

Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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incidence

Cervical cancer is the third most common cancer in women, with an estimated 529 828 new cases and 275 128 deaths reported worldwide in 2008. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers [1]. In developing countries, the age standardized mortality rate is 10/10 000—more than three times higher than in developed countries [2].

It is common knowledge that the most important cause of cervical cancer is persistent papillomavirus infection. The human papillomavirus (HPV) is detected in 99% of cervical tumors, in particular the oncogenic subtypes such as HPV 16 and 18. While Papanicolaou smears are used in the classical primary screening technique, HPV DNA testing, introduced in 2008, is well diffused in developed countries and is taking off in developing countries with a potentially significant reduction in the numbers of advanced cervical cancers and deaths [3].

In the HPV vaccination era, we expect that the cervical cancer incidence will be reduced, especially in those developed countries where large-scale immunization has been introduced. Most developed countries have introduced HPV vaccines into routine vaccination programs and more than 60 million doses have already been distributed in 2010, which could guarantee a protection rate of ~70% [4]. However, cervical cancer still represents a major public health problem even in developed countries: 54 517 new cases of invasive cervical cancer are diagnosed in Europe every year and 24 874 women die of this disease [4].

diagnosis and pathology/molecular biology

The WHO recognizes three categories of epithelial tumors of the cervix: squamous, glandular (adenocarcinoma), and other epithelial tumors including neuroendocrine tumors and undifferentiated carcinoma. Squamous cell carcinomas account for ~70%–80% of cervical cancers and adenocarcinomas for 10%–15%. Early cervical cancer is often asymptomatic while locally advanced disease could cause symptoms including abnormal vaginal bleeding, also after coitus, discharge, pelvic pain, and dyspareunia. Gross appearance is variable. Carcinomas can be exophytic, growing out of the surface, or endophytic with stromal infiltration with minimal surface growth. Some early cancers are not appreciable and even deeply invasive tumors may be somewhat deceptive on gross examination. If examination is difficult or there is uncertainty about vaginal/parametrial involvement, this should be done under anesthesia together with a radiotherapist. Papillary tumors are more commonly adenocarcinomas.

squamous cell carcinoma

Squamous carcinomas are composed of cells that are recognizably squamous but vary in either growth pattern or cytological morphology. Originally, they were graded using the Broders' grading system; subsequently, they were classified into keratinizing, nonkeratinizing, and small-cell squamous carcinomas. In the more recent WHO classification, the term small-cell carcinoma was reserved to tumors of neuroendocrine type. Keratinizing squamous cell carcinomas are characterized by the presence of keratin pearls. Mitoses are not frequent. Nonkeratinizing squamous cell carcinomas do not form keratin pearls by definition, but may show individual cell keratinization. Clear-cell change can be prominent in some tumors and should not be misinterpreted as clear-cell carcinoma.

adenocarcinoma

The arrangement of the invasive glands is highly variable and some tumors are in part or extensively papillary. About 80% of

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adenocarcinomas of the cervix are of endocervical or usual type; unlike normal endocervical mucinous epithelium, tumor cells are not obviously mucinous and show a rather characteristic appearance having eosinophilic cytoplasm. The great majority of endocervical-type adenocarcinomas are architecturally well differentiated, but they are cytologically grade 2 or 3. Only a subset of papillary or villoglandular adenocarcinoma is considered well differentiated for their good prognosis when in pure form; tumors with an underlying component of conventional adenocarcinoma behave as adenocarcinomas of the usual type. Unlike cervical squamous cell carcinomas, differential diagnosis of early invasive

adenocarcinoma from adenocarcinoma *in situ* showing somewhat complex architecture can be difficult. In mucinous adenocarcinoma mucin-rich cells predominate; some show gastric-type features and some are of the minimal deviation type (or adenoma malignum). Rare tumors are mixed adenosquamous carcinomas and include so-called glassy cell carcinoma. The other more rare types of cervical adenocarcinoma include clear-cell carcinoma and mesonephric adenocarcinoma.

Neuroendocrine tumors include carcinoids, atypical carcinoids, and neuroendocrine carcinomas. Diagnosis is histological and can be confirmed by neuroendocrine markers.

Table 1. Comparison of TNM categories and FIGO staging

TNM categories	FIGO stages	
TX		Primary tumor cannot be assessed.
T0		No evidence of primary tumor.
Tisb		Carcinoma <i>in situ</i> (preinvasive carcinoma).
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded).
T1ac	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of ≤ 7.0 mm. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread.
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread of ≤ 7.0 mm.
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion $> T1a/IA2$.
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension.
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension.
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina.
T2a	IIA	Tumor without parametrial invasion.
T2a1	IIA	Clinically visible lesion ≤ 4.0 cm in greatest dimension.
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension.
T2b	IIB	Tumor with parametrial invasion.
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney.
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall.
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney.
T4	IV	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.
T4a	IVA	Spread of the growth to adjacent organs.
T4b	IVB	Spread to distant organs.

pathogenesis—molecular biology

HPV has been recognized as the most important etiologic factor in cervical cancer. HPV16/18 account for at least two-thirds of cervical carcinomas in all continents; HPV 31, 33, 35, 45, 52, and 58 are the next most common types in cancers globally. A prophylactic vaccine against HPV16/18 has the potential to prevent more than two-thirds of worldwide cervical carcinomas and half of high-grade squamous intraepithelial lesions. These proportions may be even higher due to cross-protection against other high-risk HPV-type infections.

Squamous cell carcinomas and their precursor, intraepithelial squamous lesions, are related to HPV infection in almost all the cases and the presence of HPV 18 DNA is associated with poor prognosis. Adenocarcinomas encompass a heterogeneous group of tumors. Endocervical adenocarcinoma of usual type and its precursor, the adenocarcinoma *in situ*, have been shown to be positive for HPV in nearly 90% and 100% of cases. HPV 18 is more common in adenocarcinomas and adenosquamous carcinomas than in squamous cell carcinomas.

Unlike endocervical adenocarcinoma of usual type, the other more rare types including clear-cell and mesonephric adenocarcinoma seem to be unrelated to HPV.

Several markers identified along the carcinogenetic pathways have been studied. P53 RAS mutations are rare in cervical carcinomas. EGFR, HER2, VEGS, COX-2, and c-myc were tested as prognostic or predictive factors, but the results were not conclusive. Similarly, estrogen and progesterone receptors do not play a significant role; however, they can be useful in differential diagnosis between endocervical type and endometrioid adenocarcinomas, together with vimentine, CEA, and p16.

staging and risk assessment

The cervical cancer Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification is based on clinical examination [5]. A comparison between TNM classification (The American Joint Committee on Cancer) and FIGO staging is shown in Table 1.

The FIGO classification is based on tumor size, vaginal or parametrial involvement, bladder/rectum extension, and distant metastases. It requires radiological imaging such as chest X-ray and intravenous pyelogram. Other imaging studies

have been used to more accurately define the extent of disease. Computed tomography (CT) can detect pathologic lymph nodes, while magnetic resonance imaging can determine tumor size, degree of stromal penetrations, vaginal extension, and corpus extension with high accuracy [6]. More recently, positron emission tomography (PET) has been seen to have the potential to accurately delineate the extent of disease, particularly in lymph nodes that are not macroscopically enlarged and in distant sites, with high sensitivity and specificity. In early-stage disease, PET/CT has a sensitivity of 53%–73% and specificity of 90%–97% for the detection of lymph node involvement, while in more advanced stages the sensitivity for detecting the involvement of para-aortic nodes increases to 75% with 95% specificity [7]. Several investigators have reported on the evaluation of sentinel lymph node in early stages to avoid complete lymphadenectomy or to increase accuracy, but no definitive conclusions can be drawn. Similarly, the need for pretreatment surgical para-aortic lymph node assessment in locally advanced cervical cancer is still a matter of debate [8].

Tumor risk assessment includes tumor size, stage, depth of tumor invasion, lymph node status, lymphovascular space involvement (LVSI), and histological subtype. Lymph node status and number of lymph nodes involved are the most important prognostic factors. In stages IB–IIA, the 5-year survival rate without lymph node metastasis and with lymph node metastasis is 88%–95% and 51%–78%, respectively [9].

management of local/locoregional disease

primary treatment

Depending on stage, primary treatment consists of surgery, radiotherapy, or a combination of radiotherapy and chemotherapy. Definitive radiation therapy should consist of pelvic external beam radiation with high-energy photons and intracavitary brachytherapy, and must be administered at high doses (>80–90 Gy) and in a short time (<55 days), with the best technological resources available.

stage IA1

Stage IA1 cervical cancer can be managed conservatively to preserve fertility, with conization without lymphadenectomy,

because the risk of nodes metastasis is <1%. The cone's margins must be free of disease. If a nonfertility-preserving therapy hysterectomy is performed, ovaries need not be removed. In the presence of LVSI, lymphadenectomy is recommended (Table 2).

stage IA2

Stage IA2 with no LVSI can be treated by conization (if fertility is to be preserved) or extrafascial hysterectomy. In case of LVSI pelvic lymphadenectomy is indicated with radical trachelectomy or radical hysterectomy. In patients with surgical contraindication, brachytherapy may represent an alternative option.

stages IB1 to IIA1

Stages IB and IIA cervical carcinoma can be cured by radical surgery including pelvic lymphadenectomy or radiotherapy. The two procedures are equally effective, but differ in terms of morbidity and type of complications.

In the only randomized trial directly comparing radical hysterectomy and radiation therapy only in 343 women with stage IB–IIA disease, overall and disease-free survivals at 5 years were similar for the two groups (83% and 74%, respectively), and 66% of the patients in the surgical arm had adjuvant radiation for the presence of risk factors. The rate of severe morbidity was 28% in the surgery group and 12% in the radiotherapy group (level of evidence I) [10].

There is no published evidence that concurrent chemoradiation would be useful in patients with early cervical cancer (stages IB1 and IIA <4 cm).

Fertility-preserving surgery consisting of radical trachelectomy or conization with/without chemotherapy can be offered to young patients with early-stage cervical cancer wishing to preserve their fertility (level of evidence IV) [11, 12].

stages IB2 to IVA

chemoradiation

Historically, radiotherapy has been the mainstay in the treatment of locally advanced cervical cancer, with a local control rate ranging between 88% and 95% for stage IB, 70%–80% for stage IIB, and 30%–40% for stage III and 5-year survival >80% for stage IB, 65% for stage IIB, and 40% for stage III [13, 14].

Table 2. Cervical cancer treatment according to stage

Stage	Treatment	Issue
IA1	Conization or simple hysterectomy ± salpingo-oophorectomy and PLND if LVSI	Conservative surgery
IA2	Conization/radical trachelectomy or modified radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB1, IIA	Radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB2, IIB–IV	Combination CT/RT with cisplatin	NACT to large bulky tumors prior CT/RT

PLND, pelvic lymphadenectomy; LVSI, lymphovascular space invasion; CT, computed tomography; NACT, neoadjuvant chemotherapy; RT, radiation therapy.

In February 1999, the NCI published a Clinical Announcement strongly recommending the use of concurrent platinum based chemoradiation in patients with locally advanced disease based on the results of five randomized clinical trials [15–19]. These data were confirmed in further reviews and meta-analysis, the most recent of which, based on individual patient data from 18 randomized trials, demonstrated an absolute 5-year survival benefit of 8% for overall disease-free survival, 9% for locoregional disease-free survival, and 7% for metastases-free survival in all stages. The advantage is also shown for nonplatinum-based chemotherapy [I, A] [20].

Optimal radiation therapy, consisting of high doses (80–90 Gy to the target) administered over a short time (<50–55 days), significantly impacts on outcome [21].

The optimal regimen for chemotherapy has yet to be defined, but weekly single-agent cisplatin at 40 mg/m²/week during external beam therapy is widely used; concurrent carboplatin or nonplatinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing schedules.

One recent study seems to indicate a significant benefit for the use of adjuvant chemotherapy following chemoradiation. Patients with locally advanced cervical cancer (stages IIB to IV) treated with cisplatin–gemcitabine, both during and after radiation therapy, demonstrated great improvement in progression-free survival and overall survival. Despite these encouraging results, systemic consolidation should only be used in clinical trials [II, C] [22].

neoadjuvant chemotherapy to radiation

A systematic review from 18 trials and 2074 patients published in 2006 demonstrated that the timing and dose intensity of cisplatin-based neoadjuvant chemotherapy before radiation could affect outcome. However, the data are heterogeneous and deserve further confirmation [II, B] [23].

neoadjuvant chemotherapy to surgery

A meta-analysis of neoadjuvant chemotherapy followed by radical hysterectomy showed an absolute improvement of 14% in 5-year survival compared with radiotherapy [23]. However,

there are several objections because patients in the control arm received radiation therapy not in combination with chemotherapy. Moreover, in a separate analysis by stage subgroups, patients with stage III did not show any significant benefit. Neoadjuvant chemotherapy followed by radical surgery could have an important role in the treatment of locally advanced cervical cancer, but the appropriate indications still need to be established. The ongoing trial EORTC 55994 will clarify whether neoadjuvant chemotherapy followed by surgery will result into a better outcome compared with chemoradiotherapy in patients with stages IB2 to IIB cervical cancer.

adjuvant treatment

Women with risk factors on the pathology specimen should receive adjuvant therapy following hysterectomy (Table 3).

Two classes of risk are defined: intermediate and high-risk patients.

intermediate-risk disease

A Gynecologic Oncology Group (GOG) trial that randomly assigned 277 women to receive pelvic RT (without chemotherapy) or no further treatment demonstrated a benefit for postoperative RT in women with the following features: deep cervical stromal invasion (to the middle or one-third depth), lymphovascular space invasion, and large tumor size (>4 cm).

With a median follow-up of 10 years, a significant benefit has been shown for progression-free survival, but not for overall survival [24] [II, B].

high-risk disease

Women with one or more worse prognostic factors such as positive or close surgical margins, positive lymph nodes, or microscopic parametrial involvement are considered to be at high risk of relapse. In this setting of patients, adjuvant chemoradiation is indicated on the basis of a clinical trial that randomly assigned 268 women IA2, IB, and IIA to adjuvant radiotherapy with or without chemotherapy (cisplatin–5-fluorouracil) for four courses [19]. The use of chemotherapy was associated with a substantially better 4-year overall survival (81% versus 71%) and progression-free survival (80% versus 63%), and the outcome was better for patients who completed three to four cycles of chemotherapy [I, A].

management of advanced/metastatic disease

Patients with metastatic or recurrent cervical cancer are commonly symptomatic. The role of chemotherapy in such patients is palliative, with the primary objective to relieve symptoms and improve quality of life. The response rates after previous chemotherapy are worse compared with

Table 3. Necessary histopathologic parameters for assessment of cervical cancer

Histopathologic evaluation
Dimensions of the tumor
Stromal invasion/depth of the wall involved
Tumor differentiation
LVSI
Status of resection margins
Status of parametria and vaginal cuff
Number and status of lymph nodes

LVSI, lymphovascular space invasion.

chemotherapy naïve patients [25, 26]. Cisplatin is considered the single most active cytotoxic agent; overall, the duration of the objective response to cisplatin in patients with metastatic or recurrent disease remains disappointing and survival in such patients is only ~7 months. There is not a clear dose-response effect. Cisplatin-based combination therapy, such as cisplatin–paclitaxel and cisplatin–topotecan, has been extensively investigated in clinical trials. Only the cisplatin–topotecan combination reported an overall survival advantage compared with monotherapy [27]. A recent phase III trial assessed four cisplatin–doublet regimens (cisplatin–paclitaxel, cisplatin–topotecan, cisplatin–gemcitabine, and cisplatin–vinorelbine) [28]. No significant differences in overall survival were seen; however, the trends for response rate, PFS, and OS suggest that cisplatin–paclitaxel is the preferred regimen. Carboplatin and paclitaxel is a more attractive combination from the point of view of toxicity, and although phase II trials have demonstrated that it is a very active regimen, this has not been confirmed in randomized studies [29]. It was confirmed in a Japanese phase III trial (JCOG0505) and presented at ASCO 2012, but only for patients previously exposed to platinum. In platinum-naïve patients paclitaxel–cisplatin still seemed preferable [30].

response evaluation and follow-up

No definitive agreement exists on the best post-treatment surveillance. A clinical visit with gynecological examination including PAP smear is usually performed every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. CT or PET/CT scan should be performed as clinically indicated.

conflict of interest

The authors have reported no potential conflicts of interest.

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