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Annals of Oncology 28 (Supplement 4): iv72–iv83, 2017
doi:10.1093/annonc/mdx220

CLINICAL PRACTICE GUIDELINES

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

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†Approved by the ESMO Guidelines Committee: January 2008, last update May 2017. This publication supersedes the previously published version—*Ann Oncol* 2012; 23(Suppl 7): vii27–vii32.

Incidence and epidemiology

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females in less developed countries. There were an estimated 527 600 new cervical cancer cases and 265 700 deaths worldwide in 2012 [1]. Nearly 90% of cervical cancer deaths occurred in developing parts of the world. The large geographic variation in cervical cancer rates reflects differences in the availability of screening (which allows for the detection and removal of precancerous lesions) and in human papillomavirus (HPV) infection prevalence.

However, cervical cancer still represents a major public health problem even in developed countries: more than 58 000 new cases of cervical cancer are diagnosed and ∼24 000 patients die in Europe every year [2]. Five-year relative survival for European women diagnosed with cervical cancer in 2000–2007 was 62%, ranging from 57% in Eastern Europe to 67% in Northern Europe. Survival was particularly low (< 55%) in Bulgaria, Latvia and Poland and highest in Norway (71%) [3]. Survival decreased with advancing age at diagnosis, from 81% for 15–44-year olds to 34% for women ≥ 75 years. Survival increased significantly from 61% in 1999–2001 to 65% in 2005–2007. FIGO stage is one of the most important prognostic factors.

The most significant cause of cervical cancer is persistent papillomavirus infection. HPV is detected in 99% of cervical tumours, particularly the oncogenic subtypes such as HPV 16 and 18.

To date, three HPV vaccines are licensed and available: the bivalent HPV virus-like particle vaccine (2vHPV), the quadrivalent HPV virus-like particle vaccine (4vHPV) and nine-valent HPV virus-like particle vaccine (9vHPV). All 3 vaccines provide protection against HPV 16 and 18. 4vHPV also includes HPV 6 and 11 which cause 90% of genital warts. Furthermore, 9vHPV covers 5 more oncogenic HPV viruses (HPV 31, 33, 45, 52 and 58) in addition to the types already included in 4vHPV, which cause an additional 15% of HPV-related cancers in women and 4% of those in men [4]. Both the 2vHPV and 4vHPV have significant cross-protective activity against other oncogenic viruses. All three are efficacious against related infection and cervical, vaginal, vulvar and anal dysplasia [5–7].

Post-licensure reports from countries with established HPV vaccination programs indicate that HPV vaccination has a beneficial effect at the population level as early as 3 years after the introduction of an HPV vaccination programme, including decreases in the incidence of high-grade cervical abnormalities, the prevalence of vaccine HPV types and the incidence of genital warts [8, 9]. Prophylactic administration of HPV vaccine can effectively prevent infection and disease associated with the vaccine HPV types. The effect of vaccination on the burden of cancer remains to be determined but, according to surrogate markers, it is expected to prevent > 70% of cervical cancers.

For many years, the Papanicolaou (Pap) test has been the standard method for cervical cancer screening, reducing the incidence by 60%–90% and the death rate by 90%. However, the limitations of this cytology-based test are the sensitivity (∼ 50%) and significant proportion of inadequate specimens. More recently, an HPV test has been introduced as a screening tool as HPV deoxyribonucleic acid (DNA) is present in almost all cervical cancers and it has demonstrated higher sensitivity for high-grade cervical intraepithelial neoplasia (CIN2+) than that achieved by cytology in several studies. A pooled analysis of four randomised controlled trials of HPV-based cervical screening versus conventional cytology showed that HPV-based cervical screening provides 60%–70% greater protection against invasive

cancer compared with cytology-based screening [10]. Findings support HPV-based screening with triage at prolonged intervals, starting at age 30 years. Especially in a vaccinated population when dysplastic lesions will be less frequent, screening with Pap tests will be more difficult. Pap cytology has significant limitations. It is based on the subjective interpretation of morphological alterations present in cervical samples that must be collected with proper attention to sampling cells of the transformation zone. Also, the highly repetitive nature of the work of screening many smears leads to fatigue, which invariably causes errors in interpretation.

Therefore, primary prevention of cervical cancer is now possible via immunisation with highly efficacious HPV vaccines [II, A] and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programmes [II, A].

Diagnosis and pathology/molecular biology

Abnormal cervical cytology or a positive high-risk HPV test should lead to colposcopy and biopsy or excisional procedures such as loop electrosurgical excision and conisation. 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 easily detected and even deeply invasive tumours may be somewhat deceptive on gross examination. If examination is difficult or there is uncertainty about vaginal/parametrial involvement, examination should preferably be done under anaesthesia by an interdisciplinary team including a gynaecological oncologist and a radiation oncologist.

The World Health Organization (WHO) recognises three categories of epithelial tumours of the cervix: squamous, glandular (adenocarcinoma) and other epithelial tumours including adenosquamous carcinoma, neuroendocrine tumours and undifferentiated carcinoma (Table 1). Squamous cell carcinomas account for ~70%–80% of cervical cancers and adenocarcinomas for 20%–25%.

Squamous cell carcinoma

Squamous carcinomas are composed of cells that are recognisably squamous but vary in either growth pattern or cytological morphology. Originally, they were graded using Broders' grading system; subsequently, they were classified into keratinising, non-keratinising and small-cell squamous carcinomas. In the more recent WHO classification, the term small-cell carcinoma was reserved for tumours of neuroendocrine type. Keratinising squamous cell carcinomas are characterised by the presence of keratin pearls. Mitoses are not frequent. Non-keratinising squamous cell carcinomas do not form keratin pearls by definition, but may show individual cell keratinisation. Clear-cell changes can be prominent in some tumours and should not be misinterpreted as clear-cell carcinoma.

Table 1. WHO histological classification of tumours of the uterine cervix

Epithelial tumours	
1. **Squamous tumours and precursors**	
Squamous cell carcinoma, not otherwise specified	8070/3
Keratinising	8071/3
Non-keratinising	8072/3
Basaloid	8083/3
Verrucous	8051/3
Warty	8051/3
Papillary	8052/3
Lymphoepithelioma-like	8082/3
Squamotransitional	8120/3
Early invasive (microinvasive) squamous cell carcinoma	8076/3
Squamous intraepithelial neoplasia	
Cervical intraepithelial neoplasia (CIN) 3/ squamous cell carcinoma *in situ*	8077/2 8070/2
Benign squamous cell lesions	
Condyloma acuminatum	
Squamous papilloma	8052/0
Fibroepithelial polyp	
2. **Glandular tumours and precursors**	
Adenocarcinoma	8140/3
Mucinous adenocarcinoma	8480/3
Endocervical	8482/3
Intestinal	8144/3
Signet-ring cell	8490/3
Minimal deviation	8480/3
Villoglandular	8262/3
Endometrioid adenocarcinoma	8380/3
Clear cell adenocarcinoma	8310/3
Serous adenocarcinoma	8441/3
Mesonephric adenocarcinoma	9110/3
Early invasive adenocarcinoma	8140/3
Adenocarcinoma *in situ*	8140/2
Glandular dysplasia	
Benign glandular lesions	
Müllerian papilloma	
Endocervical polyp	
3. **Other epithelial tumours**	
Adenosquamous carcinoma	8560/3
Glassy cell carcinoma variant	8015/3
Adenoid cystic carcinoma	8200/3
Adenoid basal carcinoma	8098/3
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	
Mixed epithelial and mesenchymal tumours	
Melanocytic tumours	
Miscellaneous tumours	
Lymphoid and haematopoetic tumours	
Secondary tumours	

Morphology code of the International Classification of Diseases for Oncology (ICD-O) {921} and the Systematized Nomenclature of Medicine (http://snomed.org).
WHO, World Health Organization.

Adenocarcinoma

The arrangement of the invasive glands is highly variable and some tumours are in part or extensively papillary. About 80% of adenocarcinomas of the cervix are of endocervical or usual type; unlike normal endocervical mucinous epithelium, tumour cells are not obviously mucinous and show a rather characteristic appearance having eosinophilic cytoplasm. The most common type is the mucinous type which comprises endocervical, intestinal and gastric subtypes. 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; tumours 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 tumours are mixed adenosquamous carcinomas and include the so-called glassy cell carcinoma. The other rarer types of cervical adenocarcinoma include clear-cell carcinoma and mesonephric adenocarcinoma.

Other cervical carcinoma

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

Pathogenesis—molecular biology

HPV has been recognised as the most important aetiological factor in cervical cancer. HPV 16/18 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 of cancers globally.

HPV vaccines have a great impact on cervical cancer and HPV-associated cancers in males and females, thus leading to an annual reduction of 90% of cervical cancer, 85% of vaginal cancer HPV correlates, 87% of vulvar cancer HPV correlates, 92% of anal cancer HPV correlates and 85% of penile cancer HPV correlates [11–13].

Squamous cell carcinomas and their precursor, intraepithelial squamous lesions, are related to HPV infection in almost all cases and the presence of HPV 16 DNA is associated with poor prognosis. Adenocarcinomas encompass a heterogeneous group of tumours. 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, respectively. HPV 18 is more common in adenocarcinomas and adenosquamous carcinomas than in squamous cell carcinomas. Unlike endocervical adenocarcinoma of usual type, the other rarer types including clear-cell and mesonephric adenocarcinoma seem to be unrelated to HPV.

Staging and risk assessment

Cervical tumours are staged using the Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) and the Union for International Cancer Control (UICC) TNM staging classifications (8th edition) shown in Table 2. Cervical cancer is the only gynaecological cancer that is clinically staged based on tumour size, vaginal or parametrial involvement, bladder/rectum extension and distant metastases. It requires examination under anaesthesia, radiological imaging such as chest X-ray and intravenous pyelogram. These have been widely replaced by more timely diagnostic tools. Other imaging studies are used routinely to more accurately define the extent of disease and to allow tailoring of treatment, but do not affect the clinical stage. Computed tomography (CT) can detect pathological lymph nodes, while magnetic resonance imaging (MRI) can determine tumour size, degree of stromal penetrations, parametrial involvement, vaginal extension and corpus extension with high accuracy [14]. 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 [15]. The need for pretreatment surgical para-aortic lymph node assessment in locally advanced cervical cancer (LACC) is still a matter of debate [16].

Tumour risk assessment includes tumour size, stage, depth of tumour invasion, lymph node status, lymphovascular space invasion (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 rates without lymph node metastasis and with lymph node metastasis are 88%–95% and 51%–78%, respectively [17].

Controversy exists as to whether histological type is an independent prognostic factor for survival. Although some studies have shown no differences in survival between adenocarcinoma and squamous cell carcinoma, the majority have shown that adenocarcinoma carries a worse prognosis with 10%–20% differences in 5-year overall survival (OS) rates.

Cervical small-cell neuroendocrine carcinoma is a rare disease, accounting for only up to 2% of all invasive cervical cancers but has a particular propensity to spread distantly, which is similar to small-cell carcinoma of the lung. As a result, patients can present with systemic symptoms such as weight loss. In addition, patients may present with a paraneoplastic syndrome such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing syndrome, hypercalcaemia or a neurological disorder. The most commonly involved organs include the liver, adrenals, bone, bone marrow and the brain.

Management of local/locoregional disease (Figure 1)

Primary treatment

Surgery. Surgical therapy in cervical cancer is adapted to the stage of disease according to FIGO and TNM classification (Table 2). Microinvasive cervical cancer (stage IA1) without LVSI can be managed with conisation or simple trachelectomy to preserve

Table 2. The staging of cervical tumours is by the Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) and TNM classification (Union for International Cancer Control) [61]

TNM clinical classification

TNM categories	FIGO stages	Definition
T – Primary Tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma *in situ* (preinvasive carcinoma)
T1	I	Tumour confined to the cervix[a]
T1a[b,c]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[d]
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less[d]
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumour with parametrial invasion
T3	III	Tumour involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumour involves lower third of vagina
T3b	IIIB	Tumour extends to pelvic wall, or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[e]
N – Regional Lymph Nodes[f]		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M – Distant Metastasis[f]		
M0		No distant metastasis
M1		Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes metastasis to vagina, pelvic serosa, and adnexa

[a]Extension to corpus uteri should be disregarded.
[b]The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.
[c]All macroscopically visible lesions even with superficial invasion are T1b/IB.
[d]Vascular space involvement, venous or lymphatic, does not affect classification.
[e]Bullous oedema is not sufficient to classify a tumour as T4.
[f]No FIGO equivalent.
TNM, tumour, node and metastasis.
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fertility [I, B] [18]. Simple hysterectomy can be offered if the patient does not wish to preserve fertility. In stage IA1 with LVSI, surgical assessment of pelvic lymph nodes should be discussed with the patient, including the sentinel lymph node (SLN, see below).

In patients with FIGO stage IA2, IB and IIA, radical hysterectomy with bilateral lymph node dissection (with or without SLN) is standard treatment, if the patient does not wish to preserve fertility [I, B]. This can be carried out either by laparotomy or laparoscopy (which can be robotically assisted). The minimally invasive approach is gaining increasing relevance and is standard in most centres, since it appears to offer similar oncological safety with favourable surgical morbidity [19].

Sentinel lymph node dissection in cervical cancer. SLN dissection (SLND) is standard in the treatment of breast cancer as well as vulvar cancer and increasing evidence also suggests an important role for SLND in cervical cancer. While the evidence is still evolving and guideline recommendations are not yet clearly defined, it should be considered in FIGO stage I

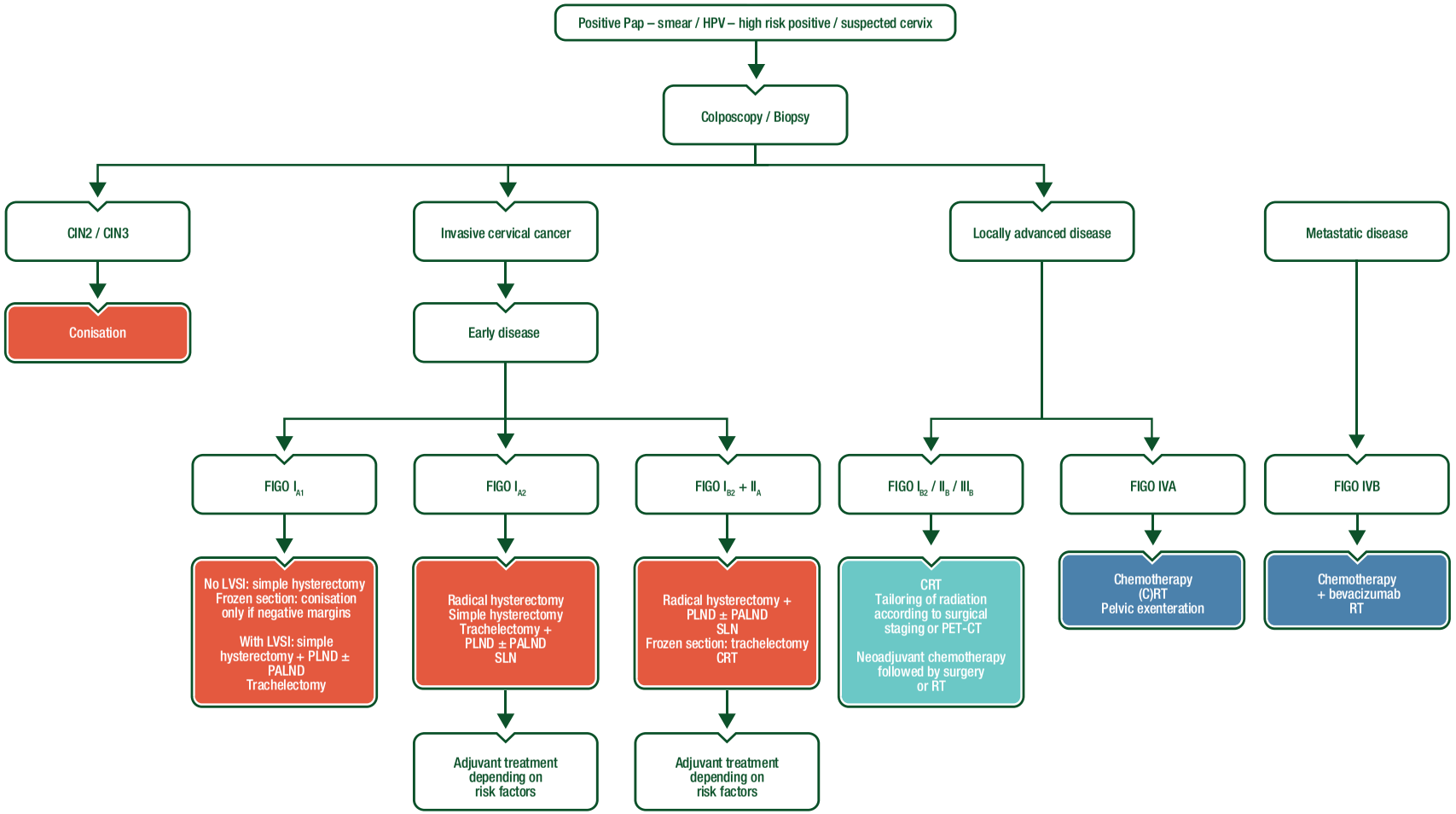

Figure 1. Treatment algorithm for cervical cancer.
CIN, cervical intraepithelial neoplasia; CRT, chemoradiotherapy; FIGO, Féderation Internationale de Gynécologie et d'Obstétrique; HPV, human papillomavirus; LVSI, lymphovascular space invasion; PALND, para-aortic lymph node dissection; Pap, Papanicolaou; PET-CT, positron emission tomography/computed tomography; PLND, pelvic lymph node dissection; RT, radiotherapy; SLN, sentinel lymph node.

patients with tumours of ≤ 4 cm. Some evidence suggests that the detection rate is highest if the tumour is < 2 cm. Tracer is injected directly into the cervix, and blue dye, technetium radiocolloid or fluorescent indocyanine green is used. SLND should be done only in centres with enough expertise and training. Sentinel nodes should be detected on both sides [II, B] [20].

Surgical therapy of the uterus. Since radiotherapy (RT) and surgery are equally effective in early stages, surgery should only be considered in patients with earlier stages (up to FIGO IIA) without risk factors necessitating adjuvant therapy, which results in a multimodal therapy without improvement of survival but increased toxicity [I, A].

It is important to note that the currently established radical hysterectomy with extensive parametrial resection most likely constitutes overtreatment in many patients, especially those with small and locally restricted tumours. Large randomised studies such as the SHAPE study are currently enrolling patients to compare simple hysterectomy with radical hysterectomy in this population [21].

Neoadjuvant chemotherapy to surgery. The rationale for the use of neoadjuvant chemotherapy (NACT) includes: (i) reduction of the primary tumour size, allowing operability; (ii) eradication of micrometastatic disease; and (iii) potential increase in tumour vascularisation and reduction of the number of hypoxic cells [22–24].

In a meta-analysis, NACT followed by radical surgery showed a highly significant 35% reduction in the risk of death compared with RT alone [hazard ratio (HR) = 0.65; $P = 0.0004$], with an absolute improvement of 14% in survival at 5 years, increasing from 50% to 64% [25]. The analysis included data from 872 patients with LACC enrolled in five different trials. The largest trial included in a second meta-analysis, enrolled 441 FIGO stage IB2–III cervical cancer patients and compared platinum-based NACT followed by radical surgery with conventional RT. The main criticism of this study is related to the suboptimal RT administration; almost 27% of patients did not receive intracavitary RT; 11% of patients received less than 60 Gy of external pelvic beam radiation total dose at point A and the median total dose delivered was 70 Gy, while the optimal treatment is considered to be 80–90 Gy at point A.

Moreover, in all of these studies, the control arm, RT alone without concomitant chemotherapy, does not represent the current standard of care for LACC. In addition, the RT total dose and the median time of RT administration were sometimes suboptimal.

There are two randomised phase III trials that have explored the role of NACT followed by surgery versus chemoradiotherapy (CRT), but the results are not yet available (EORTC Protocol 55994 and NCT00193739) [26, 27].

Moreover, a recent meta-analysis comparing NACT followed by surgery versus surgery alone confirmed that patients treated with NACT had higher local control [odds ratio (OR) = 0.67; 95% confidence interval (CI): 0.45–0.99; $P = 0.04$)] [28]. Exploratory analysis of pathological response showed a significant decrease in adverse pathological findings with NACT (OR = 0.54; $P < 0.0001$ for lymph node status; OR = 0.58; $P = 0.002$ for parametrial infiltration). However, a significant percentage of patients will not have surgery because of treatment toxicity or insufficient response.

These results indicate that NACT may offer a benefit over surgery alone in cervical cancer patients (borderline LACC, nodes positive, parametrial invasion at MRI), reducing the need for adjuvant RT [I, C].

Chemoradiotherapy in locally advanced cervical cancer. CRT has been the standard of care for patients with bulky IB2–IVA disease for almost two decades. The near simultaneous publication of five randomised trials, three in LACC, collectively demonstrating an improvement in both disease-free survival (DFS) and OS with concomitant chemotherapy and RT over standard RT/hydroxyurea (endorsed by the National Cancer Institute) changed clinical practice worldwide [I, A] [29–33]. However, concerns were raised about the applicability of the results in view of patient selection, protracted overall treatment time, the lack of a RT-only control arm and the poor outcome in the control group. An individual patient data meta-analysis was undertaken to address these issues [34]. The authors identified 18 randomised trials with an RT-only control arm from 11 countries with the subsequent analysis limited to 13 trials. The analysis confirmed the benefit of CRT but with a smaller effect. The HR for OS and DFS was 0.81 and 0.78, respectively, which translates into an absolute improvement of 6% and 8% in OS and DFS, respectively. The estimated absolute survival benefit for CRT compared with RT alone was 10% for those with FIGO stage I/II disease, compared with 3% for those with FIGO stage III/IVa. The most commonly used regimen is weekly cisplatin 40 mg/m^2, although the meta-analysis also reported significant benefits with non-platinum agents [I, A] [34].

More recently, colleagues in Mexico reported on a large randomised phase III trial comparing standard CRT with a more intensive concomitant approach with gemcitabine/cisplatin followed by an additional two cycles of adjuvant chemotherapy [35]. Yet, despite a reported 9% improvement in progression-free survival (PFS) at 3 years with treatment intensification, this approach has not been widely adopted amid concerns about toxicity [II, C]. Meanwhile two international trials of additional chemotherapy delivered either before (INTERLACE) or after CRT (OUTBACK) are ongoing and will hopefully answer the question as to whether this approach will improve OS further.

Technical advances in imaging and in RT planning have facilitated a move towards increased precision in brachytherapy practice. This approach has been championed by groups in Austria, Denmark and France with the dual aim of improving outcome through dose escalation while reducing the toxicity to the surrounding normal tissues [36]. A recently published multicentre cohort study (RetroEMBRACE) demonstrated excellent local control rates of 93% and 79% for patients with FIGO stage IIB and IIIB disease, respectively, at 3 years [37]. However, the 5-year actuarial OS was 65% and, while this is better than historical controls, it remains to be seen whether this truly represents an improvement in survival over standard CRT with lower RT doses. With a median follow up of 43 months, the actuarial 5-year G3–G5 morbidity was 5%, 7% and 5% to the bladder, gastrointestinal tract and vagina, respectively, confirming that the improved local control was achieved with a low risk of morbidity [I, B]. Given the rarity of small-cell neuroendocrine carcinoma, there are limited data to guide treatment of this type of cervical cancer. Most clinicians favour: the use of combined modality therapy (surgery followed by chemotherapy or combined CRT) for limited-stage potentially

resectable disease; definitive CRT for locoregionally advanced unresectable but non-metastatic disease; and palliative chemotherapy alone for those with metastatic disease, using chemotherapy regimens that are typically used for small-cell lung cancer.

Neoadjuvant chemotherapy and radiotherapy. The concept of delivering chemotherapy before RT (neoadjuvant or induction chemotherapy) has been explored in clinical trials with conflicting results. An individual patient data meta-analysis was undertaken of 18 randomised trials involving over 2000 patients [38]. Heterogeneity in trial design precluded a unified analysis. However, the authors identified cycle length and platinum dose intensity as important factors in determining the impact of NACT on outcome. The trials that delivered short-cycle chemotherapy ($\leq$ 14 days) gave a pooled HR of 0.83, equivalent to an improvement of 7% in 5-year survival. In contrast, the trials with longer chemotherapy cycles ($>$ 14 days) gave a pooled HR of 1.25, equivalent to an absolute detriment in survival of 8% at 5 years. Accelerated repopulation of resistant cancer cells during prolonged intervals (up to 6 weeks in some studies) between NACT and RT may account for the detrimental effect seen in some studies. The ongoing INTERLACE trial, which is randomising patients with LACC between standard CRT alone and 6 weeks of induction chemotherapy followed immediately in week 7 by standard CRT, seeks to address some of these issues by studying the use of a dose-dense schedule, incorporating a taxane and eliminating the interval between induction chemotherapy and RT.

Lymph node staging and radiotherapy. In patients with LACC, RT treatment planning relies on accurate staging information. Pelvic MRI and clinical examination is essential to determine the local extent of the tumour for both external beam RT and brachytherapy planning. Information on para-aortic nodal status is also essential for treatment planning, particularly in determining the superior extent of the external beam RT portal. FIGO staging does not take account of the nodal status and this is one of the weaknesses of this system. Surgical series suggest that the incidence of para-aortic nodal involvement increases with stage from about 5% in patients with stage I disease to 25% in those with stage III disease [39].

There is much debate concerning the best way to assess the para-aortic nodes. In some parts of the world, PET/CT is routinely used for staging while elsewhere there is a reliance on surgical exploration of the para-aortic region. It is hoped that the ongoing randomised trials will address this issue further [40]. This is particularly important in the light of the findings from a multicentre, randomised trial demonstrating an excellent outcome in patients with negative PET scans and metastasis $\leq$ 5 mm detected histologically after surgical removal and subsequently treated with extended-field CRT [41].

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. However, intermediate-risk factors such as LVSI, large tumour size and deep stromal invasion (DSI) do not significantly increase the recurrence rate alone but, when combined, the risk of recurrence is increased to 15%–20%, similar to that of high-risk factors.

Table 3. Necessary histopathological parameters for assessment of cervical cancer

Histopathological evaluation
Dimensions of the tumour
Stromal invasion/depth of the wall involved
Tumour differentiation
Lymphovascular space invasion
Status of resection margins
Status of parametria and vaginal cuff
Number and status of lymph nodes

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), LVSI and large tumour size ($>$ 4 cm). With a median follow-up of 10 years, a significant benefit has been shown for PFS (HR 0.54), but not for OS (HR 0.7; $P = 0.07$) [42].

High-risk disease. Women with one or more negative 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 CRT is indicated based on a clinical trial that randomly assigned 268 women IA2, IB and IIA to adjuvant RT with or without chemotherapy (cisplatin–5-fluorouracil) for four courses [33]. The use of chemotherapy was associated with a substantially better 4-year OS (81% versus 71%) and PFS (80% versus 63%) and the outcome was better for patients who completed three to four cycles of chemotherapy [I, A].

Cervical cancer patients with intermediate-risk disease do not need further adjuvant therapy [II, B], whereas adjuvant CRT is recommended in high-risk patients [I, A].

Management of advanced/metastatic disease (Figure 1)

Metastatic or recurrent cervical cancer is usually a symptomatic and devastating situation for the patient. Palliative chemotherapy with the aim of relieving symptoms and improving quality of life is indicated if the patient has a performance status (PS) $\leq$ 2 and no formal contraindications. Cisplatin 50 mg/m^2 every 3 weeks was, for two decades, the standard of care. However, the global efficacy was disappointing due to a low response rate (20%), short median PFS (2.8–3.2 months) and OS (6.2–8.0 months).

Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS [43, 44]. Cisplatin combined with topotecan showed superior OS compared with cisplatin alone. Both trials also demonstrated that the response rate was clearly inferior in patients previously exposed to CRT. In addition, retrospective pooled analysis suggested that black race, pelvic location rather

than non-pelvic, PS 1 or 2 and first relapse within 1 year of diagnosis may also be poor prognostic factors associated with lower response [45].

The three-drug combination of paclitaxel–ifosfamide–cisplatin (TIP) has shown promising responses (overall response rate 62%, with complete response 26%) and is regarded as an active regimen with acceptable toxicity in advanced/relapsed cervical cancer [46]. A large randomised phase III trial (GOG-204) comparing four different cisplatin-based doublets with paclitaxel, topotecan, gemcitabine or vinorelbine was unable to demonstrate the superiority of any regimen. Nevertheless, paclitaxel–cisplatin showed the highest response rate (29%), median PFS (5.8 months) and median OS (12.8 months) and was considered the preferred regimen based on the balance between efficacy and toxicity profile [II, B] [47].

Tumour angiogenesis plays a significant role in the progression of cervical cancer and has been associated with a poor prognosis. Bevacizumab prevents tumour angiogenesis by blocking vascular endothelial growth factor and was shown to be active in a phase II study (GOG-227C) in recurrent cervical cancer [48]. Based on this observation, the GOG-240 study explored the addition of bevacizumab to chemotherapy in a randomised phase III trial with a 2 $\times$2 factorial design in which OS was the primary endpoint. Patients with primary stage IVB or recurrent/persistent, good PS (0 or 1) and measurable disease were randomised to paclitaxel–cisplatin or paclitaxel–topotecan, both with or without bevacizumab. Two main conclusions were obtained from this study: first, the median OS is significantly prolonged by the addition of bevacizumab (16.8 versus 13.3 months; HR 0.765; 95% CI: 0.62–0.95; $P = 0.0068$) and second, non-platinum doublet is not superior to cisplatin–paclitaxel, even in the population previously treated with cisplatin. Patients treated with bevacizumab had a higher risk of grade $\geq$ 2 hypertension (25% versus 1.8%), grade $\geq$ 3 venous thromboembolic events (8.2% versus 1.8%) and grade $\geq$ 2 fistula (8.6% versus 1%), and these side-effects must be carefully monitored during treatment [49].

The combination of paclitaxel and carboplatin could be considered an alternative for patients that are not candidates for cisplatin. Although a Japanese randomised clinical trial which compared the two regimens showed a similar efficacy, the combination with cisplatin was superior to carboplatin in patients without previous exposure to cisplatin [50]. The combination of carboplatin/paclitaxel/bevacizumab is being studied in a multicentre, single-arm, interventional trial (CECILIA), to evaluate the safety and efficacy of the combination in recurrent and/or metastatic cervical cancer (NCT02467907).

Paclitaxel and cisplatin combined with bevacizumab is considered the preferred first-line regimen in metastatic or recurrent cervical cancer based on the balance between efficacy and toxicity profile [I, A].

In patients progressing following first-line therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated (Table 4). However, response rates are low and duration of responses is short. Therefore, no recommendation can be given about the most effective second-line treatment (Table 4).

Some patients develop small lung metastases only, which do not rapidly progress and can be managed with stereotactic RT and/or a watchful waiting policy, frequently delaying systemic chemotherapy for a significant period of time.

Table 4. Second-line therapy for metastatic cervical cancer

Agent	N	CR+PR (%)	PFS (months)	OS (months)
Bevacizumab [48]	46	11	3.4	7.3
Topotecan [62, 63]	94	13-19	2.1-2.4	6.4-6.6
Vinorelbine [64]	44	14	-	-
Gemcitabine [65]	22	5	2.1	6.5
Albumin-bound paclitaxel [66]	35	29	5.0	9.4
Docetaxel [67]	23	9	3.8	7.0
Pemetrexed [68, 69]	72	14-15	2.5-3.1	7.4-8.8
Irinotecan [70]	42	21	4.5	6.4
Sunitinib [71]	19	0	3.5	-
Erlotinib [72]	28	0	1.9	5.0
Lapatinib [73]	78	5	4.2	9.7
Pazopanib [73]	74	9	4.5	12.7
Pegylated liposomal doxorubicin [74]	27	11	3.2	8.9

CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response.

RT can play an important role in patients with recurrent disease, in the case of oligometastatic disease and for patients with only nodal metastasis in the pelvic, periaortic and/or supraclavicular regions, as high-dose RT often leads to long-term disease control and a prolonged progression-free interval. Short-course palliative RT is used to treat symptoms from distant metastases.

Local recurrence of cervical cancer following radical surgery

The therapeutic options for patients who relapse in the pelvis following primary surgery are either radical RT or pelvic exenteration. The reported survival rates range from 6% to 77%; patients with central recurrences have better prognoses than those with pelvic side wall recurrence. Patients with central recurrences had a 10-year survival rate of 77%, for those with no palpable tumour, and a 10-year survival rate of 48% if the recurrence was $<$ 3 cm; there were no long-term survivors among patients with bulky ($>$ 3 cm) central recurrence in one series. The major prognostic factors associated with survival following salvage radiation in patients with recurrent pelvic disease include disease-free interval, site of recurrence (i.e. central versus pelvic side wall), and size. Higher doses of RT can be delivered with brachytherapy and increase the likelihood of local control for patients with small volume central recurrences. Patients with large volume central or pelvic side wall recurrences have poor prognoses, and efforts should be made to detect pelvic recurrences early to increase the chance of long-term survival [51].

Fertility sparing

More than 40% of women with early cervical cancer are affected during reproductive age and wish to remain fertile. Thus, many patients demand a more conservative policy for managing these lesions in order to increase the chance of having an uneventful pregnancy in the future.

Table 5. Summary of recommendations

Incidence and epidemiology

- Primary prevention of cervical cancer is now possible via immunisation with highly efficacious HPV vaccines [II, A] and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programs [II, A].

Staging and risk assessment

- Tumour risk assessment includes tumour size, stage, depth of tumour invasion, lymph node status, LVSI and histological subtype. Lymph node status and number of lymph nodes involved are the most important prognostic factors.

Management of local/locoregional disease

Surgery

- Surgical therapy in cervical cancer is adapted to the stage of disease according to FIGO and TNM classification (see Table 2).
- Microinvasive cervical cancer (stage IA1) without LVSI can be managed with conisation or simple trachelectomy to preserve fertility [I, B]. Simple hysterectomy can be offered if the patient does not wish to preserve fertility.
- In stage IA1 with LVSI, surgical assessment of pelvic lymph nodes should be discussed with the patient, including the SLN.
- In patients with FIGO stage IA2, IB and IIA, radical hysterectomy with bilateral lymph node dissection (with or without SLN) is standard treatment, if the patient does not wish to preserve fertility [I, B].
- Increasing evidence suggests an important role for SLND in cervical cancer. Sentinel nodes should be detected on both sides [II, B].
- Surgery should only be considered in patients with earlier stages of cervical cancer (up to FIGO IIA) without risk factors necessitating adjuvant therapy, which results in a multimodal therapy without improvement of survival but increased toxicity [I, A].
- Study results indicate that NACT may offer a benefit over surgery alone in cervical cancer patients, reducing the need for adjuvant RT [I, C].

Chemoradiotherapy in locally advanced cervical cancer

- CRT has been the standard of care for patients with bulky IB2–IVA disease for almost two decades, demonstrating an improvement in both DFS and OS with concomitant chemotherapy and RT over standard RT/hydroxyurea [I, A].
- The most commonly used regimen is weekly cisplatin 40 mg/m^2, although the meta-analysis also reported significant benefits with non-platinum agents [I, A].

Adjuvant treatment

- Women with intermediate- and high-risk factors on the pathology specimen should receive adjuvant therapy following hysterectomy (see Table 3).
- Cervical cancer patients with intermediate-risk disease do not need further adjuvant therapy [II, B], whereas adjuvant CRT is recommended in high-risk patients [I, A].

Management of advanced/metastatic disease

- Palliative chemotherapy with the aim of relieving symptoms and improving quality of life is indicated if the patient has a PS $<$ 2 and no formal contraindications.
- Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS.
- Paclitaxel and cisplatin combined with bevacizumab is considered the preferred first-line regimen in metastatic or recurrent cervical cancer based on the balance between efficacy and toxicity profile [I, A].
- The combination of paclitaxel and carboplatin could be considered an alternative for patients that are not candidates for cisplatin.
- For FIGO Stage IA1 patients, conisation is recommended as a first diagnostic and curative step for microscopic tumours in the presence of negative margins and the absence of clinical contraindications to surgery. PLND is recommended for patients with LVSI, who have an increased risk of lymph node involvement. Sentinel node biopsy or trachelectomy [II, B] should be considered in some patients.
- For FIGO Stage IA2 patients wishing to preserve fertility, cone biopsy or radical trachelectomy with PLND is the standard procedure.
- Scientific evidence shows that trachelectomy with pelvic lymphadenectomy is the most appropriate surgical treatment of fertility sparing in patients with tumours measuring $\leq$ 2 cm in diameter (FIGO Stage IB1 $<$ 2 cm) [II, B]. For tumours $>$ 2 cm, NACT followed by conisation or trachelectomy may also be a valid choice.

Follow-up, long-term implications and survivorship

- Follow-up visits with a complete physical examination including a pelvic–rectal exam and a patient history should be conducted by a physician experienced in the surveillance of cancer patients.
- CT or PET/CT scan should be carried out as clinically indicated. A reasonable follow-up schedule involves follow-up visits every 3–6 months in the first 2 years and every 6–12 months in years 3–5.
- Patients should return to annual population-based general physical and pelvic examinations after 5 years of recurrence-free follow-up [III, C].

CRT, chemoradiotherapy; CT, computed tomography; DFS, disease-free survival; DNA, deoxyribonucleic acid; FIGO, Féderation Internationale de Gynécologie et d'Obstétrique; HPV, human papillomavirus; LVSI, lymphovascular space invasion; NACT, neoadjuvant chemotherapy; OS, overall survival; Pap, Papanicolaou; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; PLND, pelvic lymph node dissection; PS, performance status; RT, radiotherapy; SLN, sentinel lymph node; SLND, sentinel lymph node dissection; TNM, tumour, node and metastasis.

FIGO stage IA1

According to most international guidelines, the first diagnostic and curative step for microscopic tumours is conisation [52]. In the presence of negative margins and the absence of clinical contraindications to surgery, the cone biopsy may represent definitive treatment. For patients with LVSI, who have an increased

Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .)., optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [75].

risk of lymph node involvement, pelvic lymph node dissection (PLND) is recommended [52]. Sentinel node biopsy should be considered. Moreover, for these patients, some authors suggest trachelectomy, a surgical procedure in which the uterine cervix and adjacent tissues are removed [II, B].

FIGO stage IA2

For patients wishing to preserve fertility, cone biopsy or radical trachelectomy with PLND is the standard procedure [53]. Sentinel node biopsy is under validation but may be considered [II, B].

FIGO stage IB1 < 2 cm

Scientific evidence shows that trachelectomy with pelvic lymphadenectomy is the most appropriate surgical treatment of fertility sparing in patients with these tumours. Tumours > 2 cm are clearly associated with a higher risk of recurrence (3% for lesions ≤ 2 cm versus 17% for lesions > 2 cm); thus, international guidelines stress that this procedure is valid mostly for tumours measuring ≤ 2 cm in diameter [II, B] [54, 55].

Currently, as documented by most international guidelines, radical trachelectomy is considered a standard fertility-sparing procedure in patients with early cervical cancer and tumours < 2 cm. However, the low incidence of parametrial involvement reported in patients with tumours < 2 cm and no nodal disease or LVSI suggest that less radical treatment may be a valid choice for fertility sparing also in these lesions (lower morbidity, higher pregnancy rate).

Some studies have reported in the absence of residual disease in trachelectomy specimens in the range of 60%–65%, questioning the need for radical surgery in patients with low-risk tumours [56].

Finally, some authors have suggested conisation with/without NACT in this tumour setting as well [II, C] [55, 57–60].

FIGO stage IB > 2 cm

For tumours > 2 cm, NACT followed by conisation or trachelectomy may also be a valid choice, but downstaging by NACT in IB1 and IB2 cervical cancer before fertility-sparing surgery is still an experimental procedure [I, C].

Personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

Follow-up, long-term implications and survivorship

No definitive agreement exists on the best post-treatment surveillance of cervical cancer. At a minimum, follow-up visits with a complete physical examination, including a pelvic–rectal exam and a patient history, should be conducted by a physician experienced in the surveillance of cancer patients. There is little evidence to suggest that vaginal vault cytology adds significantly to the clinical exam in detecting early disease recurrence. Routine use of various other radiological or biological follow-up investigations in asymptomatic patients is not advocated, because the role of those investigations has yet to be evaluated in a definitive manner. CT or PET/CT scan should be carried out as clinically indicated. A reasonable follow-up schedule involves follow-up visits every 3–6 months in the first 2 years and every 6–12 months in years 3–5. Patients should return to annual population-based general physical and pelvic examinations after 5 years of recurrence-free follow-up [III, C].

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 5. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

CM and MMC have reported honoraria and participation at advisory boards for Roche; SM has reported consulting for

Roche, Clovis, Sensor Kinesis, MEDAC, AstraZeneca and has received grants from Roche, Pharmamar, Tesaro, MEDAC, AstraZeneca and honoraria from Roche, Pharmamar, Clovis, Tesaro, Sensor Kinesis, MEDAC and AstraZeneca; AGM has received honoraria from Roche, AstraZeneca and PharmaMar; NC is a member of Roche speakers' bureau; FL has reported no conflict of interest.

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