CHAPTER

24 Genital Malignancy

CHAPTER OUTLINE

GENERAL CONSIDERATIONS

There is wide range of geographical variation in the incidence of major genital malignancies, the reason is far from clear. In US (1985), cancer of the breast, ovary, and uterus accounts for 51% of all cancers among females. These sites accounted for 28% of all deaths caused by cancer. In most of the developed countries, cancer of the breast tops the list in female malignancies; **whereas in the developing countries, including India, genital malignancies top the list (Table 24.1)**.

VULVAR CARCINOMA

INCIDENCE

The lesion is rare, about 1.7 per 100,000 females. The distribution varies from 3–5% amongst genital malignancies.

ETIOLOGY

The etiology remains unclear. But the following factors are often related.

- **Advanced age:** Postmenopausal women with a median age of 60.
- More common amongst whites.
- Increased association with obesity, hypertension, diabetes, and nulliparity.
- Associated vulvar epithelial disorders (lichen sclerosus) (4–7%).
- **Infection** with high risk oncogenic HPV (type 16, 18, 31, 33, and 45) has been detected (20–50%) in patients with invasive vulvar cancer.

TABLE 24.1: Lifetime risk of pelvic malignancy.

	Carcinoma cervix	*Carcinoma body*	*Carcinoma ovary*
US			
▪ Black ▪ White	1.9 0.9	1.2 2.7	1.0 1.4
UK (Scotland)	1.2	0.8	1.3
Japan	1.8	0.3	0.5
India (Mumbai)	2.2	0.2	0.8

- **Others:** Smoking, immune deficiency, other STIs, syphilis, and lymphogranuloma venereum.
- Other primary malignancies have been observed in about 20% of cases with vulvar cancer. Cervix is most commonly affected; other sites are breast, skin or colon.

RISK FACTORS FOR VULVAR CANCER

- Infection with high risk oncogenic HPV
- Non-neoplastic chronic epithelial disorders (lichen sclerosis 4–7%)
- Immunocompromised state
- Smoking
- Advanced age
- Immune deficiency
- Presence of cervical neoplasia
- Melanoma
- Paget's disease
- Presence of VIN (5–96%)

PATHOLOGY

Sites

The most common site is labium majus followed by clitoris and labium minus. Anterior two-thirds are commonly affected. Malignant ulcer on the contralateral side may be multifactorial (Figs. 24.1 and 24.2).

Naked Eye

- **Ulcerative:** The features are raised everted edges, sloughing base with surrounding induration. This is common.
- **Hypertrophic:** The overlying skin may be intact or it ulcerates sooner or later. This is rare.

HISTOLOGICAL TYPES OF VULVAR CANCERS

- Squamous cell carcinoma—90% (Fig. 24.3)
- Melanoma—8–10%
- Adenocarcinoma (Bartholin's gland)
- Basal cell carcinoma
- Sarcoma (leiomyosarcoma)
- Metastatic cancers to vulva
- Yolk sac tumors

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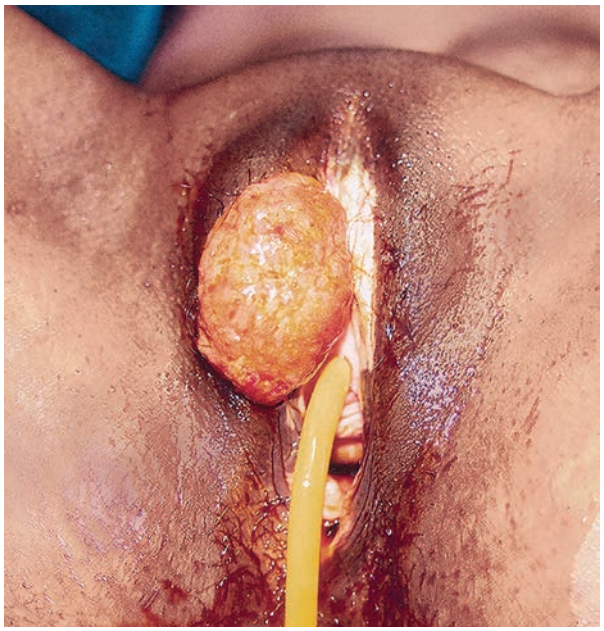

Fig. 24.1: Vulvar carcinoma on labium majus (most common site).

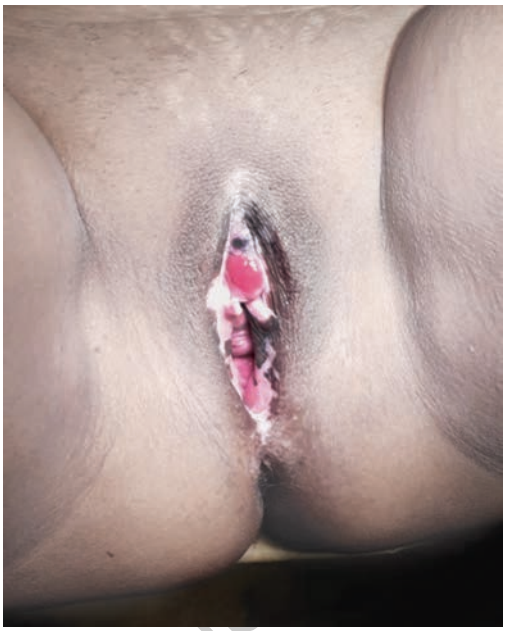

Fig. 24.2: Carcinoma clitoris (second common site of vulvar malignancy).

(*Courtesy:* Prof SN Banerjee Dept. IPGME & R, Kolkata)

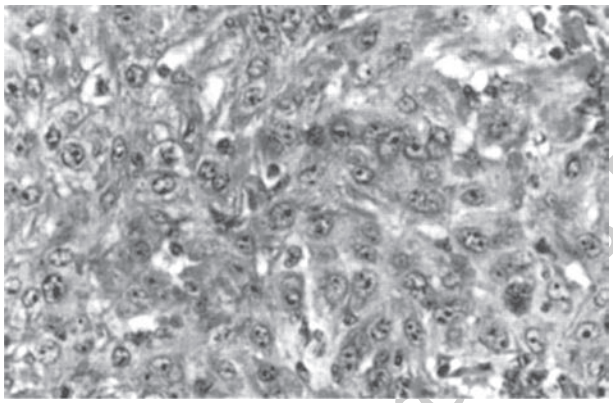

Fig. 24.3: Histological picture of vulvar squamous cell carcinoma.

SPREAD

Direct

The direct spread occurs to the urethra, vagina, rectum and even to pelvic bones. As the disease progresses, other sites in the vulva may develop neoplasia, so that multifocal sites do occur.

Lymphatics

It is the most common method of spread of lesion. It is estimated that in about 50%, the lymph glands are involved by the time the patient consults the physician.

The following facts are to be borne in mind:

- The lymphatic spread is primarily by embolization and only at a later stage, the spread is by permeation to fill the lymphatic channels.
- Contralateral metastases are not infrequent (25%) as the lymphatics of the vulva cross the midline.
- When the ipsilateral nodes are not involved from a lesion located on one side, spread to the contralateral groin node is very unlikely.
- The lymph node involvement follows a sequential pattern. The lymphatics of labia → superficial inguinal lymph nodes → deep inguinal lymph nodes → pelvic nodes.
- Pelvic nodes are secondarily involved in about 20% with affected inguinal nodes. The **nodes involved are** obturator, external iliac, hypogastric, and common iliac.
- Lymphatics of the clitoris, anus, and rectovaginal septum may drain directly into the pelvic lymph nodes.
- Involvement of pelvic nodes, bypassing the inguinal lymph nodes, is less than 3%.
- Incidence of lymph node involvement is directly related to the site, size of the lesion, and the depth of stromal invasion (Table 24.2). Chance of bilateral lymph node involvement also increases when the midline structures (clitoris, perineum) are involved.
- Histologically proved groin node involvement is present in 25% when missed on clinical assessment. In almost 25%, the nodes are histologically negative when clinically thought to be involved. Approximate incidence of lymph node involvement is given in Table 24.2.
- **Regional lymph nodes** are assessed clinically and also by using MRI (p. 100), **sentinel node lymphoscintigraphy** (p. 285), ultrasound, and PET (p. 101).

TABLE 24.2: Depth of stromal invasion and groin lymph node involvement in squamous cell carcinoma of vulva.

Depth of invasion (mm)	*Percent with positive nodes*
<1	0
1–2	7.5
2.1–3	10.0
3.1–5	30

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Hematogenous
This is rare but may occur in advanced cases.

CLINICAL FEATURES

Patient profile: The patients are usually postmenopausal, aged about 60 years often with obesity, hypertension, and diabetes.

Symptoms
- Asymptomatic
- Pruritus vulvae
- Swelling with or without offensive discharge
- Difficulty in urination
- Vulvar ulceration
- Bleeding
- Inguinal mass
- Pain

Signs
- Vulvar inspection reveals an ulcer or a fungating mass on the vulva. The ulcer has a sloughing base with raised, everted, and irregular edges and it bleeds to touch. Surrounding tissue may be edematous and indurated.
- Associated vulvar lesions mentioned earlier may be present.
- Inguinal lymph nodes of one or both the sides may be enlarged and palpable. The enlargement may also be due to infection.
- Clinical examination of the pelvic organs, including the cervix, vagina, urethra, and rectum must be done. This is due to the coexistence of other primary cancers in the genital tract.

Diagnosis
The diagnosis is confirmed by **biopsy**.
- When a definite growth is present, the biopsy is to be taken from the margin.
- Cystourethroscopy, proctoscopy CT/MRI scan (for regional nodes and metastatic disease) may be needed.
- **Colposcopic examination** of the vulva (vulvoscopy) is done by the following application of 3% acetic acid for 5 minutes. Biopsies from the most suspicious aceto-white areas are taken.
- In cases of vulvar dystrophy, the biopsy sites are from multiple areas usually from the persistent red areas or from stained areas following toluidine blue test.

DIFFERENTIAL DIAGNOSIS

The lesion needs differentiation from:
- Condyloma accuminata
- Syphilitic ulcer
- Tubercular ulcer
- Lymphogranuloma venereum
- Soft sore.

STAGING

The staging is based on clinical examination **and includes only the primary carcinoma, excluding melanoma**. The FIGO classification is widely used (Table 24.3).

TABLE 24.3: FIGO staging of carcinoma of the vulva (modified 2009).

STAGE I	**$T_{1/2}$, N_0, M_0. Tumor confined to the vulva**
IA	Tumor confined to the vulva or perineum, ≤2 cm in size with stromal invasion ≤1 mm*, negative nodes
IB	Tumor confined to the vulva or perineum, >2 cm in size or with stromal invasion >1 mm*, negative nodes
STAGE II	**T_3, N_0, M_0. Tumor of any size with adjacent spread (1/3 lower urethra, 1/3 lower vagina, anus), negative nodes**
STAGE III	**T_{1-3}, $N_{1/2}$, M_0. Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguinofemoral lymph nodes**
IIIA	Tumor of any size with positive inguinofemoral lymph nodes ■ With 1 lymph node metastasis (≥5 mm) or ■ With 1–2 lymph node metastasis(es) (<5 mm)
IIIB	■ With 2 or more lymph nodes metastases (≥5 mm) or ■ 3 or more lymph nodes metastases (<5 mm)
IIIC	With positive node(s) with extracapsular spread
STAGE IV	**Any T, any N, MI. Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures**
IVA	Tumor invades any of the following: ■ 2/3 upper urethra, 2/3 upper vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone or ■ Fixed or ulcerated inguinofemoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

*The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

CAUSES OF DEATH
- Uremia from ureteric obstruction due to enlarged common iliac and para-aortic nodes.
- Rupture of the femoral vessels by the overlying involved inguinal lymph node.
- Sepsis.

MANAGEMENT

Prophylactic
- Adequate therapy for non-neoplastic epithelial disorders of the vulva (Ch. 18).
- Adequate therapy for persistent pruritus vulvae in postmenopausal women.
- Multiple biopsies in conservative treatment of vulvar intraepithelial neoplasia (VIN).
- Simple vulvectomy in postmenopausal women with VIN where follow-up facilities are not available.

Definitive Treatment
- **Microinvasive lesion (Stage IA):** The invasion is less than 1 mm (stage IA), wide local excision with or without ipsilateral groin lymphadenectomy may be done with follow up. Generally, there is no lymph gland involvement (Table 24.2). Tumor free surgical margin should be 1–2 cm to prevent local recurrence.

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There is increased incidence of lymph node involvement in lesion of more than 1 mm invasion. It is thus prudent to perform **radical vulvectomy with bilateral groin node dissection in all cases of stromal invasion more than 1 mm**.

- **Early invasive stage:** Stage IB and II of vulva and clinically negative nodes. Radical resection (1–2 cm surgical margin) of the primarily tumor and ipsilateral inguinofemoral lymphadenectomy is done. Occasionally, a radical complete vulvectomy may be needed, depending on tumor size and location (midline) (p. 501).

Three separate incision (one for radical vulvectomy and one each for groin node dissection) approach is currently preferred instead of en-block approach (Fig. 35.17).

Pelvic node metastases are rare unless inguinofemoral nodes are involved. Pelvic lymphadenectomy in cases of positive deep node involvement is omitted in preference to external radiation on the groin and pelvis—in the form of 4500–5000 cGy, usually 4–6 weeks after surgery.

Negative **sentinel lymph node** biopsy for micrometastasis may avoid extensive lymphadenectomy. Radical vulvectomy is often associated with major long-term morbidity, sexual dysfunction and loss of body image. Radical local excision of the vulva with wide margins (1–3 cm) is considered to be an alternative to radical vulvectomy with equal result.

- **Advanced vulvar cancer (stage III to IV) or if the general condition is poor and/or in presence of comorbid conditions.**

The following principles may be adopted:

- Two stage operation is preferred. Total vulvectomy followed by at a later date, bilateral inguinofemoral lymphadenectomy.
- Total vulvectomy followed by full pelvic and groin irradiation (megavoltage therapy).
- **Stage III** cases with resectable tumors may undergo radical vulvectomy with inguinofemoral lymphadenectomy (nodal debulking) and postoperative pelvic and inguinal growth irradiation. Platinum-based concurrent chemotherapy with radiation therapy is found to be effective. Radical vulvectomy may be done 5 weeks after the completion of chemoradiation therapy.
- **Neoadjuvant chemotherapy**—followed by surgery, radiotherapy or both.
- ***Technically inoperable or recurrent lesion***

  Multimodal approach is made to provide palliation.
  - **Chemotherapy** (cisplatin, gemcitabine bleomycin, 5-FU) can be used as radiation sensitizer.
  - **Chemoradiation therapy** may be combined as primary therapy or following surgical excision of the tumor.
  - **Radiotherapy:** Intensity modulated radiotherapy (IMRT) offers greater sculpting art of covering of radiation delivery to minimize toxicity.
  - **RESULTS**
- **With negative groin nodes**, the 5-year survival rate for invasive carcinoma ranges from 90–100%.

TABLE 24.4A: 5-year survival rate of vulval carcinoma by stage.

Stage	*Survival (%)*
I	90–100
II	65–75
III	35–45
IV	20–30

TABLE 24.4B: 5-year survival rate by node status.

Nodes	*Survival (%)*
Negative nodes	80–100
Positive inguinal femoral nodes	30–50
Positive pelvic nodes	10–20

- **With positive groin nodes**, the survival rate falls to 20–55%.
- **With positive pelvic nodes**, the survival rate falls even below 20%.

PROGNOSIS

Approximate 5-year survival rate in squamous cell carcinoma is tabulated in Tables 24.4A and B.

Prognostic Factors

- Clinical stage of the disease
- Site of the tumor
- Depth of stromal invasion
- Lymphovascular space involvement
- Lymph node involvement (inguinofemoral and pelvic)
- Tumor diameter and differentiation (grade)
- DNA ploidy status.

MELANOMA

It is the second most common vulvar cancer. The common sites are the clitoris and labia minora. It may arise from a junctional nevus. Radical vulvectomy and bilateral regional lymphadenectomy (en-block) is the preferred treatment. Pelvic lymph adenectomy does not alter the prognosis. Radiation therapy, adjuvant chemotherapy, or immunotherapy (α interferon) are of limited benefit. Overall prognosis is poor.

BARTHOLIN'S GLAND CARCINOMA

Primary malignancy can be adenocarcinoma, squamous cell carcinoma or transitional cell carcinoma. The surgery is like that of squamous cell carcinoma of the vulva. The surgery is radical vulvectomy with inguinofemoral lymphadenectomy. Postoperative radiation reduces the recurrence. In addition, part of the lower vagina, levator ani, and the ischiorectal fat are to be removed. Prognosis in a case of Bartholin gland carcinoma is similar to squamous cell carcinoma when compared to stage of the disease.

Basal cell carcinoma of the vulva is rare (2%) of all vulvar carcinomas. It is generally ulcerated. Wide local excision of the lesion with wide surgical margin (2–3 cm) is the treatment and the disease is cured.

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VAGINAL CARCINOMA

PRIMARY VAGINAL CARCINOMA

Incidence

The incidence of primary vaginal carcinoma is very rare (about 0.6 per 100,000 women). It constitutes about 1% of genital malignancies. **The primary vaginal carcinoma should fulfill the following criteria.**

- The primary site of growth is in the vagina.
- The cervix and the vulva must not be involved.
- There must not be clinical evidence of metastatic disease.
- Carcinoma of vagina is mostly metastatic.

Etiology

Exact etiology is unknown. Following factors are often related:

- HPV may have a causal relationship.
- Progression from VaIN.
- Women with history of cervical cancer (multicentric neoplasia).
- Diethylstilbestrol (DES) is related with clear cell adenocarcinoma of the vagina. This is found in those who had history of intrauterine exposure to diethylstilbestrol.
- Previous irradiation therapy to the vagina or immunosuppression.
- Prolonged use of pessary.
- More common amongst whites than blacks.

Pathology

Site: The most common site is in the upper-third of the posterior wall (Fig. 24.4).

Naked eye: The growth may be ulcerative or fungative.

Histopathology: **Squamous cell carcinoma** accounts for more than 90% of the cases. The rest are adenocarcinoma (8–10%), melanoma, fibrosarcoma, sarcoma botryoides and malignant mixed mullerian tumors.

Spread is by direct continuity, by lymphatics (p. 13 anatomy) and rarely, blood borne. Inguinofemoral lymph nodes and pelvic lymph nodes are commonly involved. Lymphatics spread of upper vagina drain to the pelvic and para-aortic nodes, mid vagina, to the pelvic and groin nodes and the lower vagina to the inguinofemoral nodes. Imaging studies, MRI or PET-CT can assess the extent of spread and the lymph node metastasis. Hematogenous spread involves the lungs, liver or the bones.

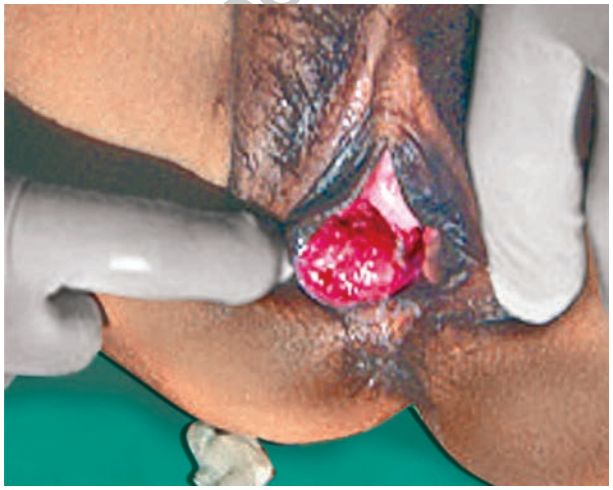

Fig. 24.4: Vaginal carcinoma.

Clinical Features

The mean age of the patient is about 55 years.

Symptoms

- May be asymptomatic, being accidentally discovered during routine screening procedures.
- Abnormal vaginal bleeding including postcoital bleeding is conspicuously present as an early symptom.
- Foul smelling discharge per vaginum.

Signs

- Speculum examination reveals an ulcerative, nodular or exophytic growth.
- The cervix looks apparently normal.

Diagnosis

- During cytology, screening procedure to detect abnormal cells.
- Colposcopic examination and targeted biopsy are helpful for patients with abnormal cytology or unexplained vaginal bleeding.
- Cystourethroscopy, proctosigmoidoscopy, CT/MRI/PET (for nodes and metastases), are done.
- Biopsy from clinically suspected lesion.

Staging

The clinical staging as outlined by FIGO is tabulated on Table 24.5.

Treatment

Primary prevention: Primary vaccination against HPV 16, 18 is effective.

Secondary prevention: Vault smear following hysterectomy due to persistent high-grade squamous intraepithelial lesions (HSIL), is to be done.

Tertiary prevention: Management of precancerous lesion of the vagina is to be done.

Radiotherapy or surgery or the combination is the accepted modality of therapy for invasive primary

TABLE 24.5: Staging of vaginal carcinoma FIGO (1995).

Stage 0	Carcinoma in situ
Stage I	Carcinoma is limited to the vaginal wall
Stage II	Carcinoma has involved subvaginal tissue but has not extended to the pelvic wall
Stage III	Carcinoma has extended to the pelvic wall
Stage IV	Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. a. Adjacent organs are involved (bladder, rectum) b. Distant organs are involved

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carcinoma of the vagina. Choice depends on the age, clinical stage, anatomical location, and size of the lesion.

Stage I:

- **Growth limited to the upper-third**: Radical hysterectomy, partial vaginectomy, and bilateral pelvic lymphadenectomy is the treatment of choice (as that of stage IB carcinoma cervix).
- **Growth limited to the lower-third:** Radical vulvectomy with removal of bilateral inguinofemoral lymph nodes along with vaginectomy.

Stage II–IV: Radiation, chemoradiation is done by external beam therapy with intracavity or interstitial radiation. Concurrent cisplatin based chemoradiation is thought to have higher efficacy. Care is to be taken to prevent bladder or rectal injury.

Pelvic exenteration operation (p. 293) is done when there is failure with radiation therapy.

Cure Rate

Overall 5-year survival rate ranges from 80% for stage I disease to 10% for stage IV disease.

SECONDARY CARCINOMA OF THE VAGINA

Secondary vaginal malignancy follows carcinoma vulva, cervix or urethra by direct spread. Metastases in the lower-third of the anterior vaginal wall or vault occur in cases of choriocarcinoma (Fig. 24.16) or endometrial carcinoma.

POINTS

- In most of the developed countries, cancer of the breast tops the list in female malignancies, whereas in the developing countries including India, genital malignancies (cancer cervix) top the list.
- **Vulvar cancer** usually occurs in postmenopausal women with median age of 60 years. Vulvar cancer accounts for 3–5% of all genital malignancies.
  The most common site is labia majora followed by clitoris and labia minora. Ulcerative type is more common than the hypertrophic type. In 90%, it is well-differentiated squamous cell carcinoma. The spread is predominantly by lymphatics both ipsilateral and contralateral (25%). Involvement of pelvic nodes bypassing the inguinal is less than 3%.
  Causes of death are due to uremia, rupture of the femoral vessels and sepsis.
  Microinvasive lesion of less than 1 mm requires wide local excision and follow up as metastasis to regional nodes are rare. Invasion of more than 1 mm requires radical vulvectomy with bilateral groin node dissection.
  Frank invasive carcinoma should be dealt with by radical vulvectomy with bilateral inguinofemoral lymphadenectomy. Pelvic lymphadenectomy is omitted in preference to radiation to the groin and pelvis—4500 to 5000 cGy 4–6 weeks after operation. With negative groin nodes, the 5-year survival ranges from 90–100%; with positive groin nodes, the survival rate falls to 20–55% and with positive pelvic nodes, the survival rate is only 20%.
- **Prognosis of vulvar carcinoma** depends on many factors. HPV positive younger patients tend to have a better prognosis.
- **Melanomas** comprise 5% of vulvar cancer and overall 5-year survival is about 50%. **Basal cell vulvar carcinoma** is treated by wide local excision.
- **Primary carcinoma of vagina** is rare and most vaginal cancers are metastatic. It constitutes 2% of gynecological cancers. The most common site is in the upper-third of the posterior wall. The mean age is 55 years. Squamous cell carcinoma accounts for 90% of the cases. 5-year survival rate is about 40–45%.
  Clear cell adenocarcinoma is seen in adolescent girls, who have had history of intrauterine exposure to diethylstilbestrol. Radical hysterectomy, vaginectomy with pelvic lymphadenectomy is the surgery.
- **Surgery** is the treatment of choice for upper vaginal, low stage tumor in younger patients. However, chemoradiation is used widely as a primary therapy. Ideally, 7000–7500 cGy is administered in less than 9 weeks.

CARCINOMA CERVIX

MAGNITUDE OF THE PROBLEM

- Cancer cervix is the lead cause of cancer and the cancer related deaths in women worldwide. More than 5,27,600 new cases and 2,65,700 deaths are recorded annually. More than 85% of these cases and deaths occur in low and middle income countries (LMICs).
- In India cervical cancer is a major public health problem. In India, carcinoma cervix is the second most common gynecological malignancy.

  It is expected to improve with organized screening program.
- Pap smear has reduced the incidence of cervical cancer by nearly 80% and death by 70%.
- HPV vaccine is safe and effective. It is expected to reduce the incidence of cervical cancer by 90–100%. Cervical cancer is an entirely preventable disease as the different screening, diagnostic and therapeutic measures are effective.
- Improvement is needed in the areas of economic resources. It needs changes in culture and implementation of organized screening programs. Disease could be treated in the preinvasive phase as it lasts several years before it becomes invasive and incurable.

Incidence

In India, twelve population-based cancer registries (PBCRs) showed cancer breast was the most common followed by cancer of the cervix (ICMR – 2004). Amongst female cancers, relative proportion of cancer breast varied between 24% and 28% whereas that of cancer cervix was

between 14 and 24%. In India, an overall incidence of 23.5/100,000 has been observed (WHO – 2008).

EPIDEMIOLOGY

In India, the prevalence is more amongst the comparatively younger age group (45 years). Carcinoma cervix is rare in women who are sexually not active (nuns, virginal women). Male circumcision is partially protective against cervical carcinogenesis.

GROSS PATHOLOGY

The site of the lesion is predominantly in the ectocervix (80%) and the rest (20%) are in the endocervix.

Naked Eye

- **Exophytic:** These arise from the **ectocervix** and form friable masses almost filling up the upper vagina in late cases. It has a cauliflower like appearance.
- **Ulcerative:** The lesion excavates the cervix and often involves the vaginal fornices (Fig. 24.5).
- **Infiltrative (endophytic):** These are found in **endocervical** growth. They cause expansion of the cervix, so that it becomes barrel-shaped. Diagnosis is often late.

Histopathology

The most common variety is squamous cell carcinoma (80–85%) either well-differentiated or moderately or poorly differentiated (Fig. 24.6). These arise from the ectocervix. **The sources of the squamous epithelium which turn into malignancy are**—squamocolumnar junction, squamous metaplasia of the columnar epithelium.

Squamous cell carcinomas (80–85%)	*Adenocarcinomas (15–20%)*
▪ Large cell (keratinizing or nonkeratinizing) ▪ Small cell (poor prognosis) ▪ Verrucous (warty tumor) ▪ Neuroendocrine tumor (highly aggressive) ▪ Glassy cell carcinoma (virulent variety)	▪ Endocervical ▪ Endometrioid ▪ Clear cell ▪ Adenoma malignum (good prognosis) ▪ Adenosquamous ▪ Mixed carcinomas
	Others
	Large cell, nonkeratinizing are common, sarcomas, lymphomas are rare

MODE OF SPREAD

Direct Extension

The growth spreads directly to the adjacent structures, to the vagina and to the body of the uterus. It extends laterally to the parametrium, paracervical and paravaginal tissues. Here, the tumor cells surround and compress the ureter. It may spread backwards along the uterosacral ligament, to involve the rectum or forwards to involve the base of the bladder, especially in endocervical growth.

Lymphatic

The primary group involved are—parametrial nodes, internal iliac nodes, obturator, external iliac nodes, rectal and sacral nodes. The secondary nodes involved are—common iliac group, the inguinal nodes, and para-aortic nodes (Table 24.6 and Fig. 24.7). Obturator nodes are commonly involved (19%). Left supraclavicular nodes (scalene nodes) are involved after the para-aortic nodes.

Sentinel lymph node (SLN) is the first node that drains the primary tumor. In most cases (85%) there is a single sentinel lymph node (Ch. 38). This node can be detected by intraoperative lymphatic mapping injecting methylene blue dye into the tumor or lymphoscintigraphy using technetium 99.

Hematogenous

Blood-borne metastasis is late and usually by veins rather than the arteries. Lungs, liver or bone are usually involved.

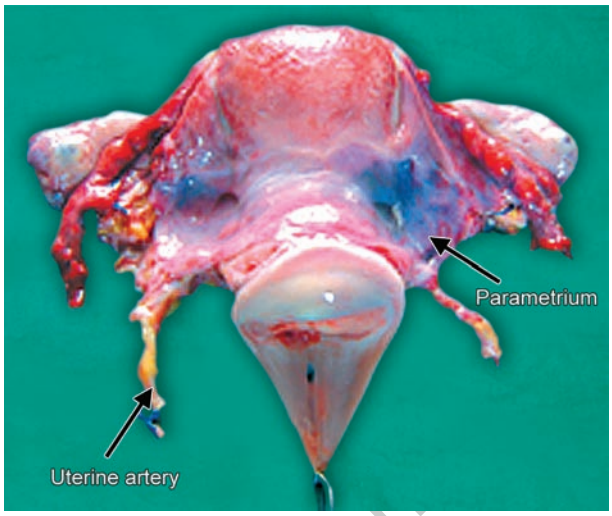

Fig. 24.5: Ulcerative type of cervical malignancy with a friable growth on the posterior lip. Radical hysterectomy done. Uterine arteries are ligated at origin (p. 507).

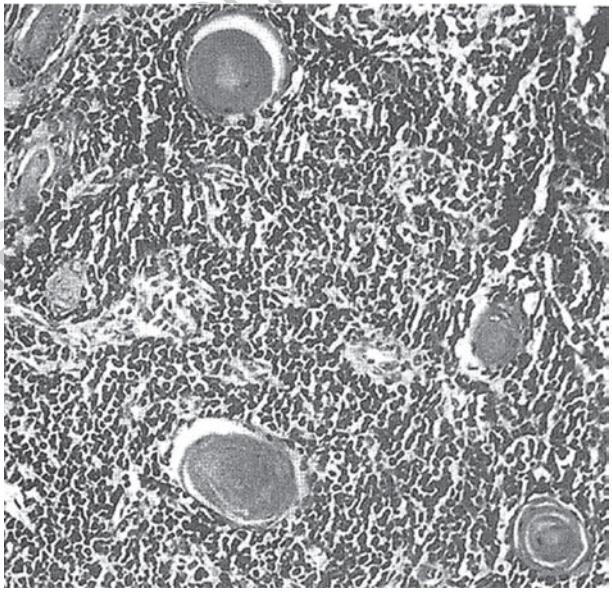

Fig. 24.6: Histology of squamous cell carcinoma of the cervix (small cell type). Keratin pearls within the nests of malignant cells are seen.

TABLE 24.6: Involvement of lymph nodes in different stages (Approximate).

Stage	Pelvic nodes (%)	Para-aortic nodes (%)
0	0	0
Ia_1 (<3 mm)	0–0.5	0
Ia_2 (3–5 mm)	5	<1
Ib	16	2
II	30	15
III	44	30
IV	55	40

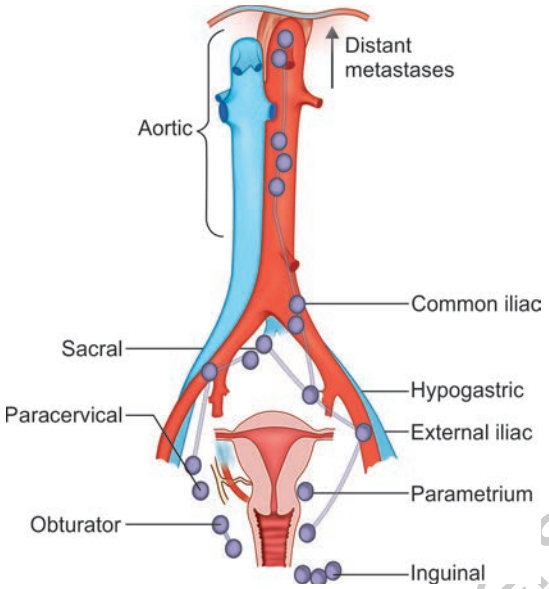

Fig. 24.7: Lymph node involvement in cervical cancer.

TABLE 24.7: Staging procedures allowed by FIGO.

- Inspection of cervix and vagina (speculum examination)
- Pelvic examination (vaginal, rectovaginal) under anesthesia

PROCEDURE USED	DETECTION
• Lymph node palpation	Enlargement and site
• Colposcopy	(*see* above)
• Hysteroscopy	Extension and depth of tumor spread
• Cystoscopy	
• Biopsy	
• Endocervical curettage	
• Conization	
• Chest X-ray	Pulmonary metastasis
• Skeletal X-ray	Bone metastasis
• Intravenous urogram/USG	Hydronephrosis
• Barium enema	Large bowel involvement
• Proctoscopy	Rectal involvement
• CT	Lymph node, metastasis, tumor size, depth of stromal invasion
• MRI	Lymph node metastases, tumor size, depth of stromal invasion, vaginal and parametrial extension
• FDG-PET	Lymph node (FDG-PET)—superior to CT/MRI
• PET-CT	Metabolic and anatomic spread of the disease

Direct Implantation

Direct implantation of the cancer cells at operation on the vault of the vagina or abdominal or perineal wound is very rare.

The risk of ovarian metastases in stage I squamous cell carcinoma of the cervix is 0.5% and it is 1.7% for adenocarcinoma.

STAGING

The purposes of staging are to determine the prognosis, to formulate the line of treatment and to compare the results of one to the other.

- **Staging of cervical cancer is based principally on clinical examination.** In cases with suspected pelvic inflammation, a course of antibiotic should be given prior to clinical staging.
- **Final staging cannot be changed once therapy has begun.**
- When doubt exists as to the correct stage, the lower stage should be assigned.
- **CT, MRI, positron emission tomography (PET), lymphangiography (p. 100 and 101)** can detect involvement of the pelvic parametrial or periaortic lymph nodes. MRI is helpful to detect parametrial extension and to define the tumor volume (Table 24.7).

Imaging and pathology can be used where available, to supplement the clinical findings. Notations are to be added: r (imaging) and p (pathology) to indicate the findings. The type of imaging modality or pathology technique used should always be documented.

The clinical staging as recommended by FIGO is tabulated in Table 24.8 and shown in Figure 24.8.

PROGNOSIS

Poor prognostic indicators:

- Tumor size (≥4 cm), involvement of the lymph nodes and positive lymph vascular invasion (LVSI)
- Extra cervical spread (≥10 mm), deep stromal invasion (>70%).
- Adenocarcinoma patients have poorer prognosis compared to patients with squamous cell carcinoma.
- Patients with higher serum values of squamous cell carcinoma antigen (SCA) have poorer survival rate.
- Poor prognosis with the presence of HPV mRNA in the blood of the patient.

Lymph node involvement (pelvic and para-aortic) reduces the survival rate by 50%.

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TABLE 24.8: FIGO staging of carcinoma of the cervix uteri (2018).

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.

[a]Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.

[b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r, and if confirmed by pathologic findings, it would be stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

SURGICAL STAGING OF CANCER CERVIX

There are often discrepancies between clinical staging and surgicopathological findings. Assessment of the pelvic and para-aortic nodes is done by laparoscopy.

DIAGNOSIS

- Early carcinoma (stage IA, IB, IIA)
- Advanced carcinoma (stage IIB–IVB).

The stage once made after all the imaging and pathology report cannot be altered later.

Histopathology grades

1. GX: Cannot be assessed
2. G1: Well differentiated
3. G2: Moderately differentiated
4. G4: Undifferentiated.

Early Carcinoma

Nomenclature: The concept of early carcinoma of the cervix is not well-defined. Presumably, it should include those lesions which have got minimal morbidity and deaths with the best available therapy and a maximal 5-year survival rate. With these criteria, the following stages as per FIGO classification are included in the category of early carcinoma.

Preclinical

There may not be any symptom nor any pelvic finding to raise any suspicion. The cervix may look apparently healthy. The diagnosis is made by the following:

- During screening procedures.
- Incidental on histological examination of tissues removed by biopsy, portio amputation or removal of the uterus.

Stage IA (microinvasive carcinoma)

Microinvasive carcinoma is one which is predominantly intraepithelial carcinoma, except that **there is disruption of the basement membrane**. The mean age is 38–42 years.

In majority, the entity is asymptomatic. There may be blood stained discharge, intermenstrual, postcoital or postmenopausal bleeding. The cervix may look abnormal like ectopy, eversion or cervicitis.

The diagnosis is made only on biopsy of the cervix. Initial screening may be done with cytology, colposcopy, and directed biopsy along with endocervical curettage (ECC).

Clinical

Stage IB (overt)

Symptoms

The duration of symptoms is not proportionate to the stage of the disease.

- Menstrual abnormalities in the form of contact bleeding or bleeding on straining (during defecation), intermenstrual bleeding are very much suspicious, especially over the age of 35.
- Excessive white discharge which may be at times offensive. This is often detected during the screening procedure.

Signs

Speculum examination reveals

- Either a red granular area which looks like an ectopy (erosion) extending from the external os or a **nodular**

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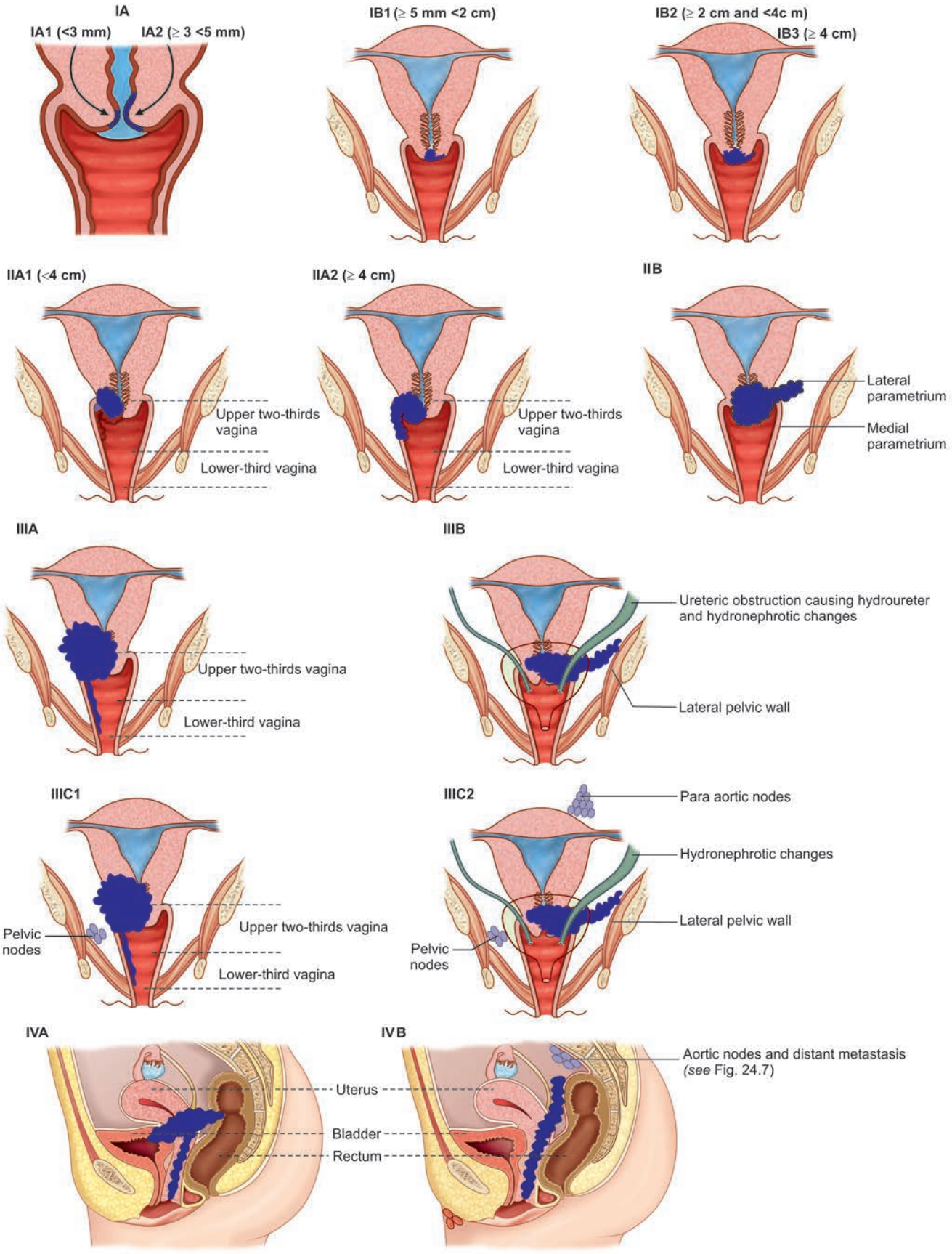

Fig. 24.8: Diagrammatic representation of staging of carcinoma cervix according to FIGO.

growth or an ulcer. The lesion bleeds on friction. **Speculum examination should be done prior to bimanual examination.** The cervical lesion may not be visible due to bleeding from the friable lesion caused by digital examination.

Bimanual examination reveals the lesion is indurated, friable, and bleeds to touch. Cervix is freely mobile.

Rectal examination reveals the parametrium absolutely free.

Confirmation of diagnosis is by biopsy

Ancillary aids for confirmation of staging:

- Cystoscopy
- X-ray chest
- Intravenous pyelography
- Proctoscopy
- USG, CT or MRI, PET-CT.

All these give usually a negative finding and as such, the clinical staging of IB is thereby confirmed.

Other investigations permitted to use for FIGO staging

- **MRI:** Useful to measure tumor size, tumor extent, bladder, rectum, parametrium, and lymph node involvement.
- **CT** is commonly used to detect nodal involvement and distant metastasis. However CT, MRI, PET may be used for FIGO staging.
- **PET (p. 101):** FDG-PET is superior to CT or MRI for detection of node metastasis (size > 5 mm). PET is used for planning the field of radiation, or planning palliative chemotherapy.

Advanced/Late Carcinoma

All cases of carcinoma with stage II B and onwards are arbitrarily called advanced carcinoma considering the reduced 5-year survival rate compared to earlier stages. In fact, in India, this group comprises about 80% of the total cervical carcinoma patients attending the hospitals for treatment.

PATIENT PROFILE

The patients are usually multiparous, in premenopausal age group. They have previous history of postcoital or intermenstrual bleeding which they ignored. Most of them do not have Pap smear screening.

Symptoms

- **Irregular or continued vaginal bleeding** which may at times be brisk.
- **Offensive vaginal discharge.**
- **Pelvic pain** of varying degree: This may be either due to involvement of uterosacral ligament leading to backache or deep seated pain due to involvement of sacral plexus.
- **Leg edema** is due to progressive obstruction of lymphatics and/or iliofemoral veins by the tumor.
- **Bladder symptoms** include frequency of micturition, dysuria, hematuria or even true incontinence due to fistula formation.
- **Rectal involvement** is evidenced by diarrhea, rectal pain, bleeding per rectum or even rectovaginal fistula.
- **Ureteral obstruction** is due to progressive growth of tumor laterally. There may be frequent attacks of pyelonephritis due to ureteric obstruction.

Ultimately, the patient may be **cachectic, anemic with edema legs. Ultimately uremia develops.**

Speculum examination reveals the nature of the growth, ulcerative or fungating which bleeds to touch.

Bimanual examination reveals the induration and extent of the growth to the vagina and to the sides. The induration of the bladder base may be felt through the anterior fornix in advanced cases.

Rectal examination is invaluable to note the involvement of the parametrium and its extent in relation to the lateral pelvic wall. Nature of induration is to be noted carefully. **If it is smooth**, the possibility of inflammation has to be excluded and antibiotics has to be given prior to final assessment for staging. **In malignancy, the induration is nodular**. Incidental involvement of the rectum has to be noted.

For confirmation of diagnosis, *biopsy* is mandatory. If the lesion is small, wedge biopsy is taken which should include a portion of the healthy tissue as well. If it is big, a bit may be taken (punch biopsy) from a comparative non-infective area. There may be brisk hemorrhage which can be effectively controlled by plugging.

Sentinel lymph node mapping and excision can be done. Lymphazurin or isosulfan blue is injected in the cervix (3 and 9 o'clock position). The radioactive blue nodes are identified. Serial node sectioning and immune histochemistry stains identifies the disease volume.

For staging of the disease—procedures (*see* above).

DIFFERENTIAL DIAGNOSIS

The growth needs to be differentiated from:

- Cervical tuberculosis
- Syphilitic ulcer
- Cervical ectopy
- Products of conception in incomplete abortion
- Fibroid polyp.

COMPLICATIONS

The following complications may occur sooner or later, as the lesion progresses.

- **Hemorrhage.**
- **Frequent attacks** of ureteric pain, due to pyelitis and pyelonephritis and hydronephrosis.
- **Pyometra** especially with endocervical variety.
- **Vesicovaginal fistula**.
- **Rectovaginal fistula:** This is comparatively rare because of the interposition of the pouch of Douglas. The rectum may be involved either through the uterosacral ligament or through rectovaginal septum.

CAUSES OF DEATH

The patient may die of:

- **Uremia:** This is due to ureteric obstruction following parametrial involvement. There is hydroureter and

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hydronephrosis. Infection supervenes, thereby further compromising kidney functions.

- **Hemorrhage:** The vaginal bleeding from the growth may be brisk or continuous. This leads to anemia and ill health.
- **Sepsis:** Localized pelvic or generalized peritonitis may occur which may be fatal.
- **Cachexia:** The cumulative effect of the factors mentioned leads to cachectic condition. The cancerous tissues have got depressant action on general metabolism.
- **Metastases** to the distant organs commonly observed are—lung (36%), lymph nodes (30%), bone (16%) and abdominal cavity (7%). These may be fatal.

MANAGEMENT OF CARCINOMA CERVIX

- **Preventive**
- **Curative**

Preventive

Primary Prevention

It involves identifying the causal factors and eliminating or preventing those from exerting their effects. Initiation of population based, organized screening program [cervical cytology, primary HPV testing or visual inspection with acetic acid (VIA)] is urgently needed.

- **Identifying 'high-risk' female**
  - Women with high-risk HPV infection (p. 270)
  - Early age of first pregnancy
  - High parity
  - Too many births/too frequent birth
  - Long-term use of combined oral contraceptives (COCs)
  - Low socioeconomic status
  - Poor maintenance of genital hygiene.
- **Sexual behavior**
  - Early sexual intercourse
  - Multiple sexual partners
  - Previous wife died of cervical carcinoma.
- **Prophylactic HPV vaccine** (p. 274) is approved to all school girls (12–18 years) and women (16–25 years). Two or three doses are usually to be given (bivalent 0–2–6 month or quadrivalent 0–1–6 month).
- **Use of condom** during early intercourse, raising the age of marriage and of first birth, limitation of family, maintenance of local hygiene, and effective therapy of sexually transmitted infections (STIs) are the positive steps in prevention.
- **Removal of cervix during hysterectomy** as a routine for benign lesion is a definite step in prevention of stump carcinoma. The incidence may be as high as 1%.

Secondary Prevention

It involves identifying and treating the disease earlier in the treatable stage.

This is done by screening procedures. The details have been described in Ch. 9 and 23. It takes 10–15 years for progression of premalignant condition to the invasive carcinoma. The abnormal cervical pathology likely to progress to invasive carcinoma can be detected. Its effective therapy reduces dramatically the incidence of invasive carcinoma. Early detection and treatment of cervical carcinoma can improve the 5-year survival rate by 80–100%.

Downstaging Screening (WHO, 1986)

Downstaging for cervical cancer is **defined as** "the detection of the disease at an earlier stage when it is still curable. Detection is done by nurses and other paramedical health workers using a simple speculum for visual inspection of the cervix".

Compared to cytological screening it is suboptimal. But in places where prevalence of cancer is high and cytological screening is not available, "downstaging screening" is useful. **The strategy is, however, not expected to lower the incidence of cancer cervix, but it can certainly minimize the cancer death through early detection.**

Once the abnormality is suspected, the case is referred to a center where diagnosis and treatment of premalignant and malignant lesions are done.

Curative

Ideally, the management of the patient with cervical cancer is a team approach. Due consideration should be given to:

- General condition of the patient
- Stage of the disease
- Facilities available—surgical and radiotherapy
- Involvement of a gynecologic oncologist
- Radiation oncologist
- Wish of the patient to be judiciously complied with.

Pretreatment Evaluation

Irrespective of the treatment modalities (surgery or radiotherapy) the following evaluations are to be made apart from those already done (Table 24.7) for staging purposes.

Serum Marker (p. 438)

Commonly used serum tumor markers are: Squamous cell carcinoma antigen (SCCA), cancer antigen 125 (CA-125), and carcinoma embryonic antigen (CEA). Elevated levels of SCCA correlate with tumor size, stage, stromal invasion, and lymph node status. This antigen is not specific. However, it has been used as a means to monitor treatment response and to predict tumor recurrence.

Pretreatment Preparations

Irrespective of the methods of treatment, general health of the patient must be improved. Due attention is to be paid to correct anemia and malnutrition. This not only makes the patient sufficiently fit to withstand surgery but rise in hemoglobin percentage improves the tissue oxygenation needed for effective ionizing effect of irradiation.

Perioperative use of leg stockings, prophylactic doses of heparin or low-molecular-weight heparin (LMWH) are used to reduce thromboembolism. Prophylactic antibiotics are to be used.

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TREATMENT MODALITIES OF CARCINOMA CERVIX

Management of Cervical Cancer

Modalities: (A) Surgery; (B) Radiation therapy; (C) Chemotherapy; (D) Combination therapy (Tables 24.9A and B).

Surgery is suitable for early stage disease. Types of surgery depending on stages are: (a) Cervical conization; (b) Trachelectomy; (c) Simple hysterectomy; (d) Radical hysterectomy; (e) Pelvic exenteration.

Surgery

The types of surgery employed in invasive carcinoma are:

Radical Hysterectomy and Pelvic Node Dissection (Fig. 24.9)

John Clark (1898) first did the operation while working as a resident in Johns Hopkins Hospital. This operation is commonly done abdominally and is known by different names (**Wertheim** of Viena—1898, **Okabayashi** of Japan—1921, **Meigs** of USA—1944). **Extensive vaginal operation** was subsequently developed to minimize the mortality and morbidity from abdominal approach. Pelvic lymph nodes are removed by bilateral extraperitoneal approach. This operation is also popularly known by different names (**Schauta** of Viena—1902, and **Mitra** of India—1957). There have been several modifications of the techniques of radical hysterectomy and bilateral pelvic lymphadenectomy at present.

Radical hysterectomy as defined by Piver and Rutledge are followed. Type I, II and the III are commonly done compared to type IV and V (Table----). Class II is usually known as Meigs Wertheim hysterectomy. It is done for stage IB and rarely for stage IIA carcinoma cervix. For class III radical hysterectomy, uterine artery is ligated at its origin from the anterior division of the hypogastric artery. In class IV, complete dissection of the ureter from its bed is done. Superior vesical artery is sacrificed. Querleu and Morrow described another classification that is based on lateral dissection with nerve preservation to reduce bladder dysfunction (Ch. 38).

The surgery includes (Fig. 38.68) removal of the uterus, tubes and ovaries of both the sides (ovaries may be spared in young women), upper half of vagina, parametrium (most of cardinal and uterosacral ligaments), and the draining primary cervical lymph nodes (parametrial, obturator, internal and external iliac groups, and sometimes common iliac. **Sacral group is not removed**). **Ovarian function may be preserved in younger patients. Ovariopexy to be done when postoperative radiation is needed.** Para-aortic lymph node evaluation is done. Any enlarged para-aortic lymph node is sampled and sent for frozen section biopsy. Para-aortic lymphadenectomy is done when found positive. Postoperative radiation therapy is to be considered if lymph nodes are found involved. Generally, **negative sentinel lymph nodes may allow omission of lymphadenectomy of the nodal basin.**

Surgery for pelvic and para-aortic lymphadenectomy can detect metastatic spread of the disease more accurately. It is superior to radiologic imaging. Lymph node dissection can avoid unnecessary over treatment or under treatment of radiation therapy. It is expected that with optimum assessment of disease spread, can have a significant survival benefit from subsequent therapy with chemotherapy and/or extended field of radiation. Laparoscopic procedure of lymphadenectomy is superior

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TABLE 24.9A: Management options of carcinoma cervix.
Microinvasive (Stage IA), Early Invasive (Stage IB, IIA) and Advanced (Stage IIB–IV) Carcinoma.

Stage	*Patient characters*	*Management option*
IA1 (microinvasive carcinoma) (<3 mm, –LVSI <3 mm, +LVSI)	▪ Young women, fertility preservation desired: LVSI present/absent	▪ Cervical conization and close follow up with cytology screening Or ▪ Mod Rad Trachel
	▪ Elderly women, family completed • LVSI—absent • LVSI—present	• Total extra-fascial hysterectomy • Mod Rad Hyst + Pelvic Lymph Or SLNB
	Method and route of surgery: Abdominal, vaginal, laparotomy, laparoscopy	
IA2 (microinvasive carcinoma) (≥3 mm, <5 mm)	▪ Low risk cases ▪ Others— • LVSI-present • Young patient, fertility desired	▪ Mod Rad Trachel Or Mod Rad Hyst + Pelvic Lymph Or SLNB • Mod Rad Hyst or more radical surgery, pelvic lymphadenectomy • Cervical conization and laparoscopic extraperitoneal pelvic lymphadenectomy Or • Radical abdominal, vaginal or Lap Trachel with Pelvic Lymph
	▪ Post-treatment follow-up with cytology (Ch. 23)	
Invasive carcinoma IB1, IB2, IIA1	▪ **Surgical treatment is preferred** ▪ **Routes:** Open or MIS (laparoscopic or robotic)	▪ Rad Trachel Or Type III Rad Hyst + Pelvic Lymph Or SLNB ▪ For stage with IB3 (≥ 4 cm)—chemoradiation (pelvic field) is the option.
IB1 (≥5 mm, < 2 cm)	▪ **Low risk:** Largest diameter <2 cm, stromal invasion <50%, no node on imaging	▪ As above or modified Rad Hyst and Pelvic Lymph
	▪ Young women, desiring fertility	▪ Rad Trachel (stage IA2-IB1)
	Route: Open-abdominal, vaginal or MIS	
	Node negativity to confirm with Lap Pelvic Lymph Or SLNB prior to Rad Trachel.	

Contd...

Contd...

TABLE 24.9B: Management options of carcinoma cervix.

Stage	*Management options*
IB2–IIA1 **IB2: ≥2 cm <4cm;** **IB3: ≥4 cm;** **IIAI: <4 cm + upper vagina**	**Primary modality: Surgery or radiotherapy, both have similar result.** Type III radical hysterectomy (Uterus + parametrium + upper vagina + part of para colpium + pelvic lymph nodes)
IB3 and IIA2 **IB3: ≥4 cm** **IIAI: <4 cm + upper vagina** **IIA2: ≥4 cm + upper vagina**	■ **Surgery is discouraged due to high morbidity** ■ Concurrent platinum based chemoradiation therapy (CCRT) ■ Neoadjuvant chemotherapy (NACT) can be used where radiotherapy facilities are scarce ■ Advantages
IIB–IVA	■ CCRT is the standard treatment for patients with locally advanced cervical cancer (LACC). ■ Radiation therapy to cover Pelvic and the extended field for stages IIIB and above. Systemic chemotherapy is given for cases stage IIIC2 and above.
Stage IVA	■ Only central disease without pelvic or side wall recurrence or distant spread: Pelvic exenteration. It has poor prognosis ■ Advanced diseases: Radiotherapy with modern development, can provide improved outcome and reduced toxicity
Stage IVB + Distant organs	CCRT may have better response with overall disease free survival (69%). Carboplatin-paclitaxel combination or cisplatin—topotecan, gemcitabine or vinorelbine found to be effective ■ Palliative chemotherapy ■ And/or Radiotherapy/supportive care (hospice)

(LVSI: lymphovascular space invasion; Modi: Modified; Rad: Radical; Trachel: Trachelectomy Hyst: Hysterectomy; SLNB: sentinel lymph node biopsy; lymph: lymphadenectomy)

Management is individualized based on the patient's disease stage, health condition and the available resources

to laparotomy. This has less morbidity with subsequent radiation therapy. However, survival benefit of extensive surgical debulking of retroperitoneal modes are 4–6%.

Limitation

It is ideally limited to early stage disease. **Radical hysterectomy** could be done by abdominal or vaginal route or by laparoscopic, robotic assisted method, depending upon the patient's fitness and surgeon's experience.

Advantages of Surgery over Radiotherapy

- Spread of the disease can be determined more thoroughly by surgicopathological staging.
- Surgical staging (laparotomy or laparoscopy) and assessment of para-aortic and pelvic nodes, can predict the survival rate accurately.

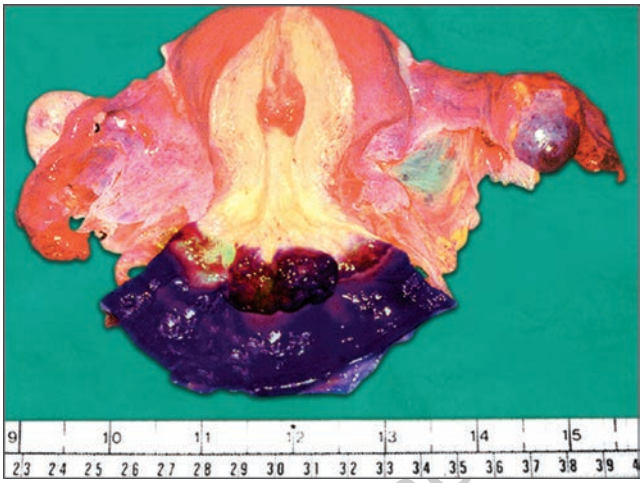

Fig. 24.9: Exophytic type of cervical squamous cell carcinoma—radical hysterectomy done.

- Preservation of ovarian function, if desired, especially in a young woman.
- Ovaries may be transposed out of the radiation field if radiation is considered in the postoperative period.
- Retention of more functional and pliable vagina for sexual function.

Psychologic benefit to the patient in that her cancer bearing organ has been removed.

Special indications: As previously mentioned, there is no superiority of surgery over radiotherapy when the patients are placed in ideal circumstances. But, there are conditions where **radiotherapy is contraindicated** and only the surgical treatment has to be provided.

Contraindication of Radiotherapy

- Associated pelvic inflammatory disease (PID)—acute or chronic, diabetes, inflammatory bowel disease, pelvic kidney.
- Associated myoma, prolapse (procidentia), ovarian tumor or genital fistula, adnexal mass.
- Young patient (to preserve ovarian function).
- Vaginal stenosis—placement of radiation source is inadequate.
- Cases with adenocarcinoma or adenosquamous carcinoma—surgery is preferred.

Complications of Surgery

See complications (below). Women with comorbidities (obesity, heart disease) are at risk for surgery.

Postoperative complications

Major postoperative complications as observed following total abdominal hysterectomy have been discussed (p. 498). **Other complications include:** Ureteric fistula (about 1%), vesicovaginal fistula (0.5%), bladder dysfunction, cystitis pyelonephritis, small bowel obstruction and rectal dysfunction. There may be lymphocyst in the pelvis, lymphedema of one or both the legs, dyspareunia, and recurrence. The mortality rate of the procedure is less than 1%.

Bladder dysfunction (atony) is a known complication. This is due to damage of the sympathetic and parasympathetic fibers to and from the bladder and

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urethra. Continuous catheterization for bladder drainage is maintained for a period of 6–10 days.

Neuropathies due to nerve injuries (femoral, obturator, sciatic, genitofemoral, ilioinguinal, lateral femoral cutaneous, and pudendal nerves).

Lymphocyst formation is a frequent complication. Tissue fluid, lymph and blood are collected to form the cyst following radical hysterectomy. Lymphocyst is best diagnosed by ultrasound. Rarely, it may be of large size to cause pain and ureteral or venous obstruction. Adequate suction drainage of the retroperitoneal space postoperatively is an important preventive measure. Majority resolve spontaneously. Sometimes, it may drain through vagina. Rarely, needle aspiration is needed when the size is large or it produces symptoms.

Pelvic Exenteration

This type of ultraradical surgery is named after **Brunschwig**. This procedure is done in a very selective cases only:

- Stage IVA disease.
- Central pelvic recurrent carcinoma (biopsy proven) without any metastasis as established by PET/CT scan.
- Completely resectable tumor mass.

Contraindications of pelvic exenteration are extra-pelvic spread of disease with distant metastasis to liver, lungs or bones.

Types

- **Anterior exenteration:** It consists of radical hysterectomy, removal of urinary bladder, and implantation of ureters either in the sigmoid colon or into an artificial bladder made from an ileal loop (ileal bladder).
- **Posterior exenteration:** It consists of radical hysterectomy, removal of rectum and a permanent colostomy.
- **Complete or total:** It consists of combination of anterior and posterior exenteration with a permanent colostomy and an ileal bladder.

  The operative mortality of such type of operation is about 10–20% and with a 5-year survival rate of about 50%.
- **Laparoscopic radical hysterectomy (LRH) with pelvic and aortic lymphadenectomy** is done for early invasive disease (stage I, IIA). The specimen is removed vaginally. Vaginal cuff is closed by endostitch. Pelvic and aortic lymphadenectomy is done.

Primary Radiotherapy

Cancer of the cervix was the first cancer of an internal organ to be treated with ionizing radiation using radium by Margaret Cleves in 1903. **Primary therapy (chemo-radiation)** is given in locally advanced (stage IIB to IVA) disease.

External photon beam radiation and brachytherapy are the two main methods (p. 426 and 427).

Both external beam radiation therapy (EBRT) and brachytherapy are delivered. External beam radiation usually proceeds intracavitary therapy (brachytherapy). EBRT is commonly given in 25 fractions during 5 weeks (40–50 Gy).

Hormone replacement therapy following radiation or surgery can be used for women with menopausal symptoms following counseling.

Advantages of Primary Radiotherapy

- Wider applicability in all stages of carcinoma cervix.
- Survival rate 85%, comparable with that of surgery in early stages.
- Less primary mortality and morbidity.
- Individualization of dose distributions/requirement possible.

Principles of Brachytherapy

Technique (Table 24.10) (discussed in Ch. 31): External beam radiation therapy (EBRT) is given in fractions usually 180 cGY/day, 5 days/week to destroy the tumor without affecting the normal tissues. This covers entire pelvis including the regional pelvic nodes. The local implant (brachytherapy) delivers radiation locally to the cervix, vagina, paravaginal and paracervical tissues. Usually tandem and ovoids or a tandem and ring are inserted in the vagina. A pack is placed in the vagina to stabilize the apparatus.

After the position of the application is confirmed by imaging, The radioactive source, such as Cesium 137 or Iridium 192 is inserted (after loading technique). Intracavitary radiation therapy ICRT may be low dose rate or a high dose rate. Both have similar survival rate and toxicity. High dose rate is commonly used and is given as on OPD basis. It is done for 3 to 4 hours.

The container is made up of platinum, gold or alloy steel to absorb alpha and beta particles and allowing the gamma rays to sterilize the cancer cells. In carcinoma cervix, the tandems are inserted in the uterine cavity and the ovoids and colpostats are placed in the vaginal vault under anesthesia. Different methods of brachytherapy are in vogue (Figs. 24.10A to C). High dose **brachytherapy** is safe and effective (NICE – 2010).

In Paris and Manchester techniques, the source strength is smaller but exposure time is increased. The vaginal source is away from the cervix. They are used with either preloaded or afterloaded special applicators. One treatment period in Paris technique is 96–200 hours as compared to Stockholm technique where each application is 24–28 hours in duration. Manchester system, which is a modification of the Paris technique, delivers

TABLE 24.10: Brachytherapy techniques.

Technique	*Amount of radium placement*	*No. of application*	*Duration*
Paris	Intrauterine tandem 33.3 mg—one Vaginal ovoid 13.3 mg—two or three	One	120 hours
Manchester	Intrauterine tandem 30–50 mg Vaginal colpostat 30–50 mg	Two	72 hours each at interval of 7 days
Stockholm	Intrauterine tandem 50 mg—one Vaginal plaque—65–80 mg	Three	24 hours each at weekly interval

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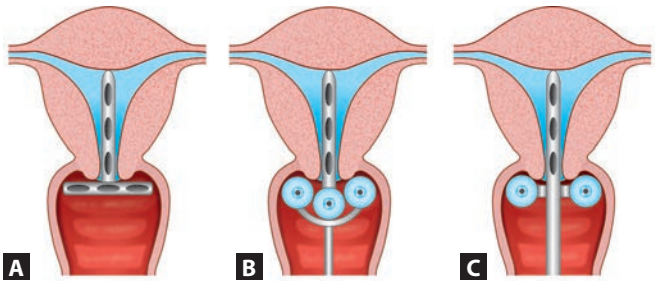

Figs. 24.10A to C: Different methods of brachytherapy: (A) Stockholm technique; (B) Paris technique; (C) Manchester technique.

constant isodose at different depths, regardless of the size of the uterus and vagina.

In Stockholm technique (Fig. 24.10A), large high intensity source with less exposure time is given, but the vaginal source is closer to the cervix.

These three basic techniques are followed all through the world in the brachytherapy for carcinoma cervix. After loading remote control technique is used for calculated dose distribution and to prevent radiation hazard. Fletcher-Suit afterloading modification system is widely used these days.

Disadvantages of Radiotherapy

Intestinal and urinary strictures, fistula formation (2–6%), vaginal fibrosis and stenosis causing dyspareunia, radiation menopause, fibrosis of bowel and bladder. **Ovarian transposition (ovariopexy)** well out of the range of pelvic irradiation may be done to avoid radiation menopause. For other complications of radiation (p. 428).

Calculation of the dose (p. 427): In calculating the doses, two reference points A and B are used (Ch. 31). Total dose calculation depends on tumor stage. Normal cervix is resistant to radiation. It can tolerate doses up to 200 to 250 Gy over 2 months. However for bladder maximum radiation is 80 Gy, rectum is 65 Gy and bowels 45 to 50 Gy. **Point A** is 2 cm cephalic and 2 cm lateral to the external os and is the point of crossing of the uterine artery and ureter. **Point B** is 2 cm cephalic and 5 cm lateral at the same plane and is approximately the site of obturator gland (Fig. 31.3).

It has been calculated that point A gets about 7000–8000 cGy and point B 2000 cGy. Taking into consideration that cancerolytic dose is approximately 7000–7500 cGy, the rest of the dose at point B is supplemented by external beam irradiation of 4000 cGy spreading over another three weeks. For external irradiation, linear accelerator with energy of 4 million electron volts or more is commonly used.

In the immediate vicinity of the source, the vagina and cervix get and tolerate about 20,000–30,000 cGy. Bladder, ureter, and rectum can tolerate up to 7000 cGy. Small gut on the other hand has a tolerance limit of only 4500 cGy.

With the advent of computer dosimetry, exact calculation of the doses on each patient for each application is being provided. **Intensity modulated external radiation therapy (IMRT),** based on computer generated algorithms can distinguish accurately the target tissue volume and normal tissue. IMRT can preferentially limit the dose of radiation to normal tissues and can deliver higher doses to tumor tissues. Treatment planning is done on 3D imaging using CT, MR, and PET to determine the tumor volume. Linear acceletors or conformational radiotherapy techniques (CRT) with 3D-CRT and IMRT are more effective. Normal tissues are spared. Toxicity is reduced. ICRT is given using a tandem and ovoids or tandem and ring. Dose system may be low dose rate (LDR), high dose rate (HDR) or pulsed dose rate (PDR). All the system results in comparable survival rate. Interstitial brachytherapy should be used when ICRT is not feasible due to distorted anatomy. It consists of insertion of multiple needles into the primary tumor and parametrium through the perineum. It is done under USG guidance. It is recommended that entire radiotherapy treatment (EBRT) should be completed within 8 weeks.

- **Advanced cases:** As the blood supply is poor, the resultant anoxia may be overcome by irradiating these cases in a special chamber under condition of hyperbaric oxygenation.
- **Recurrent cervical carcinoma:** Incidence of recurrence or persistent disease after therapy is about 35%. Cases following surgery, whole pelvic irradiation with external beam radiotherapy or chemoradiation has been advocated.
- **Carcinoma cervix detected after simple hysterectomy:** Subsequent management of such patient depends upon the following factors: (a) Microinvasive cancer; (b) Tumor confined to the cervix and the margins are negative; (c) Positive surgical margins but no gross residual tumor; (d) Gross residual tumor by clinical examination and documented by biopsy or patient with recurrent disease.
- **Treatment options are:** (a) To perform radical operation and to remove all the tissues including the pelvic lymph nodes. This may be done especially in younger women; (b) Radiation therapy—(i) No residual disease—brachytherapy to the vaginal apex, (ii) Gross residual disease—full intensity radiotherapy.
- Patients with gross residual disease have poor survival outcome.
- ***Surgery Followed by Radiotherapy***
- This is indicated in cases with **positive lymph nodes** detected following surgery.
- **Accidental discovery of invasive carcinoma cervix** of a uterus removed by simple hysterectomy.
- When **positive tissue resection margin** is present. The objective of this form of therapy is to sterilize the cancer cells in the pelvic lymph nodes. The fact remains that even by pelvic lymph node dissection it is not possible to remove all the positive nodes. Radiation dose is reduced to 4500 cGy in 24 fractions over 5 weeks.
- **Postoperative adjuvant chemoradiation therapy** (extended field radiation and platinum-based chemotherapy) significantly improved the survival rate when given following radical hysterectomy.

Radiotherapy Followed by Surgery

- **Endocervical carcinoma** with barrel-shaped cervix.
- **Bulky tumor:** Radiotherapy controls sepsis, the growth shrinks and the tumor resectability is improved.

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Neoadjuvant chemotherapy (NACT)

NACT has the following advantages: (a) Reduces tumor volume; (b) Reduces micrometastatic disease; (c) Improves in tumor resectability; (d) It is an alternative therapy when access to radiotherapy is limited or absent; (e) Improved survival rate when compared to radiotherapy alone; (f) It improves survival rate when NACT is combined with surgery. It is especially useful in young women with bulky stage IB–IIB disease desiring for FSS. Neoadjuvant chemotherapy is followed by radiotherapy.

Three cycles of platinum-based combination chemotherapy with radiation therapy followed 3–6 weeks by radical hysterectomy and lymphadenectomy is done. This has improved the resectability of the bulky ≥4 cm (stage IB2 and bulky IIA) disease. This regimen had shown better overall disease free survival rate and reduced recurrence. Due to fibrosis, surgery may be difficult. Risk of ureteric fistula may be more. **The drugs used are in combination of cisplatin, ifosfamide or paclitaxel.**

Concurrent chemoradiation includes radiation and weekly cisplatin-based combination (cisplatin and paclitaxel) chemotherapy. **Cisplatin-based concurrent chemoradiation** is used as a treatment of choice in: (a) Early stage (IA2, IB, IIA) disease after radical hysterectomy; (b) As a primary treatment for patients with bulky (≥4 cm) tumor (stage IB and IIA); (c) Locally advanced (stage IIB to IVA) disease as a primary therapy. Chemotherapy sensitizes the cancer cells to radiation and improves the survival rate.

Fertility Sparing Surgery

- **Laparoscopic assisted vaginal radical trachelectomy with pelvic and aortic lymphadenectomy (LARVT)** was designed (Daniel Dargent, 1987) to treat early invasive cervical cancer. This is done in a **young woman where childbearing function is to be preserved** (fertility sparing surgery). Initially, pelvic and aortic lymph node dissection is done. **Vaginal radical trachelectomy is done only when these nodes are negative**. Laparoscopic approach is similar to LARVH. Vaginal part includes resection of cervical, vaginal, paracervical, and paravaginal tissues. Vaginal cuff is resected circumferentially about 2 cm below the cervicovaginal junction. Ideally, the resected cervical tissue margins should be free of disease as evaluated by frozen section. Cervical permanent cerclage operation is done to prevent miscarriage and preterm labor.

Indications of Trachelectomy

- Preservation of fertility
- Early stage disease (stage IA1, A2, IB1)
- Small tumor volume (<2 cm)
- No pelvic node metastasis
- Cancer margin is at 1 cm below the internal os on MRI

PLANNING OF TREATMENT MODALITIES

A. **Early stage disease:** *See* Tables 24.9A and B.

For **early stage disease**, the survival rate following treatment by either radical hysterectomy and pelvic lymphadenectomy or with primary radiation with concurrent chemoradiation are almost equal.

B. **Advanced stage disease (Table 24.11)**

COMPREHENSIVE PALLIATIVE CARE

Principles of management are: (a) Control of symptoms; (b) Care focused on individual basis; (c) To maintain dignity and quality of life.

Common symptoms of a patient with advanced cervical cancer: (a) Pain; (b) Hemorrhage; (c) Features due to renal failure and uremia with ureteric obstruction; (d) Vaginal discharge (malodorous); (f) Problems related to fistula formation (RVF/VVF); (e) Lymphedema.

Pain control to be done as tiered approach basis. Oral morphine need to be given. Involvement of NGOs, hospice is needed.

Palliative radiotherapy may be used for uncontrolled vaginal bleeding, pelvic pain and metastatic disease pain. Usually, a dose of 20 Gy in five fractions over a week is given. ICRT may be used when EBRT fails.

CARCINOMA OF CERVIX AND PREGNANCY

Incidence of invasive carcinoma of the cervix is about one in 2,500 pregnancies.

Diagnosis is often late. Cone biopsy may be necessary for confirmation. **Complications of cone biopsy include:** Hemorrhage, abortion, preterm labor, and infection. LEEP has no superiority over cone biopsy.

Management

The following points are taken into consideration before actual management: (A) Period of gestation; (B) Survival of the fetus; (C) Wishes of the patient; (D) Histology.

A. **Patient with microinvasive carcinoma** may be followed up to term. Patient is re-evaluated following delivery and treated as in the nonpregnant state.

B. **Advanced stage:** Before 20 weeks, treatment modality is the same as in the nonpregnant state: Either surgery or chemoradiation. In late pregnancy, following maturity, fetus is delivered by classical cesarean section. Subsequent treatment with either radical surgery or radiotherapy or chemoradiation is the same as in the nonpregnant state.

Prognosis

Clinical stage (FIGO) of the disease is the single most important prognostic factor. Stage for stage survival outcome appears to be no different between pregnancy and nonpregnant state (for details see author's Textbook of Obstetrics, Ch. 21).

RESULTS OF THERAPY FOR CARCINOMA CERVIX

The result of therapy is expressed in terms of 5-year survival rate. The overall 5-year survival rate is tabulated in Table 24.11.

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TABLE 24.11: 5-year survival rate.

Stage	*5-year survival rate (%)*
IA	95.01
IB	80.1
II	64.2
III	38.3
IV	14

Recurrent Cervical Cancer

Risk factors for recurrent disease are: Large tumor size, lymphovascular space invasion, positive lymph nodes, advanced stage disease. Over all recurrence is about 30% after 5-years. A patient is declared cured if she remains well even after 10 years following initial therapy.

Most common site of recurrence is central pelvis and the pelvic side wall. Features of disease recurrence are: Pain in the pelvis, back, unilateral leg edema, ureteral obstruction, vaginal bleeding, palpable tumor in the pelvis, and lymphadenopathy. Single agent or multiagent chemotherapy with cisplatin, paclitaxel or ifosfamide is used. Palliative radiation therapy may be used to those who have been treated initially with surgery.

Follow up: The majority of the recurrences occur in the first 2 years. As such, the follow up protocols should be at 3–4 months interval for the first 2 years then at 6 months interval for next 2 years and thereafter annually. Thorough physical examination is done including examination of supraclavicular and inguinal lymph nodes. Cervical or vaginal cytology is performed. Chest X-ray is done annually. Imaging studies (CT/MRI) are done as needed.

Stump Carcinoma

When the carcinoma develops in the cervical stump left behind after subtotal hysterectomy, it is called stump carcinoma. **In true stump carcinoma**, malignancy develops 2 years after primary surgery. If it occurs earlier to that, it is presumed that the carcinoma was present at the time of primary surgery and, as such it is called coincidental, residual or false stump carcinoma.

The incidence may be as high as 1%. It is difficult to stage the disease.

There is also difficulty in the **treatment.** Dense adhesions of bladder, rectum and also ureters with the stump make the operation difficult and risky. The radiation therapy is also technically difficult, because of absence of uterus and close proximity of bladder and rectum to the radiation source. Radical parametrectomy, removal of cervix, upper vagina and pelvic lymphadenectomy is done in early stage disease.

External beam radiation therapy is given when the cervix is short. Vaginal radium application (vaginal cone) is also used. The prognosis is unfavorable. The 5-year survival rate varies from 30–60%.

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POINTS

- In most of the developing countries, **carcinoma of the cervix is the most common malignancy** in females. It ranks first, the second being breast carcinoma. The site of lesion is predominantly ectocervix (80%). The most common histologic type is squamous cell carcinoma (85–90%) and about 10–15% are adenocarcinomas.
  Squamous cell carcinomas have a viral (HPV) and veneral association unlike that of adenocarcinomas.
  The primary groups of lymph node involvement are parametrial, internal iliac, obturator, external iliac and sacral nodes.
  Preclinical invasive carcinoma is diagnosed by cytology, colposcopy and directed biopsy. If positive lesion is found, diagnostic conization and serial section has to be performed to establish the diagnosis.
  Definitive diagnosis of microinvasive carcinoma is made by cervical conization. The cone margins must be free of disease when conservative therapy is undertaken.
  Clinical presentation of early carcinoma includes menstrual abnormalities—intermenstrual bleeding or contact bleeding or excessive white discharge. Speculum examination reveals the lesion on the ectocervix which bleeds on friction.
  Causes of death are uremia, hemorrhage, sepsis, cachexia and metastases to the lung.
  Primary prevention includes identifying 'high risk' women, and 'high risk' males, sexual behavior, prophylactic **HPV vaccine**, use of condom, and removal of cervix during hysterectomy. **Secondary prevention** involves screening program and identifying the precancerous lesions or invasive lesion at its treatable stage.
- **The prognosis of carcinoma** cervix depends on many factors of which stage of the disease is important. Cancer cervix is a locally invasive tumor. It spreads primarily to pelvic tissues, then to pelvic and para-aortic lymph **nodes**. Rarely hematogenous spread to liver, lungs and bones may occur. Currently, radiation is combined with chemotherapy **(chemoradiation)** to optimize the results. Cisplatin 40 mg/m^2 weekly is used along with radiation (teletherapy and brachytherapy). **Complications** of radiotherapy may occur more than 1 year after therapy.
  Microinvasive carcinoma when treated by total hysterectomy gives 5-year survival rate of almost 100%.
  Radical hysterectomy can be performed up to stage IIA. This is especially used for a younger patient to preserve her ovarian function and to avoid vaginal fibrosis.
  Survival outcome of treatment following surgery or radiation for stage IB/IIA is the same (85%). Extraperitoneal lymphadenectomy has improved survival advantage.
  Results of therapy in terms of 5-year survival is gratifying in early stages—95% in stage Ia, reduced to 70% in stage II and 50% in stage III and 20% in stage IV (Table 24.11). HPV positive younger patients have better prognosis.
  Radical trachelectomy can be done in young women to preserve fertility as an alternative to radical hysterectomy. The disease must be in early stage (IA2 or small IB1 ≤2 cm). A therapeutic lymphadenectomy is also performed.

Contd...

Contd...

Radical trachelectomy can be done through vaginal or abdominal route. It can be done by open surgery, laparoscopic or robotic methods.

- **Leg pain** along the distribution of sciatic nerve and unilateral leg swelling are suggestive of pelvic recurrence of carcinoma cervix.
- The incidence of **stump carcinoma** is about 1%. The 5-year survival rate is 30–60%.
- For women with **carcinoma cervix during pregnancy**, survival rate is not different stage for stage when compared with the non-pregnant state.

ENDOMETRIAL CARCINOMA

INCIDENCE

The incidence is higher amongst the white population of the United States and lowest in India and Japan. In North America, amongst the whites, carcinoma body is the leading site of genital malignancy followed by ovary and cervix. In India, it ranks third amongst genital malignancy next to cervix and ovary.

While in the western countries, there has been increased incidence of carcinoma body relative to cervical one and the ratio becomes almost 1:1 in India, the incidence still remains low and the ratio ranges *between 1:8 and 1:15.*

The higher incidence in the western countries may be real or apparent. **The real one** is due to high expectation of life, rising obesity and use of estrogen in postmenopausal women and the **apparent one** is due to its detection, out of increased awareness amongst the gynecologists.

ETIOLOGY

The following are found to be related to carcinoma body of the uterus:

- **Estrogen**—persistent stimulation of endometrium with unopposed estrogen is the single most important factor for the development of endometrial cancer.
- **Age**—about 75% are postmenopausal with a median age of 60 (c.f. carcinoma cervix is more common in perimenopausal period). About 10% of women with postmenopausal bleeding have endometrial cancer.
- **Parity**—it is quite common in unmarried and in married, nulliparity is associated in about 30% (c.f. carcinoma cervix is associated more with multiparae).
- **Late menopause**—the chance of carcinoma increases, if menopause fails to occur beyond 52 years.
- **Corpus cancer syndrome**—encompasses obesity, hypertension, and diabetes.
- **Obesity** leads to high level of free estradiol as the sex hormone binding globulin level is low.
- **Unopposed estrogen stimulation** in conditions such as functioning ovarian tumors (granulosa cell) is associated with increased risk of endometrial cancer. **Unopposed estrogen replacement therapy in postmenopausal** women is associated with increased risk of endometrial cancer. Use of cyclic progestin reduces the risk. Prior use of combined oral contraceptives reduces the risk significantly (50%).
- **Polycystic ovarian disease** increases the risk due to the persistent hyperestrogenic state.
- **Tamoxifen** is antiestrogenic as well as weakly estrogenic. It is used for the treatment of breast cancer. Increased risk of endometrial cancer is noted when it is used for a long time due to its weak estrogenic effect.
- **Family history:** Hereditary nonpolyposis colorectal cancer (HNPCC) (AD syndrome) is due to the mutations in mismatch repair genes (MLH1, MSH2). Mutation carriers have the risk of developing endometrial cancer (40–60%). *BRCA1* and *BRCA2* mutation carriers have a slight increased risk.
- **Fibroid** is associated in about 30% cases.
- **Endometrial hyperplasia** precedes carcinoma in about 25% cases (Type 1).

PATHOLOGY

Naked Eye

The uterus may be smaller, normal or even enlarged (due to myohyperplasia, myometrial involvement, pyometra or associated fibroid). Two varieties are found: **Localized and diffuse.**

1. **Localized:** The usual site is on the fundus. It is either sessile or pedunculated. Myometrial involvement is late.
2. **Diffuse:** The spread is through the endometrium. The myometrium is commonly invaded; may invade to reach the serosal coat (Fig. 24.11).

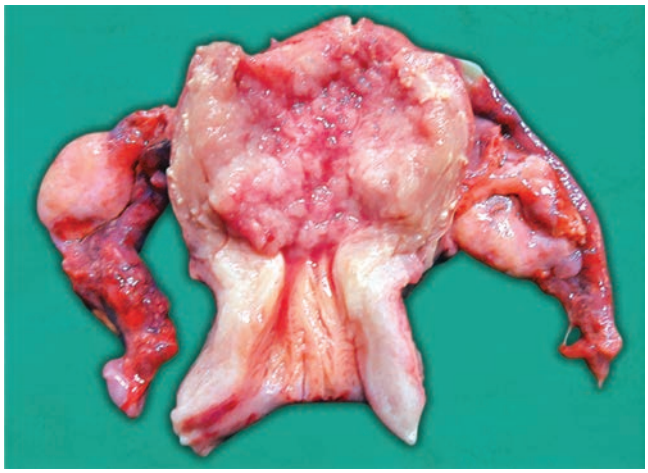

Fig. 24.11: Diffuse type of endometrial carcinoma.

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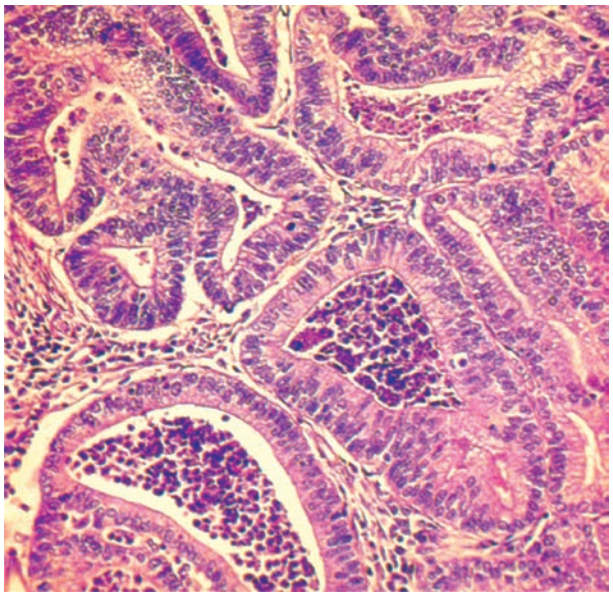

Fig. 24.12: Adenocarcinoma of the endometrium, the most common histologic type. There is significant cellular mitotic activity. The glands are arranged back-to-back.

Microscopic Appearances

The following varieties are noted:

- Adenocarcinoma [endometrioid (80%)] (Fig. 24.12)
- Adenocarcinoma with squamous elements
- Papillary serous carcinoma (5–10%) (virulent)
- Mucinous adenocarcinoma (1–2%)
- Clear cell adenocarcinoma (<5%)
- Secretory carcinoma (1%)
- Squamous cell carcinoma
- Mixed cell carcinoma
- Undifferentiated carcinoma (1–2%).

Endometrial carcinoma are of two types based upon biological and histological behavior (Table 24.12).

TABLE 24.12: Differentiating features of type I and II endometrial carcinoma.

Clinical characters	*Type I*	*Type II*
Risk factor	Unopposed estrogen	Age
Age	Perimenopause	Postmenopause
Endometrial hyperplasia	Present	Absent
Tissue differentiation	Well	Poor
Myometrial invasion	Minimal	Deep
Histology	Endometrioid	Serous, clear
Molecular characters		
Ploidy	Polyploid	Aneuploid
Her2/neu over expression	No	Yes
P-53	No	Yes
PTEN mutations	Yes	No
Prognosis	Favorable	Not favorable

SPREAD

Direct

Common modes of spread are (Type 1): (a) Lymphatic; (b) Direct; (c) Hematogenous; (d) Intraperitoneal exfoliation.

As it is slow growing, it is confined to the stroma for a long time but eventually, it spreads in all directions. Thus, it may infiltrate the myometrium and spread to the parametrium or into the peritoneal cavity through the tubes. It may spread downwards to **involve the cervix in about 15%.**

Lymphatic

Most common mode of spread is through lymphatic route. Lymphatics from the (a) Tubes and the ovaries (infundibulo pelvic ligaments) all drain in the para-aortic nodes; (b) Few lymphatics run along the round ligament drain in the inguinal and femoral nodes; (c) The lymphatics from the broad ligament drain in the pelvic nodes. The pelvic and the para-aortic nodes are the most important clinically.

Lymph node metastasis depends on the degree of tumor differentiation, myometrial invasion, tumor size, and the surgical pathological stage of the disease. Pelvic lymph node involvement in stage I disease varies from about 4% in grade 1 and 2 disease with superficial myometrial involvement to about 40% with grade 3 tumor with deep myometrial invasion. Approximately, 50% of the patients with pelvic lymph nodes will have para-aortic lymph node metastasis. In stage II disease incidence of pelvic lymph node metastasis increases to 30–45%. Lymph node metastasis is the most important prognostic factor.

The **tubes and ovaries** are involved (3–5%) either by direct spread or by lymphatics.

The vagina is involved in about 10–15% cases. The metastasis to the lower-third of the anterior vaginal wall is probably through lymphatic or by retrograde venous flow. The vault metastasis following hysterectomy may be due to direct implantation or may be explained by previous lymphatic or venous embolism.

Hematogenous

Blood borne spread occurs late. The common sites of metastases are lungs, liver, bones, and brain.

Port site metastasis is a rare type of cancer spread (0.33%).

The extent of lymph node metastases (pelvic and para-aortic) varies with histologic grade of the tumor and also with depth of myometrial invasion. Higher the grade and depth of invasion the more is the lymph node metastasis and the risk of recurrence.

Staging: The staging is based on endometrial histology and surgical evaluation, adopted by FIGO (2009). Approximately 75% patients present with stage I disease.

CLINICAL FEATURES

Patient profile: The patient is usually a nullipara, likely to be postmenopausal. There may be history of

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TABLE 24.13: 'High-risk' factors for endometrial cancer.

- Late menopause (RR: 2–4)
- Nulliparity (RR: 2–3)
- Unopposed estrogen therapy (RR: 4–8)
- History of persistent anovulation (PCOS)
- History of irregular and excessive premenopausal bleeding
- Obesity (RR: 2–10), diabetes, hypertension
- Personal or family history of breast, ovary, colon or endometrial cancer (Lynch syndrome) (RR: 20)
- Atypical endometrial hyperplasia (RR: 8–29)
- Tamoxifen therapy
- Radiation menopause

(RR: relative risk)

delayed menopause. She may be obese—likely to have hypertension or diabetes (Table 24.13).

Symptoms

- Postmenopausal bleeding (75%) which may be slight, irregular or continuous. The bleeding at times may be excessive.
- In premenopausal women, there may be irregular and excessive bleeding.
- At times, there is watery and offensive discharge due to pyometra.
- Pain is not uncommon. It may be colicky due to uterine contractions in an attempt to expel the polypoidal growth.
- Few patients (<5%) remain asymptomatic.
- In late cases there may be pelvic pressure, pain or abnormal bleeding.

Signs

The patient presents with the features as mentioned in patient profile. There may be varying degrees of pallor.

Pelvic examination: Speculum examination reveals the cervix looking healthy and the blood or purulent offensive discharge escapes out of the external os.

Bimanual examination reveals—the uterus is either atrophic, normal or may be enlarged due to spread of the tumor, associated fibroid or pyometra. The uterus is usually mobile unless in late stage, when it becomes fixed.

Rectal examination corroborates the bimanual findings.

Regional lymph nodes and breasts are examined carefully.

DIAGNOSIS OF ENDOMETRIAL CARCINOMA

The following guidelines are prescribed:

- **A case of postmenopausal bleeding** is considered to be due to endometrial carcinoma unless proved otherwise.
- Finding a benign condition to account for postmenopausal bleeding does not negate a thorough investigation to rule out carcinoma. **The two lesions may coexist.**
- **History and clinical examination** are to be recorded, as mentioned earlier.
- **Tumor marker:** Serum CA 125, elevated level indicates advanced disease. In cases with uterine papillary serous carcinoma (UPSC), it is helpful to monitor therapy and post-treatment follow up.
- **Papanicolaou smear** is not a reliable diagnostic test for endometrial carcinoma. It is positive only in 30% cases of endometrial cancer. LBC or ECC may detect glandular abnormalities.
- **Endometrial biopsy—**using a Sharman curette or **aspiration biopsy**, using a soft, flexible, plastic suction cannula (Pipelle) has been done with reliability (>90%). This is done as an outpatient procedure (Fig. 9.21). Histology is the definitive diagnosis.
- **Ultrasound and color Doppler (TVS):** Findings suggestive of endometrial carcinoma are—(a) Endometrial thickness ≥4 mm; (b) Hyperechoic endometrium with irregular outline; (c) Increased vascularity with low vascular resistance; (d) Intracavitary fluid. However, it cannot replace definitive biopsy.
- **Hysteroscopy:** It helps in direct visualization of endometrium and to take target biopsy.
- **Fractional curettage: It is the definite method of diagnosis** and can detect the extent of growth. This is done under anesthesia with utmost gentleness to prevent perforation of the uterus. If pyometra is detected, the procedure is withheld for about 1 week to avoid perforation and systemic infection.

The orderly steps for fractional curettage:

- Endocervical curettage.
- To pass an uterine sound to note the length of the uterocervical canal.
- Dilatation of the internal os.
- Uterine curettage at the fundus and lower part of the body. The endometrial tissue is usually profuse and often dark color.
- Finally, a polyp forceps is introduced in case any endometrial polyp has escaped the curette.

The specimens, so obtained, should be placed in **separate containers**, labeled properly and submitted for histological examination.

The results of **endometrial biopsy** (EB) correlate well with endometrial curettings. EB is accurate to detect cancer in 91–99%. For these reasons, cases where endometrial biopsy cannot be obtained (cervical stenosis) or results are nondiagnostic should be followed up by dilatation and curettage (fractional curettage).

- **Chest radiography** to detect spread of the disease.
- **Computed tomography (CT) scan** of pelvis and abdomen may be used to detect lymph node metastases (p. 100).
- **Magnetic resonance imaging (MRI)** can detect myometrial invasion, lymph node status and endocervical spead (Fig. 38.88). It is useful for women desiring fertility sparing surgery (to exclude myometrial invasion).
- **Positron emission tomography (PET-CT) (p. 101)** is the best imaging method for assessment of the spread of the disease.

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SURGICAL STAGING

Cases with endometrial cancer are staged on surgical pathological basis (FIGO, 2018) following laparotomy (hysterectomy and BSO). MIS staging is safe, feasible and is now recommended (Tables 24.14 and 24.15).

PROTECTIVE FACTORS

- Weight reduction
- Exercise
- Long-term use of COCs (50%)
- Use of progestins
- LNG-IUS
- Smoking (RR: 0.5)

TABLE 24.14: FIGO staging of carcinoma of the endometrium (2008).

Stage[a]	*Characteristics*
Stage I	**Tumor confined to the corpus uteri**
Stage[a] IA	No or less than half myometrial invasion[a]
Stage[a] IB	Invasion equal to or more than half of the myometrium[a]
Stage II	**Tumor invades cervical stroma, but does not extend beyond the uterus[b]**
Stage[a] III	**Local and/or regional spread of the tumor[a]**
Stage IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae[c, a]
Stage IIIB	Vaginal and/or parametrial involvement[c, a]
Stage IIIC	Metastases to pelvic and/or para-aortic lymph nodes[c, a]
Stage IIIC1	Positive pelvic nodes[a]
Stage IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	**Tumor invades bladder and/or bowel mucosa, and/or distant metastases[a]**
Stage IVA	Tumor invasion of bladder and/or bowel mucosa[a]
Stage IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes[a]

Histopathologic criteria for assessing grade:
G1: ≤5% of a nonsquamous a nonmorular solid growth pattern
G2: 6–50% of nonsquamous a nonmorular solid growth pattern
G3: >50% of nonsquamous a nonmorular solid growth pattern
[a]Either G1, G2, or G3
[b]Endocervical glandular involvement only should be considered as stage I and no longer as stage II
[c]Positive cytology has to be reported separately without changing the stage

TABLE 24.15: Distribution of endometrial cancer (FIGO – 2006).

FIGO stage	*Percentage*
I	73
II	11
III	13
IV	3

MANAGEMENT OF ENDOMETRIAL CARCINOMA

- **Preventive**
- **Curative**

Preventive

Primary Prevention Includes

- **Strict weight control** beginning early in life.
- **To restrict** the use of estrogen after menopause in nonhysterectomized women. If at all it is needed, cyclic administration of progestogen preparations are added and continued under supervision.
- **Prophylactic surgery:** Women with Lynch syndrome (HNPCC) may be considered for prophylactic hysterectomy to reduce the risk from 60% to nil. Bilateral salpingo-oophorectomy should be done to reduce the risk of ovarian cancer (10–12%).
- **Education** as regard the significance of irregular bleeding per vaginam in perimenopausal and postmenopausal period and to report to the physician.

Secondary Prevention

Screening of '**high risk**' women at least in menopausal period to detect the premalignant or early carcinoma is a positive step. There is no role for routine screening. Annual screening in high risk women (p. 275) at age >35 years is recommended.

Methods

- The cytologic specimens are obtained by either endometrial aspiration or endometrial lavage. If suspicious cells are detected, histological specimen is obtained by uterine curettage.
- The presence of abnormal endometrial cells in vaginal pool cytology requires a diagnostic curettage.
- Judicious hysterectomy in premalignant lesions of the corpus (p. 275).

Curative

Pretreatment Work up

As the patients are usually aged, obese and often complicated with medical disorders, careful systemic examination and necessary investigations are mandatory before formulating the line of treatment. Along with a gynecologic oncologist, a physician's help may be needed.

Pretreatment Preparations (Table 24.16)

The same protocol as mentioned in cases of carcinoma cervix is to be followed.

TABLE 24.16: Preoperative evaluation.

- Blood examination—complete hemogram, postprandial sugar, urea, creatinine, and electrolytes
- Liver and renal function tests
- Urine—routine examination for protein, sugar, and pus cells
- ECG and X-ray chest for cardiopulmonary assessment
- Abdominal and pelvic ultrasonography for ascites, metastasis (liver), pelvic/para-aortic nodes
- MRI/CT imaging (optional) to assess the extrauterine spread of the disease and the degree of myometrial invasion
- Steroid receptor status

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TREATMENT MODALITIES OF CARCINOMA ENDOMETRIUM

- **Surgery**
- **Radiotherapy**
- **Chemotherapy**
- **Combined therapy**

Surgery

Extrafascial hysterectomy is the preferred treatment for endometrial carcinoma confined to the body. The surgery includes removal of the uterus, tubes, and ovaries of both the sides and cuff of vagina. Removal of vaginal cuff is not essential as it neither improves the survival nor reduces the recurrence rate.

Traditionally, laparotomy has been the approach. Currently laparoscopic and robotic surgery are also recommended.

In Stage I, Surgery is the Mainstay of Treatment

Surgical procedures [surgical staging (page 300)]

- **Incision** longitudinal midline or paramedian is of choice for better exposure.
- **Peritoneal washings** (pouring 100 mL of saline) are taken for cytology.
- **Thorough exploration** of liver, diaphragm, omentum, pelvic organs, pelvic and para-aortic lymph nodes, is done.
- Suspicious lesions are biopsied.
- **Not to hold** the uterus by a vulsellum. Instead, traction is given by placing long straight artery forceps on either side of uterine cornu (Fig. 35.6B).
- **Procedure:**
  1. Type 1 hysterectomy (extrafascial): Total abdominal hysterectomy with bilateral salpingo-oophorectomy is done.
  2. **Uterus** is cut open in the operating room—for evaluation of tumor size, cervical extension, and myometrial invasion by gross examination. It may be done by microscopic frozen section.
  3. Patients with stage I G1 tumor postoperative radiation (vaginal brachytherapy or EBRT) may be given when deep myometrial invasion is there.
  4. **High-risk woman: Presence of big tumor (>2 cm),** cervical extension, G3 tumor, and myometrial invasion (>1/2 thickness) as determined by frozen section biopsy, indicates pelvic and para-aortic lymphadenectomy.
- **Lymph node sampling** of the following areas is done: (a) Common iliac; (b) External iliac; (c) Internal iliac; (d) Obturator; (e) Para-aortic.
- **Vaginal hysterectomy** may be done selectively (stage I, with well-differentiated tumor) in patients with uterovaginal prolapse or with extreme obesity.
- **Laparoscopic or laparoscopic assisted robotic** hysterectomy (p. 518) with bilateral salpingo-oophorectomy and lymph node sampling are done for staging and treatment of endometrial carcinoma (stage I).

In Stage II, Carcinoma

Management options are:

A. **Radical hysterectomy** bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy.
B. **Combined radiation and surgery:** Radiation (external and intracavitary) followed 6 weeks by extrafascial total abdominal hysterectomy and bilateral salpingo-oophorectomy.
C. **Initial surgery** simple hysterectomy followed by external and intravaginal radiation.

Radiotherapy

The primary treatment by radiotherapy is indicated in:

- Women found unfit for surgery.
- Women with significant medical comorbidities.
- Surgically inoperable disease.
- Those with high-risk of recurrence.
- Patients with advanced disease for paliation therapy.

Intracavity brachytherapy with or without external beam pelvic radiation is commonly used.

Contraindications of radiotherapy: Presence of a pelvic mass, pelvic kidney, pyometra, pelvic abscess, previous laparotomies, and/or adhesions with bowel and prior pelvic radiation.

Combined Therapy (Surgery and Radiation)

Combined therapy has shown high degree of success in this disease.

TAH-BSO followed by adjuvant radiotherapy 4–6 weeks after surgery, in a selected case, is done **to prevent locoregional recurrence.**

- **No myometrial invasion stage IA (G1, 2):** Observation only.
- **Myometrial invasion <1/2 thickness (stage IA, G2 disease):** Vaginal vault radiation (5000–6000 cGy) using colpostats afterloading techniques.
- **Myometrial invasion >1/2 thickness (stage IB):** Whole pelvis external beam radiation (4500–5000 cGy) over 5–6 weeks plus vaginal cuff boost.
- **Adnexal spread and/or intraperitoneal disease:** Whole abdominal radiation or chemotherapy (TAP).
- **Radiation therapy:** Adjuvant rediotherapy (brachytherapy and pelvic radiation) reduces locoregional recurrence in cases with high risk endometrial cancer.

Stage III and IV, Endometrial Cancer

In locally advanced disease: Adjuvant chemotherapy followed by pelvic radiation is done. Combination chemotherapy is commonly used. **Drugs comprise:** Doxorubicin paclitaxel (Taxol), adriamycin and cisplatin (TAP).

External pelvic and intracavitary radiation followed by extended hysterectomy 6 weeks later in cases of:

- Highly anaplastic tumor
- Uterine papillary serous carcinoma (UPSC)
- Clear cell carcinoma.

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These tumors have got high rate of recurrence both locoregional and systemic.

Chemotherapy

Chemotherapy is used in advanced and recurrent cases or in metastatic lesions.

- **Cytotoxic drugs** are being tried either singly or in combination. **The drugs commonly used are doxorubicin, cisplatin, carboplatin, paclitaxel, and ifosfamide** (Ch. 31, Table 31.7).

Hormonal Therapy

- **Progestogens**—are widely used. Women with presence of steroid hormone receptors [(progesterone receptor (PR) and estrogen receptor (ER)] have significantly high response to progestin therapy.
  Any one of the drugs—17 hydroxyprogesterone caproate (1 g/week IM), medroxyprogesterone acetate (1 g/week IM or 150 mg/day oral) or megesterol acetate (160 mg/day orally) is of use. The drug is to be continued for at least 3 months. If responsive, may be continued for longer period with reduced doses. In cases with early stage disease (stage IG1) with poor surgical risk LNG-IUS may be useful.
- **Selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AI):** Tamoxifen is a nonsteroidal agent with antiestrogenic as well as weakly estrogenic properties. It is used 10 mg twice daily along with progestogen therapy. It blocks the tissue estrogen receptor. It modulates progesterone receptors. It is found very effective when used adjunctively with progesterone (p. 448).

RECURRENT DISEASE

Common sites for recurrence are the vagina and the pelvis. The extrapelvic metastases are seen in the lung, lymph nodes (aortic), liver, brain, and bones. Majority (60%) of recurrences are seen within 2 years of initial therapy.

- Radiation therapy is the choice for isolated recurrence following surgical treatment.
- **Targeted therapy:** Drugs (mTOR inhibitors) including temsirolimus, everolimus and ridaforolimus are found to be effective in cases with recurrence. Combined therapy with everolimus and letrozole is found encouraging.

Follow-up of Patients

Following initial therapy, patient is examined every 4 months for the first 2 years, every 6 months for next 3 years and thereafter, annually (ACOG – 2005). Evaluation of symptoms, thorough clinical examination and X-ray chest (annual) are essential. Other investigations are: Mammography (annual) and CT, MRI when clinically indicated. Regular estimation of serum CA 125 may be helpful in cases with UPSC.

Place of Hormone Replacement Therapy

Its use is limited. In a patient with severe postmenopausal symptoms progestin (medroxyprogesterone acetate, 5–10 mg daily) may be a choice. Nonhormonal therapy (clonidine) can also be used. Urogenital symptoms can be improved using topical estrogen.

Prognosis

Elderly patients, higher stage (FIGO), poorly differentiated tumor, greater degree of myometrial penetration, lymph vascular space invasion are prognostically poor. Aneuploid tumors are prognostically worst. Histologically non-endometrioid tumors are aggressive and carry increased risk of recurrence. The prognostic factors to be considered are tabulated in Tables 24.17 and 24.18.

Fertility Sparing Therapy

Ovarian preservation in a woman with endometrial carcinoma: (a) Young women; (b) Fertility preservation needed; (c) Low grade disease; (d) Early stage disease; (e) Mandatory follow up with a compliant patient.

Fertility sparing therapy without hysterectomy is an option in a carefully selected woman. Myometrial invasion (or adnexal disease) is excluded with imaging studies. Woman with stage I G1 tumor are the candidates. Progestins are used, MPA (oral or IM) or LNG-IUD are the options. Hysterectomy and staging should be done when the lesion fails to regress with hormonal therapy.

TABLE 24.17: Poor prognostic factors in endometrial adenocarcinoma.

- **Age** at diagnosis (older the patient poorer the prognosis).
- **Advanced stage** of the disease.
- **Histologic type** (typical adenocarcinomas—better prognosis, papillary serous, clear cell carcinoma—poor prognosis)
- **Histologic differentiation**
- **Histologic grade**: Grade 3 tumors have 5 times more risk of recurrence and low 5-year survival rate
- **Increased myometrial invasion**
- **Lymphovascular** space invasion
- **Lymph node** metastasis
- **Extension** to cervix
- **Peritoneal cytology**—positive
- **Tumor size** (>2 cm → more lymph node metastasis)
- **Hormone receptor** status (receptor positive tumors have got better prognosis)
- **Ploidy status**—aneuploid tumors have got poor prognosis compared to diploid tumors
- **Oncogene expression** — HER-2/neu, poor prognosis
- **Type II endometrial cancer:** Poor prognosis

TABLE 24.18: 5-year survival rate (FIGO – 1998).

Stage	*Overall survival rate (%)*
IA	90.9%
IB	88.2%
II	71.6%
III	51.4%
IV	8.9%

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POINTS

- **Carcinoma body** ranks third amongst genital malignancies next to cervix and ovary. In USA, it is the leading site of genital malignancies followed by ovary and cervix. 75% are postmenopausal with the median age of 60. Nulliparity is associated in 30%.
  Endometrial cancer can be estrogen dependent (type-1) and nonestrogen dependent (type II). Prognosis of type I carcinoma is favorable compared to type II.
  Women with Lynch syndrome have 40–60% lifetime risk of endometrial cancer.
- **Use of combined oral contraceptive** is a known protective factor whereas chronic unopposed estrogen stimulation is a known predisposing factor for endometrial carcinoma (Tables 24.14 and 24.16).
  Corpus cancer syndrome encompasses obesity (BMI >30), hypertension and diabetes. Fibroid is associated in 30%. Endometrial hyperplasia precedes carcinoma in 25%. The most common histological type is adenocarcinoma. The pelvic and/or para-aortic glands are involved in about 10% in stage I.
  Postmenopausal bleeding is the predominant feature (75%). In premenopausal women, irregular bleeding is too often related. Once suspected, hysteroscopy and endometrial biopsy or fractional curettage is to be done, not only to diagnose but also to determine the extent of the lesion. The important primary prevention includes restriction of injudicious use of estrogen after menopause in nonhysterectomized women.
  Secondary prevention includes screening of 'high risk' women at least in menopausal period and prophylactic hysterectomy in premalignant lesions of the corpus and in women with Lynch syndrome (HNPCC).
  Diagnosis of endometrial carcinoma includes history, clinical examination, endometrial biopsy and imaging studies.
  Mainstay in the treatment of carcinoma body is total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node sampling. In stage II, radical hysterectomy has to be done. Adjuvant radiation is considered depending on the surgical stage of the disease, myometrial invasion and histologic grade.
- **Primary radiotherapy** is the treatment in surgically risk patients and in advanced stages.
- **Multimodality approach** (chemo and radiation therapy) is used in advanced and recurrent cases or in metastatic lesions.
- **Progestogens are** widely used in well-differentiated carcinoma with adequate estrogen and progesterone receptors. Antiestrogen, tamoxifen is often used along with progestogens to improve the result.
- **Prognosis of endometrial** cancer depends on many factors (Table 24.17) of which depth of myometrial invasion and tumor grade are the most important ones. Younger women with endometrial cancer have a better prognosis when compared with the older women.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease (GTD) is a heterogeneous spectrum of diseases with abnormal trophoblastic proliferation ranging from benign to malignant state. It has varying degree of spread from local invasion to distant metastasis.

Diagnosis of postmolar GTN is made when the hCG level plateaus for 3 or more consecutive weeks or re-elevates. **This may occur in 15–20% following hydatidiform mole.** Some, however, follow abortion, ectopic, and even normal pregnancy.

RISK FACTORS FOR DEVELOPMENT OF GTN

1. Advanced maternal age (>40 years)
2. β-hCG >100,000 IU/L
3. Increased uterine size
4. Bilateral ovarian enlargement (>8 cm)
5. USG—uterine invasion
6. Increased uterine vascularity (USG Doppler)

PERSISTENT GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)

Persistent GTN is evidenced by persistence of trophoblastic activity following evacuation of molar pregnancy. **This is clinically diagnosed** when the patient presents with (a) Irregular vaginal bleeding; (b) Subinvolution of the uterus; (c) Persistence of theca lutein cysts; (d) Level of hCG either plateaus or re-elevates after an initial fall. After molar evacuation serum β-hCG becomes normal in about 7–9 weeks.

Postmolar GTN of serious nature may be either invasive mole or choriocarcinoma but **GTN after nonmolar pregnancy is always a choriocarcinoma.**

Classification of GTD and risk factors are discussed in Tables 24.19A and B.

TABLE 24.19A: Classification of GTD (WHO).

Classification
A. Benign trophoblastic lesions
▪ Placental site nodule
▪ Exaggerated placental reaction
B. Hydatidiform moles (HM)
▪ Complete hydatidiform mole
▪ Partial hydatidiform moles
C. Gestational trophoblastic neoplasia
▪ Invasive mole
▪ Choriocarcinoma
▪ Placental site trophoblastic tumor
▪ Epithelioid trophoblastic tumors

TABLE 24.19B: Risk factors of GTD.

Risk factors
▪ **Race:** Asians compared to North Americans or Europeans
▪ **Age:** Extremes of age (<16 and >45)
▪ **Parity:** Increasing parity
▪ **Diet:** Risks of CHM is increased when dietary intake of animal fat, beta-carotene or vitamin A is less
▪ **Genetics:** Autosomal recessive disorder (familial recurrent HM) chromosome 19q
▪ **Risk of recurrence** is increased up to 25% when there is previous 2 or more molar pregnancy

(CHM: complete hydatidiform mole)

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Incidence

The incidence of GTN is about 1 in 5,000 pregnancies in oriental countries and 1 in 50,000 in Europe and North America. More than 50% occur after molar pregnancy, about 25% after abortion and/or ectopic pregnancy and a few after normal pregnancy. **Nonmetastatic (locally invasive) lesions develop in 15% and metastatic lesions develop in about 4% of patients after molar evacuation.**

PLACENTAL SITE TROPHOBLASTIC TUMOR

The tumor arises from the trophoblast of the placental bed. Incidence is less than 1% of all patients with GTN. 40–50% of these patients develop metastases. Syncytiotrophoblast cells are generally absent, instead intermediate trophoblast cells are predominant. β-hCG secretion is low but human placental lactogen (hPL) is secreted and this is monitored during the follow up. **The entity is not responsive to chemotherapy. Hysterectomy is the preferred treatment. Serial serum hPL** may be a reliable marker and hPL is useful for immunohistochemical staining to confirm the diagnosis.

Epithelioid trophoblastic tumor (ETT): It is a variant of PSTT (WHO, 2003). Both are relatively chemoresistant and recurrence rate for the both are high (20–30%) despite surgery or chemotherapy.

INVASIVE GTN (CHORIOADENOMA DESTRUENS)

Invasive mole comprises about 15% of all GTN.

The prominent features of this type of mole are invasive and destructive potentialities. Invasive mole shows abnormal penetration through the muscle layers of the uterus. The uterine wall may be perforated at multiple areas showing purple, fungating growth with massive intraperitoneal hemorrhage. The neoplasm may invade the pelvic blood vessels and metastasizes to vagina or distant sites as like those in choriocarcinoma.

Diagnosis

- **On laparotomy:** (a) Perforation of the uterus through which purple fungating growth is visible; (b) Hemoperitoneum.
- **Histology:** There is penetration of the uterine wall by the hyperplastic trophoblastic cells which **still retain villus structures. There is no evidence of muscle necrosis** (Fig. 24.13). The materials for uterine curettage are often deceptive as the lesion may be deep inside the myometrium.
- **Persistent high level** of urinary or serum hCG.

CHORIOCARCINOMA

Choriocarcinoma is a highly malignant tumor arising from the chorionic epithelium (Fig. 24.14). It should be remembered that it is not a tumor of the uterus which is secondarily involved.

About 3–5% of all patients with molar pregnancies develop choriocarcinoma. Amongst all patients with

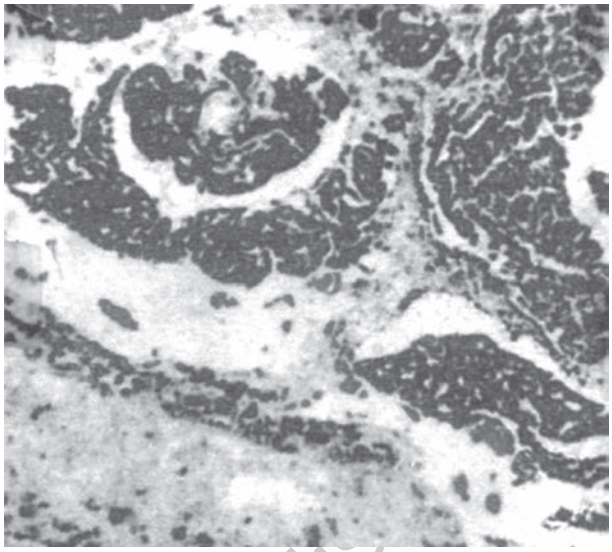

Fig. 24.13: Histological section of invasive mole showing structures of villi with marked trophoblastic proliferation deep in myometrium.

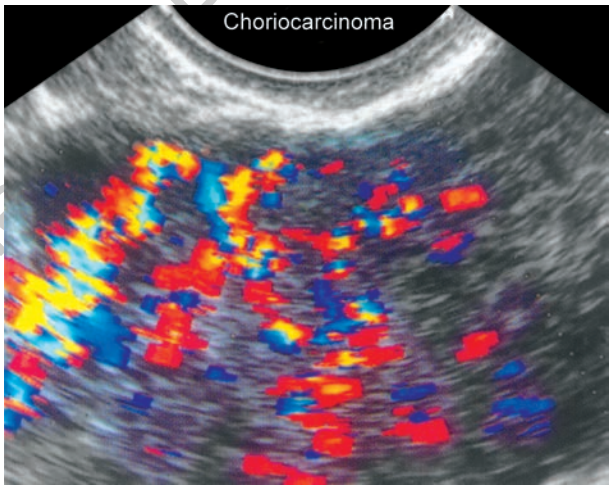

Fig. 24.14: Transvaginal color Doppler scan of choriocarcinoma showing randomly dispersed vessels.

choriocarcinoma, around 50% develop following a hydatidiform mole, 30% occur after a miscarriage or an ectopic pregnancy and 20% after an apparently normal pregnancy. **Trophoblastic disease following a normal pregnancy is either choriocarcinoma or PSTT and not a benign or invasive mole.**

Pathology

The primary site is usually anywhere in the uterus. Rarely, it starts in the tube or ovary. Ovarian choriocarcinoma (nongestational) may also be associated with malignant teratoma or dysgerminoma.

Naked Eye Appearances (Fig. 24.15)

The lesion is usually localized nodular type. It looks red, hemorrhagic, and necrotic. At times, the lesion is diffuse involving the entire endometrium. The nodular type may be located deep in the myometrium with overlying

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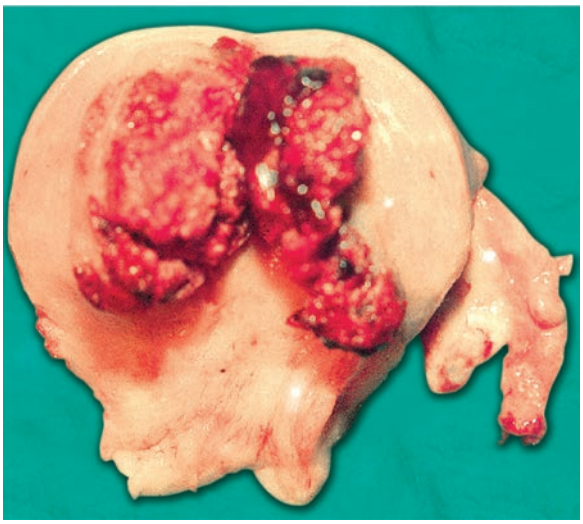

Fig. 24.15: Choriocarcinoma of diffuse type.

endometrium intact. This often gives the false-negative diagnosis on uterine curettage.

Microscopic Appearance (Fig. 24.16)

There are anaplastic sheets or columns of trophoblastic cells invading the uterine musculature. There are **evidences of necrosis and hemorrhage. Villus pattern is completely absent.**

Ovarian Enlargement

Bilateral lutein cysts are present in about 30%. These are due to excessive production of chorionic gonadotropin.

SPREAD OF GTN

Apart from the local spread, vascular erosion takes place early and hence distant metastases occur rapidly. **The common sites of metastases are** lungs (80%), anterior vaginal wall (30%), brain (10%), liver (10%), and others.

CLINICAL FEATURES OF GTN

The clinical features depend on the location of the primary growth and on its secondary deposits.

Patient Profile

There is usually a history of molar pregnancy in recent past. Rarely, its relation with a term pregnancy, abortion or ectopic pregnancy may be established. **GTN after a nonmolar pregnancy is always a choriocarcinoma.**

Symptoms

The following are the usual symptoms:

- Persistent ill health
- Irregular vaginal bleeding, at times brisk
- Continued amenorrhea.

Other symptoms due to metastatic lesions are:

Lung: Cough, breathlessness, hemoptysis
Vaginal: Irregular and at times brisk hemorrhage
Cerebral: Headache, convulsion, paralysis or coma
Liver: Epigastric pain, jaundice.

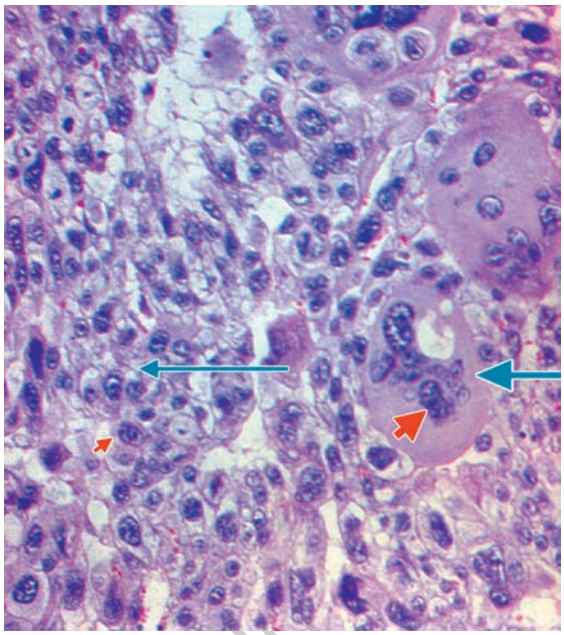

Fig. 24.16: Histologic picture of choriocarcinoma. The cytotrophoblast cells are well-defined with clear cytoplasm (thin arrow). The syncytiotrophoblast cells are arranged in sheets of multinucleated cytoplasm (thick arrow).

Signs

- Patient looks ill
- Pallor of varying degrees.

Physical signs are evident according to the organ involved.

Bimanual examination reveals subinvolution of the uterus. There may be a purplish-red nodule in the lower-third of the anterior vaginal wall (Fig. 24.17). Unilateral or bilateral enlarged ovaries may be palpable through lateral fornices.

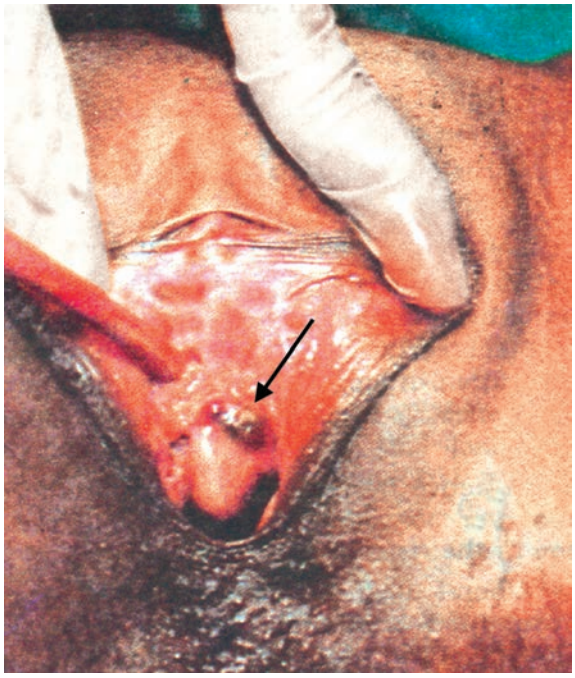

Fig. 24.17: Note the purplish-red metastatic nodule in the lower third of anterior vaginal wall (suburethral). Metastases may occur in vaginal fornices also.

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SPECIAL INVESTIGATIONS

The methods extended are not only to establish the diagnosis but also to note the metastatic sites which help in staging.

Metastatic brain lesion is suspected when the ratio of hCG in spinal fluid/in serum is more than 1:60.

DIAGNOSTIC CRITERIA FOR POSTMOLAR GTN (FIGO)

Levels of serum β-hCG are followed up.

- ≥ Four values of plateaued hCG (±10%) over at least 3 weeks time (D:1, 7, 14, 21).
- A rise of hCG of >10% for >3 values over at least 2 weeks time.
- Histologic diagnosis of choriocarcinoma.
- Persistence of hCG beyond 6 months of mole evacuation.

Chest X-ray

X-ray shows 'cannon ball' shadow or 'snow storm' appearance due to numerous tumor emboli (Fig. 24.18). Pleural effusion may be present.

Pelvic Sonography

Sonography helps not only to localize the lesion but to differentiate GTN from a normal pregnancy.

Diagnostic Uterine Curettage

Pretherapy D and C reduces the intrauterine tumor bulk. However, routine D and C for histologic diagnosis is not required. It reveals the characteristic histological pattern. It is emphasized that, the curetted material may not reveal the diagnosis in all the cases, as the lesion may be deep in the myometrium or the uterus may not be the primary site. One should be very careful and alert while doing uterine curettage as brisk hemorrhage may occur for which a lifesaving hysterectomy may have to be done.

Histopathology

Choriocarcinoma, on histology shows sheets of anaplastic trophoblastic tissue with cytotrophoblast and syncytiotrophoblast cells without chorionic villi.

Absence of paternal DNA within the tumor differentiates nongestational choriocarcinoma from gestational choriocarcinoma. Extragonadal germ cell tumors originate from midline loctations such as anterior mediastinum, retroperitoneum, and have no primary tumor in the ovaries. They secrete β–hCG. PSTT secrete HPL (50–100%) and it is lesser in amount (10%) to that of hCG.

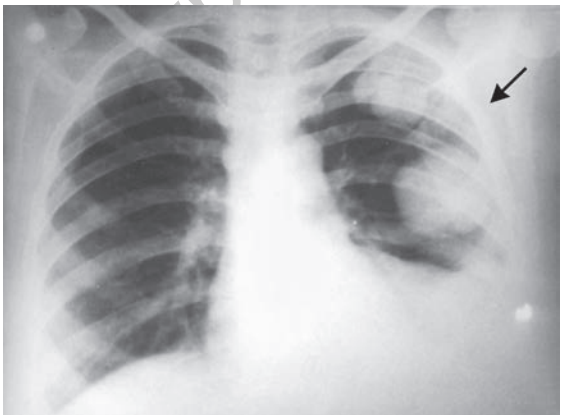

Fig. 24.18: Cannon ball shadow in the left apical and midregion of the lung with pleural effusion in choriocarcinoma.

(*Courtesy:* Eden Hospital, MCH, Kolkata)

DIAGNOSIS OF METASTASES

Vaginal nodules

Excision biopsy or biopsy should not be done. Massive hemorrhage following resection may need packing or selective embolization.

Cerebral

- The ratio of hCG levels in spinal fluid and serum is higher than 60.
- CT scan or MRI.

Liver: CT scan; ultrasonography.

Chest: X-ray (metastasis); CT may show micrometastases which are not visible on a chest radiograph.

Metastases to other sites are uncommon when pelvic examination and chest X-ray are normal.

WHO prognostic scoring system of gestational trophoblastic disease is discussed in Table 24.20.

STAGING

The anatomic staging for gestational trophoblastic tumors (GTT) as described by FIGO is tabulated in Table 24.21.

TABLE 24.20: WHO prognostic scoring system of gestational trophoblastic disease as modified by FIGO (2000).

Parameter	*Score*			
	0	**1**	**2**	**4**
Age (years)	<40	>40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval (month)*	<4	4–6	7–12	≥13
Pretreatment hCG (IU/L)	$<10^3$	10^3– $<10^4$	10^4 – $<10^5$	$\geq 10^5$
Largest tumor (cm)	<3	3–4	>5	—
Site of metastases	Lung pelvis	Spleen, kidney	GI tract, liver	Brain
No. of metastases detected	—	1–4	5–8	>8
Prior chemotherapy	—	—	Single drug	Multiple drugs

Total score: <6 is low risk and a total score ≥7 is high risk.
*__Interval:__ Time between antecedent pregnancy and start of chemotherapy. This scoring is not applicable to PSTT and ETT.

TABLE 24.21: FIGO anatomic staging for GTT.

Stage I	The lesion is confined to the uterus
Stage II	The lesion spreads outside the uterus but is confined to the genital organs
Stage III	The lesion metastasizes to the lungs
Stage IV	The lesion metastasizes to sites such as brain, liver or gastrointestinal tract

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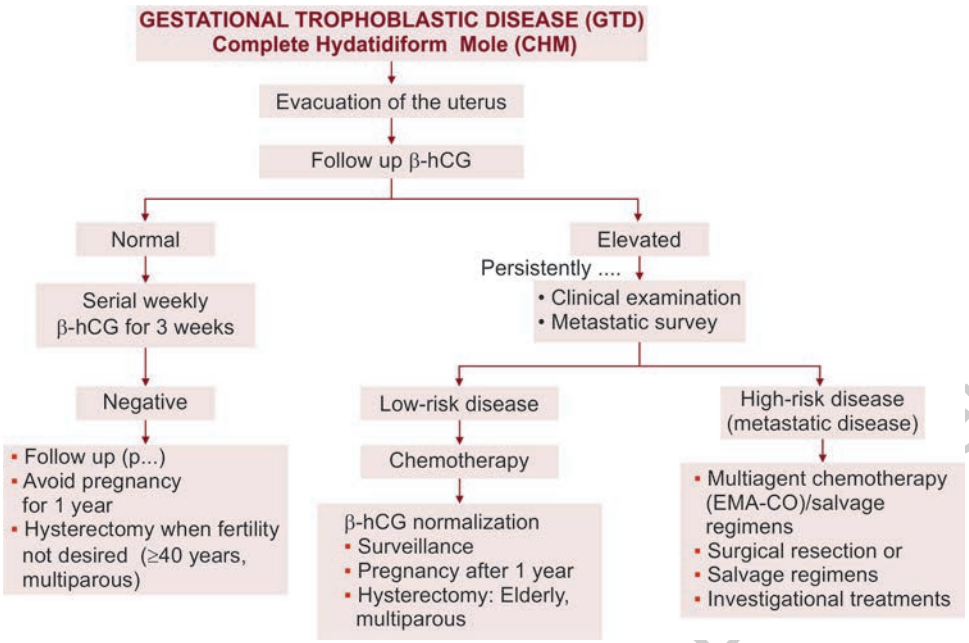
Flowchart 24.1: Management of gestational trophoblastic disease (GTD).



MANAGEMENT OF GTN

- **Preventive**
- **Curative**

Preventive

- **Prophylactic chemotherapy** in 'at risk' women following evacuation of molar pregnancy may be considered. It prevents uterine invasion or metastasis. 'At risk' women are:
  - Age of patient > 40 years.
  - Initial levels of serum hCG ≥ 100,000 IU/mL.
    - hCG level fails to become normal by 7–9 weeks time or there is re-elevation.
    - Histologically diagnosed as infiltrative mole.
  - Evidence of metastases irrespective of the level of hCG.
  - Previous history of a molar pregnancy.
  - Woman who is unreliable for follow up.

Disadvantage of routine chemotherapy is unnecessary exposure of the toxic drugs to all women who may not need it. Majority (80–90%) of women do not develop persistent GTN.

- **Meticulous follow up** following evacuation of hydatidiform mole is essential for at least 6 months to detect early evidence of trophoblastic reactivation. **A single agent chemotherapy is highly effective in nonmetastatic and low-risk metastatic GTN.**
- **Selective hysterectomy** in hydatidiform mole over 35 years. There is 4-fold reduction in the risks of choriocarcinoma.
- In suspected cases, serum hCG is to be determined.

Curative

- **Chemotherapy**
- **Surgery**
- **Radiation**

Chemotherapy

The advent of chemotherapy has revolutionized the treatment of both the nonmetastatic and metastatic lesion of choriocarcinoma. Chemotherapy is now the mainstay in the treatment (Flowchart 24.1).

Whether a single agent (Table 24.22) or multidrug regimen (Tables 24.23 and 24.24) is to be used, depends on the risk factors present. **In general, patients with nonmetastatic (low risk) and good prognosis disease are treated effectively with single agent therapy (methotrexate or actinomycin). The patients with poor prognosis metastatic disease should be treated with combination drug regimen (EMA-CO regimen).**

- **Management of GTN** needs thorough assessment of the extent of the disease. **Chemotherapy regimen is decided** on WHO prognostic scoring.
- In high risk metastatic disease, best results are obtained with EMA-CO protocol (Table 24.24).

Ultra high risk GTN (WHO): Patients in the group are: (a) FIGO high risk group with score of ≥13; (b) Patients with

TABLE 24.22: Single drug regimen in low-risk cases.

Methotrexate	1–1.5 mg/kg	IM/IV	Days 1, 3, 5, and 7
Folinic acid	0.1–0.15 mg/kg	IM	Days 2, 4, 6, and 8

The courses are to be repeated at interval of 7 days.

TABLE 24.23: Mac protocol in low-risk cases.

Methotrexate	1–1.5 mg/kg	IM/IV	Days 1, 3, 5, and 7
Folinic acid	0.1–0.15 mg/kg	IM	Days 2, 4, 6, and 8
Actinomycin D	12 mg/kg	IV	Days 1–5
Cyclophospha-mide	3 mg/kg	IV	Days 1–5

The courses are to be repeated at interval of 2 weeks.

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TABLE 24.24: EMA-CO protocol in high risk metastatic GTN.

Days	Drug	Dose
Day 1	Etoposide	100 mg/m^2 in 200 mL saline infused over 30 minutes
Day 1	Actinomycin D	0.5 mg IV bolus
	Methotrexate	100 mg/m^2 bolus followed by 200 mg/m^2 IV infusion over 12 hours
Day 2	Etoposide	100 mg/m^2 in 200 mL saline infused over 30 minutes
	Actinomycin D	0.5 mg IV bolus
	Folinic acid	15 mg IM every 12 hours for 4 doses beginning 24 hours after starting methotrexate
Day 8	Cyclophosphamide	600 mg/m^2 IV in saline over 30 minutes
	Vincristine (Oncovin)	1 mg/m^2 IV bolus

The course will restart after 7–14 days, if possible. Generally two additional courses are given after the hCG levels become normal.

metastases in liver, brain or extensive metastasis. These patients tolerate poorly with first line multiagent chemotherapy. This multiagent therapy causes sudden tumor collapse. Many of these patients suffer severe hemorrhage, metabolic acidosis, myelosuppression, septicemia, multiorgan failure and death.

Management: Complications can be avoided by giving initial minimal agents like EP regimen. Etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2 are given and repeated weekly for 1–3 weeks. Thereafter the usual full dose regimen EMA-CO is started.

Salvage therapies: Patient failing EMA-CO are mostly salvaged with paclitaxel and etoposide alternating with paclitaxel and cisplatin (TE/TP) or with EP/EMA.

All tests are repeated before each cycle: Quantitative estimation of β-hCG level, complete blood count (CBC), RFT, LFT, thyroid function and imaging studies are to be done. β-hCG levels are high in invasive mole and choriocarcinoma (100–1000,000 mIU/mL), low levels are seen in PSTT, ETT.

Treatment course should not be repeated if:

- WBC <3,000 cu mm
- Polymorphonuclear leukocytes <1500 cu mm
- Platelet counts <100,000 cu mm
- Significant elevation of BUN, SGPT

Continue treatment at 1–3 weekly interval until three consecutive negative weekly hCG titers.

SURVEILLANCE DURING AND AFTER THERAPY OF GTN

Serum hCG value monitoring every week → once negative → every 2 weeks for 3 months → every month for 1 year → every 6–12 months for life or at least 3–5 years.

- **Remission:** 3 consecutive normal weekly hCG values.
- **Response:** >10% decline in hCG during one cycle treatment.
- **Plateau:** ±10% change in hCG during one cycle.
- **Resistance:** 10% rise in hCG during one cycle or plateau for two cycles of chemotherapy.

Place of Hysterectomy

Primary hysterectomy has got a limited place. Chemotherapy alone is successful in curing 85% of patients with nonmetastatic and good prognosis metastatic GTN.

In patients with nonmetastatic or good prognosis metastatic disease, **hysterectomy decreases the number of courses of chemotherapy.**

INDICATIONS OF HYSTERECTOMY

- Lesions confined to the uterus in women aged >35 years, not desirous of fertility.
- Placental site trophoblastic tumor.
- Intractable vaginal bleeding.
- Localized uterine lesion resistant to chemotherapy.
- Accidental uterine perforation during uterine curettage.

It is preferable to start chemotherapy → surgery on day 3 → followed by chemotherapy as per schedule.

Types of Surgery

- Total hysterectomy is enough. The ovaries are usually not involved and if involved, can be effectively cured with postoperative chemotherapy.
- Lung resection (thoracotomy) in pulmonary metastasis in drug resistant cases.
- Craniotomy for control of bleeding.

Radiation

Patients with brain metastases require whole-brain radiation therapy (3000 cGy over 10 days). Intrathecal high dose methotrexate may be administered to prevent hemorrhage and for tumor shrinkage.

Liver Metastasis

Interventional radiology (hepatic artery ligation or embolization) or whole liver radiation (2000 cGy over 10 days) along with chemotherapy may be effective. Hepatic metastasis has a poor prognosis.

Transplacental metastases to the fetus is rare and the prognosis is poor.

Prognosis

The cure rate is almost 100% in low risk and about 70% in high risk metastatic groups.

Recurrences

Overall recurrences are 3% for stage I; 8% for stage II; 4% for stage III and 9% for stage IV. Meantime for recurrence is 6 months. Recurrence rate for PSTT and ETT are about 20–30%.

Prevention of Recurrent Disease

Additional cycle of chemotherapy following normalization of hCG level, should be given as follows: For nonmetastatic disease—one cycle; for good prognosis metastatic disease—two cycles; for poor prognosis metastatic disease—three cycles.

Future Childbirth

There is no adverse effect on the subsequent pregnancy provided the conception occurs after 1 year of completion

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of chemotherapy. **Pregnancy** should be confirmed by USG early and hCG level is to be measured 6 weeks after delivery to exclude persistent GTN. Incidence of placenta accreta is increased.

Surveillance and follow up is mandatory for all patients at least for 2 years. Serum hCG is measured weekly until it is negative for three consecutive weeks. Thereafter, it is measured monthly for 6 months and 6 monthly thereafter for life.

Increased risk for the development of secondary malignancies like leukemia, colon cancer, and breast cancer has been observed. This is common after treatment with multiple agent chemotherapy. Etoposide is reserved for resistant and high-risk cases only.

Phantom β-hCG: In some patients persistent mildly elevated levels of β-hCG serum persist for a long time. But in reality there is no true β-hCG or no trophoblastic disease is present. This 'phantom' β-hCG is due to heterophile antibodies in the patient's serum that interfere with the β-hCG immune assay and cause a false positive result.

In such a situation patient does not need any active management neither chemotherapy nor hysterectomy. The diagnosis can be confirmed by doing the urine test that will be negative. Heterophile antibodies are not filtered in the urine as these are large glycoprotein molecule.

Quiescent GTN: Following treatment of a HM and choriocarcinoma, persistence of low level (1–300 IU/L) of β-hCG has been observed in few patients for a period of 3 months or longer. There is no evidence of GTN on clinical, radiologic or biochemical study. It is known as quiescent GTN.

This is also considered as premalignant condition as 25% of these cases progress to choriocarcinoma over a period of 6 months to 10 years. Presence of hyperglycosylated hCG (hCG-H) is a marker of invasive cytotrophoblasts. hCG-H can be detected in many cases of quiescent GTD. Majority of these cases do not need any treatment as these are self-resolving. These cases need follow up. Cases with elevated levels of hCG on follow up, need chemotherapy.

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POINTS

- **Gestational trophoblastic neoplasia** (GTN) encompasses persistent hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumor.
- The **incidence of GTN** is about 1 in 5,000 pregnancies in Oriental countries and 1 in 50,000 in Europe and North America. 50% occur after molar pregnancy, 25% after abortion and ectopic and 25% after normal pregnancy. Nonmetastatic lesions develop in 15% and metastatic lesions develop in about 4% of patients after molar evacuation.
- **Trophoblastic cells** normally regress within 3 weeks following delivery. Women treated for GTN should not become pregnant for 6–12 months after the treatment. This helps to assess the level of β-hCG and treatment response. Diagnosis of postmolar GTN is made when the hCG level plateaus for 3 or more consecutive weeks or re-elevates.
- **The invasive mole** is diagnosed on laparotomy and on histology showing hyperplastic trophoblastic cells maintaining villous structures without evidences of muscle necrosis. In choriocarcinoma, the hyperplastic trophoblastic column of cells invades the muscles. There are evidences of hemorrhage and muscle necrosis. The villous pattern is lost.
  The most common site of metastases is lung, followed by anterior vaginal wall, brain and liver.
- **Recurrence rate of GTN** following treatment (hCG level reached normal) is 5% for metastatic good prognosis cases and is 1–2% for nonmetastatic cases (Tables 24.19A and B).
- **hCG monitoring:** All forms of hCG (hCG, core hCG, C- terminal hCG, nicked free beta and the hyperglycosylated) are monitored. To exclude false positive result retest with another assay kit or test for urine hCG may be used.
- **Heterogenicity of β-hCG molecules in GTN** is increased compared to a normal pregnancy. hCG molecules in GTN has higher proportion of nicked β-hCG, β core fragment and free β-hCG. A β-hCG assay for follow up must detect both β-hCG as well as its all the fragments and metabolites. An assay with poor sensitively may fail to detect low levels of β-hCG, leading to incorrect decision and management result. Ultimately there is disease persistence. Patients, following complete remission, have normal pregnancy and live births.
- **Chemotherapy is now the mainstay of treatment (p. 307)**.
- **Primary surgery** has got limited place. Hysterectomy is indicated in women aged more than 35 years to improve the efficacy of chemotherapy or to control intractable bleeding. Total hysterectomy is to be done on day 3 of a course of chemotherapy.
- **There is no adverse effect** on subsequent pregnancy, if it occurs after 1 year of chemotherapy. Pregnancy should be confirmed by USG early and serum hCG should be measured 6 weeks after delivery to exclude persistent GTN.
- **Prophylactic chemotherapy** can prevent uterine invasion and metastasis. But it is given selectively.
- **Low-risk GTN cases** (Tables 24.19A and B) are usually treated by single-agent chemotherapy whereas high-risk metastatic cases are treated with multiple-agent chemotherapy. Nonmetastatic and low-risk metastatic GTN cases are completely curable by chemotherapy.
- **Surveillance during and after therapy** of GTN is essential (p. 308).

MALIGNANT TUMORS OF THE OVARY

INCIDENCE

Ovarian malignancy constitutes about 15–20% of genital malignancy. It is the leading cause of cancer death in women next to breast cancer in US and Scandinavian countries. It is much less in Oriental or Latin American and Asian countries including Japan and India. **Approximately, 1 in every 70 newborn females in the United States will live to develop ovarian cancer** and 1 woman in 100 will die of

TABLE 24.25: Variations in incidence, mortality rates and disease burden for ovarian cancer.

Countries	Incidence (ASR) per 100,000	Mortality rate (ASR) per 100,000
Less developed	5.0	3.1
More developed	9.2	5.0
World average	6.1	3.7

(ASR: age-standardized incidence rates)

the disease. 20% of ovarian neoplasms are malignant. **It is more common amongst nulliparous.** It is the fourth most common cause of cancer deaths in women exceeded only by breast, colon and lung malignancies. Ovarian cancer has the highest mortality of all gynecologic cancers. World wide, there are 2,39,000 new cases and 152,000 deaths from ovarian cancer each year.

EPIDEMIOLOGY AND ETIOLOGICAL FACTORS (TABLE 24.25)

Highest incidence is recorded in the industrialized countries (Sweden, USA, and UK). There is significant reduction in the risk with increasing parity.

- **Nulligravidas** carry a higher risk for ovarian malignancy.
- **Incessant ovulation theory** (Fathalla, 1971) suggests repeated ovulatory trauma to the ovarian epithelial lining is a promoting factor for carcinogenesis. Combined oral contraceptive pills reduce the risk significantly as also repeated pregnancies.
- The role of **ovulation inducing drugs** is yet uncertain. Use of coffee, tobacco, alcohol, and dietary fat has been implicated. Association of ovarian cancer with **talc and asbestos** has also been mentioned. Breastfeeding, tubal ligation, and hysterectomy have been associated with reduction in the risk.

GENETICS AND OVARIAN MALIGNANCY

Hereditary ovarian cancer occurs in two forms:

- **Hereditary breast ovarian cancer (BOC) syndrome** is observed in 80–95% cases of all familial ovarian cancers. *BRCA1* (chromosome 17q21) and *BRCA2* (chromosome 13q12) gene mutations are observed in majority of such cases (serous not mucinous carcinoma). These patients present at an earlier age.
- **Hereditary nonpolyposis colorectal cancer (HNPCC)**—is an autosomal dominant transmission. Women with HNPCC (Lynch II syndrome) have life time risk of about 50% for endometrial cancer and 12% for ovarian cancer. The risks of other cancers like genitourinary in addition to HNPCC are high. It is due to mutations in three DNA mismatch repair genes (MLH1, MSH2, and MSH6).
- A first degree relative: Mother, sister, daughter of an affected individual
- A second degree relative: Maternal or paternal aunt or grandmothers
- **Concept of distal fallopian tube origin (Fig. 24.19)**

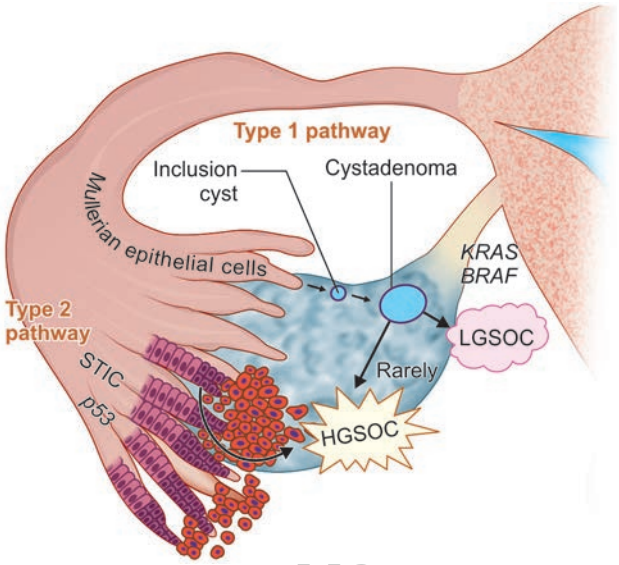

Fig. 24.19: The schematic presentation of distal fallopian tube origin of ovarian carcinoma. The concept of LGSOC and HGSOC with STIC and p53 mutation are shown.

TABLE 24.26: Dualistic pattern of ovarian carcinogenesis.

	Type 1	Type II
Carcinogenesis	Incorporation of Müllerian epithelial cells on the ovary causing ovarian endometriosis, cortical inclusion cyst	Incorporation of serous tubal intraepithelial carcinoma (STIC) with exfoliation of cells on the ovarian surface or in the peritoneal cavity
Type of tumor	Borderline tumors; Low-grade serous ovarian cancers (LGSOC), clear cell cancer, mucinous carcinoma	▪ High-grade serous ovarian carcinoma (HGSOC) ▪ Undifferentiated carcinoma
Stage at presentation	Early stage	Advanced stage
Gene mutation	KRAS, BRAF or PTEN, not p-53	P-53 mutations in 100% of cases
Clinical course	Indolent	Highly aggressive from the outset

The two important carcinogenic pathways are shown in Table 24.26.

CATEGORIES OF OVARIAN MALIGNANCY

Categories of ovarian cancer (Table 24.27).

GENERAL CONSIDERATIONS

Malignant epithelial tumors constitute about 90% of all primary ovarian carcinomas. The nonepithelial malignant tumors such as gonadal stromal or germ cell tumors are indeed rare, present special problems in extremes of age and are of pathologist's curiosity. These will be dealt separately. **Thus, in the discussion to follow, only the malignant epithelial tumors will be described.**

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TABLE 24.27: Categories of ovarian cancer (PRAT – 2012).

Epithelial (80–85%)	*Germ cell (5%)*	*Sex cord stromal (1%)*	*Metastatic disease (5%)*	*Hereditary (10–15%)*
■ High-grade serous (70%) ■ Mucinous (10%) ■ Endometrioid (10%) ■ Low-grade serous (5–10%) ■ Clear cell (5%)	■ Teratoma (immature) (36%) ■ Dysgerminoma (33%) ■ Endometrial sinus tumor (15%) ■ Embryonal carcinoma (4%) ■ Choriocarcinoma (2%) ■ Gonadoblastoma ■ Mixed germ cell (5%)	■ Granulosa cell (70%) ■ Thecoma ■ Fibroma ■ Sertoli-Leydig cell ■ Gynandroblastoma	■ GI tract 39% ■ Breast (28%) ■ Endometrium (20%) ■ Lymphoma	■ Hereditary breast and ovarian cancer syndrome ■ Lynch syndrome

PRIMARY EPITHELIAL

Malignant epithelial tumors include both cystic and solid types. **These are bilateral in about 50%** (Fig. 24.24). Cystic is more common than solid. These may arise de novo as malignant or more commonly, they result from malignant changes of benign cystic tumors.

Endometrioid carcinoma is associated with endometrial carcinoma in 20 % and ovarian endometriosis in 10% cases. In less than 5%, it may arise from the endometrial cyst.

Cystic

Naked eye appearances: The wall of the cystic tumor becomes shaggy. There may be papillary projection at places. Cut section shows solid areas with hemorrhage at places. The papillae become friable, the base becomes broad and indurated. In mucinous type, it is filled up with gelatinous material (Fig. 24.20).

Microscopic picture: The histologic appearance in each type is tabulated in Table 24.28 and shown in Figure 24.21.

Solid (Fig. 24.22)

It attains a moderate size. The external surface is smooth and often lobulated. Subserous blood vessels may be prominent. Cut section shows grayish granular appearance, at times brain-like. There may be irregular cystic spaces due to necrosis.

Microscopic appearance reveals adenocarcinoma or carcinoma without adenomatous pattern.

TABLE 24.28: Epithelial ovarian tumor and histologic appearance.

Tumor types	*Histology*	*Occurrence all ovarian*
Serous cyst carcinoma	Adenocarcinoma	35–40
Mucinous cyst carcinoma	Adenocarcinoma	10–15
Endometrioid or adenoacanthoma	Adenocarcinoma	15–25
Malignant dermoid	Squamous cell carcinoma	Rare
Others: Clear cell adenocarcinoma, malignant Brenner tumor, squamous cell carcinoma, undifferentiated carcinoma.		

FIGO STAGING OF CARCINOMA OVARY (P. 307)

The staging aims at:

- Better choice of adjuvant therapy
- Better assessment of prognosis.

The staging is done following laparotomy (staging laparotomy) and is followed as per FIGO, 2014 (Table 24.29).

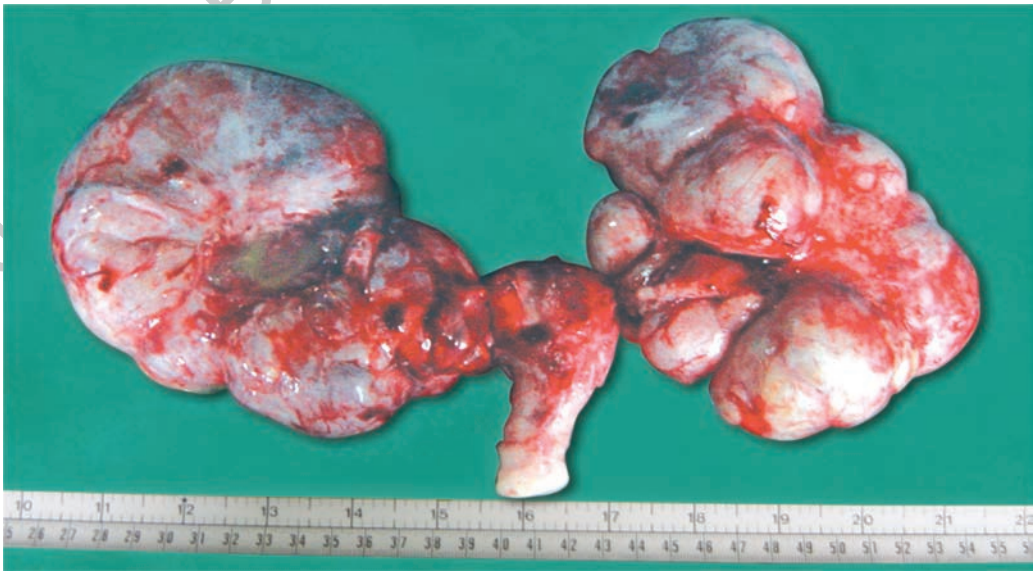

Fig. 24.20: Photograph of a surgical specimen of a huge bilateral mucinous cyst adenocarcinoma. The tumors are lobulated and with areas of hemorrhage and necrosis are seen.

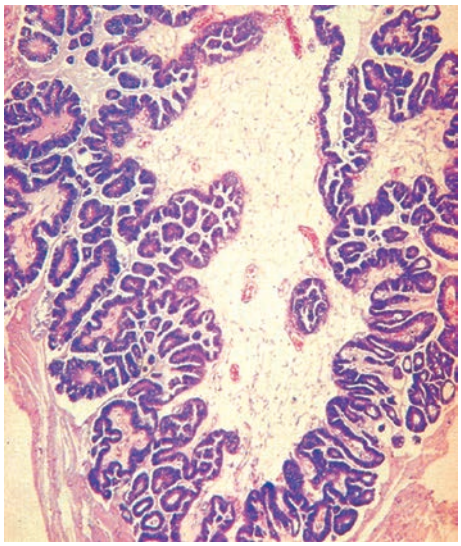

Fig. 24.21: Histologic picture of serous cyst adenocarcinoma. Long papillary outgrowths are seen. There is considerable cellular mitotic activity. This lace-like pattern characterized by slit-like spaces between the papillae is due to extensive coalescence of papillae.

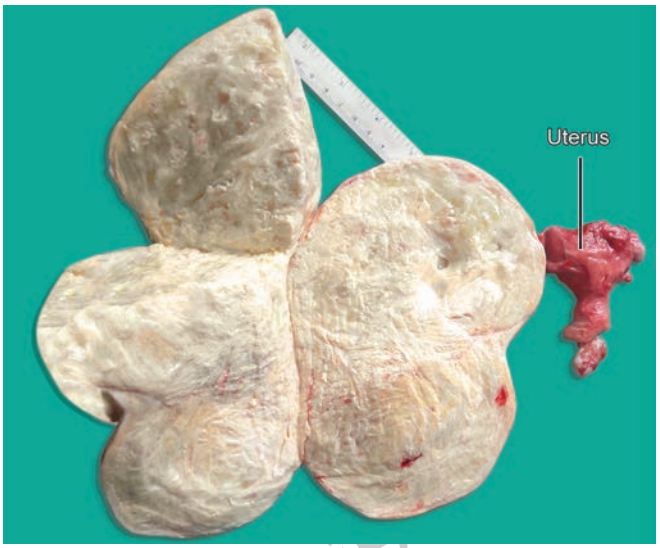

Fig. 24.22: 55-year-old lady presented with pelvic heaviness and AUB. MRI revealed solid ovarian mass. Solid ovarian tumor is cut opened. Histology confirmed ovarian fibroma. The uterus is seen by the side.

TABLE 24.29: FIGO staging of carcinoma of the ovary, tube and peritoneum (2018).

Stage I: Tumor confined to ovaries or fallopian tube(s).
T1-N0-M0
IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1a-N0-M0
IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1b-N0-M0
IC: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:
IC1: Surgical spill
T1c1-N0-M0
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c2-N0-M0
IC3: Malignant cells in the ascites or peritoneal washings
T1c3-N0-M0
Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
T2-N0-M0
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
T2a-N0-M0
IIB: Extension to other pelvic intraperitoneal tissues
T2b-N0-M0
Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
T1/T2-N1-M0

Contd...

Contd...

IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1(i) Metastasis up to 10 mm in greatest dimension
IIIA1(ii) Metastasis more than 10 mm in greatest dimension
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3a2-N0/N1-M0
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
T3b-N0/N1-M0
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
T3c-N0/N1-M0
Stage IV: Distant metastasis excluding peritoneal metastases
Stage IVA: Pleural effusion with positive cytology
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)
Any T, any N, M1

Regional lymph nodes (N)	**Distant metastasis (M)**
1. NX: Regional lymph nodes (N) cannot be assessed	1. MX: Distant metastasis cannot be assessed
2. N0: No regional lymph node metastasis	2. M0: No distant metastasis
3. N1: Regional lymph node metastasis	3. M1: Distant metastasis (excluding peritoneal metastasis)

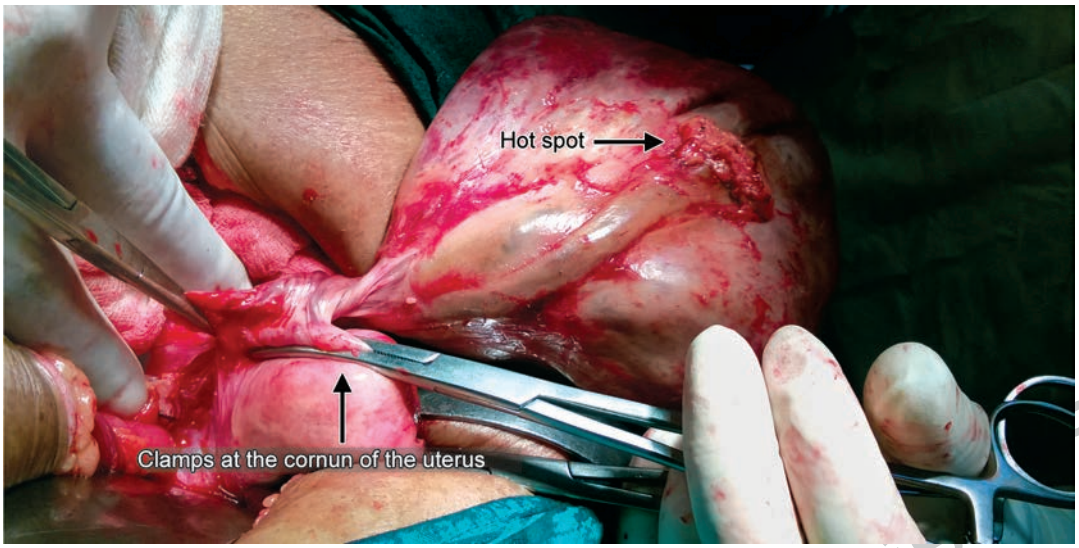

Fig. 24.23: Intraoperative photograph of a huge ovarian serous cyst adenocarcinoma. Note the tube is stretched over the tumor surface. The junction of the peritoneum (arrow) with the fimbrial epithelium [(tubal-peritoneal junction (TPJ)], is the site of carcinogenesis. TPJ is also known as 'hot spot' as that of SCJ for CIN.

SPREAD

Natural path of spread: The tumors spread **along the peritoneal surface** to involve ovarian, parietal and intestinal peritoneal surfaces as well as the undersurface of the diaphragm, particularly on the right side. **The modes of spread are:**

- **Transcelomic (exfoliation of cells)**
- **Lymphatic**
- **Direct**
- **Hematogenous**

Transcelomic

Implantation of malignant cells occurs by:

- Direct exfoliation of cells as in papillary cyst adenocarcinoma.
- Penetration of tumor capsule.
- Rupture of the capsule.

The **exfoliated cells** in the peritoneal fluid flow along the paracolic gutters.

Multiple secondary deposits are formed on the peritoneal surfaces especially in the pouch of Douglas, in the omentum, diaphragm, retroperitoneal nodes, and serous surfaces of the abdominopelvic organs (Fig. 24.23).

Lymphatics

The lymphatic spread is to the draining lymph nodes namely para-aortic and superior gastric nodes. The pelvic nodes may be involved through utero-ovarian, round ligament and peritoneal permeation into the subperitoneal lymphatics (Table 24.30) external iliac, internal iliac, common iliac and inguinal nodes. **The left supraclavicular nodes are enlarged due to** obstruction of the efferent lymphatic channel of the nodes by the tumor emboli, as it enters the thoracic duct just prior to its drainage into the left subclavian vein.

Lateral lymphatic spread through the broad ligament to the pelvic nodes may occur. Retrograde lymphatic spread in advanced disease may occur to the inguinal nodes through the round ligament.

Lymphatics of peritoneal surfaces drain through the diaphragm. Other metastatic sites are: Peritoneum, omentum, liver, pleura (effusion) and the diaphragm.

TABLE 24.30: Lymph node involvement in ovarian malignancy (%).

Stage	*Para-aortic (%)*	*Pelvic (%)*
I and II	20	30
III and IV	65	67

Direct

After the capsule is broken, the spread occurs directly to the adjacent organs such as tubes, broad ligament, intestines, omentum, and uterus.

Hematogenous

The bloodstream metastasis is late and the involved organs are lungs, liver parenchyma, brain, bones, etc.

CLINICOPATHOLOGIC EXPLANATION

Ascites

Ascites is due to obstruction of peritoneal fluid outflow principally through the diaphragm. There is also increased transudation of serum across the peritoneal surfaces. The secretion is not from the tumor bearing peritoneum but from the tumor-free areas.

Liver

The involvement of liver parenchyma is usually blood-borne when the guts are involved.

Contralateral Ovary (Fig. 24.24)

The contralateral ovary is involved in majority of metastatic ovarian malignancy. Even in primary malignancy, the contralateral involvement may be due to retrograde

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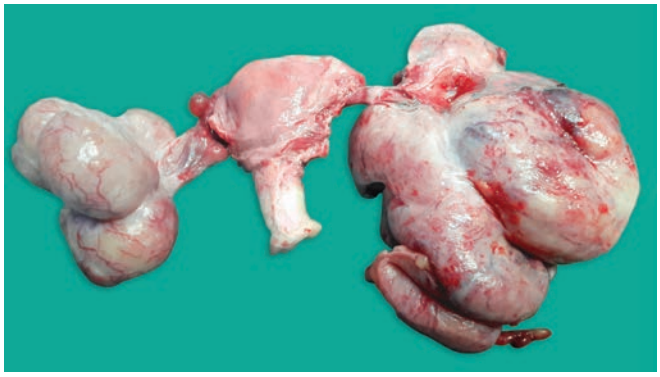

Fig. 24.24: Bilateral malignant epithelial tumors of the ovary. Both the ovaries are enlarged, lobulated in appearance with areas of hemorrhage and necrosis. Histology confirmed mucinous cystadenocarcinoma.

(*Courtesy:* Dr Biswajit Ghosh, Burnpur, WB)

lymphatic spread through para-aortic glands. Direct implantation or multicentric origin may also be a possibility.

Uterus

The body is mostly affected either due to lymphatics or through transtubal spread. The cervical involvement is rare.

Right-sided pleural effusion: More ascitic fluid reaches the right subdiaphragmatic space along the wider right paracolic gutter. This is facilitated by the increased negative suction created by liver during respiration. The fluid so collected can pass freely across the diaphragm. This is because of free communication of submesothelial network of lymphatic capillaries with the corresponding plexuses on the thoracic surface of the diaphragm underlying the pleura on the right side → right pleural effusion. Alternatively, there is more presence of wide pleuroperitoneal sinuses on the right side and hence producing right pleural effusion.

CLINICAL FEATURES

Patient Profile

Although no age is immune to ovarian malignancy, but about 60% of ovarian neoplasms in postmenopausal and about 20% in premenopausal women are malignant. There is increased association of nulliparity and with a family history.

Symptoms

In its **early stage**, ovarian carcinoma is a notoriously silent disease (asymptomatic). The presenting complaints are usually of short duration and insidious in onset. Symptoms are not specific.

- Feeling of abdominal distension and vague discomfort.
- Features of dyspepsia such as flatulence and eructations and pelvic pain.
- Loss of appetite with a sense of bloating after meals.
- In pre-existing tumor:
  - Appearance of dull aching pain and tenderness over one area.
  - Rapid enlargement of the tumor.

Gradually, more pronounced symptoms appear. These are:

- Abdominal swelling which may be rapid.
- Dull abdominal pain.
- Sudden loss of weight.
- Respiratory distress—may be mechanical due to ascites or due to pleural effusion.
- Menstrual abnormality is conspicuously absent except in functioning ovarian tumors (mentioned later in the Ch.).

Signs

The following are the findings in an established case of ovarian malignancy.

- **General examination reveals**
  - Cachexia and pallor of varying degree.
  - Jaundice may be evident in late cases.
  - Left supraclavicular lymph gland (Virchow's) may be enlarged (Fig. 24.25).
  - Edema leg or vulva is characteristic of malignant and not of benign neoplasm.
- **Per abdomen**
  - Liver may be enlarged, firm and nodular.
  - A mass is felt in the hypogastrium; too often it may be bilateral. It has got the following features (Table 21.4, p. 249):
    - Feel—solid or heterogeneous.
    - Mobility—mobile or restricted.
    - Tenderness—usually present.
    - Surfaces—irregular.
    - Margins—well-defined but the lower pole is usually not reached.
    - Percussion—usually dull over the tumor; may be resonant due to overlying intestinal adhesions.

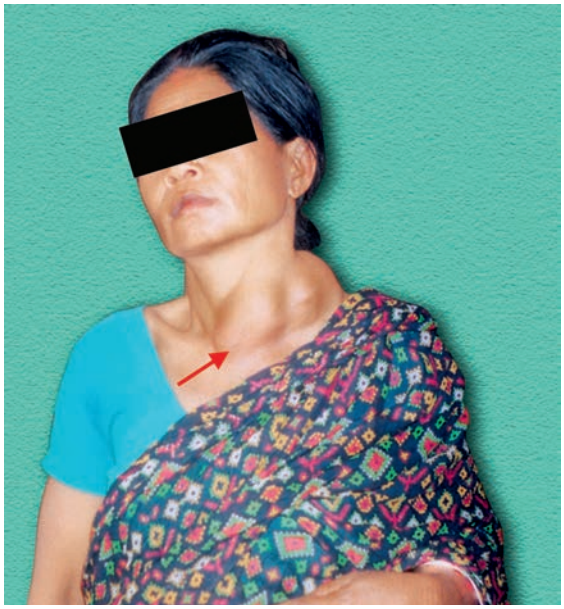

Fig. 24.25: Case of advanced ovarian malignancy with enlarged left supraclavicular glands (Virchow's gland).

(*Courtesy:* Professor S Pati, Dr A Halder, Associate Professor, Department of Gynecology and Obstetrics, NBMCH, Darjeeling)

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- **Per vaginam**
  - The uterus may be separated from the mass felt per abdomen.
  - Nodules may be felt through the posterior fornix. If it is more than 1 cm, the diagnosis of malignancy is almost certain.

SPECIAL INVESTIGATIONS

Investigation aims at:

- To confirm malignancy preoperatively
- To identify the extent of lesion
- To detect the primary site.

To Confirm Malignancy

- Cytologic examination for detection of malignant cells is carried out from the fluid collected by abdominal paracentesis or "cul-de-sac" aspiration.
- Tumor marker: In epithelial carcinoma, there is no specific tumor marker. But, elevated CA-125 level >65 U/mL with a pelvic mass may be suggestive. Other biomarkers: HE4, CA-19-9, CA-15-3, OVXI may also be suggestive.

To Identify the Extent of Lesion

- **Straight X-ray** chest to exclude pleural effusion and chest metastasis.
- **Barium enema** to detect any colon or rectal cancer.
- **Cytologic examination** of thoracocentesis fluid.
- **Paracentesis** is done in women with ascites for malignant cell cytology.
- **Ultrasound imaging:** Features suggestive of malignancy are: Multiloculation with thick-walled septa, nodular areas (>6 cm), papillary surface projections or neovascularization (on Doppler study). It can be used to detect involvement of the omentum or contralateral ovary.
- **Computed tomography (CT)** is helpful for retroperitoneal lymph node assessment and detection of metastasis (liver, omentum). It helps in staging of ovarian carcinoma (Fig. 24.26).
- **Magnetic resonance imaging (MRI)** is helpful to determine the nature of ovarian neoplasm and also for the retroperitoneal lymph nodes and detection of metastasis. It can also detect recurrence of the tumor following initial treatment (Fig. 24.27).
- **Positron emission tomography (PET)** can differentiate normal tissues from cancerous tissues. It is more sensitive than CT or MRI (p. 101). CT/PET scans are especially useful for diagnosis of disease recurrence.
- **Intravenous pyelography**.
- Examination under anesthesia.
- Diagnostic uterine curettage.

To Detect the Primary Site

- Barium meal X-ray
- Gastroscopy/colonoscopy
- Mammography.

DIAGNOSIS

- Clinical
- Investigations
- Operative findings
- Histologic confirmation.

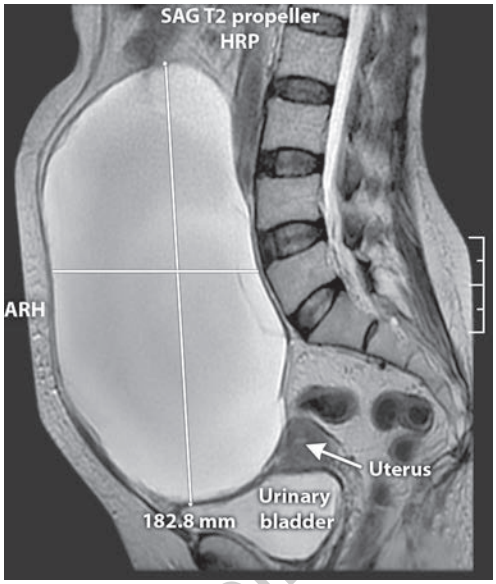

Fig. 24.26: MRI scan of a 47-year-old woman, showing a huge ovarian tumor. Sagittal view of the tumor is seen. Preoperative MRI can detect the anatomic regions that the tumor occupies and presence of any involvement of the surrounding organs and the nodal survey.

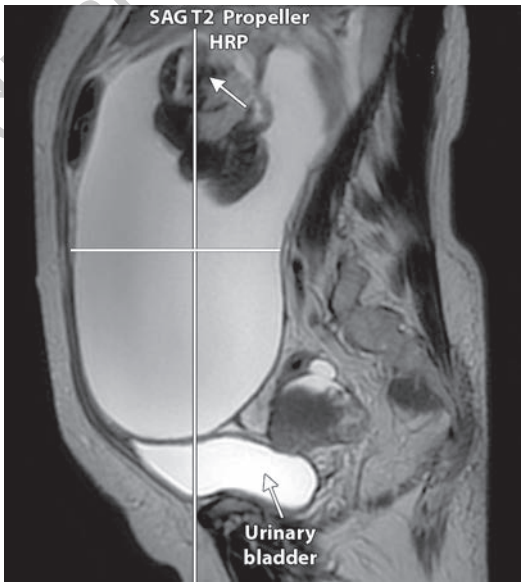

Fig. 24.27: Sagittal view of a MRI image of a 51-year-woman showing a large ovarian tumor. The tumor is heterogeneous in nature. MRI is a nonradioactive imaging modality with excellent soft tissue contrast resolution. It can detect metastatic deposits in liver, peritoneum and retroperitoneal nodes. Tumor showed a solid area in the upper part of the mass (*see* arrow). No lymph nodes are seen to be enlarged.

Clinical

Clinical diagnosis in early stage is very much deceptive because of:

- **No age specificity:** Although more prevalent beyond the age of 45 (40% of ovarian neoplasms are malignant), no age is immune to ovarian cancer. All physicians must be aware of the possible significance of persistent gastrointestinal symptoms in women over the age of 40 with a history of ovarian dysfunction.
- **No specific symptom:** It may remain asymptomatic in about 15% when first diagnosed.

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- **Unrelated to duration of symptoms: Even with symptoms** of short duration may have extensive spread, conversely a long-standing tumor may remain benign.
- **Unrelated to the size of the tumor:** A big tumor may remain benign for a long time whereas, a small enlarged ovary may be found malignant.

The cumulative effects of such vagaries explain the fact that at the time of diagnosis, about 70% of patients with epithelial carcinomas have metastases outside the pelvis. **The most common sites of metastases are—peritoneum (85%), omentum (70%), contralateral ovary (70%), liver (35%), lung (25%) and uterus (20%).**

In established and/or advanced cases of malignancy, the clinical features as mentioned earlier are enough to arrive at a diagnosis.

Ancillary Aids

- **Detection of malignant cells** from the ascitic fluid collected by abdominal paracentesis or cul-de-sac aspiration is a positive proof of abdominal malignancies. When combined with presence of a pelvic mass almost confirms ovarian malignancy.
- **Noninvasive methods** such as MRI or CT scan have not yet proved to be much useful in diagnosis. Transvaginal sonography improves the detection rate (p. 100).
- Examination under anesthesia may be useful in doubtful cases, especially in an obese patient.
- Laparoscopy too has got limited scope in confirmation of malignancy. It can just detect a neoplasm.
- Elevation of serum CA 125 beyond 35 U/mL may be suggestive.

Operative Findings

- Nature of peritoneal fluid: While hemorrhagic fluid is very much suggestive but a clear or straw color fluid cannot rule out malignancy.
- Nature of the tumor: Differentiation between a benign and malignant tumor may be possible clinically, with laparotomy findings and with ultrasonographic criteria (p. 249).
- Metastatic nodules on the peritoneal surfaces and omentum.

Histological Diagnosis

All ovarian tumors irrespective of their nature must be subjected to histologic examination. This not only confirms the diagnosis but also identifies the type and grade of malignancy.

MANAGEMENT OF EPITHELIAL OVARIAN CANCER

- **Preventive**
- **Curative**

Preventive

Primary Prevention of Epithelial Ovarian Cancer

Prevention and risk reduction of ovarian cancer is done in three ways: (1) Surveillance; (2) Chemoprevention, (3) Risk reducing surgery.

1. **Surveillance:**
   - Tumor markers screening for ovarian cancer is currently done with serum CA-125, HEP4, OVX1. Multimodal screening (TVS and serum CA-125) and longitudinal biomarker algorithms rather than a predefined cut off value (CA-125 >35 IU/mL) is important.
   - Transvaginal ultrasonography
2. **Chemoprevention: Combined oral contraceptive pills** as a preventive (chemoprevention) measure is recommended to a woman especially belonging to Lynch type II families.
3. **Risk reducing surgery**
   - Opportunistic bilateral salpingectomy
   - Bilateral salpingectomy
   - Risk reducing salpingectomy and delayed oophorectomy in high risk women
   - Opportunistic salpingectomy in general population (family planning)
   - Salpingo-oophorectomy.
4. **Genetic screening for *BRCA1* and *BRCA2*** for women with high risk for ovarian and breast cancer.

The estimated lifetime risks of breast cancer with *BRCA1* and *BRCA2* mutation are 50% and 25% respectively.

Bilateral salpingo-oophorectomy in women following completed child bearing with BRCA mutation can reduce the risk of ovarian cancer significantly. It reduces the risk of breast cancer also.

Guidelines for Management of an Enlarged Ovary

- An ovarian enlargement of 8 cm during childbearing period deserves careful follow up.
- In postmenopausal women, any ovarian enlargement should be assessed by serum CA-125 and transvaginal sonography.
- Cysts that are simple, unilocular, ≤8 cm in diameter with normal serum CA-125—can be managed conservatively. Women should be under follow up with ultrasound scan and serum CA-125 at an interval of 4 months.
- Early laparotomy is indicated in following cases:
  - The ovary enlarges progressively beyond 8 cm while under observation.
  - Any symptomatic ovarian tumor regardless of size.

Secondary Prevention (Screening for Ovarian Cancer)

Natural history of the disease is unknown. There is no preinvasive stage like that of cervical intraepithelial neoplasia. As such, screening aims at detecting early ovarian malignancy in asymptomatic women. Till date no specific method of screening for early detection of epithelial ovarian cancer is available.

Screening procedures

- **Clinical:** Regular and periodic clinical examination of the 'high risk' group is done (Table 24.31). Bimanual pelvic examination in an asymptomatic woman may detect an adnexal mass. However, clinical examination is not very specific.

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TABLE 24.31: Women with 'high risk' factors for ovarian cancer.

- **Age** group 40–60 years
- **Familial cancers**: Breast, endometrial, ovarian, colorectal
- **History** of removal of benign ovarian tumor or breast carcinoma
- Women with *BRCA1* and *BRCA2* mutation
- Postmenopausal palpable ovary (volume >8 cm^3)
- Nulliparity
- Early menarche, late menopause
- Relative or absolute infertility
- Dysgenetic gonad
- Fertility drugs use (incessant ovulation)
- Women with BMI >30
- Women workers in asbestos related industries
- Pelvic inflammatory disease

TABLE 24.32: Clinical association of raised serum CA-125.

Cancer	*Disease*	*Others*
Ovarian (serous)	Endometriosis	Normal (1%)
Peritoneal, tubal	Peritonitis	Pregnancy
Colon, uterine	Pancreatitis	Mid menstruation
Breast, lung	PID	
Stomach, lung, liver	Leiomyomata	

- **Tumor markers:** CA-125 (Table 24.32) is a glycoprotein, which has been used for screening of epithelial (nonmucinous) cancers of the ovary. Value more than 35 U/mL is suggestive of epithelial ovarian cancer. It is also used for monitoring a patient during chemotherapy and for follow up. But it is not a tumor specific antigen. There are several other conditions, where level of CA-125 is raised.
- **Multimodal screening** (serum CA-125 and TVS) is important. Longitudinal biomarker algorithms rather than a predefined cut off value (>35 IU mL) is more important (UKCTOCS – 2018).

The serum level of CA-125 falls after surgical resection of the tumor or following chemotherapy. Elevated level indicates bulky residual disease or tumor recurrence or resistant clones to chemotherapy. Serum half-life of CA-125 is 20 days.

HE 4 (Human Epididymis 4 protein) is elevated in the serum of woman with serous epithelial ovarian cancer. It is useful in the early stage ovarian cancer. Combination of CA-125 and HE 4 biomarkers study is superior to any other marker in the diagnosis and management of ovarian serous cancers.

Other tumor markers are: Macrophage colony-stimulating factors (M-CSF), OVXI, HER-2/neu, and inhibin.

- **Ultrasound imaging:** Transvaginal color Doppler imaging has been able to differentiate benign from malignant tumors by assessment of its vascular supply and intratumoral blood flow. Increased neoangiogenesis in ovarian malignancy causes central neovascularity. Study of **vascular parameters,** e.g. pulsatility index (PI) <1.0 or resistive index (RI) <0.4 increases the risk of malignancy.

Three-dimensional, contrast enhanced, power Doppler sonography is found to be more diagnostic.

- **Opportunistic bilateral salpingectomy** at the time of surgery for benign adenexal disease or hysterectomy.
- **Risk of malignancy index (RMI): RMI = U × M × CA 125**; U = USG score (one point each for: Multilocular cyst; solid areas; metastasis; ascites; bilateral lesions), M = 3 (postmenopausal women) and CA-125 level in U/mL. The risk of cancer is 75% when the RMI value is > 250.
- **Genetic testing (p. 437).**

PROTECTIVE FACTORS FOR OVARIAN MALIGNANCY

- Combined oral contraceptives
- Pregnancy
- Tubal ligation, hysterectomy
- Breastfeeding
- Low fat and high fiber diet
- DMPA

TREATMENT OF MALIGNANT OVARIAN TUMOR

- **Surgery**
- **Chemotherapy**
- **Radiotherapy**
- **Combined therapy**

Surgical Treatment of Ovarian Cancer

Surgery is the keystone in the primary treatment of ovarian malignancy.

The aims are:

- To stage the disease (staging laparotomy) accurately, thereby allowing better choice of adjuvant therapy and a better assessment of prognosis.
- To perform effective surgical removal.

Surgical Staging for Ovarian Malignancy

- Methods
  - Laparotomy
  - Laparoscopy
  - Laparoscopic assisted robotic sugary
- Procedures
  - **Omentectomy:** From transverse colon
  - **Cytoreduction:** Maximum to reduce the residual disease <1 cm.

Practical Guidelines

- **Liberal vertical incision** to minimize chance of rupture of the tumor and to facilitate better exploration.
- **To note the character of the ascitic fluid**, if any, and to collect sample for cytology. If appreciable fluid is not available, then a sample of peritoneal wash with 100 mL saline in the subdiaphragmatic area and paracolic gutter is to be collected.
- **A systematic (visual and manual) exploration (clock wise)**—palpation of liver, gastrointestinal tract, subdiaphragmatic area, omentum, and para-aortic lymph nodes. This is done in a clockwise fashion starting from the cecum.
- **Pelvic exploration**—nature of the tumor, extent of adhesions, condition of the contralateral ovary, uterus and tubes, and palpation of pelvic lymph nodes.
- **Any metastatic deposit** over the peritoneal surfaces, under surface of the diaphragm should be **biopsied**.

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TABLE 24.33: Commonly used regimen for chemotherapy in cases with ovarian epithelial cancer.

Drug	Dose	In fusion time	Cycle	Interval	Toxicity
Carboplatin or	400 mg/m^2 or AUC 5	1 hour	6 cycles	3 weeks	Nephrotoxic, neurotoxic, myelosuppression
Paclitaxel or	175 mg/m^2	3 hour	6 cycles	3 weeks	Neurotoxic, myelosuppression
Docetaxel	75 mg/m^2	1 hour	6 cycles	3 week	Neurotoxic (less), myelosuppression

Pelvic and para-aortic lymph node sampling should be done.

- **In the absence of any metastatic disease**, multiple peritoneal biopsy, scraping from the diaphragm for cytology should be taken. Occult metastasis has been found in about 10–40% of early stage (stage I and II) epithelial ovarian cancer.

Primary Surgery

- **Early stage disease (Stage Ia, G1, G2):**
  - **Young woman** → unilateral oophorectomy (fertility sparing surgery) → routine follow up and monitoring → completion of family → removal of the uterus and the other ovary.
  - **Elderly woman** → hysterectomy and bilateral salpingo-oophorectomy.
  - **In stage Ia, G3 disease and others stage I diseases:** Staging laparotomy → hysterectomy and bilateral salpingo-oophorectomy. Chemotherapy is considered for most patients.
- **Advanced stage disease:** Exploratory laparotomy → **cytoreductive or debulking surgery.** This includes: Total abdominal hysterectomy bilateral salpingo-oophorectomy, complete omentectomy, retroperitoneal lymph node sampling and resection of any metastatic tumor (Figs. 38.64A to C). **Optimum cytoreductive surgery** is aimed to reduce the residual tumor load ≤1–2 cm in diameter. Lesser the residual tumor (optimally debulked) volume (<1 cm), better is the survival.

Maximum cytoreductive surgery may need resection of a segment of bowel, bladder or the lymph nodes. Removal of omental cake by cytoreductive surgery improves the result of subsequent chemotherapy or radiotherapy. Surgery includes resection of large volume diaphragmatic disease. Diaphragmatic stripping, resection of diaphragm full thickness or half thickness, splenectomy, hepatic resection for parenchymal metastatic disease, bowel resection need to be done. Place of retroperitoneal lymphadenectomy is yet to be decided. Appendectomy is done in cases with mucinous ovarian cancer.

ADJUVANT CHEMOTHERAPY

- **In stage Ia (Grade I)** epithelial carcinoma → no adjuvant chemotherapy.
- **In all other stage I disease** → adjuvant chemotherapy with carboplatin and paclitaxel for six cycles.
- **Advanced stage disease.**
  - **Chemotherapy:** Chemotherapy is used widely following surgery to improve the result in terms of survival. Drugs are given for five or six cycles at 3–4 weekly interval (p. 427).
  - **Combination chemotherapy:** Paclitaxel (175 mg/m^2) and carboplatin (400 mg/m^2) are commonly used (Table 24.33).

    Carboplatin is excreted by the kidney. Its effective serum concentration is calculated from Calvert formula. Carboplatin total dose = Desired AUC (area under the curve) × (GFR + 25); AUC value of 5 to 7.5.

    Patients who are hypersensitive to paclitaxel, topotecan 1 mg/m^2 for 1–3 days, every 3 weeks or Gemcitabine 800 mg/m^2, every 3 weeks is given (p. 433
- **Platinum compounds (cisplatin, carboplatin) are the most effective drugs** in terms of tumor response and survival rate. Like alkylating agents they cause cross linkage of DNA strands. **They can be used either singly (Table 24.34) or in combination with paclitaxel (*see* below).**
- **Taxane derivatives** (paclitaxel, docetaxel) are found to be very effective in ovarian cancer (p. 433). Paclitaxel is derived from the bark of the pacific yew tree. Docetaxel is semisynthetic and its side effects are less (peripheral neuropathy). Taxane derivatives prevent cell division by polymerization of microtubules and making them excessively stable. They are found to be effective even in cisplatin resistant ovarian cancer. **Paclitaxel is recommended as the primary treatment of all epithelial ovarian cancer following optimal cytoreductive surgery.**
- **Combination chemotherapy:** Drugs acting in different ways on the cell cycle (p. 433), with different toxicities, are combined. Therefore efficacy is expected to be more and chance of drug resistance is low. **Currently paclitaxel and carboplatin combination chemotherapy is found to have better survival rate in advanced ovarian cancer (Table 24.33).**

  Efficacy of **docetaxel** has been found similar to paclitaxel. **Gemcitabine** or **Topotecan** has got similar efficacy (p. 433).

The recommended drugs and doses for chemotherapy of ovarian carcinoma (CAP and CP) are discussed below.

Drugs: Combining paclitaxel, carboplatin either with gemcitabine or pregylated liposomal dexorubicin are used. It is found to be toxic.

- **Maintenance therapy** with agents like pazopanib, oral tyrosine kinase inhibitor (TK1) of VEGFR, PDGFR,

TABLE 24.34: Recommended drugs and doses used as a single agent.

Drug	Dose	Route	Cycle	Interval
Cisplatin	75 mg/m^2	IV	6	4 weeks
Carboplatin	400 mg/m^2	IV	6	4 weeks
Paclitaxel	175 mg/m^2	IV	6	4 weeks
Docetaxel	75 mg/m^2	IV	6	4 weeks

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FGFR and poly-ADP (ribose) polymerase (PRAP) inhibitors have been tried (p. 432).

- **Platinum resistence disease** may be treated with: Pegylated liposomal doxorubicin (PRD), topotecan, gemcitabine, etoposide, docetaxel or paclitaxel.
- **Intraperitoneal chemotherapy** is used only for minimal (<2 cm) or microscopic residual disease. The drugs can penetrate only few millimeters. Moreover, serum levels are similar to those seen after IV chemotherapy. Currently both platinum (cisplatin) and taxanes (docetaxel) are used. There is distinct benefit of intraperitoneal cisplatin and docetaxel over their intravenous use.

Primary chemotherapy for advanced ovarian cancer is done either by IV (docetaxel or paclitaxel and carboplatin) or by intraperitoneal chemotherapy to improve the overall survival.

- **Neoadjuvant chemotherapy (NACT) and interval cytoreductive surgery:** Biopsy confirmation is done before chemotherapy.
- **Interval debulking surgery (IDS):** Patients with a advanced stage (stage III and IV) disease, often are at increased risk of primary surgery. 3–4 cycles of NACT followed by IDS and additional chemotherapy are found to improve the survival outcome.

Indications of NACT are:

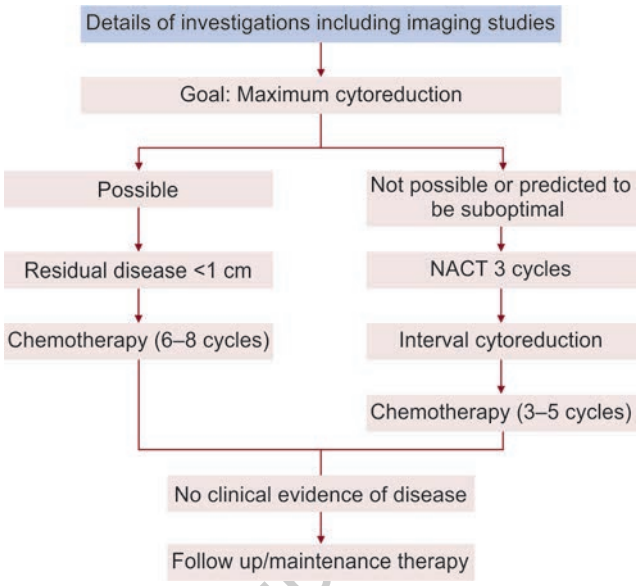
- Advanced epithelial ovarian cancer (as in imaging studies).
- High risk for surgery.
- Associated comorbid conditions (pleural effusion).
- Predicted (imaging studies) to be suboptimally resected.

  Patient should have histological diagnosis of the tumor (biopsy).
- Following a failed attempt of primary surgery.

Benefits of neoadjuvant chemotherapy are:

- Rapid clinical improvement.
- Subsequent surgery is easier and morbidity is reduced
- Optimum cytoreduction with minimal residual disease may be possible (Flowchart 24.2).
- **Radiotherapy:** There is very little scope of radiotherapy as an adjunct to surgery because of the advent of chemotherapy.
- **Radioactive isotopes (p. 426):** In early cases of ovarian cancer, radioactive phosphorus (^{32}P) is instilled into the peritoneal cavity. The isotopes are taken up by macrophages and the radiation effects are limited to superficial 4–6 mm of peritoneal lining. ^{32}P acts by emitting β-rays. Bowel complications are increased.
- **Hormone therapy:** Tamoxifen, leuprolide acetate (GnRH agonist), aromatase inhibitors are being studied in relapsed cases of ovarian tumor.
- **Immunotherapy:** With the use of *Corynebacterium parvum* and BCG cytokines, interferon or interleukin-2 is under trial. Herceptin, an antibody, when used along with chemotherapy improves the response rate (p. 436). All patients need to be followed up after completion of treatment. Serum level of CA-125 is reviewed. CT evaluation may be needed when there is suspicion of recurrent disease (50–90%).

Flowchart 24.2: Management outline for ovarian carcinoma



- **Gene and molecular therapy** (page 437).
- **Fertility sparing surgery (FSS):** Could be done in selected cases when the disease is confined to one ovary (stage IA). Unilateral adnexectomy has got excellent long-term survival. Postoperative chemotherapy may be needed in a few without an adverse effect to these child bearing.

PLACE OF UNILATERAL SALPINGO-OOPHORECTOMY (FSS)

- Tumor confined to one ovary
- Disease stage IA G1
- Capsule intact
- Contralateral ovary clinically normal
- Negative peritoneal washing
- Negative omental biopsy
- Young woman, fertility desired
- Strongly motivated for follow up

Secondary cytoreductive surgery may be done in some selected cases following completion of first line chemotherapy. Selected cases are: (a) Tumor sensitive to platinum based chemotherapy; (b) Prolonged disease free interval; (c) Isolated site recurrence; (d) Absence of ascites; (e) Following initial subopitimal debulking procedure.

REASONS FOR POOR OUTCOME IN OVARIAN CANCER

- Late diagnosis
- No preinvasive stage of the disease
- No effective screening procedure
- No correlation of symptoms with the tumor size
- Extent of tumor spread is often unknown
- Limitations of cytoreductive surgery
- Variable chemosensitivity
- Radiation dose restriction by neighboring organs
- Tumor cells are freely mobile within the peritoneal cavity

A laparoscopy prior to laparotomy is advised. Currently, CT, MRI, and serum CA-125 are being evaluated as an alternative to second look laparotomy. Better survival rate following second look surgery is however questionable.

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FAVORABLE PROGNOSTIC FACTORS

- Younger age
- Well differentiated tumor
- Small volume tumor
- Minimal residual tumor after primary cytoreductive surgery
- Absence of ascites
- Cell type other mucinous and clear cell

PROGNOSTIC FACTORS IN OVARIAN MALIGNANCY

- Surgical stage of the disease—worse beyond stage II (Tables 24.35 and 24.36).
- Histological type—endometrioid tumor has got a higher survival rate than serous type because the former tumor is highly well-differentiated.
- Histological grade of the tumor—higher the grade, poorer the prognosis.
- Peritoneal cytology—positive malignant cells, higher the risk.
- Presence of ascites—higher the risk.
- Presence of metastatic disease before cytoreductive surgery—poor the prognosis and shorter the survival.
- Volume of residual tumor after primary surgery—when <5 mm better the prognosis.
- Ploidy status—diploid tumors are prognostically better compared to aneuploid tumors.
- Degree of oncogene expression (p. 431, Ch. 31).

TABLE 24.35: Epithelial ovarian cancer (NIC – 2011C).

Stage	*5-year survival (%)*
Localized (confined to primary site)	92
Regional (regional nodes involved)	72
Distant (metastasis)	27
Unstaged	22

TABLE 24.36: Carcinoma of the ovary 5-year survival rate (FIGO stage).

Stage	*5-year survival rate (%)*
IA	94
IB	92
IC	85
IIA	78
IIB	73
IIIA	59
IIIB	52
IIIC	39
IV	17

PRIMARY PERITONEAL CARCINOMA

Papillary serous carcinoma of the peritoneum is a rare type of primary peritoneal adenocarcinoma (PPA). It constitutes 7–20% of all epithelial ovarian carcinoma.

Criteria for Diagnosis of PPA (GOG – 1993)

- The ovaries are either absent or physiologically normal in size (<4 cm diameter).
- Extraovarian sites are more involved than that of the ovarian surfaces.
- Microscopically, the ovaries are either not involved or exhibit cortical implants <5 mm in depth. There no stromal involvement.
- The histologic and cytologic tumor character is serous type. FIGO staging for ovarian carcinoma is followed. Management is according to ovarian carcinoma grade and staging. Prognosis is similar to that of epithelial ovarian cancer.
- When it is not possible to designate the primary site for ovarian, fallopian tube and peritoneal cancer, it defined as "undesignated".

GERM CELL TUMORS OF THE OVARY

Germ cell tumors constitute about 15–20% of all ovarian neoplasms and they are the second common ovarian tumors. For classification page 241. They have got varying degrees of malignant potentiality. Mature cystic teratoma (dermoid cyst) is the most common germ cell ovarian tumor (95%) and it is benign. Germ cell tumors have the following feature: (1) Occur predominantly in children and young adults. (2) Most are early stage disease, and (3) Usually have good prognosis due to chemoresponsiveness; (4) Fertility sparing surgery may be possible. About 5% of these tumors are malignant. They arise from embryonic germ cells.

IMMATURE TERATOMA

Immature teratomas are derived from the three germ layers — ectoderm, mesoderm and endoderm. These are less common and constitute 35% ovarian teratomas. **It is the most common germ cell malignancies.** It is commonly (50%) seen in women between the ages of 10 and 20 years and rarely seen after menopause. Immature teratomas are almost never bilateral.

Pathology

Varying grades of undifferentiated tissue elements are present. Prognosis depends on the quantity of immature neural tissue elements. The prognosis of immature teratoma depends mainly on the tumor grade and the stage of the disease. Grade 3 tumor has poor prognosis. Serum AFP and LDH levels may be raised. Other tumor markers: CA-125, CA 19–9, CEA are to be done. Mature teratoma carries excellent prognosis.

Treatment

Unilateral oophorectomy with surgical staging is the optimum treatment when the tumor is confined to one ovary. For elderly women hysterectomy and bilateral salpingo-oophorectomy is ideal. **Adjuvant chemotherapy** for patients beyond stage Ia GI is indicated. BEP (*see* above) is preferred, though VAC regimen is also effective.

DYSGERMINOMA

Dysgerminoma is the second most common (33%) malignant germ cell tumor. It arises from undifferentiated form of germ cells. It is often (5%) associated with

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dysgenetic gonad (Ch. 28). The counterpart of dysgerminoma in male is seminoma. Majority (75%) of the tumors occur before the age of 30 years.

hCG assays are often positive, confusing the diagnosis with pregnancy. It may coexist with pregnancy (20–30%). Dysgerminoma may be associated with choriocarcinoma or endodermal sinus tumor. **Tumor markers** LDH, hCG, lactate dehydrogenase (LDH) may be positive. Karyotyping is needed (presence of Y chromosome) especially when a premenarchal girl presents with a pelvic mass.

Pathology

The shape is usually round or oval and is usually 5–15 cm in diameter; feel is boggy, at times, it is firm rubbery. It may be bilateral (10–20%). Cut section shows pink or yellow color. Microscopic appearance reveals uniform large round cells (monotonous pattern), arranged in cords or clumps with abundant clear cytoplasm. Nuclei are large, irregular, and hyperchromatic with varying degree of mitosis. There is intense infiltration of lymphocytes and plasma cells in the fibrous septum (Fig. 24.28). Lymphocytic infiltration indicates favorable prognosis. In more than 50%, they are potentially malignant.

Clinical features are not specific for the tumor.

Treatment

Majority (75%) of dysgerminomas are confined to one ovary and are stage I at the time of diagnosis.

In a young patient where preservation of fertility is desired, laparotomy for surgical staging should be done. Conservative surgery, unilateral salpingo-oophorectomy may done in early stage I disease. Routine biopsy of normal contralateral ovary should be avoided. The tumor

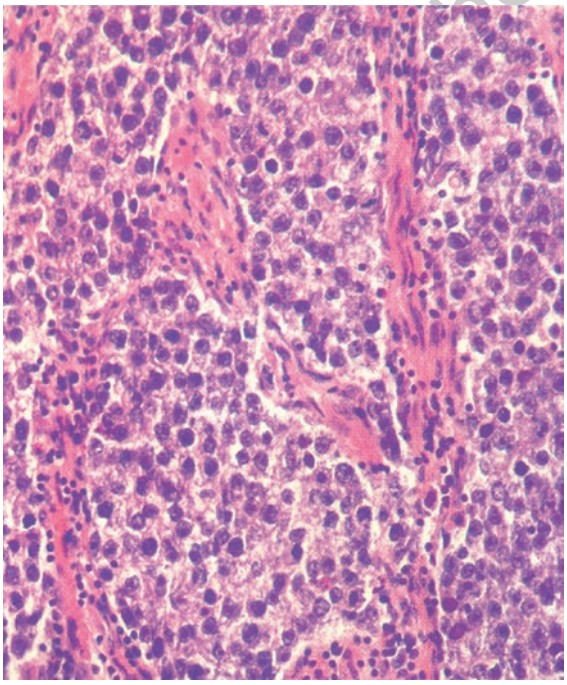

Fig. 24.28: Histologic picture of dysgerminoma cells are mostly uniform (monotonous pattern) in size. The stroma is dense with lymphocytic infiltrate.

TABLE 24.37: Recommended drugs and doses of chemotherapy (BEP, VBP).

Drugs	*Dose*	*Schedule*
Bleomycin (B)	15 units/m^2	Every week
Etoposide (E)	100 mg/m^2	On days 1–3, every 4 weeks
Cisplatin (P)	100 mg/m^2	Every 3 weeks
Vinblastin (V)	12 mg/m^2	Every 3 weeks
Drugs are given IV for 3–4 cycles, combinations used are BEP and VBP		

is sensitive to both chemotherapy and radiotherapy. **Systemic chemotherapy is the treatment of choice, where fertility is to be preserved, even in the presence of metastatic disease.**

Different chemotherapeutic agents are used either singly or in combination (Ch. 31) (Table 24.37). Carboplatin 400 mg/m^2, IV, every 4 weeks, for 6 courses have been used as a single agent therapy where the tumor has been removed completely. BEP (bleomycin, etoposide, and cisplatin), **VBP** (vinblastin, bleomycin, and cisplatin), **VAC** (vincristine, actinomycin, and cyclophosphamide) are the commonly used drugs for the germ cell tumors. The most effective chemotherapeutic regimens used are BEP, VBP and VAC (Table 24.34 and p. 433). Combination chemotherapy has significantly improved the survival rate.

Patient with Y chromosome as detected on karyotyping should have both the ovaries (gonads) removed.

Radiotherapy: Loss of fertility is a problem with radiation therapy. So, radiation therapy is not used in young patients.

Recurrent disease is treated either with combination chemotherapy or radiation therapy. Combination chemotherapy with POMB-ACE (vincristine, bleomycin, methotrexate, cisplatin, etoposide, actinomycin D, and cyclophosphamide) is preferred (p. 433). Radiation therapy is considered for patients who had been treated with combination chemotherapy earlier.

Overall survival following unilateral oophorectomy in early stage (stage Ia) disease 100% and following cisplatin-based combination chemotherapy in advanced disease is 75%.

ENDODERMAL SINUS TUMOR

These tumors arise from the primitive yolk sac.

It is observed mostly between 15 and 20 years of age. **It is the third common (20%) malignant germ cell tumor of the ovary**. Yolk sac tumors are unilateral and are usually solid, more than 10 cm in diameter.

Characteristic histological feature is the presence of cystic spaces lined by flattened epithelium. Within this space a tuft of vascular tissue is often seen. This is called **Schiller-Duval body**. Eosinophilic, hyaline bodies containing alpha fetoprotein and other proteins are also

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constant microscopic features. Tumor markers are AFP and LDH.

It is highly malignant and spreads to the adjacent structures rapidly. It is usually solid and cut section shows gelatinous or hemorrhagic areas. It is composed of yolk sac endoderm and extraembryonic mesoblasts. Association with dysgerminoma should be kept in mind. Yolk sac tumor patient may present with acute abdomen as these tumors are friable, necrotic and often hemorrhagic serum tumor markers are AFP and LDH.

Treatment

Surgical staging and unilateral salpingo-oophorectomy is generally the treatment of choice. All patients need subsequent chemotherapy. Total hysterectomy and contralateral salpingo-oophorectomy do not improve the prognosis in any way.

Chemotherapy: Routine use of combination chemotherapy has improved the survival significantly. Different combination regimens (VAC, VPB and POMB–ACE) are used (p. 427, 428). Combinations containing platinum-based compounds are associated with better response and survival. Overall 5 year disease specific survival for stage I disease is below 93%.

The tumor produces alpha fetoprotein which is an useful marker (serum level above 20 μg/mL) to monitor regression and detect recurrence.

NONGESTATIONAL OVARIAN CHORIOCARCINOMA

Ovarian choriocarcinoma may be gestational, arising from ovarian pregnancy or metastases from the uterine choriocarcinoma. It may be nongestational arising from one element of a solid teratoma. Pure nongestational choriocarcinoma of the ovary is extremely rare. Most patients present before 20 years of age. Isosexual precocious puberty is common (50%). It consists of both cytotrophoblasts and syncytiotrophoblasts and **secretes gonadotropins (hCG) which is utilized as a marker** in diagnosis and follow up. Nongestational choriocarcinoma is differentiated from gestational choriocarcinoma only by the absence of paternal DNA in the tumor.

Unlike gestational choriocarcinoma, it is not so sensitive to methotrexate. As such, surgery is the primary treatment to be followed by chemotherapy. Combination chemotherapy (MAC, BEP) have been used. Prognosis is poor.

Embryonal carcinoma: Constitutes 4% of all malignant ovarian germ cell tumors. It is seen at a mean age of 15 years. It is a highly aggressive malignant ovarian tumor. The serum tumor markers are AFP, hCG and estrogen. Histology show solid sheets of large polygonal cells with pale eosinophilic cytoplasm with a syncytial pattern.

GONADOBLASTOMA

It is a rare ovarian tumor. It consists of germ cells and gonadal stromal cells. Dysgerminoma is present in 50% of cases. Patients often present with primary amenorrhea, virilism or genital abnormalities. Karyotype is usually 45,X or 46,XX/46,XY. It is bilateral in 30% of cases.

Treatment is surgical removal of the tumor and also the contralateral ovary. Prognosis is excellent.

MIXED GERM CELL TUMORS

Presence of more than one germ cell element (at least two) is considered in this group. Dysgerminoma is the most common (70–80%) tissue element, other is yolk sac tumor. Serum markers for hCG, AFP are to be estimated. Complete surgery followed by chemotherapy (VBP, MAC or VAC) is advised.

Chemotherapy in Germ Cell Tumor

Combination chemotherapy has improved the survival following conservative surgery in advanced malignant germ cell tumors of the ovary. Patients with advanced stage-IA grade I disease need close follow up only. Following combination regimens have been used most commonly. BEP (bleomycin, etoposide, and cisplatin), VBP (vinblastin, bleomycin, and cisplatin) MAC (methotrexate, actinomycin-D, and cyclophosphamide), VAC (vincristine, actinomycin-D, and cyclophosphamide) and POMB-ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin-D, cyclophosphamide and etoposide). For details p. 433.

Menstrual function, fertility and other endocrine functions have been found to be normal following use of these drugs.

SEX CORD STROMAL TUMORS

Types

- **Granulosa cell tumors (70%)**
- **Thecomas, fibromas**
- **Sertoli-Leydig cell tumors (androblastoma)**
- **Gynandroblastoma (mixed)**
- **Unclassified.**

Sex cord stromal tumors (SCSTs) constitute 6–10% of all ovarian neoplasms. Peak incidence is over the age of 50. Patients with these tumors often present with features of excess estrogen or androgen. SCSTs are generally confined to one ovary. Majority have slow rate of growth and low malignant potential. **Surgical excision** is the primary treatment. Chemotherapy is less required. **Overall prognosis** of ovarian SCST is excellent. Commonly evaluated **tumor markers** for ovarian SCSTs with malignant potential are inhibin A and B, estrodiol and αFP. They are also known as *'functioning tumors.'*

GRANULOSA CELL TUMORS

Granulosa cell tumors constitute 2% of all ovarian neoplasms. Nearly 70% of all ovarian SCSTs are granulosa cell tumors. Adult form is about 95% and juvenile is 5%. The tumor originates from the 'rests' of primitive granulosa cells unused in folliculogenesis. **It is the most common ovarian stromal tumor.**

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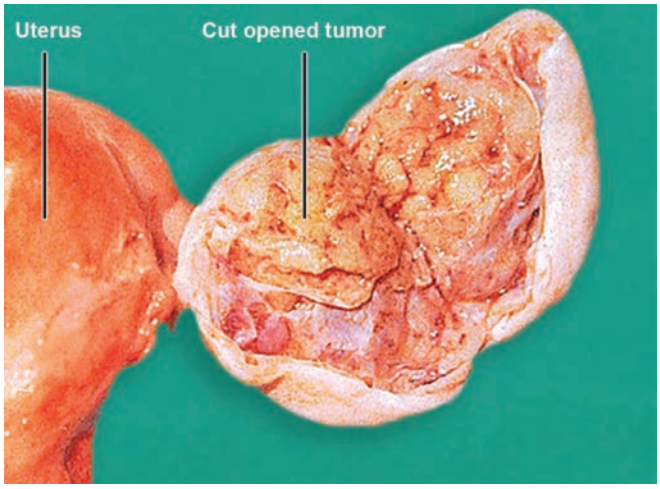

Fig. 24.29: Granulosa cell tumor. Left sided ovary cut opened to show the tumor. Histology confirmed granulosa cell tumor.

It is bilateral only in 2% of cases and is a slow growing tumor. The size varies, so also the consistency—may be solid or cystic. **Cut section** is characteristically yellow or orange (Fig. 24.29) due to its lipid content.

Microscopic Appearance (Fig. 24.30)

The cells are round or polygonal with granular eosinophilic cytoplasm with ill-defined borders. The tumor cell nuclei are variable in size but they are pale, usually grooved or folded and are called **"Coffee bean" nuclei**. Some cells are luteinized containing large polyhedral lipid cells. The cells are arranged in a number of architectural pattern but commonly in folliculoid type. The granulosa cells are arranged in small clusters around a central cavity. These structures are called **Call-Exner bodies and are pathognomonic of granulosa cell tumor.** The juvenile tumor has less number of Call-Exner bodies and less number of "Coffee bean" nuclei compared to the adult variety. The tumor cells secrete **inhibin (inhibin B)** and it is an useful marker for the disease (see Tumour Markers).

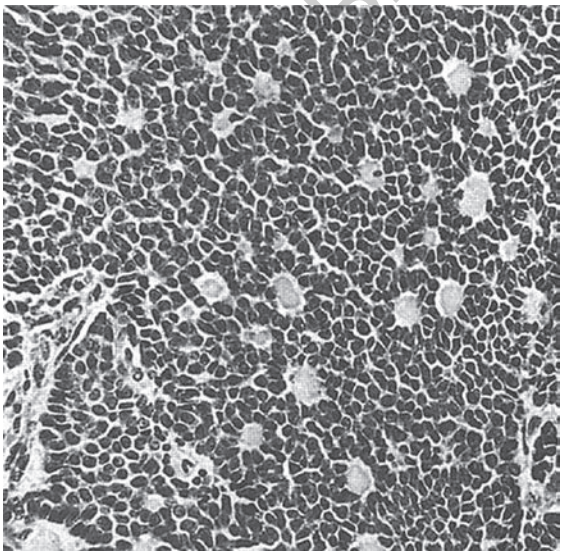

Fig. 24.30: Histologic picture of granulosa cell tumor. Presence of Call-Exner bodies (microfollicular pattern) are diagnostic.

The tumor produces estrogen and AMH. There may be associated endometrial hyperplasia (50%). Unopposed estrogenic stimulation leads to development of endometrial carcinoma in about 5–10% of cases.

Clinical Features

It occurs in all ages, 10% prior to puberty, 40% during child-bearing period, and 50% in postmenopausal women. Apart from the nonspecific features due to tumor mass, it produces **effects caused by hyperestrinism which differs with ages.** These tumors infrequently secrete androgens and may cause virilization.

- **Prior to puberty:** Precocious puberty—commonly iso sexual (p. 40).
- **Childbearing period:** Abnormal uterine bleeding.
- **Postmenopausal:** Bleeding. Associated endometrial hyperplasia or adenocarcinoma is present in 20–30% of cases.

The features of precocious puberty revert back to normal after removal of the tumor. Patient may present with **acute abdomen as** these tumors have the propensity to rupture.

Treatment

Laparotomy and surgical staging is done. Unilateral salpingo-oophorectomy is the optimum treatment for children or women in the reproductive age. Metastatic disease and recurrences have been treated with BEP chemotherapeutic regimens. Overall prognosis is good. Overall 5-year survival rate for stage I disease is about 95%. Life time follow up is essential as recurrence can occur as late as 30 years.

THECOMA-FIBROMA GROUP

Thecoma is predominantly a lesion of postmenopausal age. It may occur as a distinct entity or mixed with granulosa cell tumor. External appearance looks like a fibroma. Cut surface shows islands of yellow tissue separated by gray fibrous septa (Fig. 24.31). Microscopic picture reveals cells like that of cortical stroma with areas of granulosa cells.

Due to excess **estrogen** (tumor marker) production, there is endometrial hyperplasia and often associated with endometrial carcinoma. It is responsible for postmenopausal bleeding. Rarely, it may cause ascites or Meig's syndrome. Often the thecal cells are luteinized. These luteinized thecal cells are either inactive or may produce androgens to induce masculinization.

Treatment

It is surgical removal—total hysterectomy with bilateral salpingo-oophorectomy. In younger age group, conservative surgery may be employed considering the fact that it is mostly benign.

Fibroma in the ovary is usually observed in the postmenopausal women. It is derived from the stromal cells

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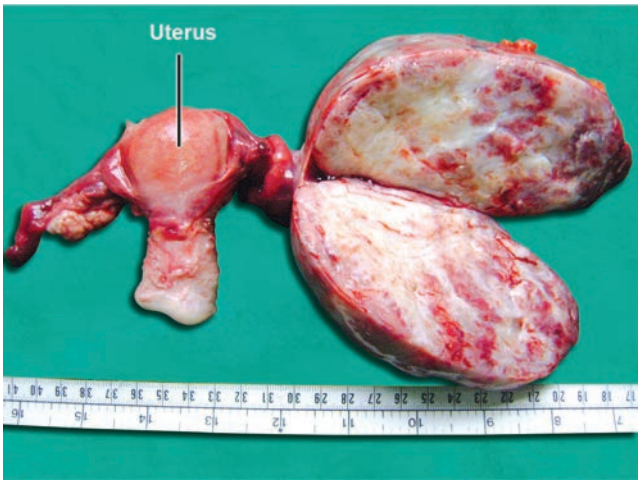

Fig. 24.31: Photograph of a surgical specimen from a 49-year-old woman who suffered abnormal uterine bleeding. The specimen had been halved to show the solid nature of the tumor. Histology revealed thecoma-fibroma.

and are similar to thecomas. Less than 10% are bilateral. Meig's syndrome (ascites, pleural effusion, and ovarian fibroma) is seen in about 1% of cases (p. 241, 545). Excision of fibromas is usually the treatment especially in young women. Fibromas showing increased cellularity and pleomorphic features and mitotic activity may be of low malignant potential. Fibrosarcoma is found in about 1% of cases.

SERTOLI-LEYDIG CELL TUMOR (ANDROBLASTOMA, ARRHENOBLASTOMA)

Sertoli-Leydig cell tumor is very rare and accounts for less than 0.5% of all ovarian tumors and less than 5% of all SCSTs.

They probably arise from the male directed cell rests in the hilum of the ovary, from granulosa cells or from teratomas. The tumor produces predominantly androgens (80%) and, in some cases estrogen 80%. Other tumor markers are: Inhibin and AFP. 80% are stage 1 and most are benign.

The tumors are small, usually unilateral (90%) and solid in consistency. Cut surface shows yellowish tinge with areas of hemorrhage and necrosis. Microscopic picture often resembles to various testicular cells such as Sertoli and Leydig cells. Immunostaining is invaluable to confirm diagnosis.

Clinical Features

The androgens produced by the tumor first lead to **defeminization**—atrophy of the breasts and uterus and amenorrhea followed by **masculinization (50%)**. This is evidenced by male type of distribution of hair, hoarseness of voice, breast atrophy, hirsutism, baldness and clitoral enlargement. Serum testosterone level is elevated.

Treatment is surgical removal of the tumor. The menstruation and fertility may return but the virilizing features fail to regress. Unilateral oophorectomy for younger age group is optimum. For older patients total hysterectomy with bilateral salpingo-oophorectomy is ideal. Adjuvant therapy is needed for poorly differentiated tumor. Combination chemotherapy (VAC or VBP) is needed for recurrent disease. Tumor removal results in rapid resolution of most hormonal effects except deepening of voice and clitoromegaly.

GYNANDROBLASTOMA

This is a very rare type of tumor. It contains both granulosa cell (estrogenic) or Sertoli-Leydig cell (androgenic) types. Usually, it has got a benign course. Surgical removal is the optimum treatment.

Follow-up

All patients of ovarian SCSTs need to be followed up. Stage I disease has got excellent prognosis following surgery. Women with higher stage disease may need adjuvant chemotherapy.

During surgery for ovarian SCSTs, staging laparotomy should be done in cases with: Granulosa cell, Sertoli-Leydig cell, fibrosarcoma, and steroid cell tumors. Well differentiated tumors like fibroma, thecoma, gynandroblastoma may not need staging laparotomy.

METASTATIC TUMORS OF THE OVARY

Metastatic tumors of the ovary constitute about 5% of all ovarian tumors.

The common primary sites from where metastases to the ovaries occur are gastrointestinal tract (pylorus, colon, and rarely small intestine), gallbladder, pancreas, breast, and endometrial carcinoma.

The mode of spread from the primary growth is through retrograde lymphatics or by implantation from metastases within the peritoneal cavity. The malignant cells from the stomach reach the superior gastric group of lymph glands which also receive the lymphatics of the ovaries. Hematogenous spread is also there.

These are usually bilateral, solid with irregular surfaces (Fig. 24.34). Peritoneal metastases are present, so also ascites. The omentum is involved and becomes solid.

Typical: Histologic picture same as that of primary one.

Atypical: The **atypical one is Krukenberg tumor** in which the histological picture differs from that of the primary one.

Metastatic tumors from the GI tract can be associated with sex hormone (estrogen and androgen) production. Patient may present with postmenopausal bleeding.

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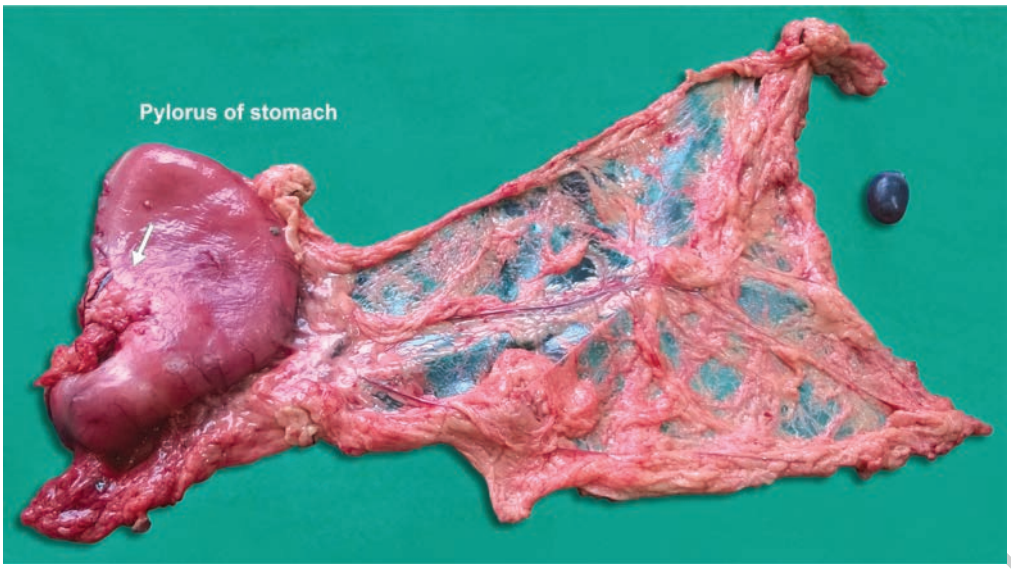

Fig. 24.32: Postoperative photograph of a specimen following partial gastrectomy and omentectomy for carcinoma of the pylorus of the stomach (see arrow).

Case history

Mrs JB 37-year-old lady underwent laparotomy for pelvic abdominal lump with the provisional diagnosis of ovarian tumors. She remained mostly asymptomatic and only late that vague symptoms of upper abdominal discomfort, dyspepsia, fullness and associated pelvic heaviness.
She underwent laparotomy for partial gastrectomy, omentectomy (Fig. 24.32) and total hysterectomy and bilateral salpingo-oophorectomy (Fig. 24.33).
Histology confirmed metastatic ovarian tumors (Krukenberg's tumor).

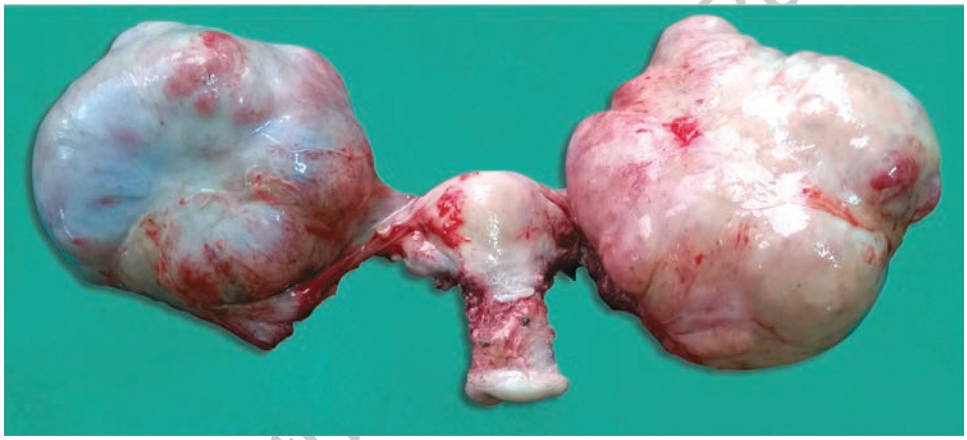

Fig. 24.33: Postoperative photograph of metastatic ovarian tumors following hysterectomy and bilateral salpingo-oophorectomy (Krukenberg's tumor). Primary site of origin was the stomach (the same patient described above). The lesions are usually diagnosed late until the primary disease is advanced. In few cases primary site is not found.

Naked Eye Appearance

The tumor is usually bilateral, solid with smooth surfaces and usually maintaining the shape of the ovary. They typically form rounded or reniform, firm white masses. Sometimes they are bosselated and may attain a big size. There is no tendency of adhesion (i.e. capsule remains intact) (Fig. 24.33).

The cut surfaces usually look yellow or white in color with cystic space at places due to degeneration. Cut surface has waxy consistency.

Histologically, the stroma is highly cellular. The mucin within epithelial cells compresses the nuclei to one pole, producing *'signet ring'* appearance. The scattered **'signet ring' looking cells are characteristic of Krukenberg tumor (Fig. 24.34).**

In most patients with Krukenberg's tumors, the prognosis is poor. Median survival being less than a year. Rarely, no primary site can be identified and the Krukenberg's tumor may be a **primary tumor.**

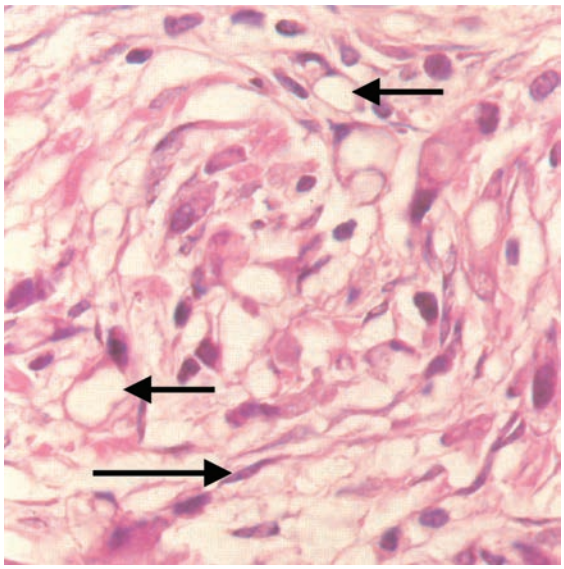

Fig. 24.34: Histologic picture of Krukenberg tumor showing characteristic 'signet ring' appearance. The signet ring cells contain the eccentric nuclei and abundant pale cytoplasm.

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POINTS

- There is wide geographical variation in the incidence of ovarian malignancy. Incidence is high in Scandinavian countries and US, low in Asian countries (India, Japan). In US about, 1 in every 70 newborn females will line to develop ovarian cancer.
- **The concept of ovarian tumerogenesis** with the distal fallopian tube origin is considered indisputable.
- **Serous cystadenomas** are the most common epithelial tumors. Serous adenocarcinomas have the worst prognosis of epithelial adenocarcinomas.
- About 20% of ovarian neoplasms are malignant. Malignant epithelial tumors constitute about 90% of all primary ovarian carcinomas. The primary mode of spread of epithelial ovarian carcinoma is transcoelomic and it spreads to the visceral and parietal peritoneum, diaphragm and to the retroperitoneal nodes. Most ovarian carcinomas are diagnosed in stages III or IV.
- **Endometrioid carcinoma** is associated with endometrial carcinoma in 20% and ovarian-endometriosis in 10% cases.
- **Patients with familial cancer syndrome** (Lynch type I and II) have a higher risk of developing epithelial ovarian cancer. Mutations of BRCA 1 gene (17 q) and BRCA 2 gene (13 q) have been observed. Inherited ovarian malignancies account for about 10–15% of epithelial ovarian cancers.
- **Incessant ovulation theory** is thought to be factor for carcinogenesis due to repeated ovulatomy trauma.
  The efficacy of screening procedure is not well-documented. However, periodic internal examination supplemented by transvaginal color Doppler sonography to note the ovarian volume, blood flow and estimation of CA-125 in 'high risk' population, can reveal the lesion at the early stage. Gene mutation study for detection of genetic inheritance is not currently recommended.
  Women with high risk factors are: Family history of ovarian, endometrial or breast carcinoma, history of removal of ovarian or breast neoplasm, use of fertility drugs, women with BRCA mutations, nulliparity, and postmenopausal palpable ovary (volume > 8 cm^3) (Table 24.31).
- **Protective factors** for ovarian epithelial adenocarcinomas are: Combined oral contraceptives, pregnancy, tubal ligation, prophylactic salpingectomy, hysterectomy and breastfeeding.
- **Ovarian enlargement less than 8 cm** in diameter in a menstruating women is most commonly functional.
- **Surgery** is the keystone in the primary treatment of ovarian malignancy. The aims are staging of the disease and to perform maximum surgical removal.
- **The ideal definitive surgery** is total hysterectomy with bilateral salpingo-oophorectomy with infracolic omentectomy with pelvic and para-aortic lymph node sampling. In exceptional cases, conservative surgery of unilateral salpingo-oophorectomy is justified.
- **Debulking surgery** with residual tumor nodules <1 cm confers better survival advantage even in advanced stage disease. CT, MRI and PET are effective for detecting residual tumor and the retroperitoneal nodes.
- **Second look surgery** either by laparoscopy or laparotomy is employed either after 12 courses of chemotherapy or after 1 year of primary therapy.
  The 5-year survival rate for patients with borderline epithelial ovarian cancer (grade 0) is close to 100%. For other stages *see* Table 24.35.
- Place of minimally invasive surgical staging of early stage ovarian cancer is accepted. About 15% of women with EOC have early stage disease at diagnosis. MIS for staging and management of early ovarian cancer is safe, feasible and effective when done by a gynecologic oncologist. The outcomes are comparable with that of laparotomy.
- **Chemotherapy** is being widely used following cytoreductive surgery to improve the result in terms of survival.
- **Platinum-based compounds** (cisplatin, carboplatin), either alone or in combination with taxane, prolong the survival rate. Taxane derivatives (paclitaxel, docetaxel) are effective in cisplatin resistant ovarian cancer. Treatment with carboplatin and paclitaxel for 3–6 cycles is desirable for most patients.
  Neoadjuvant chemotherapy is an alternative mode of chemotherapy when preoperative disease assessment is such that optimal cytoreduction is not possible.
- Chemotherapy is given before definitive surgery to debulk cancer. Benefits of this method is that the future surgical intervention is more successful and and is less complicated. Women with advanced ovarian cancer with medical complications are considered for neoadjuvant chemotherapy.
- **The ovarian antigen** CA-125 is useful to monitor the patient during chemotherapy and for follow up.
- **The prognosis of epithelial ovarian carcinoma** depends on many factors. Overexpression of oncogene (HER-2/neu) has been associated with poor prognosis.
- **Germ cell tumors** occur in young women. They are the second most common type of ovarian neoplasm. Most common germ cell tumor is the benign cystic teratoma (dermoid). It is bilateral in 10–15% cases.
  Dysgerminoma is the most common malignant germ cell tumor. It is bilateral in 10% cases. The tumor is highly sensitive to radiation. Multiagent chemotherapy (ectoposide, platinum with or without bleomycin) results in complete remission.
- **Fibroma** is the most common benign solid ovarian tumor.
- **Endodermal sinus tumor** is highly malignant occurring at a median age of 19. Alpha fetoprotein is the tumor marker. Treatment is surgery followed by chemotherapy.
- **Nongestational ovarian choriocarcinoma** is highly malignant. hCG is the tumor marker. It is not responsive to chemotherapy. The treatment is surgery followed by chemotherapy.
- **Multiagent chemotherapy** (BEP, VAC, VBP, CAP) has improved the survival rate as well as childbearing function in patients with malignant germ cell tumors.

Contd...

Contd...

- **Granulosa cell tumor** produces estrogen and may be associated with endometrial hyperplasia or endometrial carcinoma. It occurs 10% prior to puberty and 40% in postmenopausal period. It produces precocious puberty and postmenopausal bleeding. Thecoma is predominantly postmenopausal. There is excess estrogen production.
  Sertoli-Leydig cell tumor (previously called arrhenoblastoma) is very rare. It arises from the male directed cell rests in the hilum of the ovary, from granulosa cells or from teratomas. The tumor produces androgens (80%) and in some cases estrogen.
- **Primary prevention of ovarian cancer:** Current recommendations are to consider: (a) Opportunistic bilateral salpingectomy at the time of surgery for hysterectomy for benign disease or (b) Bilateral salpingo-oophorectomy in women with high risk factors (BRCA mutation), following completed family or (c) Bilateral salpingectomy and delayed oophorectomy.
- **The common primary sites** of metastatic ovarian malignancies are gastrointestinal tract, gallbladder, breast, and endometrial carcinoma. The tumor may be typical or atypical (Krukenberg). The primary sites of Krukenberg are stomach, large bowel and breast. The spread to the ovaries is by retrograde lymphatics. Histologically, it is confirmed by presence of 'signet ring' looking cells.

FALLOPIAN TUBE CARCINOMA

PRIMARY FALLOPIAN TUBE CARCINOMA

Primary carcinoma of the fallopian tube is very rare. The incidence of tubal carcinoma is less than 0.5% of gynecological malignancies.

Predisposing factors: Infertility, nulliparity and family history of ovarian cancer. Similar to ovarian cancer, the association with gene mutations (*BRCA1*, *BRCA2*), the high risk factors and the protective factors are the same.

Pathology

The site is usually in the ampullary part and the mucosa is commonly affected. The fimbrial end usually gets blocked resulting in hydrosalpinx or hematosalpinx (Fig. 38.57 and 38.58). It is mostly unilateral (80%).

Microscopic appearance: It is mostly adenocarcinoma (papillary serous) 90%.

Spread

Apart from **direct spread**, the **lymphatic** spread to the regional lymph glands (para-aortic) usually occurs. **Blood borne** spread to distant organs can occur in late stages. Transcoelomic spread with exfoliation of cells also occur.

Choriocarcinoma can occur in the fallopian tube following ectopic pregnancy or tubal hydatidiform mole.

Clinical Features

Patient profile: The patients are usually postmenopausal and nulliparous. History of infertility and pelvic infection may be there.

Symptoms

- Vaginal (postmenopausal) bleeding.
- Intermittent profuse watery discharge (hydrops tubae profluens).
- Colicky pain in lower abdomen.

Signs

Bimanual examination reveals a unilateral mass which may be tender. If reduced in size on compression, along with a watery discharge through the cervix, it is very much suspicious.

Diagnosis

- Most often accidentally discovered on laparotomy and histologic examination of the excised tube.
- **Clinical features**—as mentioned earlier.
- Suspected features are:
  - Persistent postmenopausal bleeding with uterine pathology being excluded by curettage.
  - Persistent positive Papanicolaou smear with a negative cervical and endometrial pathology.
  - Serum CA 125 is elevated in most cases (85%).
  - USG: Fluid-filled ovoid mass.
- **Laparoscopy:** In cases of persistent postmenopausal bleeding with a negative uterine pathology.
- **Ultrasound:** A fluid-filled sausage shaped mass separate from the uterus and ovary is seen. Ascites may be present.
- **Other imaging studies:** CT, MRI and PET may be used to differentiate fallopian tube from peritoneal cancer.

Stage

FIGO stage (2018) for fallopian tube cancer is as with the stage for ovarian and peritoneal cancers.

Treatment

Prophylactic surgery in high risk cases needs bilateral salpingo-oophorectomy once child bearing is completed (p. 312).

Actual treatment: Staging laparotomy is similar to ovarian cancer (p. 317). Total hysterectomy with bilateral salpingo-oophorectomy along with omentectomy. This should be followed by **platinum based (carboplatin and paclitaxel) combination chemotherapy** as an adjuvant therapy. In advanced cases, radiotherapy is considered (Ch. 31).

Prognosis

The prognosis is unfavorable mostly due to late diagnosis. The 5-year survival rate ranges between 25 and 40%.

SECONDARY FALLOPIAN TUBE CARCINOMA

This is more common (90%) than the primary. **The common primary sites are** ovary, uterus, breast, and gastrointestinal tract.

The mode of spread from the ovary or uterus is probably by lymphatics rather than a direct one.

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SARCOMA UTERUS

Incidence

Sarcoma of the uterus is rare and constitutes about 3% of uterine malignancy.

CLASSIFICATION OF UTERINE SARCOMAS

Pure sarcoma	*Carcinosarcoma (malignant mixed Müllerian tumor)*
A. Homologous ■ Smooth muscle tumors • Leiomyosarcoma (40%) • Others ■ Endometrial stromal sarcomas (10–15%) • Low grade • High grade **B. Heterologous** ■ Rhabdomyosarcoma ■ Chondrosarcoma ■ Osteosarcoma, others	**A. Homologous** ■ Carcinoma + Homologous sarcoma **B. Heterologous** ■ Carcinoma + heterologous sarcoma ■ Müllerian adenosarcoma ■ Lymphoma **C. Müllerian adenosarcoma** **D. Lymphoma**

Leiomyosarcomas are 1–2% of uterine malignancies. **Intravenous leiomyomatosis**—where benign smooth muscle grows into venous channels within the broad ligaments, uterine and iliac veins. Prognosis following surgery is excellent.

Histopathologic diagnostic criteria for uterine leiomyosarcoma depends on the number of mitotic figures (>5 MF/10 HPF), nuclear atypia and presence of coagulative necrosis.

Endometrial stromal tumors arises from endometrial stromal cells. **Endometrial stromal tumors** have chromosomal stromal aberrations observation (6p and 7p). These tumors are less common (10–15%). **Depending on mitotic activity endometrial stromal tumors are of three types:** (1) Endometrial stromal nodule (mostly benign); (2) Endolymphatic stromal myosis (low grade malignancy); (3) Endometrial stromal sarcoma (high grade malignancy).

Undifferentiated sarcoma: These high grade tumors are aggressive (mitosis >10 MF/10 HPF) and have poor prognosis.

Leiomyomatosis peritonealis disseminata—where benign smooth muscle nodules grow over the peritoneal surfaces. It is thought to arise from the metaplasia of subperitoneal mesenchymal stem cells to smooth muscle, fibroblasts, myofibroblasts under the influence of estrogen and progesterone.

Sarcomatous change of fibroid occurs in about 0.1% cases. When it does, the fibroid becomes soft. The cut section shows yellowish appearance with hemorrhage and cystic degeneration. **The whorl appearance is lost (Fig. 24.35).**

Malignant mixed Müllerian tumors (MMMT) of the uterus usually forms a large fleshy mass protruding into the uterine cavity with a broad base. Majority (90%) presents with postmenopausal bleeding.

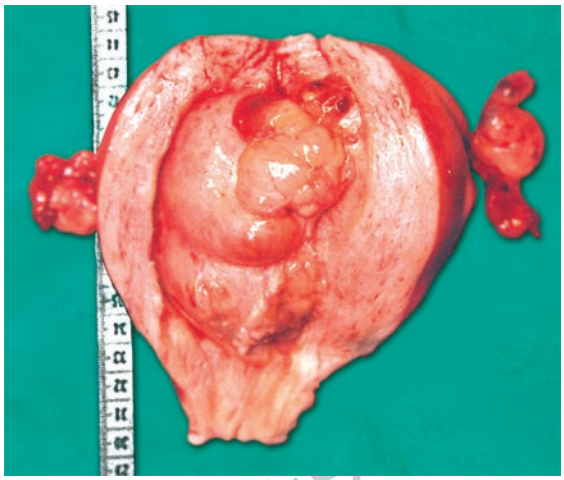

Fig. 24.35: Endometrial stromal sarcoma of uterus.

MICROSCOPIC APPEARANCE

Uterine sarcomas may be pure (single cell type) or mixed (more than one cell type). The tumor is termed *homologous when* the tissue elements are native (smooth muscle) or *heterologous when* tissue elements are not native (cartilage, striated muscle, bones). This is due to the totipotent nature of endometrial stromal cells.

Histologically, three types of cells are seen—spindle, round or combination of the two along with giant cells**. The most common is spindle cell type (Fig. 24.36).**

Malignant mixed Müllerian tumor is evidenced by presence of **both the structures of sarcoma and carcinoma (carcinosarcoma).**

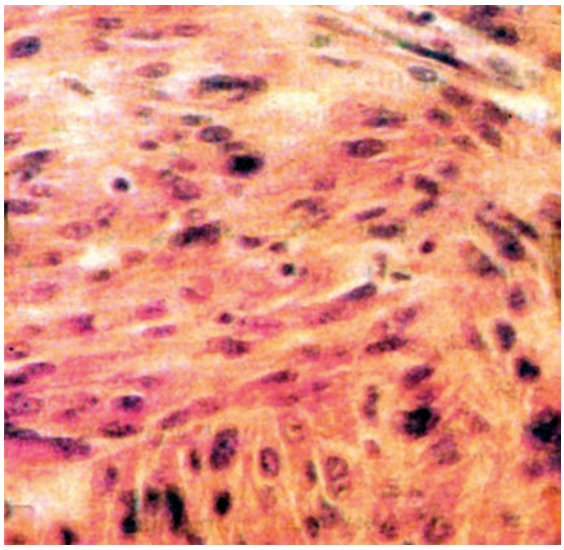

Fig. 24.36: Microscopic picture of leiomyosarcoma showing large spindle-shaped cells with pleomorphic nuclei. There is moderate cellular atypia.

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SPREAD

- **Blood borne:** This is the most common mode of spread. The organs involved are liver, lungs, kidneys, brain, bones, etc.
- **Directly** to the adjacent structures.
- **Lymphatic** spread to the regional (pelvic and para-aortic) lymph nodes.

Clinical Features

Patient profile: The age is usually between 40 and 60 years. There may be history of pelvic irradiation either for induction of menopause or malignancy.

Symptoms: There is no specific symptom.

- Irregular premenopausal or postmenopausal vaginal bleeding.
- Abnormal vaginal discharge—offensive, watery foul smelling discharge associated at times with expulsion of fleshy necrotic mass.
- Abdominal pain—due to involvement of the surrounding structures.
- Pyrexia, weakness, and anorexia.
- **Suspected sarcomatous change in a fibroid is evidenced by:**
  - Postmenopausal bleeding
  - Rapid enlargement of fibroid
  - Recurrence following myomectomy or polypectomy.

Pelvic Examination

There is no specific finding. The uterus may be enlarged and irregular. Parametrium may be thickened and indurated.

Speculum examination may reveal a polypoidal mass protruding out through the external os.

DIAGNOSIS

- MRI may be helpful when the uterus is large (Fig. 24.37).
- Diagnosis is made usually following histological examination of the removed uterus.

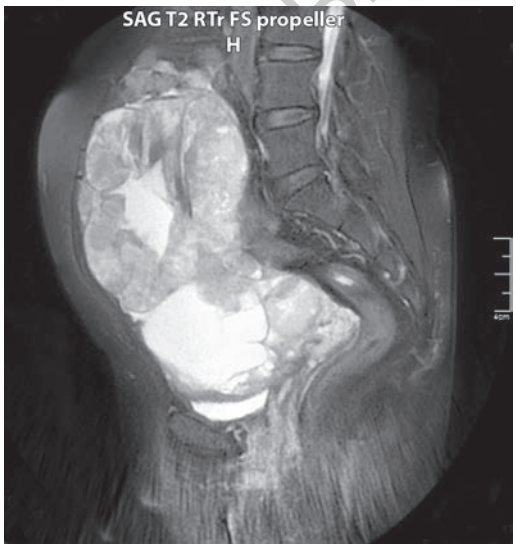

Fig. 24.37: MRI showing a huge pelvic mass (leiomyosarcoma) arising from the uterus with no normal tissue planes for resection.

- Diagnostic uterine curettage and endometrial biopsy may reveal the mucosal form of sarcoma.
- Histologic examination of the removed polyp.
- Serum CA-125 levels may be elevated in cases with carcinosarcoma. CA-125 values may be a useful marker to monitor the disease response.

TREATMENT

- Total hysterectomy with bilateral salpingo-oophorectomy is to be done. This may be followed by adjuvant external pelvic radiation.
- If **the cervix** is also involved, radical hysterectomy should be done.
- **Radiation therapy** (adjuvant) preoperative or postoperative is helpful to decrease the pelvic recurrence in endometrial stromal sarcoma and MMMT.
- **Several chemotherapeutic agents** have been tried in cases with metastatic disease. Doxorubicin, cisplatin gemcitabine, docetaxel and ifosfamide are the drugs used either singly or in combination with varying response.
- Watchful expectancy may be extended in cases of sarcoma detected accidentally from the well-capsulated fibroid following myomectomy.
- Complete resolution has been observed with progestin (provera), letrozole therapy in cases with endometrial stromal tumors.

PROGNOSIS

The prognosis is unsatisfactory. The 5-year survival rate ranges from 10–30%. Sarcoma in fibroid has got a better prognosis.

SARCOMA BOTRYOIDES (EMBRYONAL RHABDOMYOSARCOMA)

Embryonal rhabdomyosarcoma of the cervix is the most common malignant tumor of the vagina in infants and children. It is a highly aggressive tumor. Most are the subtypes of sarcoma botryoides. It is seen almost exclusively in girls below the age of 5 years. In the middle aged women it is seen within the cervix and after menopause within the uterus.

Patients with embryonal rhabdomyosarcomas have improved prognosis. The subtype sarcoma botryoides has the best chance of cure.

Clinical Features

The presenting features are:

- Blood stained watery vaginal discharge.
- Anemia and cachexia.
- Vaginal examination reveals pinkish, "grape-like" polypoidal edematous soft growth arising from the cervix. It may often fill up the whole vagina. It may be pedunculated to protrude outside.

Diagnosis is confirmed by histologic appearances of loose myxomatous stroma, pleomorphic malignant cells with striated rhabdomyoblasts.

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Treatment

With the use of multimodality treatment using chemotherapy, surgery and radiation therapy outcome of these patients have improved. Primary chemotherapy followed by conservative surgery to excise the residual tumor have been done. Many patients respond well to primary chemotherapy even without surgery.

Intravenous administration of VAC therapy (vincristine, actinomycin-D, cyclophosphamide) and radiation has been found very much effective. The drugs should be administered every 3 weeks over a period of 6 months. Chemotherapy with local resection of the disease gives better result. Radiation therapy may be needed. The results of multimodality approach are better.

Prognosis

Embryonal rhabdomyosarcomas have the poor prognosis. However, the subtype sarcoma botryoides has been best chance to cure following treatment.

Pseudosarcoma botryoides is a rare, benign vaginal polyp resembling sarcoma botryoides. It is found in vagina of infants and pregnant woman. Large atypical cells may be present but strap cells are absent. Local excision is effective.

POINTS

- **Primary carcinoma of the fallopian tube** is rarest (<1%) gynecological malignancy. It is mostly unilateral (80%). Associated hematosalpinx is often present. Classic traid of adnexal mass, intermittent profuse watery discharge (hydrops tubae profluens) and vaginal bleeding is considered pathognomonic for tubal carcinoma. USG/laparoscopy is suggestive and biopsy is confirmatory. Persistent postmenopausal bleeding and/or positive vaginal cytology for adenocarcinoma, in the absence of endometrial carcinoma, the diagnosis of tubal carcinoma should be considered.
- **Total hysterectomy with bilateral salpingo-oophorectomy along with omentectomy is done.** This is followed by platinum based combination chemotherapy as the adjuvant treatment. The prognosis is not good.
  Secondary carcinoma (metastatic) is common (90%), the primary sites are from ovary, uterus, breast or gastrointestinal tract.
- **Uterine sarcoma** comprise less than 5% of uterine malignancies. The most common site of uterine sarcoma is the intramural part.
- **The most common mode of spread** is blood borne. Total hysterectomy with bilateral salpingo-oophorectomy is the surgery. This is followed by multiagent chemotherapy and external pelvic radiation. Mitotic figure is an important prognostic factor for leiomyosarcoma of the uterus. Patients with mitotic rate of less than 5/10 HPF behave as a benign lesion but mitotic rate of more than 10 per 10 HPF are frankly malignant and have got worst prognosis.
- **Sarcoma botryoides** is a special type of mixed mesodermal tumor arising from the cervix. The child, before the age of 8, may be affected. Multimodality approach (multiagent chemotherapy with surgical removal and occasionally radiation) gives better result.

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