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Solid Tumour Section

Review

Uterus Tumours: an Overview

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Identity

Note

Anatomically, uterine neoplasms may be localized at the corpus, isthmus (the transition between the endocervix and uterine corpus) and cervix. The fallopian tubes and uterine ligaments may also undergo tumour tranformation. This overview will focus on uterine cervix and corpus tumours, including benign, pre-malignant and malignant lesions. They may affect the endometrium, muscles or other supporting tissue. Uterine tumours may be histologically typed according to several classification systems. Those used most frequently are based on the WHO (World Health Organization) International Histological Classification of Tumours and on the ISGYP (International Society of Gynecological Pathologists). The most widely-accepted staging system is the FIGO (International Federation of Gynecology and Obstetrics) one.

Classification

According to WHO recommendations, the main UTERINE CERVIX categories are:
- Epithelial tumours,
- Mesemchymal tumours,
- Mixed epithelial and mesenchymal tumours,
- Secondary tumours.

The main UTERINE CORPUS categories, once again according to WHO recommendations, are:
- Epithelial tumours,
- Mesenchymal tumours,
- Mixed epithelial and mesenchymal tumours,
- Trophoblastic tumours,
- Secondary tumours.

Clinics and pathology

Note

Female pelvic gynaecological malignancies account for almost 15% of all cancers in women. Uterine cancer is the most common, specifically endometrial cancer of the uterine corpus.

UTERINE CERVIX NEOPLASIA

Note

In countries that have well-developed screening programs using the Papanicolaou smear test to detect premalignant lesions, the incidence of invasive cervical cancer continues to decline. Age-standardised incidence rates vary from about 10 per 100,000 in most developed countries to more than 40 (up to 100) per 100,000 in many of the developing countries. Worldwide, invasive cervical cancer is the second most common female malignancy after breast cancer, with 500,000 new cases diagnosed each year. Among benign lesions, endocervical polyps are the most common, while among malignant lesions, account for approximately 90%, and adenocarcinomas for approximately 10% of cervical cancers. Due to considerable ongoing evolution in understanding the pathobiology of cervix precursor lesions, there is a lack of uniform clinical, cytological and histological terminology, the most widely accepted being the modifications incorporated into the Bethesda System of cytological diagnosis.

Etiology

Carcinomas of the uterine cervix are thought to arise from precursor lesions, and different subtypes of human papilloma virus (HPV) are major etiological factors in disease pathogenesis. Only certain types of

HPV cause cervical cancer: HPV 16, 18, 33, 35, 45, 56, called "high-risk" types, are associated with high-grade Squamous Intraepithelial Lesions (SIL) and invasive carcinomas, whereas "low- risk" HPV 6, 11, 42, 44 are associated with genital condyloma and low-grade SIL. 5% of cervical cancers are HPV DNA-negative.

Epidemiology

Epidemiologic studies report that factors increasing the likelihood of exposure to HPV, such as young age at first intercourse, a large number of sexual partners, race, high parity and low socioeconomic status, favour cervical cancer development. Latin America, the Caribbean, southern Asia, Southeast Asia, and sub-Saharan Africa are areas with the highest incidence.

Clinics

Early cervical cancer is usually asymptomatic. Approximately 80-90% of patients with cervical cancer experience abnormal vaginal bleeding. HPV causes a large spectrum of lesions ranging from relatively benign condyloma acuminatum to invasive squamous cell carcinomas.

Pathology

Epithelial neoplasia:

Endocervical polyp is the most common benign lesion found in the uterine cervix. It appears as a focal hyperplastic protrusion of the endocervical folds, including the epithelium and the stroma. Microscopically, a variety of histologic patterns are observed, depending on the prevalence of the tissue type. In situ or invasive carcinomas do not usually arise from this lesion.

Fibroepithelial polyp, or stromal polyp, is a benign exophytic proliferation of the cervical stroma. It is composed of stellate-shaped cells growing chaotically, covered by stratified squamous epithelium, and is often seen in pregnant women.

Microglandular hyperplasia is a common cervical lesion associated with oral contraception or with pregnancy in young women.

Squamous intraepithelial lesion (SIL) is a precursor of squamous cell carcinoma and usually remains inactive for more than 20 years before it becomes invasive. SIL usually affects the transformation zone near the endocervical epithelium.

Three different diagnostic systems are used:

- CIN (Cervical Intraepithelial Neoplasia, CIN I, CIN II, CIN III),
- SIL (Low grade SIL -LSIL - High grade SIL - HSIL),
- Mild, Moderate or Severe Dysplasia.

These systems correspond to:

CIN I / LSIL / Mild dysplasia
CIN II / Moderate dysplasia
CIN III / Severe dysplasia
CIN II and CIN III / HSIL

Adenocarcinoma In Situ (AIS) is a precursor of invasive cervical adenocarcinoma, showing endocervical glandular atypia. 30-60% of AIS are associated with SIL. 50-90% of cases are associated with HPV 16 or 18.

Squamous cell carcinoma (SCC) accounts for 80-90% of all cervical malignancies and for 60-80 % of invasive carcinomas. There are two major forms: microinvasive and invasive SCC. Diagnosis of the former is based on the presence of microinvasion foci. The invasive form may show heterogeneity at the microscopic level, and in most cases, infiltrating nests and clusters are characterised by an irregular, ragged contour.

Adenocarcinoma accounts for 5-20% of all cervical malignancies, and has increased during the past 20-30 years, particularly among women under 35. The tumour possibly originates from the pluripotential cells of the subcolumnar endocervical epithelium. It appears in a variety of histologic patterns, including mucinous, endometrioid, clear cell, well- differentiated villoglandular and serous adenocarcinoma.

Mesenchymal neoplasia:

Leiomyomas are rarer than those appearing in the uterine corpus and have a similar macroscopical and microscopical appearence. They account for approximately 8% of all uterine smooth muscle tumors.

Leiomyosarcoma is very rare.

Mixed epithelial and mesenchymal neoplasia:

Adenomyoma and papillary adenofibromas are rare polyp-like lesions composed of an admixture of fibroconnective tissue, smooth muscle and glandular elements. Adenomyomas may recur but behave benignly.

Malignant Mullerian Mixed Tumour (MMMT) is rarely seen in the cervix, compared with its much more common uterine counterpart. This lesion occurs in postmenopausal women and typically forms polypoid or peduncolated masses. Its histologic appearence differs from that of its uterine counterpart.

Mullerian adenosarcoma is rare. It is microscopically characterized by papillae covered by typical endocervical epithelium and malignant mesenchymal elements.

Secondary tumours are uterine cervix tumours originating outside the cervix.

Treatment

Precancerous changes in the cervix may be treated with cryosurgery, cauterization or laser surgery. Cervical conization may eventually prove to be therapeutic in many patients. Depending on the stage of the disease, surgery (early invasive cancer), combined with radiation, thermotherapy or chemotherapy (more advanced cases), are treatments of choice.

Prognosis

Early-stage cervical cancer and precancerous cervical conditions are almost 100% curable. The five-year relative survival rate for earliest-stage cervical cancer is

91%. Although death rates fell by 74% between 1955 and 1992 and continue to drop by about 2% a year, invasive cervical cancer continues to register significant morbidity and is a major cause of cancer deaths in women worldwide. Very recently, a "predictive score" system that separates the thermoradiosensitive group from the thermoradioresistant group of advanced cervical cancer has been developed on the basis of the expression profiles of 35 genes, selected by cDNA microarray analysis.

UTERINE CORPUS NEOPLASIA

Note

Uterine cancer is the fourth most common malignancy in women, following breast cancer, lung and colorectal cancer. However, as it is usually detected in early stages, it is not a common cause of cancer deaths. The most common corpus malignancy is the endometrial carcinoma (approximately 95 %.); sarcomas represent only 4% and heterologous tumors such as rhabdomyosarcomas, osteosarcomas and chondrosarcomas the remaining 1%.

The most common corpus benign tumor is leiomyoma, a proliferation of mesenchymal origin, occurring in approximately 77% of women of reproductive age, according to a study on serial uterine sections.

Etiology

The main risk factors for uterine corpus malignancy are obesity, nulliparity, late menopause, diabetes, and hypertension and radiation therapy. 10-25% of patients with mesenchymal malignancy report the administration of pelvic radiation 5 to 25 years earlier. Benign endometrial neoplasia, such as endometrial polyps, hyperplasia and adenocarcinoma, may be associated with tamoxifen therapy, possibly mediated through its agonistic estrogenic properties. As regards leiomyoma, evidence supports genetic susceptibility. Concerning gestational trophoblastic diseases, hydatiform moles arise from abnormal conceptions and most choriocarcinoma and placental site trophoblastic tumours develop following complete moles.

Epidemiology

The incidence of uterine malignancy varies widely throughout the world, with lower rates occurring in developing countries and higher rates in industrialized ones.

Benign neoplasia, specifically leiomyomas, most commonly occurs in women aged 35-49 years, but can be seen at any time between menarche and menopause. They are more common in black than in white women (3-9:1).

Clinics

Onset is frequently accompanied by metrorrhagia, menometrorrhagia, spotting and irregular bleeding, for both benign and malignant lesions, including trophoblastic diseases. Early pathological proliferation may sometimes be asymptomatic. Pain and pelvic pressure are usually manifestations of advanced disease.

Pathology

Epithelial neoplasia:

Endometrial polyps are present in 24% of the general female population, mainly in women over 40 years of age. They may show morphologically diverse patterns, related to patient hormone status, and consist of hyperplastic, cystically dilated glands in a fibrous stroma with large, thick-walled blood vessels. Endometrial polyps originate from monoclonal proliferation of mesenchyme and are not precancerous lesions, but endometrial epithelial invasive cancer (EIC) may be found in benign endometrial polyps, and endometrial polypoid masses may be malignant (adenosarcoma, malignant Mullerian mixed - MMMT - , endometrial stromal tumor). They may be associated with long-term tamoxifen therapy.

Endometrial hyperplasia (EH) is defined as a proliferation of glands of irregular size and shape with an increased gland/stroma ratio compared with proliferative endometrium. Morphologic alterations range from benign changes to premalignant disease. EH develops as a result of unopposed extrogenic stimulation. Association with polycystic ovarian disease has been described, but this entity is still a subject of debate. The WHO classification (adopted in 1994 and currently in use) distinguishes: typical (simple and complex) and atypical (simple and complex) hyperplasias. The latter confers signifcantly higher risk of progression to arcinoma.

Intraepithelial Carcinoma (EIC) is characterized by markedly atypical nuclei, identical to those seen in invasive serous carcinoma

Endometrial carcinoma is defined as an epithelial tumor, usually with glandular differentiation, arising in the endometrium and which has the potential to invade the myometrium and spread to distant sites. Type-I (related to estrogen) and Type-II (unrelated to estrogen) lesions are distinguished with respect to their biology and clinical course. Endometrioid carcinoma and serous carcinoma are the respective prototypes of the two groups. Major genetic alterations (see genes) seem to distinguish the two types, and histological classification of endometrial carcinoma may currently benefit from molecular analysis.

Endometrioid carcinoma is the most common endometrial malignancy, accounting for more than 75% of all endometrial cancers, and is relatively rare in pre-menopausal women. The histologic pattern resembles proliferative-phase endometrium and has less than 10% of squamous, serous, mucinous or clear differentiation. Both architectural and nuclear appearence are unavoidable criteria for grading lesions

Serous carcinoma is a highly aggressive carcinoma, usually post-menopausal, accounting for 10% of endometrial carcinomas. Geographical distribution is worldwide, although a lower incidence is reported in Norway and Australia. Papillary architecture with cells showing marked cytologic atypia is common.
Clear cell carcinoma comprises 1.6% of all uterine carcinomas and may have different architectural patterns, such as solid, papillary tubular and cystic.
Mucinous carcinoma is defined by the presence of more then 50% of cells containing periodic acid-Shiff positive, diastase-resistant intracytoplasmic mucin. It is rare, and usually has a glandular architectural pattern.
Squamous cell carcinoma is extremely rare and is microscopically similar to its cervix counterpart
Mixed carcinoma is defined as an endometrial carcinoma showing at least one other component comprising at least 10% of the tumour.
Transitional cell carcinoma is very rare and is defined by the presence of more than 90% of cells resembling urothelial transitional cells.
Small cell carcinoma is very uncommon and resembles small cell carcinoma of the lung.
Undifferentiated carcinoma includes approximately 1-2% of tumours lacking either glandular or squamous differentiation.
Mesenchymal neoplasia:
These tumours arise primarily from two distinct tissues: myometrial muscle (leiomyosarcoma) and endometrial stroma (mesodermal and stromal sarcomas).
Leiomyoma is a very common uterine smooth muscle proliferation, usually detected in women over 30 years old. Its growth is hormone- dependent and typical nodules are composed of whorled, anastomosing fascicles of smooth muscle cells. Less typical lesions are grouped into specific subtypes.
Endometrial stromal nodule is a rare lesion present in women aged 23-75 years. The lesion may protrude into the uterine cavity or grow within the myometrium. Microscopically, the cells resemble normal proliferative-phase endometrial stromal cells. The lesion is benign, but a hysterectomy may be necessary in order to evaluate the margin.
Leiomyosarcoma accounts for 1.3% of all uterine malignancies. Most of them are intramural, and nuclear atypia, high mitotic index and cell necrosis are the main diagnostic criteria.
Endometrial stromal sarcoma (ESS) is a rare tumor (0.2% of all uterine cancers) invading, by definition, the miometrium. It is typically subdivided into low-grade (fewer than 5-10 mitoses per 10 HPF and minimal cellular atypia) and high-grade stromal sarcoma, although this division has recently been questioned.
Miscellaneous mesenchymal tumors show no predominant muscle smoot or stromal differentiation and comprise: endometrial stromal and smooth muscle tumour (composed of an admixture of endometrial stromal and smooth muscle cells), adenomatoid tumour (a benign lesion of the uterine serosa and myometrium originating from the mesothelium and forming gland-like structures), other rare mesenchymal tumours (benign and malignant, such as lipoma, haemangioma, limphangioma, rhabdomyoma, rhabdomyosarcoma, liposarcoma, osteosarcoma, alveolar soft part sarcoma, etc) histologically identical to their counterparts arising in the usual sites.
Mixed epithelial and mesenchymal neoplasia:
Adenofibroma usually occurs in postmenopausal women and tends to recur. It presents an admixture of epithelial and mesenchymal cells.
Carcinofibroma is a very rare lesion whose behaviour is not yet clear. It is composed of an admixture of malignant epithelial and benign mesenchymal cells.
Adenosarcoma is a rare biphasic tumour which may occur at any age. It is a low-grade neoplasm, with a potential for recurrence and metastasis. It is charaterized by benign epithelial and saromatous mesenchymal components.
Carcinosarcoma (malignant mixed mesodermal sarcoma - MMMT), is still a debated entity: formerly classified among sarcomas, nowadays it is considered a variant of carcinoma, on the basis of recent clinical, histopathological, cytogenetic and molecular evidence. It accounts for 5% of all uterine corpus malignancies and is found in postmenopausal women. Microscopically it shows an admixture of carcinomatous and sarcoma-like elements, resulting in a characteristic biphasic appearance. It appears as a large, soft, polypoid mass involving the endometrium and myometrium. The carcinomatous component may be composed of papillary serous, endometrioid or clear cells, the stromal component of round or spindle cells.
Gestational trophoblastic tumors:
Gestational trophoblastic tumors are neoplastic disorders arising from placental trophoblastic tissue after abnormal fertilization.
Partial hydatiform mole is an abnormal placenta grossly characterised by an admixture of normal and hydropic chorionic villi.
Complete hydatiform mole is an abnormal placenta characterised by abnormal throphoblastic proliferation involving most chorionic villi.
Invasive hydatiform mole, usually subsequent to a complete mole, is composed of hydatiform mole villi within the myometrium.
Gestational choriocarcinoma is a highly malignant, often metastatizing neoplasm composed of a disordered array of syncytiotrophoblastic and cytotrophoblastic elements, without chorionic villi.
Placental site tumour is a rare neoplasm deriving from intermediate trophoblast cells in the placenta.
Secondary tumours are uterine corpus tumours originating outside the uterus.

Treatment

The vast majority of uterine corpus malignant tumours are highly curable since they present early symptoms and may often be diagnosed precociously. Knowledge of the surgicopathologic, as well as clinical, staging is crucial in developing an appropriate management plan. Surgical therapy is usually necessary for the majority of endometrial malignancies. Other adjuvant/adjunctive therapies such as radiation therapy, chemotherapy and hormonal therapy may be considered.
Treatment for benign uterine corpus lesions depends on the symptoms, tumor size and location and age of the patient.

Prognosis

Prognostic significance of hormone receptors in endometrial cancer has been reported; moreover, immunohistochemistry for both estrogen and progesterone receptors has been shown to correlate with FIGO grade as well as survival. HER-2/neu overexpression has been reported to be associated with a poor prognosis. Endometrioid adenocarcinoma and adenosquamous carcinoma have the highest overall 5-year survival rates. (respectively 76% and 68%), clear cell and papillary serous carcinomas the lowest (respectively 51% and 46%). The evolution of sarcoma depends primarily on the extent and stage of the disease at diagnosis. Recurrences are very frequent. The overall 5-year survival rate is 15-25%.
Among benign neoplasias, endometrial polyps may undergo malignant tranformation, while leiomyomas usually do not.

Cytogenetics

Note

The vast majority of endometrial cancers are sporadic. However, hereditary predisposition to develop uterine carcinoma is associated with hereditary non-polyposis colorectal carcinoma (HNPCC) and Cowden syndrome. Germline mutations of the FH (fumarate hydratase) have been found to be involved in syndromes associated with uterine leiomyomas. Evidence supports the existence of genetic factors predisposing to non-syndromic uterine leiomyoma, although susceptibility genes have not yet been identifed.

Cytogenetics Morphological

UTERINE CERVIX:

Karyotypic analysis on uterine cervix lesions is limited. No specific chromosome changes have been reported, although most lesions show cytogenetic abnormalities, including polyploidy. Chromosomes 5 and 17 are those most frequently involved in changes in carcinomas.

UTERINE CORPUS:

Endometrial polyps may show abnormal karyotypes, usually with a single or few changes. Three main cytogenetically-abnormal subgroups have been observed: (a) rearrangements in the 6p21-p22 region; (b) rearrangements in the 12q13-15 region; (c) rearrangements in the 7q22 region. At least for the subgroup with 6p21 rearrangement, it has been demonstrated that karyotypically aberrant cells belong to the stromal component of endometrial polyps.
Endometrial carcinomas do not show specific chromosome changes. Most of them are characterized by a hyperdiploid modal chromosome number. The majority show numerical chromosome changes, but cases with both numerical and structural abnormalities have been observed in the context of complex karyotypes. Non-random gains of 1q and 8q are frequently found. Correlations between karyotypic aberration patterns and histological differentiation have recently been reported, with the identification of different copy number changes among the different grades of type I carcinomas, between serous papillary and clear-cell carcinomas of type II, as well as between homologous and heterologous carcinosarcomas.
Endometrial stromal tumours are cytogenetically heterogeneous. The most common karyotypic changes involve chromosomes 6, 7, and 17. A subgroup of stromal lesions, including low-grade endometrial stromal sarcomas (more rarely in high-grade ESS) and endometrial stromal nodules are characterized by t(7;17)(p15;q21) translocation, resulting in the fusion of JAZF1 and JJAZ1 genes.
In **Endometrial Malignant Mullerian Mixed Tumours**, chromosome 8 or 8q. gains have been suggested to characterize a distinct cytogenetic subgroup.
Benign smooth muscle tumors are associated with abnormal karyotypes in almost 40-60% of cases. Different cytogenetically-abnormal subgroups have been recognized. Chromosomal structural changes at the 6p21, 12q13-15; 7q22, and trisomy 12 define those most frequently found; chromosome regions 1q42-44, 3q, and 10q are non-randomly involved in changes in a minority of cases.
Uterine leiomyosarcomas have complex cytogenetic karyotypes with numerical and structural aberrations and cytogenetic intratumoral heterogeneity.
Hydatiform moles have peculiar karyotypes: complete moles usually have a 46,XX karyotype of paternal origin, arising from an anuclear oocyte fertilized by an haploid 23,X sperm which undergoes replication. More rarely a 46,XY karyotype is found, arising from the fertilizaion of an anuclear oocyte by two haploid sperm. Incomplete moles (more than 90%) have a triploid karyotype and the presence of both maternal and paternal chromosomal material, due to ferilization of an haploid oocyte by two haploid sperm.

Cytogenetics Molecular

UTERINE CERVIX. A pronounced chromosomal instability in advanced cervical carcinomas has been

observed by comparative genomic hybridization (CGH.). CGH profiles show 2q33-q37 deletions and 3q gains as characteristic changes. FISH analysis on squamous cell carcinoma showed an increased DNA copy number in chromosomes 3 and X in the development and progression from HSIL to cervical carcinoma.

UTERINE CORPUS. CGH data on **endometrial cancer** confirm G-banding results, pinpointing a central role of 8q gains in the pathogenesis of carcinosarcomas and endometrial adenocarcinomas. CGH observation shows that **atypical endometrial hyperplasia** shares genomic abnormalities with endometrioid carcinoma, whereas simple **endometrial hyperplasia** shows no genomic imbalances.

Genes involved and proteins

Note

Notch1 exerts specific protective effects against HPV-induced transformation through suppression of E6/E7 expression. In high-grade HPV-positive **cervical lesions,** down-regulation of the cell signaling molecule Notch1 allows for increased expression of E6 and E7 oncogenes, which promote malignant cervical cell transformation.

A putative progression model for sporadic **endometrioid adenocarcinoma** developing through atypical endometrial hyperplasia has recently been proposed. Tumour initiation and progression are characterized by the acquisition of various molecular alterations. In this model, the most frequent, earliest events are the mutation of PTEN and K-ras, possibly followed by inactivation of e-cadherin (playing a role in progression) and later by p53 mutations, overexpressin of her/neu and inactivation of p16. An alternative pathway may lead directly to a high-grade tumour type by p53 mutation and her2/neu amplification, respectively.

Mutations in the MSH2/MSH6 complex seem to play a central role in **endometrial carcinoma associated with HNPCC.**

Fusion of the JAZF1 and JJAZ1 genes is found in endometrial stromal lesions, possibly restricted to the classic histologic subset.

Intragenic PTEN mutations are involved in the genesis of **uterine carcinosarcomas** with endometrioid-type carcinoma components.

Complete moles show overexpression of several growth factors, including c-myc, epidermal growth factor, and c-erbB2, as compared to a normal placenta. On rare occasions, complete moles may be familial, inherited as an autosomal trait: they are biparental in origin and result from misexpression of imprinted genes. A candidate region of chromosome arm 19q13.4 has been identified.

Germline mutations of the fumarate hydratase (FH) gene, located at 1q42.1, are involved in **syndromic uterine leiomyomas**. Very recently, loss of the FH gene has been demonstrated in a subgroup of **nonsyndromic uterine leiomyoma** characteried by 1q rearrangements.

Dysregulation of the HMGA2 (12q15) and HMGA1 (6p21.3) genes has been observed in **uterine leiomyomas**, as well as in **endometrial polyps**.

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