clinical practice guidelines

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

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incidence

The crude incidence of cervical cancer in the European Union is 13.2/100 000 and the crude mortality rate is 5.9/100 000 women/year. Nearly 500 000 cervical cancer new cases are occurring worldwide each year, responsible for 274 000 deaths. Cervical cancer represents the third most common cause of female mortality. The mortality is 10 times higher in developing countries, where ~80% of new cases occur, compared with developed countries, since screening and treatment programmes are frequently inaccessible to women in developing countries. The screening capacity is satisfactory in most European Union member states, even if, based on data from available screening registers, the coverage of the screening test is <80% in all programmes, ranging from 10% to 79%. Early age at first sexual intercourse and early pregnancies have been recently evidenced as risk factors for cervical cancer in developing countries. High-risk persistent infection with sexually transmittable human papillomavirus is responsible for virtually all cases of cervical cancer. HPV-16 and HPV-18 are the most prevalent of the oncogenic types. In addition to screening techniques including conventional Papanicolaou smear and HPV DNA testing, primary prevention via vaccination against HPV is now available. The high efficacy of the vaccines may dramatically decrease cervical cancer, preventing up to 70% of newly diagnosed cases. The cost of the vaccine, however, precludes its widespread implementation and may increase the difference in mortality with developing countries.

diagnosis

Pathological diagnosis should be made according to the World Health Organization classification based on a surgical biopsy.

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staging and risk assessment

Clinical examination represents the basis for Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification, which is the most widely used classification. This classification is based on tumoral extension, clinically assessed, depending on tumour size, vaginal and/or parametrial involvement, and bladder/rectum tumoral extension (Table 1). FIGO classification has been recently reviewed and has integrated sub-division in IIA tumours, based on clinical tumour size assessment. FIGO classification requires basic complementary examinations including chest X-ray and intravenous pyelogram. Nowadays, magnetic resonance imaging (MRI) is considered the reference complementary examination as it is superior to computed tomography (CT) scan for tumour extension assessment and equal to CT scan for nodal involvement assessment. MRI should be preferred to CT scan and include pelvic and abdominal imaging. MRI and CT have low sensitivities for nodal involvement. Ultra-small particles of iron oxide (USPIO), used as MRI contrast agent, seem to improve sensitivity. USPIO is currently under investigation by the Gynecology Oncology Group. Positron emission tomography (PET) has been reported to have sensitivity and specificity of 100% and 99%, respectively. PET is still under evaluation, and is compared with surgical nodal staging. A thoracic CT scan may be included for metastasis assessment.

Surgical pelvic and para-aortic nodal staging are optional. In early stage cervical cancer, sentinel node procedure is currently under study. This technique seems to be a feasible method of lymph node assessment with a high detection rate, and low false-negative rate, and may even represent a more sensitive procedure than pelvic lymphadenectomy.

Tumour risk assessment includes tumour size, stage, nodal involvement, lymphovascular space involvement and histological subtype. Squamous cell carcinoma is the most frequent histological type, accounting for 80%–90% of the cancers. Adenocarcinoma represents 10%–20% of cervical cancer histologies, with an increase in relative distribution of adenocarcinoma compared with squamous cell carcinoma in developed countries. Adenocarcinoma has significantly lower survival rates compared with squamous cell carcinoma stage to stage, with higher distant failure rates.

Table 1. FIGO staging

0	Carcinoma *in situ* (preinvasive carcinoma)
I	Cervical carcinoma confined to the uterus; invasive carcinoma diagnosed by microscopy
IA	All macroscopically visible lesions—even with superficial invasion—are stage IB
IA1	Stromal invasion ≤3.0 mm in depth and ≤7.0 mm in horizontal spread
IA2	Stromal invasion >3.0 mm and ≤5.0 mm with a horizontal spread ≤7.0 mm
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
II	Tumour beyond the uterus but not to pelvic wall or to lower third of the vagina
IIA	without parametrial extension
IIA1	clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	clinically visible lesion >4.0 cm in greatest dimension
IIB	with parametrial extension
III	Tumour extends to pelvic wall and/or involves lower third of the vagina and/or with hydronephrosis or non-functioning kidney
IIIA	Tumour involvement of the lower third of the vagina without extension to the pelvic wall
IIIB	Tumour extension to the pelvic wall and/or causes hydronephrosis or non-functioning kidney
IVA	Tumour involvement of rectal and/or bladder mucosa and/or extends beyond true pelvis
IVB	Distant metastasis

treatment

Multidisciplinary treatment planning is mandatory, based on tumour size and extension.

FIGO stage IA1

Standard treatment consists of conization with free margins or simple hysterectomy (according to patient age). In case of lympho-vascular space involvement, pelvic lymphadenectomy is recommended. In patients with at least two high-risk factors (deep stromal invasion, lymphovascular space involvement, large primary tumours) postoperative pelvic radiotherapy with or without concomitant chemotherapy should be considered. In patients with positive margins, parametrial involvement or pelvic node involvement, standard treatment consists of complementary concomitant chemoradiation.

FIGO stage IA2

Surgery is the standard. Options consist of conization or trachelectomy in young patients and simple or radical hysterectomy in other patients. Pelvic lymphadenectomy is required. In patients with positive margins, parametrial involvement or pelvic node involvement, standard treatment consists of complementary concomitant chemoradiation.

FIGO stage IB1

There is no standard treatment. Options consist of surgery, external irradiation plus brachytherapy or combined radio-surgery.

Standard surgery consists of radical hysterectomy, bilateral oophorectomy and pelvic lymphadenectomy. Conservative fertility-sparing surgery can be proposed in young patients with tumour presenting excellent prognostic factors, consisting of radical trachelectomy. Potential candidates are patients with tumours having largest diameter of <20 mm, without lymphovascular space involvement and without lymph node involvement. A review of 548 patients treated with radical trachelectomy and lymphadenectomy reported a recurrence rate of ∼5%, in accordance with what has been reported for standard colpohysterectomies. Pregnancy outcomes were reported to be within the range 41%–78%. These data however, do not represent a Level I of treatment evidence.

Combined radio-surgery, which represents a therapeutic option, usually consists of preoperative brachytherapy followed 6–8 weeks later by surgery. In patients treated with upfront surgery presenting positive margins, disease within parametria or pelvic node involvement, standard treatment consists of complementary concomitant chemoradiation.

FIGO stage IB2–IVA

Concomitant chemoradiation represents the standard. This modality is superior to radiotherapy alone for local control, metastasis rate, disease-free and overall survival. A meta-analysis was recently performed, based on 18 trials with individual patient data, collecting a total of 3452 patients. Cisplatin-based chemotherapy was used in 85% of the patients. The results demonstrated a 6% improvement in absolute 5-year survival (from 60% to 66%) and 8% improvement in 5-year disease-free survival with chemoradiotherapy. A larger benefit was seen in two trials in which chemotherapy was given after chemoradiotherapy with an absolute improvement of 19% at 5 years. Patients with advanced stage IB2–IIA/B may benefit more from chemoradiotherapy than patients with stage III and IVA, translating to a 5-year survival benefit of 10% for women with stage IB–IIA, 7% for women with stage IIB and 3% for women with stage IIIB–IVA. Non-platinum-based regimens for chemoradiation appear to be as efficient as platinum-based chemotherapy. The most common regimen, however, is cisplatin monotherapy 40 mg/m^2 on a weekly schedule. Chemoradiotherapy increases acute toxicity, particularly gastrointestinal and haematological side-effects. Late effects of this combined treatment have not been extensively studied in the literature. The role of adjuvant chemotherapy after concomitant chemoradiation remains unclear and should be included in further clinical investigations. One randomized

study has recently been presented showing the benefit of adjuvant chemotherapy with cisplatin–gemcitabine after concomitant chemoradiation.

The use of recombinant human erythropoietin to increase haemoglobin levels in the context of concomitant chemoradiation within the frame of a randomized study failed to show any therapeutic ratio, as the trial was prematurely closed, due to an excess of thromboembolic events in the erythropoietin arm. Less than 25% of the planned patients had entered the study and the difference in thromboembolic events was not statistically significant between the two randomized arms.

External irradiation is combined with brachytherapy and the total treatment duration should remain <55 days. MRI 3-D based brachytherapy seems to improve local control. Complementary extra-fascial hysterectomy after radiotherapy has been evaluated within the frame of a randomized trial by the RTOG group. There was no survival difference between the two arms, with a potential benefit among patients with persistent disease. This complementary surgery can therefore be considered as an option for patients with persistent disease.

Neoadjuvant chemotherapy remains controversial and is currently under investigation by the EORTC (55994). A systematic review with individual patient data meta-analysis has demonstrated the superiority of neoadjuvant chemotherapy followed by surgery over radiotherapy in terms of overall survival. In spite of these results, neoadjuvant chemotherapy has not been considered as a standard for two reasons: one is the inferiority of the control arm (radiotherapy alone) compared with the present standard of concomitant chemoradiation arm in this meta-analysis and second is the results of the GOG 141 study, showing no advantage of neodjuvant chemotherapy with vincristine and cisplatin before radical hysterectomy and pelvic/para-aortic lymphadenectomy in bulky stage IB.

FIGO stage IVB

Platinum-based combination chemotherapy has a potential benefit. A statistically significant benefit on median overall survival, median progression-free survival, and overall response rate was evidenced with a combination of cisplatin plus topotecan, compared with cisplatin alone in a randomized trial conducted by the GOG. Another randomized trial conducted by the GOG compared four cisplatin doublets. No regimen was superior to cisplatin and paclitaxel. Although this regimen showed a trend in favour of response rate and progression-free survival, there were no statistically significant differences. Differences in chemotherapy schedules should take into account pre-existing morbidity and potential toxicity for individualized treatment.

locoregional and metastatic recurrence

For most patients palliative chemotherapy is the standard option. Pelvic surgery (exenteration in most cases) is an option in selected cases of central pelvic recurrence. Salvaged radiotherapy should be considered as an option for patients with pelvic recurrence without prior irradiation.

follow-up

The most appropriate follow-up strategy has not been clearly stated. Clinical with gynaecological examination including PAP smear are usually performed every 3 months for the first 2 years, every 6 months for the next 3 years and yearly thereafter. SCC dosage in squamous cell carcinoma may be useful in patients' follow-up if initially increased. PET/CT might have a role in early local recurrence and metastasis detection.

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