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A Review on Ovarian Malignancy

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ABSTRACT

Ovarian cancers are the seventh most common cancers are seen in women. It is seen more frequently in old age group women's. The survival depends on the stage of identification and many of the patient's present in advanced disease when the prognosis becomes dismal. The dilemma is to distinguish them from benign disease so that the unwanted laparotomies could be saved. Biomarkers and radiological categorization may play a role in categorizing benign from malignant and deciding on the management. There is no screening method to identify ovarian cancers and the patient presents with nonspecific complaints missing them in early stages. Optimal cytoreduction is required for better survival, development free survival and response to adjuvant chemotherapy. Those women having history of breast, ovary, and endometrial, colorectal cancers should be screened for malignancies and genetic testing is advised. Surgery is the mainstay of treatment followed by chemotherapy. Risk decreasing salpingoophorectomy can be offered to women having BRCA1 and BRCA2 mutation carriers after they complete their family. The area of target therapies is the latest and promising in treatment of ovarian cancer. They are coming in forefront when chemotherapy toxicity, drug resistance are big hurdles in treatment of ovarian cancer. Latest advances and understanding of the biology of ovarian cancer have led to clinical trials of targeted agents. The angiogenesis inhibitors and polyadenosine diphosphate-ribose polymerase (PARP) inhibitors are the most developed.

Keywords: Ovarian cancers, Salpingoophorectomy, Neoplasia, PARP, etc.

INTRODUCTION

Ovarian tumors are frequently occurring tumors in ovaries because of the propensity of ovaries for neoplasia. It is estimated that 5% to 10% of women in the United States in their lifetime will undergo a surgical procedure for a suspected ovarian neoplasm, and 13% to 21% of these women will be found to have an ovarian malignant neoplasm.[1] It is important to identify preoperatively whether patient is high risk for ovarian malignant disease to limit the number of surgical procedures. Ovarian cancer is the most lethal of all gynaecologic cancers. Ovarian cancer accounts for 5% of all cancers among women and 7th most common cancer in women.[2] Elderly women are more likely to develop ovarian cancer than young women. Worldwide there are 3,00,000 new cases of Ovarian Cancer and 1,85,000 ovarian

cancer related deaths annually.' Although 5 years survival in stage 1 and 2 is 80- 85%, unfortunately most cases (75%) are diagnosed in advanced stages 3 and 4 in whom 5 years survival is only 25%. Therefore, the overall 5 years survival falls to less than 45%." Ovarian tumour can be classified into benign, malignant and metastatic. The classification of ovarian tumors is based on their histogenesis. The world health organization histological classification for ovarian tumors separates ovarian neoplasms according to the most probable tissue of origin: surface epithelial (65%), germ cell (15%), sex cord-stromal (10%), metastases (5%), miscellaneous. Surface epithelial tumors are further classified by cell type (serous, mucinous, endometrioid, etc) and atypia (benign, borderline [atypical proliferation, low malignant potential] or malignant. The majority (85%-90%) of malignant ovarian tumors are epithelial. Whereas malignant germ cell tumors are most commonly seen in girls younger than age 20 years, epithelial cancers of the ovary are primarily seen in women older than age 50 years.

❖ WHO CLASSIFICATION OF OVARIAN TUMOR‘s

1. Surface epithelial-stromal tumors

Serous tumors:
Benign (cystadenoma)
Borderline tumors (serous borderline tumor)
Malignant (serous adenocarcinoma)

2. Mucinous tumors, endocervicamike and intestinal type

Benign (cystadenoma),
Borderline tumors (mucinous borderline tumor),
Malignant (mucinous adenocarcinoma)

3. Endometrioid tumors

Benign (cystadenoma),
Borderline tumors (endometrioid borderline tumor)
Malignant (endometrioid adenocarcinoma).

4. Clear cell tumors

Benign, borderline tumors
Malignant (clear cell adenocarcinoma).

5. Transitional cell tumors

Brenner tumor, Brenner tumor of borderline malignancy
Malignant Brenner tumor
Transitional cell carcinoma (non-brenner type).

6. Epithelial-stromal

Adenosarcoma Carcinosarcoma (formerly mixed Müllerian tumors)

7. Sex cord-stromal tumors

Granulosa tumors: Fibromas, fibrothecomas and thecomas

Sertoli cell tumors, Leydig cell tumors.

8. Sex cord tumor with annular tubules:

Gynandroblastoma and steroid (lipid) cell tumors

9. Germ cell tumors

Teratoma: Immature, mature, solid, cystic (dermoid cyst), monodermal (e.g., struma ovarii, carcinoid), dysgerminoma, yolk sac tumor (endodermal sinus tumor) and mixed germ cell tumors.

- **NON-NEOPLASTIC OVARIAN MASSES**

a. Functional cyst

This is commonly occurring enlargement of ovary in reproductive years. When ovulation doesn't occur, a cyst lined by granulosa cells is formed which may persist for few days to 2 weeks. When ovulation occurs, a corpus luteum is formed and if hemorrhage occurs in this, it may get enlarged to form a cyst. This may give rise to pain and discomfort. On ultrasonography, it may show a thin- walled, simple-appearing, anechoic cyst without solid component. A hemorrhagic cyst on USG may show complexity because of fibrin and blood stranding. Corpus luteum, follicular, and theca-lutein cysts are benign lesions occurring in view of exaggerated physiologic response of the ovary. In most instances, they involute over time, but they do need to be included in the differential diagnosis.

b. Endometriotic cysts

Endometriosis is a condition in which endometrial glands and stroma are implanted outside their normal location in the uterine cavity. It usually occurs in 35 to 45 years of age. The most common sites for endometriosis are the ovaries, the supporting ligaments of the uterus, and the peritoneum of the cul-de-sae and bladder. In patients with Endometriotic cysts, there will be symptoms suggestive of endometriosis, including dysmenorrhea, pelvic pain, or infertility. In examination, there may be nodularity of the uterosacral ligaments. Pelvic pain is by far the most usual symptom of endometriosis. Ultrasonography may show a homogenous echo, sometimes referred to as having a "ground-glass appearance and septations with nodularity may be misinterpreted as a solid mass. CA-125 levels are also frequently elevated in patients with endometriosis. The complex mass on ultrasonography along with CA-125 level elevations may be misdiagnosed as ovarian malignancy on work up.'

- **BENIGN OVARIAN NEOPLASMS**

The ovary is composed of tissue derived from coelomic epithelium, germ cells, and mesenchyme and tumors may arise from them. Neoplasms can be divided into solid and cystic types based on ultrasonography and gross appearances. The most common benign cystic neoplasms of the ovary are serous and mucinous cyst adenomas and cystic teratomas (dermoids). Benign cyst adenomas may vary in size from 5 to 50 cm and are thin walled, ovoid, and frequently unilocular. Benign neoplasms do not metastasize nor do they spontaneously regress.'

a. Serous cyst adenoma

Serous cyst adenomas are more common than the mucinous type of tumor. On gross evaluation, the cyst fluid is usually thin, watery, and yellow tinged. They are bilateral in 10% of cases. The surface of the cyst is usually smooth and it is mostly unilocular but septations dividing the cyst can be seen. Some serous tumors may have small papillary projections on the surface of the cyst wall. Large, frond like solid projections or nodules or areas of necrosis are seen in malignancy. On microscopic examination, psammoma bodies are characteristic feature of this tumor. Psammoma bodies are calcified granules arising as a result of degeneration of the papillary implants.

b. Mucinous cystadenoma

Mucinous cyst adenomas may become very large in size. On gross evaluation, the masses are round or ovoid, usually translucent or bluish to whitish gray with smooth capsules. The loculi are present by number of discrete septa that contains a clear, viscid fluid. Papillae are rarely noted. On microscopic examination, the lining of the epithelium is of a tall, pale-staining secretary type with presence of goblet cells is common. This type of cyst usually arises from simple metaplasia of the germinal epithelium. It may rarely arise from a teratoma or from a Brenner tumor in which there has been mucinous transformation of the epithelium.

c. Dermoid cyst (Benign cystic teratoma)

These neoplasms are thought to arise from early ova that have been triggered by some type of parthenogenesis process. Dermoid cyst occurs in young age group. These are generally <10 cm and are bilateral in 15-25% cases. On gross evaluation, the wall is thick, opaque, whitish. On opening of the cyst, one frequently finds hair, bone, cartilage, and a large amount of greasy sebaceous fluid. The cyst may grow in size, rupture and malignant degeneration can occur. Malignant degeneration can occur in teratomas in 1% to 3% of these tumors, and it is usually of a squamous type. Teratomas can be evaluated easily by imaging. For example, abdominal radiographs may demonstrate calcifications (teeth, bone) and CT imaging is helpful in showing fat densities commonly seen with dermoid. In ultrasound, hyperechoic areas with complex cyst may be seen. In young patient, only cyst may be removed to preserve fertility. During surgery, the spillage of cystic fluid should be avoided to prevent the development of chemical peritonitis.[7]

d. Fibroma

These are benign solid tumor of the ovary and usually of connective tissue origin (fibromas, thecomas, or Brenner tumors). They are usually firm in consistency, slightly irregular in contour, and mobile. They may present as small nodules to extremely large, filling the entire pelvis and lower abdomen. The tumors are characterized by their firmness and resemblance to myomas, and they are frequently misdiagnosed as such. Meigs syndrome is characterized by ascites, hydrothorax, and an ovarian tumor that was originally believed to be specifically a fibroma; however, many other types of ovarian tumors are now known to be associated with this syndrome, such as Brenner tumors and Krukenberg tumors. The cause of Meigs syndrome is not completely understood. They are most commonly occurred in menopausal age group and may be associated with menstrual irregularity because of estrogenic stimulus [8]

e. Brenner tumor

Brenner tumor is grossly identical to a fibroma. The tumor is found as an incidental finding in an otherwise unremarkable ovary. On microscopic examination, there is markedly hyperplasic fibromatous matrix interspersed with nests of epithelioid cells. The epithelioid cells show a “coffee bean” pattern caused by the longitudinal grooving of the nuclei under high magnification. Brenner are uniformly benign, but there have been reports of malignant Benner tumors. Several cases of endometrial hyperplasia are associated with Brenner tumors as a result of its estrogenic effect. These lesions are managed by simple excision.’

- **MALIGNANT OVARIAN TUMORS**

Ovarian neoplasms consist of various histologic subtypes. Epithelial ovarian cancers are the most common subtype and are present in above 90% of cases. The incidence of ovarian tumor enhances with increasing age number and it is more common in sixth to seventh decade. Median age at diagnosis is 63 years. Most ovarian cancers are diagnosed after pathological examination of specimen after surgery or biopsy preoperatively, intra-operatively and post-operatively. Fine needle aspiration is not done in early stage cancers to avoid the risk of spillage. It may be required in advanced stage in patients not fit for surgery.

a. Germ cell tumors

These malignant tumors include dysgerminoma, immature teratoma, embryonal carcinoma, endodermal sinus tumors. They mainly occur in girls, adolescents and young women and are diagnosed in age 16 to 20 years age group. [10] In first two decades, 60% of the neoplasm are germ cell tumors and one third of them are malignant. They generally present in early stage. Ovarian malignant germ cell tumors constitute 2.5 % of all malignant tumors of ovary while 95% of them are epithelial ovarian malignancy.[11] They have excellent prognosis as they are sensitive to chemotherapy. Dysgenetic gonads are a risk factor.'[2] Dysgerminomas produce b-hCG in 5% of cases because of the presence of multinucleated syncytiotrophoblastic giant cells and also occasionally produce lactic dehydrogenase (LDH). Embryonal carcinoma and poly-embryoma produce a-fetoprotein and b-hCG.[1'] Depending on the component present, mixed germ cell tumors may secrete b-hCG, a- fetoprotein. Dysgerminoma is the ovarian counterpart to testicular seminoma. It is the most common germ cell tumor. Most of the patients with Germ cell

tumors are symptomatic and most commonly present with pain abdomen, bloating or fullness and menstrual disturbaances.[1]

- **EVALUATION OF OVARIAN TUMOR**

a. Clinical presentation

Patient with ovarian tumor may present with various clinical settings. Patient may present with symptoms such as pelvic pain or mass causing pressure symptoms. The most common symptoms associated with ovarian cancer are abdominal bloating, increased abdominal size, pelvic pain, abdominal pain, feeling full quickly, and difficulty eating. Urinary symptoms are also frequently present. When these symptoms occur for more than 12 days per month and are of new onset, then ovarian cancer should be considered as a possibility. [16] Others may have a mass identified as a part of work up for another condition such as ultrasonography for back pain.' They can also get detected during routine gynaecological examination.

- **IMAGING MODALITIES**

a. Pelvic ultra-sonography

It is the most valuable initial tool and should be considered as the first investigation to evaluate for ovarian tumor. RCOG recommends pelvic ultrasound (trans-vaginal, trans-abdominal or both) as the single most effective way to evaluate ovarian masses. Many tools have been designed to increase the sensitivity and specificity of ultrasonography to recognize malignant ovarian lesion and to avoid unnecessary staging laparotomy. Trans-abdominal ultrasound is preferred for lesions extending out of pelvis. Trans-vaginal scan may be used to visualize the internal features such as papillary projections and for small lesions in cul-de-sac. The ultrasonography shows size, unilateral or bilateral involvement, mass morphology (septae, unilocular/ multilocular and associated findings such as ascites.[1] The sensitivity of morphologic analysis with US in predicting malignancy in ovarian tumors has been shown to be 85%-97%, whereas its specificity ranges from 56% to 95%.[2]

- **INTERNATIONAL OVARIAN TUMOR ANALYSIS SIMPLE RULES AND SIMPLE RULES RISK CALCULATION[2]**

In 2008, international ovarian tumor analysis (IOTA) group formulated simple rules. It is based on 5 B (benign) features and 5 M (malignant) features.

B1: Unilocular
B2: Presence of solid components with largest diameter <7 mm
B3: Presence of acoustic shadows
B4: Smooth multilocular tumor with largest diameter <100 mm
B5: No blood flow
Ml: Irregular solid tumor
M2: Presence of ascites
M3: At least four papillary structures
M4: Irregular multilocular solid tumor with largest diameter >l00 mm
M5: Very strong blood flow.

It is said to be benign or malignant if only B or M features are present respectively or as inconclusive when no or both B and M features apply.

- **Doppler US Estimation**

Color Doppler US of ovarian masses helps identify vascularized tissue and can assist in differentiating solid tumor tissue from non-vascularized structures. Its wave form analysis of vessels can be used to distinguish between benign and malignant. Benign lesions tend to initiate new tumor blood vessel formation peripherally from pre- existing host vessels, whereas malignant tumors tend to initiate new tumor blood vessel formation structures in the centre. The neovascularity within malignant mass results in low pulsatality index, low resistance index, high time-averaged maximum velocity and absence of diastolic notch i.e.,

less than 1,leass than 0.4 & greater than 15cm/s respectively. [22]

- **Cancer antigen 125 (CA 125)**

CA 125 is a tumor associated antigen used to monitor patients with ovarian carcinoma. The value that is considered significantly above 35 units/ml. It is elevated in approximately 80% of patients with non-mucinous, epithelial ovarian cancers and 50% of stage I ovarian cancers. CA-125 testing has limited sensitivity and specificity because it is raised in several benign gynaecological and non-gynaecological conditions like benign ovarian, endometriosis, liver cirrhosis, pelvic inflammatory disease, uterine fibroids etc. It is raised in 1% of healthy women and it also varies with normal menstrual cycle, age and smoking status. Even in postmenopausal women single CA 125 value has a low positive predictive value of around 6%. The change in CA125 level overtime may be more helpful than a single value and therefore it is useful for follow up of patients of ovarian cancer after treatment.[2']

- **Risk of malignancy index (RMX)**

It combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score. The RMI is a product of the ultrasound scan score, the menopausal status and the serum CAl 25 level (IU/ml).

RMI= U^M•CA-125 level.

Where,
U= ultrasound score (higher-risk morphology=3, low-risk morphology=1)
M= menopausal status (postmenopausa1=3, premenopausal=1), and CA-125 level is the actual testing value.

If score greater than 250, then high chances of malignancy.[24]

- **HE4**

FDA has approved the use of HE4 for evaluating the risk of malignancy in a case of pelvic mass.

- **Other tumor markers**

CA 19 9, CEA may be raised in mucinous ovarian tumor. It may also be raised in GIT malignancies. In such cases ratio of CA125/CEA if more than 25 indicates ovarian pathology. Beta HCG, LDH, Alpha fetoprotein is other markers which are raised in germ cell tumors.[25]

- **The OVA1 test**

It is a biomarker panel that measures five proteins (CA- 125, §2-microglobulin, apolipoprotein Al, prealbumin, and transferrin); it was approved by the food and drug administration in 2009 to better classify adnexal masses to assist physicians with making referral to gynaecologic cancer specialists. A high probability of malignancy is defined as a score of greater than 5.0 in premenopausal women and greater than 4.4 in postmenopausal women. It is indicative of increased risk of malignancy. This test has 96% sensitivity, 35% specificity, 40% positive-predictive value (PPV), and 95% negative-predictive value (NPV).[26]

- **CT or magnetic resonance imaging (MRI)**

CT may provide additional information on the anatomy of mass, upper abdominal findings, and information on lymphadenopathy and ureteral patency. It can help in finding out the extent of disease preoperatively. MRI can be useful in the diagnosis of mature cystic teratomas, endometriomas, and leiomyomas because of excellent contrast resolution and tissue characterization. NCCN guideline recommends PET/CT or MRI for indeterminate lesions if results will alter management. CT/ MRI can be used to see the response of primary treatment in ovarian cancer post operative1y.[2]

- **Colonoscopy and endoscopy**

May be helpful in patients presenting with symptoms upper or lower intestinal involvement.

- **Differential diagnosis**

Other non ovarian apparent adnexal masses which may mimic an ovarian tumour are diverticulitis, tubo-ovarian abscess, carcinoma caecum, sigmoid, pelvic kidney, and uterine or ligamentary myomas careful evaluation is done to exclude these conditions.

- **RISK FACTORS FOR OVARIAN CANCER**

The strongest risk for ovarian cancer is family history of breast and ovarian cancer. 10-15% of ovarian cancers are due to genetic predisposition and up to 20% of high grade serous ovarian carcinomas are due to genetic causes. Therefore, national comprehensive cancer network (NCCN) recommends genetic testing for all ovarian cancer. Other risk factors are older age, null parity, smoking, alcohol, obesity and long-term use of hormone replacement therapy (HRT). HRT users have a 20% higher risk than never users. Smoking increases the risk for mucinous tumors more than other histopathology.[2]

- **Familial ovarian cancer** [9]

Familial hereditary ovarian cancer currently falls into three categories. Site-specific familial ovarian cancer, hereditary breast-ovarian cancer syndrome, in which there is an increased incidence of breast and ovarian carcinomas alone or in combination. Lynch syndrome type II, in which family members may develop a variety of cancers, including colorectal, endometrial, and ovarian cancer. Inherited genetic mutations are seen in approximately 10% of women who develop ovarian cancer. These mutations are autosomal dominant and have maternal or paternal transmission and multiple family members are involved over several generations. In hereditary breast-ovarian cancer syndrome, there is inherited germ line mutation of brcal and BRCA2. In brcal mutations are located on long arm of chromosome l7q and BRCA2 are located on l3q12. There is estimated risk of ovarian cancer of 39% to 46% for carriers of the brcal mutation but a lower rate of 10% to 20% for carriers of the BRCA2 mutation." In Lynch II syndrome, there is inherited mutation in a family of DNA repair genes (MSH2, mlhl, PMS1, PMS2). In a consensus statement of the cancer genetics studies, in BRCA1 mutation carriers-annual or semi-annual screening with transvaginal ultrasonography (TVS) and determination of serum carcinoma antigen 125 (CA-125) levels beginning at age 25 to 35 years are recommended. National institutes of health (NIH) consensus conference recommended that women with two or more first-degree relatives with ovarian carcinoma be offered prophylactic oophorectomy after completion of childbearing or age 35 years. Prophylactic oophorectomy does not prevent subsequent primary peritoneal cancer.[32]

FACTORS PROTECTIVE AGAINST OVARIAN CANCER

Certain factors that decrease the risk of ovarian malignancy are following: Pregnancy, birth control pills (These decrease risk by 35-50% after 5 years of use), fallopian tube ligation (Decrease the risk by 30%), salpingectomy (Decrease the risk by 60%), breast feeding (Decrease the risk 40%), hysterectomy (Decrease the risk 40-50%).

BORDERLINE OVARIAN TUMOURS (BOTS)

Comprise about 15%-20% of all epithelial ovarian malignancies with incidence of 1.8-4.8 per 100,000 women per year. BOTs differ significantly from ovarian carcinomas with regard to percentile distribution of tumor histo-types, lower FIGO stage, excellent overall prognosis, younger age distribution, and a lower frequency of BRCA mutations. The increased risk of BOTs may also be associated with the use of fertility drugs. The majority of BOTs are serous tumors (53.3%), followed by mutinous tumors (42.5%) and less common histo-types. BOTs are mainly diagnosed at an earlier stage (75% at FIGO stage I) in contrast to ovarian cancer (25% at FIGO stage I).”

MANAGEMENT OF OVARIAN TUMOR

Complete evaluation of patient is done after analyzing and assembling information from history, examination, imaging and tumor markers. One aim is to see the characteristics of malignancy. Management depends on age of the patient, menopause status and morphological characteristics of mass

by ultrasound, clinical findings and patient desires. The features of benign mass are absence of symptoms (pain, nausea, vomiting, weight loss), unilateral, unilocular in ultrasound, normal CA 125. Masses that raise the suspicion of malignancy should be considered for surgical intervention. Surgery should be considered in following conditions: Bilateral adnexal masses, masses associated with elevated tumor markers, Symptomatic masses, complex masses, especially containing solid components, thick septations/mural nodules. Premenopausal patients with complex masses that persist or grow after period of observation. Postmenopausal patients with simple masses larger than 5 cm or complex masses of any size.

MANAGEMENT OF OVARIAN CARCINOMA

In case of ovarian carcinoma, surgical staging is done and it is based on surgery and pathologic finding. Needle biopsy for tissue diagnosis is not advised as it may lead to spillage in case of malignant ovarian tumor. Most important factor in prognosis is stage of the disease. Survival is affected by the cancer stage, grade of differentiation, gross findings at surgery, amount of residual tumor after surgery, and additional treatment required. Majority cases of epithelial ovarian cancer demands a comprehensive surgical staging unless contraindicated due to poor surgical outcome or has a low optimal cyto-reductive potential, the primary treatment in such cases is a neo-adjuvant therapy.

Stages IA, IB, and IC

Careful surgical staging is critical in the management of stage I invasive ovarian cancer and should include bilateral salpingo oophorectomy, hysterectomy, omentectomy, and pelvic and aortic lymph node sampling, with peritoneal biopsies and washings. Open laparotomy with vertical midline incision is recommended. Minimally invasive technique can be used under experienced hands in surgical treatment of early-stage disease. Sampling of ascetic fluid, if any or peritoneal washings are obtained by instilling and recovering 50 to 100 dL of saline from the cul-de-sac, each paracolic gutter, and from beneath each hemi diaphragm and should be sent for cytological examination in a heparinised vial. Scrapings from the undersurface of the diaphragm are obtained by using an Ayer's spatula. Systematic bilateral pelvic and Para-aortic lymph node dissection up to the left renal vein has to be performed.

In the young woman with stage IA and grade 1 disease (except in carcinosarcoma or clear cell tumor and grade III tumor) that is desirous of further childbearing, unilateral salpingo-oophorectomy may be done. It is associated with minimal increased risk of recurrence, provided a careful staging procedure is performed."

Patients with stage I, grade 3 and stage IC disease treatment with platinum-based combination chemotherapy for 3 to 6 cycles is given postoperatively. Utilization of carboplatin (AUC=5 or 6 on day 1) with weekly paclitaxel (60-80 mg/m^2 days 1, 8, and 15) on either a 21-day (continuous) or 28-day (one week without treatment) schedule is reasonable.

Stages IIA, HB, and COC

Staging surgery followed by platinum-based combination chemotherapy is given. Comprehensive surgical staging and optimal debulking is ideal for successful planning in this stage. Retrospective studies have strongly suggested that the survival rate in these patients depends on the amount of residual tumor and grade of the disease.[4] The patients with no macroscopic residual tumor appear to have the best prognosis after primary chemotherapy. Optimal debulking is done so that no macroscopic visible to the chemo-therapeutic agent. Cyto-reduction produces lesions or tumor tissue is reduced to <1cm in greatest smaller residual masses with a relatively higher growth dimensions. Bulky tumors have large proportion of cells in fraction and this also reduces total no. of chemotherapy the resting or G0 phase thus rendering them less sensitive cycles and prevents acquired chemo resistance.

Table 1: Staging classification of ovarian carcinoma using the federation of international gynaecologists and obstetricians (FIGO) nomenclature.[7]

AJCC Stage	FIGO Stages	Stage grouping	Stage description
I	I	T1	The cancer is only in the ovary or fallopian tube.
		N0	It has not spread to nearby lymph nodes.

		M0	It has not spread to distance sites.
IA	IA	T1	The cancer is in one ovary, and the tumor is confined to the inside of the ovary; or the cancer is in one fallopian tube, and is only inside the fallopian tube. There is no cancer on the outer surfaces of the ovary or fallopian tube. No cancer cells are found in the fluid (ascites) or washings from the abdomen and pelvis.
		N0	It has not spread to nearby lymph nodes.
		M0	It has not spread to distant sites.
IB	IB	T1b	The cancer is in both ovaries and fallopian tubes but not on their outer surfaces. No cancer cells are found in the fluid (ascites) or washings from the abdomen and pelvis.
		N0	It has not spread to nearby lymph nodes.
		M0	It has not spread to distant sites.
IC	IC	T1c	• The tissue (capsule) surrounding the tumor broke during surgery, which could allow cancer cells to leak into the abdomen and pelvis (called surgical spill). This is stage IC1. • Cancer is on the outer surface of at least one of the ovaries or fallopian tubes or the capsule (tissue surrounding the tumor) has ruptured (burst) before surgery (which could allow cancer cells to spill into the abdomen and pelvis). This is stage IC2. • Cancer cells are found in the fluid (ascites) or washings from the abdomen and pelvis. This is stage IC3.
		N0	It has not spread to nearby lymph nodes.
		M0	It has not spread to distant sites.
II	II	T2	The cancer is in one or both ovaries or fallopian tubes and has spread to other organs (such as the uterus, bladder, the sigmoid colon, or the rectum) within the pelvis or there is primary peritoneal cancer.
		N0	It has not spread to nearby lymph nodes.
		M0	It has not spread to distant sites.
IIA	IIA	T2a	The cancer has spread to or has invaded (grown into) the uterus or the fallopian tubes, or the ovaries.
		N0	It has not spread to nearby lymph nodes.
		M0	It has not spread to distant sites.
IIIA1	IIIA1	T1	The cancer is in one or both ovaries or fallopian tubes.
		T2	There is primary peritoneal cancer.
		N1	It may have spread or grown into nearby organs in the pelvis.
		M0	It has not spread to distant sites.
IIIA2	IIIA2	T3a	The cancer is in one or both ovaries or fallopian tubes or there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. During surgery, no cancer is visible in the abdomen (outside of the pelvis) to the naked eye, but tiny deposits of cancer are found in the lining of the abdomen when it is examined in the lab.
		N0/ N1	The cancer might or might not have spread to retroperitoneal lymph Nodes.
		M0	It has not spread to distant sites.

IIIB	IIIB	T3b	There is cancer in one or both ovaries or fallopian tubes or there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. The deposits of cancer are large enough for the surgeon to see, but are no bigger than 2 cm (about 3/4 inch) across.
		N0/ N1	It may or may not have spread to the retroperitoneal lymph nodes but it has not spread to the inside of the liver or spleen.
		M0	It has not spread to distant sites.
IIIC	IIIC	T3c	The cancer is in one or both ovaries or fallopian tubes or there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. The deposits of cancer are larger than 2 cm across and may be on the outside (the capsule) of the liver or spleen.
		N0/ N1	It may or may not have spread to the retroperitoneal lymph nodes but it has not spread to the inside of the liver or spleen.
		M0	It has not spread to distant sites.
IVA	IVA	Any T	-
		Any N	
		M1a	Cancer cells are found in the fluid around the lungs with no other areas of cancer spread such as the liver, spleen, intestine, or lymph nodes outside the abdomen.
IVB	IVB	Any T	-
		Any N	
		M1b	The cancer has spread to the inside of the spleen or liver, to lymph nodes other than the retroperitoneal lymph nodes, and/or to other organs or tissues outside the peritoneal cavity such as the lungs and bones.

SPECIAL CIRCUMSTANCES

Fertility sparing surgery (preserving uterus and contra lateral ovary or bilateral salpingo-oophorectomy conserving uterus) can be considered for early-stage cancers/low risk tumors (early stage invasive epithelial tumors, malignant germ cell tumors, mutinous or malignant sex chord stromal tumors, low malignant potential) who wish to preserve fertility.[3,]

Mutinous tumors of the ovary are not common. Thus, the upper and lower gastrointestinal tract should be evaluated to rule out occult primary. Appendix should be inspected and if appears abnormal, appendectomy is to be performed.

Chemotherapy in the present era, platinum-based compounds have proved to be most successful in treatment of ovarian malignancy. The combination of paclitaxel and cisplatin became the standard for combination first-line chemotherapy for the treatment of epithelial ovarian carcinoma.

PRIMARY SYSTEMIC THERAPY FOR EPITHELIAL OVARIAN CANCER FOR STAGE I DISEASE[7]

i. Paclitaxel and carboplatin (preferred)

Day 1: Paclitaxel 175 mg/m^2 IV over 3 hours, followed by: day 1: Carboplatin AUC 5-6 IV over 30 minutes. Repeat cycle every 3 weeks for 3-6 cycles. Or days 1, 8 and 15: Paclitaxel 80 mg/m^2 IV over 1 hour, followed by: day 1: Carboplatin AUC 5-6 IV over 30 minutes.
Repeat cycle every 3 weeks for 6 cycles, or day 1: Paclitaxel 60 mg/m^2 IV over 1 hour, followed by: day 1: Carboplatin AUC 2 IV over 30 minutes.

Repeat cycle weekly for 18 weeks.

ii. Docetaxel and carboplatin

Day 1: carboplatin AUC 5 IV.
Day 1: Liposomal doxorubicin 30 mg/m^2 IV.
Repeat every 4 weeks for 3-6 cycles for stage I disease or 6 cycles for stage II-IV disease or high-grade stage I disease.

iii. Paclitaxel and cisplatin (IV7IP)

Day 1: Paclitaxel 135 mg/m^2 IV over 3 hours or IV continuous infusion over 24 hours.
Day 2: cisplatin 75-100 mg/m^2 intra-peritoneal (IP) infused as rapidly as possible via IP ported,
Day 8: Paclitaxel 60 mg/m^2 IP infused as rapidly as possible via IP Porte.
Repeat cycle every 3 weeks for 6 cycles.

PRIMARY SYSTEMIC THERAPY FOR EPITHELIAL OVARIAN CANCER FOR STAGE H-IV DISEASE[7]

- **Paclitaxel, carboplatin and bevacizumab**

Day 1: Paclitaxel 175 mg/m^2 IV over 3 hours, followed by: day 1: Carboplatin AUC 5-6 IV over 30 minutes,
Day 1: Bevacizumab 7.5 mg/kg IV.
Repeat cycle every 3 weeks for 5-6 cycles and continue maintenance bevacizumab for up to 12 additional cycles. Or day 1: Paclitaxel 175 mg/m^2 IV over 3 hours, followed by: day 1: Carboplatin AUC 6 IV over 1 hour.
Repeat cycle every 3 weeks for 6 cycles.
Starting day 1 of cycle 2: Bevacizumab 15 mg/kg IV over 30-90 minutes every 3 weeks for up to 22 cycles.

- **HIPECJ**

Cisplatin 100 mg/m^2 IP over 90 minutes at time of debulking surgery.
In elderly patients (>70 years) and/or those with comorbidities:
Day 1: Carboplatin AUC 5 IV over 30 minutes.
Repeat cycle every 3 weeks.

MAINTENANCE THERAPY FOR EPITHELIAL OVARIAN CANCER FOR STAGE II- IV DISEASE

Day 1: Bevacizumab 15 mg/kg IV or Bevacizumab 7.5 mg/kg IV.
Repeat cycle every 3 weeks.

WHEN BEVACIZUMAB IS NOT USED IN PRIMARY THERAPY

Days 1-28: Olaparib 300 mg (tablet formulation) twice daily.
Repeat cycle every 4 weeks.

SYSTEMIC CHEMOTHERAPY REGIMES IN MALIGNANT SEX CHORD STROMAL CELL TUMOR

- **BEP (Bleomycin, etoposide and cisplatin)**

Days 1-5: Cisplatin 20 mg/m^2 IV over 60 minutes,.
Days 1- 5: Etoposide 100 mg/m^2 IV over 60 minutes.
Days 1, 8, 15: bleomycin 30 units IV over 10 minutes.
Repeat cycle every 3 weeks for 3-4 cycles.

- **Paclitaxel and carboplatin**

Day 1: Paclitaxel 175 mg/m^2 IV over 3 hours; Followed by:
Day 1: carboplatin AUC 5 IV over 30 minutes.
Repeat cycle every 3 weeks for 6 cycles.

TARGETED THERAPIES

The area of target therapies is the most recent and promising in treatment of ovarian cancer. They are coming in forefront when chemotherapy toxicity, drug resistance is big hurdles in treatment of ovarian cancer. With recent advances and understanding of the biology of ovarian cancer have led to clinical trials of targeted agents. The angiogenesis inhibitors and polyadenosine diphosphate- ribose polymerase (PARP) inhibitors are the most developed.

Tyrosine kinase inhibitors, which target vascular endothelial growth factor receptors (VEGFR), inhibit an important target in ovarian cancer. In this category, Cediranib is being further evaluated in the phase III randomized trial ICON-6 in conjunction with carboplatin and paclitaxel in the primary setting.

ROLE OF PARP INHIBITORS

In SOLO1 trial PARP inhibitors like Olaparib have shown benefit in maintenance therapy following response to platinum chemotherapy in newly diagnosed advanced BRCA mutated ovarian cancer without the use of Bevacizumab. Recently in PAOLA-1 trial olaparib has been used in the maintenance setting after first line therapy including bevacizumab and there was survival benefit even in those without BRCA mutation. Olaparib monotherapy is found useful in BRCA1 or BRCA2 mutation carriers with recurrent ovarian cancer and three or more lines of therapy, including a 30% response in platinum-resistant tumors, leading to FDA approval for this indication."

Inhibition of the epidermal growth factor receptor (EGFR), which affects cell proliferation, angiogenesis, and apoptosis, has emerged as a possible therapeutic option for patients with ovarian cancer. Agents in this category may inhibit EGFR through tyrosine kinase inhibition (erlotinib, gefitinib, CI-1033) and monoclonal antibodies (trastuzumab, cetuximab).

MALIGNANT GERM CELL TUMORS

Fertility sparing surgery is recommended for those desiring of fertility regardless of stage of the disease. In children and adolescents with early-stage germ cell tumors, comprehensive surgical staging may be omitted. After surgery, 3-4 cycles of chemotherapy (BEP regime) are given.

SYSTEMIC CHEMOTHERAPY REGIMES IN MALIGNANT GERM CELL TUMOUR

- **BEP (Bleomycin, etoposide and cisplatin*)***

Days 1-5: Cisplatin 20 mg/m^2 IV over 60 minutes,
Days 1-5: Etoposide 100 mg/m^2 IV over 60 minutes.
Days 1, 8 and 15: Bleomycin 30 units IV over 10 minutes.
Repeat cycle every 3 weeks for 3-4 cycles.

- **Etoposide and carboplatin lfor patients with stage IB-IM resected dysgerminoma for whom minimizing toxicity is critical*)***

Day 1: Carboplatin 400 mg/m^2 IV over 30 minutes,
Days 1-3: Etoposide 120 mg/m^2 IV over 60 minutes.
Repeat cycle every 4 weeks for 3 cycles.

FOLLOW UP OF OVARIAN CARCINOMA

The patients are followed 2-4 months for 2 years, then 3-6 months for 3 years and then annually after 5 years. In every visit, physical examination and pelvic examination is done. CA125, and other tumor markers are done if they were initially raised. Hemogram and blood chemistry is done. Chest X ray, CT/MRI/PET CT is advised depending on the clinical condition of the patient.

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