Thanks to the early detection program, the incidence of cervical cancer is declining. Every woman from the age of 20 is admitted once a year and includes various examinations. If a malignant disease is suspected, further diagnostic steps should be taken and a treatment plan adapted to the patient should be developed. The following article will help you to diagnose cervical cancer reliably and to initiate the right steps in the therapy.

Diagnosis of Cervical Cancer

Anamnesis and clinical evaluation of cervical cancer

In anamnesis it is important to check for symptoms. As pre- and early stages of cervical cancer are usually asymptomatic, they usually represent a random finding. In 90% of the cases, however, advanced cancers show symptoms like contact bleeding, lymphoedema of the legs, ureteral stenosis, ileus symptoms or back pain.
Gynecological examination in cervical carcinoma

Though the recommended age at first screening suggested by WHO is 30 years, age at first screening varies between countries. In Germany, it’s 20 years, and in the US it’s 21. Screening includes the direct visualization of the cervix by adjusting the speculum and using acetic acid or Lugol’s iodine to highlight precancerous lesions so they can be viewed with the “naked eye”, assessment of epithelial atypia on the portio surface or the cervical canal and the cytological smear diagnostics.

In this case, smears are taken from the endo- and ectocervix, and then evaluated microscopically according to Papanicolaou staining (“Pap smear”).

In addition, colposcopy can be performed, in which the portio is viewed through a colposcope in 6 to 40-fold magnification. For an extended investigation, the portio can be dabbed with acetic acid or Lugol-iodine solution (Schiller-iod sample). In the case of the latter, normal epithelium becomes brown, while atypical, altered epithelium remains bright.

A detailed description of the various diagnostic steps of gynecological examination can be found here: Diagnostics of female genitalia.

The following abnormal findings indicate the presence of atypia:

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Cytological smear</td>
<td>Changes in the nucleus (e.g., polymorphic, multiple nuclei), changes in the plasma, shift of the nuclear-plasma ratio in favor of the nucleus</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>Vesicular epithelium, mosaic, puncture, bleeding nodular surface, ulcer, exo- / endophytic tumor</td>
</tr>
</tbody>
</table>
Further Studies in Cervical Cancer

HPV diagnostics

HPV infection can be detected by **PCR test**. Since papillomaviruses are found in 98% of the invasive carcinomas, a negative test result almost excludes an **oncological** hazard. However, a positive finding only indicates a **potential disease risk**. Thus, HPV diagnostics are suitable for **supplementary examination** in suspicious findings, but not as a screening method.

![Diagram of cell cycle](image)

**Image**: “In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.” by OpenStax College - Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013. Licence: CC BY 3.0

Histology

In the case of significant findings, it is necessary to confirm them **histologically**. Here tissue is taken from suspicious areas. This can be done by selective **biopsy** under **colposcopy** or **cervical curettage**.

Another, **more invasive** method is **conization**. In this case, pathological tissue, which should contain both the **endocervix** and the **ectocervix**, is removed either by means of a **scalpel (knife conization)** or **electric loop (loop conization, LEEP)**. Because of the typical tumor localization (sexually mature women: portio surface, older women: cervical canal), the cones taken should be flat in **premenopausal** women and high and narrow in **postmenopausal** cases. Disadvantage of this method is the risk of **bleeding** and **late complications**, such as **cervical stenosis** and **insufficiency**.

Pretherapeutic staging

In addition to direct visualization of the cervix via a speculum and palpation, the evaluation of the **spread of the tumor** is also mandatory in histologically confirmed cancer. For this purpose, **transvaginal** and **renal** ultrasounds should be performed.
Vaginal Ultrasound

Stage 1A                  Stage 1B
Stage 2A                  Stage 2B                  Stage 3B
Cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system, which is based on clinical examination, rather than surgical findings. It allows only the following diagnostic tests to be used in determining the stage: palpation (feeling with the fingers), inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton, and cervical conization.

An MRI is also considered:

Patients with histologically confirmed cervical cancer FIGO stage from 1B2 up to and including III should receive a baseline MRI for the assessment of locoregional tumor spread.

If necessary, rectoscopy and cystoscopy can be performed and, in FIGO IB2, a CT of thorax and abdomen can be used to assess the extrapelvic tumor spread.

Therapy of Cervical Cancer

The therapy of cervical cancer consists in a complex *individual* treatment planning, which must be adapted to the individual case. In addition to the *stage classification*, factors such as child planning, patient age and risk factors play a role.

*Note:* The therapy of the cervical cancer must be adapted to each patient individually!

Treatment of cervical intraepithelial neoplasia (CIN)

The spontaneous recovery rate of CIN I and II is high, which is why a *follow-up cytology* should be performed after three months.

If the changes remain over 12 months or if a CIN III is present, an *operative* therapy must be considered.

Most frequently carried out is a *conization* (see above). The cut margins are then assessed *histologically:* if they are free from atypia, the probability of recurrence for a CIN is 1-2%; if atypia are found, they are 15-20%.

Another method is *laser surgery*, in which the pathological tissue is destroyed by a laser beam at a depth of 5 to 7 mm. This method is only slightly *invasive*, but *histological* assessment is not possible.
In case of postmenopausal women, completed family planning or other diseases of the uterus, a **hysterectomy** is considered.

**Treatment of early stages of cervical cancer**

*Cancer with early stromal invasion* can be cured by a **hysterectomy** (see below). In the case of a **microcarcinoma** (FIGO 1A2), the removal of the **pelvic lymph nodes** is also considered. If a child’s wish is required, a **conization** can be sufficient.

**Surgical Treatment of Invasive Cervical Cancer**

**Abdominal radical operation**

Operative therapy is the therapy of choice in the FIGO stages IB-IIB. **Radical hysterectomy (abdominal radical surgery)** is used as standard.

Depending on the present tumor findings, a different **radicality** of the operation is to be sought. According to Piver et al., there are the following stages:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Restricted Radicality: Extrafascial hysterectomy without complete mobilization of ureters</td>
</tr>
<tr>
<td>II</td>
<td>Modified-radical hysterectomy = extrafascial hysterectomy with resection of parametria medial to the ureters: discontinuation of the uterine artery to the crossover of the ureter and the Ligg. uterosacralia / cardinalia halfway to the crossbones / pelvic wall. Resection of the upper vaginal third and preparation of the ureter (without detachment from Lig. pubovesicale).</td>
</tr>
<tr>
<td>III</td>
<td>“Classical” radical hysterectomy (equivalent to Wertheim-Meigs operation): discontinuation of the uterine artery at the origin and the Ligg. uterosacralia and cardinalia close to origins (Os sacrum, pelvic wall). Resection of the upper vaginal third (up to the vaginal half) and preparation of the ureter (up to the mouth in the bladder, while preserving a small lateral portion of the Lig. pubovesicale).</td>
</tr>
<tr>
<td>IV</td>
<td>Like grade III, in addition complete release of the ureters from Lig. pubovesicale (a). Resection of the A. vesical superior (b) and up to 3/4 of the vagina (c).</td>
</tr>
<tr>
<td>V</td>
<td>Resection of parts of the bladder or distal ureter with ureteral implantation</td>
</tr>
</tbody>
</table>

The removal of the **uterus** with **parametrium** and **vaginal cuff** through **pelvic**
lymphadenectomy is called Wertheim-Meigs operation and is most frequently performed in Germany. In pelvic lymph nodes and larger carcinomas, which are positive at frozen sections, para-aortic lymphadenectomy should be performed.

If a squamous cell carcinoma is present, the removal of the adnexa is not necessary in premenopausal women. In the case of adenocarcinoma, however, this should be considered. Reason is the higher metastasis probability.

**Note:** Removal of the adnexa is not obligatory!

After radical hysterectomy the occurrence of the following complications is possible: fistulae (bladder-vagina, ureter-vagina), lymphedema, lymphoceles, bladder emptying disorders and ureteral stenoses.

**Alternative Operations**

A less invasive alternative is laparoscopic lymphadenectomy followed by radical vaginal hysterectomy.
"Uterus prior to hysterectomy." by Hic et nunc. Licence: CC BY-SA 3.0

"Laparoscopic hysterectomy." by Hic et nunc. Licence: CC BY-SA 3.0

"Cervical stump (white) after removal of the uterine corpus at laparoscopic supracervical hysterectomy." by Hic et nunc. Licence: CC BY-SA 3.0

"Transvaginal extraction of the uterus in total laparoscopic hysterectomy." by Hic et nunc. Licence: CC BY-SA 3.0

"End of an laparoscopic hysterectomy." by Hic et nunc. Licence: CC BY-SA 3.0
In the case of small tumors (<2 cm), negative lymph nodes and squamous cell carcinoma as a type of tumor, trachelectomy (cervicectomy) can be performed to maintain the ability to bear children. In doing so, the uterus and a part of the cervix are left behind and attached to the vagina. Removal of the lymph nodes is performed laparoscopically.

In FIGO stage IV, an exenteration may be considered. The vagina, urinary bladder and uterus (anterior exenteration) or vagina, rectum, uterus (posterior exenteration) and stoma system are removed depending on the disease.

Radiotherapy for cervical cancer

When the cervical limits (FIGO stage III) are exceeded, a primary surgical procedure can not be attempted. Here, primary radiation therapy with the combination of platinum-based chemotherapy (cisplatin) is the method of choice. It may be indicated as of stage IIB.

Optimal radiotherapy results are achieved by combination of teletherapy (percutaneous irradiation) and brachytherapy (contact therapy).

In brachytherapy, a radionuclide carrier is introduced into the cavum uteri by the afterloading method. In this way surrounding structures such as urinary bladder and
rectum are spared.

In case of inoperable patients, or if a preservation of the ovarian function is not attempted, primary radiotherapy can also be performed in smaller carcinomas, since this is equivalent to the operation.

Postoperative irradiation is indicated when the carcinoma can not be completely removed by surgery.

Complications of radiation therapy may include: colpitis, cystitis, proctitis, dyspareunia, fistula (vagina-bladder, vagina-rectum) and loss of ovarian function

Chemotherapy for cervical cancer

In contrast to other genital carcinomas (e.g., ovarian carcinoma), the cervical carcinoma is less responsive to chemotherapy. In stage IVB, palliative systemic therapy is the means of choice.

A neoadjuvant chemotherapy can be used to reduce the tumor size (down-staging) prior to surgery or irradiation.

Aftercare and Prognosis of Cervical Cancer

Tumor aftercare in case of cervical cancer

For aftercare, the current guidelines recommend the following:

Women who have had a total hysterectomy (removal of the uterus and cervix) should stop screening. Women who have had a supra-cervical hysterectomy (cervix intact) should continue screening according to guidelines. (American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP); 2012)

Optional studies include colposcopy, vaginal ultrasound, renal ultrasound and HPV testing.

A control of tumor markers (SCC, CEA) is not recommended due to lack of evidence.

Prognosis in cervical cancer

The prognosis of cervical cancer depends on various factors, including tumor stage, lymph node involvement, resection margins and tumor size. Thus the mean 5-year survival rates of the different stages differ as follows:

- Stage I: 80 %
- Stage II: 70 %
- Stage III: 45 %
- Stage IV: 15 %

If vascular invasion occurs, the 5-year survival rate drops from 80% to 30%, in the case of lymph node metastasis from 85% to 50%. A young age is also a negative prognostic factor.
Prevention of Cervical Cancer

Primary prevention of cervical cancer

Primary prevention of the cervical carcinoma involves the prevention of risk factors (promiscuity, smoking, infections) and the possibility of vaccination against HPV viruses. This should be done as early as possible and before the start of sexual activity. It is indicated for girls and boys alike.

The following vaccines are currently available:

- **Gardasil**: against HPV 6, 11, 16, 18
- **Cervarix**: against HPV 16, 18

Secondary prevention of cervical cancer

The secondary prevention is used to detect already existing atypia. This includes the screening test, which can be claimed once a year by women from the age of 21, including a cytologic smear (see above).

Review Questions

1. Which statement regarding cervical cancer is correct?
   
   1. A positive finding in HPV diagnostics indicates advanced cervical cancer.
   2. In the case of conization, the removed conus should be flat in postmenopausal women and high and narrow in premenopausal cases.
   3. Treatment of cervical cancer is always based on a standard treatment plan independent of individual factors.
   4. Adnectomy is obligatory for any surgical method.
   5. The HPV vaccine is part of the primary prevention of cervical cancer.

2. Which diagnostic method for early detection of cervical cancer or pre-therapeutic classification does not make sense?
   
   1. Cytological smear
   2. Radiological examination
   3. Speculum evaluation
   4. Transvaginal ultrasound
   5. MRI investigation

3. A 28-year-old female (0 Gravida, 0 Para) consults her gynecologist because of contact bleeding after sexual intercourse. After detailed diagnosis, a cervical carcinoma is found in FIGO stage III. What is the most effective therapy?
   
   1. Chemotherapy alone
   2. Knife conization
   3. Radical hysterectomy with pelvic lymphadenectomy without removal of the adnexa
   4. Radical hysterectomy with pelvic lymphadenectomy with removal of the adnexa
   5. Radiotherapy in combination with platinum-containing chemotherapy

References

Switzerland: Springer.


**Correct answers:** 1E, 2B , 3E

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