National Guidelines in Histopathology

Handling & reporting of Gynaecological Malignancies

Second edition
2021

Ministry of Health, Sri Lanka
and College of Pathologists of Sri Lanka

National Guidelines in Histopathology

Handling & Reporting of Gynaecological Malignancies

Second edition, 2021

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Message by the Director General, Health Services

Ministry of Health, Sri Lanka

Cancer is one of the leading non-communicable diseases in Sri Lanka. With the establishment of national cancer policy on cancer prevention and control, there has been a commendable improvement in the cancer services provided island-wide.

The pathologists play a major role in the diagnosis of cancer and it is of utmost importance to formulate new guidelines as well as to update existing guidelines to improve the quality of diagnosis and to predict the prognosis of the disease in cancer patients.

These guidelines on handling tumours of the gastrointestinal tract, breast and gynaecological region as well as the guidelines on specimen handling and transport appear to be comprehensive guides to the histopathologists practicing in Sri Lanka and hope that these guidelines will help to improve the quality and the consistency of the histopathology reports across the country.

I am very grateful to the College of Pathologists of Sri Lanka for having identified the need and have been able to accomplish this difficult task amidst many hardships faced during the Covid-19 pandemic. I wish to thank the editors, authours and the clinicians who have contributed to these guidelines for their commitment in formulating these guidelines.

As these guidelines will be available in a freely available, easy to use, electronic format and I hope that these will help to improve the quality and delivery of diagnostic services to cancer patients in Sri Lanka.

I wish the College of Pathologists of Sri Lanka all the success in their future endeavours to improve the quality of histopathology services in the country.

Dr. Asela Gunawardena
Director General of Health Services
Ministry of Health
Sri Lanka

Message by the Deputy Director General Laboratory Services

Ministry of Health, Sri Lanka

In the provision of health care services, the laboratory sector plays a vital role by providing timely and accurate test results enabling the clinicians in diagnosis and treatment. Cancer is one of the leading health issues in Sri Lanka which needs effective curative and preventive diagnostic services. In order to achieve this, the contribution of histopathologists is invaluable.

The Laboratory Services Unit, Ministry of Health works with a vision to achieve standards for medical laboratories set by the international organizations for standardization and a mission to provide timely, reliable, high-quality diagnostic services to relevant health care providers. These guidelines published by the College of Pathologists, Sri Lanka have given a valuable contribution to achieving our mission and improving the services provided by the histopathology laboratories to the public.

I am pleased to note that the availability of these guidelines in electronic format hence histopathologists working all over the country will be able to get the maximum use of it.

I wish the College of Histopathologists, Sri Lanka all the success in their future endeavors to provide a tremendous service to uplift the health of the citizens in Sri Lanka.

Dr. Sudath K. Dharmaratne
Deputy Director General-Laboratory Services
Ministry of Health
Sri Lanka

Message by the President

College of Pathologists of Sri Lanka

Since the first series of the National Guidelines in Histopathology were published in 2007, the necessity to revise these guidelines and formulate new guidelines was considered to keep pace with the rapid advancements occurring in the field of histopathology worldwide. The College of Pathologists has been able to complete and publish this new series of guidelines with the objective of improving the diagnostic services in histopathology and histopathology reporting across the country. I am extremely happy that we were able to accomplish this task during the Covid-19 pandemic, utilizing the lockdown periods effectively.

The guidelines have been formulated after extensive discussion by the members of the guideline committees and clinicians in the relevant fields, conforming to the latest, accepted international guidelines in histopathology reporting. These offer a comprehensive guide to the pathologists when handling tumours of the gastrointestinal tract, breast and genaealogical region as well as to specimen handling and transport.

The structure of the guidelines has been made similar to the first series wherever possible with X, Y and Z denoting the mandatory, desirable and optional recommendations respectively. (X; Mandatory; recommendations that can be carried out in most of the institutions in Sri Lanka, Y; Desirable; investigations that can be carried out in selected institutions in Sri Lanka including the private sector and Z; Optional; investigations that are not freely available in Sri Lanka which may be performed in the private sector or abroad).

The guidelines will be in the electronic format to allow maximum visibility to the histopathologists working across the country.

On behalf of the College of pathologists of Sri Lanka, I wish to acknowledge the contributions made by the series editors, content editors, authours, clinicians and all the members of the guideline committees and thank them for their commitment to formulate these guidelines to be on par with international guidelines.

I am also grateful to the Director General of Health Services Dr. Asela Gunawardena and the Deputy Director General Laboratory Services, Dr. Sudath Dharmaratne for facilitating the electronic publication process of these guidelines.

I hope that the histopathologists working across the country will make full use of these guidelines to improve the quality of diagnostic services and reporting in histopathology.

Prof. Dulani Beneragama
President, College of Pathologists of Sri Lanka, 2021.

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OVERVIEW

Introduction

With rapid advances taking place in all the disciplines of medicine it has become necessary to streamline histopathology services, in order to provide meaningful information to clinicians that would directly have an impact on patient management.

This hand book provides the guidelines for handling and histopathological reporting of surgical specimens removed for gynecological malignancies. The main purpose of this guideline is to improve the quality of clinical care provided in health institutions. All the contents are evidence based and define the minimum standards for reporting of gynecological malignancies. Data would conform to a standard format. The proforma may be used as the main reporting format or may be combined with free text as required.

Histopathologists should be members of multidisciplinary teams dedicated to the diagnosis and management of patients. Optimal reporting of gynecological specimens requires a partnership between the pathologist, surgeon and oncologist. The surgeon can help the pathologist by providing necessary information, orientating the specimen in relevant instances and ensuring that specimen containers are labeled correctly. . Regular clinico-pathological discussions and correlation with pre-operative imaging studies are important to maintain and develop this partnership. Histopathological findings which include tumour type, grade and stage are essential to determine the management plan.

These guidelines have been approved by the College of Pathologists of Sri Lanka and we advise its use as a minimum data set. Minimum data sets are effective in maintaining uniformity and ensuring that all necessary data are provided for clinical management of the patient.

Cervical cancer is the third most common cancer in women worldwide. In Sri Lanka, it is the third most common cancer in females (Cancer incidence data 2014, National cancer control program, Sri Lanka). Precancerous dysplastic changes of the cervical epithelium can be easily detected in a routine Pap smear and is completely treatable. Precancerous lesions of the cervix can progress to invasive cervical carcinoma which has the potential to spread to other sites. Human papilloma virus infection is the cause in more than 90% of cervical carcinoma. Health education programs, screening tests and HPV vaccination can markedly reduce the total number of deaths due to cervical carcinoma worldwide.

Endometrial cancer is the most common female genital tract malignancy occurring in the Western World. In Sri Lanka it is the second most common malignancy of the female genital tract. The tumours affect a wide age range, but most arise in postmenopausal women. Most endometrial malignancies (80-85%) are related to sustained unopposed oestrogen stimulation of the endometrium. The typical malignancy is endometrioid adenocarcinoma, classified as two types. Type 1 is low grade, co-exists with atypical endometrial hyperplasia, is confined to the uterus at the time of diagnosis (70%) and have a relatively good prognosis.

The non-endometrioid endometrial malignancies, or Type 2, affect older women, are oestrogen independent, arise in an atrophic endometrium, and have a poor prognosis. Type 2 tumours include both serous and clear cell carcinomas. The term 'minimal carcinoma' is applied to both in situ and superficially invasive serous carcinoma, as metastases have been found despite minimal if any stromal invasion.

Ovarian cancer is the fourth commonest malignancy in Sri Lankan females and account for 8% all female cancers. Numbers for fallopian tube cancers are much less, however this figure will change with current criteria for diagnosis of such lesions.

Vulval malignancies are rare and account for approximately 4% of all gynaecological cancers. Over 85% of vulval cancers are squamous cell carcinomas. Vulval melanoma, adenocarcinoma, basal cell carcinoma, lymphoma and sarcomas are miscellaneous rare tumours accounting for the remainder. Vulval cancer is associated with a high morbidity and mortality due to its frequent late diagnosis.

Gestational trophoblastic neoplasms (GTN) are malignant lesions that arise from placental villous and extra villous trophoblast. GTN occurs in 1:40,000 pregnancies and is more common in Asia than in Europe or North America.

Prof. Bimalka Seneviratne

Chairperson, Committee to formulate National Guidelines in Histopathology on Gynaecological Malignancies, 2nd edition.

CHAPTER 1

Clinician's role in optimizing reporting of gynaecological malignancies

The following measures are to be taken into consideration before dispatching malignant gynecological specimens to the histopathology laboratory: **[X]**

- Specimens to be completely immersed in the formalin fixative (usually 10% formalin, ideally 10% neutral buffered formalin), when submitting for routine histological assessment.
- Dispatch in suitable containers with tight fitting lids to avoid spilling of contents.
- Clear label with identification details.
- Relevant clinical details including radiological findings to be included in the request form.
- Details of previous biopsies and histological diagnoses, to be mentioned.
- Orientation of specimens when necessary.
- Cervical biopsies from different sites to be appropriately labeled and sent in separate containers
- Cone biopsies (cervix) to be oriented with a suture at 12 o'clock position.
- Presence of macroscopically visible tumour and the site of tumour needs to be clearly stated in the request form.
- Macroscopic tumour extension and operative findings to be mentioned.
- State the clinical staging of visible tumours in the request form.
- Lymph node biopsies from different sites should be labeled separately and sent in different containers.
- Vulvectomy specimens to be pinned out on a cork board and oriented for the identification of margins
- Clinician's contribution to optimize reporting of gestational trophoblastic disease (*mention in requisition form*):
  - Past history of gestational trophoblastic disease
  - History of prior chemotherapy for known gestational trophoblastic disease
  - Serum β- HCG levels
  - Ultrasound scan findings

CHAPTER 2

Histopathological assessment of cervical malignancy

Specimen collection and transport

Refer National Guidelines in Histopathology – Collection, Handling and Transport of Surgical Specimens (second edition, 2021).

2.1 Handling and reporting of cervical biopsy specimens

Specimen identification details and labeling should be checked before commencing the cut-up procedure.

2.1.1 Specimen handling (macroscopic description / grossing) [X]

Points to note include:

- Specimen type
  - Punch biopsies
  - Endocervical curettage
  - LLETZ biopsy / LEEP biopsy (cone is much smaller than that obtained by the conventional method)
  - Cone biopsy (cervical conization)
- Number of specimen containers
- Specimen condition – fresh, in fixative etc.
- Site / anatomic location – identify separately if the specimen has been oriented (anterior lip, posterior lip etc.)
- Specimen dimensions
- Colour & shape
- Gross abnormalities – ulcers, erosions, irregularities, etc.

Punch biopsy

- Record the number of pieces (carefully search the container and the undersurface of the lid for minute fragments of tissue).
- Do not cut the specimen unless the individual pieces are greater than 4 mm in diameter. Identify the mucosal surface. If the fragments are tiny wrap them in filter paper or place them in a biopsy bag before placing in the tissue cassette.
- It is important to process all of the tissue received, no matter how small.
- Submit the material in its entirety.

- If specimens are received with a special identification (eg: anterior lip, posterior lip), label and submit them separately.
- Prepare histology sections at 3 levels.

Endocervical curettage

Endocervical curettage is performed to evaluate the presence of endocervical neoplasms, cervical neoplasia in the endocervical canal or to determine whether endometrial carcinoma has spread into the cervix.

- Measure in aggregate.
- Note down any other abnormality
- Process all wrapped in filter paper or in a biopsy bag.
- Examine histology sections at three levels.

LLETZ (large loop excision of transformation zone) / LEEP (loop electro excision procedure)

Cone is much smaller and orientation may be difficult.

- Size and shape, number of pieces (fragmented or intact)
- Identify the mucosal surface
- Identify gross abnormalities (irregularities, erosions, ulcers etc.)
- Make thin, parallel slices (2-3 mm), ensuring that the epithelium is present in each section. Move in a clockwise manner (with accompanying drawing).
- Process all tissue
- Prepare histology sections at 3 levels & examine all sections.

Cone Biopsy (Figure 1)

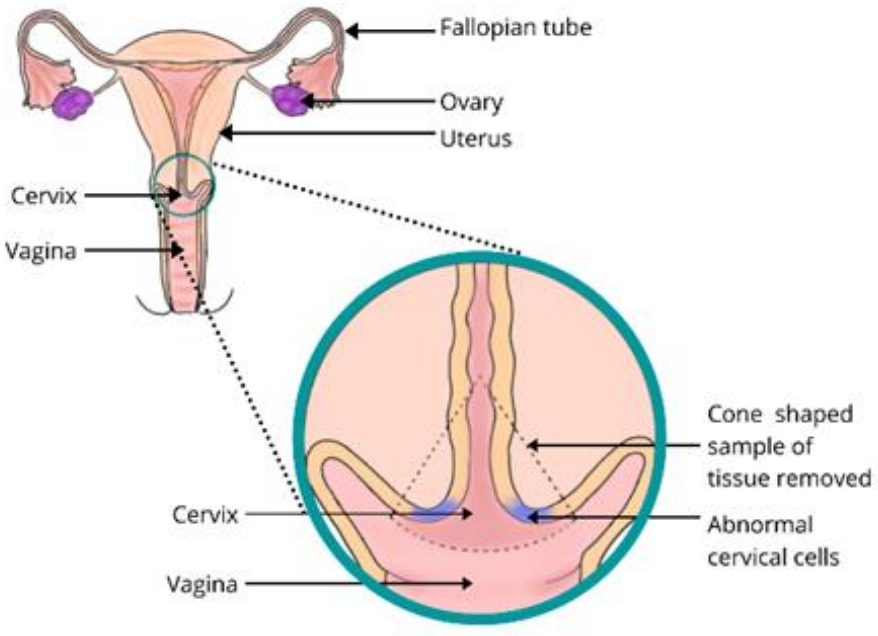

Figure 1. Cone biopsy – Cone shaped wedge of tissue from the cervix

- Ideally the specimen should be received intact with a suture indicating the 12 o'clock position.
- **Note**
  - Size (diameter & depth) and shape of the cone; complete or fragmented.
  - Epithelium: colour, irregularities, erosions, cysts, previous biopsy site.
- Open the specimen by inserting a sharp, pointed scissors into the cervical canal and cutting it longitudinally along the 12 o'clock position (Figure 2).
- If the specimen has not been oriented, open at any site.
- Pin on a corkboard with the mucosal side up and fix in formalin for several hours.
- Paint both surgical margins with India ink.
- Cut the entire cervix by making parallel sections, 2-3 mm apart, along the plane of the endocervical canal starting from 12 o'clock position and moving clockwise.
- Sections should be taken in a way that the epithelium is present in each section, including the squamo-columnar junction.
- Some trimming of the stroma may be allowed.

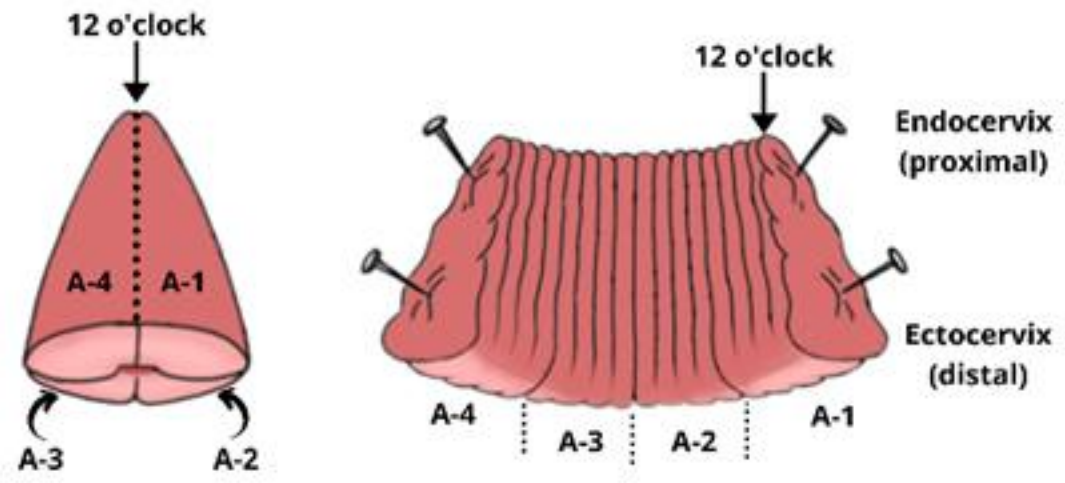

Figure 2. Slicing a cone biopsy.
A-1 – sections from 12 to 3 o'clock
A-2 – sections from 3 to 6 o'clock
A-3 – sections from 6 to 9 o'clock
A-4 – sections from 9 to 12 o'clock

- **Block selection**
  - All the tissue must be submitted (except for trimmed stroma).
  - If the cone has been oriented, identify the 12 o'clock position.
  - Submit sections as in figure 1, with accompanying drawing.

2.1.2 Microscopy & conclusion [X]

Histological tumour type	Refer tumour types in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Tumour grade	Tumours are graded according to RCPA standards and datasets for histopathological reporting of cervical neoplasia; March 2021 **G1** - Well differentiated **G2** - Moderately differentiated **G3** - Poorly differentiated **G4** – Undifferentiated
Tumour site	Based on the clock face quadrant (e.g., right superior quadrant ,12 to 3 o'clock, right inferior quadrant , 3 to 6 o'clock)
Tumour size	All dimensions are important
Stromal invasion	Depth of invasion & horizontal extension or extent of spread cannot be assessed
Lymphovascular invasion	Present /Absent
Associated pathology	Koilocytes, inflammation, etc.
Margins	Adequacy of local excision should be assessed. Comment on endocervical and ectocervical margins and deep margin: ▪ Margin(s) cannot be assessed or ▪ Involved / uninvolved by intraepithelial neoplasia / invasive carcinoma: – Focal / diffuse – Specify location if possible

2.1.3 Immunohistochemistry [Y]*

* Although mentioned as category Y due to the stains being unavailable widely at present, this category **will be X whenever p16 stain is available**, to be able to classify cervical malignancies according to the WHO Classification of tumours (5th edition, Female Genital Tumours).

2.1.4 Molecular HPV typing [Z]

Desirable wherever relevant according to the WHO Classification of tumours (5th edition, Female Genital Tumours).

2.2 Handling & reporting of hysterectomy specimens of cervical carcinoma

Radical hysterectomy and lymph node dissection is the usual surgical procedure for cervical carcinoma. Radical hysterectomy specimens include a vaginal cuff depending on the extent of tumour spread, broad strips of parametria, a variable proportion of broad, round and uterosacral ligaments. In young women adnexae are often spared. Systematic and thorough examination and handling should be done to provide a complete and accurate pathological report.

2.2.1 Specimen handling (macroscopic description / grossing) [X]

- Orientate the specimen – anterior / posterior, right / left.
- Take appropriate measurements in three dimensions - uterus, cervix, vaginal cuff, right and left adnexa.
- If visible area of previous loop or cone biopsy is present record dimensions and site.
- Look for macroscopic parametrial and paracervical tumour involvement.
- Ink parametrial, paracervical, anterior and posterior cervical resection surfaces from the vaginal cuff to the peritoneal reflections.
- Open the uterus laterally into anterior and posterior halves or coronally in to right and left halves allowing optimal visualization of the cervical tumour (can be done according to the individual pathologist's preferences).
- If the tumour is small amputate the cervical stump and dissect in a similar way as for a cone biopsy or loop biopsy (Figure 3).
- Record the appearance of the tumour (polypoid, ulcerative).
- Measure the size of the macroscopically visible tumour (in 3 dimensions).
- Record the tumour site (anterior, posterior etc.).
- Record the macroscopic distances to
    - radial (circumferential) resection margin (including the paracervical tissue thickness)
    - vaginal (inferior) resection margin
- Record macroscopic margin involvement (position and extent).
- Dissect out lymph nodes (usually sent in separate bottles) and note down the number.

Block selection

- The entire circumference of the vaginal resection margin (if the length of the vaginal cuff is short, submit together with the cervix)
- Sample the tumour adequately to represent maximum extent
  - deepest point of invasion
  - relationship to the margins
  - full thickness of cervical wall
  - interface with adjacent cervix with or without CIN or CGIN
  - all quadrants
- Sample one block per one centimeter of greatest tumour dimension
- Sample the lower uterine segment, immediately proximal and adjacent to the tumour
- Sample paracervical (in continuity with tumour) and parametrial tissue
- Sample uterine corpus and adnexa according to standard protocols. (Rosai & Ackerman's Surgical Pathology, 10th edition).
- Sample lymph nodes according to standard protocols (Rosai & Ackerman's Surgical Pathology, 10th edition):
  - If grossly involved- one block
  - If node less than 5 mm in size - bisected or processed whole
  - Large node - in more than one block

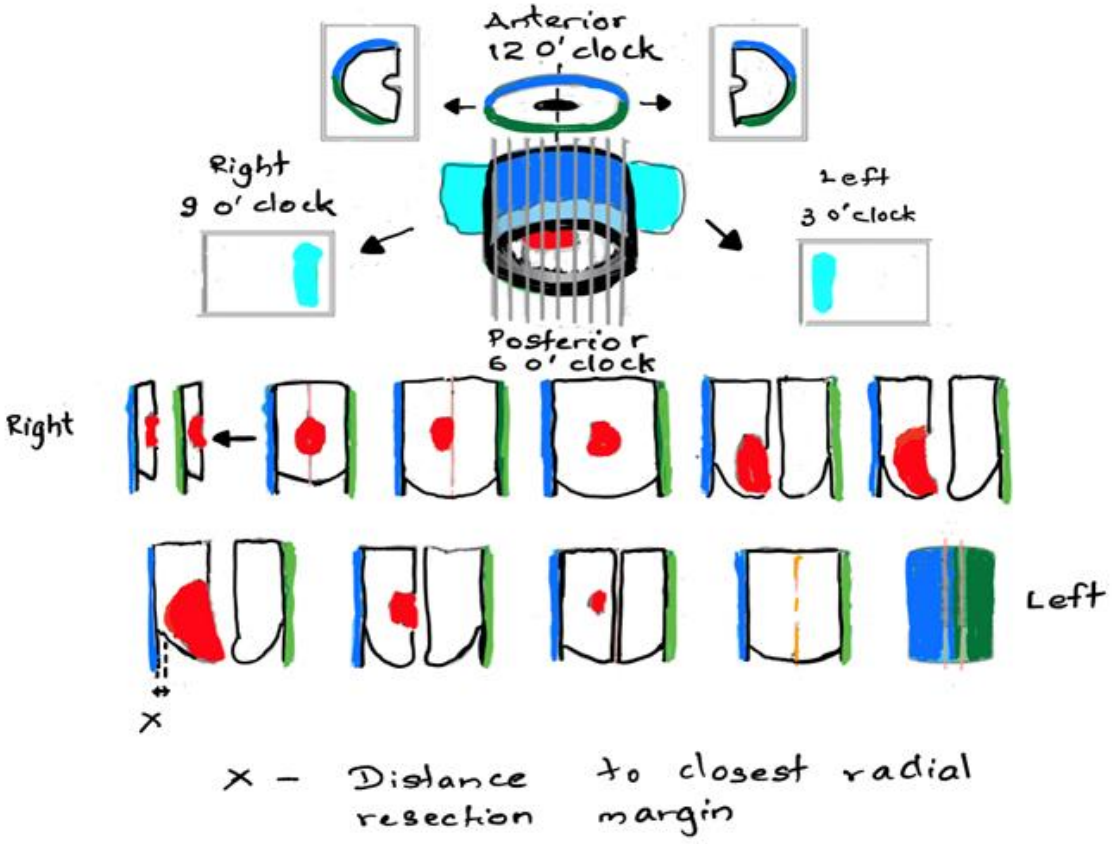

Figure 3. Handling of cervical cone biopsy specimen.

2.2.2 Microscopy & conclusion [X]

Histological tumour type	Refer tumour types in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Tumour grade	Tumours are graded according to RCPA standards and datasets for histopathological reporting of cervical neoplasia; March 2021 ▪ Squamous cell carcinoma Grade 1 = Well differentiated (keratinizing) Grade 2 = Moderately differentiated Grade 3 = Poorly differentiated Grade X = grade cannot be assessed - e.g.: very early minimally invasive carcinoma. However, current WHO recommendations for cervical cancer tumour classification, 5th edition, does not include grading as it has not shown any prognostic significance. ▪ Neuroendocrine carcinoma - considered as high-grade
Tumour size	Tumour size should be measured in millimeters in three dimensions and two measurements should be provided in the report. ▪ Maximum horizontal dimension (Figure 4) o Direct measurement or calculation by multiplying the number of block thickness. o Multiple tumours - each measured separately, and the staging done on the largest). ▪ Maximum depth of invasion (Figure 4) o Measured from the basement membrane of the adjacent (dysplastic or non-dysplastic) epithelium. o In difficult situations e.g. adenocarcinoma, ulcerated tumours, polypoid carcinomas, tumour thickness can be taken and should be mentioned in the report.

- If surface ulceration is present measure from the ulcerated surface to the deepest point of invasion.
- The thickness of the cervical wall (a) in the maximum area of invasion (Figure 4), should be documented.
- The fraction of the cervical wall invasion; invasive depth (numerator) / cervical wall thickness (denominator) is used as a component to calculate the Gynecologic Oncology Group (GOG) score.

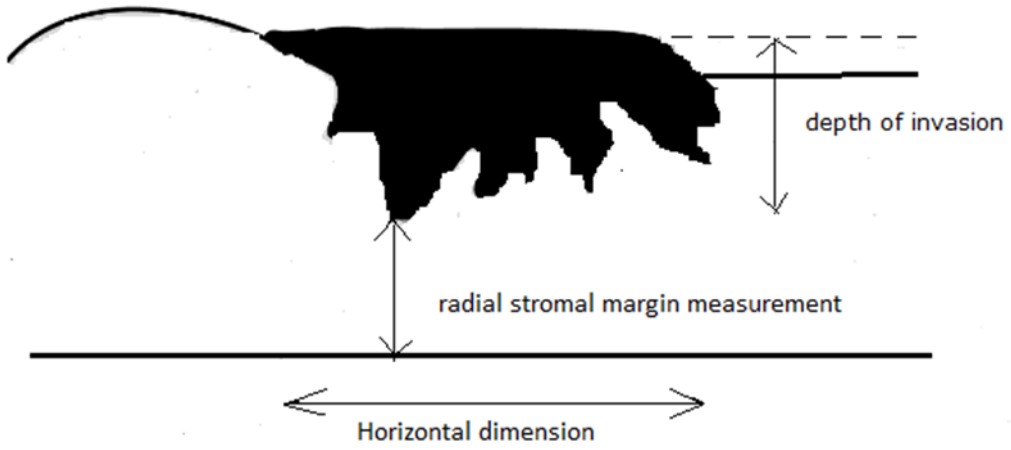

Figure 4. Measurement of size in cervical carcinoma

Resection Margins

Specific margins:

- Radial (circumferential) margin: minimal thickness of uninvolved cervical stroma or, if the minimal radial margin is lateral add the paracervical tissue thickness or previously trimmed paracervical tissue thickness.
- Inferior margin (vaginal or cervical).

Status of Margins: Involved / uninvolved / indeterminate

- Involved (tumour at the margin or less than 1mm)
- Uninvolved – measure the distance from margins
- Indeterminate (e.g.: cautery artifact)

State the position of the closest margin.

Lymphovascular invasion	Present / absent / indeterminate.
Paracervical and parametrial involvement	Involved / uninvolved.
Precursor lesions (CIN / AIS)	Distance to the margins Severity (Low grade / High grade)
Other tissues and organs - involved / uninvolved	▪ Endometrium ▪ Myometrium ▪ Right adnexa ▪ Left adnexa
Regional lymph nodes status	Pelvic nodes- obturator, internal, external and common iliac nodes Record the total number of lymph nodes/ number of positive nodes If parametrial nodes identified- include in the final node count Extranodal extension - present / absent Dimensions of all involved nodes
Provisional tumour stage	Refer annexure II for the 8th AJCC/TNM and FIGO staging currently in use in 2021.

2.2.3 Immunohistochemistry [Y]

p16 immunohistochemical marker is highly desirable to differentiate HPV associated from HPV unassociated squamous and glandular malignancies of the uterine cervix (see section 2.1.3)

ER, Vimentin, CEA, p16 in relevant cases to differentiate cervical from endometrial adenocarcinoma.

2.3 Reporting proforma for cervical carcinoma [X]

Specimen type and dimensions	:	
Histological type of tumour	:	
Histological grade	:	
Tumour size	:	Maximum horizontal dimension (mm) Maximum depth (mm)
Tumour site	:	
Extent of local spread	:	
Cervical wall thickness (include paracervical tissue thickness)	:	_____ mm
Distance to closest radial resection margin (include paracervical tissue thickness	:	_____ mm
Vaginal involvement	:	Yes / No Distance from distal vaginal margin: _____mm
Paracervical involvement	:	Yes / No
Parametrial involvement	:	Yes / No
Lymphovascular invasion	:	Yes / No
CIN	:	Yes / No Grade 1 / 2 / 3
CGIN	:	Yes / No Grade: Low / High
Pelvic lymph nodes	:	This group includes obturator, internal, external and common iliac nodes. Total number: Number involved: Extranodal spread: Yes / No
Para-aortic lymph nodes	:	Positive / Negative for tumour Extranodal spread: Yes / No
Other tissues and organs	:	Endometrium Myometrium Right adnexa Left adnexa
Pathological tumour stage	:	

Annexures

Annexure I. WHO classification of tumours of the uterine cervix in 5th edition of WHO classification of Female Genital Tumours, currently in use in 2021.

- Squamous epithelial tumours
  - Low-grade squamous intraepithelial lesion
  - High-grade squamous intraepithelial lesion
  - Squamous cell carcinoma, HPV- associated
  - Squamous cell carcinoma HPV-independent
  - Squamous cell carcinoma NOS

- Glandular tumours & precursors
  - Adenocarcinoma in situ NOS
  - Adenocarcinoma in situ, HPV-associated
  - Adenocarcinoma in situ, HPV independent
  - Adenocarcinoma NOS
  - Adenocarcinoma, HPV associated
  - Adenocarcinoma, HPV independent, gastric type
  - Adenocarcinoma, HPV independent, clear cell type
  - Adenocarcinoma, HPV independent, mesonephric type
  - Adenocarcinoma, HPV independent, NOS
  - Endometrioid adenocarcinoma NOS
  - Carcinosarcoma, NOS
  - Adenosquamous carcinoma
  - Mucoepidermoid carcinoma
  - Adenoid basal carcinoma

- Carcinoma, undifferentiated, NOS

- Mixed epithelial and mesenchymal tumours
  - Adenomyoma NOS
    - Mesonephric-type adenomyoma
    - Endocervical-type adenomyoma
  - Adenosarcoma

- Germ cell tumours NOS
  - Mature teratoma
  - Dermoid cyst
  - Endodermal sinus tumour
  - Yolk sac tumour
  - Choriocarcinoma

Annexure II. AJCC/ TNM 8th edition & FIGO staging of Tumours of the cervix uteri, currently in use in 2021.

* TNM stages are based on clinical and/or pathological classification. FIGO stages are based on surgical staging (subdivision of stage 1 in to 1A-1B1 are mainly pathological)

* The definitions of the T, N and M categories correspond to the FIGO stages. Both systems are included for comparison.

TNM stage	FIGO stage	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis	0	Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5 mm measured from the base of the epithelium and horizontal spread of 7 mm or less.
T1a1	IA1	Stromal invasion 3mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
Note: The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.		
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a / IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4 cm in greatest dimension
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of the vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	With parametrial invasion

T3	III	Tumour extends to pelvic wall, involves lower third of vagina, or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumour involves lower third of vagina
T3b	IIIB	Tumour extends to pelvic wall or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumour invades mucosa of bladder or rectum or extends beyond true pelvis
N - Regional Lymph Nodes		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M - Distant Metastasis		
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
pTNM Pathological classification		

The pT and pN categories correspond to the T and N categories.

pN0: Histological examination of a pelvic lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1, T2, T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

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CHAPTER 3

Histopathological assessment of malignancies of the uterine corpus

Specimen collection and transport

Refer National Guidelines in Histopathology – Collection, Handling and Transport of Surgical Specimens (second edition, 2021).

3.1 Handling and reporting of biopsy specimens of endometrial malignancy

Specimen identification details and labeling should be checked before commencing the cut-up procedure.

3.1.1 Specimen handling (macroscopic description / grossing) [X]

Specimen type

- Endometrial curetting
- Endometrial biopsy
- Pipelle biopsy
- Other, specify

Macroscopy

- Specimen dimensions
  - Curetting: Measure aggregate size in three dimensions (mm)
  - Biopsies with minimal fragments and polyps
    - Number of pieces submitted
    - Maximum dimension (mm) each fragment
    - If intact polyp(s) are present, measure each in three dimensions (mm)
- Colour & texture

Grossing procedure

Dissection is not required in most circumstances. Large polyps maybe bisected longitudinally if required.
If the fragments are tiny, place them on filter paper.
It is important to process all of the tissue received, no matter how small.

3.1.2 Microscopy & conclusion [X]

Histological tumour type	Refer tumours of the endometrium in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Tumour grade	Refer FIGO grading (Annexure II)
Associated pathology	

3.2 Handling and reporting of hysterectomy specimens of endometrial malignancy

3.2.1 Specimen collection and transport

Refer National Guidelines in Histopathology – Collection, Handling and Transport of Surgical Specimens (second edition, 2021, Chapter 1 section F on fixation).

Specimen identification details and labeling should be checked before commencing the cut-up procedure.

3.2.2 Specimen type

- Abdominal hysterectomy: Total abdominal hysterectomy & bilateral salpingo-oophorectomy (TAH + BSO) (includes uterus, cervix, both ovaries, both fallopian tubes. This is the most common specimen for endometrial malignancy.
- Radical hysterectomy - Includes all above with parametria and vaginal cuff.
- Laparoscopic hysterectomy - should be specified as balloon manipulators used may cause artefactual vascular pseudo-invasion.
- Vaginal hysterectomy
- Additional specimens
  - Omentum
  - Lymph nodes
  - Peritoneal biopsy (+/-)
  - Peritoneal fluid /washings

3.2.3 Specimen handling (macroscopic description / grossing) [X]

Macroscopy

- Orientation of the specimen: identify the anterior and posterior walls of the uterus using anatomic landmarks such as the peritoneal reflection and the round ligament/ovaries.
  Note: If the specimen cannot be oriented, contact the surgeon or designate one serosal aspect of the uterus 'A' and the other 'B'.
- Gross photography of the specimen if possible **[Y]**
- The uterus must be opened into two equal halves whether sent in formalin or fresh. The uterus should be opened along the lateral uterine walls (3 and 9 o'clock).

Note: Uterus should be opened immediately as soon as possible upon receipt in the pathology laboratory and placed immediately in formalin.

- The above method provides maximum exposure of the endometrial surface in a flat plane which allows better visualization and measurement of the tumor.
- The surgical margins and any abnormal serosal surfaces of the uterus must be marked with ink in order to assess areas suspicious for tumour involvement.
- Document site of the tumour - fundal, isthmic / lower uterine segment, anterior, posterior wall, cornua etc.
- Measurements
  - Uterus in three dimensions in mm.
    - Midline fundal - serosa to ectocervix / intercornual distance /anterior to posterior dimension.
  - Ovaries / fallopian tubes / omentum / peritoneal biopsies
  - Size of the tumour-
    - Tumour should be measured in 3 planes in mm.
    - The third measurement is tumour thickness and the depth of invasion into the myometrium.
  - Myometrial thickness should be measured at point of maximal invasion.
  - Dimensions in all three planes of all visible abnormalities (especially thickening of the endometrium or polyps) must be recorded.

Note: Using the word 'edge' to refer to the periphery of a lesion and 'margin' to refer to the surgical specimen margins will avoid misunderstanding.

- The external appearance of the uterus /cervix/ovaries/fallopian tubes
  - Uterus - intact or opened
  - Any nodules or roughening of the ovarian surface
  - Any lesions in the cervix

  - Any dilatation of a fallopian tube or a previous tubal interruption (e.g. ligation)
- Look for macroscopic parametrial tumour involvement
- Examine the peritoneal surfaces with attention paid to the vaginal peritoneal reflection of the Pouch of Douglas to exclude possible metastatic tumour deposits.
- A diagram / photograph will be helpful.
- The closest distance of the endometrial tumour from the inferior surgical resection margin must be measured.
- The tumour with full thickness of the underlying myometrium in consecutive, serial sections taken perpendicular to the serosal surface.
- The thickness of the adjacent normal myometrial wall must be recorded.
- If no endometrial abnormality is seen on gross examination, the tumour may have been totally removed by a previous curettage. In such cases the endo-myometrium is serially sliced in the longitudinal plane to check for an endophytic tumour component.
- If no areas suspicious for myoinvasion are discovered, then all the endometrial tissue must be blocked.
- Each cornual recess must be sampled for any occult tumour.
- Cervix: The surface of the cervical canal and the underlying stroma is examined for tumour involvement.
- Record the extension of invasive tumour or isolated foci of tumour involving the cervix.
- The tumour dimensions and the shortest distance from the inferior surgical margin and the external anatomical os must be recorded.
- The maximum tumour invasive depth and the normal thickness of the cervical wall must be recorded.
- Lymph nodes: Maximum diameter of each lymph node
  (if multiple nodes found then a size range must be recorded)
- Record any additional relevant macroscopic abnormalities.

Block selection

- The selection of the specific tissue blocks is dictated by the lesion identified on gross examination and performed in a systematic manner to ensure that a microscopic estimate of tumour size is possible (Figure 1).
- Representative sections of the tumour including the deepest focus of myometrial invasion, at least 4 sections of the tumour should be taken.
- Transverse section through the lower uterine segment immediately proximal to the endocervix.
- A longitudinal section through the lower uterine segment.
- Sections through both cornu.

Note: In cases with biopsy proven carcinoma, but no visible tumour, cornual blocks must be taken; the entire endometrium may need to be blocked depending on the histological findings in the initial sections.

- Single midline sections through the anterior and posterior cervical lips. Entire endocervical canal must be sampled.
- Vaginal cuff if included in the specimen with margin blocked separately.
- In the case of large endometrial tumours, contiguous sections to include the most inferior part of the tumour and the external anatomical os. This will allow microscopic confirmation of any cervical stromal involvement.
- Normal or uninvolved endometrium.
- Left and right parametria.
- Appropriate sampling of other abnormalities (e.g. fibroids).
- Ovaries and tubes - One section, each from both ovaries and tubes if normal.
  - Fimbrial ends of the tubes should be sampled. Any abnormal areas should be sampled accordingly.
  - If on clinical or pathological grounds, there is any knowledge or suspicion of a hereditary cancer syndrome, then all of the ovarian and tubal tissue must be processed.
- Omental tissue
  - One block from omentum if there is macroscopic tumour.
  - If no abnormality is seen 2- 4 blocks should be taken.
  - Any abnormal or suspicious areas are sampled.
- Peritoneal biopsy: Peritoneal biopsy should be totally processed.
- Lymph nodes
  - All lymph nodes should be blocked
  - If there is macroscopic involvement one block is adequate

Note:

  - All nodes ≥ 3mm in size, section in 2 mm slicing perpendicular to the long axis, submitting in their entirety.
  - All nodes ≤ 2 mm in size submit whole.
  - Count total number of lymph nodes in each group as this gives some indication to specimen adequacy.

- Representative blocks should be taken from any other submitted tissue.

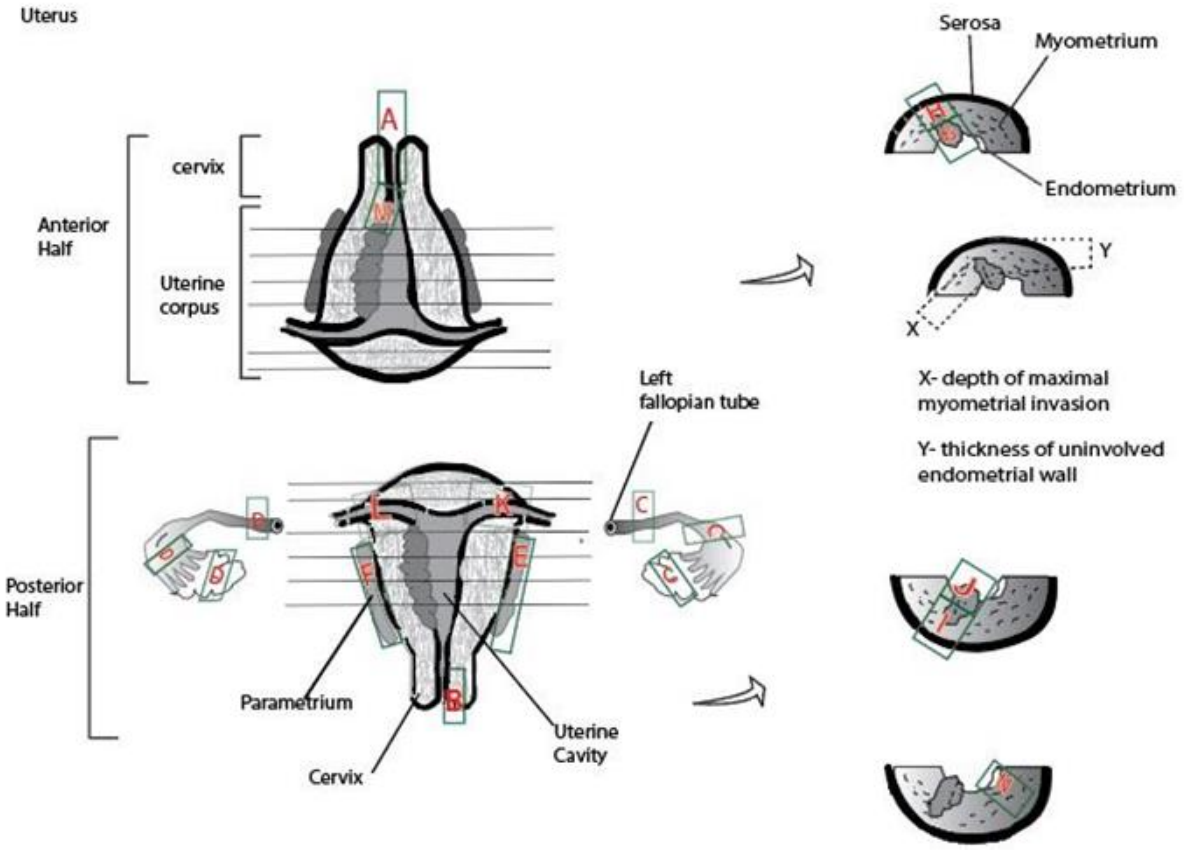

Figure 1. Block selection - Total hysterectomy and bilateral salpingo-oophorectomy for endometrial cancer

3.2.4 Microscopy & conclusion [X]

Hysterectomy specimen	
Histological tumour type	Refer tumour types in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Tumour grade	Refer FIGO grading currently in use in 2021 (Annexure II)
Myometrial Invasion	Defined as the depth of myometrial invasion from the endo-myometrial junction to the deepest focus of invasive carcinoma in comparison to the overall myometrial thickness. **Note:** ▪ The uterine wall in the cornual region is thin and blocks from this region should not be used for evaluation of depth of invasion, unless the tumour is

	located wholly in this region or it reaches / breaches the serosa only in this region. ▪ If the absolute depth of myometrial invasion cannot be ascertained, myometrial infiltration that reaches the arcuate vascular plexus of the uterus usually indicates > 50% myometrial invasion.
Lymphovascular invasion	Present / absent.
Microcystic elongated and fragmented (MELF) pattern of invasion	Presence should be reported.
Involvement of cervical tissue	The depth of invasion into cervical stroma is measured in mm and should be documented in relation to the full thickness of the cervical wall (mm). This may be expressed as a fraction or percentage of the cervical wall thickness.
Involvement of vaginal tissue	Present / absent.
Uterine serosal involvement	The uterine serosa is considered involved when tumour is seen to penetrate through the serosal layer.
Parametrial involvement	Parametrium when received in a radical or modified radical hysterectomy specimen, should be totally processed.
Adnexal involvement	Adnexal involvement by endometrial carcinoma should be distinguished from synchronous independent carcinomas involving the uterus and one or both ovaries or fallopian tubes.
Omental involvement	Present / absent.
Lymph node involvement	

Peritoneal involvement	Although not included in the 2009 revision of FIGO staging, peritoneal involvement must be documented with reference to site. Involvement of bladder, sigmoid serosa and cul-de-sac is FIGO Stage IVA. Involvement of abdominal peritoneum is FIGO Stage IVB (Annexure III).

Conclusion:

Hysterectomy specimen

- Specimen type
- Dimensions
- Tumour type and Grade
- Tumour site
- Tumour size
- Myometrial invasion thickness
- Thickness of adjacent normal myometrium
- Distance from tumour to serosal surface
- Lymphovascular invasion
- MELF pattern of invasion
- Non-neoplastic endometrium
- Tumour extension
  - Ovaries left / right
  - Fallopian tubes left / right
  - Cervix - glands and stroma
  - Vaginal cuff
  - Parametria left / right
  - Omentum
  - Peritoneal biopsy
  - Lymph nodes
- Pathological tumour stage: Refer annexure III for the 8th AJCC/TNM and FIGO staging currently in use in 2021.

3.2.5 Immunohistochemistry

Refer annexure V for specific situations where immunohistochemistry is of importance in the diagnosis of endometrial carcinomas.

3.3 Reporting proforma for endometrial carcinoma excision specimens [X]

Macroscopy		
Specimen components with dimensions	:	Adnexa / Vaginal cuff / Parametrium / Others (specify)
Accompanying specimens with dimensions	:	Omentum Lymph nodes: Pelvic / Para-aortic / Other (specify)
Microscopy		
Tumour type	:	
FIGO grade	:	1 or 2 or 3 (non-endometrioid / mucinous tumours automatically grade 3)
Tumour site		Fundus / body / lower uterine segment
Maximum dimension of tumour	:	_____mm
Myometrial invasion	:	None / <50% / ≥50%
Thickness of adjacent myometrium	:	_____mm
MELF pattern of invasion	:	Present / Not identified
Lymphovascular invasion	:	Present / Not identified
Microscopic involvement of: ▪ Cervical stroma ▪ Vagina ▪ Adnexa	:	 Involved / Not involved / Not assessable Involved / Not involved / Not assessable Involved / Not involved / Not assessable
If adnexa involved, is this considered to be a separate primary neoplasm?	:	Yes / No / Uncertain
Uterine serosa	:	Involved / Not involved / Not assessable
Parametrium	:	Involved / Not involved / Not assessable

Non neoplastic endometrium	:	
Lymph nodes ▪ Right pelvic lymph nodes ▪ Left pelvic lymph nodes ▪ Para-aortic lymph nodes	:	Not sampled / Sampled (no. positive / total no.) _____/_____ (no. positive / total no.) _____/_____ (no. positive / total no.) _____/_____
Omentum	:	Not sampled / Involved by tumour / Not involved by tumour
Peritoneal involvement		Involved / Not involved / Not assessable If involved, site of involvement: Pelvic / Abdominal
Distant metastases		Yes / No / Not assessable
Pathological tumour stage	:	

Annexures

Annexure I. WHO classification of tumours of the uterine cervix in 5th edition of WHO classification of Female Genital Tumours, currently in use in 2021.

Epithelial tumours & precursor lesions

- Endometrial hyperplasia without atypia
- Atypical hyperplasia of the endometrium
- Endometrioid carcinoma NOS
- Serous carcinoma NOS
- Clear cell adenocarcinoma NOS
- Carcinoma, undifferentiated NOS
- Mixed cell adenocarcinoma
- Mesonephric adenocarcinoma
- Squamous cell carcinoma NOS
- Mucinous carcinoma, intestinal type
- Mesonephric-like adenocarcinoma
- Carcinosarcoma NOS

Integrated histomolecular endometrial carcinoma (EC) classification -

- POLE-Ultramutated endometrioid carcinoma
- Mismatch repair- deficiency endometrioid carcinoma
- p53 mutant endometrioid carcinoma
- No specific molecular profile (NSMP) endometrioid carcinoma

Note: The diagnostic algorithm for the integrated histomolecular carcinoma classification can be applied for all endometrial cancer histological subtypes (including carcinosarcomas) (WHO Classification of Female Genital Tumours, 5th edition page 246)

Mesenchymal tumours

- Leiomyoma (and variants)
- Intravenous leiomyomatosis
- Smooth muscle tumour of uncertain malignant potential
  - Epithelioid smooth muscle tumour of uncertain malignant potential
  - Myxoid smooth muscle tumour of uncertain malignant potential
  - Spindle smooth muscle tumour of uncertain malignant potential
- Metastasizing leiomyoma
- Leiomyosarcoma NOS
  - Spindle leiomyosarcoma

- Epithelioid leiomyosarcoma
- Myxoid leiomyosarcoma
- Endometrial stromal nodule
- Endometrial stromal sarcoma, low grade
- Endometrial stromal sarcoma, high grade
- Undifferentiated sarcoma
- Uterine tumour resembling ovarian sex cord tumour
- Perivascular epithelioid tumour, benign
- Perivascular epithelioid tumour, malignant
- Inflammatory myofibroblastic tumour
  - Epithelioid myofibroblastic sarcoma

Mixed epithelial and mesenchymal tumours

- Adenomyoma NOS
- Atypical polypoid adenomyoma
- Adenosarcoma

Miscellaneous tumours

- Primitive neuroectodermal tumour NOS
- Germ cell tumours NOS
  - Yolk sac tumour NOS
  - Mature teratoma NOS
  - Immature teratoma NOS

Note:

- Accurate typing is important on both biopsies and resection specimens.
- Serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated
- Carcinoma and grade 3 endometrioid carcinoma are aggressive tumours.
- Endometrioid carcinomas and mucinous adenocarcinoma (endometrioid carcinoma with > 50% of tumour showing intracytoplasmic mucin) have a better prognosis.
- If multiple histological types are identified then the approximate relative percentages of each type must be stated.
- Serous EIC is an intraepithelial neoplasm that usually arises in atrophic endometrium or in an endometrial polyp. The cytology and immunophenotype is similar to uterine serous carcinoma but the tumour is confined to the pre- existing endometrial epithelium with no invasion of the endometrial stroma or myometrium. Even in the absence of demonstrable invasion, serous EIC can shed cells and metastasize to extrauterine sites; this is

the rationale for including this as a subtype of endometrial carcinoma in the WHO 2014 classification.

- Carcinosarcomas (Malignant Mixed Mullerian tumours) are now classified as epithelial neoplasms that have undergone sarcomatous metaplasia. They are staged like other endometrial cancers.
- Undifferentiated carcinoma may occur in pure form or in combination with a low-grade (grade 1 or 2) endometrioid adenocarcinoma; the combination of a low-grade endometrioid adenocarcinoma and undifferentiated carcinoma is referred to as dedifferentiated carcinoma.
- Neuroendocrine tumours may occur in pure form or in association with another morphological subtype of endometrial carcinoma.
- Mixed carcinoma refers to a tumour composed of more than one morphological type, at least one of which should be non-endometrioid / mucinous, typically serous carcinoma.
- The non-dominant type of differentiation must comprise at least 5 % of the tumour.
- It is recommended that all morphological types are mentioned in the pathology report along with the approximate percentage of each component, even if the minor component comprises less than 5 % of the neoplasm.

Annexure II. Histological (FIGO) grading.

The FIGO grading system is primarily based on the architectural arrangement of the neoplastic cells that characteristically produce glands. Any squamous elements should be excluded from the assessment.

G1	5% or less of a non-squamous or non-morular solid growth pattern
G2	6-50% of a non-squamous or non-morular solid growth pattern
G3	More than 50% of a non-squamous or non-morular solid growth pattern

Note:

- Nuclear atypia, which exceeds that which is routinely expected for the architectural grade, increases the tumor grade by 1.
- Serous carcinoma, clear cell carcinoma, and carcinosarcoma, undifferentiated carcinoma endometrioid carcinoma grade 3 are considered high grade or grade 3 tumours.
- In cases where there is a significant discrepancy between the reported tumour grade / type in the biopsy and in the hysterectomy, especially when there is no or minimal residual tumour in the hysterectomy specimen, it is necessary to review the prior biopsy and take this into account when assigning the final tumour grade / type. (The tumour grade on from the formalin-fixed

hysterectomy specimen is more reliable than that of the pre-operative pipelle sample, endometrial curettage, or frozen section).

Annexure III. AJCC/ TNM 8th edition & FIGO staging for tumours of the uterus - endometrium, currently in use in 2021.

* TNM stages are based on clinical and/or pathological classification. FIGO stages are based on surgical staging

* The definitions of the T,N and M categories correspond to the FIGO stages. Both systems are included for comparison.

TNM stage	FIGO stage	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1	I[a]	Tumour confined to uterine corpus
T1a	IA[a]	Tumour limited to endometrium or invading less than half of myometrium
T1b	IB	Tumour invades one half or more of myometrium
T2	II	Tumour invades cervical stroma, but does not extend beyond uterine corpus
T3	III	Local and / or regional spread as specified below.
T3a	IIIA	Tumour invades the serosa of the corpus uteri or adnexae (direct invasion or metastasis)
T3b	IIIB	Vaginal or parametrial involvement (direct invasion or metastasis)
N1, N2	IIIC	Metastasis to pelvic or para-aortic lymph nodes
N1	IIIC1	Metastasis to pelvic lymph nodes
N2	IIIC2	Metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes
T4	IV	Tumour invades bladder / bowel mucosa
N - Regional Lymph Nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis to pelvic lymph nodes	
N2	Regional lymph node metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes	

Note:

- Histological examination of a pelvic lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.
- Regional lymph nodes are the pelvic (hypogastric [obturator, internal iliac], common and external iliac, parametrial, and sacral) and the para-aortic nodes.

M - Distant Metastasis	
M1	Distant metastasis microscopically confirmed (excluding metastasis to vagina, pelvic serosa, or adnexa, including metastasis to inguinal lymph nodes, intra-abdominal lymph nodes other than para aortic or pelvic nodes)

Note: pMX and pM0 are not valid categories.

Stage grouping – Endometrial carcinoma			
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1, T2, T3	N1, N2	M0
Stage IIIC1	T1, T2, T3	N1	M0
Stage IIIC2	T1, T2, T3	N2	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Annexure IV-A. AJCC/ TNM 8th edition & FIGO staging for leiomyosarcoma & endometrial stromal sarcomas, currently in use in 2021.

* TNM stages are based on clinical and/or pathological classification. FIGO stages are based on surgical staging

* The definitions of the T,N and M categories correspond to the FIGO stages. Both systems are included for comparison

TNM stage	FIGO stage	
T1	I	Tumour limited to the uterus
T1a	IA	Tumour 5 cm or less in greatest dimension
T1b	IB	Tumour more than 5 cm
T2	II	Tumour extends beyond the uterus, within the pelvis
T2a	IIA	Tumour involves adnexa
T2b	IIB	Tumour involves other pelvic tissues
T3	III	Tumour infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
N1	IIIC	Metastasis to regional lymph nodes
T4	IVA	Tumour invades bladder or rectum
M1	IVB	Distant metastasis

Annexure IV-B. AJCC/ TNM 8th edition & FIGO staging for adenosarcoma, currently in use in 2021.

TNM stage	FIGO stage	
T1	I	Tumour limited to the uterus
T1a	IA	Tumour limited to the endometrium / endocervix
T1b	IB	Tumour invades less than half of the myometrium
T1c	IC	Tumour invades more than half of the myometrium
T2	II	Tumour extends beyond the uterus, within the pelvis
T2a	IIA	Tumour involves adnexa
T2b	IIB	Tumour involves other pelvic tissues
T3	III	Tumour infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
N1	IIIC	Metastasis to regional lymph nodes
T4	IVA	Tumour invades bladder or rectum
M1	IVB	Distant metastasis
N - Regional Lymph Nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant Metastasis		
M0	No distant metastasis	
M1	Distant metastasis (excluding adnexa, pelvic & abdominal tissues)	
pTNM Pathological classification		
The pT and pN categories correspond to the T and N categories.		
pM: Distant metastasis		
pM1	Distant metastasis microscopically confirmed	
Note: pM0 and pMX are not valid categories.		

Stage grouping – Uterine sarcomas			
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC*	T1C	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0

Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1, T2, T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Annexure V. Specific situations where immunohistochemistry is of importance in the diagnosis of endometrial carcinomas.

1. **To distinguish between endometrial and endocervical adenocarcinoma:** more often necessary in biopsies than in resection specimens

	Vimentin	**ER**	**PR**	**CEA**
Endometrial adenocarcinoma	Positive (strong)	Positive (strong)	Positive (strong)	Negative
Cervical adenocarcinoma	Negative	Negative	Negative	Positive

- Vimentin expression in endometrioid adenocarcinomas is usually strong and expressed on the lateral membranes, but endometrial carcinomas with mucinous differentiation express vimentin less frequently.
- CEA expression in cervical adenocarcinomas of the usual type is characteristically, although not always, diffuse with cytoplasmic and luminal border reactivity, whereas endometrioid adenocarcinomas of the uterus may exhibit weak, luminal CEA positivity.
- Squamous elements in endometrioid adenocarcinomas often show strong positivity with CEA.
- p16 staining may be useful in the distinction between an endometrioid adenocarcinoma of the uterine corpus and a usual cervical adenocarcinoma; the former is usually patchily positive and the latter diffusely immunoreactive.

2. **To distinguish between endometrioid and serous adenocarcinoma.**

- Grade 3 endometrioid adenocarcinomas show clinical behaviour similar to that of serous carcinomas.
- Grade 3 endometrioid adenocarcinoma may be difficult to differentiate from serous carcinoma, but it is usually solid and shows less pronounced nuclear pleomorphism.
- Grade 3 endometrioid adenocarcinomas generally show a greater incidence of expression of ER and PR, whilst expression of p53 and p16 is commoner is serous carcinomas.
- Serous carcinomas almost always exhibit aberrant p53 staining (intense nuclear staining of almost all nuclei or totally negative staining).

3. To differentiate endometrial adenocarcinoma from clear cell adenocarcinoma.

	CEA	HNF-1B	Napsin A	AMACR
Endometrioid Adenocarcinoma	Negative	Negative	Negative	Negative
Clear cell adenocarcinoma	Positive	Positive (67-100%)	Positive (56-93%)	Positive (75-88%)

- Serous carcinoma of the endometrium can be difficult to distinguish from clear cell carcinoma, the latter being extremely uncommon within the uterus. Aberrant p53 expression (diffuse and strong or totally absent) and diffuse p16 expression favours the diagnosis of serous carcinoma.

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CHAPTER 4

Histopathological assessment of tumours of the ovary, fallopian tubal & primary peritoneal malignancies

Introduction

Ovarian cancer is the fourth commonest malignancy in Sri Lankan females. Recent evidence indicates that the precursors of high grade serous carcinoma (HGSC) originate in the fallopian tube in patients with germline BRCA1 mutations, and also for many sporadic tumours. Therefore, in the presence of serous tubal intraepithelial carcinoma (STIC) or invasive high grade serous carcinoma in the tubal mucosa, assignment of a fallopian tube origin is now recommended. In approximately 15-10% of cases of HGSC, the fallopian tube is normal with an ovarian mass. Such lesions are classified as ovarian tumours.

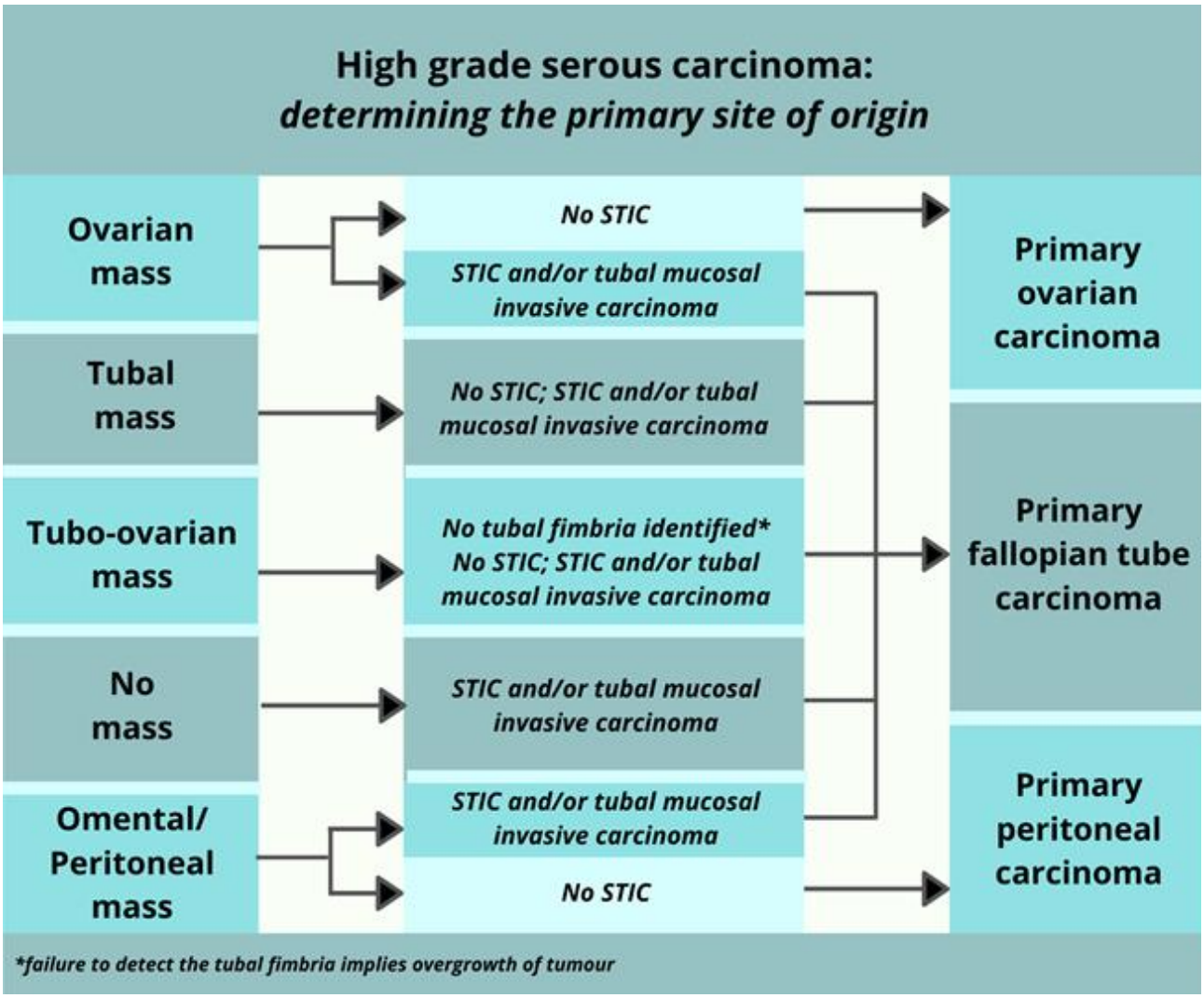

Figure 1. High grade serous carcinoma: determining the primary site of origin

Cases should be categorized as primary peritoneal carcinoma by the conventional criteria below and only after complete examination of the fallopian tubes (including the non-fimbrial portions) has excluded the presence of STIC or a small tubal HGSC.

The criteria are as follows;

- Both ovaries must be normal in size or enlarged by a benign process
- The involvement in the extra-ovarian sites must be greater than the involvement on the surface of either ovary.
- The ovarian tumour involvement must be non-existent, confined to the ovarian surface without stromal invasion or involve the cortical stroma with tumour size less than 5 x 5 mm.

4.1 Handling and reporting of tumours of the ovary, fallopian tube & primary peritoneal malignancies

4.1.1 Specimen collection and transport

Refer National Guidelines in Histopathology – Collection, Handling and Transport of Surgical Specimens (second edition, 2021).

4.1.2 Specimen handling (macroscopic description / grossing) [X]

OVARIAN MALIGNANCIES

- Specimen type
- Neo adjuvant chemotherapy given/not given
- Dimensions - three dimensions in mm
- Ovary- unilateral/bilateral involvement
- External surface – capsule - implants, rupture, adhesions
- Cut surface - cystic/ solid, unilocular/ multilocular cystic, presence of necrosis, papillae, calcification, colour, presence or absence of normal ovary
- Uterus and cervix- look for any abnormalities, serosal tumour deposits
- Fallopian tubes - fimbriae present/ absent, tumour present/absent
- Omentum - any hard areas, nodules, size of largest nodule
- Appendix - tumour present/absent, if tumour present distance from proximal margin.

TUBAL MALIGNANCIES

Mention the size, site of tumour (isthmus, ampulla, fimbria) and serosal involvement.

PERITONEAL MALIGNANCIES

- Number of tumour deposits, if present and/or approximate area (%) of specimen involved by tumour
- Maximum dimension of largest metastatic deposit (mm)

Block selection

- Paint the ovarian surface
- Take 1 block per 10 mm of tumour with ovarian surface, normal ovary, fallopian tube, residual ovary and other suspicious papillary areas.
- Borderline mucinous tumours may require further extensive sampling to exclude invasive tumour foci.
- Omentum, representative sections 5-6 blocks recommended.
- The sampling of fimbrial end of each fallopian tube in total, if no gross lesion is present, is recommended for patients with ovarian tumours.
- In primary peritoneal carcinoma - sample whole ovary and tube
- Prophylactic / risk-reducing salpingo-oophorectomy- sample the entire ovary and tube
- Appropriate handling implies that all ovarian and tubal tissue should be serially sectioned and submitted. For fallopian tubes, amputate the fimbrial ends and section parallel to the long axis of the fallopian tube to maximize the amount of tubal epithelium available for histological examination. The remainder of the fallopian tube is submitted as serial cross-sections. Fixation for 1 to 2 hours prior to sectioning and/or manipulation may help prevent sloughing of the epithelium.
- SEE-FIM protocol for sectioning and extensively examining the fimbriated end of the fallopian tube (Figure 2). The infundibulum and the fimbrial segment (distal 2 cm) are cut longitudinally to allow maximal exposure of tubal plicae. The isthmus and ampulla are cut transversely at 2-3 mm intervals.

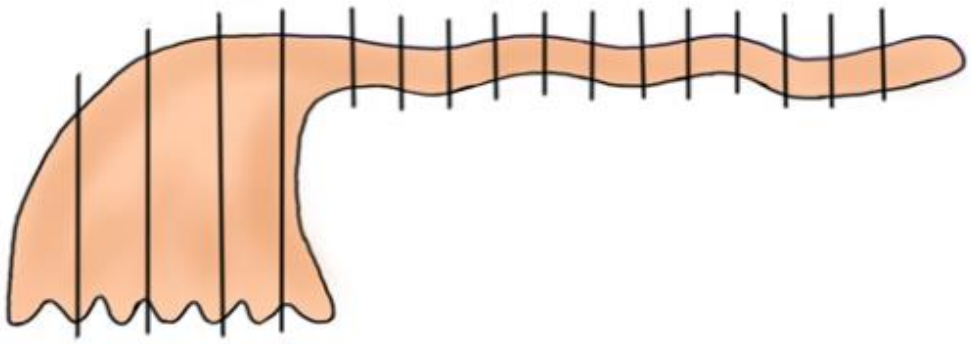

Figure 2. SEE-FIM protocol for sectioning and extensively examining the fimbriated end of the fallopian tube.

4.1.3 Microscopy & conclusion [X]

Primary tumour site	
Histological tumour type	Refer tumours of the ovary, tube and peritoneum in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Tumour grade	If relevant to the tumour, grade it according to tumours of the ovary, tube and peritoneum in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021)
Ovarian surface involvement	If applicable
Borderline tumour	Absent / Serous / Mucinous / Endometrioid / Other
Microinvasion (upper limit 5 mm)	Present / Absent
Intraepithelial carcinoma for mucinous borderline tumour	Present / Absent
Micropapillary architecture for serous borderline tumour	Present * / Absent * at least 5 mm in one dimension
Dimensions of largest omental deposit	If applicable
Serous tubal intraepithelial carcinoma (STIC)	Present / Absent
Involvement of other tissues / organs	If present
Peritoneal cytology status	
Lymph node status	
Borderline tumour - implants and type	Document if present.
Chemotherapy response	If applicable (Annexure II)
Pathological tumour stage	Refer annexure IV for the 8th AJCC/TNM and FIGO staging of tumours of the ovary, fallopian tube and primary peritoneal malignancies currently in use in 2021.

4.1.4 Immunohistochemistry [Y]

Refer annexure III for specific situations where immunohistochemistry is of importance in the diagnosis of ovarian carcinomas.

4.2 Reporting proforma for ovarian, tubal & primary peritoneal malignancy [X]

OVARIAN MALIGNANCY		
Macroscopy		
Specimen type	:	
Ovaries		
Right		
▪ Dimensions	:	_____ mm
▪ Tumour involvement	:	Yes / No
▪ Capsule	:	Intact / Disrupted / Involved by tumour / Not assessable
▪ Surface involvement	:	Yes / No
Left		
▪ Dimensions	:	_____ mm
▪ Tumour involvement	:	Yes / No
▪ Capsule	:	Intact / Disrupted / Involved by tumour / Not assessable
▪ Surface involvement	:	Yes / No
Fallopian tubes		
Right		
▪ Length	:	_____ mm
▪ Normal /Abnormal	:	_____
▪ Comment	:	_____
Left		
▪ Length	:	_____ mm
▪ Normal /Abnormal	:	_____
▪ Comment	:	_____
Uterus		
▪ Dimensions	:	_____ mm
▪ Normal /Abnormal	:	_____
▪ Comment	:	_____

Cervix	:	Normal /Abnormal
Omental biopsy / Omentectomy		
▪ Dimensions	:	_____ mm
▪ Involved by tumour	:	Yes / No
▪ If involved, size of the largest tumour nodule	:	_____ mm
▪ Comment	:	_____
Peritoneal biopsies	:	Not received / Received
Lymph nodes	:	Not received / Received
Others	:	Other involved organs received
Microscopy and conclusion		
Right ovary		
▪ Borderline tumour	:	Absent / Serous / Mucinous / Endometrioid / Other
▪ Microinvasion	:	Present / Absent
▪ Intraepithelial carcinoma	:	Present / Absent
▪ Micropapillary architecture	:	Present / Absent
▪ Invasive carcinoma	:	Present / Absent
▪ If invasive carcinoma is present, tumour subtype	:	
▪ Tumour differentiation (for endometrioid carcinoma)	:	**GX**: Cannot be assessed **G1**: Well differentiated **G2**: Moderately differentiated **G3**: Poorly differentiated
Note: o Serous carcinoma: low grade / high grade only, o Clear cell/ Undifferentiated/carcinosarcoma: automatically considered grade III. o Mucinous carcinoma: the pattern of invasion should be noted as expansile / confluent or infiltrative / destructive. Mucinous carcinoma grading is optional.		
Left ovary	:	Same items as for right ovary.
Fallopian tubes:		
▪ Right	:	Not involved / Involved
▪ Left	:	Not involved / Involved
▪ STIC	:	Present / Absent

Endometrium	:	Normal / Abnormal Comment_____
Myometrium	:	Normal / Abnormal Comment_____
Uterine serosa	:	Not involved / Non-invasive borderline implants / Invasive carcinoma / Invasive implants
Omentum	:	Not involved / Non-invasive borderline implants / Invasive carcinoma / Invasive implants
Lymph nodes	:	
Peritoneal cytology sample (if received)	:	Not involved / Involved / Equivocal
Provisional FIGO stage	:	
Pathological TNM stage	:	

FALLOPIAN TUBAL MALIGNANCY

Macroscopy

Fallopian tubes

Right

- Length : _____ mm
- Normal / Abnormal :
- Size of tumour : _____ mm
- Site of tumour Isthmus/ Ampulla / Fimbrial
- Serosal involvement : Yes / No

Left

- Length : _____ mm
- Normal / Abnormal :
- Size of tumour : _____ mm
- Site of tumour Isthmus/ Ampulla / Fimbrial
- Serosal involvement : Yes / No

Ovaries

Right

- Dimensions : _____ mm
- Tumour involvement : Yes / No

Left

- Dimensions : _____ mm
- Tumour involvement : Yes / No

Uterus and cervix		
▪ Normal /Abnormal	:	_____
▪ Comment	:	_____
Microscopy and conclusion		
Right fallopian tube		
▪ Borderline tumour	:	Absent / Serous / Mucinous / Endometrioid / Other
▪ Microinvasion	:	Present / Absent
▪ Invasive carcinoma	:	Present / Absent
▪ If invasive carcinoma is present, tumour subtype	:	
▪ Tumour differentiation (for endometrioid carcinoma)	:	**GX**: Cannot be assessed **G1**: Well differentiated **G2**: Moderately differentiated **G3**: Poorly differentiated
Note: o Serous carcinoma: low grade / high grade only, o Clear cell/ Undifferentiated/carcinosarcoma: automatically considered grade III. o Mucinous carcinoma: the pattern of invasion should be noted as expansile / confluent or infiltrative / destructive.		
Left fallopian tube	:	Same items as for right ovary.
Ovaries:		
▪ Right	:	Not involved / Involved
▪ Left	:	Not involved / Involved
Endometrium	:	Normal / Abnormal Comment_____
Myometrium	:	Normal / Abnormal Comment_____
Uterine serosa	:	Not involved / Non-invasive borderline implants / Invasive carcinoma / Invasive implants
Omentum	:	Not involved / Non-invasive borderline implants / Invasive carcinoma / Invasive implants
Lymph nodes	:	
Peritoneal cytology sample (if received)	:	Not involved / Involved / Equivocal
Provisional FIGO stage	:	
Pathological TNM stage	:	

PRIMARY PERITONEAL MALIGNANCY

Macroscopy

Nature and site of specimen/s	:	
Dimensions	:	_____ mm
Involved by tumour	:	Yes / No
Size of the largest tumour nodule	:	_____ mm
Ovaries		
Right		
▪ Dimensions	:	_____ mm
▪ Tumour involvement	:	Yes / No
Left		
▪ Dimensions	:	_____ mm
▪ Tumour involvement	:	Yes / No
Fallopian tubes		
▪ Right	:	Normal / Abnormal
▪ Left	:	Normal / Abnormal
▪ Comment	:	_____
Uterus and cervix		
▪ Normal /Abnormal	:	_____
▪ Comment	:	_____

Microscopy and conclusion

Peritoneum		
▪ Borderline tumour	:	Absent / Serous / Mucinous / Endometrioid / Other
▪ Microinvasion	:	Present / Absent
▪ Invasive carcinoma	:	Present / Absent
▪ Tumour subtype and differentiation	:	Serous / Clear cell / Carcinosarcoma / Undifferentiated / Endometrioid / Mucinous / Transitional
Omentum		
▪ Borderline tumour	:	Absent / Serous / Mucinous / Endometrioid / Other
▪ Microinvasion	:	Present / Absent
▪ Invasive carcinoma	:	Present / Absent
▪ Tumour subtype and differentiation	:	Serous / Clear cell / Carcinosarcoma / Undifferentiated / Endometrioid / Mucinous / Transitional

Microscopic features of other tissues		
Ovaries ▪ Right ▪ Left	: :	 Not involved / Involved Not involved / Involved
Fallopian tubes ▪ Right ▪ Left	: :	 Pathology other than STIC present / absent Pathology other than STIC present / absent
Ovaries: ▪ Right ▪ Left	: :	 Not involved / Involved Not involved / Involved
Endometrium	:	Normal / Abnormal Comment_____
Myometrium	:	Normal / Abnormal Comment_____
Uterine serosa	:	Not involved / Borderline changes / Invasive carcinoma
Lymph nodes	:	Sites _____ Not sampled / Number harvested / Number involved
Peritoneal cytology sample (if received)	:	Not involved / Involved / Equivocal
Comments / additional information	:	
Provisional FIGO stage	:	
Pathological TNM stage	:	

Annexures

Annexure I. Tumours of the ovary, peritoneum & fallopian tube in WHO classification of Female Genital Tumours, 5th edition currently in use in 2021.

OVARIAN TUMOURS

Serous tumours

- High grade serous carcinoma
- Low grade serous carcinoma
- Serous cystadenoma / adenofibroma / surface papilloma
- Serous borderline tumor
- Serous borderline tumor- micropapillary variant

Seromucinous tumours

- Seromucinous borderline tumour
- Seromucinous cystadenoma
- Seromucinous adenofibroma

Mucinous tumours

- Mucinous cystadenoma NOS
- Mucinous cystadenofibroma NOS
- Mucinous borderline tumor / atypical proliferative mucinous tumor
- Mucinous adenocarcinoma

Endometrioid tumours

- Endometrioid cystadenoma / adenofibroma
- Endometrioid borderline tumor
- Endometrioid adenocarcinoma NOS
- Seromucinous carcinoma

Clear cell neoplasms

- Clear cell cystadenoma
- Clear cell adenofibroma
- Clear cell borderline tumour
- Clear cell adenocarcinoma NOS

Brenner tumours

- Brenner tumor NOS
- Brenner tumour borderline
- Brenner tumour malignant

Other carcinomas

- Mesonephric -like adenocarcinoma
- Undifferentiated carcinoma
- Dedifferentiated adenocarcinoma
- Carcinosarcoma NOS
- Mixed cell adenocarcinoma

Mesenchymal tumours

- Endometrioid stromal sarcoma low grade
- Endometrioid stromal sarcoma high grade
- Leiomyoma NOS
- Smooth muscle tumour of uncertain malignant potential
- Leiomyosarcoma NOS

Mixed epithelial and mesenchymal tumours

- Adenosarcoma

Sex cord -stromal tumours

- Pure stromal tumours
- Fibroma NOS
- Cellular fibroma
- Thecoma NOS
- Thecoma luteinized
- Microcystic stromal tumor
- Sclerosing stromal tumor
- Signet ring stromal tumour
- Leydig cell tumor (NOS)
- Steroid cell tumor (NOS)
- Steroid cell tumour malignant
- Fibrosarcoma NOS

Pure sex cord tumours

- Granulosa cell tumor-adult
- Granulosa cell tumor-juvenile
- Sertoli cell tumor NOS
- Sex cord tumor with annular tubules

Mixed sex cord -stromal tumours

- Sertoli-Leydig cell tumor NOS
- Sertoli-Leydig cell tumor well differentiated
- Sertoli-Leydig cell tumor moderately differentiated
- Sertoli-Leydig cell tumor poorly differentiated
- Sertoli-Leydig cell tumor retiform
- Sex cord stromal tumour NOS
- Gynandroblastoma

Germ cell tumours

- Teratoma benign
- Immature teratoma NOS
- Dysgerminoma
- Yolk sac tumour NOS
- Embryonal carcinoma NOS
- Choriocarcinoma NOS
- Mixed Germ cell tumour NOS
- Monodermal teratomas and somatic-type tumours arising from a dermoid cyst
- Struma ovarii
- Struma ovarii malignant
- Teratoma with malignant transformation
- Strumal carcinoid
- Cystic teratoma NOS

Germ cell -sex cord -stromal tumours

- Gonadoblastoma
- Mixed Germ cell- sex cord -stromal tumour NOS

Miscellaneous tumours

- Adenoma of rete ovarii
- Adenocarcinoma of rete ovarii
- Wolffian tumour
- Solid pseudopapillary tumour of ovary
- Small cell carcinoma, hypercalcemic type
- Small cell carcinoma, large cell variant
- Wilms tumour

TUMOURS OF THE FALLOPIAN TUBE

Epithelial tumours

- Serous adenofibroma NOS
- Serous borderline tumour NOS
- High grade serous carcinoma
- Endometrioid adenocarcinoma NOS
- Carcinosarcoma NOS

Mixed epithelial and mesenchymal tumours

- Adenosarcoma

Germ cell tumours

- Mature teratoma NOS
- Immature teratoma NOS

TUMOURS OF THE PERITONEUM

Mesothelial tumours

- Adenomatoid tumour
- Well differentiated papillary mesothelioma, benign
- Mesothelioma, malignant
    - Epithelioid mesothelioma, malignant
    - Sarcomatoid mesothelioma
    - Mesothelioma, biphasic, malignant

Epithelial tumours

- High grade serous carcinoma
- Low grade serous carcinoma
- Serous borderline tumour

Mesenchymal tumours

- Leiomyomatosis peritonealis disseminata
- Abdominal fibromatosis
- Calcifying fibrous tumour
- Gastrointetinal stromal tumour
- Solitary fibrous tumour NOS
    - Fat forming Solitary fibrous tumour
    - Giant cell rich Solitary fibrous tumour

    - Dedifferentiated Solitary fibrous tumour
    - Solitary fibrous tumour malignant
- Endometrial stromal sarcoma low grade
- Endometrial stromal sarcoma high grade
- Desmoplastic small round cell tumour

Annexure II. Chemotherapy Response Score (CRS).

Score	Criteria
1	**No or minimal tumour response.** Mainly viable tumour with minimal regression, associated fibro-inflammatory changes* limited to a few foci (> 95% tumour viable)
2	**Partial tumour response.** Multifocal or diffuse regression associated fibro-inflammatory changes*, with viable tumour ranging from diffuse sheets, streaks or nodules to extensive regression with multifocal but easily identifiable residual tumour.
3	**Complete or near-complete response.** Mainly regression, with few irregularly scattered individual tumour cells or cell groups (all measuring less than 2 mm), or no residual tumour identified (< 5% tumour viable).

* Regression associated fibro-inflammatory changes: fibrosis associated with macrophages, including foam cells, mixed inflammatory cells and psammoma bodies; to be distinguished from tumour-related inflammation or desmoplasia.

Annexure III. Specific situations where immunohistochemistry is of importance in the diagnosis of ovarian carcinomas **[Y]**

Carcinoma type	PAX 8	WT 1	TP 53 mutant type	ER	PR
LGSC	100%	100%	0	96%	50%
HGSC	96%	92%	93%	80%	30%
MC	50-60%	0%	50%	6%	0%
EC	84%	4%	11%	86%	72%
CCC	99%	0%	12%	13%	6%

LGSC- low grade serous carcinoma, HGSC- high grade serous carcinoma, MC- mucinous carcinoma, EC- endometrioid carcinoma, CCC- clear cell carcinoma.

Brenner tumours - CK 7 and P 63 positive, CK 20 and WT 1 negative.

Germ cell tumours - Alpha fetoprotein, PLAP, CD 117, HCG, CD 30.

Sex cord / stromal tumours - Inhibin, Calretinin, CD 99, Melan A.

Metastatic carcinoma - Most ovarian carcinomas with mucinous and endometrioid morphology should always raise suspicion and might need IHC markers to exclude metastatic carcinomas. At least CK7 and CK20 are recommended as preliminary markers.

Tumour site	IHC markers
Ovary	CK 7 > CK 20, PAX 8 positive, ER / PR for endometrioid tumours
Appendix, colo-rectum	CK 20 > CK 7, CDX 2 positive, ER/PR negative
Pancreato-biliary	CK 7 > CK 20, PAX 8 negative, CK 19 & CA 19-9 positive
Gastric	CK 7 / CK 20 variable,
Breast	CK 7 positive, CK 20 negative, mammoglobin, GCDFP-15, ER and PR

Annexure IV. AJCC / TNM 8th edition & FIGO staging of tumours of the ovary, fallopian tube and primary peritoneal malignancies, currently in use in 2021.

* TNM stages are based on clinical and / or pathological classification. FIGO stages are based on surgical staging

* The definitions of the T, N and M categories correspond to the FIGO stages. Both systems are included for comparison

TNM stage	FIGO stage	
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1	I	Tumour limited to the ovaries (one or both) or fallopian tube(s)
T1a	IA	Tumour limited to 1 ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings.
T1b	IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings.
T1c	IC	Tumour limited to 1 or both ovaries or fallopian tubes, with any of the following:

T1c1	IC1	Surgical spill
T1c2	IC2	Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
T1c3	IC3	Malignant cells in ascites or peritoneal washings
T2	II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal malignancy.
T2a	IIA	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovary(ies).
T2b	IIB	Extension to other pelvic tissue, including bowel within the pelvis.
T3 and/or N1	III[a]	Tumour involves one or both ovaries or fallopian tubes or primary peritoneal carcinoma with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.
N1		Retroperitoneal lymph node metastasis only
N1a	IIIA1i	Lymph node metastasis not more than 10 mm in greatest dimension.
N1b	IIIA1ii	Lymph node metastasis more than 10 mm in greatest dimension.
T3a any N	IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without retroperitoneal lymph nodes, including bowel involvement.
T3b any N	IIIB	Macroscopic peritoneal metastasis beyond pelvic brim 2 cm or less in greatest dimension, including bowel involvement outside the pelvis with or without retroperitoneal lymph node metastasis.
T3c	IIIC	Peritoneal metastasis beyond the pelvic brim > 2 cm in greatest dimension and or retroperitoneal lymph node metastasis (including extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ).
M1	IV	Distant metastasis
N - Regional Lymph Nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
N1	IIIA1	Retroperitoneal lymph nodes metastasis only.
N1a	IIIA1i	Lymph node metastasis no more than 10 mm in greatest dimension.
N1b	IIIA1ii	Lymph node metastasis more than 10 mm in greatest dimension

Note: Regional lymph nodes include the following:
External iliac, internal iliac (hypogastric), obturator, common iliac, para-aortic, pelvic NOS and retroperitoneal NOS lymph nodes

M - Distant Metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
M1a	IVA	Pleural effusion with positive cytology.
M1b	IVB	Liver or splenic parenchymal metastases. Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity). Transmural involvement of intestine.

Stage grouping – Ovary, fallopian tube and primary peritoneal malignancies			
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1C	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA1	T1/2	N1	M0
Stage IIIA2	T3a	N0, N1	M0
Stage IIIB	T3b	N0, N1	M0
Stage IIIC	T3c	N0, N1	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

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CHAPTER 5

Histopathological assessment of vulvo-vaginal malignancy

5.1 Handling and reporting of vulval malignancies

5.1.1 Specimen collection and transport

Refer National Guidelines in Histopathology – Collection, Handling and Transport of Surgical Specimens (College of Pathologists of Sri Lanka, 2021).

Specimen identification details and labeling should be checked before commencing the cut up procedure.

5.1.2 Specimen handling (macroscopic description / grossing) [X]

- Specimen type
  - Vulva biopsy
  - Hemivulvectomy (unilateral)
  - Partial vulvectomy (no deep fascia)
  - Simple or total vulvectomy (with deep fascia)
  - Total radical vulvectomy (with lymph nodes)
  - Others: as specified by the gynaecologist

Note: All vulvectomy specimens should have an accompanying diagram depicting the anatomical relationships.

- If received in fresh state, after the initial inspection and description, the specimen should be pinned out to a cork board and allowed to fully fix in large quantity of formalin before dissection.
- Paint the entire peripheral margin and deep surface of the specimen with two different colours of ink.
- Orientate and identify anatomical features present in the specimen; urethral and vaginal orifices, clitoris and labia majora.
- Record additional orientation or information provided by the operating clinician.
- Photograph the intact specimen to locate the tumour and its relationship to the margins.

- Describe and measure the anatomical components:
  - Vulva in three dimensions; right-left x anterior-posterior x thickness
  - Clitoris, vaginal orifice, labial folds
  - Others
- Surface
  - Hair-bearing skin
  - Hairless skin/mucosa
  - Both hair-bearing skin and hairless skin
  - Undetermined
- Specimen integrity
  - Intact and complete
  - In fragments
  - Other (specify)
- Tumour
  - Absent or present - if absent, record whether a scar is present.
  - Number - if more than one tumour is present, record the distance between tumours (mm)
- Tumour site
  - Laterality - right / left
  - Labia minora
  - Labia majora
  - Clitoris
  - Other (specify)
- Tumour size (mm) - in three dimensions
- Tumour growth type - fungating, ulcerative, others (specify)
- Tumour appearance - Colour, shape, contour, border
- Margins
  - Involved/ uninvolved
  - Distance to margins (mm)
- Adjacent skin abnormalities
  - Present / absent
  - Describe (white, red, thickened, pigmented, others)

Note: Vulval specimens with macroscopic tumour and without macroscopic tumour are handled slightly differently after the initial steps.

VIN excision biopsies without macroscopic tumour:

Microscopic cancers occur in VIN excision specimens in about 20%. Early invasion arising in VIN has a diagnostic significance similar to that of macroscopic tumour.

Once invasion has been identified, measuring depth of invasion correctly is crucial as this is the single best predictor of groin lymph node metastases and will largely determine whether to excise lymph nodes or not.

Vulvar intraepithelial neoplasia (VIN): Submit all tissue if possible. If not , submit all sections from previous excision or biopsy site (identified by suture or scar). If the scar is long , submit representative sections particularly the most raised areas.

Excision specimens with macroscopic tumour:

These need to be confirmed as carcinoma. There are some benign lesions such as keratoacanthoma, pseudoepitheliomatous hyperplasia or prurigenous nodule, that could mimic malignancy.

Serially section the specimen horizontally from anterior (12 o'clock) to posterior (6 o'clock) ends ensuring that the mid-point (deepest point) of the tumour is demonstrated.

After sectioning the following should be noted;

- Macroscopic depth of invasion (mm)
- Measurement of depth of invasion into the subcutaneous fat.

If depth of invasion is not accessible macroscopically, mention distance to margins (mm)

If inguinal fat is attached, locate all lymph nodes and mention:

- site(s)
- total number retrieved
- maximum diameter of each (mm)

Block selection [X]

- Small specimen (<10mm): submit all
- Larger specimen with small tumour (<10mm): submit all sections of tumour demonstrating the relationship with adjacent skin.
- Large specimen with large tumour (>20mm):
  - Submit representative sections of surgical margins
  - Submit perpendicular sections of 12 o'clock and 6 o'clock margins
  - If the entire circumferential margin is sampled, ensure that the surface demonstrating the outer limit is embedded en face (face downwards in a cassette). Circumferential margin will be visible in the first paraffin section.

  - Submit entire cross section of tumour demonstrating the deepest point of tumour invasion, using composite blocks if required.
  - Submit blocks demonstrating relationship of tumour with the closest margin
  - Submit blocks demonstrating interface of tumour with adjacent skin
  - Submit blocks demonstrating areas of tumour with different appearances
- Sentinel lymph node: bisect transversely across the long axis of the node. Submit all sections.
- Small, macroscopically uninvolved lymph nodes: bisect transversely across the long axis of the node. Submit all sections.
- Large, macroscopically uninvolved lymph nodes: section transversely at 3mm intervals across the long axis of the node. Submit all sections.
- Macroscopically involved lymph nodes: section transversely at 3 mm intervals across the long axis of the node; submit sections demonstrating relationship with the capsule to allow microscopic evaluation of any possible extracapsular invasion.
- Remaining tissue should be stored with orientation maintained in case further sections are required.

Table 1. Sample block summary

Specimens with tumour		
Cassette	Site	No. of pieces
A	12 o'clock margins, perpendicular sections	
B	6 o'clock margins, perpendicular sections	
C	Tumour, deepest point of invasion	
D	Tumour and closest margin	
F	Tumour and adjacent skin	
G-H	Tumour, raised /ulcerated areas	
I+	Lymph nodes	
Specimens without apparent tumour		
Cassette	Site	No. of pieces
A-C	Sections from area of previous biopsy / suture / scar	
VIN specimens		
Cassette	Site	No. of pieces
A-E	All or representative sections as applicable.	

5.1.3 Microscopy and conclusion [X]

Type of vulval specimen	
Histological tumour type	Refer tumours of the vulva in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Differentiation and tumour grade	Grade 1: Well differentiated Grade 2: Moderately differentiated Grade 3: Poorly differentiated Grade 4: Undifferentiated
Tumour size	▪ Maximum horizontal dimension: _____mm ▪ Depth of invasion: _____mm ▪ Tumour thickness: _____mm
Lymphovascular invasion	Present / absent.
Perineurial (intraneural) invasion	Present / absent.
Margins	Involvement. Distance to the closest margin: _____mm
Associated features	High-grade VIN / HSIL Paget disease
Non-neoplastic epithelial disease	Lichen sclerosus / Lichen planus / Squamous hyperplasia.
Lymph node involvement	
Adnexal involvement	Adnexal involvement by endometrial carcinoma should be distinguished from synchronous independent carcinomas involving the uterus and one or both ovaries or fallopian tubes.
Omental involvement	Present / absent.
Lymph node involvement	
Pathological tumour stage	Refer annexure IV for the 8th AJCC/TNM and FIGO staging currently in use in 2021.

5.2 Handling & Reporting of vaginal malignancies

Primary malignancies of the vagina are rare, most carcinomas involving the vagina represent direct extension from cervical carcinoma. Microscopically, approximately 95% of vaginal carcinomas are conventional squamous cell carcinomas of varying degrees of differentiation. Less common types of vaginal malignancies include adenocarcinoma, sarcoma, melanocytic tumours and endodermal sinus tumour.

The sites of primary vaginal cancers in order of frequency are upper third of the vagina (56%), the lower third (31%) and the middle third (13%). Tumours of upper two third of vagina drain mainly to pelvic nodes and lower third drains to inguinal nodes.

Vaginal specimens are rare, as surgeons are reluctant to perform vaginectomies, and when encountered as a complete organ they are usually part of an exenteration specimen. Most specimens from the vagina are biopsies.

5.2.1 Specimen collection and transport

Refer National Guidelines in Histopathology – Collection, Handling and Transport of Surgical Specimens (second edition, 2021).

5.2.2 Specimen handling (macroscopic description / grossing) [X]

- Specimen type
  - Biopsies
  - Wide local excision
  - Vaginal resections
    - Partial and total vaginectomy – vaginal epithelium is removed without disruption of the adjacent tissue.
    - Radical vaginectomy - removal of the vagina with supporting tissue around.
  - Trachelectomy specimens – vagina with cervix without removing uterus
  - Vaginectomy specimens with hysterectomy
  - Vaginectomy with TAH & BSO
  - Lymphadenectomy specimens with any form of surgical specimens mentioned above.
  - Pelvic exenteration specimens

Vaginal biopsies

Follow cervical biopsy guidelines and procedure.

Wide local excision

Follow vulval wide excision procedure.

Vaginal resections (vaginectomy)

- Look for orientation (sutures, clips)
- Measure the specimen in three dimensions
- Cut up can follow two procedures:
  1. Open the vaginal specimen along one side (lateral border) , ink resection margins (deep, inferior and superior), pin out on a cork board, and fix and, handled in the same manner as a large skin excision.
  2. Stuff the cavity with formalin soaked gauze, fix overnight, ink resection margins (deep, inferior and superior) and cut in half.
- Describe the specimen: colour, shape and mucosal appearance.
- Examine and measure the lesion - shape, colour, erosion, heamorrhage etc.
- Measure the distance from the lesion to margins.
- Take a photograph.
- Take sections as for skin excision specimens.
- If the specimen is large there are two possible sectioning methods:
  1. Perpendicular margins – preferred method; the specimen is serially sectioned parallel to the short axis.
  2. En face margins - when the margins are > 5mm away from the lesion macroscopically - superior and inferior margins are sectioned and submitted, deeper margin (circumferential) can be submitted as a shave.

Pelvic exenteration

These specimens are handled in the same manner as radical hysterectomies for cervical cancer. If the uterus has been previously removed, the resulting vaginal pouch can be opened along one side and handled in the same manner as vaginectomy specimens.

Total pelvic exenteration includes the bladder, uterus with attached adnexa, vagina, and rectum. The evaluation of these specimens includes both a separate and an integrated approach.

Anterior exenteration: If the bladder is included with the uterus.

Posterior exenteration: if the rectum is included with the uterus.

- Fill the vagina with formalin-soaked gauze pads and distend the bladder and rectum with formalin. Submerge the entire specimen in formalin and fix overnight.
- The fixed specimen is bisected in the sagittal plane to demonstrate the tumour and its relationship to surrounding structures. This is best

accomplished by using probes in the urethra and in the uterine canal as midline guides.

- After the specimen has been sectioned, a diagram can facilitate the description of the tumour, including its extension and both cut surfaces photographed.

Block selection [X]

Sections should be taken to demonstrate the greatest depth of tumor invasion, the tumor with adjacent normal appearing mucosa, and the relationship of the tumor to the cervix.

With the added structures, additional sections need to be taken to include the extent of tumor involvement of the bladder or rectal wall, and an evaluation of their respective surgical margins.

- **Vaginal resection (vaginectomy):** Submit entirely unless the specimen is very large or an incidental resection.
  Large specimens:
  - Margins - superior, inferior, circumferential (deep) - obtain either shave margins or with tumour.
  - Representative sections from tumour -– obtain serial sections from tumour.
  - Section from adjacent normal mucosa with tumour.

Table 2. Sample block summary

Cassette	Site	No. of pieces
A	Superior margin	
B	Inferior margin	
C	Deep(Circumferential) margin.	
D	Tumour, deepest point of invasion.	
F	Tumour and closest margin	
G-H	Tumour and adjacent skin	
I+	Tumour, raised/ulcerated areas	

- **Trachelectomy and hysterectomy specimens:** Follow procedure as for hysterectomy
- **Pelvic exenteration for vaginal malignancy:**
  Sections for histology – Figure 1.
  - Greatest depth of tumour invasion
  - Tumour with adjacent normal appearing area

- Sections of the tumour to demonstrate invasion of the adjacent viscera (bladder, urethra, rectum, paravaginal tissue).
- Vaginal and paravaginal soft tissue margins with perpendicular or shave sections.
- Lymph nodes
- Surgical margins - vaginal, urethral, ureteral, proximal and distal bowel margins
- Standard hysterectomy sections: ovaries, tubes, endometrium, myometrium, cervix.

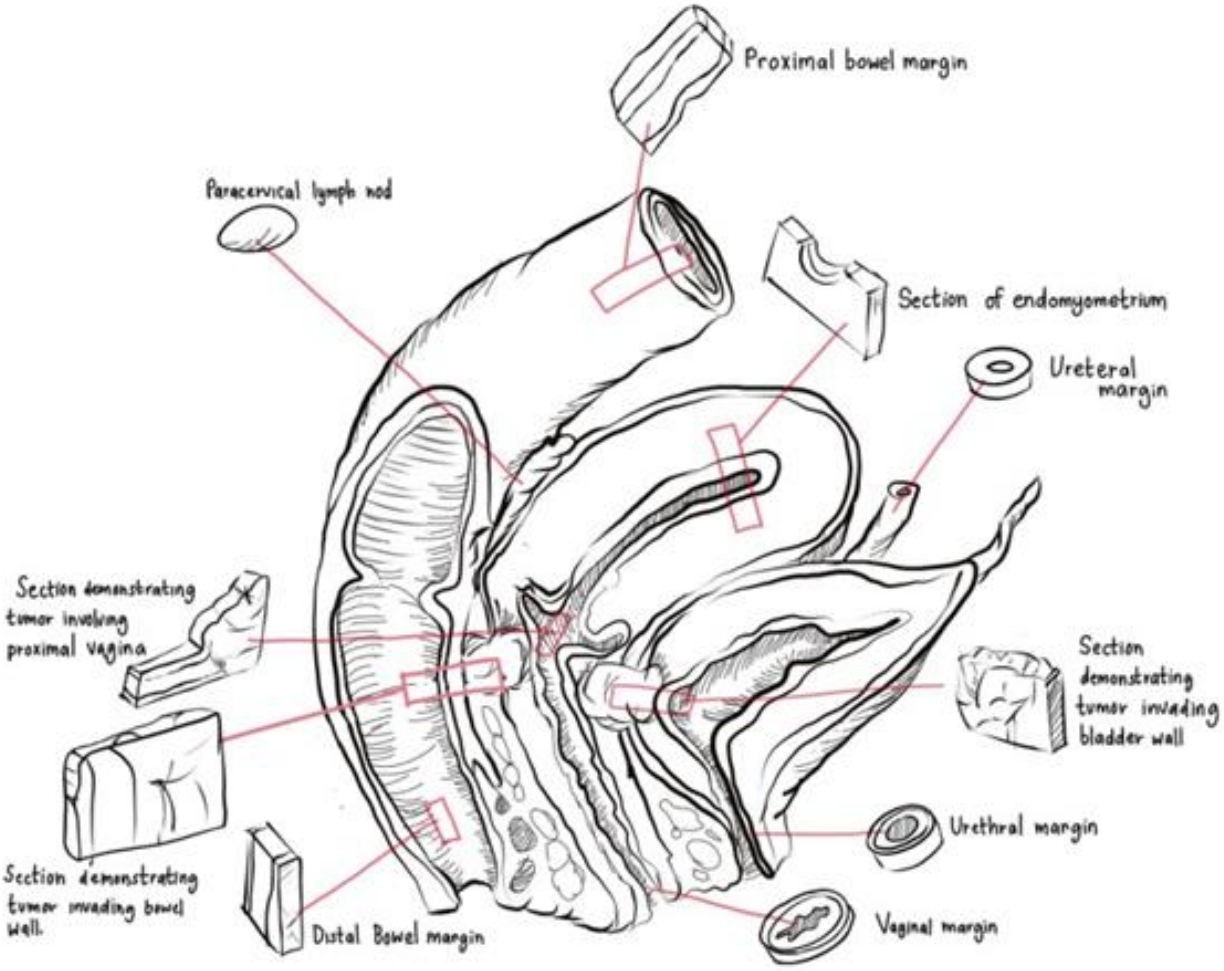

Figure 1. Representative samples to be obtained from pelvic exenteration specimen for vaginal malignancy:

5.2.3 Microscopy and conclusion [X]

Type of specimen	
Site of the tumour	
Size of the tumour	
Histological tumour type	Refer tumours of the vagina in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Histological grade CAP guidelines Vagina 4.3.0.1 November 2021	Grade 1: Well differentiated Grade 2: Moderately differentiated Grade 3: Poorly differentiated Other (specify): _____ GX: Cannot be assessed Not applicable
Involvement of other organs by the tumour	Specify the extent of tumor involvement in these structures
Associated pathology	
Radiaiton changes	
Lymph node involvement	
Pathological tumour stage	Refer annexure V for the 8th AJCC/TNM and FIGO staging currently in use in 2021.

5.2.4 Immunohistochemistry [Y]

p16 immunohistochemical marker is highly desirable to differentiate HPV associated from HPV unassociated squamous malignancies of the vagina and HPV associated adenocarcinoma of the vagina.

CK 7, CEA, CAM 5.2, EMA, GCDFP-15 for primary vulval Paget disease which-usually expresses these markers.

5.3 Reporting proforma for vulvo-vaginal malignancy

5.3.1 Reporting proforma for vulval malignancy resection specimens [X]

Macroscopy		
Type of specimen	:	
Specimen size	:	_____ mm
Tumour site	:	Labium major: left / right Labium minor: left / right Clitoral
Maximum macroscopic tumour dimension	:	_____ mm
Nearest macroscopic margin (specify)	:	
Nearest macroscopic margin distance	:	_____ mm
Microscopy		
Tumour type	:	
Tumour differentiation / grade	:	Grade 1: Well differentiated Grade 2: Moderately differentiated Grade 3: Poorly differentiated GX: Cannot be assessed Other (specify): _____ Not applicable
Tumour size	:	Maximum horizontal dimension: ____mm Depth of invasion: ____mm
Lymphovascular invasion	:	Present / absent
Perineurial (intraneural) invasion	:	Present / absent
Margins	:	Extension to margin: Yes / No Distance of the tumour to the closest margin: ____mm
Precursors of squamous cell carcinoma of vulva	:	Squamous intraepithelial lesions, HPV-associated and vulvar intraepithelial neoplasia, HPV–independent: Present / Not identified
Paget disease	:	Present / Not identified

Non-neoplastic epithelial disease	:	Lichen sclerosus / Lichen planus / Squamous hyperplasia
Lymph nodes, if received	:	Left / Right Number received Number positive Sentinel lymph nodes Size of sentinel lymph node deposit(s): ____mm Inguinofemoral lymph nodes Pelvic lymph nodes Other, specify _____ Largest lymph node deposit: ____mm Extranodal extension: Yes / No
Histological evidence of distant metastasis	:	Present / absent
HPV staining (if done)	:	
Pathological tumour stage	:	

5.3.2 Reporting proforma for vulval malignancy biopsy specimens [X]

Macroscopy		
Type of specimen	:	Punch biopsy Wedge biopsy Other (specify)
Specimen size	:	_____ mm
Tumour site	:	Labium majus: left / right Labium minus: left / right Clitoral
Maximum macroscopic tumour dimension	:	_____ mm
Nearest macroscopic margin (specify)	:	Specify margin Distance to tumour _____ mm
Microscopy		
Tumour type	:	
Tumour differentiation / grade	:	Grade 1: Well differentiated Grade 2: Moderately differentiated Grade 3: Poorly differentiated Grade 4: Undifferentiated Not applicable
Tumour size	:	Maximum horizontal dimension: ____mm

		Depth of invasion: ____mm
Lymphovascular invasion	:	Present / absent
Perineurial (intraneural) invasion	:	Present / absent
Margins	:	Extension to margin: Yes / No Distance of the tumour to the closest margin: ____mm
Precursors of squamous cell carcinoma of vulva	:	Squamous intraepithelial lesions, HPV-associated and vulvar intraepithelial neoplasia, HPV–independent: Present / Not identified
Paget disease	:	Present / Not identified
Associated pathology	:	

5.3.3 Reporting proforma for vaginal malignancy (vaginal biopsy, vaginal resection, pelvic exenteration) [X]

VAGINAL BIOPSY		
Type of specimen	:	Incisional biopsy Other (specify)
Tumour site	:	Upper third Middle third Lower third
Histological tumour type	:	
Histological tumour grade	:	Well differentiated Moderately differentiated Poorly differentiated Undifferentiated
Tumour extension	:	Stromal invasion Muscle invasion
Margins (if excisional)	:	
Additional pathological findings	:	
VAGINAL RESECTION		
Type of specimen	:	Wide excision Partial / total / radical vaginectomy Other (specify)
Tumour site	:	Upper third Middle third Lower third

Tumour size	:	Greatest dimension (mm)
Histological tumour type	:	
Tumour grade	:	Well differentiated Moderately differentiated Poorly differentiated Undifferentiated
Other tissue / organ involvement	:	
Margins	:	Peripheral margin: Deep margin:
Lymphovascular invasion	:	Present / absent
Associated pathological changes	:	
Pathological tumour stage	:	

PELVIC EXENTERATION

Macroscopy		
Specimen type	:	Full / anterior / posterior pelvic exenteration
Received state	:	Fresh / in formalin Intact / disrupted / previously incised
Specimen measurements	:	Specimen measuring ____ x ____x ____ cm in greatest overall dimensions Bladder: Bowel: Right ureter: Left Ureter: Uterus: Cervix: Vagina:
Tumour size	:	
Extension of tumour	:	Into adjacent viscera /f extension present, distance from to the inked soft tissue margin
Lymph nodes	:	Specify groups and number of nodes in each group.
Microscopy		
Site of the tumour	:	
Size of the tumour	:	

Histological tumour type	:	
Tumour grade	:	
Other organs involved by the tumour	:	Specify the extent of tumour involvement into these structures
Lymphovascular invasion	:	Present / absent
Radiation effects	:	Present / absent
Associated pathology	:	
Pathological tumour stage	:	

Annexures

Annexure I. Microscopic measurement of vulval tumours.

- **Maximum horizontal tumour size:** Microscopic horizontal size of tumour has to be correlated with macroscopic measurements in large tumours (If a tumour extends across seven or more blocks the tumour is greater than 20 mm in diameter, FIGO stage II or greater).
- **Depth of invasion and tumour thickness:** Depth of invasion is measured in millimeters from the adjacent most superficial dermal papilla to the deepest point of invasion (Figure 2). If this is not possible, it can be estimated by subtracting the distance of the surface to the epithelial stromal interface of the most superficial dermal papilla, from the distance between the surface and the deepest point of invasion.
- **Tumour thickness** is measured from the granular layer (in keratinized tumours) or from the base of the ulcer (in the case of ulcerated tumours) to the deepest point of invasion (Figure 3).

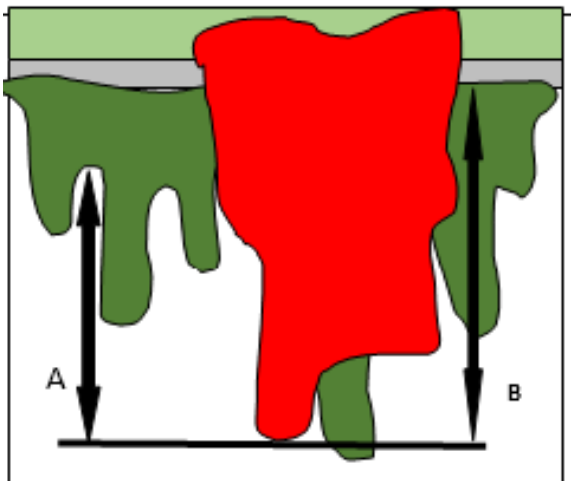

Figure 2. Measurement of tumour thickness and depth of invasion.
A - Depth of invasion
B - Tumour thickness

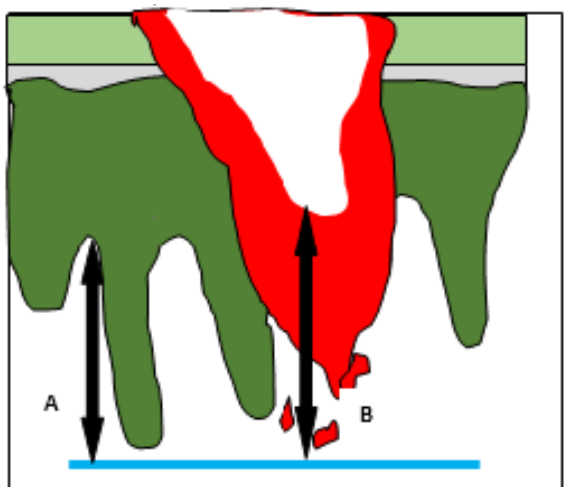

Figure 3. Measurement of tumour thickness and depth of invasion in an ulcerated tumour.
A - Depth of invasion
B - Tumour thickness

Annexure II. Classification of Tumours of the Vulva in 5th edition of WHO classification of Female Genital Tumours, currently in use in 2021.

Epithelial tumours

Benign Squamous lesions

- Seborrheic keratosis
- Condyloma acuminatum

Squamous cell tumours and precursors

- Squamous intraepithelial lesions, HPV-associated, of the vulva
- Vulvar intraepithelial neoplasia, HPV-independent
- Squamous cell carcinoma, HPV-associated, of the vulva
- Squamous cell carcinoma HPV-independent, of the vulva
- Squamous cell carcinoma NOS of the vulva
- Basal cell carcinoma

Glandular tumours and cysts

- Mammary-type glandular lesions
  - Papillary hidradenoma
  - Chondroid syringoma
  - Fibroadenoma
  - Phyllodes tumour
  - Adenocarcinoma of mammary gland type
- Bartholin gland cyst lesions
  - Bartholin gland cyst
  - Bartholin gland hyperplasia, adenoma and adenomyoma
  - Bartholin gland carcinomas
- Other cysts of the vulva

Adenocarcinoma of other type

- Paget disease
- Carcinomas of sweat gland type
- Adenocarcinoma of intestinal type

Germ cell tumours

- Germ cell tumours of the vulva

Annexure III. Classification of Tumours of the Vagina in 5th edition of WHO classification of Female Genital Tumours, currently in use in 2021.

Epithelial tumours

Benign squamous lesions

- Condyloma acuminatum (see tumours of the vulva)
- Squamous papilloma of the vagina
- Atrophy of the vagina
- Tubulosquamous polyp

Squamous cell tumours and precursors

- Squamous intraepithelial lesions of the vagina
- Squamous cell carcinoma, HPV-associated, of the vagina
- Squamous cell carcinoma, HPV-independent, of the vagina
- Squamous cell carcinoma NOS of the vagina

Benign glandular lesions

- Villous adenoma
- Mullerian papilloma of the vagina
- Vaginal adenosis
- Endocervicosis of the vagina
- Cysts of the vagina

Glandular tumours

- Adenocarcinoma, HPV-associated, of the vagina
- Endometrioid carcinoma of the vagina
- Clear cell carcinoma of the vagina
- Mucinous carcinoma, gastric type, of the vagina
- Mucinous carcinoma, intestinal type, of the vagina
- Mesonephric adenocarcinoma of the vagina
- Carcinosarcoma of the vagina

Other epithelial tumours

- Mixed tumours of the vagina
- Adenocarcinoma of Skene gland origin
- Adenosquamous carcinoma of the vagina
- Adenoid basal carcinoma of the vagina

Mixed epithelial and mesenchymal tumours
▪ Adenosarcoma of the vagina
Miscellaneous tumours
▪ Germ cell tumours of the vagina

Annexure IV. AJCC/ TNM 8th edition staging of tumours of the vulva , currently in use in 2021.

* TNM stages are based on clinical and/or pathological classification. FIGO stages are based on surgical staging

* The definitions of the T, N and M categories correspond to the FIGO stages

T = Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ (preinvasive carcinoma)
T1	Tumour confined to vulva or vulva and perineum
T1a	Tumour 2 cm or less in greatest dimension and with stromal invasion no greater than 1.0 mm [a]
T1b	Tumour greater than 2 cm and/or with stromal invasion greater than 1.0 mm [a]
T2	Tumour of any size with extension to adjacent perineal structures – lower third of urethra, lower third of vagina, anus
T3 [b]	Tumour of any size with extension to the following structures: upper 2/3rd of urethra, upper 2/3rd of vagina, bladder mucosa, rectal mucosa or fixed to the pelvic bone

Note:

[a] The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

[b] T3 is not used in FIGO staging.

N = Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis with the following features:
N1a	1 or 2 lymph node metastasis each less than 5 mm
N1b	1 lymph node metastasis 5 mm or greater

N2	Regional lymph node metastasis with the following features:
N2a	3 or more lymph node metastases, each less than 5 mm
N2b	2 or more lymph node metastases, 5 mm or greater
N2c	Lymph node metastasis with extracapsular spread
N3	Fixed or ulcerated regional lymph node metastasis
M = Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis (including pelvic lymph node metastasis)
pTNM Pathological classification	
The pT and pN categories correspond to the T and N categories.	
pN0	Histological examination of an inguinofemoral lymphadenectomy specimen will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative but the number ordinarily examined is not met, classify as pN0.
pM: Distant metastasis	
pM1	Distant metastasis microscopically confirmed
Note: pM0 and pMX are not valid categories.	

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T1/2	N1a/b	M0
Stage IIIB	T1/2	N2a/b	M0
Stage IIIC	T1/2	N2c	M0
Stage IVA	T1/2	N3	M0
	T3	Any N	M0
Stage IVB	Any T	Any N	M1
Note: FIGO no longer includes stage 0 (Tis)			

Annexure V. AJCC/ TNM 8th edition & FIGO staging of carcinoma of vagina, currently in use in 2021.

* TNM stages are based on clinical and/or pathological classification. FIGO stages are based on surgical staging.

* The definitions of the T and M categories correspond to the FIGO stages. Both systems are included for comparison

TNM	FIGO	
T = Primary tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumour confined to vagina
T2	II	Tumor invades paravaginal tissues (paracolpium)
T3	III	Tumour extends to pelvic wall
T4	IVA	Tumour invades mucosa of bladder or rectum, or extends beyond the pelvis
M1	IVB	Distant metastasis
N = Regional lymph nodes		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M = Distant metastasis		
M0		No distant metastasis
M1		Distant metastasis (including pelvic lymph node metastasis)
pTNM Pathological classification		
The pT and pN categories correspond to the T and N categories.		
pN0		Histological examination of an inguinal lymphadenectomy specimen will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative but the number ordinarily examined is not met, classify as pN0.
pM: Distant metastasis		
pM1		Distant metastasis microscopically confirmed
Note: pM0 and pMX are not valid categories.		

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1/2/3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

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CHAPTER 6

Histopathological assessment of gestational trophoblastic neoplasms

Gestational trophoblastic neoplasms (GTN) are malignant lesions that arise from placental villous and extra villous trophoblast. GTN occurs in 1:40,000 pregnancies and is more common in Asia than in Europe or North America.

6.1 Handling and reporting of specimens of gestational trophoblastic neoplasms

6.1.1 Specimen handling [X]

- **Curettings and products of conception**
  - Both samples need to be submitted for histology wrapped in a filter paper, or in a biopsy bag
  - Curettings: The entire specimen needs to be processed
  - Products of conception: Representative sections to be processed
- **Hysterectomy specimen for gestational trophoblastic neoplasms**
  - These include invasive hydatidiform mole, epithelioid trophoblastic tumour, placental site trophoblastic tumour, choriocarcinoma NOS, choriocarcinoma combined with other germ cell elements
  - Hysterectomy specimens need to be received fresh **[Z]**
  - Uterus can be opened in the sagittal plane or coronally according to the preference of the reporting pathologist.
  - Note the presence or absence of parametrial tissue and vaginal cuff
  - Fix the specimen in formalin
  - Photograph the cut surface **[Z]**
  - Identify the designated tumour site: Fundus, anterior wall, posterior wall, lateral walls (specify if known)

6.1.2 Macroscopy

- Specimen type: Curettings / products of conception / hysterectomy specimen depending on the type of surgery
- Specimen size:
  - Curettings and products (in mm)
  - Hysterectomy specimen: measurements include those of the uterine corpus, cervix, ovaries and tubes, and vaginal tissue (if present)
- Tumour size:
  - Maximum tumour dimension (in mm)
  - Other dimensions (in mm)

- Tumour extension: Presence or absence of gross myometrial invasion
- Cervical involvement
- Vaginal involvement
- Uterine serosal involvement
- Parametrial involvement
- Fallopian tube involvement
- Involvement of the ovaries
- Involvement of the broad ligament
- Tumour extension in to other non-genital organs (specify organ)
- Lymph nodes: No regional nodal designation (N classification) in the staging of gestational trophoblastic disease.

6.1.3 Block selection

- Curettings: The entire specimen needs to be submitted
- Products of conception: Representative sections need to be submitted
- Hysterectomy specimen (Figure 1):
  - Select at least four sections from the tumour including,
    - full thickness of the uterine wall,
    - maximum myometrial invasion,
    - section with serosal involvement (if present)
  - One block from the lower uterine segment
  - Cornual blocks when there is an adnexal involvement
  - Parametrial tissue should be blocked in its entirety
  - Two longitudinal blocks from each lip of cervix with entire length of endocervical canal.
  - One or two blocks each of both ovaries and tubes if grossly normal; take adequate blocks if there is macroscopic involvement.
  - One block from vaginal tissue if it is included in the sample and macroscopically normal; take adequate blocks if there is macroscopic involvement
  - Appropriate blocks to sample other abnormalities

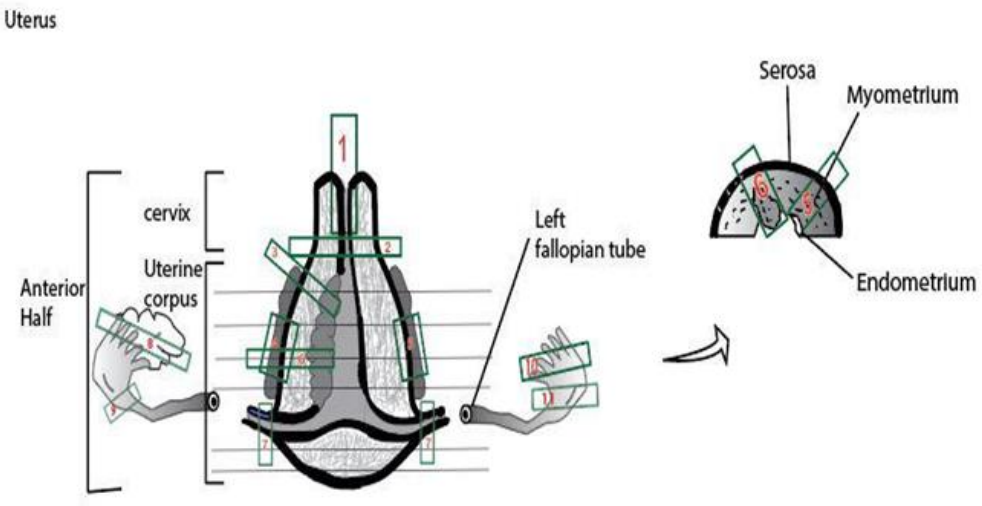

Figure 1. Representative samples to be obtained from a hysterectomy specimen with gestational trophoblastic neoplasm.

- Sample block key:
  1. Sections from cervix
  2. Section from lower uterine segment
  3. Tumour with full thickness of myometrium
  4. Right parametrial shave margin
  5. Left parametrial shave margin
  6. Tumour with maximum depth of myometrial invasion
  7. Right and left cornu
  8. Right ovary
  9. Right fallopian tube
  10. Left ovary
  11. Left fallopian tube

6.1.4 Microscopy and conclusion [X]

Histological tumour type	Refer classification of Gestational Trophoblastic disease in WHO Classification of tumours (5th edition of Female Genital Tumours, currently in use in 2021 - Annexure I)
Microscopic tumour extension	▪ Tumour confined to uterus (pT1) ▪ Tumour extends outside the uterus but limited to the genital structures (pT2) ▪ Tumour extends to other non-genital organs or structures (specify) ▪ Specify organs with separate metastasis and number of metastasis identified
Note: Direct extension or metastasis to any non-genital structure is taken as metastatic disease.	
Resection margins	▪ Margins cannot be assessed ▪ Not involved by tumour ▪ Involved by tumour /specify margins
Lymphovascular invasion	Cannot be assessed / present / absent.
Foetal tissue	Present / absent.
Foetal anomalies	Presence should be reported.
Metastatic disease	Present / absent. If present, specify sites of metastasis

Additional pathological findings	
Ancilliary studies	Refer annexure IV
Pathological tumour stage	Refer annexure II for the 8th AJCC / TNM and FIGO staging currently in use in 2021.
WHO risk scoring system	Refer Annexure III for WHO scoring system currently in use in 2021

6.1.5 Immunohistochemistry [Y]

Refer annexure IV for Immunohistochemistry to differentiate intermediate trophoblastic tumour (ITT) from primary cervical carcinoma and choriocarcinoma.

6.2 Reporting proforma for gestational trophoblastic diseases [X]

Gross description		
Type of specimen	:	
Type of procedure	:	e.g., TAH & BSO, Laparoscopic hysterectomy & BSO
Specimen dimensions	:	▪ Dimensions of the uterus in mm ▪ Dimensions of both ovaries and tubes in mm
Site of tumour	:	
Maximum tumour diameter	:	_____ mm
Additional tumour dimensions	:	_____ mm
Macroscopic tumour involvement in other genital organs	:	
Microscopy and conclusion		
Histological tumour type	:	

Microscopic tumour extension	:	▪ Not applicable ▪ Tumour confined to the uterus ▪ Tumour extends outside the uterus but is limited to genital structures, which includes extension to: o Fallopian tubes o Ovaries o Broad ligament o Vagina o Cervix ▪ Tumour extends to other non-genital organs : Specify organ/s
Margin involvement	:	Present/ absent (specify margin)
Lymphovascular invasion	:	Present / absent
Foetal tissue	:	Note macroscopic and microscopic presence / absence
Foetal anomalies	:	
Metastatic disease	:	Present / absent If present, site/s and number
Additional pathological findings	:	
Ancilliary studies	:	
Provisional pathological Pathological tumour stage	:	TNM / FIGO – see annexure II
WHO risk scoring system	:	Refer annexure III

Annexures

Annexure I. Classification of Gestational Trophoblastic disease in 5th edition of WHO classification of Female Genital Tumours, currently in use in 2021.

- Tumour like lesions
  - Exaggerated placental site reaction
  - Placental site nodule/plaque
- Abnormal non molar villous lesions
- Molar pregnancies
  - Partial hydatidiform mole
  - Complete hydatidiform mole
  - Invasive hydatidiform mole
- Gestational trophoblastic neoplasms
  - Trophoblastic tumour- epithelioid
  - Placental site trophoblastic tumour
  - Choriocarcinoma NOS
  - Choriocarcinoma combined with other germ cell elements

Annexure II. AJCC / TNM 8th edition & FIGO staging (adopted in 1992 and updated in 2002) of primary gestational trophoblastic neoplasms currently in use in 2021.

TNM stages are based on clinical and/or pathological classification. FIGO stages are based on surgical staging.

* The definitions of the T and M categories correspond to the FIGO stages. Both systems are included for comparison

TNM	FIGO	
T = Primary tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1	I	Tumour confined to uterus
T2	II	Tumour extends to other genital structures (ovary, tube, vagina, broad ligament) by metastasis or direct extension
M = Distant metastasis		
M0		No distant metastasis
M1a	III	Metastasis to lungs
M1b	IV	Other distant metastasis

pTNM Pathological classification	
The pT and pN categories correspond to the T and N categories.	
pM: Distant metastasis	
pM1	Distant metastasis microscopically confirmed

Note:

- pM0 and pMX are not valid categories.
- This staging system applies to following categories of Gestational trophoblastic disease:
  - Choriocarcinoma
  - Invasive hydatidiform mole
  - Placental site trophoblastic tumour
- There is no regional nodal designation (N classification) in the staging of gestational trophoblastic tumours.
  - Nodal involvement of these tumours is extremely rare but has an extremely poor prognosis.
  - Any lymph node metastasis should be classified as metastatic (M1b) disease.
- Stage I – IV are subdivided into A & B according to the prognostic score.
- Genital metastasis (vagina, ovary, broad ligament, and fallopian tube) is classified as T2.
- Any involvement of non-genital structures, whether by direct invasion or by metastasis is described using M classification.
- “y" prefix indicates those cases in which classification is performed during or after initial multimodality therapy (neoadjuvant chemotherapy, radiotherapy or both) = ypTNM
- "r" prefix indicates a recurrent tumour when staged after a documented disease-free interval = rTNM
- Additional descriptor - Residual tumour (R):
  Tumour remaining in a patient after therapy with curative intent (e.g., surgical resection for cure) is categorize by a system known as R classification.

Rx	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Annexure III. WHO risk scoring system.

A prognostic scoring index, which is based on factors other than the anatomical extent of disease is used to assign cases to high risk and low risk categories, and these categories are used in stage grouping.

WHO risk factor scoring with FIGO staging	**0**	**1**	**2**	**4**
Age (years)	< 40	> 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval from index pregnancy	< 4 months	4 - 6 months	7 – 12 months	> 12 months
Pretreatment HCG	< 10^3 mIU/ml	> 10^3 – 10^4	> 10^4 – 10^5	> 10^5
Largest tumour size including uterus	-	3 - 4 cm	> 5 cm	-
Sites of metastasis including uterus	Lung	Spleen Kidney	GIT	Brain Liver
Number of metastases identified	-	1 - 4	5 - 8	> 8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

Annexure IV. Immunohistochemistry.

A. Immunohistochemistry to differentiate intermediate trophoblastic tumour (ITT), primary cervical carcinoma and choriocarcinoma:

Note: This table shows the percentage of positivity of each marker.

	CD10	**CK5/6**	**hCG**	**CEA**	**P63**
ITT	100	13	87	33	40
Cervical carcinoma	20	100	10	80	80
Choriocarcinoma	100	-	100	-	70

B. Immunohistochemistry for differential diagnosis of placental trophoblastic neoplasms:

Gestational chorio-carcinoma	Non-gestational chorio-carcinoma	Placental site trophoblastic tumour	Epithelioid trophoblastic tumour	Trophoblastic proliferation in early gestation / complete mole
Diffuse hCG positivity	Diffuse hCG positivity	hCG positivity in multinucleated giant cells	Diffuse p63 positivity	hCG positivity in multinucleated giant cells
Ki67 > 90%	-	Ki67 5 - 10%	Ki67 > 10%	Ki67 < 5%

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