CERVICAL CANCER [1,2]

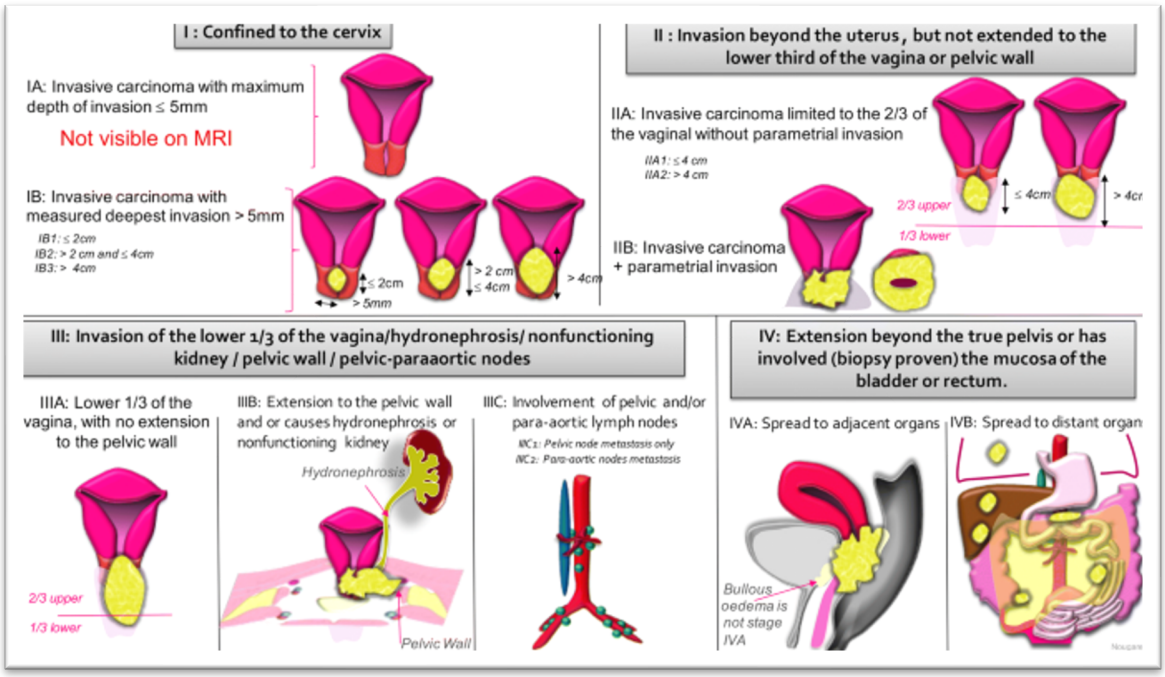
General Overview

- 4th most common cancer in women worldwide
  - Highest incidence between 35-44 years
  - Highest incidence in low-income countries due to a lack of screening
- Risk factors: HPV infection (immune suppression, history of sexual transmitted disease, multiple partners), smoking, low socio-economic status
- Pathophysiology: persistent HPV infection (70% = HPV type 16 and 18)
- Findings/symptoms: abnormal cells on pap smear, bleeding, vaginal discharge, pelvic pain
- Two main histological subtypes: squamous cell carcinoma and adenocarcinoma
- Prevention:
  - Primary: vaccination (Gardasil 9® - nonavalent vaccine), most effective in HPV-naïve patients, number needed to treat for vaccination to prevent new HPV-infections/precursor lesions after HPV-exposure: 1/42, no reimbursement after age of 19 years in Belgium (cost: €150 per vaccine, 3 vaccines needed)
  - Secondary: screening (pap smear and HPV detection) and treatment (LLETZ) of precursor lesions (CIN 2-3)

Staging (2018 FIGO classification) and Prognosis

- Physical examination (if necessary under anesthesia) with pap smear and biopsy
- Disease extent: transvaginal ultrasound, MRI of the pelvis, (PET-)CT
- Full lab including SCC tumor marker

Figure 1: 2018 FIGO classification



FIGO 2018 classification

Stage 1: The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)

IA: Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm
- **IA1:** Measured stromal invasion ≤3 mm in depth
- **IA2:** Measured stromal invasion >3 and ≤5 mm in depth

IB: Invasive carcinoma with measured deepest invasion >5 mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter
- **IB1:** Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
- **IB2:** Invasive carcinoma >2 and ≤4 cm in greatest dimension
- **IB3:** Invasive carcinoma >4 cm in greatest dimension

Stage 2: The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall

IIA: Involvement limited to the upper two-thirds of the vagina without parametrial involvement
- IIA1: Invasive carcinoma ≤4 cm in greatest dimension
- IIA2: Invasive carcinoma >4 cm in greatest dimension

IIB: With parametrial involvement but not up to the pelvic wall

Stage 3: The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes

IIIA: The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall

IIIB: Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)

IIIC: Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases), irrespective of tumor size and extent (with r and p notations)
- **IIIC1**: Pelvic lymph node metastasis only
- **IIIC2:** Para-aortic lymph node metastasis

Stage 4: The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV

IVA: Spread of the growth to adjacent pelvic organs

IVB: Spread to distant organs

- Prognosis depends on stage of the disease
  - 5-year overall survival stage IIB-IVA: 73-20%
  - Risk of recurrence: 45% in first 2 years
  - Median survival after recurrence: 12 months

Figure 2: 5-year overall survival

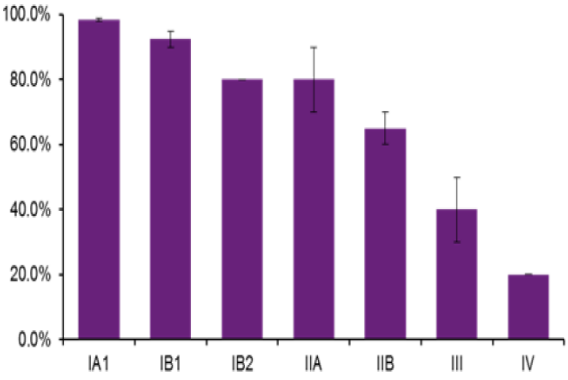
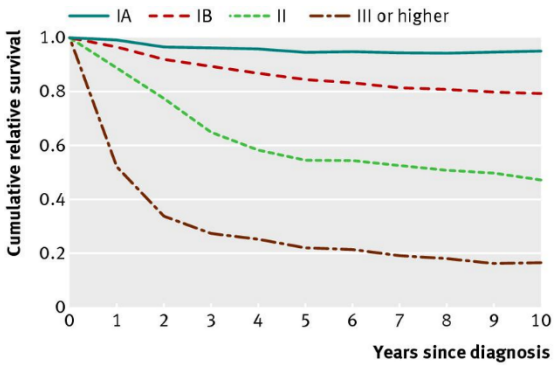


Figure 3: relative survival ratios of cervical cancer for women of all ages, by FIGO stage



	Relative survival ratios		
	1 year	5 year	10 year
IA	99 (97 to 100)	95 (91 to 97)	95 (91 to 98)
IB	97 (95 to 98)	85 (81 to 88)	80 (74 to 84)
II	89 (83 to 93)	54 (47 to 62)	47 (36 to 59)
III or higher	52 (46 to 58)	22 (17 to 28)	17 (12 to 22)

Treatment

SURGERY

- Indication: tumors ≤ 4 cm without lymph node (LN) involvement
- Technique:
  - FIGO stage IA: conization/LLETZ +/- sentinel node procedure (if LVSI +)
  - FIGO stage IA2-IB1 (≤ 2cm): simple hysterectomy with sentinel node procedure [3,4]
  - FIGO stage IB2-IIA1: radical hysterectomy + sentinel node procedure +/- pelvic lymphadenectomy; via open surgery (better OS compared to minimally invasive) [5]
  - Consider fertility sparing surgery in young patients after discussion of potential risks: trachelectomy + sentinel node procedure +/- cerclage
- Sentinel node procedure: two step procedure [6]
  - Step 1: sentinel node excision + ultra-staging
  - Step 2:
    - if LN negative: completion of (radical) hysterectomy
    - if LN positive: chemoradiation
- Adjuvant treatment:
  - High risk patients (LN +, involvement of surgical margins, parametrial involvement): adjuvant chemoradiation (with cisplatin) +/- brachytherapy
  - Intermediate risk patients (cfr. Sedlis criteria [7]): adjuvant radiation therapy

Sedlis criteria		
Lymphovascular space invasion	**Stromal invasion**	**Tumor size by clinical palpation**
+	Deep 1/3	Any
+	Middle 1/3	≥ 2cm
+	Superficial 1/3	≥ 5cm
-	Middle or deep 1/3	≥ 4cm

CHEMORADIATION THERAPY

- Stage IB3-IVA and inoperable stage IB1-IIA1
  - External beam radiation therapy (EBRT, 25x1.8Gy + 25x 0.4/0.5Gy on lymph nodes that appear pathological on imaging) + concomitant cisplatin (40mg/m² q1w during radiation therapy) + brachytherapy (2x14Gy), aim for total treatment time < 7 weeks
  - Addition of induction chemotherapy (carboplatin AUC2 + paclitaxel 80mg/m² q1w x 6 weeks) improves PFS and OS [8] (patients with FIGO 2018 stage IB3, II, IIIB, IIIC, and IVA disease)
  - Consider para-aortal lymph node dissection if negative on imaging to determine extent of the radiation field
- Neo-adjuvant chemotherapy followed by radical surgery:
  - No difference in OS but better DFS in chemoradiation group: chemoradiation therapy is preferred [9,10]

LOCAL TREATMENT OF RECURRENT DISEASE

- Surgical exenteration (anterior/posterior/both) when treated with radiation therapy before, associated with high risk of major complications (21%) and poor prognosis (5y OS 38%)
- Definitive chemoradiation if sidewall pelvic recurrence after primary surgery in radiotherapy naïve patients

SYSTEMIC THERAPY

- Indication: stage IVB or systemic recurrent disease
- First line: cisplatin 50mg/m² q3w + paclitaxel 135mg/m² q3w [11] or carboplatin AUC5 q3w + paclitaxel 175mg/m² q3w [12]
    - preference for cisplatin if not received prior
    - + bevacizumab 15mg/kg q3w if no infiltration in rectum/bladder [13]
    - + pembrolizumab 200mg q3w if PD-L1 CPS ≥ 1 [14]
- Second line:
    - cemiplimab: if not received prior IO, regardless of PD-L1 status [15]
    - chemotherapy: response rates 0-29%, PFS 2-5 months, OS 5-12 months with different agents, no agent is specifically recommended

Follow-up

- Pelvic MRI 8-12w after chemoradiation therapy
- Physical examination every 3-4 months in the first 2 years, then every 6 months in year 3-5
- No evidence to support follow-up with pap smear and HPV detection, especially not in patients treated with chemoradiation therapy
- To consider: CT thorax every year, other imaging studies only on indication

What's new

- Locally advanced setting:
    - KEYNOTE-A18 trial: association of pembrolizumab to chemoradiation therapy followed by pembrolizumab improves PFS and OS in patients with FIGO 2018 stage III-IVA cervical cancer [16, ESMO 2024]
- Metastatic/recurrent setting:
    - BEATcc trial: addition of atezolizumab to cis/carboplatin + paclitaxel + bevacizumab in 1st line improves PFS and OS regardless of PD-L1 status, no reimbursement in Belgium yet [17]
    - Innova301 trial: tisotumab vedotin vs TPC improvement of PFS, OS and ORR in second/third line [18], ongoing trials are testing TV + carboplatin in 1st line and TV + pembrolizumab in 2nd and 3rd line

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