CHAPTER
17 Gynecologic Malignancies

Globally, gynecologic malignancies present a major oncologic problem. Worldwide (Ferlay et al, 2010), these cancers constitute about 9% of all cancers and about 18% of all female cancers. Worldwide, cervical cancer is the 7th (4.2%), uterine corpus is the 12th (2.3%), and ovarian cancer the 17th (1.8%). Regarding female cancers, cervical cancer is the third after breast and colorectum constituting 8.8% of all female cancers, uterine corpus is 6th (4.8%), and ovary the 8th (3.7%). More than 85% of the global burden of cervical cancer occurs in developing countries, where it accounts for 13% of all female cancers, due to high risk of HPV infection and lack of preventive and early detection methods. However, the profile of gynecological cancer shows a marked geographic variation (Table 17-1). Thus in USA, gynecological malignancies constitute about 6% of all cancers (Ries et al, 2007) and endometrial carcinoma predominates. In Egypt, gynecological malignancies constitute about 9.8% of all cancers and ovarian cancer predominates (NCI Cairo Data 2003-2004). In less developed countries, gynecological cancer constitutes 10.2% of all cancers and cervical cancer predominates (Ferlay et al, 2010).

OVARIAN CANCER

Incidence

Ovarian cancer is the most common gynecologic malignancy in Egypt (4.7% of all female cancers, ranking 3rd, and 40.7% of gynecologic cancers). Globally it constitutes 3.7% of all female cancers and ranks the eighth. In USA, it constitutes about 3.1% of all cancers in women, ranking as the ninth amongst female cancers. Ovarian cancer related mortality is 4.2% of all female cancer deaths. It is the seventh leading cause of cancer-related death in females, and despite attempts at early detection, 60% of patients have extrapelvic spread of the disease at the time of diagnosis. The lifetime risk of developing ovarian cancer is 1.5% (or 1:70), and one woman in 100 will die of the disease. The median age incidence is 55 years, but younger (22 years) in germ cell tumors, granulosa and Sertoli cell tumors.

Etiology

Malignant transformation of ovarian surface epithelium have been explained by the *incessant ovulation theory*. Accordingly, repeated ovulation will traumatize surface epithelium and leads to its proliferation. This theory is supported by the rare incidence of ovarian cancer in nulliparous women,

Table 17-1 Comparative Relative Frequency (%) of Gynecological Cancer in USA, Egypt and The Less Developed Countries

Site	USA*	Egypt**	Less Developed Countries***
Endometrium	42.9	23.3	20
Ovary	31.2	40.7	17.3
Cervix	20.9	27.9	62.7
Vulva	4.0	4.7	NA
Vagina	1.0	3.5	NA
Total (No)	102648	894	723626

(*Ries et al, 2007, SEER Data, ** NCI Data 2002-2003, *** Globocan 2008 Data, Ferlay etal, 2010)

as well as, patients with anovulatory cycles or users of contraceptive pills.

Risk factors for ovarian cancer include: *age* (cancer risk increases steadily from age of 30 to plateau at the age of 75-80). In USA the median age is 63 years. *Reproductive factors* (early menarche and late menopause increase risk but high parity and oral contraceptive use are protective specially for clear cell and endometrioid carcinomas). *Chronic inflammation* (incited by ovulation induced injury, retrograde menstruation-induced salpingitis or by introduction of foreign material through vagina and uterine cavity) may play a role. Other weak or inconclusive factors exist, the most important of which is protective role of *low-fat diet*.

Familial ovarian cancer accounts for 5-10% of the total. This includes: (1) the *breast-ovary syndrome* (BRCA-1 and BRCA-2 gene mutation), by age of 70 years, the risk of developing ovarian cancer is estimated as 40% and 18%, respectively, (2) the *colon-ovary syndrome* or Lynch-II syndrome (mismatch repair gene mutation or microsatellite instability). Individuals with this syndrome show a risk for colon cancer without polyposis and endometrial carcinoma and to lesser extent of other sites including ovary (about 2% of ovarian cancer). Ovarian cancers of this type were found to arise at an earlier age than sporadic cases (mean 40 years) and tended to be well or moderately differentiated and relatively low stage (FIGO stage I or II) at diagnosis, and (3) *Site-specific ovarian cancer* is recognized in families in which two or more first- or first- and second-degree relatives have ovarian carcinoma. The lifetime risk of ovarian carcinoma is approximately three fold higher in these families than in the general population. This type of *hereditary predisposition* is currently considered an "ovarian-specific" variant of hereditary breast/ovarian cancer, as no susceptibility gene other than BRCA1 and BRCA2 has been identified. It is noteworthy that the increased frequency of ovarian cancer in relatives of women with ovarian cancer is not paralleled by an increase among relatives of women with "borderline" or mucinous ovarian tumors.

Pathogenesis

The histogenesis of ovarian tumors is derived from four main sources, namely: surface epithelium, germ cells, sex cord-stromal cells and metastases (Fig 17-1). The surface epithelium of the ovary is mesodermal in origin, the same origin of müllerian duct. This explains the müllerian- like differentiation observed in surface epithelial ovarian tumors (e.g. tubal, endometrioid and endocervical mucinous differentiation). The germ cells originate from embryonic stem cells then migrate into the gonads. The profile of ovarian germ cell tumors is basically similar to testicular germ cell tumors. But, in contrast to testicular teratomas, ovarian teratomas are commonly benign and cystic. The ovarian stroma is mesenchymal in origin and has two components, namely: a specialized hormone-secreting stroma, as well as, an ordinary supporting stroma. Metastases to the ovary are common (Krukenberg tumors) and the routes of spread are mainly lymphatic or hematogenous from a gastric, colonic or breast primary.

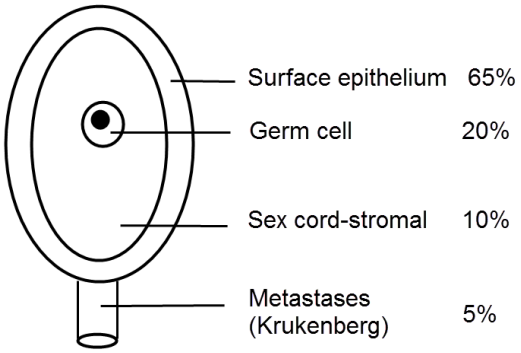

Fig 17-1 *Histogenesis and relative frequency of ovarian tumors.*

Time-honored concepts in epithelial ovarian cancer (EOC) oncogenesis include the following: (1) They presumably originate from ovarian surface epithelium (OSE) which is of mesodermal origin (multipotential stem cell), (2) Ovarian cancer begins in the ovary and spreads systematically to the pelvis, abdomen, and then distant sites, (3) Ovarian carcinoma, over time, progresses from well to poorly differentiated. Benign, borderline, and malignant ovarian tumors reflect sequential steps in malignant transformation, regardless of their type of differentiation (i.e., serous, mucinous, endometrioid, or clear cell). Hence, the different histological types of ovarian tumors are essentially interchangeable.

Molecular Oncogenesis

Advances in molecular biology correlated with morphologic studies aimed at investigating the relationship of borderline tumors to invasive carcinoma have shed new light on the pathogenesis of ovarian carcinoma and have challenged these aforementioned time-honored concepts of

ovarian neoplasia. Mounting clinicopathologic and molecular genetic data have led to the proposal of a new model of ovarian carcinogenesis that reconciles the differing relationships of borderline and malignant tumors that exist among the different cell types of ovarian cancer. This model divides surface epithelial tumors into two broad categories: Type I and Type II, based on their clinicopathologic features and characteristic molecular genetic changes (Table 17-2). Type I and Type II refer to tumorigenic pathways and are not histopathological diagnostic terms (Kurman and Shih 2008, and Li et al, 2012).

Type I tumors

They are low grade, relatively indolent neoplasms that arise from well-characterized precursor lesions (atypical proliferative (borderline) tumors in case of low grade serous and all mucinous carcinomas and endometriosis for low grade endometrioid and clear cell carcinomas), and usually present as large stage I neoplasms (as they grow slowly from benign precursors with delayed transformation). They constitute 20% of ovarian carcinomas. Clear cell carcinoma, although it exhibits most of the features of the Type I tumors, is typically high grade unlike the other Type I tumors. Nonetheless, preliminary molecular genetic data show a greater similarity of clear cell carcinoma to Type I as compared to Type II tumors. Type I tumors often harbor somatic mutations of genes encoding protein kinases including KRAS (low grade serous and mucinous carcinomas), BRAF (low grade serous), PIK3CA (clear cell carcinoma), and ERBB2, as well as other signaling molecules including PTEN and CTNNB1 (β-catenin) in low grade endometrioid carcinoma. Chromosomal instability is low in category I tumors. The atypical proliferative or borderline serous and mucinous tumors in turn appear to develop from cystadenomas, while the atypical proliferative endometrioid and clear cell tumors arise from endometriosis, typically endometriotic cysts (endometriomas) (Kurman et al, 2011).

Table 17-2 Categories of Ovarian Cancers According to the New Model of Carcinogenesis.

Type I tumors
Low-grade serous CA
Low-grade endometrioid CA
Clear cell CA
Mucinous CA
Type II tumors
High-grade serous CA
High-grade endometrioid CA
Undifferentiated CA
Carcinosarcoma

(Modified from Cho et al, 2009)

Type II tumors

The vast majority is high-grade serous carcinomas, which are aggressive, high grade neoplasms from the outset. It was believed that theses tumors arise "de novo." Recent data, however, suggest that high-grade serous carcinomas arise from tubal serous intraepithelial carcinomas (TSIC), and express homeobox (Hox) genes (Kantargian, 2011). Till present, it is not clear what proportion of high-grade serous carcinomas arises from the tube. More than 75% of Type II carcinomas have TP53 mutations. The few examples of stage I high -grade serous carcinomas that have been studied have been shown to harbor same mutations of TP53 thus supporting the postulate that these tumors are aggressive from the outset. Further support came from the detection of TP53 mutations in TSIC. Moreover, a recently described tubal precursor lesion of TSIC termed "p53 signature" is shown to overexpresses p53, and can harbor a p53 mutation, despite being morphologically normal. These findings highlight the importance of p53 mutation in the early development of high-grade serous carcinoma. Due to their failure to detect this early event, the current use of vaginal ultrasound and serum CA125 as screening tests for ovarian cancer is not associated with detection of these high grade tumors in their early Stage I. These tests lack the sufficient sensitivity and specificity to effectively detect category II ovarian cancer at a curable stage as they are dependent upon bulkiness of disease which is coupled with high stages in contrast to category I tumors which are bulky where they are still in stage I (Kurman et al, 2011).

The anatomical progression of ovarian carcinoma is poorly understood. It is generally assumed that carcinoma originates in the ovary, is confined to the ovary for a period of time, and then disseminates to the pelvis, followed by the abdominal cavity before spreading to distant sites. This view underlies the basis of the International Federation of Gynecology and Obstetrics (FIGO) staging

system in which tumors confined to the ovary are stage I, those involving the pelvic organs stage II, with involvement of abdominal organs stage III, and when spread occurs to distant sites stage IV. There are, however, significant problems with this assumption. Clinicopathologic comparison of stage I with stage III carcinomas shows that stage I tumors are predominantly Type I and non-serous, while stage III tumors are predominantly Type II and most often high-grade serous; furthermore, stage I tumors tend to be significantly larger, an observation that would suggest that ovarian carcinomas get smaller with progression (Kurman et al, 2011).

Classification

The classification of ovarian cancer (WHO, 2003) and relative frequency of the main histologic types are presented in (Table 17-3, Fig 17-1). Table 17-3 also presents a list of photographs illustrating gross and microscopic features of these tumors. The frequency of biologic subcategories of ovarian tumors in the various histologic types is shown in (Table 17-4) and the incidence of bilaterality is presented in (Table 17-5). The highest incidence of malignancy (25%) is encountered in serous epithelial tumors and metastases are most common to present bilaterally (65%).

1. *Carcinomas of surface epithelium* constitute the majority of malignant tumors. The comparative histologic features of these carcinomas are outlined in (Table 17-6) and illustrative photos are listed in (Table 17-3). It is important to recognize tumors of borderline malignancy (atypical proliferative tumors) because of their vastly better prognosis even in non-destructive metastatic cases. Borderline tumors differ from benign tumors by the presence of a stratified lining, epithelial atypia and mitosis. It also differs from conventional malignant tumors by the absence of stromal invasion and when metastasis occurs it is non destructive (lacking desmoplastic reaction). About 90% of low malignant potential (LMP) tumors are serous and 10% are mucinous.

2. *Germ cell tumors* constitute approximately 20% of ovarian malignancies. They are most common in young women and children. They characteristically show trisomy of chromosome 12. Dysgerminoma accounts for about one half of all malignant germ cell tumors, with a median age of 22 years. Ovarian teratomas are commonly benign and cystic.

3. *Sex cord-stromal tumors* are interesting neoplasms because of their hormonal activity. Granulosatheca cell tumor (2% of malignant tumors) secretes estrogen, whereas, Sertoli-Leydig cell tumor and hilum cell tumors are androgenic, but gynandroblastoma secretes both estrogens and androgens.

Spread

Ovarian cancer spreads by 4 main routes, namely: (1) *Local spread*: with invasion of capsule reaching surface of ovary. (2) *Trans-peritoneal* implantation, first affecting pelvic peritoneum then abdominal peritoneum. Omentum is the most favorable site for growth of implants (omental cake). With time, tumor implants will infiltrate the underlying structures, such as : intestine, bladder and retroperitoneum. (3) *Lymphatic spread* to paraaortic lymph nodes (Fig 17-2). (4) Distant *hematogenous* spread to lungs, pleura and liver parenchyma.

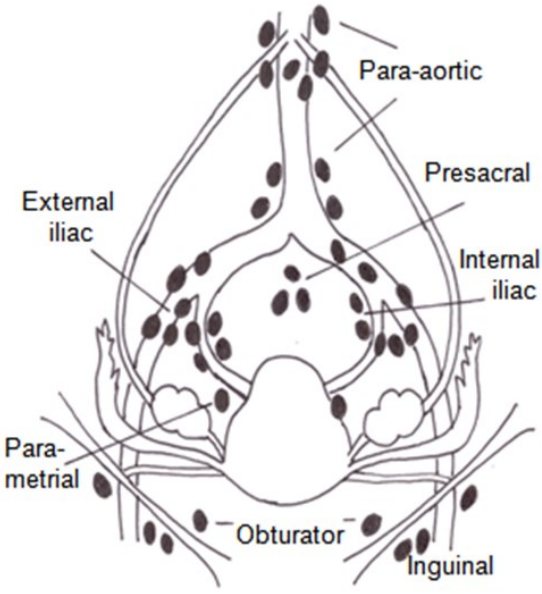

Fig. 17-2 *Lymphatic drainage of female genital organs. The vulva and lower vagina drain to inguinal nodes, the upper vagina, cervix and endometrium drain to pelvic nodes, the ovary and fallopian tubes drain to paraaortic nodes.*

Table 17-3 WHO Classification of Ovarian Tumors

Surface epithelial Tumors (65%)

- Benign serous cystadenoma (P 18-1, P 18-2)
- Benign serous cystadenofibroma (P 18-3, P 18-4)
- Borderline serous tumor (=atypical proliferative serous tumor) (P18-5)
- Serous papillary adenocarcinoma (P 18-6, P 18-7)
- Benign mucinous cystadenoma (P 18-8)
- Borderline mucinous tumor (=atypical proliferative mucinous tumor) (P 18-9)
- Mucinous adenocarcinoma (P 18-10, P 18-11)
- Transitional (Brenner) tumor (P 18-12, P 18-13)
- Endometrioid cystadenoma and cystadenofibroma
- Borderline endometrioid tumor (=atypical prolifer-Ative endometrioid tumor)
- Endometrioid adenocarcinoma (P 18-14, P 18-15)
- Clear cell adenocarcinoma (P 18-16)

Germ cell tumors (20%)

- Mature teratoma (P 18-17, P 18-18)
- Monodermal teratoma (P 18-19, P 18-20)
- Immature teratoma (P 18-21)
- Dysgerminoma (P 18-22, P 18-23)
- Embryonal carcinoma (P 18-24)
- Yolk sac tumor (P 18-25)
- Choriocarcinoma (P 18-26)

Sex cord-stromal tumors (10%)

- Granulosa cell tumor (P 18-27, P 18-28)
- Granulosa-theca cell tumor (P 18-29)
- Sertoli cell tumor (P 18-30)
- Sertoli-Leydig tumor (P 18-31)
- Gynandroblastoma
- Thecoma/fibroma (P 18-32)
- Lipid or steroid cell tumor (P 18-33)

Combined or mixed tumors

- Gonadoblastoma (P 18-34)
- Mixed müllerian (P 18-35)

Primary Extranodal lymphoma (P 18-36)

Metastatic tumors (Krukenberg)(P 18-37)

(Tavassooli and Devilee, 2003)

Table 17-4 Frequency of Biologic Subcategories of Ovarian Tumors (%)

Type	Benign	Borderline	Malignant
Serous	60	15	25
Mucinous	80	10	10
Brenner	96	2	2
Teratoma	90	-	10
Granulosa-theca	85	-	15
Sertoli-Leydig	99	-	1

Table 17-5 Bilaterality of Ovarian Tumors

Benign		Malignant	
Tumor Type	%	Carcinoma Type	%
Serous	25	Metastatic	65
Teratoma	10	Serous	50
Mucinous	5	Endometriotic	30
Granulosa	5	Mucinous	20
Sertoli	3	Dysgerminoma	20

Table 17-6 Comparative Histologic Features of Ovarian Carcinoma

	Serous	Mucinous	Endometrioid
1. Frequency	75%	10%	15%
2. Epithelium	cuboidal	columnar basal nuclei	columnar central nuclei
3. Mucin	luminal border	abundant	luminal
4. Squamous metaplasia	–	–	50%
5. Cilia	frequent	–	–
6. Psammoma bodies	30%	–	–

Staging

The original staging system of International Federation of Gynecology and Obstetrics (FIGO, 2002) is generally used (Fig 17-3 and Table 17-7).

Prognosis

The most important predictors of prognosis are the stage of the disease, histologic type and some biologic markers. The prognosis is excellent if the tumor is confined to the ovaries (Stage I). At all stages of the disease, tumors of borderline malignancy are also associated with excellent prognosis (Table 17-8). High grade carcinomas, clear cell carcinomas and choriocarcinoma are associated with unfavorable prognosis. Also, aneuploidy and oncogene expression of tumors are poor prognostic factors.

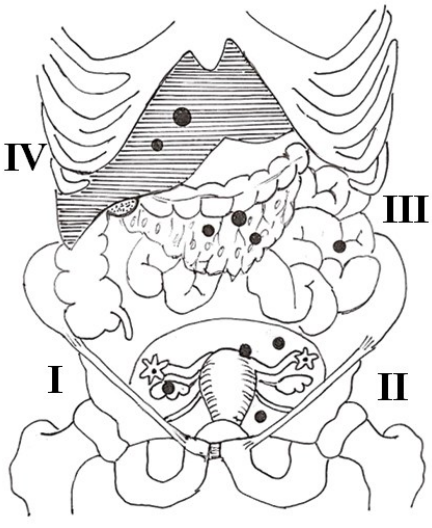

Fig 17-3 *FIGO stages of ovarian carcinoma, stage I confined to ovary (stage I is subclassified into IA unilateral confined to ovary, IB bilateral involvement of ovaries and IC capsular invasion, rupture, tumor on ovarian surface or malignant ascites), stage II pelvic disease, stage III abdominal or nodal spread and stage IV distant metastasis (Edge et al, 2010).*

Table 17-7 Carcinoma of the Ovary: FIGO Clinicopathologic Staging

Stage I	**Growth limited to the ovaries**
Ia	Growth limited to one ovary; no malignant cells-containing ascites present. No tumor on the external surface; capsule intact
Ib	Growth limited to both ovaries; no malignant cells-containing ascites present. No tumor on the external surfaces; capsules intact present containing malignant cells, or with positive peritoneal washings
Ic	Tumor either stage Ia or Ib, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites
Stage II	**Growth involving one or both ovaries with pelvic extension**
IIa	Extension and/or metastases to the uterus and/or tubes
IIb	Extension to other pelvic tissues
IIc	Tumor either stage IIa or IIb, but with tumor on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
Stage III	**Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis**
IIIa	Tumor grossly limited to abdominal peritoneal seedling detected only by microscopy
IIIb	Tumor of one or both ovaries with gross abdominal peritoneal seedling <2 cm
IIIc	Gross abdominal peritoneal seedling >2 cm or positive retroperitoneal or inguinal lymph nodes
Stage IV	**Growth involving one or both ovaries with distant metastases**. If pleural effusion is present, there must be positive cytology to allot a case to stage IV; parenchymal liver metastasis equals stage IV

(Edge et al, 2010) N.B. The original FIGO for ovarian cancer was not updated

Table 17-8 Relative Survival Rates of Ovarian Carcinoma by Original FIGO Stage and Histology (SEER Data, 1988-2001)

Stage	Malignant (23634 cases)		Borderline (5092 cases)	
	5-year	10-year	5-year	10-year
Stage I	**89**	**84**	**99**	**98**
Ia	94	89	100	99
Ib	91	79	100	91
Ic	80	76	97	96
Stage II	**66**	**56**	**98**	**94**
IIa	76	67	97	90
IIb	67	57	98	93
IIc	57	50	98	95
Stage III	**34**	**22**	**96**	**88**
IIIa	45	31	97	89
IIIb	39	25	97	91
IIIc	35	23	97	85
Stage IV	**18**	**10**	**77**	**70**

(Ries et al, 2007)

Early Detection

Since most ovarian cancer is diagnosed at an advanced stage, efforts should be made for the early detection of the disease during its preclinical phase. The available methods include: physical examination, pelvic ultrasonography and biomarkers (CA-125). Periodic examination is started by the age of 40 years and repeated annually.

Of the various techniques for imaging, pelvis transvaginal sonography (TVS) has been extensively studied and is probably superior to abdominal ultrasonography, with a yield of one per thousand and a specificity of 98.7%. One strategy to improve the effectiveness of ovarian cancer screening is to target high risk population such as those with a family history of ovarian cancer. In such cases the yield of TVS is increased to 4 per 1000.

Of the biomarkers described in ovarian cancer, CA-125 has been the most extensively studied. It is a glycoprotein of unknown function that is detectable in 80% of cases of epithelial ovarian cancer, values above 35 U/ml are considered abnormal. The sensitivity of CA-125 is about 60% and specificity is 95% in premenopausal patients, hence, it is advisable to combine this test with other modalities of detection.

A presumptive goal of screening should be to detect high-grade serous carcinoma in stage I. Unfortunately, screening trials have generally identified stage I non-serous tumors, borderline tumors, non-epithelial tumors, and advanced stage serous carcinomas, with the identification of stage I high-grade serous carcinoma an exceedingly rare event, even in series focusing on high-risk women (Meeuwissen et al, 2005 and van der Velde et al, 2009). As stated earlier in the pathogenesis section, an understanding of the new model of ovarian cancer pathogenesis sheds light on such discouraging reality. According to this model, high-grade serous carcinomas (type II ovarian cancer), which account for the vast majority of ovarian cancer deaths, are usually relatively small at their site of origin even when they are widely disseminated. Both vaginal ultrasound and serum CA125 lack sufficient sensitivity and specificity to effectively detect them at a curable stage, if one even exists. To complicate the picture more, Type II ovarian tumors, which are amenable to detection at stage I by current screening methods, only constitute 20% of ovarian carcinomas.

EXTERNAL GENITALIA

Cancer of vulva

It accounts for 5% of all gynecologic cancer. All premalignant lesions of squamous epithelium of the vulva are now grouped together under the term vulvar intraepithelial neoplasia (VIN). It is graded into three grades and is etiologically related to HPV type 16 (this is opposed to types 6 and 11 usually found in condyloma acuminatum, P 17-38). Vulvar intraepithelial neoplasia includes: Lichen sclerosus (P 17-39), Bowen disease, Paget disease and melanoma in situ. The common invasive carcinomas of vulva include: squamous carcinoma (96%), adenocarcinoma of Bartholin gland (2%), malignant melanoma and sarcomas (2%).

Vaginal cancer

It contributes 2% of gynecologic malignancy. It is commonly squamous cell carcinoma (P 17-40). However, about 10% are adenocarcinoma (P 17-41) which may be related to exposure to diethylstilbestrol (DES) in utero. The vagina is a common site of sarcoma botryoides in children (P17-42). It is also a common site for metastases (e.g. choriocarcinoma).

CERVICAL CARCINOMA

Incidence

The decreasing frequency of cervical cancer in the West is due to the adoption of screening programs by Pap test. In USA, it constitutes only 1.6% of female cancer. Worldwide it constitutes 8.8% of female cancer and in Egypt it is only 1.5% (possibly due to religious sexual restrictions). But, cervical carcinoma continues to be a leading cause of cancer mortality in many developing countries e.g. central and South America, eastern and southern Africa, south-central Asia . It contributes about 8.2% of cancer-related death worldwide while in Mexican females it is responsible for 12.8% of cancer deaths (incidence is 15.5% of female cancer). Cervical cancer is 20.9% of gynecological cancer in the USA, and 27.9% in NCI, Cairo and 62.7% in less developed countries. The high relative frequency of cervical cancer in relation to gynecological cancer at NCI Cairo as compared to its low incidence in the general Egyptian female population is possibly attributable to the fact that cancer cervix surgery is a sophisticated one that is not preferred by gynecologists who usually prefer to refer it to specialized centers as NCI.

The majority of women with invasive SCC are diagnosed in their mid-40s or 50s; however, cervical carcinoma can occur at almost any age between 17 and 90 years (Pino and Crum, 2000). Patients with invasive SCC are 15–23 years older than patients with high-grade squamous intraepithelial lesion (SIL) and 8 years older than patients with microinvasive carcinoma. In recent years there has been increased recognition that cervical cancer can occur in women under 35 years. Women under 35 years account for 22.1% of all patients with invasive cervical cancer in the United States.

Etiology

1. *Extrinsic factors*: (a) human papilloma virus (HPV) types 16 and 18, and (b) co-factors are: associated herpes simplex virus infection (HSV-2) smoking and oral contraceptives.

2. *Host factors*: (a) early sexual contact and multiparity, (b) multiple partners and uncircumcised males, (c) low socioeconomic standard, and (d) immunosuppression.

Pathogenesis

The normal histology of cervix and basal cell hyperplasia are illustrated in (P 17-43 and P 17-44). Molecular, clinical, and epidemiological studies have implicated HPV infection in the pathogenesis of cervical carcinoma. More than 90% of cervical carcinoma contains DNA sequences of specific HPV types, especially HPV 16 and HPV 18 (Gliford et al, 2006) as opposed to the types usually found in condylomas (types 6 and 11)(P 17 -45). The distribution of HPV types in invasive cervical cancers shows only minor geographic variations. Globally, HPV 16 is most frequently detected in invasive cervical cancer, followed by HPV 18. HPV types 31, 33, 35, 45, 52, and 58 are the next most common types found in cancers globally with minor variations seen in their relative importance by region (Munoz et al, 2003). In patients with metastatic cervical carcinoma, HPV DNA can also be identified in distant metastases, with viral DNA hybridization patterns frequently matching those of the primary cervical tumor. Based on the strength of the molecular and epidemiologic evidence linking HPV to invasive squamous cell carcinoma of the cervix, 13 high-risk types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56,

58, 59, and 66) have been classified as carcinogenic to humans by the WHO.

Molecular oncogenesis

In HPV 6 and 11 the virus remains outside DNA (episomal state) but undergoes intranuclear replication with synthesis of new virus particles. The infected squamous cells show characteristic perinuclear vacuole (koilocytosis, P 17-45). Conversely, in HPV 16 and 18, integration of virus into DNA occurs with arrest of viral replication and start of the carcinogenesis process in squamous cells (Fig 17-4). The integrated virus starts to produce E6 and E7 oncoproteins which combine and inhibit p53 and Rb tumor suppressor phosphoproteins respectively leading to cell immortalization. A potential cofactor in this process is the herpes simplex virus (HSV-2) which may play an initiating role with HPV acting as a promoter.

Cancer cervix is thought to arise in preexisting areas of epithelial atypia over a period of 10 to 20 years. The classification, terminology and histopathology of these lesions (Table 17-9 and Fig 17-5) have undergone major changes during the past decades, from dysplasia and carcinoma in situ (Reagan, 1953), to cervical intraepithelial neoplasia CIN (Richart, 1968) and finally to squamous intraepithelial lesion SIL (the Bethesda system, 1989). Cervical SIL is classified into low-grade LSIL (including koilocytosis, mild dysplasia and CIN-I) and high-grade HSIL (including moderate and severe dysplasia, carcinoma in situ and CIN-III). LSIL is mostly a reversible lesion related to HPV type 6 and 11, composed of diploid cells with progression to carcinoma in only 5% of cases. Conversely, HSIL is related to HPV type 16 and 18, composed of aneuploid cells, with a risk of malignant change of 33%.

Macroscopy

The gross appearance depends on the site of tumor origin in the uterine cervix (P 17-51). Thus, *ectocervical* carcinoma may be ulcerating or exophytic (papillary). Whereas, *endocervical* carcinoma may be nodular or barrel-shaped.

Histopathology

The World Health Organization (WHO) histological classification of carcinomas of the uterine cervix is presented in (Table 17-10). Also presented in this table their relative frequency and illustrative photomicroscopic pictures (P 17-52 to P 17-59).

Squamous cell carcinoma (SCC) is by far the most common (80%) of cervical carcinoma, of which large cell non-keratinizing subtype predominates (70%). Less frequent subtypes are: adenocarcinoma (10%) and miscellaneous subtypes (10%).

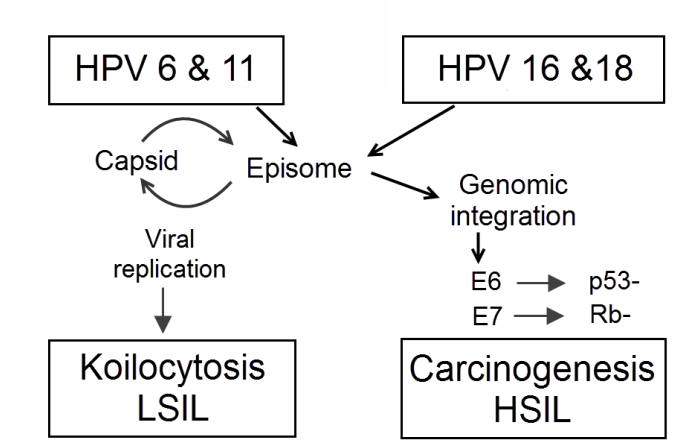

Fig 17-4 *Human papilloma virus (HPV) subtypes and genesis of cervical pathology. HPV6 and 11 replicate outside DNA, producing low grade squamous intraepithelial lesion (LSIL), but HPV16 and 18 integrated in DNA resulting in high-grade squamous intraepithelial lesion (HSIL) and cancer*

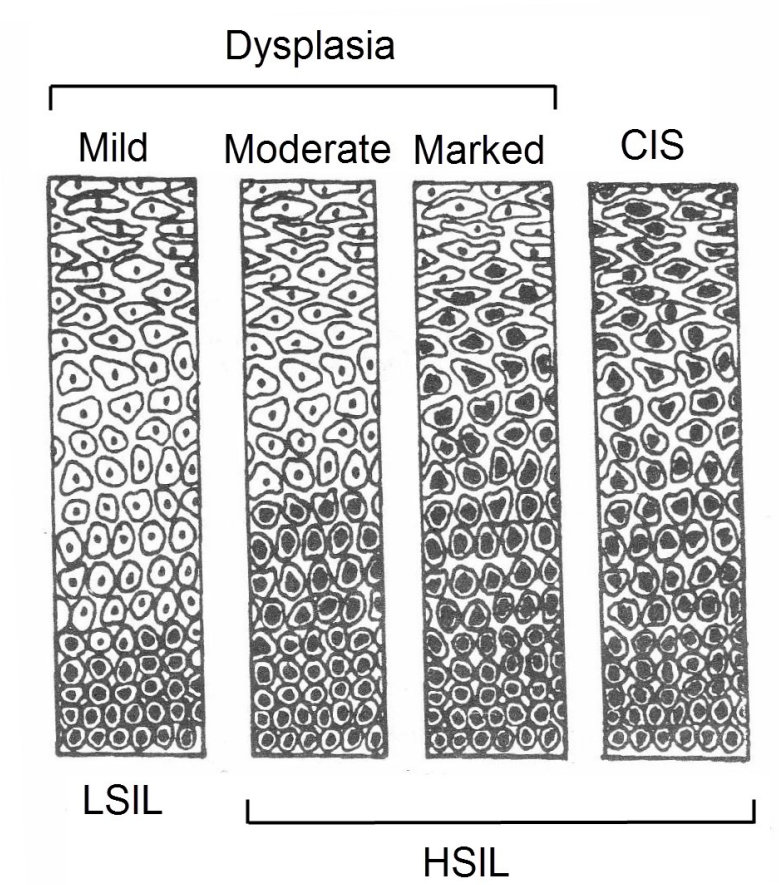

Fig 17-5 *Classification and terminology of atypical squamous lesions of uterine cervix. Abbreviations: CIS carcinoma in situ, LSIL low-grade squamous intraepithelial lesion and HSIL high-grade squamous intraepithelial lesion. These atypical changes are most marked at the squamo-columnar junction of the cervix (transformation zone).*

Table 17-9 Interrelation of Classifications for Atypical Epithelial Lesions of the Uterine Cervix

Dysplasia (Reagan, 1953)	CIN (Richart, 1968)	SIL (Bethesda, 1989)	Picture No.
Mild	CIN-I	LSIL	P 17-45, P 17-46
Moderate	CIN-II		P 17-47
Marked	CIN III	HSIL	P 17-48, P 17-49,
CIS			P 17-50

Abbreviations: CIN cervical intraepithelial neoplasia, LSIL low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesion.

Table 17-10 Modified World Health Organization (WHO) Histological Classification of Invasive Carcinomas of the Uterine Cervix

Squamous cell carcinoma (80%)
Microinvasive (early invasive) squamous cell carcinoma (P 17-52)
Invasive squamous cell carcinoma
Keratinizing 25% (P 17-53)
Nonkeratinizing (large cell 70% and small cell 5%) (P 17-54)
Basaloid
Verrucous
Warty
Papillary
Squamotransitional
Lymphoepithelioma-like carcinoma
Adenocarcinoma (10%)
Usual type adenocarcinoma
Mucinous adenocarcinoma
Endocervical type (P 17-55)
Intestinal type
Signet-ring type
Minimal deviation (P 17-56)
Villoglandular
Endometrioid adenocarcinoma
Clear cell adenocarcinoma (P 17-57)
Serous adenocarcinoma
Mesonephric adenocarcinoma (P 17-59)
Other epithelial tumors (10%)
Adenosquamous carcinoma (P 17-58)
Glassy cell variant
Adenoid cystic carcinoma
Adenoid basal carcinoma
Neuroendocrine tumors
Carcinoid
Atypical carcinoid
Small cell carcinoma
Large cell neuroendocrine carcinoma
Undifferentiated carcinoma

(Tavassooli and Devilee, 2003)

Spread

1. *Local*: to body of uterus, parametrium, ureters and vagina.

2. *Lymphatic spread* (Fig 17-3) to pelvic nodes, microinvasive lesions <3 mm (FIGO IA1) rarely metastasize, but 5% of tumors 3-5 mm (FIGO IA2) have positive lymph nodes.

3. *Hematogenous spread* to lungs and liver.

Staging

The original FIGO staging system (1988) is the one generally adopted (Table 17-11, Fig 17-6). In developed countries cervical carcinoma is diagnosed by cytology in its preclinical stage with disease still confined to the cervix (stage I). This stage is subdivided into four substages: (1) IA1: Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread, (2) IA2: Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less, (3) IB1: Clinically visible lesion 4.0 cm or less in greatest dimension, and (4) IB2: Clinically visible lesion more than 4.0 cm in greatest dimension.

Prognosis

The overall 5-year relative survival rate for all the stages is 71.5% (Ries et al, 2007). But, survival varies according to SEER stage (Table 17-12) and histology (Table 17-13). It is 90.9% for localized disease (confined to cervix), 57.1% for regional disease (spread to regional lymph nodes) and only 16.1% for distant stage with metastases (SEER data 2003-2009, accessed on May 7th, 2012).

Factors that have been reported to increase an individual's risk for nodal metastases, recurrence, and death are (1) depth of stromal invasion, (2) presence of lymphovascular invasion, (3) tumor volume, and (4) involvement of the resection margin.

Early Detection

Annual Pap test with a pelvic examination is recommended starting from age 20 or earlier if sexually active. After three consecutive examinations with normal findings, the checkup may be done less frequently.

Table 17-11 The Original FIGO Staging of Carcinoma of the Cervix Uteri (1988)

Stage I	Cervical carcinoma confined to uterus (extension to the corpus disregarded)
IA	Invasive carcinoma diagnosed only by microscopy; all macroscopically visible lesions, even with superficial invasion, are stage IB
IA1*	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
Stage II	Tumor invades beyond the uterus but not to pelvic wall or to lower third of the vagina
IIA	Without parametrial invasion
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIA1	Clinically visible lesion less than or equal to 4.0 cm in greatest dimension
IIB	With parametrial invasion
Stage III	Tumor extends to the pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney
IIIA	Tumor involves lower third of vagina with no extension to pelvic wall
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or regional node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

(Tavassooli and Devilee, 2003) * In updated FIGO IA <5 mm in depth

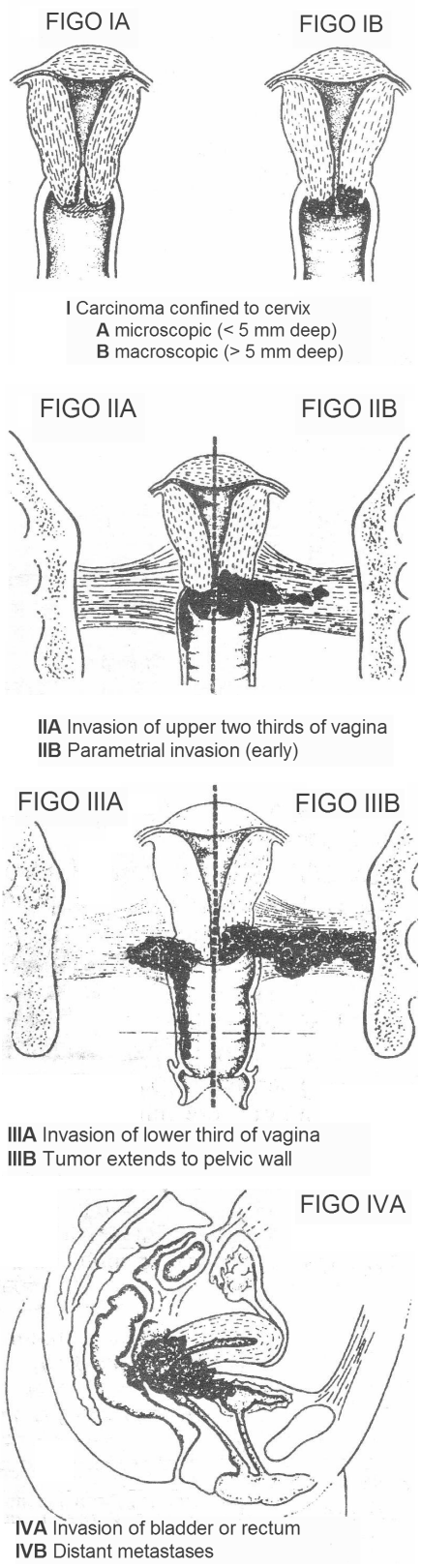

Fig 17-6 *Updated staging of cervical carcinoma according to the International Federation of Gynecology and Obstetrics (Edge et al, 2010).*

Table 17-12 Relative Survival Rates of Cervical Carcinoma by FIGO Surgical Stage

Stage	5-year	10-year
Stage IA	99	97
Stage IB	90	86
Stage II	54	45
Stage III	39	28
Stage IV	14	10

(SEER Data 3656 patients, Ries et al, 2007)

Table 17-13 Relative Survival Rates of Cervical Carcinoma by Histology and FIGO Surgical Stage

Stage	5-year (%)	10-year (%)
Squamous carcinoma		
Stage I	91	87
Stage II	61	53
Stage III	47	41
Stage IV	16	12
Adenocarcinoma		
Stage I	92	89
Stage II	54	45
Stage III	39	28
Stage IV	14	10

(SEER Data 3656 patients, Ries et al, 2007)

Differential Diagnosis

1. *Microglandular adenosis* (P 17-60): This is an incidental finding in cervical specimens which can mimic invasive adenocarcinoma. Glands are small and crowded but they are superficial and lack atypia and no evidence of mitotic activity.

2. *Squamous metaplasia of endocervix* (P 17-61): This lesion could simulate microinvasive squamous carcinoma especially when it involves ducts of the endocervical glands. Careful examination will show involvement of surface epithelium by the same metaplastic changes and residual basal columnar epithelium can be seen. Associated basal cell hyperplasia is often present.

3. *Tunnel clusters of endocervix* (P 17-62): Can be mistaken for mucinous adenocarcinoma. It is a hyperplastic lesion composed of crowded and microcystic glands filled with mucin and are lined by flat bland epithelium. Lobular pattern is preserved.

4. *Ectopic decidual tissue* (P 17-63): It may be misdiagnosed as glassy or clear cell carcinoma, but the cells show small uniform nuclei and are immunoreactive for CD56.

ENDOMETRIAL CARCINOMA

Incidence

Endometrial carcinoma is the most common carcinoma of the female genital tract in western reports (Ries et al, 2007). It is the 6th most common female cancer worldwide constituting 4.8%. In the USA it contributes about 5.8% of all female cancers (coming fourth after breast, lung and colorectum) and about 43% of gynecological cancer. In Egypt, it comes in the 13th rank among female cancer representing 1.6%. At NCI it is the third most common gynecological cancer after ovary and cervix constituting about 23%. Fortunately, the curability is high (about 80% in stage I). The median age is 60 years.

Etiology

Most of the cases are related to hyperestrinism such as: infertility, late menopause, nulliparity, anovulatory cycle, complex atypical endometrial hyperplasia (CAH), estrogen therapy, tamoxifen therapy and estrogen secreting ovarian tumors. Other risk factors are obesity, diabetes and hypertension.

Pathogenesis

From a pathogenetic viewpoint, two different forms of endometrial carcinoma with distinct clinicopathologic features have been identified: a low grade *endometrioid carcinoma (type I)* which is estrogen-related is usually associated with endometrial hyperplasia and occurs in younger perimenopausal women. The risk of progression into endometrioid adenocarcinoma is increased in atypical hyperplasia (Table 17-14). The second variants, *endometrial carcinoma (type II)* is a more aggressive type of different histology (serous, clear or adenosquamous) unrelated to estrogen stimula-

Table 17-14 The Risk of Progression of Endometrial Hyperplasia to Endometrial Carcinoma

Type	Without atypia	With atypia
Simple	4.3%	7.4%
Complex	16.1%	47.0%

(Kantarjian et al, 2012)

Table 17-15 Comparison of Clinicopathological Types of Endometrial Carcinoma

Feature	Type I	Type II
Frequency	80%	20%
Age (years)	Premenopausal (50 y)	Postmenopausal (65 y)
Estrogen	Related	Unrelated
Molecular Oncogenesis	Microsatellite PTEN, K-RAS, β-catenin, Lynch	p53, p16
Histologic types	Endometrioid, mucinous	Serous, clear, squamous and undifferentiated
Biologic Grade	Low	High
Hormone receptor	Positive	Negative
Associated endometrium	Hyperplasia	Atrophy
Immunophenotype	Vimentin +	p53, p16
Myometrial invasion	Minimal	Deep
Hormone therapy	Dependent	Independent
Prognosis (5-y survival)	Favorable (90%)	Unfavorable (35%)

(Kantarjian et al, 2012 / Nucci and Oliva, 2009)

tion and occurs in older women. Table 17-15 shows the clinicopathological features of these two variants of endometrial carcinoma.

Molecular Oncogenesis

The carcinogenic mechanism varies according to the histologic type of carcinoma (DeVita, 2011). In *type I carcinoma* (endometrioid and mucinous types), oncogenesis is mainly related to PTEN (a negative regulator of cell cycle), K-RAS (a proto-oncogene) and β-catenin (a mitogenic agent whose mutations tend to increase its stability, prevents its degradation leading to its accumulation and nuclear translocation). Conversely, in *type II endometrial carcinoma* (serous and clear cell types), oncogenesis is related to mutation of tumor suppressor genes (p53 and p16), HER2 amplification and Bcl-2 expression.

Macroscopy

Endometrioid carcinoma is almost uniformly exophytic even when deeply invasive. The neoplasm may be focal or diffuse. At times the tumor may appear to be composed of separate polypoid masses. Necrosis usually is not evident macroscopically in well-differentiated carcinomas but may be seen in poorly differentiated tumors, sometimes in association with ulcerated or firm areas. Myometrial invasion by carcinoma may result in the enlargement of the uterus, but a small

atrophic uterus may harbor carcinoma diffusely invading the myometrium. Uteri containing serous endometrial adenocarcinoma often are small and atrophic. Generally the tumor is exophytic and has a papillary appearance. The depth of invasion is difficult to assess on macroscopic examination.

Histopathology

Table 17-16 shows the WHO classification of endometrial carcinoma as well as the corresponding illustrative pictures. Endometrioid adenocarcinoma is the most common (80%) histologic type. It is composed of tubular glands lined by stratified non-mucin-secreting epithelium. Rarely, basal or suprabasal vacuolization may be evident (secretory endometrioid carcinoma).

Staging

In 1988, the International Federation of Gynecologists and Obstetricians (FIGO) introduced their initial staging system for endometrial carcinoma (Fig 17-7). In 2009 this staging was updated to incorporate four major changes: (1) Previous stages IA and IB were combined as stage IA, and previous IC changed to IB (2) Stages IIA and IIB of cervical invasion were combined together as IIA in the new system. (3) Previous stage IIIC was sub-classified in the new system into IIIC1 (positive pelvic nodes) and IIIC2 (positive paraaortic nodes). (4) Positive peritoneal cytology is no longer a factor in the updated FIGO classification (Edge et al, 2010).

Table 17-16 Histologic Classification of Endometrial Carcinoma and its Variants

Type	%
Type I	
Endometrioid Carcinoma, P17-64	80
with squamous metaplasia, P17-65	
villoglandular	
secretory	
Ciliated	
Mucinous Carcinoma	5
Type II	
Papillary serous carcinoma, P17-67	5
Clear cell carcinoma, P17-66	5
Small cell carcinoma	1
Squamous cell carcinoma	1
Undifferentiated carcinoma	1
Mixed carcinoma	

(Tavassoli and Devilee, 2003/Nucci and Oliva, 2009)

Prognosis

Prognostic determinants of endometrial carcinoma include the following clinical pathological factors, and molecular biomarkers: (1) *Age*: The prognosis is more favorable in younger patients (5 -y survival 92% in patients below 50 years and 60% in patients > 70 years old), (2) *Grade* and myometrial invasion (Table 17-17 and Table 17-18), (3) *Histological type* (Table 17-19), type I is more favorable, (4) *FIGO stage* (Table 17-18 and Table 17-20), (5) *Lymphatic spread*: Lymphovascular invasion (5-y survival 84% if absent and 65% if present) and lymph node metastasis (5-y DFS 90% if negative and 54% if positive) and (6) *Biomarkers*: Hormone receptors, DNA ploidy, Ki67 index, K-RAS and p53.

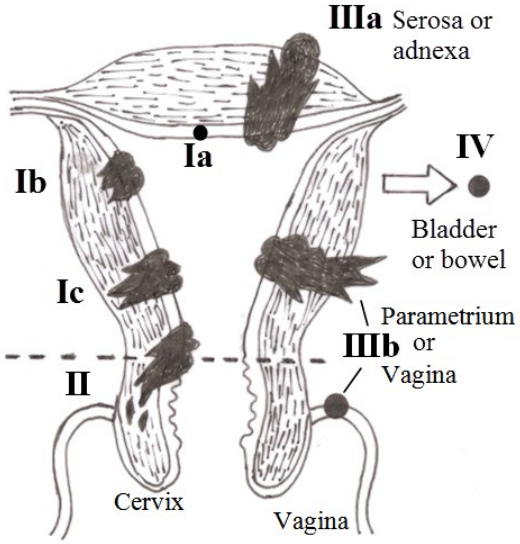

Fig 17-7 *Original FIGO staging of endometrial carcinoma (1988). Stage IA endometrial intraepithelial neoplasia (EIN), IB invasion of inner half of myometrium, IC invasion of outer half of myometrium, II cervical invasion, IIIA serosa, adnexa, IIIB parametrium and vagina, IVA invasion of bladder or bowel and IVB distant metastasis. In the updated FIGO staging (Edge et al, 2010), stages IA and IB are combined together as stage IA and IC changed to IB. Also, stages IIA and IIB are combined as stage II. Positive pelvic lymph nodes are considered stage IIIC1 and positive paraaortic lymph nodes stage IIIC2. Positive peritoneal cytology is no longer a factor in staging.*

Differential Diagnosis

A. Carcinoma mimics

1. Endometrial hyperplasia (P 17-68 to P 17-71).
2. Adenomyoma (P 17-72).
3. Müllerian adenofibroma (P 17-73).

B. Other carcinomas

This includes endocervical and ovarian carcinoma as well as metastatic carcinoma from colon and breast. Table 17-21 shows the differentiating immunostaining panel that can be useful in this respect.

Table 17-17 Prognosis by Grade of Endometrioid Endometrial Carcinoma

Grade	Histological Criteria	5-year survival (%)
I	Solid area < 5%	94
II	Solid area 5-50%	84
III	Solid area > 50%	72

(Nucci and Oliva, 2009) N.B. In the updated FIGO 2009, tumor anaplasia and mitotic activity are taken in consideration in grading.

Table 17-18 Five-Year Survival Endomerioid Endometrial adenocarcinoma by FIGO Stage and Grade

Grade	FIGO Stage	
	Confined to uterus (Stage I)	Extrauterine (Stages II to IV)
Low (G1and2)	76-100%	76%
High (G3)	67%	26%

(Nucci and Oliva, 2009)

Table 17-19 Prognosis of Histologic Types of Endometrial Carcinoma

Type	5-y survival
Mucinous Carcinoma	95
Endometrioid Carcinoma with squamous metaplasia	94
Endometrioid Carcinoma	91
Clear cell carcinoma	65
Squamous cell carcinoma	61
Papillary serous carcinoma	45

(US-SEER Data, Ries et al, 2007)

Table 17-20. Recurrence Rate of Endometrial Carcinoma by Combined Grade and FIGO Stage

Grade	Ia	Ib
I	24	53
II	11	45
III	7	35

(Nucci and Oliva, 2009)

Table 17-21 Differential Diagnosis of Endometrial Carcinoma

Carcinoma	PR	CEA	Vimentin	CK	WT1
Endometrial	+	-	+	7	-
Endocervical	-	+	-		
Ovarian	+			7	+
Metastatic colon	-	+		20	
Metastatic breast	+	+		7, 8, 18	

(Bartosch et al, 2011)

SARCOMAS OF UTERUS

Uterine sarcomas arise from mesenchymal stem cells which may be unipotential or bipotential (carcinosarcoma). Uterine sarcomas account for 10% of malignant tumors of uterine corpus. *In adults*, the three main uterine sarcomas are: endometrial stromal sarcoma, leiomyosarcoma and mixed sarcomas of müllerian origin (carcinosarcoma and adenosarcoma), all present in the uterine corpus. Their age incidence, relative frequency and prognosis are presented in Table 17-22. About 33% of patients present with a locally advanced or metastatic disease (Ries et al, 2007). Endometrial stromal sarcoma is the least common and least aggressive. *In children*, embryonal rhabdomyosarcoma (botryoid sarcoma) is the main mesenchymal sarcoma and contrary to adults, it affects the uterine cervix or vagina.

1. Endometrial stromal sarcoma

It is composed of densely-packed spindle cells resembling endometrial stromal cells. It is classified into low-grade and high-grade subtypes. The low-grade variant (P 17-74) is characterized by infiltration of myometrium and extensive intravascular invasions (previously named endolymphatic stromal myosis, P 17-75). The high grade variant shows more mitotic activity (>10 per 10 HPF) but angioinvasion is absent.

2. Leiomyosarcoma

It accounts for one third of uterine sarcomas and it has been estimated that one of every 800 fibroids is a leiomyosarcoma. The median age is 50 years. Grossly, it is usually of large size (> 10 cm), of yellowish color, lacking the fibrous trabeculation of leiomyoma, shows focal necrosis and infiltrating border. The most significant indicator of malignancy is the mitotic activity, usually exceeding 5 per 10 HPF and associated with cytologic atypia (P 17-76).

3. Mixed müllerian tumor

It is a highly aggressive *carcinosarcoma* affecting elderly women. It arises from remnants of müllerian duct. The carcinoma component is an endometrial adenocarcinoma. The sarcoma component may be homologous (spindle cells) or heterologous (composed of foreign elements such as chondrosarcoma, osteosarcoma or rhabdomyosarcoma) (P 17-77). Epithelial component may be benign (*adenosarcoma*, P 17-78) and alternatively the benign component may be the mesenchymal looking one (müllerian *carcinofibroma* or carcinomesenchymoma).

Differential Diagnosis

Benign smooth muscle tumors of the uterus (P 17-79 to P 17-81) can pose a diagnostic difficulty especially when they show increased cellularity (cellular leiomyoma) or atypical (bizarre) cells (symplastic leiomyoma). The differentiation lies on the examination of ample material with careful counting of mitosis and exclusion of coagulative necrosis. In some instances mitosis is increased but it is below the required threshold for labeling the case as malignant (>3/10HPF for symplastic or atypical leiomyoma and > 5/10 HPF for cellular leiomyoma). In such instances malignant potential is uncertain and tumors are termed "smooth muscle tumor of uncertain malignant potential, STUMP".

Table 17-22 Sarcomas of the Uterine Corpus

	Endometrial Stromal Sarcoma	Leiomyosarcoma	Carcinosarcoma
Mean age (years)	45	55	65
Relative frequency	17%	27%	56%
5-y relative survival	64%	28%	22%

(US-SEER Data, 3519 patients, Ries et al, 2007)

GESTATIONAL TROPHOBLASTIC TUMORS (GTT)

GTT comprise a wide spectrum of neoplastic disorders that arise from trophoblastic tissue after abnormal fertilization. They account for only 1% of all gynecologic malignancies.. GTT are relatively common in East Asia. Women above the age of 40 years have a fivefold greater risk of developing these tumors.

GTT are classified into molar and non-molar (Nucci and Oliva, 2009) (Table 17-23). *Molar tumors* are associated with villi and represent abnormally developed placental tissue, whereas, *non-molar tumors* represent proliferation of trophoblastic epithelium not accompanied by villi. The most serious complications of molar pregnancy include: persistent gestation trophoblastic disease (20% of cases) and choriocarcinoma (2-5% of cases). Choriocarcinoma is highly-aggressive if untreated, but curable (90-100%) with methotrexate chemotherapy.

Molecular Oncogenesis

In moles, the excess of paternal chromosomes probably contributes to the induction of trophoblastic hyperplasia, resulting from overexpression of growth factors. However, in *choriocarcinoma*, expression of several oncogenes (HER2, C-myc, Bcl-2 and telomerase) and loss of function of tumor suppressor genes (p53 and RB) have been reported (Kantarjian et al, 2011).

Classification

1. Hydatidiform mole (HM)

A benign tumor which includes two entities: complete and partial HM, typical features of which are presented in (Table 17-24 and P 17-82) .

a. The complete hydatidiform mole develops when an empty ovum is fertilized by two sperms or by one diploid sperm. Grossly, it appears as grape-like vesicles and histologically it shows large edematous avascular villi covered by the 3 types of trophoblastic cell, syncytiotrophoblast intermediate and cytotrophoblast (Fig 17-8). The fate of the

Table 17-23 Classification of Gestational Trophoblastic Tumors

Behavior	Molar	Non-molar
Non-neoplastic		Placental site nodule
	-	Exaggerated placental site
Benign	Partial hydatidiform mole	-
	Complete hydatidiform mole	-
Intermediate (borderline)	Invasive hydatidiform mole	Placental site trophoblastic tumor
Malignant	-	Epithelioid trophoblastic tumor
	-	Choriocarcinoma

(Nucci and Oliva, 2009)

Table 17-24 Types of Hydatidiform Mole

Item	Complete	Partial
Karyotype	46XX, 46XY	69XXY
DNA cytometry	Diploid	Triploid
Fetal parts	Absent	Present
Villous edema	Diffuse	Focal
Trophoblast	Circumferential	Focal
Atypia	Present	Absent
hCG	+++	+
Pre-eclampsia	+	-
Choriocarcinoma	2%	Rare

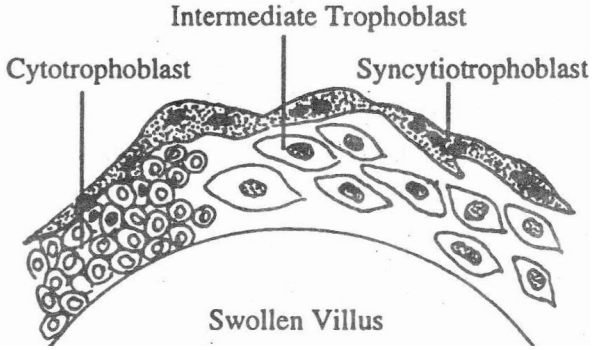

Fig 17-8 *The three cell types of trophoblasts observed in conception and trophoblastic tumors.*

mole is either to remain benign (88%), or change to an invasive mole (10%) or choriocarcinoma (2%). (b) *The partial hydatidiform mole* is the result of fertilization of a normal ovum by either two sperms or one diploid sperm resulting in triploid cells. Grossly, the vesicular pattern is focal. Histologically, trophoblastic proliferation is confined to syncytiotrophoblast only which is present on the surface, as well as, in the stroma.

2. Invasive hydatidiform mole

It is a tumor of borderline malignancy affecting patients over the age of 40 years. Histologically, it shows enlarged villi with proliferating trophoblastic cells deeply invasive in the myometrium (P 17-83) .

3. Placental site trophoblastic tumor

It is a persistent proliferation of intermediate trophoblasts in the placental implantation site (P 17-84) . The lesion follows a normal pregnancy or abortion in 95% of cases and molar gestation in 5%. One third of patients have a positive pregnancy test and 15% of cases have malignant behavior. Histologically, it is characterized by sheets of uniform, polygonal intermediate trophoblasts invading the myometrium. The cells show variable staining with immuno-histochemistry for human placental lactogen. Evidence of malignancy are necrosis and mitosis (>5 per 10 HPF). The malignant lesion is less responsive to chemotherapy and is usually treated with hysterectomy.

4. Choriocarcinoma

It is more common in Asia (1/2000 pregnancy) than in the West (1/30,000 pregnancy). The tumor originates on top of hydatidiform mole (50%), abortion (25%) or normal pregnancy (25%). Cytogenetically, the vast majority are 46 XY. Grossly it shows extensive hemorrhage and necrosis (P 17-85). Histologically, it is a biphasic tumor composed of a central core of cytotrophoblasts surrounded by a covering of syncytiotrophoblasts, with a few intermediate trophoblasts (P 17-86). Immunohistochemically, the syncytiotrophoblasts stain for hCG. Choriocarcinoma spreads locally to the vagina (30%) and hematogenous to lungs, brain, liver and kidneys. Lymphatic spread is rare.

5. Epithelioid trophoblastic tumor (ETT)

This newly-recognized tumor is distinct from placental site trophoblastic tumor and choriocarcinoma; with risk of metastasis of 10-20%. Histologically, it is composed of intermediate trophoblast with epithelioid features (resembling squamous carcinoma), focal necrosis, and high Ki-67 labeling index (>10%). Tumor cells are immunoreactive to hCG and CK18.

Staging

In the FIGO staging for gestational trophoblastic tumors (Table 17-25), stage I is assigned to tumors confined to uterus and this is subclassified to three substages (A, B and C) according to lack (IA absent) or association (IB one risk and IC two or more of risk factors, namely: age >40 years, antecedent abortion or term pregnancy, interval of >4 months from index pregnancy, pretreatment hCG of >40,000, tumor size >5 cm, and finally previous failed chemotherapy). In stage II, tumor extends outside uterus but it is limited to genital organs. Stage II with absent risk factors is IIA, with one risk IIB and with two risks IIC. In stage III tumor extends to lungs with or without genital tract involvement. Stage III with no risk factors is IIIA, with one risk is IIIB and with two risk factors is IIIC. Stage IV is metastasis to sites other than lungs. If this is without risk factors then it is stage IVA, with one risk it is IVB and with two risk factors it is IVC (Kohorn, 2001).

Table 17-25 FIGO Staging of Gestational Trophoblastic Tumors (GTT)

Stage I	GTT confined to uterus
Stage II	Extrauterine spread to adnexa
Stage III	Lung metastases
Stage IV	Other metastatic sites

High risk factors include: old age (>40), antecedent full-term pregnancy, duration >4 months, hCG level >40,000 mIU/ml, tumor size (>5 cm), brain or liver metastases and prior failed chemotherapy.

Final stages: are subclassified into 3 main subgroups (A, B, C) according to absence of risk factors, presence of one risk factor and presence of two risk factors respectively.

(Kohorn, 2001 and Edge et al, 2010)

Prognosis

More than 50 years ago, metastatic gestational trophoblastic disease was invariably fatal. At present, the cure rate exceeds 90% (Kantarjian et al, 2011). This success is the result of a combination of factors, namely: effective combination chemotherapy, the ability to diagnose and monitor therapy by using β-hCG levels and identification of risk factors and their use in risk-adapted therapy.

Placental tumors

Vascular tumors are the most common tumors of placenta (Table 17-26). Other rare benign tumors may arise from ectopic tissues in placenta. Malignant tumors are invariably metastatic, mainly melanoma and lymphoma.

Table 17-26 Placental Tumors

Benign
Angioma (chorangioma)
Hemangioendothelioma
Teratoma
Giant melanotic nevus
Adrenal adenoma
Hepatocellular adenoma
Leiomyoma
Malignant (metastatic)
Melanoma
Lymphoma

(Kurman et al, 2011)

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