PATHOLOGY AND STAGING CERVICAL AND ENDOMETRIAL CANCER

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MGIMS

WHO HISTOLOGICAL CLASSIFICATION

- **Epithelial tumours**
  - **Squamous tumours and precursors**
    - Squamous cell carcinoma, not otherwise specified
      - Keratinizing
      - Non-keratinizing
      - Basaloid
      - Verrucous
      - Warty
      - Papillary
      - Lymphoepithelioma-like
    - Squamotransitional carcinoma
    - Early invasive (microinvasive) squamous cell carcinoma
    - Squamous intraepithelial neoplasm
    - Cervical intraepithelial neoplasm
    - Cervical squamous carcinoma “in situ ”
    - Benign squamous cell lesions
      - Condyloma accuminatum
      - Squamous papilloma
      - Fibroepithelial polyp

- **Glandular tumours and precursors**
  - Adenocarcinoma
    - Mucinous adenocarcinoma
      - Endocervical
      - Intestinal
      - Signet-ring cell
      - Minimal deviation
      - Villoglandular
    - Endometroid adenocarcinoma
    - Clear cell adenocarcinoma
    - Serous adenocarcinoma
    - Mesonephroid adenocarcinoma
  - Early invasive adenocarcinoma
  - Adenocarcinoma “in situ”
  - Glandular dysplasia
    - Benign glandular lesions

- **Other epithelial tumours**
  - Adenosquamous carcinoma
  - Glassy cell carcinoma
  - Adenoid cystic carcinoma
  - Adenoid basal carcinoma
- **Neuroendocrine tumours**
  - Carcinoid
  - Atypical carcinoid
  - Small cell carcinoma
  - Large cell neuroendocrine carcinoma
- Undifferentiated carcinoma

- **Mesenchymal tumours and tumour-like conditions**
  - Leiomyosarcoma
  - Endometrioid stromal sarcoma, low grade
  - Undefferentiated endocervical sarcoma
  - Sarcoma botryoides
  - Alveolar soft part sarcoma
  - Angiosarcoma
  - Malignant peripheral nerve sheath tumour
  - Leiomyoma
  - Rhabdomyoma

- **Mixed epithelial and mesenchymal tumours**
  - Carcinosarcoma (Malignant mixed Müllerian tumour)
  - Adenosarcoma
  - Wilms tumour
  - Adenofibroma
  - Adenomyoma
- **Melanocytic tumours**
  - Malignant melanoma
  - Blue naevus
- **Miscellaneous tumours**
  - Tumours of germ cell type
    - Yolk sac tumour
    - Dermoid cyst
    - Mature cystic teratoma
- **Lymphoid and haematopoetic**
  - Malignant lymphoma - (specify type)
  - Cervical leukaemia (specify type)
- **Secondary tumours**

PROGNOSTIC FACTORS

	Value
Histopathology	Varying response and prognosis with SCC, adeno, adeno-squamous variants
Grading	Nuclear grade of differentiation could be of progonostic value
EGFR	Cell surface staining of EGFR and cytoplasmic staining of pEGFR are predictive of response and survival
COX-2	Expression may hold value in predicting response and disease-free survival
HPV/p-16	p16 (as a surrogate for HPV infection) or the detection of HPV DNA could be predictive of tumour behaviour, sensitivity and survival
MMP	MMP-2 & MMP-9 could be surrogates for tumour invasiveness and metastatic potential

Test	Value
EMMPRIN	Predictive of invasive and metastatic potential
Cathepsin-B	Predictive of invasiveness and nodal involvement
NF-kB	Predictive of loco-regional and distant failure
CXCR4/CCR7	Predictive of nodal involvement and survival
SCC- Ag (Serum)	Ag Predictive of nodal involvement, response and relapse-free survival
CEA (Serum)	May compliment SCC-Ag
CA-125 (Serum)	Potential value in adenocarcinoma for predicting LN involvement and survival.

General rules for staging

- **T** describes the primary tumor site
- **N** describes the regional lymph node involvement
- **M** describes the presence or otherwise of distant metastatic spread.
- Use of the TNM system can generate a large number of different subcategories. To simplify, therefore, they are grouped together as an anatomical stage classification and given a Roman numeral stage (stage I, II, III, and IV).
- Occasionally prognostic factors other than the anatomical extent of disease are included to develop an anatomical/prognostic group classification.

General rules for staging

- **TNM or cTNM**: pre-treatment extent of disease. Is determined with information collected from examination, laboratory tests, imaging and biopsy.
- **pTNM**: Additional information from surgical excision and pathological examination of the entire primary tumour
- In general TNM is used to determine initial treatment strategy, while pTNM is used to determine the requirement for post surgical adjuvant therapy and follow up.
- Patients should have the clinical stage determined before any treatment commences.
- **yTNM** : If neoadjuvant therapy is given prior to surgical resection, the cTNM or pTNM category is identified by a.
- The **ypTNM** considers only viable tumour cells and not signs of regressed tumour tissue such as scars, fibrotic areas, mucin lakes etc.

ADDITIONAL DESCRIPTORS

- **x:** is used to record the category when T, N cannot be assessed if clinical examination and results of investigations have not been performed or recorded.
- **R** : may be used to describe the extent of residual disease after treatment usually after surgical resection. The additional descriptor **r** describes the extent of disease at time of recurrence (e.g. **r**T0,N1,M0).
- **i and sn**: Isolated tumour cells (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest dimension that are usually detected by immunohistochemistry or molecular methods, but which may be verified with H&E stains. ITCs do not typically show evidence of metastatic activity or penetration of vascular or lymphatic sinus walls. pN0(i+) No regional lymph node metastasis histologically, positive morphological findings for ITC. pN0(mol+) No regional lymph node metastasis histologically, positive non-morphological findings for ITC. Cases with or examined for isolated tumour cells (ITC) in sentinel lymph nodes can be classified with the addition of (sn) suffix

TNM and FIGO Classifications for Cervical Cancer

Primary tumor (T)		
TNM	**FIGO**	**Surgical-Pathologic Findings**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (preinvasive carcinoma
T1	I	Cervical carcinoma confined to the cervix
T1a	IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification

T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension

T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
T4	IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
T4a	IVA	Tumor invades mucosa of bladder or rectum (bullous edema is not sufficient to classify a tumor as T4)
T4b	IVB	Tumor extends beyond true pelvis

Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Distant metastasis (M)		
M0		No distant metastasis
M1		Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal, or para-aortic lymph nodes; and lung, liver, or bone)

Shortcomings of the FIGO Staging System

- Does not consider tumour volume beyond Stage-IIA onwards, though volume of disease can influence local control, survival and may correlate with risk of extra-pelvic metastasis
- Does not regard lymph nodal involvement even though lymph-nodal involvement drastically decreases survival
- Does not regard uterine corpus extension even though uterine corpus extension may be predictive of lymph-nodal involvement and poorer outcome
- Does not take histology into consideration, though non-squamous histologies are associated with poorer response and survival
- Large intra-stage variations can occur, extent of parametrial involvement may be minimal to massive, but still stage remains un-altered.

WHO HISTOLOGICAL CLASSIFICATION OF TUMOURS OF THE UTERINE CORPUS: EPITHELIAL TUMOURS

Endometrial carcinoma

- Endometrial (endometrioid) adenocarcinoma
  - Variant with squamous differentiation (adenoacanthoma).
  - Secretory variant.
  - Ciliated cell variant.
- Mucinous adenocarcinoma
- Serous adenocarcinoma/uterine papillary serous carcinoma (UPSC)
- Clear cell adenocarcinoma
- Mixed cell adenocarcinoma (adenosquamous carcinoma)
- Squamous cell carcinoma.
- Transitional cell carcinoma.
- Small cell carcinoma.
- Undifferentiated carcinoma

- Pleomorphic tumours
- Mesenchymal tumours
- Mixed epithelial and mesenchymal tumours
- Gestational trophoplastic disease
- Miscellaneous tumours

International Federation of Gynecology and Obstetrics (FIGO) histological grading

- Endometrial carcinoma is graded as low grade (well differentiated) or high grade (poorly differentiated), based on histopathology and evaluation of the tumour cell morphology and growth pattern
- Some will also use 3 levels of grading based on histological tumour pattern:

- G1: non-squamous or non-morular solid growth pattern of 5% or less
- G2: non-squamous or non-morular solid growth pattern of 6% to 50%
- G3: non-squamous or non-morular solid growth pattern of more than 50%.

Patient phenotype

Type I endometrial carcinoma

- Most commonly seen in the classical clinical setting of an obese patient with hyperlipidaemia, hyperoestrogenism, insulin resistance, and infertility.
- Also common in women with uterine bleeding and late onset of menopause associated with oestrogen-induced endometrial hyperplasia.
- These lower grade hormone receptor-positive endometrioid cancers more commonly occur in older women

Type II endometrial carcinomas

- More typically arise in atrophic endometrium.
- Associated with p53 mutations.
- More common in black women

Tumour hormone receptor status

Oestrogen receptor (OR) and progesterone receptor (PR) status is only evaluated for potential palliative use of hormonal therapy in advanced or recurrent tumours, but does have prognostic value:

- Presence of progesterone receptors (PR positive)
- Presence of oestrogen receptors (OR positive)
- Clinical response to a trial of progestogen (typically medroxyprogesterone).

TUMOUR BIOMARKER STATUS

Used increasingly in order to sub-classify endometrial carcinoma and for the purposes of treatment and prognosis.

- PTEN (phosphatase and tensin homologue)
- Mismatch-repair genes MLH1, MSH2, MSH6, and PMS2
- p53
- K-ras
- BRCA
- HER-2/neu
- Phospho-AKT is controversial.

TNM Classification for Endometrial Cancer Primary tumour

TNM	FIGO stages	Surgical-pathologic findings
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one half of the myometrium
T1b	IB	Tumor invades one half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus**
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement

	IIIC	**Metastases to pelvic and/or para-aortic lymph nodes**
	IV	Tumor invades bladder mucosa and/or bowel mucosa, and/or distant metastases
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

*FIGO no longer includes stage 0 (Tis)
**Endocervical glandular involvement should only be considered as stage I and no longer as stage II

Regional lymph nodes (N)		
TNM	FIGO stages	Surgical-pathologic findings
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

Distant metastasis (M)		
TNM	FIGO stages	Surgical-pathologic findings
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, or lung, liver, or bone metastases; it excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)

THANK

YOU