Cervix uteri
Cervix uteri

- anatomy
- histology
- ectopy / ectropion
- Nabothian cysts
- cervicitis
- precancerous lesions
- carcinoma
Cervix – anatomical relationships
Cervix uteri - anatomy

- **vaginal portion**
  - projects into the cavity of the vagina
- **ectocervix / exocervix** – the part of the cervix visible from inside the vagina during a gynecologic examination
- **endocervix (endocervical canal)** – a tunnel through the cervix
- **supravaginal portion**
  - the part of the cervix above the vaginal vault
vaginal cuff

external os

exocervix
Cervix - histology

- **ectocervix** – covered by stratified noncornified squamous epithelium

- **endocervical canal** – lined by single layer of mucin-secreting columnar epithelium

- **squamocolumnar junction** = the junction of the endocervical mucosa with the squamous epithelium

- **transformation zone** = part of the cervix covered by metaplastic squamous epithelium
Squamocolumnar junction prior to puberty.

Metaplastic change of endocervical epithelium in the transformation zone

Eversion of the endocervical epithelium at puberty and/or first pregnancy

Relocation of SCJ in the endocervical canal after the menopause

source: http://www.eurocytology.eu
Ectopy / ectropion

- Endocervical mucinous epithelium is not exclusively limited to the anatomic area of endocervix
- May occupy significant regions of the anatomic ectocervix:

  - after onset of puberty (mechanical reasons – swelling of the stroma in response to hormonal stimulation)
  - during pregnancy
  - when using contraceptive pills
  - after the delivery
  - remains on the ectocervix until near the menopause
Ectopy / ectropion

Ectopy/ectropion appears red and ulcerated to the naked eye – it also has been interpreted (mistakenly) as an erosion. But erosion is a different process accompanied by wearing away of the mucosal tissue.

causes of erosion:
- trauma
- chemicals
- infections
- carcinoma
Squamous cell metaplasia

- Mucin-secreting endocervical epithelium is gradually replaced by squamous epithelium.
- This area is known as the transformation zone.
- Constant exposure to acidic vaginal pH levels are triggers of the squamous metaplasia process (hyperplasia of the reserve cells – immature squamous metaplasia – mature squamous metaplasia).
- Transformation zone is the most common area of pathological changes (dysplasia, inflammation, erosion).
Definition of metaplasia

- Metaplasia is a process by which one fully differentiated type of epithelium changes into another.
- It is usually an adaptive change which occurs in response to longstanding (chronic) irritation of any kind, or in response to hormonal stimuli.
- Metaplastic change is reversible and theoretically, transformed epithelium should revert to its original form after the stimulus is removed, but this does not always happen.
- Metaplasia occurs at many body sites, e.g., gastric mucosa, bladder, bronchi, etc.
Nabothian cysts

- mucinous retention cysts
- develop within the TZ secondary to squamous metaplasia, covering and obstructing endocervical glands
- up to 1.5 cm in diameter
- usually disappear, some can persist indefinitely
- rarely can be symptomatic
## Cervicitis

### Noninfectious cervicitis
- chemical or mechanical in nature
- inflammatory response is nonspecific
- common causes:
  - chemical irritation (douching)
  - local trauma (foreign bodies – tampons, pessaries, IUD)

### Infectious cervicitis
- common disease
- central role in the pathogenesis of pelvic inflammatory disease and endometrial infections
eiology:
  - bacteria
  - viruses
  - fungi
  - protozoa, parasites
Microorganism causing infectious cervicitis

- **Bacteria**
  - Chlamydia trachomatis
  - Neisseria gonorrhoeae
  - Mycoplasma hominis
  - Ureaplasma ureolyticum
  - Gardnerella vaginalis
  - Actinomyces israeli
  - Treponema pallidum
  - Mycobacterium tuberculosis
  - Group B Streptococcus

- **Viruses**
  - Human papillomavirus - HPV
  - Herpes simplex virus

- **Fungi**
  - Candida albicans
  - Aspergillus

- **Protozoa and parasites**
  - Trichomonas vaginalis
  - Ameba
  - Schistosomes
Infectious cervicitis

- initial event of PID
- primary infectious focus in postpartum and postabortal endometritis
- concurrent bacterial infection have been directly related to:
  - spontaneous abortion
  - premature delivery
  - chorioamniiitis
  - stillbirth
  - neonatal pneumonia and septicemia
Precancerous lesions of the cervix
Human oncogenic viruses

- Viruses are associated with nearly 20% of the human cancer cases worldwide
- The most common virus-associated cancer:
  1. Cervical carcinoma
  2. Liver carcinoma

<table>
<thead>
<tr>
<th>Virus family</th>
<th>Causal role in human cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accepted</td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>HBV</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td></td>
</tr>
<tr>
<td>Gammaherpesviruses</td>
<td>EBV</td>
</tr>
<tr>
<td>Papovaviridae</td>
<td>HPV (high-risk types)</td>
</tr>
<tr>
<td>Papillomaviruses</td>
<td></td>
</tr>
<tr>
<td>Polyomaviruses</td>
<td></td>
</tr>
<tr>
<td>Adenoviridae</td>
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</tr>
<tr>
<td>Poxviridae</td>
<td></td>
</tr>
<tr>
<td>Molluscipoxvirus</td>
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<tr>
<td>Leporipoxvirus</td>
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<tr>
<td>Retroviridae</td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td>HTLV-I</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>HCV</td>
</tr>
</tbody>
</table>

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HPV

- the most common cause of sexually transmitted diseases (STD)
- infection by high-risk genotypes HPV plays a critical role in the pathogenesis of cancer:
  - cervix uteri
  - vagina
  - vulva
  - anus
  - penis
  - orofacial region

- HPV includes about 130 genotypes to date
- about 15 anogenital HPVs have been classified (by the IARC) as oncogenic – most common types:
  - 16, 18, 31, 33, 51, 52, 53, 58

<table>
<thead>
<tr>
<th>Lokalizace</th>
<th>Onemocnění</th>
<th>Typy HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kůže</td>
<td>Verruca vulgaris</td>
<td>2, 4, 1, 7, 26, 29</td>
</tr>
<tr>
<td></td>
<td>Verruca plana</td>
<td>3, 10, 27, 23, 41</td>
</tr>
<tr>
<td></td>
<td>Verruca plantaris</td>
<td>1, 2, 4</td>
</tr>
<tr>
<td></td>
<td>Epidermodysplasia verruciformis</td>
<td>5, 8, 17, 20, 36, 9, 12, 14-15, 19, 21-25, 38, 46</td>
</tr>
<tr>
<td>Anogenitální oblast</td>
<td>Condyloma acuminatum</td>
<td>6, 11, 1, 2, 10, 16, 30, 44, 45, 54, 55</td>
</tr>
<tr>
<td></td>
<td>Dysplasie adenokarcinomu důložního čípku</td>
<td>16, 18</td>
</tr>
<tr>
<td>Ústní dutina</td>
<td>Hyperplasie epitalu</td>
<td>13, 32</td>
</tr>
<tr>
<td>Larynx</td>
<td>Papilom</td>
<td>6, 11</td>
</tr>
<tr>
<td>Oční spojivka</td>
<td>Papilom</td>
<td>11</td>
</tr>
</tbody>
</table>
Worldwide annual incidence of cancer caused by HPV infections
Harald zur Hausen

- born 1936
- German virologist
- he has done research on Epstein-Barr virus and contributed to finding that a virus can transform healthy cells (lymphocytes) into cancer cells
- in 1976 he published the hypothesis that HPV plays an important role in the cause of cervical cancer
- his work on HPV and cervical cancer received a great deal of scientific criticism on initial unveiling but subsequently was confirmed
- in 2008, he received the Nobel Prize in Medicine (with Luc Montagnier and Francoise Barre-Sinoussi, who discovered the HIV)
Life cycle of HPV

- Normal Cervical Squamous Epithelium
  - Mature squamous layer
  - Squamous epithelium
- New Infection
  - HPV infection
  - Microabrasions in cervical mucosa
- Infected Cervical Squamous Epithelium
  - New infectious HPV
  - Viral assembly
  - Distal movement of infected cells
  - Viral DNA replication
  - Integrated viral DNA
  - Episomal maintenance phase

JA Kahn, NEJM, 2009;361:271
Epidemiology of HPV infection

- most women become infected with HPV
- frequent pattern: multiple serial infections with different types of HPV, each infectious episode being of relatively short duration
- majority of HPV infections are transient – undergo clearance or become latent within 1-2 years
- high risk HPV tend to clear more slowly – the infection that persist for two or more years pose the greatest risk – since these are the infections that may progress to a high grade cervical precursor lesions or even an invasive cancer
Epidemiology of HPV infection

- development of invasive cancer - after 10 or more years of high-risk HPV persistent infection
- high-grade CIN (CIN2, CIN3) – 30-50% of untreated lesions progress to invasive cancer over a 30-year follow-up period
Molecular mechanisms of HPV-induced carcinogenesis

- high-risk types can integrate into the host genome
- two viral genes (E6 and E7) may be over-expressed
- E6 protein inhibits p53 (p53 controls responses to different types of cellular stress including DNA damage)
- E7 protein binds and inactivates Rb (Rb controls cell cycle progression)

- selective growth advantage
- continuous expression of these proteins can lead to the accumulation of mutations in the cellular genome that are required for malignant conversion
high-risk HPV infection

viral integration

inactivation p53

inactivation Rb

transformation of the squamous (glandular) cells, genetic instability

precancerous lesions

80% transient infection

loss of function (apoptosis, cycle cell checkpoints control)

loss of function (G1 to S phase transition, apoptosis)

invasive carcinoma
Cervical cancer prevention

**Primary prevention**
- attempts to reduce the risk of the actual development of HPV infection
- HPV vaccine
- prevention of contact with HPV
- promotion, education

**Secondary prevention**
- early detection and cure
- screening
- early detection and treatment of precancer or early invasive lesions
- PAP-smear
- colposcopy
- HPV test
Screening – PAP test

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Screening – PAP test
Cervical cancer – precursor lesions

Pathologic findings

- abnormal cellular proliferation
- abnormal maturation
- cytologic atypia:
  - nuclear pleomorphism
  - increased N/C ratio
  - hyperchromatic nuclei
  - koilocytes
  - increased mitotic activity
Classification of HPV related precursors

- a two tier system
- used for all squamous lesions of lower anogenital tract
  - vulva
  - vagina
  - cervix
  - penis
  - anus
- low grade squamous intraepithelial lesions (LSIL)
- high grade squamous intraepithelial lesions (HSIL)
**Classification of HPV related precursors**

<table>
<thead>
<tr>
<th>Current classification</th>
<th>cervix</th>
<th>vulva</th>
<th>vagina</th>
<th>penis</th>
<th>anus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VIN1</td>
<td>ValN1</td>
<td>PeIN1</td>
<td>AIN1</td>
</tr>
<tr>
<td>Former classification (but may be used as synonyms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSIL</td>
<td>CIN1</td>
<td>VIN2</td>
<td>ValN2</td>
<td>PeIN2</td>
<td>AIN2</td>
</tr>
<tr>
<td>HSIL</td>
<td>CIN2</td>
<td>VIN3</td>
<td>ValN3</td>
<td>PeIN3</td>
<td>AIN3</td>
</tr>
<tr>
<td>CIN3</td>
<td>VIN3</td>
<td>ValN3</td>
<td>PeIN3</td>
<td>AIN3</td>
<td></td>
</tr>
<tr>
<td>CIS</td>
<td>CIS</td>
<td>CIS</td>
<td>CIS</td>
<td>CIS</td>
<td>CIS</td>
</tr>
</tbody>
</table>

CIN - cervical intraepithelial neoplasia
VIN - vulvar intraepithelial neoplasia
ValN - vaginal intraepithelial neoplasia
PeIN - penile intraepithelial neoplasia
AIN - anal intraepithelial neoplasia
CIS - in situ carcinoma

Only precursors associated with HPV infection
On the vulva only a part - the so-called usual VIN (uVIN1, 2, 3); precursors of the vulva without HPV infection - differentiated VIN (dVIN), by definition high grade lesion (dVIN3 or CIS of plain type)
Precursor lesions

CIN 1

CIN 2

CIN 3

CIS
Glandular lesions - precursors

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Glandular lesions - precursors

adenocarcinoma in situ and CIN 3
## WHO Classification of Tumors

### Epithelial tumours
**Squamous tumours and precursors**
- Squamous cell carcinoma, not otherwise specified 8070/3
- Keratinizing 8071/3
- Non-keratinizing 8072/3
- Basaloid 8083/3
- Warty 8081/3
- Papillary 8092/3
- Squamous papilloma 8095/0

**Squamous intraepithelial neoplasia**
- Squamous intraepithelial neoplasia 8120/3
- Early invasive (microinvasive) squamous cell carcinoma 8076/3
- Cervical intraepithelial neoplasia (CIN) 3 / squamous cell carcinoma in situ 8070/3

**Benign squamous cell lesions**
- Condyloma acuminatum 80357/3
- Fibroepithelial polyp 80358/3

**Glandular tumours and precursors**
- Adenocarcinoma 8140/3
- Mucinous adenocarcinoma 8490/3
- Endocervical 8492/3
- Intestinal 8144/3
- Signet-ring cell 8495/3
- Papillary 8496/3
- Vaginal, vulval 8237/3
- Endometrioid adenocarcinoma 8530/3
- Clear cell adenocarcinoma 8310/3
- Serous adenocarcinoma 8441/3
- Mesonephric adenocarcinoma 9110/3

**Early invasive adenocarcinoma** 8140/3
- Adenocarcinoma in situ 8141/3
- Glanulat dysplasia 8142/3
- Benign glandular lesions 8143/3
- Mullerian papilloma 8144/3
- Endocervical polyp 8145/3

**Other epithelial tumours**
- Adenosquamous carcinoma 8560/3
- Glanulat cell carcinoma 8015/3
- Adenoid cystic carcinoma 8020/3
- Adenoid basal carcinoma 8029/3
- Neuroendocrine tumours
  - Carcinoid 8240/3
  - Atypical carcinoid 8249/3
  - Small cell carcinoma 8041/3
  - Large cell neuroendocrine carcinoma 8013/3
  - Undifferentiated carcinoma 8020/3

**Mesenchymal tumours and tumour-like conditions**
- Leiomyosarcoma 8890/3
- Endometroid stromal sarcoma, low grade 8351/3
- Undifferentiated endodermal sarcoma 8805/3
- Sarcoma botryoides 8310/3
- Alveolar soft part sarcoma 9561/3
- Angiosarcoma 9120/3
- Malignant peripheral nerve sheath tumour 9549/3
- Leiomyoma 8890/0
- Genital rhabdomyosarcoma 8850/0
- Postoperative spindle cell nodule 8852/0

**Mixed epithelial and mesenchymal tumours**
- Carcinosarcoma (malignant mullerian mixed tumour; metaplastic carcinoma) 8390/3
- Adenosarcoma 8330/3
- Wilms tumour 8961/3
- Adenofibroma 9013/3
- Adenomyoma 8953/0

**Malignant tumours**
- Malignant melanoma 8720/3
- Blue nevus 8722/3

**Miscellaneous tumours**
- Tumours of germ cell type
  - Yolk sac tumour 9071/3
  - Dermoid cyst 9064/3
  - Mature cystic teratoma 9069/0

- Lymphoid and haematopoietic tumours
  - Malignant lymphoma (specify type) 8070/3
  - Leukaemia (specify type) 8072/3

**Secondary tumours**

---

1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) (92/1) and the Systematized Nomenclature of Medicine (http://www.nlm.nih.gov). Behaviour is coded 0 for benign tumours, 1 for in situ carcinomas and grade 2 for malignant neoplasms, 3 for malignant tumours, and 4 for borderline or uncertain behaviour.

2 Intraepithelial neoplasia does not have a specific code in ICD-O. ICD-O codes are only available for lesions categorized as squamous intraepithelial neoplasia grade 3 (e.g. cervical intraepithelial neoplasia 3 = 8077/3, squamous cell carcinoma in situ = 8079/3, glandular intraepithelial neoplasia grade 3 = 8149/3, and adenocarcinoma in situ = 8149/3).
# Tumors of the uterine cervix

<table>
<thead>
<tr>
<th>Pseudotumors</th>
<th>Precursor lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>endocervical polyp</td>
<td>CIN1, CIN2, CIN3, CIS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign tumors</th>
<th>Malignant tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>fibroepithelial polyp</td>
<td>epithelial</td>
</tr>
<tr>
<td>squamous cell papilloma</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>condyloma accuminatum</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>leiomyoma</td>
<td>mesenchymal</td>
</tr>
<tr>
<td></td>
<td>leiomyosarcoma</td>
</tr>
</tbody>
</table>
Carcinoma of the cervix
Invasive cervical cancer - risk factors

- infection with high-risk types of HPV
- cigarette smoking
- oral contraceptives
- Chlamydia trachomatis infection
- low socioeconomic status

- protective factors: vegetable (tomatoes – lycopene, carrots – carotenoids, folates...?)
<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>990 cases</td>
<td>314 deaths</td>
</tr>
<tr>
<td>18,8 / 100 000 women</td>
<td>6 / 100 000 women</td>
</tr>
<tr>
<td>2,6% (of all cancer)</td>
<td>2,6% (of all cancer)</td>
</tr>
</tbody>
</table>

source: http://www.uzis.cz
Worldwide incidence of cervical cancer

source: http://info.cancerresearchuk.org
Worldwide incidence of cervical cancer

- Cervical cancer is second only to breast cancer
- Most frequent type of cancer in some developing countries
- Third leading cause of cancer mortality

Source: http://info.cancerresearchuk.org
Incidence of cancer of the uterine cervix: age-standardised rates (world) per 100,000 (all ages).

Cancer of the uterine cervix: age-standardised (world) incidence and mortality rates per 100 000 (all ages) in 18 world regions

Squamous cell carcinoma

- keratinizing
- non-keratinizing
- intercellular bridges
- nuclear atypias
- larger polygonal or oval cells
- eosinophilic cytoplasm
- usually numerous mitotic figures
Adenocarcinoma

- mucinous
- endometrioid
- clear cell
- serous

- histological features:
  - glandular architecture
  - mucus production
    (depends on histotype)
Prognostic factors

- **stage** is the most important prognostic factor
- histologic type and grade – little direct influence on survival
- other prognostic factors:
  - lymphvascular invasion (LVS!)  
  - tumor size (volume)  
  - depth of invasion  
  - parametrial involvement  
  - nodal status
<table>
<thead>
<tr>
<th>TNM classification</th>
<th>FIGO Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a IIA</td>
<td>IIIA</td>
<td>Tumour involves lower third of vagina, no extension to pelvic wall</td>
</tr>
<tr>
<td>T3a</td>
<td>IVA</td>
<td>Tumour invades mucosa of bladder or rectum or extends beyond true pelvis</td>
</tr>
</tbody>
</table>

**Note:** The presence of bullous oedema is not sufficient to classify a tumour as T4.

**M1** IVB Distant metastasis

**N** - Regional Lymph Nodes

| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

**M** - Distant Metastasis

| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>FIGO Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IA1</td>
<td>T1a1</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IA2</td>
<td>T1a2</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IB1</td>
<td>T1b1</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>T1b2</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2a</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1, T2, T3a</td>
<td>N1</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
</tr>
</tbody>
</table>

1 (51,2976).
2 A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
3 The regional lymph nodes are the paracervical, parametrial, hypogastric (internal iliac, obturator), common and external iliac, presacral, and lateral sacral nodes.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Tumor confined to uterus</td>
<td>98-99</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor confined to uterus</td>
<td>87-90</td>
</tr>
<tr>
<td>IIA</td>
<td>Tumor invades beyond uterus—not to pelvic wall of lower third of vagina; without parametrial invasion</td>
<td>62-83</td>
</tr>
<tr>
<td>IIB</td>
<td>Tumor invades beyond uterus—not to pelvic wall of lower third of vagina; with parametrial invasion</td>
<td>62-68</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>33-48</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

**TNM Classification**

T – Primary Tumour

**TNM Categories**

TX: Primary tumour cannot be assessed
T0: No evidence of primary tumour
Tis: Carcinoma in situ
T1: Invasion of myometrium
T1a: Tumour invades less than half of myometrium
T1a1: Tumour invades less than half of myometrium to within 1 mm of the myometrial-stromal junction
T1a2: Tumour invades less than half of myometrium to at least 1 mm of the myometrial-stromal junction
T1b: Tumour invades more than half of myometrium
T1b1: Tumour invades more than half of myometrium to within 1 mm of the myometrial-stromal junction
T1b2: Tumour invades more than half of myometrium to at least 1 mm of the myometrial-stromal junction
T2: Invasion of uterine serosa or endocervical stroma
T2a: Invasion of serosa without parametrial involvement
T2b: Invasion of serosa with parametrial involvement
T3: Tumour invades pelvic wall
T3a: Tumour invades pelvic wall, no extension to pelvic wall
T3b: Tumour extends to pelvic wall or causes hydronephrosis or non-functioning kidney
T4: Tumour invades mucosa of bladder or rectum or extends beyond true pelvis

**Stage**: IA (tumor confined to uterus), IB (tumor confined to uterus), IIA (tumor invades beyond uterus – not to pelvic wall of lower third of vagina; without parametrial invasion), IIB (tumor invades beyond uterus – not to pelvic wall of lower third of vagina; with parametrial invasion), III, IV.

**Stage IIIA**: T3a N0 M0
**Stage IIIB**: T1, T2, T3a N1 M0
**Stage IVA**: T4 Any N M0
**Stage IVB**: Any T Any N M1

Note: The presence of bullous oedema is not sufficient to classify a tumour as T4.

*Source: Institute of Pathology, First Faculty of Medicine, Charles University.*