chapter 10 of the expanded GGPO guideline on “Palliative Medicine in Incurable Cancer” (AWMF register no. 128/001OL, version 2.1, January 2020).

# 20. Family planning

**Major changes in the chapter on the family planning**

During revision of the guideline, this chapter has been updated as a separate chapter taken from Chapter 8. The content of the chapter has been revised.

*L. Lotz, M.C. Koch, M.W. Beckmann*

| 20.1 | Consensus-based Recommendation | new 2020 |
|---|---|---|
| EC | Women with early-stage cervical cancer who wish to have children shall be offered fertility-preserving treatment options. | |
| | Strong Consensus | |

The recommendations made in this chapter are based at the expert level, as well as the current consensus-based guideline on fertility preservation in oncological diseases (AWMF register number 015/082, version 1.0, September 2017), as there are insufficient data to allow evidence-based recommendations [764].

In patients in the reproductive phase of life (under the age of 40) with cervical carcinoma, fertility preservation plays an important role in the treatment approach, due to improving survival rates in the early stages and the postponement of family planning to a later phase of life.

## 21. Surgical procedures for organ preservation in cervical carcinoma

In patients with squamous cell carcinoma or adenocarcinoma of the cervix in FIGO stages IA1 L1 V0, IA2 V0, or IB1 and IIA1 V0 ≤ 2 cm and who wish to have children, radical cervicectomy with permanent cerclage is a fertility-preserving procedure [765]. Histopathological evidence of tumor-free pelvic lymph nodes is a prerequisite for this form of treatment. Neuroendocrine cervical carcinomas are frequently associated with recurrence, distant metastases, and low 5-year survival rates, and are therefore not suitable for radical vaginal cervicectomy (see section Chapter 8.6.2).

The adequate oncological safety of radical vaginal cervicectomy (RVC) in comparison with radical hysterectomy has been confirmed in several retrospective studies [766], [767]. Radical abdominal cervicectomy (RAC) may lead to a larger parametrial width in comparison with RVC [768]. However, parametrial infiltration is observed in only 0.4–0.6% of cases in cervical carcinomas less than 2 cm with N0 L0 V0 and stromal infiltrations less than 10 mm [315], [769]. It therefore remains questionable whether the length of the resected parametria plays a decisive role in these stages and whether radiotherapy offers any advantages over simple cervicectomy or conization. Various smaller studies of simple trachelectomy or conization have reported a low overall recurrence rate [777], [770].

Pregnancy rates after radical cervicectomy for cervical cancer vary from 24% to 66% in the literature [771], [772]. This is due to the different techniques used in the analyses and the numbers of women who actually hope to become pregnant after radical cervicectomy. According to Speiser et al. [771], the pregnancy rate after RVC is not significantly different in comparison with patients without previous surgery. Fifty of 76

women who sought pregnancy after RVC became pregnant (65.8%). In a systematic review by Bentivegna et al. [772], the fertility and live birth rates in 2777 patients with 944 pregnancies after radical cervicectomy were 55% and 70%, respectively. The live birth rate did not differ relative to the cervicectomy technique used (RVC 67% [308/460], RAC 68% [120/175], and 78% [50/649] with robot-assisted cervicectomy).

The main risk after radical cervicectomy is an increased rate of miscarriage and preterm delivery due to premature membrane rupture in chorioamnionitis. The risk of preterm delivery is 26.6–57%, with a significantly higher risk after RAC [772]. After radical cervicectomy, there is an increased risk of ascending infection and cervical insufficiency during pregnancy, with a risk of miscarriage or preterm delivery, due to the shortened cervix. Cervical stenosis occurs in 15% of cases, with problems of hematometra and also impaired fertility [773], [774].

In FIGO stages IA1 and IA2 without risk factors, conization with cervical curettage or simple cervicectomy can also be performed. The pregnancy rates are 71–75%, with an increased risk of second-trimester miscarriage in comparison with the general population (6% vs 1.6%) [777]. The rate of preterm birth appears to be much lower after conization/simple cervicectomy in comparison with radical cervicectomy. In a meta-analysis of 347 women, the risk of preterm birth was 6.8% (1.5–15.5%) vs. 26.6% (19.6–34.2%) [766].

For FIGO stage IB1 cervical carcinoma that is ≥ 2 cm, the use of neoadjuvant chemotherapy (NACT) followed by conization or cervicectomy with pelvic lymphadenectomy for organ preservation is increasingly being investigated. An analysis by Pareja et al. [775] included 394 patients with cervical carcinomas 2–4 cm in size and radical cervicectomy. The recurrence rate after RAC was 3.8% relative to all sizes and 6% for tumors larger than 2 cm, while after radical vaginal cervicectomy it was 4.2% (including all tumor sizes) and 17% for tumors larger than 2 cm, and after neoadjuvant chemotherapy followed by radical cervicectomy it was 7.6%. The highest pregnancy rates were achieved after neoadjuvant chemotherapy and radical cervicectomy (NACT+RT 30.7% vs. RVC 24% vs. RAC 16.2% [775]). In a systematic review by Bentivegna et al, pregnancy rates of 49% (22/61) were achieved after NACT and conization and 38% (39/61) after radical cervicectomy. It was also found that the preterm delivery rate was lower in patients with NACT than after RVC or RAC (11/71 [15%] vs. 113/285 [39%] and 59 /104 [57%], respectively; P [Committee, Ontario Guidelines Advisory et al. 2008]. Neoadjuvant chemotherapy combined with fertility-preserving surgery (conization/simple cervicectomy or radical cervicectomy ) for cervical carcinoma 2–4 cm in diameter is not currently standard, with case numbers that are still low and a lack of long-term follow-up data. However, the method may be discussed as an experimental procedure in individual cases in women who hope to have children.

## 21.1. Fertility protection methods (ovariopexy, cryopreservation of oocytes and ovarian tissue)

If radiochemotherapy is planned, ovariopexy is a measure that can preserve ovarian function in terms of both endocrine function and fertility (see Chapter 10, Radiotherapy). Radiotherapy has substantial effects on ovarian function. A radiation dosage of as little as 2 Gy to the ovaries (LD50) reduces follicular density by half [780]. The radiation effect on the ovaries is heavily age-dependent [781]. In 97.5% of women aged 30

years, a radiation dosage of 14.3 Gy leads to the complete elimination of ovarian function. Ovariopexy in young premenopausal patients before the start of radio(chemo)therapy, alongside modern techniques, can achieve a significant reduction in the ovarian dosage [778], [275]. Various surgical techniques have been described in the literature. Due to the inhomogeneity of the patient groups and the lack of prospective randomized studies, no reliable conclusions can be drawn in comparing the different techniques, although cranial transposition is probably the safest technique for reducing the radiation dose in pelvic irradiation. A meta-analysis including 32 publications and a total of 1189 patients reported a success rate of 80.8% (min. 17%, max. 95%) in relation to preserved ovarian function [782]. The height at which the ovaries are suspended is thought to be one of the strongest prognostic factors for preservation of ovarian function. The ovaries should be at least 2 cm above the iliac crest [783]. The risk of ovarian ischemia, which led to amenorrhea in 4% of the patients regardless of the radiation dosage, should be considered to have limited relevance in relation to the benefits of this treatment [794]. Although the overall effectiveness of ovarian transposition in preserving ovarian function is considered to be high, reports of pregnancy after radiotherapy for cervical cancer are rare [784]. Since ovariopexy usually requires complete separation of the adnexa from the uterus, assisted reproduction measures must be considered after the completion of oncologic therapy [785]. Reversing the procedure is technically difficult and is associated with a high risk of functional ovarian loss. In addition, irradiation of the uterus significantly reduces the chances of pregnancy. Organ doses to the uterus in excess of 45 Gy result in significant damage and often cause uterine infertility [779]. For women with uterine infertility (hysterectomy or uterine radiation damage) but with preserved ovarian function or cryopreserved oocytes beforehand, the option of surrogacy is available. However, surrogacy is prohibited in Germany under the Embryo Protection Law. An alternative for patients after hysterectomy is uterus transplantation. Worldwide, 13 healthy children have now been born after uterus transplantation [786], [787]. One patient underwent uterus transplantation after hysterectomy for cervical carcinoma and had two pregnancies [770]. Patients who have had organ transplantation are at increased risk of recurrence due to immunosuppression [773]. No data after uterus transplantation are available for patients in whom immunosuppressants were administered in a time-limited setting until explantation of the organ.

Prior to radiochemotherapy or neoadjuvant chemotherapy, fertility-preserving options include cryopreservation of oocytes and/or ovarian tissue.

Cryopreservation of fertilized and unfertilized oocytes is one of the established fertility protection measures in women. The success rate depends on the age at the time of cryopreservation and the underlying ovarian reserve. According to registry-based calculations, the chance of birth per stimulation and cryopreservation in women aged [Peppercorn, J. M. et al. 2011], [795]. A time window of about 2 weeks for hormonal stimulation with oocyte retrieval needs to be taken into account until the start of cytotoxic therapy.

Ovarian tissue cryopreservation is also an established method for restoring fertility after cancer treatment. The procedure can be performed at very short notice before cytotoxic therapy at any time in the cycle, and thus usually does not lead to any delay in oncological therapy. A total of over 120 births have been achieved worldwide after orthotopic transplantation of cryopreserved ovarian tissue [788], [789], [790], [791], [792]. The birth rate is currently about 30–35%. After radiotherapy of the uterus, a probably much lower pregnancy rate must be expected due to the uterine damage, although no figures on this are available. In addition, the risk of ovarian metastases

must be taken into account during transplantation, since with autotransplantation of ovarian tissue there is a potential risk of causing a recurrence with the cryopreserved tissue. Ovarian metastases in early-stage cervical carcinoma without risk factors are rare, but the risk is significantly higher with adenocarcinoma than with squamous cell carcinoma (5.31% vs. 0.79% in stages IB–IIa ) [793].

For further information on the individual methods and success rates of fertility-protective measures, reference may be made to the consensus-based guideline on fertility preservation in oncological diseases (AWMF register no.: 015/082).

# 22. Cervical carcinoma during pregnancy

**Major changes in the chapter on cervical carcinoma during pregnancy**

This chapter has been completely revised and transferred from a previous subsection into a separate chapter. No recommendations have changed. The literature has been comprehensively supplemented and updated.

*P. Wimberger, F.A. Stübs, M.W. Beckmann, M.C. Koch*

Approximately 4500 new cases of cervical carcinoma occur in Germany annually, with around one-quarter of the cases being in patients under the age of 35, so that there is a risk of cervical carcinoma in pregnancy [796]. The reported incidence of cervical carcinoma in pregnancy is low, ranging from 0.02% to 0.9% [797].

A distinction needs to be made between an initial diagnosis of cervical carcinoma before pregnancy, but in women who wish to have children, and an initial diagnosis of cervical carcinoma when pregnancy is already present. In this chapter, only the procedure for a first diagnosis of cervical carcinoma and simultaneous pregnancy is discussed. The data situation for an early cervical carcinoma outside of pregnancy with a desire to have children later, involving fertility-preserving procedures, is discussed in Chapter 20.

## 22.1. Diagnosis of high-grade dysplasia and invasive cervical carcinoma during pregnancy

During pregnancy the portio changes due to physiological hormonal influences. The cervix shows a strong increase in size towards the end of pregnancy and the transformation zone becomes more visible due to eversion of the endometrium. This allows for better visual assessment but can be confused with neoplastic changes [798]. Regardless, if pregnancy is detected, a cytological check is recommended as part of the maternity guideline.

Often cervical carcinoma in pregnant women is asymptomatic, but when symptoms do occur, they include fetid yellowish fluoride or contact bleeding. In advanced stages (≥ FIGO stage IIB), symptoms such as urinary retention and constipation may occur [798].

| 21.1 | Evidence-based Recommendation | checked 2021 |
|---|---|---|
| GoR **A** | During pregnancy, any cytological suspicion of higher-grade dysplasia or carcinoma shall be clarified using colposcopy and biopsy. | |
| LoE **2+** | [799] | |
| | | |

A Pap smear is obligatory during prenatal care. The validity of cytology during pregnancy is the same as outside of pregnancy. Women who do not otherwise take part regularly in cancer screening can thus be reached during pregnancy in particular. It is important to note the pregnancy on the cytology request, so that the cytologist does not misinterpret the physiological changes in the epithelium [800].

Abnormal Pap smears must be clarified using colposcopy (with a targeted biopsy if appropriate) [799]. The sensitivity and specificity of targeted biopsies during pregnancy are 83.7% and 95.9%, respectively [800]. Complications such as secondary bleeding (1–3%), premature delivery, and rupture of the amniotic membranes are very rare [800].

Conizations are only indicated starting in the second trimester of pregnancy when there is colposcopic or macroscopic suspicion of invasion. Reported risks here include a 5% rate of bleeding during the first two trimesters and 10% in the third trimester; miscarriage in up to 25%; premature delivery in 12%; and infections in 2%. The lowest risk of bleeding and miscarriage is in the second trimester, mainly between the 14th and 20th gestational weeks. Laser conization appears to be superior to other surgical methods in relation to the range of side effects [313], [800]. Laser vaporization and endocervical curettage are not indicated during pregnancy [800], [799], [801], [802].

The FIGO stage is determined on the basis of the clinical examination. Staging of invasive cervical carcinoma is carried out using ultrasound by an experienced ultrasonographer [94], with MRI and CT examinations in addition starting in the second trimester only after the indication has been very strictly established and following detailed consideration of the risk–benefit profile [800]. Lymph-node staging is carried out using MRI, with a good correlation between pathology and morphology [803] or using laparoscopic lymphadenectomy with low maternal and neonatal morbidity. Alternatively, lymphadenectomy can be performed as an open procedure as part of the cesarean operation [802], [804].

## 22.2. Epidemiology of and treatment planning for cervical carcinoma in pregnancy

Cervical carcinoma is the most frequent gynecological malignancy in pregnancy, with an incidence of 0.1–12 per 10,000 [802]. In Western industrialized nations, the incidence is 10–15 per 100,000 pregnancies. Around 70–80% of cervical carcinomas are diagnosed at FIGO stage I. The requirement for treatment depends on the stage of the disease, lymph-node status, histological subtype, gestational age, growth dynamics, acute symptoms (e.g., bleeding) and the patient's desire to have children and preserve fertility [802]. Randomized clinical trials are not possible, and the evidence is therefore based on case series, case reports, and expert opinion. Interdisciplinary treatment in a level 1 perinatal center and gynecological cancer center should be required [802]. There is no evidence that pregnancy accelerates cervical cancer. The stage-adapted, tumor type–specific and tumor size–specific prognosis for pregnant patients is comparable with that in nonpregnant patients [806], [805].

### 22.2.1. Treatment options for cervical carcinoma in pregnancy relative to tumor stage and gestational age

The prognosis during the early stages (up to stage IB) seems to be similar to that in nonpregnant women [805], [822].

In the case of histologically confirmed CIN III or carcinoma in situ, one can await the end of the puerperium with tightly scheduled close-meshed colposcopic and clinical check-ups until surgical therapy can then be performed.

In cases of microinvasion (stage IA1 or IA2), a delay in therapy is acceptable without influencing the course of the disease, but regular clinical check-ups on the local findings are required [807], [808]. In FIGO stages IA1–IA2, conization can be recommended between the 14th and 20th weeks of gestation, with colposcopic check-ups conducted every 4–8 weeks thereafter, bearing maximum oncological safety in mind [807], [808]. The risk of bleeding is increased before gestational week 14 and after gestational week 20.

Laparoscopic lymphadenectomy for staging provides important information on the prognosis as early as stage IA2 in the presence of risk factors such as G3 and/or L1 and/or V1, but also at stage IB. Lymphadenectomy is possible and safe in gestational weeks 13–22, bearing maximum oncological safety in mind, and is associated with a good oncological and obstetric outcome [809], [810]. After gestational week 23, the size of the uterus severely limits the radicality of lymphadenectomy, and lymphadenectomy in the context of a postponed cesarean should therefore then be considered. A good option, particularly in the case of microinvasion and risk factors, as well as with tumors [Wright, J. D. et al. 2007].

If there is proven nodal involvement, termination of the pregnancy should at least be discussed in order to initiate radiochemotherapy promptly [811]. If the patient has a very strong wish to maintain the pregnancy, neoadjuvant chemotherapy may also be considered as an individual decision in order to gain time.

Fertility-preserving surgery is possible in early stages (up to stage IB1 [Wright, J. D. et al. 2007].

In the case of macroinvasive carcinoma, from the second trimester onwards pulmonary maturity is reached, and postponement of stage-appropriate surgery in the form of radical hysterectomy and lymphadenectomy, with neoadjuvant chemotherapy as well if appropriate, is an option in order to prolong the pregnancy [812]. In the meantime, neoadjuvant chemotherapy has become the standard if maintenance of the pregnancy is desired.

Neoadjuvant chemotherapy, with the option of delaying definitive surgical therapy until gestational week 32–34 in the context of the cesarean section, should be considered. No chemotherapy should be administered in the first trimester due to mutagenicity and teratogenicity and a high rate of miscarriage [813].

Chemotherapy is possible starting from the second trimester; the risks of growth retardation, fetal ototoxicity, and myelosuppression are known. Chemotherapy with cisplatin 50–100 mg/m2 q3w [804] or carboplatin AUC5 q3w / paclitaxel 80 mg/m2 body surface area weekly are possible [796], [814]. Chemotherapy should ideally be stopped 2–3 weeks before planned delivery in order to avoid delivery at the nadir. MRI and colposcopic check-ups, and tumor marker monitoring if appropriate, are recommended for monitoring therapy. No fetal malformations or perinatal morbidity were reported with cisplatin therapy in 21 pregnant women [818]. It is assumed that there is a placental filtration mechanism for platinum, as the platinum concentrations measured in cord blood are only 23–65%, and in amniotic fluid 11–42%, of those in maternal blood [818]. Although the data on the use of carboplatin during pregnancy are sparse, they appear to indicate lower toxicity [821].

Serious malformations have been reported in only 1.3% of infants born after chemotherapy administration from the second trimester onward, so that the risk is similar to that in the general population [813].

A meta-analysis on the use of neoadjuvant platinum-based chemotherapy in the second or third trimester, including 39 studies and 88 patients, showed generally encouraging results. The tumors were diagnosed at stages I–IIa in 87.5 % of cases; 86 patients received cisplatin and only two received carboplatin [304]. Cisplatin monotherapy was administered in 62.5% of the patients and 35.2% received combination therapy — with paclitaxel in 17 cases (35%), while one patient received a combination of carboplatin plus paclitaxel and one patient received carboplatin monotherapy. Complete remission was observed in 8.7% and partial remission in 46%, and stable disease in 42%. Adverse events were documented in only 25%, grade 3 toxicities were rarely reported, with thrombocytopenia and anemia in three patients and an allergic reaction to paclitaxel in one patient [304]. Eighty-eight neonates were reported from 84 pregnancies, with one set of twins and one set of triplets; 80.7% of them were born healthy. The preterm birth rate was 97.6% and the mean gestational age was 33.1 gestational weeks. One child was diagnosed with retroperitoneal embryonal rhabdomyosarcoma during the follow-up at 5 years of age, and another was diagnosed with acute myeloid leukemia at 29 months of age [304]. Recurrent cervical carcinoma was observed in 19.8% of the mothers during the course of the disease, and unfortunately 90% died. Radical hysterectomy with lymphadenectomy was performed during the cesarean procedure in 79% of the cases. Radical hysterectomy with pelvic lymphadenectomy was planned in only 2.3% as a secondary procedure after the cesarean during the later course (in some cases only after the puerperium). Radiochemotherapy alone was administered during the course in 3.9% [304]. In Germany, neoadjuvant platinum-based chemotherapy up to the cesarean, which is then followed by radical lymphadenectomy, is a frequently used variation. This is then followed by radiochemotherapy or radical hysterectomy after the puerperium, depending on the lymph-node stage and tumor stage.

The chemotherapy regimen currently recommended is platinum-containing chemotherapy (cisplatin 75 mg/m2), preferably with paclitaxel (175 mg/m2) at a 3-week interval or carboplatin AUC5 with paclitaxel (80 mg/m2), with an acceptable short-term toxicity profile [809].

Data on late toxicities are awaited. The vast majority of children show comparable motor and cognitive development [813], [815], [816]. The greatest risks of chemotherapy for the fetus during pregnancy are prematurity and growth retardation [817]. Platinum therapies increase the risk of myelotoxicity and ototoxicity in the fetus. With taxane-containing therapy, there is a higher rate neonatal intensive care treatment being needed [819], [820]. The risks to the mother also be need to be taken into consideration, of course, with myelotoxicity, ototoxicity, polyneuropathy, thrombosis and a risk of pulmonary embolism, among others. Anticoagulation treatment during ongoing therapy is therefore recommended.

If there is a good response with neoadjuvant chemotherapy, the pregnancy can be prolonged until 34+0 gestational weeks and even up to 37+0 gestational weeks if necessary, in order to avoid delivery of the fetus at a stage of extreme prematurity, with all the known consequences of prematurity.

### 22.2.2. FIGO stages IIB, III, and IV

A first diagnosis of FIGO stages II, III, and IV is rare during pregnancy. Treatment for the mother is in the foreground here, and platinum-based radiochemotherapy with cisplatin as the radiosensitizer should be performed. However, radiotherapy is not compatible with continuation of the pregnancy. The patient's wishes and the week of gestation also need to be taken into account here. If the diagnosis is made in the second trimester, fetal pulmonary maturity can be awaited before treatment starts. Therapy consists of primary cesarean section and radiochemotherapy. If the initial diagnosis takes place at term, this procedure is the gold standard [800]. If the patient has a very strong desire to have the child, then initial neoadjuvant chemotherapy can be considered on an individual basis, with a markedly increased risk to the mother up to the time of the postponed primary caesarean and subsequent combined radiochemotherapy.

## 22.3. Mode of delivery

Vaginal delivery is not contraindicated in patients with preinvasive lesions. Spontaneous regressions during the puerperium after spontaneous birth have even been reported [800].

For microinvasive carcinomas (FIGO IA1), the data situation is unclear. Spontaneous delivery can only take place if a resection with healthy margins has been performed beforehand in the context of a conization; otherwise, a cesarean section should be performed. However, the majority of authors recommend cesarean section in this case as well.

For macroinvasive carcinomas (FIGO IB, IIA), cesarean section combined with stage-specific treatment in the form of radical hysterectomy and pelvic lymphadenectomy is the gold standard mode of delivery. A two-stage procedure is preferred. Hysterectomy is performed secondarily to reduce morbidity. In microinvasive cervical carcinoma with risk factors and stage IB [Pottharst, A. et al. 2009], [823].

## 22.4. Cervical carcinoma during pregnancy — a solvable dilemma

Diagnosis and treatment should be the same as in nonpregnant women. Therapeutic options should be discussed on an interdisciplinary basis, depending on the gestational age and the patient's preferences. Fetal maturation can often be awaited. Abortion should be considered only in exceptional cases. Treatment for patients with cervical carcinoma in pregnancy is ideally performed in a gynecological cancer center and a level I perinatal center. Centralization is extremely useful, not least due to the rarity of cases. Suspicious or enlarged lymph nodes should be confirmed histologically in view of their prognostic significance and importance for further management. Laparoscopic, robotic, or laparotomic lymph-node staging during pregnancy up to gestational week 24 has shown valid results regarding the number of lymph nodes removed, with comparatively low morbidity. Depending on the tumor stage and gestational week, the following treatment options must be discussed with the patient, including the risks and benefits of individual approaches:

- Surgery, including tumor removal (conization, simple or radical cervicectomy, up to radical hysterectomy) and lymph-node staging (SNB if appropriate), depending on the stage of the disease, with the intention to preserve the pregnancy.

- Radical hysterectomy plus pelvic lymphadenectomy or primary radiochemotherapy: by analogy with the stage without preservation of pregnancy, with or without prior pregnancy termination.
- Delay in oncological therapy until viability (if possible > gestational week 32) and start of oncological therapy immediately after delivery by cesarean section or after the puerperium.
- Neoadjuvant chemotherapy to prolong the pregnancy until at most the end of prematurity, followed by cesarean section, including the necessary oncological therapy, particularly if there is a locally advanced stage or with residual tumor after conization that cannot be completely excised. In this case, laparoscopic lymph-node staging (with sentinel lymph-node excision if appropriate) should also be discussed before the start of neoadjuvant chemotherapy. Neoadjuvant platinum-based chemotherapy can be considered starting from gestational week 14 at the earliest.
- Cesarean (if possible) after gestational week 30 is the recommended mode of delivery.
- Either at the time of cesarean or as a secondary procedure (after the puerperium at the latest), definitive stage-adjusted oncologic therapy is recommended in the same way as in a nonpregnant patient, incorporating the treatment already administered during pregnancy.
- In summary, every patient with cervical carcinoma during pregnancy should be managed by an interdisciplinary team (gynecologic oncologist, obstetrician, neonatologist, anesthesiologist, radiation oncologist, and psycho-oncologist). A consensus treatment plan should be established, including patient's intention, tumor stage, tumor biology, and gestational age at cancer diagnosis. The primary goals are oncological safety for the pregnant patient and the survival of the fetus without additional morbidity.

# 23. Incidental cervical carcinoma after simple hysterectomy

**Major changes in the chapter on incidental carcinoma after simple hysterectomy**

During revision of the guideline, this chapter has been updated as an independent chapter extracted from Chapter 8, Foundations of treatment . The chapter has undergone hardly any revision in terms of content.

*P. Hillemanns, A. Mustea, F.A. Stübs, M.C. Koch, D. Denschlag*

| 22.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | In cases of incidental cervical carcinoma after simple hysterectomy, stage-appropriate treatment shall be administered. If a radical hysterectomy would originally have been indicated, surgical staging shall be carried out, followed by either repeat surgery (parametria, vaginal cuff, lymphadenectomy) or radio(chemo)therapy. | |
| | Strong Consensus | |

Only a few published studies on this topic were available for the guideline group. They are all retrospective, and show that starting from stage IA2 additional therapy is required after incidental findings of cervical carcinoma in a simple hysterectomy [318], [824], [825], [826]. Avoidance of further treatment is associated with unacceptably high recurrence rates. In a study including 147 patients (with stages IA1 to IIA), the recurrence rate with a median follow-up period of 116 months was 34.6% in a group who received only observation, in comparison with 6.8% in the R(CH)T group and 0% in the group who underwent radical parametrectomy [825]. In another study including 90 patients (with stages Ib to IIb), the 5-year survival rate after secondary radiotherapy was 85.5% and the 10-year survival rate was 74.1% [824]. A more recent analysis of 15 studies including 238 women showed an increased rate of surgical complications with secondary parametrectomy, cranial colpectomy with pelvic lymphadenectomy [827]. However, no specific preoperative factors were identified to predict the survival rate, need for adjuvant treatments, or parametrial involvement. The studies thus do not allow any definite conclusions to be drawn regarding which form of treatment is preferable — RT, R(CH)T, or repeat surgery in the form of radical parametrectomy on analogy with radical hysterectomy (Piver II/III). Instead, several aspects suggest that the treatment options are equivalent in relation to the overall survival. However, if RT/R(CH)T can be avoided on the basis of risk factors, surgery has advantages — particularly in younger women — due to its lower long-term morbidity.

# 24. Neuroendocrine cervical carcinoma

**Major changes in the chapter on neuroendocrine cervical carcinoma**

The chapter has undergone few changes. It has been extracted from the previous Chapter 8, Foundations of therapy and updated as a separate chapter.

*T. Fehm, A. Bartens, F. Martogini, A. K. Dietl, D. Gantert*

Neuroendocrine cervical carcinoma (NECC), representing 1–1.5% of cervical carcinomas, is a particularly rare but high-risk form of cervical carcinoma [829], [830]. It frequently occurs in younger women (mean age of onset 45 years) [831], [832]. Detection of HPV, particularly HPV-16 and -18, appears to be a risk factor [833]. NECC is usually an exophytically growing tumor [141].

NECC is divided by the WHO into two main types, depending on the degree of differentiation: NECC with low differentiation (small cell and large cell neuroendocrine cervical carcinoma), and NECC with high differentiation (typical and atypical carcinoid) [393], [834]. Small cell NECC is the most common subtype, accounting for 80% of cases [393] (Chapter 7.1, Classification of invasive cervical carcinomas).

NECC has a generally poor prognosis, independently of the treatment, and also a poorer prognosis in comparison with adenocarcinoma and squamous cell carcinoma [136], [137], [835], [836], [837], [840]. The prognosis of the disease is mainly influenced by the FIGO stage and lymph-node status [838], as well as infiltration depth [835], smoking, age, and purely small cell histology [140], [840]. Even in the early stages (I to IIA), regional lymph-node or hematogenous distant metastases occur in 40–60% of the patients. Recurrence or metastasis to the lung, liver, bone, brain, or lymph nodes is common within 1 year [137], [141], [836]. The 5-year survival rate ranges from 34% to 37%, with a median overall survival of 40 months [828], [839]. The median recurrence-free survival is 16 months [828].

In early stages (FIGO I–IIA), radical hysterectomy, optionally followed by adjuvant chemotherapy (or with a primary neoadjuvant approach), is most common and appears to be associated with the best survival rates [828], [839]. By analogy with the histologically similar small cell lung cancer (SCLC), chemotherapy consisting of etoposide and cisplatin/carboplatin (PE) or vincristine, Adriamycin (doxorubicin), and cyclophosphamide (VAC) is often administered [828], [839]. In locally advanced NECC (IIB–IVB) or with recurrences, combined radiochemotherapy or chemotherapy is administered [828], [839]. With recurrences after platinum-containing primary therapy, a combination of topotecan, paclitaxel, and bevacizumab is possibly superior in comparison with PE or VAC [828]. Few studies of radiochemotherapy are as yet available. However, brachytherapy in addition to teletherapy appears to improve the median survival (48.6 vs. 21.6 months) and should be discussed when planning radiotherapy [828]. For treatment planning, the case can be presented at a specialized tumor conference for neuroendocrine tumors.

In the clinical follow-up, it should be noted that a total of 68% of the patients die in the second and third year after the disease [828].

# 25. Structures for the provision of medical care

**Major changes in the chapter on care provision structures**

This chapter has been completely revised editorially and adapted to new legal circumstances and the quality data developed through the previous guideline. No new recommendations or statements have been generated.

In the care provision structures, changes have been arisen in some places, and matters that were already anticipated in 2014 have been implemented.

The information needed has been added at the relevant points. The additions relate to the following topics:

- Current 2020 annual report of the DKG on the certification of gynecological cancer centers, with data for the year 2019.
- Summary presentation by the Working Group of German Tumor Centers on cervical carcinoma at the 2020 Cancer Congress.
- Establishment in 2014 of gynecological dysplasia consultation hours and units by the German Society for Gynecology and Obstetrics (DGGG), the Working Group on Cervical Pathology and Colposcopy (AG-CPC), the Working Group on Gynecological Oncology (AGO), and the German Cancer Society (DKG) .
- Implementation of cervical carcinoma screening in accordance with the Cancer Early Detection and Registry Law (KFRG) starting from January 1, 2020.
- Adoption of the quality indicators from the guideline on the basis of the new state of the evidence not only for the certification process, but also for the IQTIG in the framework of statutory quality assurance measures.

*M.W. Beckmann, T. Fehm, R. Wiedemann, M.C. Koch, S. Wesselmann*

## 25.1. Preliminary remarks

The state of the data on the topic of medical care structures for women with cervical carcinoma is limited to only a few studies. Clear evidence-based conclusions on the effects of care structures on patient-related outcome parameters in Germany are not possible. Cervical carcinoma is avoidable and is curable after early detection. Structures have therefore been created that will comprehensively regulate prevention, diagnosis, treatment, and follow-up and can therefore lead to better results. These are being continuously further developed, and aims for improving early cancer detection, further development of oncological care structures, ensuring effective oncological treatment and strengthening the focus on the patient have been newly included in the National Cancer Plan (http://www.bmg.bund.de/praevention/nationaler-krebsplan.html). The need to evaluate the care provision situation in Germany is clearly recognized in the plan, along with the need for research studies on long-term follow-up and on the training situation. Date for a 10-year period are now available. On the basis of the data now available, the National Cancer Plan strategies have been modified. However, no changes were made in connection with cervical carcinoma.

## 25.2. Treatment in oncological centers

| 24.1 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Patients with cervical carcinoma should be treated by an interdisciplinary team. The team should include all of the specialist disciplines necessary, in a cross-sectoral network. This is best achieved in a certified center. | |
| | Consensus | |

### 25.2.1. Interdisciplinary and cross-sectoral care

Caring for patients with suspected or diagnosed cervical carcinoma is an interdisciplinary and cross-sectoral task. To ensure that optimal treatment results are achieved for the patient, it is necessary for the various structures and individuals working in the chain of care to collaborate in a coordinated, interdisciplinary, and cooperative fashion [841], [842]. The basis for this type of care is the definition of centers stated in the framework of the National Cancer Plan: “A center consists of a network of qualified and jointly certified, interdisciplinary and trans-sectoral, possibly multiple-site, institutions (hospitals, medical practices, rehabilitation institutions), which so far as is technically appropriate reflect if possible the entire chain of care for those affected” [841]. The results of surveys in certified centers for breast cancer and bowel cancer have shown that implementing this concept of a center has positive effects from the point of view of health-care providers on the quality of care for the patients who are treated in the certified networks [843], [845], and also that the level of patient satisfaction is very high [846]. In addition, analyses of the guideline-based quality indicators in certified centers show that the content of the guidelines is being well implemented and that patients are receiving treatment in accordance with the guidelines [844].

Within this system, the aim is to achieve high-quality prevention, diagnosis, and treatment, including rehabilitation and palliation, for the patients. For this purpose, the procedures and structures within the network need to be optimized in an interdisciplinary and cross-sectoral fashion. The three-level model for centers in the National Cancer Plan — with the establishment of organ cancer centers, oncological centers, and comprehensive cancer centers with collaborating partners (such as private practices) at all levels of care — represents the foundation for this high-quality structure for the provision of care [841], [847].

Gynecological cancer centers have been certified by German the Cancer Association (DKG), the German Society for Gynecology and Obstetrics (DGGG), and the Working Group on Gynecological Oncology (AGO) since 2008.

The 2020 analysis of key figures in the annual report of the Certified Gynecological Cancer Centers for audit year 2019 – key figure year 2018 lists 155 certified centers as of December 31, 2019. At the time when the previous version of this guideline was compiled, there were 100 certified centers (in March 2014). This shows the continuous increase in certified centers that has taken place since the start of certification in 2008. Overall, 43–50% of all gynecological carcinomas are treated in certified centers [848]. In the meantime, thanks to the large numbers of treatments, the corresponding amounts of data on the implementation of the quality indicators of the individual guidelines are also available, so that the guideline committees are able to reflect on the individual data. The gynecological tumors ovarian carcinoma, cervical carcinoma, and

endometrial carcinoma are all covered by Level 3 guidelines in the German Guideline Program in Oncology. Consensus-based (Level 2) guidelines are available for vulvar carcinoma, vaginal carcinoma, and other tumors (trophoblastic tumors and sarcomas). The diagnosis, treatment, and follow-up of gynecological carcinomas are thus very well covered by guidelines.

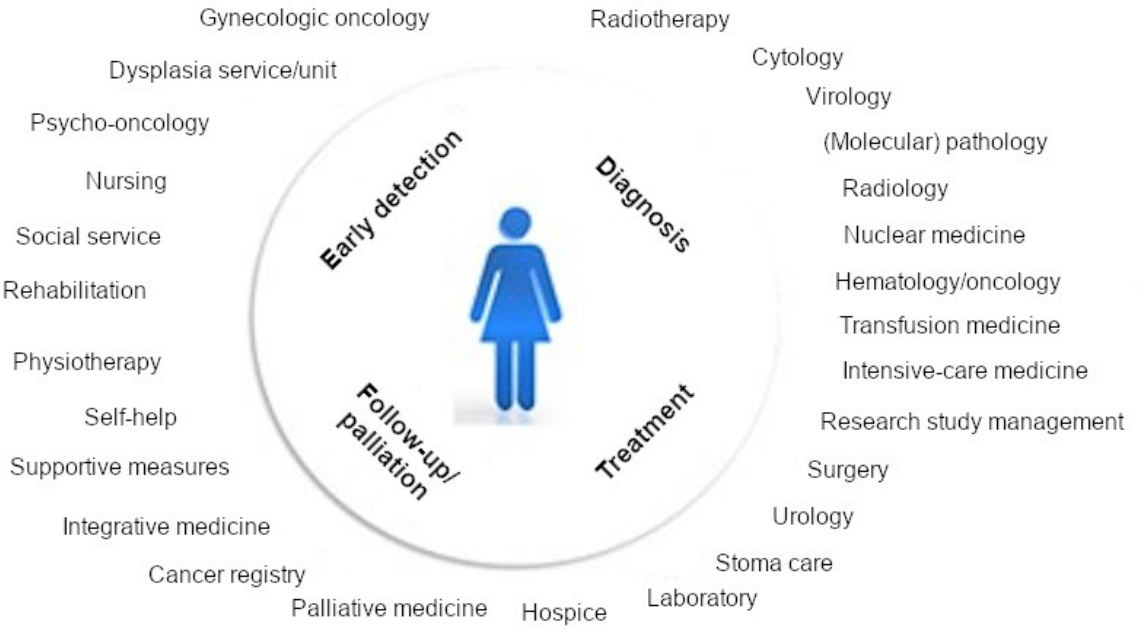



**Figure 7: Certified gynecological cancer center: network and tasks for patients with cervical carcinoma**

On analogy with the breast cancer centers, the plan here is also to establish comprehensive care, so that care for patients with cervical carcinoma can take place in a quality-assured, certified, interdisciplinary and cross-sectoral form (see Fig. Figure 7). Particularly in view of the declining numbers of cases of invasive carcinoma, interdisciplinary collaboration among recognized and assessed experts is becoming increasingly important. Certain minimum numbers of cases are necessary in order to ensure quality-assured care in accordance with the current standard [841], [851], [852], [853]. Care in specialized units [854] and by specialized surgeons (gynecological oncologists [849]) leads, for example, to a reduction in the recurrence-free interval and improved survival [854], [849]. The qualitative and quantitative expertise of the physicians providing treatment — for example, through specialization in gynecological oncology [849] and the number of surgical and systemic treatments administered — therefore needs to be demonstrated in the certified centers. The aim must be to ensure that patients with a diagnosis of cervical carcinoma have an opportunity to attend centers that present their quality level transparently and meet the relevant criteria [841], [847], [850].

## 25.2.2. Concept of the center — interdisciplinary tumor conference

| 24.2 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | The cases of all patients with cervical carcinoma shall be presented at an interdisciplinary tumor conference. | |
| | Strong Consensus | |

The interdisciplinary tumor conference is the central element for the required coordination of the various levels of care and patient-related decision-making on diagnosis and treatment in which the various partners involved in treatment take part. It is at the tumor conference that decisions are made regarding diagnostic and therapeutic procedures for patients. In order to achieve the optimal patient-related oncological treatment results while at the same time maintaining the lowest possible morbidity, a central prerequisite is to establish — in the framework of the interdisciplinary tumor conference — an agreed interdisciplinary treatment approach for patients with a first diagnosis of, or with recurrent/metastatic, cervical carcinoma. The interdisciplinary tumor conference is therefore a central point in the certification process. The interdisciplinary tumor conference on the treatment of patients with cervical carcinoma requires at least the presence of a gynecological oncologist, a pathologist, a radiologist, and a radiooncologist; additional disciplines such as a nuclear medicine specialist may be added when needed.

These center structures have to be financed in the health-care system. Care for patients should focus on units that offer the entire range of standard therapies in order to allow comprehensive, quality-assured care for patients while at the same time maintaining optimal usage of limited resources. Resources should be used in a targeted fashion, diagnosis and treatment should be in accordance with guidelines, and quality should be verifiable through the relevant documentation [847], [850].

## 25.2.3. Interdisciplinary chain of care

The first element in the chain of care is the private-practice gynecologist, who identifies a patient with cervical carcinoma either through her participation in statutory early cancer detection examinations or as a result of abnormal symptoms.

On April 3, 2013, the Cancer Early Detection and Registry Law (*Krebsfrüherkennungs- und -registergesetz*, KFRG) was passed in Germany. The framework of the law established two screening program: for cervical carcinoma and colon/rectal carcinoma, , among other things. This entitles people with statutory health insurance to free participation in organized screening, clarification of unusual findings in certified dysplasia consultations or units, and care in certified gynecological cancer centers. Due to the statutory status assigned to cancer registration, requiring the corresponding documentation, screening was implemented on January 1, 2020 after the establishment of the cancer registries.

Following the gynecological examination, and in the presence of an abnormal cytological smear and/or HPV test result, a patient with the relevant expert opinion receives further histological clarification either locally or in a gynecological dysplasia consultation or unit (see Fig. 8).

#### 25.2.3.1. Care algorithm agreed by consensus in the guideline group (2014, 2021)

Based on expert consensus; strong consensus.

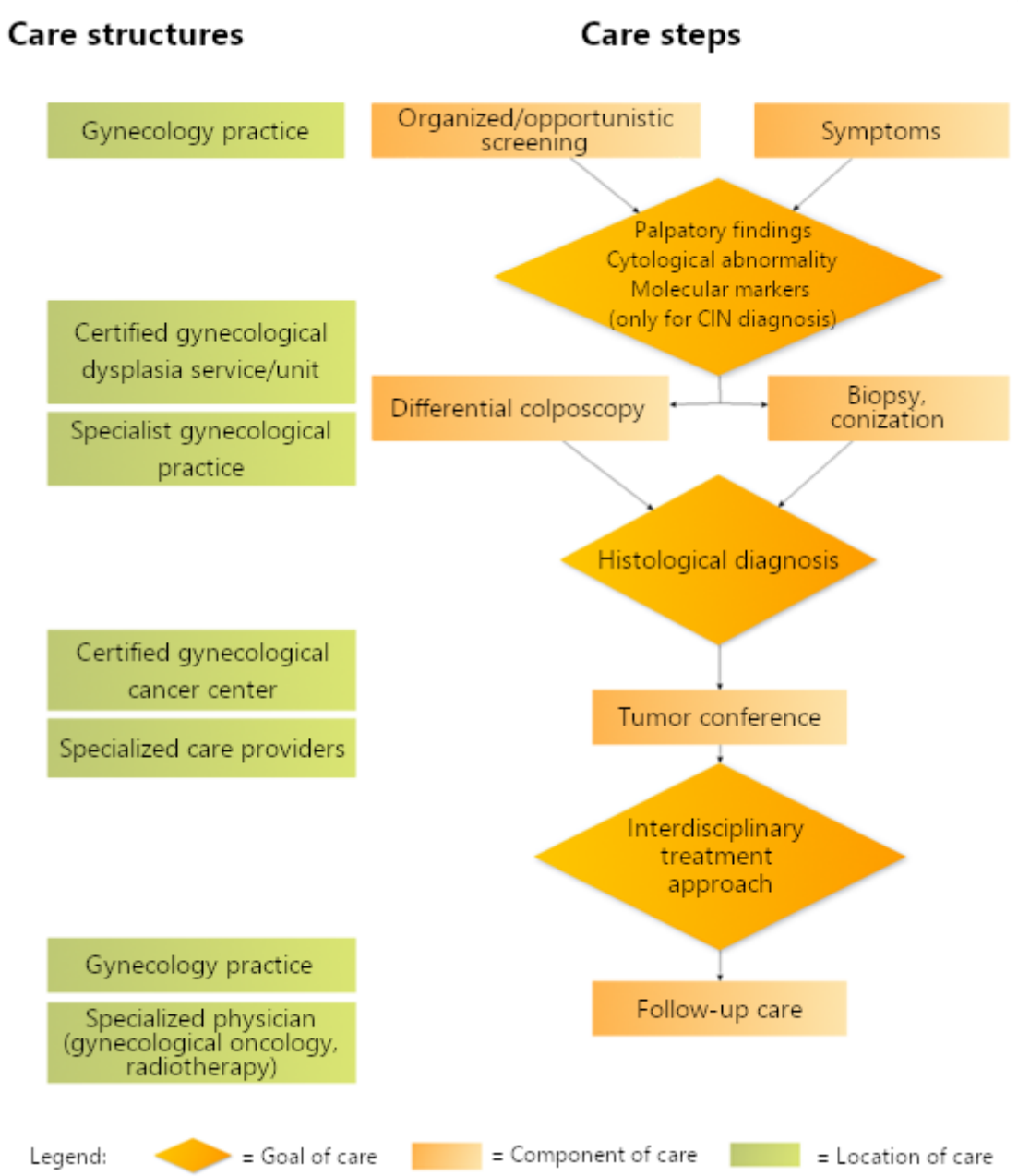



**Figure 8: Care algorithm agreed by consensus (2014, 2021)**

For this purpose, cooperative structural models (gynecological dysplasia consultation/unit), as called for in the previous version of this guideline, have been implemented by the German Cancer Association (DKG) together with the Working Group on Gynecological Oncology (AGO) and the German Association for Gynecology and Obstetrics (DGGG), along with the Working Group on Cervical Pathology and Colposcopy (*Arbeitsgemeinschaft für Zervixpathologie und Kolposkopie*, AGCPC). Differential colposcopy with targeted tissue excision is carried out for histological confirmation. Further examinations in relation to HPV diagnosis and other molecular-genetic markers

are carried out depending on the type of lesion that is present or on the pathological indication.

In contrast to care for patients with breast carcinoma and in the setting of early detection for breast carcinoma, patients with cervical carcinoma have previously only had opportunistic rather than organized screening available. In particular, the clarification of abnormal cytology or histology findings has not been uniformly defined. Although the gynecological cancer centers were established in 2008, not all of them also had the relevant specialized structures for clarifying abnormal cervical pathologies. However, these are now mandatory for the certification process.

Through the cooperation among the four societies and in the knowledge that organized cervical cancer screening was to be introduced and that dysplasia units or dysplasia consultation services would become necessary at that time, the quality criteria included in the German Cancer Society's certification system were defined in 2014, and certified dysplasia units and certified dysplasia consultation services were introduced. In the meantime, more than 120 of these certified structures have been established, and they are therefore now able to perform their function within the framework of organized cervical carcinoma screening that started on January 1, 2020. At present, however this number is far from sufficient to ensure nationwide coverage. For that, at least 400 consultation services or units are necessary to ensure comprehensive care for patients. The aim is that these certified structures should carry out guideline-compliant diagnosis and make treatment recommendations, thus completing the chain of care provided by the centers. By receiving primary screening by gynecologists in private practice, clarification and further diagnosis in certified dysplasia consultation services or units, treatment in certified gynecological cancer centers, and follow-up with gynecologists in private practice, the patient should then be able to receive the best possible care within a cohesive system [855].

When the suspected diagnosis has been confirmed histologically and the tumor stage in the FIGO classification (see Appendix, Table 21) has been established digitally, the patient is referred to a unit that will provide the relevant diagnostic procedures and treatment options. The certified gynecological cancer centers have been established for this purpose by the German Cancer Association (DKG) in collaboration with the German Association for Gynecology and Obstetrics (DGGG) and the Working Group on Gynecological Oncology (AGO) [841], [842]. Certification ensures that interdisciplinary and cross-sectoral collaboration takes place to establish the diagnostic and therapeutic algorithm for the patient in the framework of the interdisciplinary tumor conference.

If neoadjuvant or adjuvant drug treatment approaches are adopted, it is possible for them to be carried out within the certified network in an outpatient setting, by specialized gynecological oncologists (BNGO) or by hematologists and internal-medicine oncologists (BNHO).

After the completion of treatment and the relevant rehabilitation measures, the patient is returned to outpatient treatment, supervision, and care by the relevant specialist physicians.

### 25.2.4. Longitudinal documentation of patient history

The decisive element in the entire chain of care is that information from the individual areas of care is collected and systematically documented in order to allow statements to be made that are relevant to the patient's care in relation to the quality of the process, of its structure, and of its results.

This approach is adopted in the new Cancer Early Detection and Registry Law (KFRG), as it specifies that data should be compiled centrally and thus collected on both a cross-sectoral and also multiple-site basis, so that they can be used to present the quality of the results.

For this purpose, the Working Group on Data-Minimizing Standard Tumor Documentation (*Datensparsame Einheitliche Tumordokumentation*, DET), initiated by the Federal Ministry of Health (BMG), has defined a basic dataset with which the data are to be documented on a cross-sectoral basis. This basic dataset also includes the data fields required to reflect the quality indicators that are acquired in the framework of the Level 3 guideline "Diagnosis, Treatment, and Follow-Up in Patients with Cervical Carcinoma" (AWMF register no. 032/033OL) and Level 3 guideline "Prevention of Cervical Carcinoma" (AWMF register no. 015/027OL), as well as quality assurance measures from the Federal Joint Committee (G-BA) and the various areas of care provision in the health-care system.

Following decentralized input from all care providers, central data documentation and analysis is intended to make the necessary information available again to the physicians and the patients they are treating.

In connection with the Eighth National Oncological Quality Conference held in 2020 at the German Cancer Congress, the existing data from the various tumor centers from the years 2000 to 2018 were summarized. Twenty-one clinical registries from 11 federal states participated. The data showed a median age at presentation of in situ carcinoma of 34 years, and for invasive cervical carcinoma of 50 years. The median age at diagnosis for invasive carcinoma is rising, while for in situ carcinoma it is falling. In addition, the ratio of in situ to invasive carcinomas is changing. It clearly shows an increase in preinvasive lesions with a simultaneous decrease in invasive carcinomas. This can be regarded as a success for cervical carcinoma prevention [856].

In terms of grading, morphology, T, N, M and UICC stages, there are no significant changes, although there has been a significant increase in the number of lymph nodes examined.

With regard to treatment approaches, a decrease in the combination of surgery and radiochemotherapy has been seen since the introduction of the guideline, as is also the case for surgery and radiotherapy alone. There has been an increase in the specification of a single treatment option — primary surgery or primary radio-chemotherapy. This shows that the guideline recommendations have been comprehensively implemented nationally [856].

### 25.2.5. Quality indicators for certification as statutory quality assurance measures

The quality cycle in oncology is a central consequence of the National Cancer Plan and combines the goals of guidelines, centers, and documentation that it sets out. The starting point for the cycle is the evidence-based guidelines with their obligatory procedure for obtaining quality indicators (QIs; for methodology, see Chapter 26 and the guideline report). These QIs are incorporated into the requirement catalogues of the certified centers — in this case, the gynecological cancer centers. The results of the QIs are published annually in the form of annual reports [861]. The 2020 annual report

includes the results for 2234 patients who received an initial diagnosis of cervical cancer in 2018, representing 51% of the incident cases [862]. The results of the QIs are discussed in the interdisciplinary and multi-profession certification committees in order to check the degree of implementation of guideline contents and to compare the real care situation with the guideline recommendations. However, the results of the QIs are also fed back to the guideline group and provide it with an overview of the degree of implementation of its work. Since QIs are primarily aimed at areas with a potential for improvement, QIs can be deleted from the set if the underlying recommendations have been comprehensively implemented and no further potential for improvement is apparent. However, new QIs are also defined, which anchor the new recommendations from the guideline update in the clinical routine in the certified centers and promote and require adaptation to the current state of the evidence or consensus.

Various publications have shown that the quality cycle — consisting of guidelines, centers, and documentation — leads, in the patients' interest, to improvements in oncological care for all cancer patients, including patient-relevant end points. Analyses of clinical cancer registries, statutory health-insurance companies' data, and rehabilitation facilities show, depending on the focus of the evaluation, an improvement in overall survival, a reduction in postoperative mortality, and an improvement in the functional outcome after surgery when the patients are treated in certified centers [863], [864], [865], [857], [858], [859], [860], [866].

## 25.2.6. Opportunities for further training

| 24.3 | Consensus-based Recommendation | checked 2021 |
|---|---|---|
| EC | Education and further training for physicians in the treatment of patients with cervical carcinoma should take place in a gynecological cancer center/oncological center. | |
| | Consensus | |

The guideline group is not aware of any meta-analyses, randomized studies, or observational studies on the training situation relative to cervical carcinoma in Germany. This section is therefore at the level of an expert consensus.

As larger numbers of patients with cervical carcinoma are nowadays often only treated in certified networks, training for physicians who treat cervical carcinoma patients is also becoming concentrated in the certified networks [841], [849], [850]. The guidelines in the 2004 further training regulations for the performance figures that have to be achieved during medical specialist training, advanced specialist training, and/or optional further training are difficult to achieve outside of these care structures, with regard to both time periods and also target numbers. Administration of brachytherapy in cervical carcinoma, major surgical procedures in the context of advanced training in gynecological oncology, and disease-specific chemotherapy procedures in the context of additional training in drug therapy for tumors can only be provided in locations where patients with these clinical pictures are being treated by physicians with the relevant further training and qualification requirements, and where there is established oncological experience in interdisciplinary care for patients with cervical carcinoma. Currently, the large number of specialists and advanced specialists in the various areas of care allows comprehensive care provision, but the numbers of authorizations for

further training are stagnating or have been declining slightly in recent years. It is becoming clear that in the future, the numbers of individuals in specialized further training will be lower, so that care for patients with cervical carcinoma is likely to become more difficult [849], [850].

# 26. Quality indicators

*J. Rückher, S. Wesselmann*

Quality indicators are measurement variables for which data are collected to assess the quality of the structures, processes, and events they represent. Quality indicators are an important tool for quality management. The aim in using them is to achieve constant improvement in medical care by presenting, critically reflecting on, and if necessary improving the results of the care provided. The present selection of quality indicators is based on the methodology of the German Guideline Program in Oncology [867]. To compile them, a Quality Indicators Working Group was set up. The group established the final set of quality indicators on the basis of the quality indicators already existing in the 2014 guideline, the new strong recommendations ("must") in the updated guideline, the results of the existing quality indicators from the German Cancer Society's certified gynecological cancer centers, and the results of research on existing national and international quality indicators. The precise procedure and composition of the Working Group are outlined in the guideline report.

Following two online meetings of the Working Group, one new quality indicator was adopted (QI 10) and one quality indicator was deleted from the previous set (QI 9, R0 resection in exenteration). The annual report of the gynecological cancer centers showed that in 2018, only 43 exenterations were performed in 23 centers nationally (range 1–8 exenterations per center), while 123 centers did not report any exenterations — so that the informative value of the indicator was rated as low [861]. The final set thus still consists of nine quality indicators.

In addition, the Working Group has asked the clinical cancer registry to provide a stage-specific figure for sentinel lymphadenectomy alone for the next update of the guideline, in accordance with Statement 8.4, Staining for sentinel lymphadenectomy alone.

Notes on the QIs: The numerator is always a subset of the denominator. Quality indicators 1, 5, 6, and 7 are to be documented using the basic oncology dataset of the cancer registries (as of October 2020).

Notes on the QIs: The numerator is always a subset of the denominator. Quality indicators 1, 5, 6, and 7 are to be documented using the basic oncology dataset of the cancer registries (as of October 2020).

**Table 20: Quality Indicators**

| Quality Indicator | Reference Recommendation | Evidence Basis / Additional Information |
|---|---|---|
| **QI 1: Presentation at the tumor conference (checked 2021)** | | |
| **Enumerator**<br><br>no. of patients presented at the tumor conference<br><br>**Denominator** | **24.2.**<br><br>The cases of all patients with cervical carcinoma shall be presented at an interdisciplinary tumor conference. | **EC**<br><br>**Quality goal:**<br><br>Presentation of patients in the tumor conference as frequently as possible. |

| Quality Indicator | Reference Recommendation | Evidence Basis / Additional Information |
|---|---|---|
| all patients with a first diagnosis, recurrence, or newly developed distant metastasis of cervical carcinoma<br><br>Participants in the tumor conference include a gyneco-oncologist, a pathologist, a radiologist, and a radio-oncologist. | | |
| **QI 2: Details given in the medical report at first diagnosis and tumor resection (checked 2021)** | | |
| **Enumerator**<br><br>no. of patients with medical reports including details on:- Histological type (WHO)- Grading- Evidence/absence of lymphatic or venous invasion (L and V status)- Evidence/absence of perineural sheath infiltration (Pn status)- Staging (pTNM and FIGO) in patients who have undergone conization, taking the conization findings into account- Depth of invasion and extent in millimeters in pT1a1 and pT1a2- Depth of invasion relative to the thickness of the cervical wall (metric or percentage) in radical hysterectomy- Three-dimensional tumor size in centimeters (starting from pT1b1)- Minimum distance to the resection margins (in pT1b tumors, endocervical stroma)- R classification (UICC)<br><br>**Denominator**<br><br>all patients with a first diagnosis of cervical carcinoma and tumor resection | **7.1.**<br><br>Tumor classification ***shall*** be carried out on the basis of the currently valid edition of the WHO classification.<br><br>**7.3.**<br><br>Staging ***shall*** be carried out in accordance with the current edition of the TNM classification.<br><br>**7.4.**<br><br>A diagnosis of microinvasive cervical carcinoma ***shall*** be based on the definitions given in the current editions of both the WHO and TNM classifications.<br><br>**7.10.**<br><br>Morphological processing ***shall*** take place in such a way that all therapeutically and prognostically relevant parameters can be assessed. The report ***shall*** be produced on the basis of the currently valid WHO classification for tumor type and the current TNM classification for staging, as well as the R classification (UICC). | **EC**<br><br>**Quality goal:**<br><br>Complete reports of findings as often as possible for initial diagnosis of cervical carcinoma and tumor resection |

| Quality Indicator | Reference Recommendation | Evidence Basis / Additional Information |
|---|---|---|
| | **7.11.**<br><br>The tracheclectomy report ***shall*** include the following details:<br><br>• Histological type (WHO)<br>• Grading<br>• Presence/absence of lymphatic or venous invasion (L and V status)<br>• Presence/absence of perineural sheah infiltration (Pn status)<br>• Staging (TNM),<br>• Depth of invasion and extent in millimeters in pT1a1 and pT1a2<br>• Three-dimensional tumor size in centimeters (from pT1b1)<br>• Minimum distance from the resection margins (endocervical stroma in pT1b tumors)<br>• R classification (UICC).<br><br>**7.12.**<br><br>Morphological processing ***shall*** take place in such a way that all therapeutically and prognostically relevant parameters can be assessed. The report ***shall*** be produced on the basis of the currently valid WHO classification for tumor type and the current TNM classification for staging, as well as the R classification (UICC).<br><br>**7.15.**<br><br>The radical hysterectomy report ***shall*** include the following details:<br><br>• WHO histological type<br>• Grading | |

| Quality Indicator | Reference Recommendation | Evidence Basis / Additional Information |
|---|---|---|
| | • Presence/absence of lymphatic or venous invasion (L and V status)<br>• Presence/absence of perineural sheath infiltration (Pn status)<br>• Staging (TNM), taking the conization findings into account in patients who have undergone conization<br>• Depth of invasion and extension in millimeters in pT1a1 and pT1a2<br>• Depth of invasion relative to the cervical wall thickness (measurement or percentage figure)<br>• Three-dimensional tumor size in centimeters (from pT1b1)<br>• Minimum distance from the resection margins (endocervical stroma in pT1b tumors, vagina in pT2a tumors, and parametrium in pT2b tumors)<br>• R classification (UICC) | |
| **QI 3: Details in the medical report with lymphadenectomy (checked 2021)** | | |
| **Enumerator**<br><br>no. of patients with medical reports including details on:- No. of affected lymph nodes relative to removed lymph nodes- Correlation with site of biopsy removal (pelvic/para-aortic)- Details of the largest extent of the largest lymph-node metastasis, in mm/cm- Details of the absence/presence of capsular penetration by the lymph-node metastasis- Details of isolated tumor cells or micrometastases | **7.17.**<br><br>In lymphadenectomy specimens obtained during surgical treatment for cervical carcinoma, all removed lymph nodes ***shall*** be histologically examined.<br><br>**7.19**<br><br>Evidence of isolated tumor cells or micrometastases ***should*** be mentioned in the histological report and included in the TNM classification. | **EC**<br><br>**Quality goal:**<br><br>Complete reports of findings as often as possible for patients with cervical carcinoma and lymphadenectomy |

| Quality Indicator | Reference Recommendation | Evidence Basis / Additional Information |
|---|---|---|
| **Denominator**<br><br>all patients with cervical carcinoma and lymphadenectomy | **7.20.**<br><br>The report on lymph nodes ***shall*** include the following details: number of affected lymph nodes relative to the number of lymph nodes removed, correlated with the location of removal (pelvic/para-aortic). | |
| **QI 4: Cytological / histological lymph-node staging (checked 2021)** | | |
| **Enumerator**<br><br>no. of patients with cytological/histological lymph-node staging<br><br>**Denominator**<br><br>All patents with cervical carcinoma in FIGO stage ≥ IA2–IVA<br><br>Cytological/histological lymph-node staging = for diagnosis; not lymphadenectomy. | **8.2.**<br><br>Treatment must be administered relative to the histological tumor stage, verified using surgical staging or interventional diagnosis. | **EC**<br><br>**Quality goal:**<br><br>Cytological/histological lymph-node staging as often as possible for cervical carcinoma in FIGO stage ≥ IA2–IVA |
| **QI 5: Cisplatin-containing radiochemotherapy (checked 2021)** | | |
| **Enumerator**<br><br>no. of patients with cisplatin-containing chemotherapy<br><br>**Denominator**<br><br>all patients with a first diagnosis of cervical carcinoma and primary radiochemotherapy | **10.4.**<br><br>In patients with cervical carcinoma in whom there is an indication for primary radiotherapy from stage IB2 onwards, the radiotherapy ***shall*** be combined with cisplatin-based chemotherapy. | **Grade of recommendation A, level of evidence 1++**<br><br>**Quality goal:**<br><br>To provide cisplatin-containing radiochemotherapy as often as possible to patients with an initial diagnosis of cervical carcinoma and primary radiochemotherapy. |
| **QI 6: Adjuvant radio(chemo)therapy (checked 2021)** | | |
| **Enumerator** | | **Derived from one of the goals in the guideline:** |

| Quality Indicator | Reference Recommendation | Evidence Basis / Additional Information |
|---|---|---|
| no. of patients with adjuvant radio(chemo)therapy<br><br>**Denominator**<br><br>all patients with a first diagnosis of cervical carcinoma and radical hysterectomy | | To ascertain the status quo in medical care, particularly with regard to quality indicator 6 on adjuvant radio(chemo)therapy, as there are no data available on how many patients are treated adjuvantly on a stage-appropriate basis with combined cisplatin-containing radio(chemo)therapy.<br><br>**Quality goal:**<br><br>Currently: ascertaining the status quo.<br><br>In the longer term: reducing adjuvant therapy in favor of primary surgery alone or radio(chemo)therapy alone in the group at risk (unimodal therapy) |
| **QI 7: Histological confirmation (checked 2021)** | | |
| **Enumerator**<br><br>no. of patients with pretherapeutic histological confirmation<br><br>**Denominator**<br><br>all patients with cervical carcinoma and treatment for a local recurrence | **16.5.**<br><br>If a locoregional recurrence is suspected, histological confirmation shall be obtained. | **EC**<br><br>**Quality goal:**<br><br>Pretherapeutic histological confirmation as often as possible in patients with cervical carcinoma and treatment for a local recurrence. |
| **QI 8: Diagnosis of spread in local recurrence (checked 2021)** | | |
| **Enumerator**<br><br>All patients with imaging diagnosis (CT of chest and abdomen) to exclude distant metastases<br><br>**Denominator** | **17.1.**<br><br>If a local recurrence develops, the appropriate imaging diagnostic procedures shall be carried out to exclude distant metastases and for treatment planning. | **EC**<br><br>**Quality goal:**<br><br>Imaging diagnosis as often as possible in patients with local recurrence of a cervical carcinoma. |

| Quality Indicator | Reference Recommendation | Evidence Basis / Additional Information |
|---|---|---|
| All patients with local recurrence of cervical carcinoma | | |
| **QI 9: Complete medical report on conization findings (new 2021)** | | |
| **Enumerator**<br><br>all patients in the denominator with medical reports on:- Type of lesion (CIN, AIS, SMILE)- Location (endocervical, ectocervical)- Extent- In case of invasion, with details of size and lymph-node invasion, vascular invasion, and perineural sheath invasion- Grading- Status of resection margins (R status)<br><br>**Denominator**<br><br>All patients with HSIL (CIN II/III), AIS, SMILE and/or cervical carcinoma who have undergone conization.<br><br>Data on this indicator are to be collected by dysplasia units/services and gynecological cancer centers. | **7.8.**<br><br>The histological report ***shall*** note the type of lesion (CIN, ACIS and its variants in the form of stratified mucin-producing intraepithelial lesions [SMILE]), its location (endocervical, ectocervical), and its extent, as well as the presence of invasive tumor. When there is evidence of invasion, details ***shall*** also be given of its extent and of lymphatic, vascular and perineural sheath invasion, as well as grading. The status of the resection margins ***shall*** also be noted. | **Quality goal:**<br><br>Complete medical report as often as possible for patients with conization. |

# 27. Research needs

In the context of the development of the S3 guideline on the diagnosis, therapy and follow-up of cervical carcinoma, deficits in the evidence base have been demonstrated. The majority of the agreed statements are consensus-based and not supported by prospective randomized studies, as is usually the case with sufficient evidence. This lack of evidence of high-quality systematic reviews and controlled randomized trials is not due to an insufficient systematic search, but to the real lack of evidence.

Thus, in the context of the initiation and primary structuring of the guideline, PICO questions of particular clinical relevance (see guideline report) were developed from the topic complexes of lymph node metastases, surgery versus radiochemotherapy, radical hysterectomy for lymph node involvement and therapy for distant metastases (pM1).

Due to financial constraints, not all of these topic complexes with underlying questions could be given to an external evidence search, so two topic complexes were focused on in the external evidence search:

Search strategy number 1:

Secondary hysterectomy, surgery versus radiochemotherapy, radical hysterectomy for lymph node involvement (see guideline report).

Search strategy number 2:

pM1, therapeutic lymphonodectomy before radiochemotherapy, lymph node metastases and neoadjuvant chemotherapy (see guideline report).

This showed that, starting with the central question namely the indication for the choice of primary therapy, there is not a single study in the databases that has investigated a prospective randomized comparison between surgery and radiatio or radiochemotherapy as the primary single therapy option. Given that cervical cancer has now been treated for over 220 years after the initial treatment description using surgical therapy, this is extremely disappointing and shows that there is actually a very great need for studies. Based on this fundamental problem, the questions of secondary hysterectomy after radiochemotherapy, the question of radical hysterectomy with proven lymph node involvement in the pelvic localization and the further surgical strategy after proven lymph node involvement in the para-aortic localization are obvious problem areas with a lack of evidence. For none of the corresponding questions are there sufficient prospective randomized studies to make a clear therapy planning based on corresponding prospective randomized studies.

Both search strategy number 1 (see above) and search strategy number 2, which covered the topic areas of neoadjuvant chemotherapy with corresponding follow-up questions about the extent of surgical procedure after neoadjuvant chemotherapy, as well as the procedure for proven pelvic or para-aortic lymph node metastases, showed an identical lack of high-quality studies that could be used as an evidence base for recommendations. Thus, these questions and topics could also only be agreed upon as consensus-based recommendations.

Only in areas involving the use of drug therapies are findings available that enable therapy planning at an evidence-based level. This concerns, for example, neoadjuvant

chemotherapy, radiochemotherapy, adjuvant chemotherapy and drug therapies for recurrence diagnosis or metastases. Appropriate studies are being developed here with the support of industry. The questions concerning the basis of therapy, namely surgery or radio(chemo)therapy, are not investigated by industry-supported studies and apparently do not receive corresponding public research funding in any country.

Thus, the need for research in the field of cervical carcinoma emphatically extends to studies comparing primary therapy (surgery versus radiochemotherapy) and the corresponding surgical modifications or modifications of diagnostic methods (surgical staging). In order to develop a clear therapy strategy with prioritization of the procedure that allows the lowest morbidity with the best recurrence-free and overall survival of the patient, corresponding public research funds must be made available.

While the incidence of cervical carcinoma is decreasing in industrialized nations, it remains the most common female carcinoma worldwide, so the research option in western industrialized nations could have a tremendous impact on non-industrialized nations.

In addition to this key clinical research need, in the absence of evidence, there is a need for research in the area of follow-up, long-term treatment consequences (including quality of life) and pathological prognostic factors and their impact on treatment choice.

Another point that is becoming increasingly important, especially in industrialized countries, is in the area of health care structures. Of particular interest here is the effect of certified structural units and centralization on patient-relevant outcome parameters and the problem of consistent education and training as the number of cases decreases. With the falling incidence of cervical carcinoma, the question of lege artis care with corresponding expertise in both the surgical and radio-oncological fields is a question of health care research that needs to be solved in the long term.

In summary, it was identified as a central need for research in cervical carcinoma, that in most areas of diagnostics, therapy, supportive measures, but also in aftercare, there is hardly enough high-quality evidence available. As these are mainly topics that are not supported by industry funding, these results can only be developed with the support of public funders. If possible, this should be addressed with an evaluation of therapy-specific quality of life as well as economic aspects.

Specifically, the guideline group addresses the following research questions for which a systematic evidence review is being conducted without usable results:

- Is percutaneous radio(chemo)therapy with or without brachytherapy, followed by secondary hysterectomy oncologically equivalent to percutaneous radio(chemo)therapy with brachytherapy?
- Does secondary hysterectomy after primary radio(chemo)therapy have an influence on the local recurrence rate, DFS, MFS, OS?
- Should secondary hysterectomy be performed as radical or simple hysterectomy?
- Are surgical therapy and radio(chemo)therapy equivalent in stages IB and II?
- Should radical hysterectomy be omitted in the case of parametranous or pelvic lymph nodes?
- Should radical hysterectomy be omitted for paraaortically affected lymph nodes? (Extent, anatomical structure, infra/supramesenteric).

- What are the options for singular metastasis (radiofrequency ablation, surgery, radiotherapy)?
- Is systematic pelvic or paraaortic LNE useful prior to primary radiochemotherapy (e.g., for pN+)? Should only debulking be performed?
- Does pelvic radiotherapy or radiochemotherapy for pN1 pelvic (incl. singular micrometastasis) after therapeutic lymphonodectomy have an impact on local recurrence rate, DFS, MFS, OS?
- Does para-aortic radiotherapy or radiochemotherapy for pM1 para-aortic (incl. singular micrometastasis) after therapeutic lymphonodectomy influence local recurrence rate, FS, MFS, OS?
- How are positive lymph nodes after neoadjuvant chemotherapy to be evaluated prognostically as well as for further therapy?

Specifically, the guideline group also addresses the following research questions, for which a systematic search has been conducted without usable results and for which, in the opinion of the experts of the guideline panel, no high-quality studies are to be expected in the near future either:

- What is the significance of pM1 (para-aortic) compared to pM1 (pulmonary, hepatic, osseous) for therapy?
- Is neoadjuvant chemotherapy followed by surgery equivalent to primary radiochemotherapy (percutaneous + brachytherapy)?
- Is neoadjuvant CHT followed by surgery equivalent to primary surgery?
- Does surgical staging of locoregional tumor spread and lymph node status alter treatment planning?
- Does surgical staging prior to neoadjuvant chemotherapy make sense?
- Should surgical staging be the basis for therapy selection?
- How should the sentinel lymph node biopsy be performed (e.g. unilateral/ bilateral, blue/radioactive, application)?
- Is sentinel lymph node biopsy alone sufficient as a staging of the lymph nodes? If so, for which tumor stages?
- Does ultrastaging (possibly in conjunction with sentinel lymph node biopsy) of the lymph nodes improve the detection rate of lymph node metastases?
- What is the significance of ultrastaging for further therapy or prognosis?
- How to proceed in case of accidental cervical carcinoma after simple hysterectomy?
- What is the prognostic significance of L1 in cervical carcinoma (preferably a prospective study of pT1b1 cases with and without lymph node metastases using a multivariate approach)?
- What is the prognostic significance of grading in cervical carcinoma (preferably a prospective study of pT1b1 cases with and without lymph node metastases with multivariate approach AND with different grading scores)?
- What is the interobserver variability related to grading in cervical carcinoma?
- What is the prognostic significance of deep stromal infiltration in cervical carcinoma (preferably a prospective study of pT1b1 and pT2a1 cases with and without lymph node metastases using a multivariate approach AND generating a ROC_curve to determine the optimal cut-off value [which was, after all, defined in the guideline as 66% infiltration of the cervical stroma])?
- Study of prognostic significance of tumor size in pT2b-CX (cases with and without LKM with multivariate approach), cut-off as in pT1b and pT2a.
- Quality control study on the completeness of pathology findings with respect to pathological-anatomical prognostic parameters and TNM-relevant information.

- What are the optimal follow-up intervals and examinations for cervical carcinoma?
- What is the impact of follow-up on PFS, MFS, OS and quality of life?
- Analysis of health-related quality of life in cervical carcinoma-associated disease.
- To provide a systematic review of studies (results) published to date on health-related quality of life in cervical cancer-associated disease.
- Identification and summary of studies that
- Report quality of life scores for various disease states,
- address quality of life in women survivors, or
- Evaluate effects of cervical cancer-related interventions on health-related quality of life.
- Gap analysis for health economic evaluation of specific interventions (diagnostics, follow-up and rehabilitation) related to cost-effectiveness in cervical cancer.
- Identification and comparative interpretation of studies on the cost-effectiveness of specific technologies relevant to cervical cancer.
- Derivation of health economic research needs in this field

# 28. Appendices

**Table 21: Overview of TNM-categories / FIGO stages (modified 2021)**

| TNM categories | FIGO-Stages (2009) | Definition | FIGO Stages (2018) | Definition |
|---|---|---|---|---|
| TX | - | Primary tumor cannot be assessed | | - |
| 0 | - | No evidence of primary tumor | | - |
| Tis | - [1] | Carcinoma in situ (preinvasive carcinoma; adenocarcinoma in situ, stratified mucin-producing lesion; SIMLE) | - [1] | - |
| 1 | I | Tumor confined to the cervix | I | Tumor confined to the cervix |
| T1a | IA | Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm, with a horizontal spread of 7.0 mm or less | IA | Invasive carcinoma diagnosed only by microscopy. Stromal invasion to a maximum depth of 5.0 mm [2] |
| T1a1 | IA1 | Stromal invasion of ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread | IA1 | Stromal invasion of ≤ 3.0 mm in depth[2] |
| T1a2 | IA2 | Stromal invasion of > 3.0 mm and ≤ 5.0 mm with a horizontal spread of 7.0 mm or less | IA2 | Stromal invasion of more than 3.0 mm but no more ≤ 5.0 mm [2] |

| TNM categories | FIGO-Stages (2009) | Definition | FIGO Stages (2018) | Definition |
|---|---|---|---|---|
| | IB | (Macroscopically) visible lesion, confined to the cervix, or microscopic lesion > T1a2 / IA2 | IB | Clinically (macroscopically) visible lesion, confined to the cervix, or microscopic lesion > T1a2 / IA2 |
| T1b1 | IB1 | Clinically (macroscopically) visible lesion, ≤ 4.0 cm in largest extent | IB1 | Clinically (macroscopically) visible lesion, ≤ 2.0 cm in largest extent |
| T1b2 | IB2 | Clinically (macroscopically) visible lesion, > 4.0 cm in largest extent | IB2 | Clinically (macroscopically) visible lesion, > 2.0 cm but ≤ 4.0cm in largest extent |
| Tb3 | - | - | IB3 | (Macroscopically) visible lesion, more than 4.0 cm in largest extent |
| | II | Tumor invading beyond the uterus, but not as far as the pelvic wall and not to the lower third of the vagina | II | Tumor invading beyond the uterus, but not as far as the pelvic wall and not to the lower third of the vagina |
| T2a | IIA | Tumor with spread into the vagina (proximal and/or middle third), but without invasion of the parametrium | IIA | Tumor with spread into the vagina (proximal and/or middle third), but without invasion of the parametrium |
| T2a1 | IIA1 | Clinically (macroscopically) visible lesion ≤ 4.0 cm at largest extent | IIA1 | Clinically (macroscopically) visible lesion ≤ 4.0 cm at largest extent |

| TNM categories | FIGO-Stages (2009) | Definition | FIGO Stages (2018) | Definition |
|---|---|---|---|---|
| T2a2 | IIA2 | Clinically (macroscopically) visible lesion > 4.0 cm at largest extent | IIA2 | Clinically (macroscopically) visible lesion > 4.0 cm at largest extent |
| T2b | IIB | Tumor with invasion of the parametrium, but not as far as the pelvic wall | IIB | Tumor with invasion of the parametrium, but not as far as the pelvic wall |
| T3 | III | Tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctional kidney | III | Tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctional kidney |
| T3a | IIIA | Tumor involves the lower third of the vagina, with no extension to the pelvic wall | IIIA | Tumor involves the lower third of the vagina, with no extension to the pelvic wall |
| T3b | IIIB | Tumor extends to the pelvic wall and/or causes hydronephrosis or nonfunctional kidney | IIIB | Tumor extends to the pelvic wall and/or causes hydronephrosis or nonfunctional kidney |
| pN1 or pM1 | IVa | Metastases in the pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent | IIIC | Metastases in the pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent |
| pN1 | IVa | Metastases only in pelvic lymph nodes | IIIC1 | Metastases only in pelvic lymph nodes[4] |
| pM1 | IVa | Metastases in paraaortic lymph nodes (independently of | IIIC2 | Metastases in paraaortic lymph nodes (independently of |

| TNM categories | FIGO-Stages (2009) | Definition | FIGO Stages (2018) | Definition |
|---|---|---|---|---|
| | | whether or not pelvic lymph nodes are involved) | | whether or not pelvic lymph nodes are involved)[4] |
| T4 | IV | Tumor invades the mucosa of the bladder or rectum or extends beyond the boundary of the lesser pelvis | IV | Tumor invades the mucosa of the bladder or rectum or extends beyond the boundary of the lesser pelvis |
| T4 | IVa | Tumor invades the mucosa of the bladder or rectum or extends beyond the boundary of the lesser pelvis | IVa | Spread into organs of the lesser pelvis |
| M1 | IVb | Distant metastases, including metastases in para-aortic lymph nodes | IVb | Distant metastases |
| | | | | |

**N classification of regional lymph nodes (pelvic):**

NX = regional lymph nodes cannot be assessed

N0 = No regional lymph node metastases

N1 = Regional lymph node metastases

**M classification of distant metastases (including para-aortic lymph nodes):**

cM0 = No clinical evidence of distant metastases

cM1 = Clinical evidence of distant metastases

pM1 = Histological confirmation of distant metastases

pM0 = Histologically confirmed distant metastases

**Lymphatic invasion (L-status):**

LX = Invasion of lymphatic vessels cannot be assessed

L0 = No lymphatic invasion

L1 = Evidence of lymphatic invasion

**Vascular invasion (V status):**

VX = Vascular invasion cannot be assessed

V0 = No vascular invasion

V1 = Evidence of vascular invasion

**Invasion of the perineural sheaths (Pn status):**

PnX = Perineural invasion cannot be assessed

Pn0 = No perineural invasion

Pn1 = Evidence of perineural invasion

- Carcinoma in situ is not included in the respective FIGO classification, but is anchored in the TNM classification.
- Horizontal extension is no longer relevant for staging in the 2018 FIGO classification. However, no rationale is given for this by FIGO, nor are any relevant studies cited.
- In the 2018 FIGO classification, para-aortic lymph nodes are now defined as regional lymph nodes; this proposal is also followed in the revised reprint of the TNM classification [868].
- It was suggested by FIGO in 2019 that adding the notation “r” (imaging) and “p” (pathology) would indicate the method by which the finding was established.

**Table 22: Overview of UICC-Stages (checked 2021)**

| UICC stage | Corresponding TNM categories | | |
|---|---|---|---|
| **0** | Tis | N0 | M0 |
| **IA** | T1a | N0 | M0 |
| **IA1** | T1a1 | N0 | M0 |
| **IA2** | T1a2 | N0 | M0 |
| **IB** | T1b | N0 | M0 |
| **IB1** | T1b1 | N0 | M0 |
| **IB2** | T1b2 | N0 | M0 |
| **II** | T2 | N0 | M0 |
| **IIA** | T2a | N0 | M0 |
| **IIA1** | T2a1 | N0 | M0 |
| **IIA2** | T2a2 | N0 | M0 |
| **IIB** | T2b | N0 | M0 |
| **III** | T3 | N0 | M0 |
| **IIIA** | T3a | N0 | M0 |
| **IIIB** | T1, T2, T3a | N1 | M0 |
| | T3B | Any N | M0 |
| **IVA** | T4 | Any N | M0 |
| **IVB** | Any T | Any N | M1 |

# 29. List of Figures

Figure 1: Morphology of cervical carcinoma. Source: Arbeitsgemeinschaft Deutscher Tumorzentren, 2021 [24] ..... 37

Figure 2: Diagnosis and definition of stages as the basis for treatment decision-making ≤ FIGO stage IIB (2014/2021) ..... 65

Figure 3: Diagnosis and definition of stages as the basis for treatment decision-making ≤ FIGO stage IIB ..... 66

Figure 4: Assessing stromal infiltration ..... 84

Figure 5: Types of treatment and combinations of them for women with primary cervical carcinoma (not all are standard procedures, and not all have been investigated in larger prospective and randomized studies) (2021) ..... 98

Figure 6: Surgical techniques and principles (2014, 2021) ..... 100

Figure 7: Certified gynecological cancer center: network and tasks for patients with cervical carcinoma ..... 214

Figure 8: Care algorithm agreed by consensus (2014, 2021) ..... 216

# 30. List of Tables

Table 1: Involved Professional Societies and Organisations ..... 15

Table 2: Abbreviations Used ..... 18

Table 3: The SIGN evidence classification scheme ..... 29

Table 4: The grade of recommendation scheme ..... 30

Table 5: Classification of strength of consensus ..... 31

Table 6: Categories for evaluating conflicts of interest ..... 33

Table 7: Relative 5- and 10-year survival rates for cervical cancer in relation to UICC stage from the Bavarian Cancer Registry (n=14,606), 1998-2011. ..... 35

Table 8: Incidence and mortality rates for carcinomas specific to women, 2021 ..... 36

Table 9: Definitions of the nomenclature for cervical carcinoma (checked 2021) ..... 56

Table 10: Histological criteria for the different invasion patterns in endocervical adenocarcinoma (the Silva system [171], [172], [173]) ..... 77

Table 11: Rio classification (2011), addendum 1 ..... 80

Table 12: International Endocervical Adenocarcinoma Criteria and Classification (IECC) for adenocarcinoma of the cervix uteri [248], [248] ..... 90

Table 13: Summary of standard factors, risk factors, and prognostic factors and their therapeutic relevance in microinvasive carcinoma (stage T1a in the TNM classification) (modified 2021) ..... 94

Table 14: Summary of standard factors, risk factors, and prognostic factors and their therapeutic relevance in macroinvasive carcinoma (stage > T1a in the TNM classification) (modified 2021) ..... 95

Table 15: Classification of radical hysterectomy (checked 2021) ..... 123

Table 16: Obligatory locoregional follow-up examinations and intervals (checked 2021) ..... 168

Table 17: Optional locoregional follow-up examinations and intervals (checked 2021) ..... 168

Table 18: Optional extended follow-up examinations and intervals (checked 2021) ..... 169

Table 19: Treatment options in recurrent cervical carcinoma (modified 2021) ..... 177

Table 20: Quality Indicators ..... 221

Table 21: Overview of TNM-categories / FIGO stages (modified 2021) ..... 232

Table 22: Overview of UICC-Stages (checked 2021) ..... 237

# 31. Bibliography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