CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/294.15(GU)

MANAGEMENT OF CERVICAL CANCER (SECOND EDITION)

Ministry of Health Malaysia

Malaysian Gynaecological Cancer Society

Malaysian Oncological Society

Academy of Medicine Malaysia

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http://www.moh.gov.my
http://www.acadmed.org.my
http://www.malaysiaoncology.org
http://www.themgcs.blogspot.com
Also available as an app for Android and iOS Platform: MyMaHTAS

STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2015 and will be reviewed in 2019 or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

In line with the current development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these CPG were from the Ministry of Health (MoH) and Ministry of Education (MoE). There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

The previous CPG entitled Management of Cervical Cancer 2003 was used as the basis for the development of the present guidelines. A literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N); Medline via Ovid, Pubmed and Cochrane Database of Systemic Reviews (CDSR). Refer to **Appendix 1** for **Example of Search Strategy**). The inclusion criteria are all literature on women with cervical cancer, regardless of study design. The search was limited to literature published in the last ten years and on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify relevant studies. All searches were conducted from 11 Jan 2013 to 20 Feb 2013. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 28 February 2015 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other CPG on cervical cancer developed by Scottish Intercollegiate Guidelines Network (SIGN) 2008. The CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 13 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 26 times throughout the development of these guidelines. All literatures retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion are resolved consensually. These CPG are based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literatures used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page).

On completion, the draft guideline was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval.

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations management of cervical cancer based on the following aspects:-

i. Diagnosis and staging of cervical cancer
ii. Treatment
iii. Referrals and Follow-up

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Inclusion Criteria

- All women with cervical cancer

Exclusion Criteria

- Pre-invasive cervical disease
- Screening of cervical cancer

TARGET GROUP/USER

This CPG is intended to guide those involved in the management of cervical cancer either in primary or secondary/tertiary care namely:-

i. Medical officers and general practitioners
ii. Allied health professionals
iii. Trainees and medical students
iv. Patients and their advocates
v. Professional societies

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

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The draft guideline was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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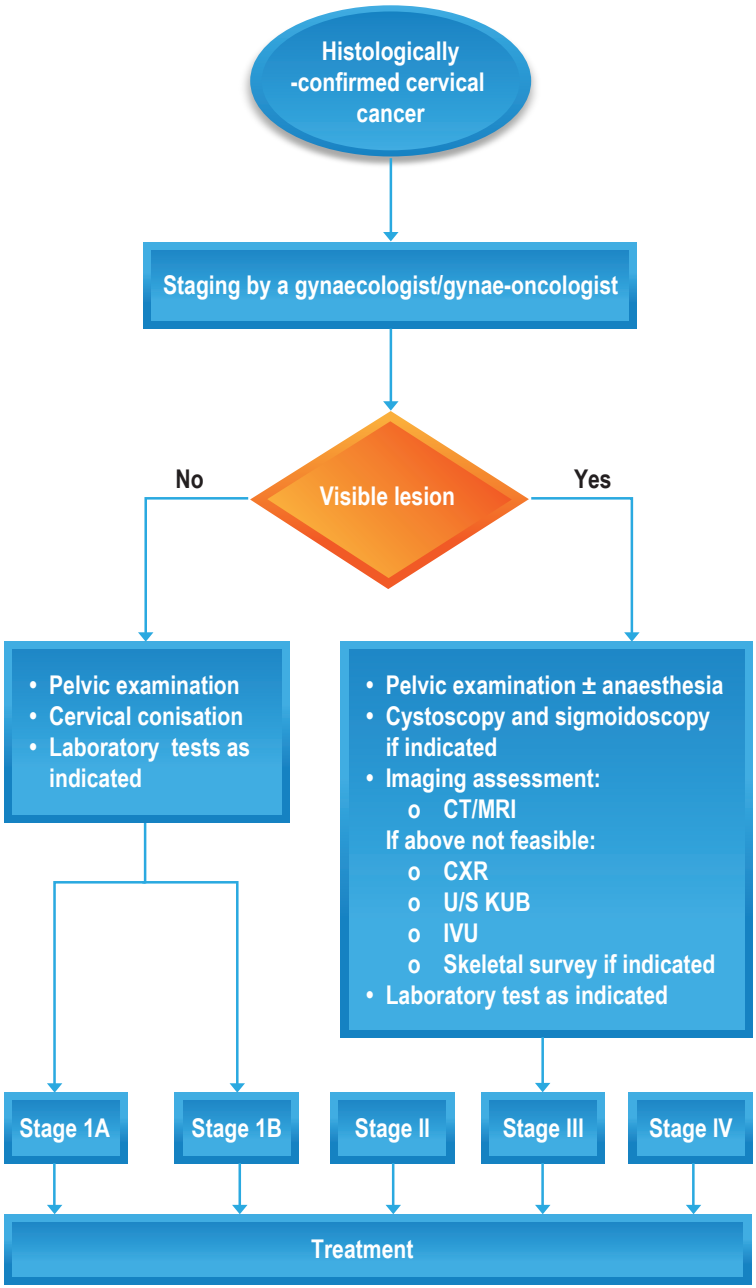
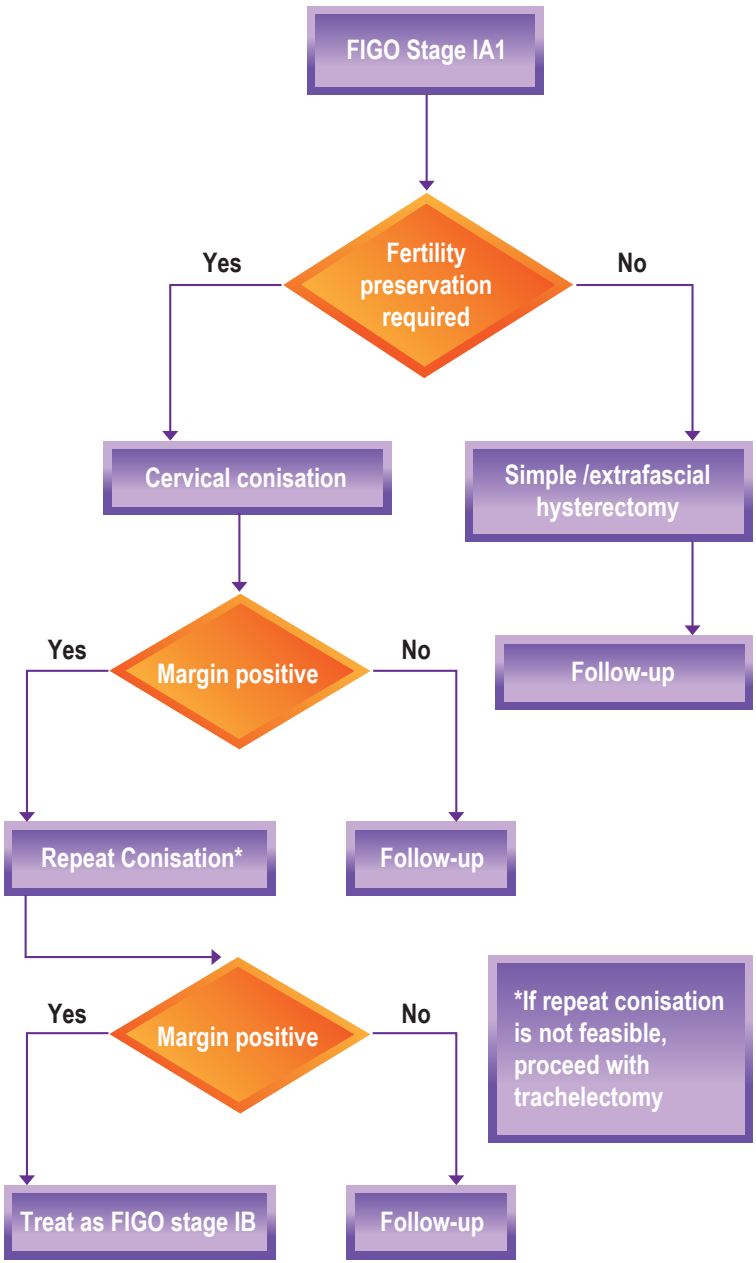
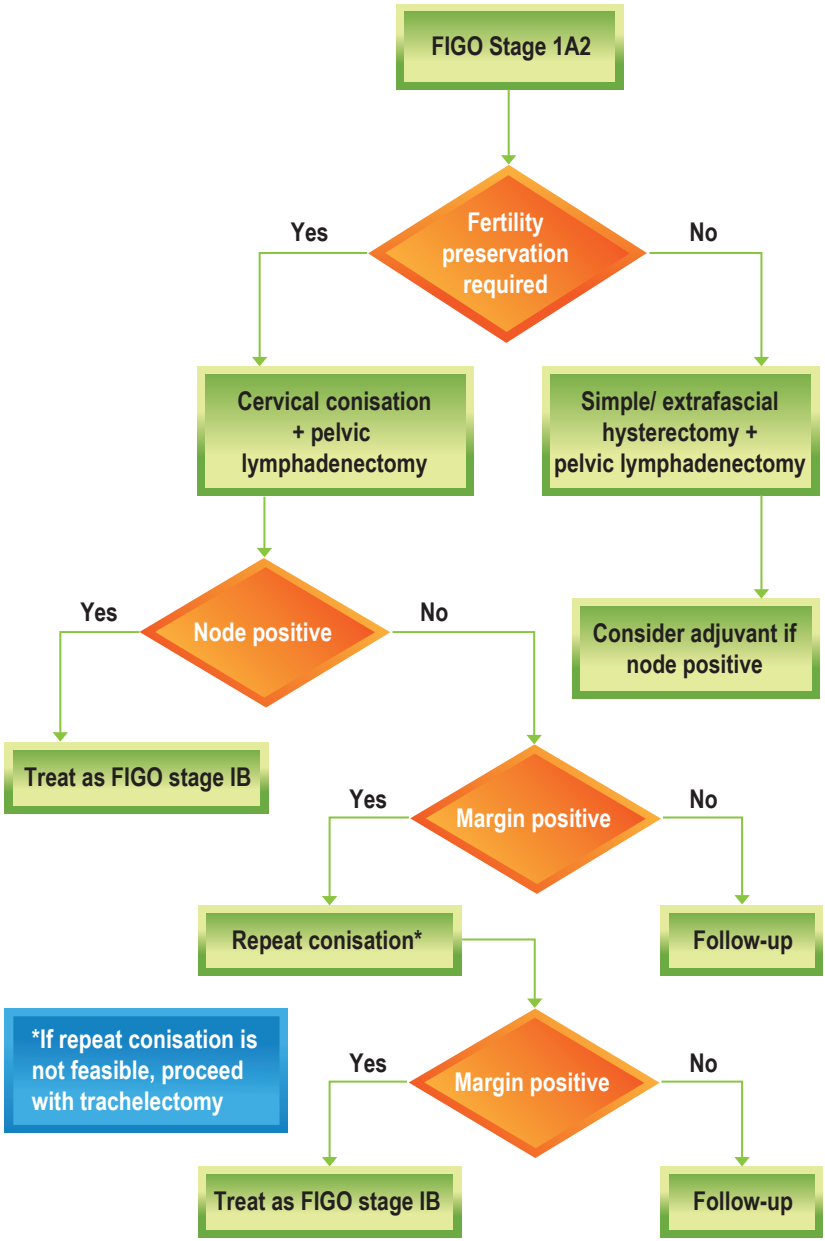
ALGORITHM 1. ASSESSMENT OF CERVICAL CANCER



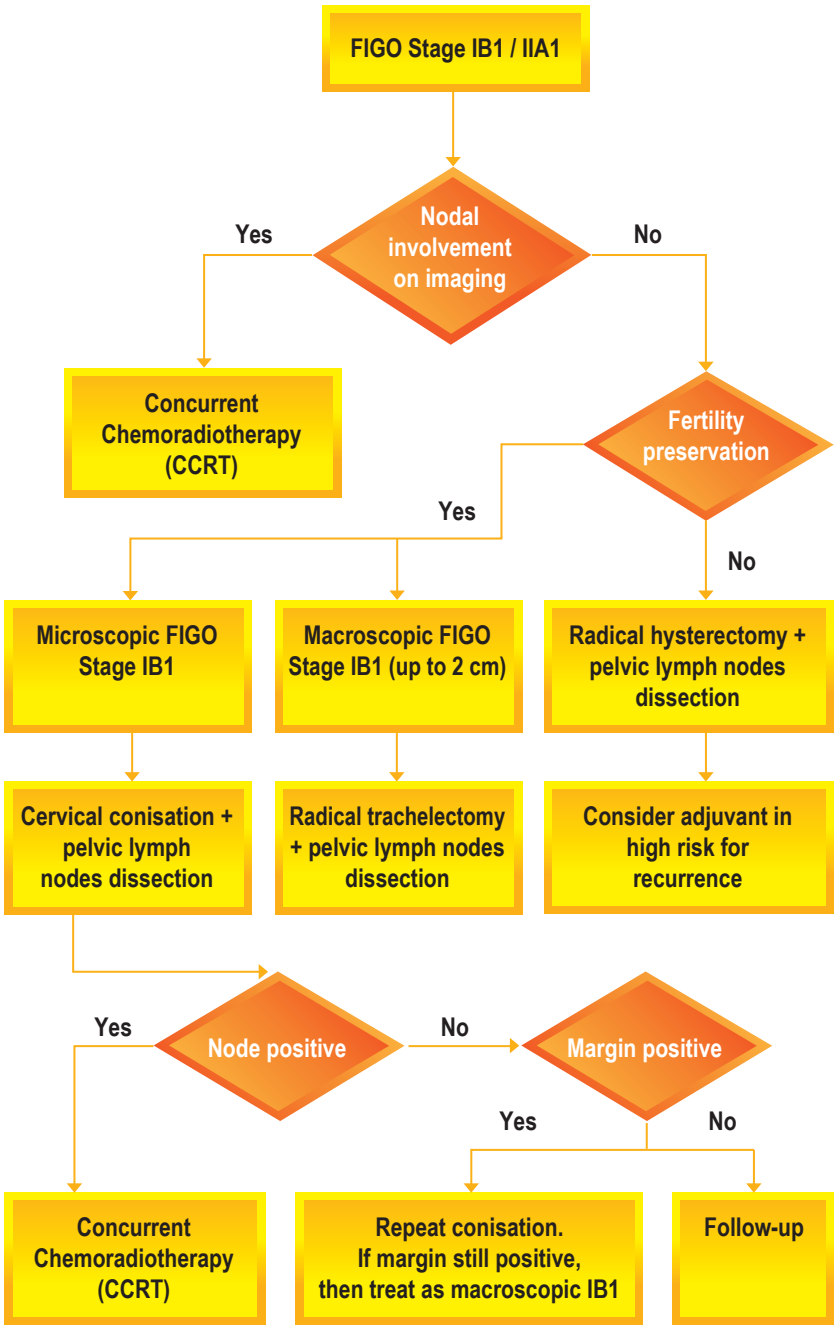
ALGORITHM 2. MANAGEMENT OF FIGO STAGE IA1



ALGORITHM 3. MANAGEMENT OF FIGO STAGE IA2



ALGORITHM 4: MANAGEMENT OF FIGO STAGE IB1 / IIA



1. INTRODUCTION

Cervical cancer remains an important health issue among women in Malaysia. Despite numerous screening programmes for early detection of pre-invasive disease of the cervix, many women have been diagnosed at invasive stage of cervical cancer. This has tremendous implications to the patients, carers and healthcare system.

The first edition of CPG on Management of Cervical Cancer was published in 2003. Many new development especially in the treatment of the condition has emerged which lead to variation in clinical practice. Based on these, the CPG have been updated using a systematic review methodology. It aims to guide healthcare providers on the evidence-based management of invasive cervical cancer in the Malaysian healthcare setting.

2. EPIDEMIOLOGY

There is an increasing trend of cancer worldwide. A total of 14.1 million new cancer cases and 8.2 million cancer deaths occurred in 2012, compared to 12.7 million and 7.6 million respectively in 2008. Cervical cancer is the fifth (3.7%) common cause of cancer following prostate (7.9%), colorectal (9.7%), breast (11.9%) and lung cancer (13.0%) globally. It is the fourth (7.9%) common cause of cancer among women after breast (25.2%), colorectal (9.2%) and lung cancer (8.8%). Seventy percent of cervical cancer cases occur in low resourced countries.[1, level III]

In Malaysia, cervical cancer is the second most common cancer among women following breast cancer.[1 - 2, level III] The age-standardised rate is highest among Indians (10.3/100,000) followed by Chinese (9.5/100,000) and Malays (5.3/100,000). The rate increases after 30 years of age and peaks at 65 - 69 years. Among all cancer deaths, cervical cancer ranked fifth.[3, level III]

In the United States, a declining overall incidence of cervical cancer has been reported; largely attributed to the decrease in the incidence of squamous cell carcinoma. However, there is an unexplained rise of adenocarcinoma (AC).[4, level II-2] There is no published local data on the trend of cervical cancer.

3. RISK FACTORS

The primary cause of cervical cancer is infection with certain types of Human Papilloma Virus (HPV) which is transmitted sexually. Multiple risk factors are associated with the development of the cancer:

- >3 sexual partners[5, level II-2]
- early sexual intercourse (<17 years old)[5, level II-2]
- >10 years' use of oral contraceptive[5, level II-2]
- first delivery before age of 17[6, level II-2]
- high parity (≥7 full term pregnancies)[6, level II-2]
- smoking[6 - 7, level II-2]
- lower socioeconomic status[8, level II-2]

4. CLINICAL PRESENTATION

The symptoms associated with cervical cancer are commonly encountered at primary care. However, most data on clinical presentations are based on research at secondary care.

Common presenting symptoms in cervical cancer are postmenopausal bleeding (84.0%), vaginal discharge (72.0%), postcoital bleeding (PCB) (64.0%) and abdominal pain (56.0%).[9, level III] The prevalence of PCB in cervical cancer ranges between 0.7% to 39%.[10, level III] In patients with PCB, cervical cancer is found in 3.6% of women with no record of smear or with normal smear and 5% of women with abnormal smear.[11, level III]

- Most patients are asymptomatic. However, common presenting symptoms that may suggest cervical cancer are:
  - postmenopausal bleeding
  - vaginal discharge
  - post-coital bleeding
  - abdominal pain

Among those with PCB:[12, level III]

- cervical cytology (conventional pap smear) has sensitivity, specificity and positive predictive value (PPV) of 50%, 86.5% and 92.8% respectively for cervical cancer
- colposcopy has sensitivity and PPV of 78.6% and 23.4% respectively for cervical cancer

Based on the Malaysian National Cancer Statistics 2007, 21% of cervical cancer patients presented at stage I, 34.7% at stage II, 25.6% at stage III and 18.7% at stage IV.[3, level III]

5. REFERRAL

Appropriate referral mechanism can improve the quality of care given to patients. Referral to gynaecology/gynae-oncology clinic after abnormal cytology/pap smear is important to establish prompt diagnosis. The proposed criteria and time frame for referral is shown in **Table 1**.

Table 1. Time frame for referral of abnormal cytology to gynaecology clinic

Time frame for referral	Criteria
Within 8 weeks	• After three consecutive inadequate samples • After three tests reported as inflammatory smear in a series • One test reported as AGC-US or AGC-H • After two tests reported as LSIL or ASCUS* * HPV DNA testing should be considered if available. If positive for high risk HPV, to refer for colposcopy.
Within 4 weeks	• One test reported as HSIL
Within 2 weeks	• One test reported as possible invasion • One test reported as possible glandular neoplasia • Women with symptoms of postcoital bleeding particularly >40 years, intermenstrual bleeding and persistent vaginal discharge

Modified:

1. Luesley D, Leeson S. editors. Colposcopy and Programme Management. Second Edition. Sheffield; NHS Cancer Screening Programme: 2010
2. Division of Family Health Development, Ministry of Health Malaysia. Guidebook for Pap Smear Screening. Putrajaya; MoH: 2004

Once diagnosed with cervical cancer, patients should receive definitive treatment within 31 days of agreeing to their care plan or within 62 days on the referral pathway.[13, level III]

6. DIAGNOSIS

a. Histopathological Examination

A definitive diagnosis of cervical cancer is made by histopathological examination of cervical tissue. Type of cervical tumour is diagnosed based on the World Health Organization (WHO) histological classification of tumours of the uterine cervix (refer to **Appendix 3**).[2, level III]

Histological reports of cervical cancers in small resection (loop/cone biopsies) and hysterectomy specimens should follow the minimum Dataset for Histological reporting of cervical neoplasia (3rd edition) of the Royal College of Pathologists. Meticulous and accurate reporting of gross pathological and histological parameters determine treatment and prognosis of the patients. Regular tumour board meetings are also advocated to optimise patient management decisions.[14, level III]

There are numerous independent histopathologic prognostic factors which are important in determining the patient's management, which includes lymph node status (p=0.0004), parametrial invasion (p=0.016), lymph vascular space invasion (LVSI), p=0.046) and histology of pure AC (p=0.012).[15, level III]

The presence of LVSI must be recorded for tumours of all types and stages. It is the only significant prognostic factor for cumulative 5-year survival rate in tumour confined to uterus (p=0.0078).[15, level III]

Based on survival analysis, patients can be stratified into three prognostic risk groups.[15, level III]

- Low risk: Tumour confined to uterus not associated with LVSI (estimated 5-year survival rate of 100 ± 0%).
- Intermediate risk: Tumour confined to uterus associated with positive LVSI or squamous/adenosquamous carcinoma associated with parametrial invasion or pelvic lymph node metastasis (estimated 5-year survival rate of 85.5 ± 3.9%).
- High risk: Pure AC associated with parametrial invasion or pelvic lymph node metastasis with common iliac/paraaortic node metastasis (estimated 5-year survival rate 25.1 ± 9.7%).

All patients with lymph node micrometastasis (LNmM), regardless of its size, are considered LVSI positive. LVSI (RR=2.64, 95% CI 1.67 to 5.49) and lymph node micrometastasis (LNmM) <2 mm (RR=2.44, 95% CI 1.58 to 3.78) has double the risk of recurrence following surgical resection of early-stage cervical cancer.[16, level III]

- Histopathological reports of cervical cancer should include core histological data, which are:[14, level III; 16, level III; 17]
  - tumour type (based on WHO classification)
  - tumour grade (based on modified Broders grading)
  - tumour dimension (depth and maximal horizontal dimension)
  - if tumour is multifocal in origin, to be indicated, staging is based on the largest focus
  - presence of LVSI
  - status of resection margins (presence of tumour, distance of tumour and location of the closest excision margin)*
  - lymph node status (number of nodes retrieved and involved), presence of micrometastases and extranodal spread*
  - involvement of other organs or tissue*
  - presence of involvement of endometrial cavity (endomyometrium)*
  - presence of involvement of paracervical, parametrial and vaginal tissue*

  * included in post-surgical specimens

Refer to **Appendix 4** for proposed **Reporting Proforma for Cervical Cancer in Excisional Cervical Biopsies/Hysterectomy Specimens**.

There is preference for avoiding the term 'microinvasive carcinoma' and using the specific The International Federation of Gynecology and Obstetrics (FIGO) stage as a descriptor.[14, level III]

Tumours should be staged according to the revised FIGO staging of 2009. The decision to use Tumour-Node-Metastases (TNM) as well as FIGO staging for cervical cancer is left to the discretion of the pathologist and the preference of their tumour board meetings.[14, level III]

b. Frozen Section Assessment

In most institutions, frozen section assessment is not used routinely for the evaluation of resection margins. However it may be performed on clinically suspicious lymph nodes to look for metastasis before proceeding with or abandoning a radical surgery.[14, level III]

Intraoperative frozen examination of sentinel node (SN) accurately predicts the status of pelvic lymph nodes and is effective for selecting intraoperatively the group of patients who will benefit from radical hysterectomy.[18, level III]

- Sensitivity and negative predictive value (NPV) of frozen section pathological examination for the detection of macrometastatic disease are 100%.
- Sensitivity for the detection for macrometastatic and micrometastatic disease, excluding isolated tumour cells, and NPV are 88.9% and 98.8% respectively.

Refer to **Chapter 8** on **Treatment (Sentinel Nodes)**.

Recommendation 1

- In cervical cancer,
  - reporting of histopathological examination for surgical specimens of radical hysterectomy should be standardised and contained core histological data*.
  - frozen section assessment of suspicious pelvic or para-aortic lymph nodes may be performed intra-operatively.

*Refer to the yellow box above.

7. STAGING

a. Clinical Staging

Staging of cervical cancer plays an important role in determining further investigations and treatment as well as survival of patients. Hence, an adequate and appropriate staging is an integral part of management for these patients.

There are two commonly used staging systems for cervical cancer namely FIGO staging[19, level III] and TNM classification.[20, level III] The latest revised FIGO staging of 2009 is currently the standard staging system used in Malaysia for all histological types (refer to **Appendix 5**).

FIGO staging is based on clinical examination. A thorough pelvic examination with/without anaesthesia is mandatory to provide information for the staging. When there is doubt as to which stage a particular cancer should be allocated, the lower stage is assigned.[19, level III]

The office pelvic examination has a weak but significant correlation with the actual extent of disease in determination of vaginal ($r=0.255$, $p<0.01$) and parametrial invasion ($r=0.174$, $p<0.01$). The overall accuracy is 70.4% for vaginal involvement and 74.5% for parametrial disease. It also has high accuracy in early FIGO stage cervical cancer (85.4% for stage IB1 and 77.4% for stage IB2) but low accuracy in FIGO stage II (35.5% for stage IIA and 20.5% for stage IIB).[22, level III]

The following examinations are permitted for the determination of FIGO staging, as indicated by presenting characteristics: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton. Blood tests should include full blood count, renal and liver function tests. Syphilis and human immunodeficiency virus serology need to be considered based on discussion with the patient about risk factors.[21, level III]

- **Initial assessment of microinvasive disease**
  - **Assessment of FIGO stage IA**

Diagnosis of both Stage IA1 and IA2 should be based on microscopic examination of excised tissue, including cone biopsy with negative margins, trachelectomy or hysterectomy. If the margins of the cone biopsy are positive for cervical intraepithelial neoplasia III or invasive cancer, a second cone biopsy should be performed or the patient treated as FIGO stage IB1 disease.[21, level III]

- **Assessment of FIGO stage IB and above**

Biopsy of the visible lesions is mandatory to confirm the diagnosis of cervical cancer.

Chest X-ray and evaluation of hydronephrosis are mandatory in grossly invasive disease. Evaluation of hydnonephrosis can be done using renal ultrasound, intravenous urography, computed tomography (CT) or magnetic resonance imaging (MRI). The bladder and rectum are evaluated by cystoscopy and sigmoidoscopy only if the patient is clinically symptomatic. The presence of bullous oedema alone on the bladder or rectal mucosa should not be assigned as FIGO stage IV. Suspected bladder or rectal involvement should be confirmed histologically.[21, level III]

CT and/or MRI with/without positron emission tomography (PET) may provide information on nodal status or systemic spread but are not mandatory.[21, level III] Refer to section on Radiological Staging for further details.

In our local context, as CT scan is widely available, the CPG DG suggests it is a preferred modality as part of the assessment of cervical cancer. In healthcare facilities where this modality is not readily available or if patients are not suitable for contrast studies, other modalities such as chest X-ray and ultrasound scan may be used.

- The staging of cervical cancer is determined at the time of the primary diagnosis and cannot be altered, even at recurrence.

b. Radiological Staging

It is important to assess prognostic factors based on radiological imaging such as tumour size, parametrial and pelvic side invasion, adjacent organ invasion and lymph node metastases to complement clinical assessment. Utilisation of different imaging modalities depends on accessibility, patients' clinical stage, clinicians' preference and cost, among others. Worldwide, CT and MRI are preferred over other modalities in cervical cancer staging. However, radiological imaging is not included in the revised FIGO staging.

In a meta-analysis of eight studies, MRI showed higher sensitivity compared to CT in locally advanced cervical cancer (LACC) in evaluating:[23, level III]

- parametrial invasion: 74% (95% CI 68 to79) vs 55% (95% CI 44 to 66), p=0.0027
- bladder invasion: 75% (95% CI 66 to 83) vs 64% (95% CI 39 to 82)
- rectal invasion: 71% (95% CI 53 to 83) vs 45% (95% CI 20 to 73%)
- lymph node involvement: 60% (95% CI 52 to 68%) vs 43% (95% CI 31 to 57), p=0.047

However, heterogeneity is an issue in this study in terms of equipment and techniques used in the primary papers.

In a diagnostic study, MRI showed sensitivity of 100% and specificity of 85.7% to 90% in detecting vaginal infiltration and tumour extension to cervical stroma with an accuracy of 92.2%.[24, level III]

Parametrial infiltration is an important parameter in determining management options of apparent early stage cervical cancer. In a diagnostic study, MRI appeared to perform better than examination under anaesthesia (EUA) although not statistically significant (NPV of 76.9% vs 65.3%, p=0.162). This evidence is limited by measurement bias.[25, level III]

In cervical cancer FIGO stage IB1, preoperative MRI-measured tumour diameter is significantly associated with pathological prognostic factors namely parametrial involvement, lymph node metastasis, deep stromal invasion and LVSI. Tumour diameter ≤20 mm may serve as a strong predictor for absence of parametrial involvement (p=0.01).[26, level II-3]

The use of transvaginal ultrasound (TVS) has recently been advocated in view of its accessibility and cost; however it is operator-dependent. In early stage cervical cancer (FIGO stage IA2 to IIA):[27, level II-3]

- TVS has better sensitivity and specificity than MRI in residual tumour detection and assessment of parametrial invasion. The results are not affected by the status of prior cone biopsies.
- TVS is comparable to MRI in tumour size and stromal invasion determination (κ of 0.81 and 0.77 respectively).
- TVS is excellent in classifying bulky tumours and detecting deep stromal invasion (κ of 0.82 and 0.81 respectively).

Diagnostic performance of PET or PET-CT for the assessment of para-aortic lymph nodes (PAN) metastases (prevalence of >15%) is acceptable when performed in those with FIGO stage III or IV.[28, level II-2] In normal-sized hypermetabolic lymph nodes, the diagnostic value of PET-CT requires further evaluation.[29, level III] Fluorodeoxyglucose (FDG) PET/CT is useful for primary evaluation of locally advanced cervical cancer (LACC), monitoring treatment response and others.[30, level III]

Pre-treatment PAN assessment surgically (laparoscopy or laparotomy) in FIGO stage IIB - IVA cervical cancer planned for pelvic radiotherapy (RT) does not offer additional survival benefit compared with standard imaging techniques (CT scan or MRI).[31, level I]

In grossly invasive disease, CT or MRI with/without PET may provide information on nodal status or systemic spread but such radiological modalities are not mandatory. Compared with CT and MRI, PET-CT is a more accurate imaging method for detecting nodal metastases that are >10 mm. Isolated and unexpected areas of PET enhancement should be confirmed histologically if possible, to confirm or exclude the presence of distant metastatic disease.[21, level III]

- The use of positron emission tomography computed tomography requires further evidence before it can be recommended in early stage cervical cancer.

In post-treatment LACC, there is a moderate correlation (r=0.68) between clinical and MRI assessments at three months which improved at six months (r=0.86).[32, level II-3]

The role of abdominal or pelvic CT, MRI PET or TVS as part of routine follow-up has not been fully evaluated in prospective studies.[33, level I]

Recommendation 2

- Clinical staging with/without anaesthesia should be performed before initiating cervical cancer treatment.
- In early stage cervical cancer, magnetic resonance imaging (MRI) may be used to complement examination under anesthesia for surgical decision-making.
- Computed tomography scan or MRI, when available, may be offered to assess nodal status and systemic spread in grossly invasive cervical cancer.

8. TREATMENT

- Patients' involvement in decision-making is essential in the management of cervical cancer.

a. Primary Treatment

Surgery is the preferred modality of treatment for early stage cervical cancer, if it is not contraindicated. Similar survival outcomes have been reported in surgically treated early stage cervical cancer compared with RT.[34, level I] It also has the advantage of preserving coital and ovarian function in young patients.

i. Surgery

- **Fertility-preserving surgery**

Cervical cancer is the third most common cancer in women younger than 40 years. Up to 42% of all cervical cancers are diagnosed in women before the age of 45 years, and up to 40% of early cervical cancers are diagnosed in young women who are potentially interested in a fertility-preserving surgery.[35, level III] Therefore, simple and radical trachelectomy has been increasingly used.[35 - 36, level III]

Fertility-preserving surgery may be considered in young patients with early stage cervical cancer. The surgical options include cervical conisation, large loop excision of transformation zone (LLETZ), simple and radical trachelectomy via vaginal or abdominal approaches. These procedures may be combined with pelvic lymph nodes dissection (PLND).

Careful patient selection is important to ensure low complication rates and optimal obstetric and oncologic outcomes. Cases should be evaluated and managed by experienced gynae-oncologists. Careful evaluation of the initial diagnostic specimens from cervical conisation or trachelectomy by experienced pathologists is needed.[35, level III]

There is no evidence retrieved specifically for the treatment of FIGO stage IA1 cervical cancer. In Malaysia, such condition is treated by cervical conisation for those who want to preserve fertility or otherwise simple hysterectomy. Pelvic lymphadenectomy is not recommended for treatment in FIGO stage IA1 disease.[17]

Cold knife conisation or LLETZ combined with PLND may be offered to women having FIGO stage IA2 and microscopic IB1 cervical cancer with no LVSI requesting fertility preservation.[17] A less radical surgery,

such as cervical conisation or simple hysterectomy, combined with pelvic lymphadenectomy in this group of patients has 100% recurrence-free survival at median follow-up of 56 months and low post-operative morbidity.[37 level II-2]

In women with FIGO stage IB1 cervical cancer who desire to preserve fertility, radical trachelectomy in combination with PLND is recommended, provided that the tumour diameter is less than 2 cm and absence of LVSI.[17] Techniques available include vaginal, abdominal, laparoscopic and robotic approaches.[35, level III] Type II radical abdominal trachelectomy (RAT) has similar obstetrics and oncologic outcomes as type III RAT with better recovery of bladder function ($p<0.01$).[36, level III]

In FIGO stage IA to IB1, radical vaginal trachelectomy (RVT) is associated with shorter hospital stay, less blood loss and significantly fewer blood transfusions, compared with radical hysterectomy (RH). The oncologic outcomes appear uncompromised. There is no statistical difference in 5-year overall survival (OS) and 5-year progression-free survival (PFS) between the two types of surgery.[38, level I] The recurrence rate is low (4.2% at median follow-up of 48 months) and obstetrics outcomes are good with 59% term delivery rate after RVT. First and second trimester loss are 13% and 19% respectively.[39, level III]

RAT has similar surgical and pathological outcomes [i.e. histologic type, residual disease in specimen, conversion to hysterectomy, median hospital stay and the use of post-operative adjuvant RT or concurrent chemoradiotherapy (CCRT)] with RVT. However, RAT allows a significantly wider parametrial resection.[40, level II-3]

The following criteria can be used as a guide for choosing modality of surgery when fertility preservation is required:

1. Cervical conisation
   - FIGO stage IA1
   - Squamous cell carcinoma (SCC), AC or adenosquamous carcinoma histological type
   - Age 40 years old or younger.

2. Simple trachelectomy
   - Age 40 years old or younger.
   - FIGO stage IA2 or microscopic FIGO stage IB1
   - Absent of LVSI
   - SCC, AC or adenosquamous carcinoma histological type.
   - No deep stromal invasion, endocervical or lower uterine segment involvement, parametrial involvement and nodal metastasis on pelvic MRI

3. Radical trachelectomy
   - Age 40 years old or younger
   - Small volume FIGO stage IB1 up to 2 cm tumour size
   - SCC, AC or adenosquamous carcinoma histological type
   - No deep stromal invasion, endocervical or lower uterine segment involvement, parametrial involvement and nodal metastasis on pelvic MRI
   - Limited endocervical extension on colposcopic evaluation

Future pregnancy plan:[35, level III]
- It is advisable to wait for 6 to 12 months after radical trachelectomy before attempting pregnancy to allow healing and to exclude early cancer recurrence.
- Pregnancy after radical trachelectomy is at higher risk of cervical stenosis, prematurity and obstetrics complications.
- Delivery is via caesarean section.

- Intra-operative frozen section is preferred to assess surgical margins and suspicious nodes during simple and radical trachelectomy with pelvic lymph nodes dissection in fertility-preserving cervical cancer surgery.

Recommendation 3
- Women with early stage cervical cancer desiring fertility preservation is preferably managed by gynae-oncologists and the following may be offered:
  - FIGO stage IA1: cervical conisation without pelvic lymph node dissection (PLND)
  - FIGO stage IA2: cold knife cervical conisation with PLND
  - Microscopic FIGO stage IB1: simple trachelectomy with PLND
  - FIGO stage IB1: radical trachelectomy with PLND

- **Non-fertility-preserving surgery**

Simple hysterectomy is the standard treatment for FIGO stage IA1 cervical cancer, while simple hysterectomy and PLND is the treatment of choice for FIGO stage IA2.

RH and PLND is the preferred treatment for FIGO stage IB1 cervical cancer, if there are no contraindications to surgery. Simple hysterectomy and PLND may be an alternative for small volume (microscopic) FIGO stage IB1 cervical cancer with excellent prognosis.[37, level II-2]

Controversy arises over the best primary management options for bulky tumour >4 cm (FIGO stage IB2 and IIA2) which can be either surgery or

CCRT. There is no recent evidence addressing this issue but the CPG DG favours CCRT, as the risk of nodal involvement is high and thus requires post-operative chemoradiotherapy.

The outcome of early stage AC (FIGO stage IA to IIB) treated with either primary RT/CCRT or surgery are comparable in terms of 5-year survival (OR=0.67, 95% CI 0.20 to 2.26), disease-free survival (OR=0.43, 95% CI 0.13 to 1.43) and complications (OR=3.32, 95% CI 0.61 to 18.12). Although not statistically significant, the trend of survival rate favours surgery.[34, level I]

Intra-operative detection of nodal metastasis in patients undergoing RH for early stage cervical cancer raises a management dilemma i.e. whether to proceed or abandon the surgery. These patients would still require RT/CCRT. However, given the lack of well-designed randomised controlled trials (RCTs), no definite conclusion can be made regarding the superiority of one approach over another.[41, level III; 42, level II-2]

- Treatment for patients with intra-operative detection of nodal metastasis should be individualised.

The incidence of ovarian metastasis in patients with early stage cervical cancer is low (0.9% - 3.7%). The most significant factor associated with the metastasis is the AC histological type.[43 - 44, level II-2; 45, level III] Other factors are older age group (>45 years old), bulky tumour size (>4 cm), FIGO stage IB2 to IIA[43, level II-2] and the presence of gross vascular erosion.[45, level III] The incidence of ovarian metastases in FIGO stages IB to IIB is higher in AC compared to SCC.[44, level III]

Ovarian preservation is safe during radical surgery in young patients with early stage SCC of cervix.[43, level II-2; 44 - 46, level III] The incidence of subsequent complication in the retained ovary is rare.[46, level III] However in AC, bilateral salphingo-oophorectomy should be performed.[44, level II-2; 46, level III]

There is no significant difference in survival rate between SCC and AC in patients with confirmed metastasis on the removed ovaries ($p>0.05$).[44, level II-2]

Recommendation 4

- In women with early stage cervical cancer who do not require fertility preservation,
  - simple/extrafascial hysterectomy should be performed for FIGO stage IA1 cervical cancer.
  - simple/extrafascial hysterectomy with pelvic lymphadenectomy may be performed for FIGO stage IA2.
  - radical hysterectomy with pelvic lymphadenectomy is the preferred treatment for FIGO stage IB1 cervical cancer.
  - concurrent chemoradiotherapy is the preferred treatment for bulky cervical cancer (FIGO stage IB2 and IIA2).
  - ovarian preservation during radical surgery may be offered in young patients with early stage squamous cell carcinoma of cervix. However in adenocarcinoma, bilateral salphingo-oophorectomy should be performed.

- **Laparoscopic and Robotic Surgery**

Laparoscopic and robotic surgeries in oncology are getting more attention with the advancement in the field of minimally invasive surgery.

In a Cochrane systematic review, there was no reliable evidence in the efficacy, safety and long term outcomes of laparoscopic-assisted vaginal radical hysterectomy in the treatment of early stage cervical cancer.[47, level I]

Laparoscopic radical hysterectomy and robotic radical hysterectomy, compared with radical abdominal hysterectomy (RAH), are associated with lesser blood loss ($p<0.05$), lower post-operative infectious morbidity ($p=0.005$) and shorter hospital stay ($p<0.05$).[48, level II-2] However, there is no evidence on long-term oncologic outcomes.[48, level II-2]

There is insufficient evidence to support surgical assessment of para-aortic nodal status (laparoscopy or laparotomy) prior to pelvic RT.[31, level I]

- Laparoscopic and robotic radical hysterectomy has short-term benefits but require further evidence on long term outcomes before any recommendation can be made.
- Laparoscopic and robotic radical hysterectomy should be performed by a trained persomels in the presence of a gynae-oncologist.

- **Sentinel Nodes (SN)**

Systematic lymphadenectomy followed by histological assessment is the standard technique currently used to detect nodal spread. In

histologically proven nodal metastases, CCRT is the primary treatment. According to the SN hypothesis, histologically tumour-negative SN predicts that the remaining lymph nodes will be tumour-free.

There is a higher probability in determining lymph node status in cervical cancer by SN biopsy compared with imaging methods such as CT scan, MRI and PET scan (OR=18.49, 95% CI 3.59 to 95.17).[49, level III] In a meta-analysis of 21 studies, the pooled sensitivity of positive SN in detecting nodal metastasis was 89% (95% CI 83 to 94) with no significant difference in detection techniques used (p=0.17).[50, level III]

There is no significant difference in the detection rate of SN using either ^{99m}Tc or blue dye and also in the methods in identifying and retrieving SN (laparotomy versus laparoscopy).[49, level III] Combined ^{99m}Tc and blue dye has a significantly higher SN detection rate compared to ^{99m}Tc or blue dye alone (97%, 88% and 84% respectively).[50, level III]

Recommendation 5
- Sentinel nodes detection may be considered to detect nodal metastasis in early stage cervical cancer where facilities are available.

ii. Definitive Chemoradiotherapy/Radiotherapy

The role of definitive chemoradiotherapy in FIGO stage IB2 and above is well established. The treatment consists of external beam radiotherapy (EBRT) 45-50.4 Gray (Gy) in 25-28 fractions over five to six weeks concurrent with weekly cisplatin-based chemotherapy and brachytherapy. The recommended total tumour dose in 2 Gy per fraction radiobiologic equivalence to Point A is 80 to 90 Gy, depending on the initial stage of the disease.

Earlier RCTs have shown that CCRT is superior to RT alone for LACC. This treatment has been the standard of care for LACC since 1999.

Two meta-analyses showed that CCRT improved OS, PFS and disease-free survival compared to RT alone in FIGO stage IB to IVA cervical cancer. Most of these trials were using platinum-based chemotherapy.[51 - 52, level I]

In a systematic review of limited quality, CCRT caused significant increase of acute haematological and gastrointestinal toxicities and no significant difference in late toxicities.[51, level I] In view of the consistent survival benefit from CCRT, the additional acute toxicities described may be justified.

Extended field RT, which involves treating the pelvis and the PAN with or without chemotherapy, may be considered for cervical cancer patients with PAN involvement at the expense of increased but manageable toxicities.[53 - 54, level II-2] The decision for this treatment should be made at the discretion of the treating oncologist.

Intracavitary brachytherapy (ICBT) is an essential part of RT for cervical cancer, treating mainly the primary tumour. High doses of radiation can be delivered to the tumour while the surrounding normal tissues, such as rectum, are relatively spared. High dose rate (>12Gy/hour) ICBT is as efficacious and safe as low dose rate (<2Gy/hour) ICBT in LACC in terms of OS, disease specific survival, relapse free survival, local regional recurrence and distant metastasis. The additional advantages of high dose rate ICBT are convenient outpatient treatment and rigid immobilisation for better accuracy of source applicator positioning.[55, level I]

The treatment time (from first fraction of RT to the last fraction of RT or brachytherapy) should not be more than 56 days as this would adversely affect the local control rate. However, this is not associated with distant failure or disease-specific mortality.[56, level II-1]

Recommendation 6

- Concurrent chemoradiotherapy should be given as the primary treatment in FIGO stage IB2 to IVA (locally advanced cervical cancer). The treatment time should not exceed eight weeks.
- Intracavitary high dose rate or low dose rate brachytherapy should be given in locally advanced cervical cancer.

b. Adjuvant Treatment

i. Surgery

The role of adjuvant post-radiation hysterectomy for patients with FIGO stage IB2 cervical cancer has been a source of controversy since this combined approach was first advocated. It is suggested that these bulky tumours and the associated tumour hypoxia was better addressed by hysterectomy than by additional intra-cavitary radiation.

In a large RCT, adjuvant surgery with extrafascial hysterectomy after radiation in FIGO stage IB cervical cancer had no clinical benefit compared with no adjuvant surgery. Even though there was a trend towards reduction in progression of disease and death but it was non-significant (RR for progression=0.77, p=0.07; RR for death=0.89, p=0.26). This may be due to lower cumulative incidence of local relapse (14% vs 27%) but higher distant progression (20% vs 16%) in the adjuvant surgery group at five years. Further analysis showed a

significant 28% reduction in progression of disease in bigger tumours (4 to 6 cm) in the adjuvant surgery group. The rates of grade 3 and 4 adverse events were similar at 10% in both group.[57, level I]

In cervical cancer patients with localised residual disease after primary radiation therapy, adjuvant hysterectomy is an effective salvage procedure even in patients with FIGO stage III disease and in those with non-SCC. The 5-year survival rate in the adjuvant surgery group is significantly higher than the group without adjuvant surgery (68.6% vs 14.5%). Apart from that:[58, level II-2]

- there is no difference in survival between SCC and non-SCC (p=0.6862).
- there is a trend for better survival of smaller tumours compared with larger tumours, although non-significant (p=0.053).

Adjuvant hysterectomy after unsuccessful ICBT does not offer advantage in recurrence-free and survival nor increase late toxicity.[59, level II-2]

- 50% of patients treated with pelvic EBRT alone have recurrent disease, whereas none among adjuvant hysterectomy patients (p=0.068).
- 43% of patients treated with pelvic EBRT alone have died of disease recurrence, whereas none among adjuvant hysterectomy patients (p=0.152).
- No patients develop late toxicity such as fistulae, wound dehiscence or bowel stenosis.

Recommendation 7

- Adjuvant surgery should not be routinely offered in cervical cancer.
- Hysterectomy after primary radiation therapy may be offered as a salvage procedure in cervical cancer with bulky primary tumour >4 cm or post-treatment localised residual tumour.

ii. Chemotherapy

Adjuvant chemotherapy is chemotherapy given after primary treatment. In a multi-centered open label RCT, the addition of gemcitabine to standard CCRT, followed by adjuvant chemotherapy with gemcitabine and cisplatin improved OS (HR=0.68, 95%CI 0.49 to 0.95) and PFS (HR=0.68, 95% CI 0.49 to 0.95). The addition of gemcitabine increased grade 3/4 acute haematological (neutropenia) and non-haematological toxicities (vomiting and diarrhoea). When further analysed, the gemcitabine-related toxicities occurred mostly during the preadjuvant phase. There was no difference in the incidence of late toxicities with or without gemcitabine.[60, level I]

In view of the different regime used as primary treatment in the RCT, further studies are warranted before any recommendation can be made on adjuvant chemotherapy in cervical cancer.

iii. Chemoradiotherapy/Radiotherapy

- Pathological factors that increase the risk of recurrence for early cervical cancer following radical surgery:[61 - 62, level I]
  - positive lymph nodes
  - parametrial or vaginal margin involvement
  - LVSI
  - lower uterine segment involvement
  - deep stromal invasion
  - non-squamous histology
  - high grade tumour
  - tumours >4 cm in size

Adjuvant platinum-based chemoradiotherapy after radical surgery may be required for high risk factors mentioned above. The modified Delgado score is accepted to stratify the risk for adjuvant chemoradiotherapy (refer to **Appendix 6**).[63]

Two meta-analyses have shown that chemoradiotherapy is more efficacious than RT alone:

- Reduces the risk of death (HR=0.56, 95% CI 0.36 to 0.87) and disease progression (HR=0.47, 95% CI 0.30 to 0.74) in early stage cervical cancer (FIGO stage IA2 to IIA).[62, level I]
- Acute grade 4 toxicity occurred more frequently in the chemoradiotherapy group (RR=5.66, 95% CI 2.14 to 14.98). However, long term data is limited.[62, level I]
- Improves OS (RR=0.74, 95% CI 0.64 to 0.86) in locally advanced, bulky FIGO stage IB or post-operative high-risk cervical cancer.[64 level I]

Adjuvant RT alone reduces risk of local recurrence (HR=0.6, 95% CI 0.4 to 0.9) without improvement of OS in FIGO stage IB cervical cancer compared to no further treatment. Adverse events are not significantly increased.[61, level I]

Recommendation 8

- Adjuvant chemoradiotherapy should be considered in cervical cancer patients with high risk of recurrence* after radical surgery.
- Patients with cervical cancer who are medically unfit for chemoradiotherapy may be offered adjuvant radiotherapy alone.

*Refer to **Appendix 6**

iv. Neoadjuvant Chemotherapy (NAC)

CCRT is the standard treatment for early stage cervical cancer with bulky disease and locally advanced cervical cancer. NAC is used to downstage the tumour prior to surgery.

In a Cochrane systematic review, NAC followed by surgery, with or without RT, improved OS (OR=0.65, 95% CI 0.53 to 0.80) compared to RT alone in FIGO stage IB - IVA cervical cancer.[52, level I]

In another Cochrane systematic review, NAC followed by surgery had significantly better OS and PFS than surgery alone in early-stage or LACC.[65, level I] However, in a more recent systematic review with a well-defined study population (FIGO stage IB1 to IIA), there was no difference in OS and PFS between NAC followed by surgery and surgery alone.[66, level I]

NAC before surgery reduces the need of adjuvant RT by significantly decreasing tumour size and distant metastasis,[66, level I] as well as reducing nodal metastasis.[65 - 66, level I] In early stage or LACC, there is less parametrial infiltration with NAC (OR=0.52, 95% CI 0.30 to 0.91).[65, level I]

In one of the reviews, there was insufficient data for quantitative analysis on the adverse effects of NAC. Three studies stated that surgical morbidity was similar between the NAC and standard treatment groups while one suggested lower surgical morbidity in the NAC group which may be due to a lower frequency of urological events.[65, level I] In the other review, data showed that serious late toxicity to the bladder, gastrointestinal tract and vagina were similar in both study groups.[52, level I]

The addition of NAC may improve survival if given in shorter cycle length (<14 days) and higher dose intensity (≥25 mg/m2/week).[52, level I; 65, level I]

Patients who achieved response to NAC before surgery have a favourable prognosis, with significant improvement in PFS and OS up to five years.[67, level II-2]

- Neoadjuvant chemotherapy is not routinely recommended for patients in cervical cancer due to debatable evidence and the decision should be made at the discretion of treating gynae-oncologist/ oncologist.

9. SPECIAL CIRCUMSTANCES

a. Pregnancy

Pregnancy does not worsen the prognosis of cervical cancer. Delaying treatment while awaiting foetal maturity in patients with early-stage disease diagnosed during first and second trimesters of pregnancy does not seem to have a major impact on patients' survival.[68, level III]

- Factors to be considered in the management of cervical cancer in pregnancy:
  - stage of disease
  - tumour size
  - nodal status
  - histology subtype
  - gestational week
  - patient's/couple's desire for pregnancy preservation (if oncologically safe)

FIGO staging is the same for non-pregnant and pregnant states. MRI is the imaging procedure of choice for assessment of locoregional spread.[69, level III] If required, CT scan can be offered and preferably done after 15 weeks gestation. PET-CT is not recommended during pregnancy.[68, level III]

Histological assessment of lymph node is the gold standard for nodal status. Laparoscopic lymphadenectomy is feasible up to 20 weeks gestation. Lymphatic mapping and SN detection are technically feasible during pregnancy.[68, level III]

The following recommendations are modified from the French Recommendations on the Management of Invasive Cervical Cancer during Pregnancy.[70, level III] In the SCC and AC histological subtypes, treatment is based on gestational age and the stage/size of tumour:

i. For FIGO stage IB1

- If tumour is diagnosed when foetal maturity is considered attained,
  - deliver foetus, optimally by caesarean section followed by cervical cancer treatment thereafter.
  - consider radical hysterectomy during caesarean section for women who are multiparous or completed family.
- If tumour is diagnosed >18 - 22 weeks gestation but before foetal maturity and patient wishes to preserve pregnancy,
  - for tumour size <2 cm, close follow-up is required including clinical and radiological imaging.
  - for tumour size of 2 - 4 cm, management should be individualised. If tumour size is close to 4 cm, offer NAC and inform of the treatment risks.

- deliver foetus once maturity attained, followed by cervical cancer treatment as per standard of care.

- If tumour is diagnosed <18 - 22 weeks gestation (when pelvic laparoscopic lymphadenectomy is technically feasible and possible) and patient wishes to preserve pregnancy,
  - consider laparoscopic pelvic lymphadenectomy for tumour size <2 cm. In the absence of nodal involvement, follow-up closely by clinical examination and imaging modality. If no disease progression, start cancer treatment as soon as foetal maturity is attained. In the presence of nodal involvement, consider termination of pregnancy (TOP) and start chemoradiation therapy thereafter.
  - consider TOP for tumour size 2 - 4 cm as there is a higher risk of nodal involvement.

ii. For FIGO stage IB2 and above, CCRT is the standard treatment,

- If tumour is diagnosed when foetal maturity is considered attained,
  - deliver foetus, optimally by caesarean section followed by cervical cancer treatment thereafter.
  - nodal staging surgery (pelvic nodes with/without para-aortic nodes for tumor >4 cm or positive pelvic nodes) at the same sitting is recommended.
- If tumour diagnosed >22 weeks gestation but before foetal maturity is attained, and without extracervical spread, offer CCRT after caesarean section once foetal maturity attained, and do not delay treatment for >6 - 8 weeks. Dissect pelvic ± para-aortic lymph nodes for tumour >4 cm or positive pelvic nodes during caesarean section.
- For tumour diagnosed <20 - 22 weeks gestation, offer CCRT after uterus is evacuated (hysterotomy or other procedure) or with foetus in utero (if expulsion impossible and bulky cervical cancer).

iii. For non-SCC and non-AC, such as the more aggressive SCC, diagnosed during first or second trimester of pregnancy, treatment is individualised and pregnancy preservation is not advisable.

Recommendations on treatment of cervical cancer in pregnancy are based on expert opinion and discussion among the CPG DG members.

Recommendation 9

- Treatment of cervical cancer (squamous cell carcinoma and adenocarcinoma) in pregnancy should be based on gestational age and stage/size of tumour.
- If tumour is diagnosed when foetal maturity is attained, deliver foetus followed by cancer treatment.
- If tumour is diagnosed before foetal maturity, for FIGO stage IB1:
  - tumour <2 cm and patient wishes to preserve pregnancy, close follow-up till maturity attained and deliver, followed by cancer treatment.
  - tumour 2 - 4 cm, consider termination of pregnancy followed by cancer treatment.
- For FIGO stage IB2 and above:
  - if tumour diagnosed <20 - 22 weeks gestation, consider termination of pregnancy followed by concurrent chemoradiation therapy.
  - if tumour diagnosed >22 weeks gestation and absence of extracervical spread, offer concurrent chemoradiotherapy after caesarean section once foetal maturity is attained.
- Neoadjuvant chemotherapy may be offered to a patient with operable cervical cancer whose surgery is delayed more than six weeks to allow optimal foetal maturity.

As cervical cancer in pregnancy is uncommon, the use of chemotherapy during pregnancy is mostly described in case reports.

In a methodologically-limited systematic review of observational studies, platinum derivatives especially cisplatin, may be used safely during the second and third trimesters as its use in the first trimester increases the risk of abortion or congenital anomalies.[71, level II-2]

Complete response (10%), partial response (63.4%) and stable disease (23.3%) were achieved after chemotherapy, whereas progression was observed in only 3.3% of cases. Chemotherapy was well tolerated with no serious adverse outcomes to both mothers and babies.[71, level II-2]

Recommendation 10

- Platinum-based chemotherapy may be considered after the first trimester in pregnant women with cervical cancer.

b. Tumour Arising from Cervical Stump

The incidence of cancer arising from the cervical stump in patients with prior subtotal hysterectomy is approximately 2%.[72 - 73, level II-3]

Cancer of the cervical stump should be managed in the same way as cervical cancer arising in an intact uterus.(17) This is supported by:

- Good OS (68% for 5-year survival rate) and low treatment morbidity (10%) when treated with either surgery followed by tailored adjuvant RT in operable disease, RT or CCRT.[73, level II-3]
- Prognosis is similar when managed with the same treatment regimen.[72, level II-3]

Recommendation 11
- Cancer of the cervical stump should be managed in the same way as cervical cancer arising in an intact uterus.

c. Cervical Cancer Diagnosed after Hysterectomy for Benign Gynaecological Disorder

Cervical cancer may be diagnosed incidentally after hysterectomy for benign gynaecological disease. Further management is based on clinical and pathological parameter. The choices are include no further treatment, further surgery with parametriectomy and lymphadenectomy and chemoradiation therapy.

Cervical cancer of FIGO stage IA1 diagnosed after simple hysterectomy can be followed up safely without further treatment regardless of LVSI status.[74, level II-2]

In FIGO stage IA2 – IIA cervical cancer,
- adjuvant treatment such as RT, CCRT or surgery [radical parametrectomy + paraaortic lymphadenectomy (RP + PLND)] significantly increases 10- year DFS compared to observation alone or chemotherapy; however, there is no significant difference in OS.[74, level II-2]
- surgery vs RT/CCRT have comparable DFS and OS with lower rate of late complications observed in surgery.[74, level II-2]
- post-operative radiotherapy gives high relapse-free and OS but has high overall treatment related complications.[75, level II-2]

Surgery (RP + PLND) alone is a safe option and achieves good OS rate in patients who fulfill these criteria,
- SCC, AC or adenosquamous cancer
- disease FIGO stage IA2 and IB1
- no evidence of deep invasion or tumour at margin and
- no clinical evidence of residual disease at vagina vault or parametrium

It avoids radiation therapy in 83% of patients and hence, preserves ovarian function and reduces sexual dysfunction.[76, level II-2]

Recommendation 12

- In cervical cancer diagnosed after hysterectomy for benign gynaecological disorder,
  - followed up safely without further treatment in FIGO stage IA1.
  - adjuvant treatment [radiotherapy, concurrent chemoradiotherapy or surgery (radical parametrectomy + pelvic lymphadenectomy] should be considered in FIGO stage IA2 - IIA.

d. Neuroendocrine Cancers

Most neuroendocrine cancers (NEC) of the cervix are small cell carcinomas, which account for up to 2% of cervical cancers.[77, level III; 78, level II-2] Median age of diagnosis is in the fifth decade. The usual presenting symptom is vaginal bleeding and a cervical mass can often be identified on examination. Some patients have abnormal pap smears.[77, level III]

In rare cases, patients may present with clinical or biochemical evidence of ectopic hormone production including corticotropin (Cushing's syndrome), vasopressin (syndrome of inappropriate anti-diuretic hormone secretion), insulin (hypoglycemia), serotonin (carcinoid syndrome) and parathyroid hormone (hypercalcemia) or myasthenia gravis.[77, level II]

There is an increased risk for LVSI and high rate of extrapelvic recurrence in NEC which correlates with poor prognosis.[77, level III; 79, level II-2] Most common sites of extrapelvic metastasis are bone, supraclavicular lymph nodes and lungs. Imaging evaluation generally includes CT scan of thorax, abdomen and pelvis or PET/CT scan. Head CT scan is not recommended on initial evaluation for small cell NEC of the cervix. [77 - 80, level III]

Surgery is primarily used either to achieve a diagnosis and for resection of early stage disease. RH, which is the standard surgery for FIGO stage IB to IIA cervical cancer of the ordinary type, has been adopted for the treatment of NEC. For early stage disease, patients with complete surgical resection should be considered for adjuvant chemotherapy. Recent data supports the use of platinum with or without etoposide in small cell and large cell NEC in improving survival.[77, level III; 79, level II-2]

CCRT is offered in non-surgical candidates (such as locally advanced disease, unfit for surgery, early disease with evidence of lymphadenopathy or FDG-avid nodal metastasis) and it is typically given with concurrent etoposide/cisplatinum.[81, level II-2] For advanced stage disease, metastatic sites are treated with platinum-based combination chemotherapy. Extrapolating from small cell lung cancer, vincristine/doxorubicin/cyclophosphamide and topotecan are considered as alternative or second-line therapies.[77, level III]

In local practice, CCRT regime is similar to other histological types; however additional adjuvant chemotherapy (cisplatin/etoposide) is given for 4 - 6 cycles.

NAC or adjuvant radiation does not improve survival. Multimodality treatment appears to produce the best outcomes for this disease. Primary tumours <4 cm and no clinical evidence of lymph node metastasis have better prognosis.[77, level III]

The follow-up is similar to other histological types with particular emphasis on periodic full body imaging with either CT or PET/CT. Brain imaging should be considered if patient is symptomatic.[77, level III]

Recommendation 13

- Neuroendocrine cancer of cervix should be managed by gynae-oncologists/oncologists.

10. FOLLOW-UP

The most appropriate follow-up strategy for clinically disease-free cervical cancer patients after receiving primary treatment varies from institution to institution.

There is modest low quality evidence to inform the most appropriate follow-up strategy. The majority of cervical cancer recurrences (62% to 89%) are detected within two years of primary treatment.[82, level III] A total of 58% of cervical cancer recurrences occur in the pelvis. Most of the patients (65%) are symptomatic at recurrence. Among them, 53% are found by exclusive pelvic examination.[83, level III] All asymptomatic pelvic recurrences are diagnosed by pelvic examination.[84 - 85, level III] A high percentage (85%) of the cancer can be diagnosed by pelvic examination and/or CT.[83, level III]

DFS for cervical cancer significantly correlates with site of relapse, type of relapse and symptoms at relapse. A better OS from relapse is observed in localised pelvic recurrence as compared to distant sites.[83, level III]

Follow-up is recommended for every three months in the first year, every four months in the second year, every six months in the third to fifth year and annually thereafter.[83, level III]

At a minimum, follow-up visits should include a complete physical examination with a patient history to detect symptomatic and asymptomatic recurrence.[82, level III] Cervical cytology or vault smears are not indicated to detect asymptomatic recurrence as it does not permit earlier detection of recurrence and does not increase survival.[82, level III; 86, level III]

Routine use of chest X-ray, abdominal and pelvic ultrasound, PET, CT, MRI, intravenous pyelography or blood analysis/tumour markers (CA 125 and SCCA) is not recommended as their role has yet to be evaluated in a definitive manner.[82, level III] MRI or CT should be considered initially to assess potential clinical recurrence in symptomatic patients. A whole body PET scan or PET-CT should be recommended on all patients in whom recurrent or persistent disease has been demonstrated on MRI or CT and in whom salvage therapy (either pelvic exenteration or RT) is being considered.

Patients should return to annual population-based general physical and pelvic examination after five years of recurrence-free follow-up.[82, level III]

Short-term hormone replacement therapy (HRT) does not appear to have an adverse effect on oncologic outcome in most gynecologic cancer survivors and improves quality of life (QOL). The treatment appears to be safe although not as effective as HRT in the treatment of

vasomotor symptoms, selective serotonin reuptake inhibitors (SSRIs) and alpha-2 adrenergic agonists are reasonable alternatives.[87, level II-2]

Recommendation 14

- After primary treatment, patients with cervical cancer may be followed up every three months in the first year, four months in the second year, six months in the third to fifth year and annually thereafter.
  - Physical examination including pelvic examination should be performed during follow-up.

11. RECURRENT DISEASE

a. Pelvic exenteration

In advanced and recurrent cervical cancer, the role of surgery is limited. In this situation, pelvic exenteration may be an option in selected group of patients.

Primary or secondary pelvic exenteration with curative or palliative intention is an effective option with high percentage of long-term survival in LACC FIGO stage IVA:

- Median survival between 29 – 30 months[88, level II-1; 89, level II-2]
- 5 - years OS ranging from 36.8% to 52%[88, level II-1; 90 - 91, level II-2]

Patients who have undergone pelvic exenteration of curative intent have higher OS compared with those of palliative intent (5-year and 10-year OS are 64% and 57% for curative intent vs 19% and 18% for palliative intent). There is no significant difference in 5-year OS when pelvic exenteration is performed in SCC or AC cervical cancer ($p>0.05$).[92, level II-1]

In a mixed population that includes cervical cancer, 61% 5-year OS is achieved when resection margin is negative.[93, level II-2]

For cervical cancer patients who have undergone pelvic exenteration, the following factors are significantly associated with lower OS:

- positive pelvic lympnode[88, level II-1; 94, level II-2]
- positive resection margin[91, level II-2; 94, level II-2]
- shorter time between primary treatment and recurrence[91, level II-2]
- surgery of palliative intent[91, level II-2]

In pelvic exenteration:

- the overall complication rates range between 51.6% and 66%.[91, level II-2; 92, level II-1; 94, level II-2]
- the early complication rates (≤30 days) range between 44.8% and 50%.[89 - 90, level II-2; 94 level II-2]
- the late complication rates (>30 days) range between 48.5% and 74%.[89 - 90, level II-2; 94, level II-2]
- the rate of major complication requiring surgical treatment is 20%.[95, level II-2]
- the rates of infectious morbidity, intestinal obstruction and fistula are 86%, 33% and 23%.[93, level II-2]
- the rate of operative mortality is 5.5%.[91, level II-2]

- Contraindication for pelvic exenteration:
  - distant metastasis/extra pelvic spread
  - pelvic side wall involvement such as hydronephrosis/hydroureter and lumbosacral plexopathy
  - poor performance status
- Common complications for pelvic exenteration are infectious morbidity, intestinal obstruction, fistula formation, anastomotic leak and prolonged hospital stay.

Recommendation 15

- In patients with cervical cancer, pelvic exenteration may be considered in locally advanced disease or in pelvic recurrence, after thorough counselling on its benefits and risks.

b. Chemotherapy

Chemotherapy with palliative intent may be an option in patients with recurrent or metastatic cervical cancer with Eastern Cooperative Oncology Group (ECOG) Performance Status grades 0 to 2 (refer to **Appendix 7**).

In recurrent or metastatic cervical cancer,

- there is no difference in response rates between platinum-containing regimens and non-platinum-containing regimens (RR=1.33, 95% CI 0.50 to 3.54).[96, level I]
- combination cisplatin-based chemotherapy has better response (complete and partial response) and improve survival compared to single-agent cisplatin chemotherapy.[96 - 97, level I]
- combination of paclitaxel and platinum chemotherapy has better response compared to non-paclitaxel-containing combination (RR=1.47, 95% CI 1.01 to 2.15).[96, level I]
- response rate towards platinum-containing chemotherapy is better in out-of-radiotherapy-field (non-irradiated site) recurrence compared to in-radiotherapy-field (irradiated site) recurrence. (RR=0.62, 95% CI 0.46 to 0.83).[96, level I]

- combination chemotherapy has more toxicities compared to single agent chemotherapy.[96 - 97, level I]

Recommendation 16
- Combination chemotherapy* may be offered to patients with recurrent or metastatic cervical cancer with good performance status.

* Refer to **Appendix 8** on Systemic Therapy of Cancer (revised edition MoH and MoE Malaysia) for suggested chemotherapy regime.

c. Salvage Radiotherapy/Chemoradiotherapy

The treatment for recurrent cervical cancer depends on the mode of primary treatment and the site and extent of recurrent disease. Salvage RT or CCRT may be a feasible treatment option for locally recurrent cervical cancer following surgery with high salvage rate (41 – 45 %) and acceptable late complication rate.[98 - 99, level II-2]

Recommendation 17
- In radiotherapy naïve cervical cancer patients with local recurrence, salvage radiotherapy to the pelvis may be offered.

12. TREATMENT COMPLICATIONS

Radiation proctitis and cystitis are known complications of radiation therapy. Acute radiation complication refers to radiation-induced injury during the time of treatment and for up to 90 days after completion of RT. This is a frequently occurring early adverse effect and the pathology is of an inflammatory process affecting the rectal or bladder mucosa, and is generally self-limiting.

Late radiation complications are complications occurring more than 90 days after completing radiotherapy treatment and are relatively rare. The underlying pathology is of submucosal injury with a combination of fibrosis, ischaemia, and subsequent ulceration, which can be localised, diffuse or full thickness penetrating the wall of the rectum. The clinical presentation may have an inflammatory component producing tenesmus, urgency, diarrhoea, constipation, anal sphincter dysfunction (affecting the control of the bowels), mucoid or bloody discharge per rectum or frank bleeding with ulceration which may perforate. These chronic and episodic symptoms will cause impaired QOL of the patients.

At present, there is no recommended standard treatment for both late radiation proctitis and cystitis in view of lack of evidence with regards to effectiveness and impact on QOL by the treatment approaches or methods. There is no recent evidence on the above issues and thus the CPG DG has decided to use the best available evidence beyond the scope of the search.

a. Radiation Proctitis

Late radiation proctitis is episodic and variable in nature. A Cochrane systematic review on non-surgical interventions for the management of late radiation proctitis had identified several treatment approaches with varying results.[100, level I]

- Rectal sucralfate showed greater clinical improvement for proctitis than anti-inflammatories (OR=14, 95% CI 1.46 to 134.26), though no difference was seen for endoscopic improvement (OR=2.74, 95% CI 0.64 to 11.76). Other effective medications were combination of metronidazole and anti-inflammatory drugs, and rectal hydrocortisone.
- Short chain fatty acid enemas did not appear to be efficacious compared to placebo.
- Thermal coagulation therapy appeared to have clinical improvement in the management of haemorrhagic radiation proctitis refractory to other treatments.
- Hyperbaric oxygen therapy improved radiation proctitis compared to placebo (RR=2.7, 95% CI 1.2 to 6.0; NNT=3).

b. Radiation Cystitis

Late radiation cystitis is relatively uncommon treatment complication. The same Cochrane systematic review found no evidence from trials determining the effects of non-surgical treatments for late radiation cystitis. Therefore, there is no standard treatment in managing patients with radiation cystitis.[100, level I]

- There is insufficient good quality evidence to recommend treatment for late radiation proctitis and cystitis in cervical cancer. Therefore, the treatment should be individualised according to the attending doctor.

c. Lymphoedema

Refer to **Chapter** on **Palliative Care** (**Lymphoedema**).

d. Chronic Bladder Dysfunction

It is a common late complication of radical hysterectomy ranging from 0-44% and the most distressing one, requiring voiding by the clock with the help of abdominal muscles and in some cases, self-catheterisation.[101]

Radicality of the surgery is closely related to post-operative bladder dysfunction. Compared with the extent of lateral parametrial resection, the extent of vaginal resection has stronger association with bladder dysfunction.[102]

Direct, nerve-sparing radical hysterectomy is a technique that spares the pelvic autonomic nerves without compromising radicality, providing another approach to improve quality of life and reduce bladder and bowel morbidity.[103, level III]

13. PALLIATIVE CARE

There is an increasing trend of integration of modern cancer care with palliative medicine. Palliative care focuses on preventing and relieving suffering, optimising symptom control, preserving hope and improving QOL.[104]

All healthcare providers should be trained to deliver basic palliative care. Specialist palliative care providers may be required for management of complex symptoms and end of life issues.[105] Inpatient specialised palliative care units and community hospices nationwide are listed in **Appendix 9**.

This chapter aims to address some common issues experienced by patients with advanced disease which include:

- pain
- malignant/malodorous wounds
- thrombosis and haemorrhage
- fistulae
- lymphoedema
- malignant ureteric obstruction
- end of life care

- Appropriate symptom management in advanced cervical cancer can be complex and a clear understanding of prognosis is essential to guide assessment and subsequent management.

a. Pain

Principles of pain management are described in the Clinical Practice Guidelines for the Management of Cancer Pain by MoH.[106]

Patients with advanced cervical cancer may experience complex neuropathic pain as a complication of RT or chemotherapy, or develop lumbar plexopathy from nerve infiltration.[107, level III]

Management of selected pain syndromes may benefit from specialist consultations for intrathecal or epidural procedures in addition to conventional analgesic medications. A combination of opioids, local anaesthetics and clonidine can be used for temporary neural blockade while neurolytic agents such as alcohol are used for permanent blockade.[17]

Malignant psoas syndrome refers to proximal lumbosacral plexopathy by painful fixed flexion of the ipsilateral hip, with radiological or pathological evidences of ipsilateral psoas major muscle malignant involvement. Treatment options include opioids, agents for neuropathic pain, muscle relaxants to counter psoas muscle spasm, agents to reduce peri-tumoural oedema and anti-tumoural agents if suitable.[108, level III]

b. Malignant/Malodorous Wounds

Patients with malodorous malignant wounds often associate the condition with advance, progressing disease. This not only causes physical discomfort, but also significant psychological and social impact, and negatively affects the woman's body image and sense of worth.[107, level III]

Malodorous discharges are generally caused by tissue breakdown from ulcerating necrotic tissue, erosion into a hollow viscous such as the bowel or urinary tract, and/or an added infection of the fluid. Benign lesions such as pressure-related breakdown can also contribute to the malodour.[107, level III]

Management involves treating infection, containing or removing fluid loss, reducing local irritation and improving QOL.(17) There is limited published evidence guiding the management of wounds in cancer patients and no evidence regarding QOL improvement.[109, level I]

Surgical methods to manage malodour may include removal or debridement of necrotic tissue, and nephrostomies or defunctioning colostomies for fistula-related urinary or faecal incontinence. Tumour burden may also be reduced by interventional radiology techniques to reduce tumour circulation, palliative RT or chemotherapy.[107, level III]

Patients using topical metronidazole, mesalt dressing, activated carbon dressing and curcumin ointment can control the odour of malignant fungating wounds.[110, level II-3] Other suggested methods include:[17, level III; 107, level III]

- systemic metronidazole
- aromatherapy
- pads and tampons
- vaginal douches
- topical steroids
- barrier creams to avoid local skin irritation and excoriation
- treatment of bacterial and fungal infections
- oral tranexamic acid 1000 - 1500 mg two to three times daily for bleeding wounds
- octreotide and hyoscine butylbromide to reduce faecal loss from enterovaginal fistulae
- suprapubic catheterisation for vesicovaginal fistulae

c. Fistulae

The risk to develop vesicovaginal and/or rectovaginal fistulae is high (22 – 48%) after curative RT with or without chemotherapy in patients with FIGO stage IVA cervical cancer.[111, level III] Fistula formation occurs between six and 48 months after RT, with possible serious complications occurring even after five years.[107, level III] The routine use

of EUA, cyctoscopy and proctoscopy at the time of initial diagnosis helps in counseling women about the likelihood of this complication. [112, level III]

Appropriate radiological investigations are often needed to establish the fistula site and its complexity. Surgical interventions may include:[17, level III; 107, level III]

- fistula repair
- formation of ileal conduit
- stoma formation for enterovaginal fistulae
- colonic stenting in bowel obstruction
- percutaneous nephrotomies or internal ureteric stents for urological fistulae

Primary exenteration surgery for selected patients in FIGO stage IVA have been suggested to avoid morbidity associated with fistula formation.[111, level III]

Patients with advance disease where non-surgical measures are more appropriate may benefit from:[17]

- octreotide, hyoscine butylbromide or glycopyrronium to reduce discharge volume
- codeine phosphate or loperamide to reduce motility and increase stool consistency
- barrier creams to prevent local irritation and excoriation
- topical steroids
- tampons and pads
- low residue diet

d. Thrombosis and Haemorrhage

Venous thromboembolism (VTE) causes high mortality and morbidity in patients with cancer, and is the second most common cause of death after cancer progression.[113, level III]

The risk of thromboembolic events is up to seven times higher in cancer patients, with the incidence being highest in the first few months of diagnosis. Others at high risk are those with metastatic disease at the time of diagnosis and after tumour recurrence.[113, level III] Cancer patients receiving anticoagulant treatment for VTE also showed a two to threefold increased risk of developing recurrent VTE.[114 - 115, level I]

The mechanisms of VTE in cancer patients can be summarised in the following table:

Table 2. Mechanism of VTE in Cancer Patients

Mechanism of VTE in Cancer Patients	
Tumour-associated	**Non-tumour associated**
• Extrinsic vascular compression and invasion	• Central venous access devices
• Tissue factor production	• Anti-neoplastic mediated platelet activation
• Cancer pro-coagulant production	• Anti-neoplastic mediated endothelial cell damage
• Accentuated platelet activation	• Anti-angiogenesis therapy
• Inflammation-mediated increases in factor VIII, vWF and fibrinogen	• Anthracycline-induced congestive heart failure
• Impaired fibrinolysis due to high PAI-1	• Immobility
• Acquired deficiencies of natural anticoagulants	

Source: Ministry of Health. Prevention and Treatment of Venous Thromboembolism. Putrajaya: MoH; 2013

- **Initial management of VTE**

For the initial management of VTE in cancer patients, low molecular weight heparin (LMWH) is superior to unfractionated heparin (UFH), with reduced risk of mortality (RR=0.71, 95% CI 0.52 to 0.98) and no significant difference in recurrent VTE events.[114, level I] Among various LMWH regimes, once daily treatment is as safe and efficacious as twice daily treatment, and is more convenient for the patient.[116, level I]

A Cochrane systematic review showed fondaparinux was as safe and efficacious as UFH, and dalteparin as safe and efficacious as tinzaparin in the initial management of VTE in cancer patients.[114, level I]

- **Long-term management of VTE**

For the long-term treatment of VTE in cancer patients, LMWH reduces recurrent VTE events (HR=0.47, 95% CI 0.32 to 0.71) but not death when compared with vitamin K antagonists (VKA).[115, level I]

If VKA is the choice of long-term treatment, current Malaysian VTE guidelines recommend starting warfarin within 24 hours of diagnosis in combination with LMWH or fondaparinux. Treatment with LMWH is to be continued for five days or until International Normalised Ratio (INR) is above 2 for at least 24 hours, whichever is longer. Anticoagulation should be continued indefinitely or until cancer is resolved.[117]

Currently, there is insufficient evidence on the usage of novel anticoagulants (such as dabigatran and rivaroxaban) in the management of VTE in cancer patients.[115, level I]

More than 50% of cancer patients have renal insufficiency, in turn affecting treatment choices and dosages. In severe renal insufficiency, UFH is used for the initial treatment, followed by VKA or long-term LMWH with anti-Xa monitoring. Tinzaparin may be a safe option for the treatment and prevention of VTE in cancer patients with renalfailure. [113, level III]

Patients with Deep Vein Thrombosis (DVT) who receive home treatment, compared with inpatient treatment, are less likely to have recurrence of VTE (RR=0.61, 95% CI 0.42 to 0.90), have a lower mortality (RR=0.61, 95% CI 0.42 to 0.90) and show a trend for fewer major bleeding complications but more minor bleeding complications.[118, level I]

Vena caval filter (VCF) usage for the prevention of pulmonary embolism increases risk of long-term lower limb DVT (HR=1.52, 95% CI 1.02 to 2.27) with no significant improvement in mortality or reduction in the rate of pulmonary embolism or DVT.[119, level I] Current Malaysian VTE guidelines list only two indications for the insertion of a VCF which are contraindication to anticoagulation and the presence of large free floating iliocaval thrombus.

- **Haemorrhage**

Patients with cervical cancer may suffer from bleeding problems due to advanced or metastatic disease. Chemotherapy causing thrombocytopaenia and myelosuppression, vitamin K deficiency and adverse drug effects are factors contributing to clotting and bleeding problems.[107, level III]

Palliative RT for cervical carcinoma results in complete cessation of vaginal bleeding in up to 45% of patients after the first radiation fraction.[120, level III] Other methods suggested to treat minor haemorrhage include fibrinolytic inhibitors such as oral or intravenous tranexamic acid.[17]

e. Lymphoedema

In patients with cervical cancer, 12.2% of them have a clinical diagnosis of lower limb lymphoedema. They are 3.5 times more likely to develop lower limb lymphoedema if they receive pelvic RT and have 3.3 times higher risk if pelvic lymph nodes are surgically removed.[121, level III] Lymph node metastases, infiltrative carcinoma and pressure from large tumours also contribute to secondary lymphoedema.

Patients report a poor QOL due to pain, changes in lower limb sensation, appearance, restriction in activities and distress.[17] Those at risk of lymphedema should be identified early, monitored and taught of self-care. Patients and carers should be offered information about lymphoedema, its prevention and management.[122, level III]

General approaches to minimise the risk of developing lymphoedema are:[122, level III]

- good care of skin and nails
- maintain optimal body weight
- eat a balanced diet
- avoid injury to area at risk
- avoid tight underwear, clothing, watches and jewellery
- avoid exposure to extreme temperatures
- use high factor sunscreen and insect repellent
- wear prophylactic compression garments, if prescribed
- perform exercise/movement and limb elevation
- wear comfortable, supportive shoes

Diagnosis criteria for lymphoedema have been identified as:[17]

- increase in limb circumference
- changes in sensation: fullness, tightness, heaviness, throbbing and shooting pains
- reduce in limb flexibility
- palpable changes to the skin or subcutaneous tissue such as fibrosclerosis that may be pitting or non-pitting

Severity of disease is classified into stages as described by the International Society of Lymphology (refer to **Appendix 10**).

The evidence for treatment of lymphoedema is poor with no clear conclusions on the efficacy of benzo-pyrones,[123, level I] and weak evidence supporting usage of multi-layer bandaging over hosiery.[124, level I]

A consensus report outlines the approach to managing lymphoedema: [122, level III]

- exercise and movement
- swelling reduction and maintenance by compression garments, multi-layer bandaging, exercise and lymphatic massage
- skin care
- pain management
- psychosocial management

Lymphoedema is best managed by specialist lymphoedema practitioners, usually physiotherapists, who are available at some healthcare settings.[122, level III]

f. Malignant Ureteric Obstruction

Obstructive renal failure occurs due to locally advanced cervical cancer. Patients may be asymptomatic, but may complain of pelvic pain or uraemic symptoms due to renal failure.[125, level II-2]

Treatment options are:[17; 126, level II-2]

- retrograde stenting
- percutaneous nephrostomy (PN) with/without antegrade stenting
- conservative management

Endoscopic placement of ureteral stents are often considered as the first-line option for relieving ureteral obstruction.[126, level II-2] If retrograde stenting is unsuccessful, alternative options would be PN and/or antegrade stenting.

PN can be of clinical benefit for patients with performance status 1 - 3 (refer to **Appendix 7**). High levels of morbidity (44%) have been reported with median OS of 8.9 weeks after the surgery. Half of the patients experience clinical benefit, as measured by recovery from uraemic symptoms, lumbar pain or generally poor renal function.[125, level II-2]

Malignant ureteric obstruction indicates poor prognosis. Palliative surgical interventions may be inappropriate if patients are terminally ill with irreversible renal failure. The high morbidity associated with palliative diversion may impair QOL. Treatment decisions should be based on clear discussions of options, prognosis, cost, complications and QOL, between patients and a multidisciplinary team.[126, level II-2]

g. Malignant Bowel Obstruction

The incidence of malignant bowel obstruction (MBO) in gynaecologic cancer appears to be commonest in ovarian cancer (54.5%), followed by cervical or endometrial cancer (27.3%).[127, level II-3] Patients often have high morbidity due to symptoms such as abdominal pain, colic, nausea and vomiting, as well as from treatment such as surgery, nasogastric tube insertion and intravenous therapy.

Management of MBO should be tailored to the underlying aetiology, stage of disease and goals of care. Treatment options may include surgical management with corrective or non-corrective laparotomies, venting tubes and stent insertions, or medical management such as symptomatic relief with opioids, anti-emetics, anti-spasmodics, anti-secretory drugs and steroids.[104, level III]

In patients with advanced gynaecologic cancers who present with MBO, treatment with dexamethasone (6 - 16 mg/day) may resolve bowel obstruction but will not improve survival. A therapeutic trial of four to five days is suggested.[128, level I] Octreotide may be considered in these patients, and will reduce overall nausea, vomiting and nasogastric drainage volume.[127, level II-3]

There are no clear recommendations for surgery in resolving symptoms of MBO in advanced gynaecologic cancer.[128, level I] Consider medical

management for patients with advanced stage cancer and a shorter time interval between cancer diagnosis and bowel obstructions.[129, level III]

h. End of Life Care

The final phase of terminal illness can be the most challenging time for the patient, their carers and healthcare providers. Increased clinical vigilance on symptom control, psychosocial and spiritual distress is needed, along with sensitive communication and decision making.[130, level III] Those closely affected by a death should be offered bereavement, emotional and spiritual support appropriate to their needs and preferences.[131]

Recommendation 18

- Patients with advanced cervical cancer should receive palliative care and be referred to a specialised palliative team if necessary.
- Low molecular weight heparin should be used for the initial and long-term treatment of venous thromboembolism in cervical cancer, where available.

14. PSYCHOSEXUAL CARE AND SOCIAL SUPPORT

In cervical cancer patients, psychological distress is often unrecognised. Therefore, a simple and practical screening tool such as the Distress Thermometer may help to identify underlying issues and make necessary referrals. Refer to **Appendix 11** for **Distress Thermometer Screening Tool**.

Following diagnosis of cervical cancer, women often experience distress in many domains of life such as:[132, level III]

- emotional (feelings of sadness, down or depressed, anxiety and worry that treatment is beyond control)
- physical (lack of energy and unable to do things they used to do)
- psychological (fears about cancer returning and spreading)
- social (concerns about the worries of close ones)

Locoregional cervical cancer survivors report chronic fatigue after RT. They also experience lower pleasure and QOL, higher discomfort and higher levels of depression and anxiety, than those without chronic fatigue.[133, level III]

Sexual dysfunction is a common problem after cervical cancer treatment. Many factors contribute to this including the loss of psychologic self-esteem, distorted physical appearance, or deterioration of organ function. Although most women resume sexual activity after radical hysterectomy, 41% of them have decreased sexual satisfaction while 36% have increased dyspareunia.[134, level III] Physical intimacy and body image are highly vulnerable to disruption after cancer diagnosis and treatment.[135, level I]

Patients should be advised that their physical and psychological functions are likely to deteriorate in the initial post-treatment period, but they should anticipate improvement thereafter.[17]

Recommendation 19

- Psychosocial assessment should be performed in all cervical cancer patients.
- Psychoeducation regarding potential deterioration and treatment outcome-related to the cervical cancer should be offered after diagnosis.
- The sexual health of women diagnosed with cervical cancer should be assessed pre-treatment and monitored during the treatment.

Women with cervical cancer require help for various needs. These needs should be identified early so that resources and intervention can be put in place as promptly as possible.[132, level III] Many women

report an increase need for emotional and physical closeness with their spouse.[135, level I]

Some women show concern about their sexual health, which include:[134, level III]

- potential harm from sexual activity on health
- appropriate time to resume sexual activity
- ways to relieve pelvic pain or increase sexual desire
- self-awareness of being feminine

Several psychological interventions for patients with cervical cancers have been evaluated. Couple-focused intervention has stronger effects compared to women-focused intervention. It improves most sexual aspects including adjustment, drive, satisfaction and intimacy. It also has strong effects for the male partners' sexual drive and satisfaction.[135, level I]

Other psychological interventions with some positive effects:

- Cognitive Behavioural Therapy on changing unhelpful thoughts or behaviour and coping skills.[136, level I]
- counselling on emotional distress including anxiety and depression.[136 level I]
- relaxation and guided imagery on emotional distress and body discomfort.[137, level III]
- information-based intervention on disease, treatment options and coping strategies.[136, level III]
- social support (including family, friend and special person) is associated with higher quality of life and lower rate of depression and anxiety.[137, level III]

- In cervical cancer:
  - couple-focused intervention is preferred over women-focused intervention to improve sexual health.
  - Cognitive Behavioural Therapy can reduce psychosocial distress.
  - social support improves quality of life and reduces negative mood symptoms, including depression and anxiety.

15. IMPLEMENTING THE GUIDELINES

It is important to standardise the management of cervical cancer at all healthcare levels in Malaysia by using an evidence-based CPG. This aims to prevent long-term morbidity and mortality.

a. Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:-

- dissemination of CPG
  - availability and dissemination of CPG to healthcare providers (hardcopies and softcopies)
  - conferences and updates on management of cervical cancer
- implementation of CPG
  - public awareness via Cervical Cancer Awareness
  - accessibility to relevant multidisciplinary teams
  - active involvement of government and non-governmental organisations

Existing barriers for application of the recommendations of the CPG are:-

- limited awareness in managing and referrals among primary care providers
- variation of practice and treatment at different levels of care
- limited facilities and human resources
- inadequate training at all levels of healthcare providers
- lack of networking between public and private health-care providers

b. Potential Resource Implications

To implement the CPG, there must be a strong commitment to:-

- distribute the CPG widespread to healthcare providers
- strengthen training on cervical cancer management for healthcare providers
- establish a cervical cancer registry in Malaysia
- develop of multidisciplinary teams in secondary and tertiary care levels

To assist in the implementation of the CPG, the following is proposed as clinical audit indicator for quality management:-

- Percentage of patients with cervical cancer receiving definitive treatment within six weeks of histological diagnosis

$$= \frac{\text{Number of patients with cervical cancer receiving definitive treatment within six weeks of histological diagnosis in a year}}{\text{Number of patients with cervical cancer with histological diagnosis in the same period}} \times 100\%$$

- Percentage of patients with cervical cancer completing CCRT within eight weeks

$$= \frac{\text{Number of patients with cervical cancer completing CCRT within eight weeks in a year}}{\text{Number of patients with cervical cancer receiving CCRT in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH. These include a Quick Reference and a Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

The following MeSH terms or free text terms were used either singly or in combination, search was limit to English, human and last 10 years:-

1. Uterine Cervical Neoplasms/
2. (uterine cervical adj1 (cancer$ or neoplasm$ or carcinoma or tumo?r$ or malignanc$)).tw.
3. (uterine cervix adj1 (cancer$ or neoplasm$ or carcinoma or tumo?r$ or malignanc$)).tw.
4. 1 or 2 or 3
5. Recurrence/
6. recurr*.tw.
7. recrudescen*.tw.
8. relaps*.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. Antineoplastic Agents/
12. ((drug* or agent*) adj1 anticancer).tw.
13. (chemotherapeutic anticancer adj1 (agent* or drug*)).tw.
14. (cancer chemotherapy adj1 (drug* or agent*)).tw.
15. chemotherapy drugs cancer.tw.
16. chemotherapy agent cancer.tw.
17. chemotherapy agents cancer.tw.
18. chemotherapy drug cancer.tw.
19. (antitumo?r adj1 (drug* or agent*)).tw.
20. antineoplastic*.tw.
21. (antineoplastic adj1 (agent* or drug*)).tw.
22. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 10 and 22
24. limit 23 to (english and humans and last 10 years)

Appendix 2

CLINICAL QUESTIONS

1. Epidemiology/Risk factors/Clinical presentation
   - 1.1 What is the epidemiology of cervical cancer?
   - 1.2 What are the risk factors of cervical cancer?
   - 1.3 What are clinical presentations of cervical cancer?

2. Referral
   - 2.1 When should the patients with cervical cancer be referred to gynae-oncology/oncology team?

3. Diagnosis and Staging
   - 3.1 What are the important histopathological parameters in the diagnosis of cervical cancer?
   - 3.2 What is the role of frozen section assessment in cervical cancer?
   - 3.3 Is clinical staging effective in the assessment of cervical cancer?
   - 3.4 What is the role of imaging in the assessment of cervical cancer?

4. Treatment
   - 4.1 Are the following modalities effective and safe in the primary treatment of cervical cancer?
     - Surgery
     - Definitive Chemoradiotherapy/Radiotherapy
   - 4.2 What are the effective and safe adjuvant therapies in cervical cancer?
     - Surgery
     - Chemotherapy
     - Chemoradiotherapy/Radiotheraphy
     - Neoadjuvant Chemotherapy
   - 4.3 What are the effective and safe management of cervical cancer in the following special circumstances?
     - Pregnancy
     - Tumour arising from cervical stump
     - Cervical cancer diagnosed after hysterectomy for benign gynaecological disorder
     - Neuroendocrine cancers
   - 4.4 What are follow-up plans for patients with cervical cancer?
   - 4.5 What are the effective and safe modalities for diagnosis, assessment and treatment of recurrent cervical cancer?
     - Surgery
     - Chemotherapy
     - Salvage radiotherapy/Chemoradiotherapy

4.6 What are the effective and safe management of complications following treatment of cervical cancer?
4.7 What are the effective and safe palliative care following treatment of cervical cancer?
4.8 What are the effective psychosexual care and social support for patients and carers?

Appendix 3

WHO histological classification of tumours of the uterine cervix

Epithelial tumours

Squamous tumours and precursors	
Squamous cell carcinoma, not otherwise specified	8070/3
Keratinizing	8071/3
Non-keratinizing	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 /	8077/2
Squamous cell carcinoma in situ	8070/2
Benign squamous cell lesions	
Condyloma acuminatum	
Squamous papilloma	8052/0
Fibroepithelial polyp	
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	
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

Leiomyosarcoma	8890/3
Endometrioid stromal sarcoma, low grade	8931/3
Undifferentiated endocervical sarcoma	8805/3
Sarcoma botryoides	8910/3
Alveolar soft part sarcoma	9581/3
Angiosarcoma	9120/3
Malignant peripheral nerve sheath tumour	9540/3
Leiomyoma	8890/0
Genital rhabdomyoma	8905/0
Postoperative spindle cell nodule	

Mixed epithelial and mesenchymal tumours

Carcinosarcoma (malignant müllerian mixed tumour; metaplastic carcinoma)	8980/3
Adenosarcoma	8933/3
Wilms tumour	8960/3
Adenofibroma	9013/0
Adenomyoma	8932/0

Melanocytic tumours

Malignant melanoma	8720/3
Blue naevus	8780/0

Miscellaneous tumours

Tumours of germ cell type

Yolk sac tumour	9071/3
Dermoid cyst	9084/0
Mature cystic teratoma	9080/0

Lymphoid and haematopoetic tumours

Malignant lymphoma (specify type)
Leukaemia (specify type)

Secondary tumours

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) {921} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
2. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are only available for lesions categorized as squamous intraepithelial neoplasia grade 3 (e.g. cervical intraepithelial neoplasia 3) = 8077/2, squamous cell carcinoma in situ = 8070/2, glandular ntraepithelial neoplasia grade 3 = 8148/2 and adenocarcinoma in situ = 8140/2.

Source: Kurman RJ, Carcangiu ML, Herrington CS et al. WHO Classification of Tumours of Female Reproductive Organs. Fourth Edition. Geneva, WHO. 2014; Chapter 5

Appendix 4

REPORTING PROFORMA FOR CERVICAL CANCER IN EXCISIONAL CERVICAL BIOPSIES / HYSTERECTOMY SPECIMENS

MACROSCOPIC

Specimen labelled as:

Type of procedure/specimen:

LLETZ ☐ **CONE Biopsy** ☐ **Trachelectomy** ☐

Radical Trachelectomy ☐ **Simple Hysterectomy** ☐ **Radical Hysterectomy** ☐

Orientation markers: ☐

Specimen gross/external appearance:

SPECIMEN MEASUREMENTS	
Length of specimen:	mm
Length of canal:	mm
Ectocervix diameter (3-9 o'clock):	mm
Ectocervix diameter (6-12 o'clock):	mm
UTERINE DIMENSION	
Cervix-fundus:	mm
Anterior-posterior:	mm
Distance between cornu:	mm
ADNEXA	Present ☐ Absent ☐ Normal ☐ Abnormal (specify) ☐
	Right ovary dimension mm
	Right fallopian tube mm
	Left ovary dimension: mm
	Left fallopian tube: mm

Vaginal cuff dimension:

____mm (length) x ____mm(width/circumferential) x ____ mm(thickness)

Parametrium included	Yes ☐ No ☐
Paracervix included	Yes ☐ No ☐
Macroscopically visible tumour	Present ☐ Absent ☐
Number of visible tumour(s)	_____
Tumour location (position)	Anterior ☐ Posterior ☐ Right ☐ Left ☐ Circumferential ☐

Gross appearance of tumour	Exophytic ☐ Endophytic ☐
Tumour size: ____mm (vertical/length) x _____mm horizontal/width) x ____mm(depth/thickness)	
Thickness of cervical wall at deepest invasion site	mm
Macroscopic involvement of vagina	Yes ☐ No ☐
Macroscopic involvement of parametrium	Yes ☐ No ☐
Macroscopic involvement of paracervix	Yes ☐ No ☐
Lymph nodes	
MICROSCOPIC **Tumour** **Multiple tumours : Present ☐ Absent ☐** **Histological tumour type : Squamous carcinoma ☐** **Adenocarcinoma ☐** **Adenosquamous carcinoma ☐** **Neuroendocrine carcinoma ☐** **Other (Specify):**	
Carcinoma subtype	
Histological tumour grade	Well / Grade 1 ☐ Moderate / Grade 2 ☐ Poor / Grade 3 ☐ Not assessable / Not applicable ☐
Maximum depth of invasion	mm
Cervical wall thickness	mm
Minimum thickness of uninvolved cervical stroma	mm
Ulceration	Present ☐ Absent ☐
Horizontal measurement	mm
Transverse measurement	mm

Associated AIS : Absent ☐ Present ☐ (If present, describe extention)	
Associated CIN : Absent ☐ Present ☐ (If present, describe grade and extention)	
Associated SMILE : Absent ☐ Present ☐ (If present, describe extention)	
EXTENT	
Lymphovascular invasion	Present ☐ Absent ☐
Parametrium	Involved ☐ Not Involved ☐ If involved: Right ☐ Left ☐ (distance from excision margin:_____ mm)
Paracervix	Involved ☐ Not Involved ☐ If involved: Right ☐ Left ☐ (distance from excision margin:_____ mm)
Vagina cuff	Involved ☐ Not Involved ☐ (distance from excision margin:_____ mm)
Involvement of other organs	Not Applicable ☐ No ☐ Yes ☐ (Please specify)
MARGIN STATUS	
Invasive tumour	
Endocervical margin	Involved ☐ Not Involved ☐ (specify distance:_____ mm)
Ectocervical margin	Involved ☐ Not Involved ☐ (specify distance:_____ mm)
Radial margin	Involved ☐ Not Involved ☐ (specify distance:_____ mm)
NON-INVASIVE COMPONENT	
Margin status of AIS	Involved ☐ Not Involved ☐ (specify distance:_____ mm)
Margin status of CIN	Involved ☐ Not Involved ☐ (specify distance:_____ mm)
Margin status of SMILE	Involved ☐ Not Involved ☐ (specify distance:_____ mm)
ANCILLARY TEST	

Appendix 5

Revised FIGO Cervical Cancer Staging 2009

Cancer of the cervix uteri[a]

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterus corpus should be disregarded).
IA	• Invasive cancer identified only microscopically (all gross lesion even with superficial invasion are Stage IB cancers). • Invasion is limited to measured stromal invasion with a maximum depth of 5 mm[b] and no wider than 7 mm. • IA1 : Measured invasion of stroma ≤ 3 mm in depth and ≤7 mm width • IA2 : Measured invasion of stroma >3 mm and <5 mm in depth and ≤7 mm width
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA • IB1 : Clinical lesions no greater than 4 cm in size • IB2 : Clinical lesions >4 cm in size
II	The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina.
IIA	Involvement up to the upper 2/3. No obvious parametrial involvement • IIA1 : Clinically visible lesion ≤4 cm • IIA2 : Clinically visible lesion >4 cm
IIB	Obvious parametrial involvement but not onto the pelvic sidewall
III	The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydroneprosis or non-functioning kidney should be included unless they are known to be due to other causes.
IIIA	Involvement of the lower vagina but no extension onto the pelvic sidewall
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or the rectum.
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

[a] Adapted from FIGO Committee on Gynecology Oncology (2)
[b] The depth of invasion should not be more than 5mm taken from the base of epithelium, either surface or glandular, from which it originates. Vascular space invasion should not alter the staging.

Source: Pecorelli S; Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009 May;105(2):103-4. Erratum in: Int J Gynaecol Obstet. 2010 Feb;108(2):176

Appendix 6

Modified Delgado's Prognostic Risk Scoring System

Relative risk of recurrence after radical hysterectomy for cervical cancer	
Variable	**Relative risk**
Depth of tumor penetration (mm)	
Superficial	
3	1.0
4	3.0
5	7.2
6	14
7	21
8	26
10	21
Middle	
5	20
6	22
7	23
8	25
10	28
12	32
14	36
Deep	
7	28
8	30
10	34
12	37
14	41
16	45
18	49
19	54
Clinical tumor size (cm)	
Occult tumor	1.0
1	1.6
2	1.9
3	2.4
4	2.9
6	4.4
8	6.6
Capillary/lymphatic space involvement	
No	1.0
Yes	1.7
The GOG score is calculated by multiplying the relative-risk for depth X tumour size x capillary/ lymphatic space involvement	

Source: Greater Metropolitan Clinical Task force. Gynaecological Cancer Guidelines 2009. Sydney: NSW Department of Health; 2009

Appendix 7

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light house work and office work
2	• Ambulatory and capable of all self-care but unable to carry out any work activities • Up and about more than 50% of waking hours•
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	• Completely disabled • Cannot carry on any self-care • Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55

Appendix 8

Systemic Therapy Cancer Protocol

CERVICAL CANCER CHEMOTHERAPY

Concurrent chemo-radiotherapy

Single agent cisplatin

	Cycle length (days) = 21		Anti-emetic = 4	
Drugs	Dose (mg/m^2)	Route	Infusion Time	Days
Cisplatin	30 - 40	IV	1 hour	1

N.B. In practice, 50 mg total dose per week of cisplatin could be used

Palliative chemotheraphy

Single agent cisplatin

	Cycle length (days) = 21		Anti-emetic = 4	
Drugs	Dose (mg/m^2)	Route	Infusion Time	Days
Cisplatin	50	IV	1 hour	1

Cisplatin-5FU

	Cycle length (days) = 21		Anti-emetic = 4	
Drugs	Dose (mg/m^2)	Route	Infusion Time	Days
Cisplatin	50 - 75	IV	1 hour	1
5Fluorouracil	750 - 1000	IV	24 hour	1 - 5

Cisplatin-MTX

	Cycle length (days) = 21		Anti-emetic = 4	
Drugs	Dose (mg/m^2)	Route	Infusion Time	Days
Cisplatin	50	IV	1 hour	1
Methotrexate	100	IV	Bolus	1 - 5

Paclitaxel-cisplatin

	Cycle length (days) = 21		Anti-emetic = 4	
Drugs	Dose (mg/m^2)	Route	Infusion Time	Days
Paclitaxel	175	IV	1 hour	1
Cisplatin	75	IV	Bolus	1 - 5

**Carboplatin can be used if the patient is unable to tolerate cisplatin*

Source: Ministry of Health & Ministry of Higher Education Malaysia. Systemic Therapy of Cancer 2nd Edition. Putrajaya: MoH & MoHE; 2008

Appendix 9

Pain Management and Palliative Care Service Providers

PAIN CLINICS		
Hospital	**Tel No.**	**Tel No.**
Hospital Selayang, Selangor	603-61203233	http://www.hselayang.moh.gov.my
Hospital Melaka, Melaka	606-2822344	http://www.hmelaka.moh.gov.my
Hospital Sultan Ismail, Johor	607-3565000	http://www.hsi.moh.gov.my
Hospital Raja Permaisuri Bainun, Perak	605-2533333	http://www.hipoh.moh.gov.my
Hospital Raja Perempuan Zainab II, Kelantan	609-7452000	http://www.hrpz2.moh.gov.my
Hospital Tengku Ampuan Rahimah, Selangor	603-33757000	http://www.htar.moh.gov.my
Pusat Perubatan Univeristi Malaya, Kuala Lumpur	603-79494422	http://www.ummc.edu.my
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur	603-91455555	http://www.ppukm.ukm.my
Hospital Universiti Sains Malaysia, Kelantan	609-7663000	http://www.hselayang.moh.gov.my
PALLIATIVE CARE UNITS		
Hospital	**Tel No.**	**URL**
Hospital Selayang, Selangor	603-61203233	http://www.hselayang.moh.gov.my
Hospital Bukit Mertajam, Kedah	604-5383333	http://www.hospbm.moh.gov.my
Hospital Duchness of Kent, Sabah	6089-212111	http://www.hdok.moh.gov.my
Hospital Melaka, Melaka	606-2707653	http://www.hmelaka.moh.gov.my
Hospital Pulau Pinang, Pulau Pinang	604-2293333	http://www.hpp.moh.gov.my
Hospital Queen Elizabeth, Sabah	6088-206258	http://www.qeh.moh.gov.my
Hospital Raja Permaisuri Bainun, Perak	605-5222245	http://www.hipoh.moh.gov.my
Hospital Raja Perempuan Zainab II, Kelantan	609-7485533	http://www.hrpz2.moh.gov.my
Hospital Sultanah Aminah, Johor	607-2231666	http://www.hsajb.moh.gov.my
Hospital Sultanah Bahiyah, Kedah	604-7303333	http://www.hsbas.moh.gov.my
Hospital Sultanah Nur Zahirah, Terengganu	609-6233333	http://www.hsnzkt.moh.gov.my
Hospital Tawau, Sabah	6089-773533	http://www.htwu.moh.gov.my
Hospital Tengku Ampuan Afzan, Pahang	609-5133333	http://www.htaa.moh.gov.my
Hospital Tuanku Ja'afar, Negeri Sembilan	606-7623333	http://www.htjs.moh.gov.my
Hospital Umum Sarawak, Sarawak	6082-208069	http://www.hus.moh.gov.my
Pusat Perubatan Universiti Malaya, Kuala Lumpur	603-79494422	http://www.ummc.edu.my
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur	603-91455555	http://www.ppukm.ukm.my

Source: Ministry of Health. Management of Cancer Pain. Putrajaya; MoH: 2010

Malaysian Hospice Directory

PERSATUAN HOSPICE ARK
No. 2, 2A, 2B Jalan Sutera Merah 3
Taman Sutera, 81200, Johor Bahru, Johor
Tel: 07-556 0878
Contact Person: Ms Alice
Email: hospice_ark@hotmail.com

PALLIATIVE CARE ASSOC. OF JOHOR BAHRU
44, Jalan Tun Abdul Razak, Susur 1
80000 Johor Bahru
Tel: 07-222 9188/222 8858 Fax: 07-222 4858
Contact Person: Ms Nancy Yee
Email: nancyyee.pcajb@gmail.com
www.pcajb.com

PERSATUAN HOSPIS KEDAH
d/a Pej Kesihatan Kota Setar, Lebuhraya Darul Aman
Jalan Bakar Bata, 05100 Alor Setar, Kedah
Tel: 04-771 3487 Fax: 04-771 0116
E-mail: sriwahyu2006@yahoo.com.my
hospiskedah.blogspot.com

PERSATUAN HOSPIS NEGERI KELANTAN
Hospital Raja Perempuan Zainab II,
15586 Kota Bharu, Kelantan
Tel: 09-745 2000 Fax: 09-747 5418
E-mail: drimisairi@klt.moh.gov.my

HOSPICE MALACCA
621-F, Jalan Delima 12, Tmn Bkt Melaka,
Bukit Beruang, 75450 Melaka
Tel : 012-6235 115
Fax: 06-2321 479
Contact Person: S/N Chong Fei Gin
E-mail: drrajagopal@hotmail.com
www.hospismelaka.org

PERTUBUHAN HOSPICE NEGERI SEMBILAN
No. 41, Off Jalan Rasah
70300 Seremban, Negeri Sembilan
Tel: 06-762 1216 Fax: 06-762 1216
Contact Person : Ms Kala
E-mail: hospicens2012@yahoo.com
pertubuhanhospicenegerisembilan.com

PERSATUAN HOSPIS PAHANG
A4614 Lorong Alor Akar 19
25250 Kuantan, Pahang
Tel / Fax: 09-5670 743
Email: hospispahang@gmail.com

PERSATUAN HOSPIS TERENGGANU
Klinik Bedah Pakar, Kompleks Rawatan Harian,
Hospital Sultanah Nur Zahirah, 20400 KT,
Terengganu
Tel /Fax: 09-6212121 ext 2058
Email: drnona31765@gmail.com

NCSM PENANG
Rumah Hospis Pulau Pinang
250A, Jalan Air Itam, 10460 Penang
Tel: 04-228 4140 Fax: 04-226 4676
Contact Person: Nor Asikin Abd Kadir
E-mail: ncsmpg@gmail.com
www.ncsmpenang.org

PENANG HOSPICE SOCIETY
c/o Rumah Hospis Pulau Pinang
250A Jalan Air Itam, 10460 Penang
Tel: 04-228 4140 Fax: 04-2264676
Contact Person : Ms Chitra Alagan
E-mail: penanghospicesociety@gmail.com
www.penanghospice.org.my

PURE LOTUS HOSPICE OF COMPASSION
73, Jalan Utama, 10460 Penang
Tel / Fax: 04-229 5481
Email: lyanshih@gmail.com
purelotushospice.org

CHARIS HOSPICE
15, Cangkat Minden, Jalan 12, 11700 Penang
Tel: 011-1246 6757, 04-6587668 Fax: 04-6587669
Email: charishospice@gmail.com
www.charishospice.com

PERAK PALLIATIVE CARE SOCIETY
54, Jalan Sultan Ahmad Shah,
31400 Ipoh, Perak
Tel/Fax: 05-546 4732
Contact Person: Ms Leong Lai Peng
E-mail: admin@ppcs.org.my
www.ppcs.org.my

TAIPING PALLIATIVE SOCIETY
48, Jalan Lim Sam Kip,
34000 Taiping, Perak
Tel/Fax: 05-807 2457
Contact Person: Ms Veronica Liew
E-mail: veraliew@hotmail.com

HOME CARE HOSPICE PROGRAMME, SABAH c/o Sabah Cancer Society No.15, Lorong Tupai 3, Teck Guan Villa, Jalan Penampang, 88300 Kota Kinabalu, Sabah Tel: 088-222 315 Fax: 088-210 377 E-mail: sabahcancersociety@yahoo.com www.sabah.org.my/scss/cancer	PALLIATIVE CARE ASSOCIATION OF KOTA KINABALU, SABAH PWD 7396 & 7397 Taman Rose, Off Jln Penampang, 88300 Kota Kinabalu, Sabah, Malaysia Tel: 088-231 505 Fax: 088- 231 506 Contact Person: Ms Grace Chong E-mail: pcakk@yahoo.com www.sabah.org.my/pcakks
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KASIH HOSPICE CARE SOCIETY No 7, Jalan 14/29 aka Jalan Dato Abdul Aziz, 46100 Petaling Jaya, Selangor Tel: 03-7960 7424 E-mail: admin@kasihfoundation.org www.kasihfoundation.org Fax: 03-7956 6442	HOSPIS MALAYSIA 2 Jalan 4/96, off Jalan Sekuci, Tmn Sri Bahtera, Jalan Cheras, 56100 Kuala Lumpur Tel : 03-9133 3936 Fax : 03-9133 3941 Email: info@hospismalaysia.org www.hospismalaysia.org

Source: Malaysian Hospice Council (available at http://www.malaysianhospicecouncil.org)

Appendix 10

International Society of Lymphology (ISL) Lymphoedema Staging

Stage	
ISL Stage 0	A subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before oedema becomes evident
ISL Stage I	This represents early onset of the condition where there is accumulation of tissue fluids that subsides with limb elevation. The oedema may be pitting at this stage
ISL Stage II	Limb elevation alone rarely reduces the swelling and pitting is manifest
ISL late Stage II	There may or may not be pitting as tissue fibrosis is more evident
ISL Stage III	The tissue is hard (fibrotic) and pitting is absent. Skin changes as such thickening, hyperpigmentation, increased skin folds, fat deposits and warty overgrowth develop

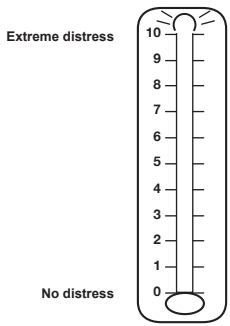
Source: Lymphoedema Framework. Best Practice for the Management of Lymphodema. International Consensus. London: MEP Ltd; 2006

Appendix 11

Distress Thermometer Screening Tool

SCREENING TOOLS FOR MEASURING DISTRESS

Instructions: First please circle the number (0-10) that best describes how much distress you have been experiencing in the past week including today.



Second, please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.

YES	NO	Practical Problems
☐	☐	Child care
☐	☐	Housing
☐	☐	Insurance/financial
☐	☐	Transportation
☐	☐	Work/school
		Family Problems
☐	☐	Dealing with children
☐	☐	Dealing with partner
☐	☐	Ability to have children
		Emotional Problems
☐	☐	Depression
☐	☐	Fears
☐	☐	Nervousness
☐	☐	Sadness
☐	☐	Worry
☐	☐	Loss of interest in usual activities
☐	☐	Spiritual/religious concerns

YES	NO	Physical Problems
☐	☐	Appearance
☐	☐	Bathing/dressing
☐	☐	Breathing
☐	☐	Changes in urination
☐	☐	Constipation
☐	☐	Diarrhea
☐	☐	Eating
☐	☐	Fatigue
☐	☐	Feeling Swollen
☐	☐	Fevers
☐	☐	Getting around
☐	☐	Indigestion
☐	☐	Memory/concentration
☐	☐	Mouth sores
☐	☐	Nausea
☐	☐	Nose dry/congested
☐	☐	Pain
☐	☐	Sexual
☐	☐	Skin dry/itchy
☐	☐	Sleep
☐	☐	Tingling in hands/feet

Other Problems: _____

_____

Source: Reproduced with permission from The NCCN 1.2010 Distress Management Clinical Practice Guidelines in Oncology. ©National Comprehensive Cancer Network, 2010. Available at: http://www.nccn.org.

Medication List

Chemotherapy Drug	Common side effects	Comments
Cisplatin	• Peripheral neuropathy • Nausea, vomiting • Myelosuppression • Nephrotoxicity • Ototoxicity	• Adequate hydration and urinary output at least 24 hours after administration • Obtain baseline renal function, then monitor renal function (SCr, CrCl) at every cycle. Observe for cumulative renal toxicity. • Recommend to perform baseline audiography and prior to each subsequent dose • Observe for anaphylactic-like reactions during infusion • Monitor renal function (SCr, CrCl) • Observe for anaphylactic-like reactions during infusion
Carboplatin	• Electrolyte imbalance (hyponatremia, hypomagnesemia, hypocalcaemia, hypokalaemia) • Nausea, vomiting • Myelosupression	• Monitor renal function (SCr, CrCl) • Observe for anaphylactic-like reactions during infusion
Paclitaxel	• Alopecia • Nausea, vomiting • Myelosuppression • Peripheral neuropathy • Arthalgia/myalgia	• Monitor for hypersensitivity reaction during infusion
Gemcitabine	• Fever • Nausea,vomiting • Myelosuppression • Increased hepatic transaminases	• Monitor liver function
Topotecan	• Myelosupression • Nausea, vomiting	• Monitor for interstitial lung disease
5-Fluorouracil	• Diarrhoea	• Monitor for hand-foot syndrome
Mitomycin-C	• Myelosuppression	• Observe for extravasation (vesicant) • Monitor for haemolytic-uremic syndrome

- To monitor FBC and serum electrolytes prior to every cycle of chemotherapy.

Source:

1. Lacy CF, Armstrong, Goldman MP et al. editors. Drug Information Handbook 2012-2013 w/International Trade Names Index , 21st Edition. Ohio: Lexi-Comp; 2012
2. Ministry of Health & Ministry of Higher Education Malaysia. Systemic Therapy of Cancer 2nd Edition. Putrajaya: MoH & MoHE; 2008

LIST OF ABBREVIATIONS

AC	adenocarcinoma
AGC-H	Atypical glandular cells - hyperplasia
AGC-US	Atypical glandular cells of undetermined significance
ASCUS	Atypical Squamous Cells of Undetermined Significance
CCRT	concurrent chemoradiotherapy
CI	confidence interval
CIN	cervical intraepithelial neoplasia
cm	centimeter
CPG(s)	clinical practice guidelines
CT	computed tomography
DVT	deep vein thrombosis
DFS	disease free survival
DG	Development Group
ECOG	Eastern Cooperative Oncology Group
EUA	examination under anaesthesia
EBRT	external beam radiotherapy
FDG-PET	Fluorodeoxyglucose positron emission tomography
FIGO	The International Federation of Gynecology and Obstetrics
Gy	Gray
HPV	Human Papilloma Virus
HR	hazard risk
HRT	hormone replacement therapy
HSIL	high-grade squamous intraepithelial lesion
HTA	health technology asessment
INR	International Normalised Ratio
ICBT	intracavitary brachytherapy
LLETZ	large loop excision of transformation zone
LACC	locally advanced cervical cancer
LSIL	low grade squamous intraepithelial lesion
LMWH	low molecular weight heparin
LNmM	lymph node micrometastasis
LVSI	lymph vascular space involvement
MoH	Ministry of Health
MRI	magnetic resonance imaging
MBO	malignant bowel obstruction
NPV	negative predictive value
NAC	neoadjuvant chemotherapy
NEC	neuroendocrine cancers
OR	odds ratio
OS	overall survival
PAN	para-aortic lymph nodes
PN	percutaneous nephrostomy
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PLND	pelvic lymph nodes dissection
PPV	positive predictive value
PCB	postcoital bleeding
PFS	progression-free survival

QOL	quality of life
RC	Review Committee
RAT	radical abdominal trachelectomy
RAH	radical abdominal hysterectomy
RH	radical hysterectomy
RP	radical parametrectomy
RVT	radical vaginal trachelectomy
RT	radiotherapy
RCT(s)	randomised controlled trials
RR	relative risk
SIGN	Scottish Intercollegiate Guidelines Network
SSRIs	selective serotonin reuptake inhibitor(s)
SN	sentinel nodes
SCC	squamous cell carcinoma
TOP	termination of pregnancy
TNM	tumor-node-metastasis
TVS	transvaginal ultrasound
UFH	unfractionated heparin
VCF	vena caval filter
VTE	venous thromboembolism
vs	versus
WHO	World Health Organization

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- Technical Advisory Committee for CPG for their valuable input and feedback
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