Cervical cancer

➢ Acknowledgments

- We would like to acknowledge the Oncology Committee of the Egyptian Health Council (EHC) Guidelines, for adapting these Guidelines.
- Chair of the Oncology Committee of Egyptian Health Council Guidelines: Prof Hussein Khaled.
- The Oncology Committee Members: Emad Hamada, Samir Shehata, Hesham Elghazaly, Hesham Tawfik, Fouad Abuotaleb, Ebtesam Saad Eldin, Ihab Khalil, Khaled Abdelkarim, Lobna EZZ Elarab, Mary Gamal, Mohamed Abdel Mooti, Mohamed Gamil, Nervana Hussein, Ola Khorshid, Omar Sherif Omar, Rasha Fahmi, Rasha Shaltout, Yousri Wasef & Yousri Rostom.

➢ Abbreviations

ASIR	Age standardize incidence rate
ASMR	Age standardize mortality rate
CRT	Concurrent chemo radiotherapy
EUA	Examination under anesthesia
FDG-PET/CT	18-Fluoro-deoxyglucose positron emission tomography
LVSI	Lympho vascular invasion
MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy

Pap	Papanicolaou
PS	Performance status
RT	Radiotherapy
SLND	Sentinel lymph node dissection

➢ Executive Summary

Diagnostic and Staging Work up	
Diagnostic and staging work up should include history and physical examination, complete blood count, as well as liver function and renal function studies.	**Good practice statement**
We recommend cervical cytology or Papanicolaou (Pap) smears and cervical biopsies for diagnosis.	**Strong recommendation**
We recommend cone biopsy (i.e., conization) if the cervical biopsy is inadequate to define invasiveness or if accurate assessment of microinvasive disease is required.	**Strong recommendation**
Recommended radiologic imaging includes pelvic MRI, and FDG-PET/CT.	**Strong recommendation**
Consider examination under anesthesia (EUA) cystoscopy/proctoscopy for cases having ≥ stage IB.	**Good practice statement**
Consider options for fertility sparing or referral to reproductive endocrinology and infertility.	**Conditional recommendation**
Staging and risk assessment.	
Tumor risk assessment should include tumor size, stage, depth of tumor invasion, lymph node status, LVSI and histological subtype.	**Strong recommendation**
Management of local/locoregional disease,	
Surgery	
Surgical therapy in cervical cancer should be adapted to the stage of disease according to FIGO and TNM classification (Appendix).	**Good practice statement**
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.	**Strong recommendation**
Microinvasive cervical cancer (stage IA1) without LVSI should be managed with conisation or simple	**Strong recommendation**

trachelectomy to preserve fertility, and simple hysterectomy is recommended if the patient does not wish to preserve fertility.	
In stage IA1 with LVSI, surgical assessment of pelvic lymph nodes is recommended.	**Strong recommendation**
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.	**Strong recommendation**
Adjuvant/neoadjuvant treatment	
Consider NACT with surgery as this may reduce the need for adjuvant RT.	**Conditional recommendation**
Intermediate-risk surgicopathologic findings, frequently referred to as Sedlis criteria, are defined by a combination of lymphovascular space involvement, depth of stromal invasion, and tumor size (Table 5, appendix), and they should be treated by whole pelvic RT delivered to a total dose of 4500 to 5040 cGy, in 180 Gy per fraction or 4000 to 4400 Gy in 200 Gy per fraction.	**Strong recommendation**
Adjuvant CRT is recommended in high-risk patients (one or more negative prognostic factors such as positive or close surgical margins, positive lymph nodes or microscopic parametrial involvement). For these patients, whole pelvic RT should be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40mg/m2).	**Strong recommendation**
Chemoradiotherapy in locally advanced cervical cancer	
We recommend CRT for patients with bulky IB2–IVA disease, and the most commonly used regimen is weekly cisplatin 40 mg/m2.	**Strong recommendation**
Patients not eligible to cisplatin may receive carboplatin or gemcitabine.	**Strong recommendation**
Brachytherapy is needed to obtain a sufficiently high dose to ensure a high rate of local control in advanced cases.	**Good practice statement**
Management of advanced/metastatic disease	
Palliative chemotherapy with the aim of relieving symptoms and improving quality of life is recommended if the patient has a PS< 2 and no formal contraindications.	**Strong recommendation**
Cisplatin-based doublets with paclitaxel or topotecan have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS.	**Strong recommendation**
Paclitaxel and cisplatin combined with bevacizumab is recommended as the preferred first-line regimen in metastatic or recurrent cervical cancer based on the balance between efficacy and toxicity profile.	**Strong recommendation**

The combination of paclitaxel and carboplatin is recommended as an alternative for patients that are not candidates for cisplatin.	**Strong recommendation**
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.	**Conditional recommendation**
Local recurrence of cervical cancer following radical surgery	
Higher doses of RT can be delivered with brachytherapy and increase the likelihood of local control for patients with small volume central recurrences.	**Strong recommendation**
Clinical indicators	
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.	**Good practice statement**
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.	**Good practice statement**
Patients should return to annual population-based general physical and pelvic examinations after 5 years of recurrence-free follow-up.	**Good practice statement**

➢ Introduction

In Egypt, there was an estimated 1302 new cases of cervical cancer with an ASIR of 2.8/100 000 normal population and ranks the 13th most common cancer among females. There were 820 (ASMR: 1.8/100 000 normal population) deaths occurred because of this disease based on GLOBOCAN 2022.

➢ Purpose and scope

These guidelines are developed to improve the quality of care for cervical cancer via providing a uniform standard of care across the country to help in early diagnosis, treatment and follow up for cervical cancer so more optimal treatment

options and improved clinical outcomes.

- **Target audience**

Clinicians who are involved in the care and treatment of patients with cervical cancer, include medical oncologists, radiation oncologists, clinical oncologist, gynecologists, surgeons, radiologists, pathologists, and palliative care specialists.

- **Methodology**

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation. inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guidelines must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence). - Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cutoff point or rank the guidelines (any guideline scoring above 50% on the rigor dimension was retained)

The NCCN, ESMO, NICE guidelines are the main sources used while formulating the national guidelines for cervical cancer.

- **Evidence assessment**

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

- **The strength of the recommendation**

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations: With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations: These are made when there is greater uncertainty about the four factors above (Table 2) or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations; when there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

- **Recommendations**

Diagnostic and Staging Work up

- Diagnostic and staging work up should include history and physical examination, complete blood count, as well as liver function and renal function studies.

Good practice statement

- We recommend cervical cytology or Papanicolaou (Pap) smears and cervical biopsies for diagnosis.

Strong recommendation, high grade evidence, (4).

- We recommend cone biopsy (i.e., conization) if the cervical biopsy is inadequate to define invasiveness or if accurate assessment of microinvasive disease is required.

Strong recommendation, high grade evidence, (5).

- Recommended radiologic imaging includes pelvic MRI, and FDG-PET/CT

Strong recommendation, high grade evidence, (6,7).

- Consider examination under anesthesia (EUA) cystoscopy/proctoscopy for cases having ≥ stage IB.

Good practice statement

- Consider options for fertility sparing

Conditional recommendation, high grade evidence, (8).

Staging and risk assessment

- Tumor risk assessment should include tumor size, stage, depth of tumor invasion, lymph node status, LVSI and histological subtype.

Strong recommendation, high grade evidence, (Table 4, appendix).

Management of local/locoregional disease

Surgery

- Surgical therapy in cervical cancer should be adapted to the stage of disease according to FIGO and TNM classification (Appendix).

Good practice statement

- 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.

Strong recommendation, high grade evidence (9).

- Microinvasive cervical cancer (stage IA1) without LVSI should be managed with conisation or simple trachelectomy to preserve fertility, and simple hysterectomy is recommended if the patient does not wish to preserve fertility.

Strong recommendations, high grade evidence (8).

- In stage IA1 with LVSI, surgical assessment of pelvic lymph nodes is recommended.

Strong recommendation, moderate grade evidence (10).

- 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.

Strong recommendation, high grade evidence, (9,11).

Adjuvant/neoadjuvant treatment

- Consider NACT with surgery as this may reduce the need for adjuvant RT.

Conditional recommendation, high grade evidence, (12,13).

- Intermediate-risk surgicopathologic findings, frequently referred to as Sedlis criteria, are defined by a combination of lymphovascular space involvement, depth of stromal invasion, and tumor size (Table 5, appendix), and they should be treated by whole pelvic RT delivered to a total dose of 4500 to 5040 cGy, in 180 Gy per fraction or 4000 to 4400 Gy in 200 Gy per fraction.

Strong recommendation, strong grade evidence, (14-16).

- Adjuvant CRT is recommended in high-risk patients (one or more negative prognostic factors such as positive or close surgical margins, positive lymph nodes or microscopic parametrial involvement). For these patients, whole pelvic RT should be delivered to a total dose of 4500 to 5040 cGy, in 180 cGy fractions, with concurrent weekly cisplatin (40mg/m2).

Strong recommendation, high grade evidence, (14,17).

Chemoradiotherapy in locally advanced cervical cancer

- We recommend CRT for patients with bulky IB2–IVA disease, and the most commonly used regimen is weekly cisplatin 40 mg/m2;

Strong recommendation, high grade evidence, (18-23).

- Patients not eligible to cisplatin may receive carboplatin or gemcitabine.

Strong recommendation, very low grade evidence (24,25).

- Brachytherapy is needed to obtain a sufficiently high dose to ensure a high rate of local control in advanced cases.

Good practice statement

Management of advanced/metastatic disease

- Palliative chemotherapy with the aim of relieving symptoms and improving quality of life is recommended if the patient has a PS< 2 and no formal contraindications.

Strong recommendation, high grade evidence, (26,27).

- Cisplatin-based doublets with paclitaxel or topotecan have demonstrated superiority to cisplatin monotherapy and should be used.

Strong recommendation, high grade evidence (26,27).

- Paclitaxel and cisplatin combined with bevacizumab is recommended as the preferred first-line regimen in metastatic or recurrent cervical cancer based on the balance between efficacy and toxicity profile.

Strong recommendation, high grade evidence, (28-30).

- The combination of paclitaxel and carboplatin is recommended as an alternative for patients that are not candidates for cisplatin.

Strong recommendation, moderate grade evidence, (31).

Strong recommendation, moderate grade evidence, (32).

- 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.

Conditional recommendation, low grade evidence, (33).

Local recurrence of cervical cancer following radical surgery

- Higher doses of RT can be delivered with brachytherapy and increase the likelihood of local control for patients with small volume central recurrences.

Strong recommendation, high grade evidence (34).

Clinical indicators

- 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.

Good practice statement

- 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.

Good practice statement

- Patients should return to annual population-based general physical and pelvic examinations after 5 years of recurrence-free follow-up.

Good practice statement

➢ **Update of this guideline**

This guideline will be updated whenever there is new evidence.

➢ **Research gaps**

- Systematic inclusion of cost-benefit analyses in clinical trials with collection of health economic analysis such as incremental cost effectiveness ratio in order to facilitate clinical decision-making.
- Predictive biomarkers: response to specific systemic targeted therapies and immunotherapy.
- Improve models for pre-clinical testing of novel drugs.
- Search for tools to assess quality of life and in clinical trials.

- Dietary supplements, nutritional counselling, physical activity recommendations and psychological support as part of an integrative healthcare approach to care for people with ovarian cancer.

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➢ Annexes

Table 4. Necessary histopathological parameters for assessment of cervical cancer (2)

- 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

Table 5. Intermediate Risk-factors for Cervical Cancer (2).

Lymphovascular space involvement	Stromal invasion	Tumor size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2 cm
Positive	Superficial 1/3	≥5 cm
Negative	Deep or middle 1/3	≥4 cm

The staging of cervical tumours is by the Fe´deration Internationale de Gyne´cologie et d'Obste´trique (FIGO) and TNM classification (Union for International Cancer Control), (2).

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
T1a	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
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
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		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M – Distant Metastasis		
M0		No distant metastasis
M1		Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes

metastasis to vagina, pelvic serosa, and adnexa

James D, Brierley JD, Gospodarowicz MK et al. (eds). TNM Classification of Malignant Tumours, 8th edition. Oxford, UK: John Wiley & Sons, Inc. 2016.