Endometrial Carcinoma

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Introduction

The uterus and the ovary are the commonest sites for female genital tract cancer with risk factors for endometrial cancer including obesity, diabetes, nulliparous status, hypertension and late menopause. The majority (>80% of cases) are type I endometrial adenocarcinoma arising as a result of unopposed exogenous or endogenous oestrogens from a background of endometrial hyperplasia, and presenting confined to the endometrium and with a good prognosis. Type II cancers occur in older women, are oestrogen independent and >50% present with extrauterine spread due to early lymphatic dissemination. Prognosis is poor, worsening in the following order: clear cell adenocarcinoma, serous adenocarcinoma and carcinosarcoma.

Most endometrial cancers present with abnormal vaginal bleeding and this is particularly significant in a postmenopausal patient with 88% of patients over 50 years and a peak incidence of 60–64 years of age. Other symptoms include an abdominopelvic mass, feeling of fullness in the abdomen and uterine prolapse. There may also be constipation or urinary frequency. Investigation is by dilatation and curettage under general anaesthetic, but now more commonly outpatient pipelle endometrial sampling. The retrieved fragments are usually very scanty and may require filtering from the formalin fixative. The role of the pathologist is not to phase the endometrium but to comment on whether any functional endometrium is actually represented, and if so, if it is benign, atypical or malignant. Atypical endometrium may represent a false negative sample of a concurrent adenocarcinoma. Investigation also includes transvaginal ultrasound scan which can relate the endometrial stripe thickness to the menopausal status (postmenopausal is usually <5 mm), and detect any focal lesions, e.g. polyps. Hysteroscopy allows direct visualisation of the uterine cavity and more extensive sampling. Transcervical resection of the endometrium (TCRE) is reserved for benign dysfunctional endometria in premenopausal patients. If there are histological features suspicious of or diagnostic of malignancy in biopsy material, MRI scan is used to assess tumour stage, in particular the depth of myometrial invasion, and the presence of cervical or extrauterine involvement. CT scan assesses more distant spread.

A significant proportion of patients with atypical hyperplasia and early stage well differentiated endometrioid adenocarcinoma may respond to progesterone therapy, although this is excluded by radiological evidence of myoinvasive disease. In general treatment of uterine cancers (adenocarcinoma, carcinosarcoma, sarcoma) is by hysterectomy and bilateral

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salpingo-oophorectomy, with peritoneal washings as part of the staging procedure. The surgical approach is often laparoscopic and vaginal. Modified radical hysterectomy (inclusive of vaginal cuff, parametria, omentectomy and limited regional lymphadenectomy) is considered for deeply myoinvasive cancers, those with cervical involvement, or high-grade cancers (serous, clear cell, undifferentiated, squamous cell). They, and cancers with lymphovascular invasion, may also require preoperative chemotherapy and/or post-operative chemoradiotherapy. Occasional locally advanced tumours are not amenable to resection and chemo−/radiotherapy is used as the first line of management. This can result in marked cytological changes, e.g. radiation atypia mimicking serous intraepithelial carcinoma, or taxane induced ring mitoses. Furthermore, significant tumour regression can lead to only microscopic residual foci of tumour masked by a necroinflammatory response, making assessment of pathological stage difficult. Vaginal vault recurrence of uterine cancer is relatively common and treated with further local surgery and/or radiotherapy. A rare, late complication is post irradiation sarcoma or carcinoma, within the field of treatment after a latent period of several years.

Gross Description

Specimen

- Curettage/pipelle sample (on an outpatient basis: some cases are also detected by routine cervical smear)/TCRE chippings.
- Subtotal/total/radical hysterectomy/bilateral salpingo-oophorectomy/limited pelvic lymph node dissection, omentectomy.
- Size (mm) and weight (g).
- Suboptimal fixation of the endometrium in a hysterectomy specimen can make accurate histological assessment problematic. This can be countered by post-surgical injection of formalin with a narrow caliber plastic stylet through the cervical os.

Tumour

Site
- Fundus, body, isthmus. Involvement of the lower uterine segment is unfavourable.

Size
- Length × width × depth (mm) or maximum dimension (mm).

Appearance
- Polypoid/papillary/solid/ulcerated/infiltrative/necrotic/haemorrhagic.
- Malignant mixed mesodermal tumours are typically fundal and polypoid in an elderly patient and may protrude inferiorly through the internal cervical os.

Edge
- Circumscribed/irregular.

Extent
- Infiltration endometrium, myometrium, serosa, cervix, parametrium.

Adjacent Endometrium
- Atrophic, hyperplastic, polypoid.

Histological Type

The vast majority of uterine cancers are *adenocarcinoma of two main types,* although there is overlap between the categories

- *Type I (prototype: endometrioid adenocarcinoma):* peri-/postmenopausal, low parity, high socio-economic status, obesity, diabetes, hypertension, hyperoestrogenism (hormonal therapy, endogenous or secreting tumour, e.g. ovarian sex cord-stromal), ER positive, background endometrial hyperplasia. Microsatellite instability/PTEN (phosphatase and tensin homologue) mutations.
- *Type II (prototypes: serous and clear cell adenocarcinomas, carcinosarcoma):* older patients, more aggressive, atrophic endometrium with precursor serous endometrial intraepithelial carcinoma (EIC), ER±. p53 mutations.

A minority of endometrial cancers are *familial*, or associated with *hereditary non-polyposis colorectal cancer (HNPCC)* where incidence (2%) approximates that of bowel cancer. Adenocarcinoma is usually of endometrioid type, but distinctive clues to these microsatellite unstable cancers are tumour in the lower uterine segment and of undifferentiated morphology with a prominent infiltrate of peri-/intratumoural lymphocytes (TILs). This can be further explored with mismatch repair immunohistochemistry. Significance as to prognosis is uncertain. Cumulative dose of *tamoxifen in patients with breast cancer* is also a risk factor for endometrial carcinoma.

Endometrioid Adenocarcinoma

- *70–80% of cases.*
- Typical: low-grade well differentiated endometrial type glandular pattern, in perimenopausal patients, and due to unopposed oestrogenic drive ± adjacent endometrial hyperplasia.
- Variants:
  – *With squamous differentiation*—up to 30% of cases. The tumour is graded on the glandular component as it can be difficult to tell if the squamous cell element is benign or malignant. Where both elements are well differentiated the previous designation of adenocanthoma is now rarely used.
  – *Secretory carcinoma*—the cells resemble secretory endometrium.
  – *Ciliated carcinoma*—rare, the cells resemble tubal epithelium.
  – *Villoglandular carcinoma*—low-grade, well differentiated and papillary. Exclude high-grade serous carcinoma (high-grade nuclear characteristics with a tufted papillary pattern).
  – *Sertoliform carcinoma.*

Serous (Papillary) Adenocarcinoma

- *5–10% of cases.*
- *High-grade* in the elderly and de-novo with no adjacent hyperplasia but associated with *serous EIC.*

- Typically shows *disproportionate lymphovascular/myometrial invasion* and *omental spread* relative to the amount of endometrial disease. This means that EIC or stage I serous carcinoma can be associated with *extensive extra-uterine spread* and present as a *primary peritoneal serous adenocarcinoma* but no clinically or radiologically obvious uterine or ovarian mass lesion.
- Potentially *multifocal* with extrauterine lesions e.g. ovary, fallopian tube.
- High-grade nuclear characteristics, usually a papillary pattern but occasionally tubuloglandular.
- Necrosis and psammoma bodies are often seen. p53 typically mutated (immunochemistry either overexpressed or "null" type), HER2, p16, PTEN, HMGA2 and Ki-67. ER ±/PR-. It is also WT-1 negative in distinction from ovarian papillary serous adenocarcinoma which is positive and this is a useful feature in differential diagnosis and staging.
- *Poor prognosis* with *30% 5 year survival.*

Clear Cell Adenocarcinoma

- *1–5% of cases;* postmenopausal. Not related to diethylstilboestrol and *aggressive* with myometrial invasion.
- >50% of the cells are clear cell, mixed solid/glandular/tubulocystic/papillary architecture.

Mucinous Adenocarcinoma

- >50% cells have stainable mucin.
- *Usually low-grade, minimally invasive and good prognosis.*
- Distinguish from cervical adenocarcinoma by differential biopsy/curettage, and exclude a gastrointestinal primary (clinical history, CK20/CDX-2 positive/CK7 negative).

Squamous Cell Carcinoma

- In old age often with cervical stenosis and pyometra; exclude spread from a cervical carcinoma.

Mixed

- Second component is >10% of the tumour area, e.g. composite endometrioid/serous/clear cell adenocarcinoma. Any carcinoma with *5–10% serous characteristics* tends to behave more aggressively and should be designated as such. Adenocarcinoma with squamous cell differentiation is excluded. Adenosquamous carcinoma (where both components are obviously malignant) is a mixed lesion with a poor prognosis.

Undifferentiated Carcinoma

- Small cell/not otherwise specified: *aggressive.*
- Spread from a cervical primary or lung primary must be excluded in small cell carcinoma.
- It can be difficult to distinguish between *high-grade endometrioid, serous and undifferentiated uterine carcinomas* and more recognisable foci should be sought with additional tissue blocks. *Undifferentiated carcinoma* shows a sheeted dyscohesive pattern of large, monomorphic, mitotically active cells sometimes with rhabdoid cells, giant cells, necrosis and myxoid stroma. It lacks a minor component of more usual serous or endometrioid cancer and is only focally cytokeratin positive. More than *50% present with advanced stage* and *ultimately fatal disease.* Occasional cases are in younger patients, in the lower uterine segment and associated with DNA mismatch repair abnormalities.

Malignant Mixed Müllerian Tumours (MMMT)

- *Low-grade malignancy:* adenosarcoma; carcinofibroma. Both are rare.
- *High-grade malignancy:* carcinosarcoma/sarcomatoid carcinoma is a carcinoma comprising either serous or endometrioid endometrial adenocarcinoma with a *biphasic pattern* and component of vimentin/cytokeratin positive malignant spindle cells. Lesions can be either *homologous* or *heterologous* (containing tissues alien to the uterus, commonly immature/malignant cartilage, striated muscle, bone). Those tumours with heterologous elements have a worse prognosis than those where the mesenchymal component is homologous. Carcinosarcoma is the commonest malignant mixed tumour and 50% contain heterologous elements. It is considered a malignancy of epithelial origin and staged as other endometrial carcinomas (see section "Other Pathology" for further discussion).

Metastatic Carcinoma

- *Direct spread:* cervix, bladder, rectum.
- *Distant spread:* infiltrating lobular breast carcinoma, kidney, malignant melanoma, stomach, pancreas. The commonest are breast, stomach, colon and pancreatic carcinomas. Often myometrial with an endometrial component, metastases can mimic primary endometrial disease e.g. infiltrating lobular breast carcinoma (endometrial stromal sarcoma), renal carcinoma (clear cell adenocarcinoma), and colorectal carcinoma (mucinous adenocarcinoma). A relevant *clinical history* and *comparison with previous histology* are crucial in making the distinction. Metastases should be considered in any endometrial cancer of unusual appearance, multinodular growth pattern, with prominent lymphovascular involvement or lack of precancerous endometrial changes.

Differentiation

- FIGO grade 1/2/3 for endometrioid adenocarcinoma. Based on architectural and nuclear features.

The glandular component of endometrioid adenocarcinomas is graded 1 (<5%), 2 (6–50%), and 3 (>50%) based on the proportion of non-squamous, non-morular solid growth pattern

(figures in parenthesis indicate percentage solid component for that grade). The presence of high grade nuclear features in >50% of the tumour raises the overall grade by 1 of architecturally grade 1 and 2 tumours: nuclear grade 1 (oval nuclei, even chromatin, inconspicuous nucleolus, few mitoses) and nuclear grade 3 (irregular, rounded nuclei, prominent nucleoli, frequent mitoses). Nuclear grade 2 is intermediate between grades 1 and 3. Some cancers show grade heterogeneity indicative of tumour progression. In tumours with squamous cell differentiation, grading is based on the glandular component. Serous, clear cell, carcinosarcoma and undifferentiated carcinomas are automatically considered overall grade 3 with nuclear grade taking precedence over architecture. Mucinous carcinomas are generally grade 1. There may be a discrepancy in grading between biopsy and resection material and a provisional grade is often provided on initial material.

Extent of Local Tumour Spread

- Border: pushing/infiltrative.
- Lymphocytic reaction: prominent/sparse.

Endometrium

- *EIN (endometrial intraepithelial neoplasia)* is an umbrella term encompassing and highlighting the diagnostic difficulties there are in distinguishing between entities on the overlap spectrum of complex endometrial hyperplasia with atypia, and, intra-endometrial adenocarcinoma. Progression along this spectrum is characterised by increased *glandular crowding and complexity*, *intraglandular necrosis* and *cytological atypia* with *reduction in intervening stroma*. An important differential diagnosis is a benign mimic with focal glandular crowding e.g. endometrial polyp (look for covering epithelium and prominent vascular stroma with thick walled vessels). Another possible consideration is atypical polypoid adenomyoma arising from the isthmus in younger patients (look for a glandular proliferation in abundant smooth muscle).
- *EIC (endometrial intraepithelial carcinoma)* is effectively serous adenocarcinoma in situ of the endometrial surface epithelium and is present *adjacent to or overlying 90% of serous adenocarcinomas*. p53 is typically mutated (either overexpressed or "null" type) and the Ki-67 proliferation index is high. It is also occasionally seen with clear cell carcinoma and even extrauterine peritoneal disease in the absence of invasive endometrial cancer.
- *EIN* and *EIC* are to be distinguished from the range of relatively commonly occurring *endometrial metaplasias* and *reactive epithelial changes*. These include ciliated tubal, mucinous, squamous morular and intestinal metaplasias, and surface syncytial, papillary, eosinophilic and clear cell changes.

Myometrium

- Proportion of wall involved <50%, ≥50%.
- If ≥50% on MRI scan a radical hysterectomy is considered. Outer myometrial involvement is seen in about 25% of cases.

Extent of myometrial invasion relates to the histological type and grade of carcinoma. True myometrial invasion must be distinguished from both a normal irregular outline or expansion of the endo-/myometrial junction (look for a continuous line of myometrial vascular structures in a compressed atrophic myometrium), and, abnormal epithelium in pre-existing adenomyosis (look for periglandular endometrial stroma—CD10 positive). Invasive stromal desmoplasia and inflammation are useful diagnostic clues although often not present in carcinoma. Alternative patterns of invasion should also be considered e.g. diffuse along a broad pushing front, or, MELF (microcystic, elongated, fragmented). Endometrial/myometrial junction and endometriosis containing carcinoma usually have a broad or lobulated front and smooth outline associated with native endometrial stroma. To some extent this dilemma is superseded by FIGO staging with stage I disease

encompassing any carcinoma confined to the endometrium or up to <50% of the myometrium. An approximate landmark for the latter is invasion less than or beyond the myometrial vascular arcuate plexus. Occasionally a patient is a non-operable surgical candidate due to co-morbidity and a TCRE specimen is provided—assessment of myoinvasion can be problematic due to the random orientation of the chippings.

Serosa

- Distance (mm) of the deepest point of invasion from the nearest serosal surface. Direct serosal spread is relatively unusual but is associated with a 40% 5 year survival rate and a tendency for recurrences in extra-abdominal sites.

Vagina

- Vaginal recurrences are not uncommon and treated by further local surgery or radiation therapy. The rare situation of clinical presentation of endometrial carcinoma with a vaginal metastasis is adverse with a median survival of 1–2 years.

Parametrium

- Parametrial involvement either by direct extension or lymphatic invasion is an *indicator of poor prognosis*. It can only be assessed when there has been a modified radical hysterectomy, i.e. for a preoperative diagnosis of a high-grade cancer or where imaging has suggested cervical or deep myometrial involvement.

Endocervix/Exocervix

- *10% of cases* usually by direct invasion, lymphatic spread or occasionally by implantation following curettage. *Stromal invasion* increases the *risk of pelvic lymph node metastases.* It must not be confused with post biopsy or cut-up arti-

factual 'carry-in', florid reactive changes following biopsy sampling or curettage, or other benign mimics of neoplasia, e.g. mesonephric remnants or tuboendometrial metaplasia. There is considerable interobserver variation in assessing whether there is tumour involvement of endocervical glands versus cervical stroma. Distinction between an *endometrial* and *cervical origin for a tumour* can be difficult clinically, radiologically and histologically in curettage samples. Some reliance is placed on the *nature of the tissue from which the carcinoma appears to be arising,* e.g. dysplastic cervix or hyperplastic endometrium. *Immunohistochemistry* may also be of help in *low-grade adenocarcinomas* in that uterine endometrioid adenocarcinoma is usually vimentin/ER positive and CEA negative while cervical adenocarcinoma shows the reverse. In addition, p16 antibody also stains more strongly in cervical adenocarcinoma. Alternatively with high-grade or undifferentiated carcinoma endometrial lesions may be p53+/p16− and cervical cancers the reverse. Cervical squamous carcinoma may also be strongly p63 positive.

Fallopian Tubes/Ovaries

- Either by direct extension or metastatic spread. Lymphovascular invasion favours the latter. If extrauterine disease is confined to the ovaries or fallopian tubes 5 year survival is still relatively favourable at 75%.

Omentum

Involved/Not involved.

FIGO

FIGO staging is recommended and applicable to uterine carcinoma and carcinosarcoma.

I Tumour confined to the corpus:
A. Invades endometrium or less than half of the myometrium
B. Invades half or more of the myometrium

II Tumour invades cervical stroma but does not extend beyond the uterus

III Local and/or regional lymph node tumour spread:

    A. Invades uterine serosa and/or adnexa(e)

    B. Vaginal and/or parametrial involvement

    C. Metastasis to pelvic (C1) and/or para-aortic (C2) lymph nodes

IV Tumour invades:

    A. Bladder and/or bowel mucosa[a] and/or

    B. Distant metastases including intraabdominal and/or inguinal lymph nodes

[a]Requires histological confirmation by biopsy. Invasion of the rectal wall or bladder wall is pT3. Positive peritoneal cytology is reported separately without changing the stage. "Frozen pelvis" is a clinical term meaning tumour extension through the parametrium to the pelvic wall(s) i.e. IIIB (Figs. 24.1, 24.2, and 24.3)

Lymphovascular Invasion

- Present/absent.
- Intra−/extratumoural. Usually at the invasive front of the carcinoma.
  - Seen particularly in *serous* and deeply *myoinvasive endometrioid adenocarcinomas.* Lymphovascular invasion in the outer myometrium is an adverse prognostic indicator but it does not upstage an otherwise superficially invasive (FIGO IA) carcinoma.
  - Beware vascular *pseudoinvasion* in laparoscopic hysterectomy (LAH) specimens and autolysis related cut-up *smear artifact.* It can also be difficult to separate true lymphovascular invasion from intramyometrial peritumoural *retraction artifact*. These distinctions are important as *lymphovascular invasion* is an *indicator for postoperative adjuvant therapy*. The presence of red blood cells, a perivascular lymphocytic infiltrate and a demonstrable endothelial lining (CD34, D2–40) are useful pointers. True vascular invasion is also unusual in early stage low-grade cancers. Note that it can also be mimicked by the cystic spaces (lined by epithelium rather than endothelium) of the MELF (Microcystic Elongated and Fragmented) pattern of myometrial invasion.

Lymph Nodes

Site/number/size/number involved/extracapsular spread.

Regional nodes: pelvic (obturator and internal iliac), common and external iliac, parametrial, sacral and para-aortic. A regional lymphadenectomy will ordinarily include a minimum of 10 lymph nodes.

The commonest sites of *extrauterine spread* are the *regional lymph nodes* and *ovaries.* Lymph node disease relates to the tumour grade, type, depth of invasion and lymphovascular involvement. *Invasion of the outer third of the myometrium* is associated with *lymph node metastasis in up to 33% of cases*. Pelvic and para-aortic lymph node metastases are associated with 65–85% and 35–45% 5 year survivals respectively. Initial spread is to pelvic lymph nodes but there can be skip metastasis to involve para-aortic lymph nodes alone. *Recurrences* are in the pelvis and vaginal vault. High-grade serous carcinoma tends to show extensive omental and pelvic disease. *Distant metastases* of uterine carcinoma are to lung, liver, bone, central nervous system and skin of the scalp.

Excision Margins

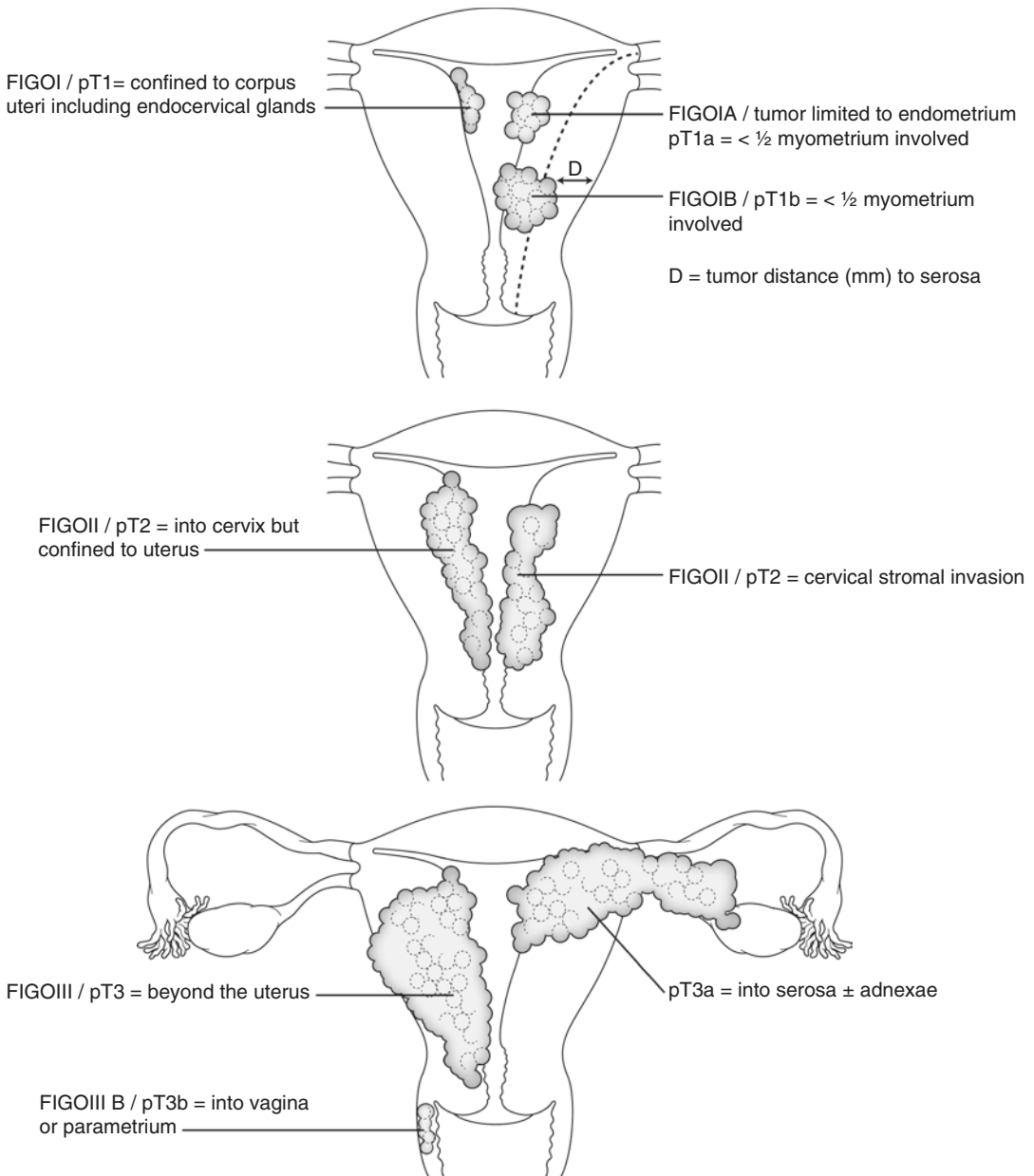Distances (mm) to the serosa, tubal and inferior vaginal limits.

Other Pathology

Uterus

- *Polyp(s), hyperplasia (simple, or, complex with architectural ± cytological atypia), adenomyosis.*

Carcinoma occasionally develops within a preexisting *endometrial polyp* although this is increased in *tamoxifen therapy* (see below). It can be of either usual low-grade endometrioid or high-grade serous type.

FIGOI / pT1= confined to corpus
uteri including endocervical glands

FIGOIA / tumor limited to endometrium
pT1a = < ½ myometrium involved

FIGOIB / pT1b = < ½ myometrium
involved

D = tumor distance (mm) to serosa

FIGOII / pT2 = into cervix but
confined to uterus

FIGOII / pT2 = cervical stromal invasion

FIGOIII / pT3 = beyond the uterus

pT3a = into serosa ± adnexae

FIGOIII B / pT3b = into vagina
or parametrium

Fig. 24.1 Uterine carcinoma. Reproduced, with permission, from *Histopathology Reporting: Guidelines for Surgical Reporting*, *2nd ed.*, © 2006, Springer

About *25% of untreated atypical hyperplasias progress to adenocarcinoma* and up to *40% are associated with concurrent disease*. Features favouring *adenocarcinoma* over complex hyperplasia with cytological atypia are: *intraglandular epithelial bridges, stroma free papillary and cribriform epithelial patterns, intraglandular* *polymorphs and necrosis, cytological atypia, mitoses and stromal elimination and invasion.* Criteria for stromal invasion include: a. irregularly infiltrating glands associated with a fibroblastic or desmoplastic response, and/or, b. extensive papillary or confluent glandular (cribriform) growth patterns. Stromal and superficial

TNM: **T4**
FIGO: IVA
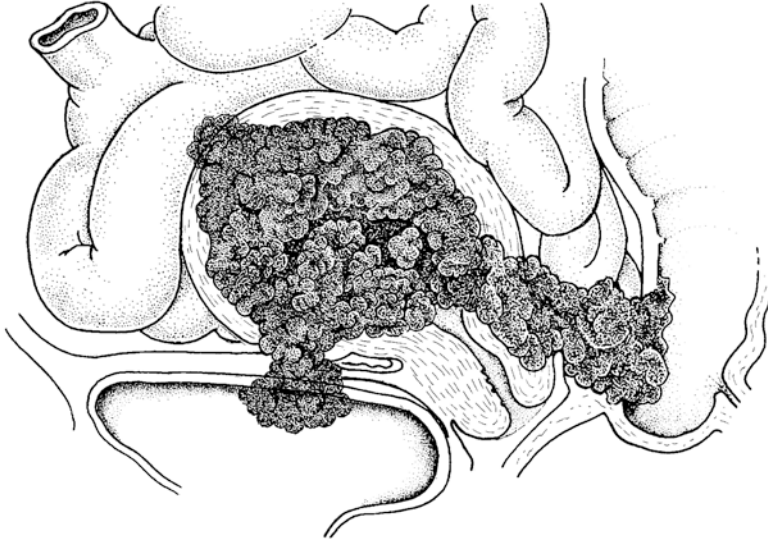
Tumour invades
bladder mucosa
and/or bowel mucosa

Fig. 24.2 Uterine carcinoma. Reproduced, with permission, from *TNM Atlas: Illustrated guide to the TNM/pTNM classification of malignant tumours, 5th ed.*, © 2005, Springer-Verlag

Fig. 24.3 Uterine carcinoma: regional lymph nodes. Reproduced, with permission, from *TNM Atlas: Illustrated guide to the TNM/pTNM classification of malignant tumours, 5th ed.*, © 2005, Springer-Verlag

Para-aortic

Common iliac

Lateral sacral

External iliac

Hypogastric
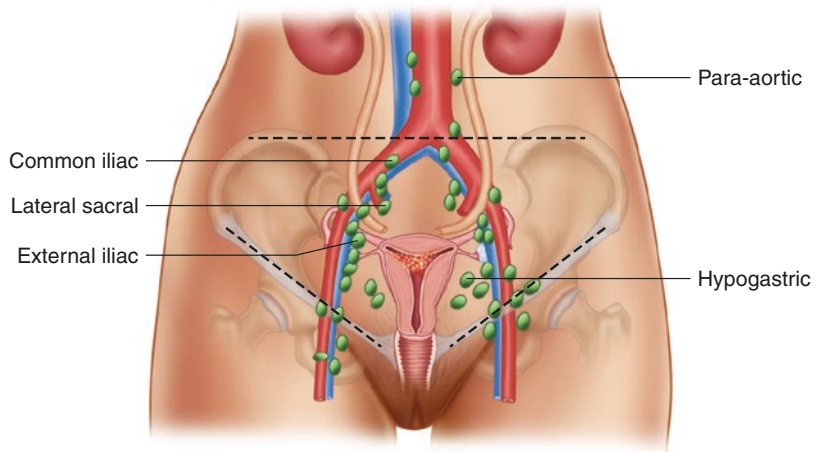
myometrial invasion are useful in distinguishing between intra-endometrial and invasive adeno-carcinoma in curettage specimens. Inhabitation of *adenomyosis* by complex hyperplasia or ade-nocarcinoma usually shows circumscribed foci with surrounding native endometrial stroma.

Ovary

- *Thecoma* and *granulosa cell tumour:* can result in oestrogenic drive to the endometrium resulting in simple or complex hyperplasia, or adenocarcinoma.

- *Accompanying ovarian carcinoma*: this is seen in 5–10% of endometrial carcinomas. Distinction between *synchronous primary lesions* and *ovarian secondaries* rests on the latter being bilateral, multinodular, often serosal and with ovarian stromal lymphovascular invasion. The uterine primary will usually be high-grade with deep myometrial and lymphovascular invasion. There is a higher frequency of *concurrent early stage primaries in endometrioid adenocarcinoma of the uterus and ovary (25%)* than in the other cancer subtypes.

Other Comments

Tamoxifen effects: tamoxifen related polyps, hyperplasia, adenocarcinoma, adenosarcoma, carcinosarcoma. Tamoxifen is an anti-oestrogen but has paradoxical oestrogenic effects on the endometrium leading to an increased frequency of a range of endometrial neoplasms some of which are prognostically adverse. Polyps can be large, multiple, necrotic, have areas of glandular, papillary or clear cell metaplasia, and may even harbour adenocarcinoma, often serous in type.

Carcinosarcoma: is often polypoid at the fundus of an elderly patient with deep myometrial and lymphovascular invasion. About *30% present with stage III/IV disease.* The carcinomatous component is usually *high-grade glandular* (endometrioid, clear cell, serous or undifferentiated), and the *sarcomatous element homologous* (cf. endometrial stroma, leiomyosarcoma, fibrosarcoma) or *heterologous* (striated muscle, cartilage, bone, fat). Heterologous elements portend a worse outcome. Immunohistochemistry for epithelial and mesenchymal markers, e.g. desmin may be necessary to confirm the diagnosis. This *aggressive neoplasm has a 20–40% 5 year survival.*

Adenosarcoma: the majority (80%) of adenosarcomas arise in the postmenopausal endometrium. They are polypoid with proliferative type glands and usually homologous stromal type sarcoma distributed in a condensed periglandular cambium layer. *Recurrence (30%)* relates to

mitoses, stromal overgrowth and myoinvasion in this *low- to intermediate-grade malignancy*.

Immunophenotype

Endometrioid adenocarcinoma usually co-expresses cytokeratins (7, 8, 18, 19) and vimentin. Oestrogen and progesterone marking is common relating to histological type and grade, and is of some use in assessing potential response to hormonal therapy in disseminated disease. CEA stains weaker than in cervical carcinoma. The squamous morules seen in endometrioid carcinoma stain positively with CDX-2. In contrast to grade 3 endometrioid adenocarcinomas, high-grade *serous adenocarcinomas* over express p53, p16, PTEN, HMGA2 and may be negative for ER/PR. These immunoprofiles may be of use in distinguishing high-grade endometrioid adenocarcinoma from serous adenocarcinoma with a tubuloglandular pattern. Uterine serous adenocarcinoma is also WT1 negative in contrast to ovarian serous adenocarcinoma. DNA aneuploidy is an index of high-grade, advanced stage tumours and over expression of Ki-67, p53 and HER2 (20–40% of cases) is adverse.

Prognosis

Radical hysterectomy is considered for endometrial carcinoma if there is ≥50% myometrial invasion with grade 2 or 3 histology, invasion of the cervix, undifferentiated, clear cell or serous adenocarcinoma, lymphovascular invasion or suspicious lymph nodes on CT scan. *Preoperative adjuvant chemo−/radiotherapy* may also be used in these circumstances. *Intraoperative frozen section* of suspicious lymph nodes is an important prequel to radical resection, and if positive a more conservative approach adopted.

Overall 5 year survival for endometrial carcinoma is *80–85%* with *type I* oestrogen-related cases arising from a background of hyperplasia typically presenting with stage I disease, and doing better than *type II* non-oestrogen-dependent lesions *(30–70% 5 year survival).* Serous,

undifferentiated, squamous cell and clear cell carcinomas are more aggressive than equivalent stage endometrioid tumours. *Lymphovascular invasion,* which correlates with progressing tumour grade, myometrial invasion and stage (cervical and extra-uterine spread), is an *adverse prognostic factor* (70–75% 5 year survival). Prognosis also relates strongly to *tumour stage:* I, 82–95% 5 year survival; II, 60–80%; III, 30–50%. *Tumour grade* has an influence in that grade 1 tumours (87% 5 year survival) fare better than grade 3 (58% 5 year survival).

Other Malignancy

Endometrial stromal lesions can be benign (stromal nodule) or malignant, the latter having infiltrating margins. Biopsy or curettage samples impose limitations in making this assessment, which is more appropriately done on a hysterectomy specimen.

Endometrial Stromal Sarcoma

- A *low-grade malignancy resembling endometrial stroma* (stromal cells/spiral arteriole vascular pattern) with infiltrative margins and variable mitoses (usually <5–10/10 high-power fields). Shows characteristic *lymphovascular invasion* (previously called endolymphatic stromal myosis). It comprises 20% of uterine sarcomas and 2% of uterine malignancies. An *80–90% 5 year survival rate* if confined to the uterus, but prone to *local pelvic or abdominal recurrence (30%) after a lag period of many years,* and may cause pressure effects, e.g. hydronephrosis. *High stage tumours* have a *40% 10 year survival rate.* Sometimes hormone responsive to adjuvant progesterone therapy.

Undifferentiated Uterine Sarcoma

- Previous and current alternate designation as high-grade endometrial stromal sarcoma.

Characterised by cellular pleomorphism, mitoses (>10/10 high-power fields) and destructive myometrial invasion with infiltrating margins and aggressive behaviour. *Size of tumour (>4 cm)* and *extrauterine extension* are adverse indicators in low- and high-grade lesions. Treatment is surgical although there is some evidence for partial response to chemotherapy and hormonal manipulation in metastatic disease.

FIGO staging for uterine sarcomas

I	Tumour confined to the uterine corpus
	A. ≤5 cm
	B. >5 cm
II	Tumour extends beyond the uterus, within the pelvis
	A. To adnexa(e)
	B. To extrauterine pelvic tissues
III	Tumour invades abdominal tissues
	A. One site
	B. Two sites
	C. Regional lymph nodes
IV	Tumour invades:
	A. Bladder and/or rectum
	B. Distant metastases.

Immunophenotype of mesenchymal tumours: endometrial stromal sarcomas are CD10, WT1, ER, PR and vimentin positive. Up to 50% are desmin positive but they are h-caldesmon negative. Low-grade lesions also preserve a pericellular reticulin pattern. Differential diagnosis of endometrial stromal sarcoma is leiomyomatous tumour (strongly desmin/h-caldesmon positive ± CD10), and that of undifferentiated uterine sarcoma is undifferentiated carcinoma (cytokeratin, EMA positive).

Leiomyomatous Tumours

- *Malignancy relates to a combination of:*
  - Infiltrative margins.
  - Cellular atypia.
  - Coagulative tumour cell necrosis.
  - Mitoses >10/10 high-power fields.
  - Leiomyosarcoma (1–3% of uterine malignancies/40–50% of uterine sarcomas) is usually a high-grade lesion with a bulky

mass, satellite nodules, areas of necrosis and variably poor outlook (20–70% 5 year survival). Surgical excision with or without adjuvant chemotherapy is the mainstay of treatment. Variants are typical (spindle cells), epithelioid and myxoid. Tumour cells are smooth muscle actin, desmin, h-caldesmon, calponin and vimentin positive with cross reactivity for cytokeratin (CAM 5.2) and variable ER expression.

- *Uncertain malignant potential:*
  - Cellular atypia and mitoses 5–10/10 high-power fields indicate probable malignancy if the atypia is moderate or severe.
- *Cellular leiomyoma:*
  - Benign; identify thick walled vessels and strong desmin positivity to distinguish from an endometrial stromal tumour.
- *Mitotically active leiomyoma:*
  - Benign if no significant cytological atypia, abnormal mitoses or coagulative tumour cell necrosis.
- *Cell type:*
  - Myxoid and epithelioid leiomyosarcomas have less tumour cell necrosis, cytological atypia and mitotic activity. Relatively bland myxoid lesions can locally recur and metastasise. An infiltrative growth pattern is a useful diagnostic feature.
- *Beware pseudomalignancy:*
  - Bizarre *symplastic leiomyoma*. Benign if the symplastic nuclear change is focal, the mitotic count is low (<3/10 high-power fields) and coagulative tumour cell necrosis is absent.
  - Changes after *gonadotrophin analogue treatment*, *viz.* haemorrhage and necrosis, symplastic type nuclear atypia and apparent hypercellularity. Extensive coagulative necrosis after uterine artery embolisation can also confuse, but other features of malignancy such as atypia and mitoses are usually absent.
  - *Intravenous leiomyomatosis* with vascular invasion and "metastases" but not malignant.

Choriocarcinoma/Placental Site Trophoblastic Tumour (PSTT)

- After abortion, normal or molar pregnancy.
- See Chap. 28.

Malignant Lymphoma/Leukaemia

- See Chap. 25.

Others

- Haemangiopericytoma, angiosarcoma, soft tissue sarcomas and germ cell tumours are all rare.

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