Review Article

Ovarian tumor: a review

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ABSTRACT

Ovarian cancers are the 7th most common cancers in women. It is found more commonly in elderly age group. The survival depends on the stage of diagnosis and many of the patients present in advanced disease when the prognosis becomes dismal. The dilemma is to differentiate them from benign disease so that the unwanted laparotomies could be saved. Biomarkers and radiological classification may play a role in differentiating benign from malignant and deciding on the management. There is no screening method to diagnose ovarian cancers and the patient presents with nonspecific complaints missing them in early stages. Optimal cytoreduction is required for better overall survival, progression free survival and response to adjuvant chemotherapy. Those women having history of breast, ovary, endometrial, colorectal cancers should be screened for malignancies and genetic testing is advised. Surgery is the mainstay of treatment followed by chemotherapy. Risk reducing salpingoophorectomy can be offered to women having BRCA1 and BRCA2 mutation carriers after they complete their family. 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 are 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.

Keywords: Ovarian cancers, Neoplasia, PARP

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.[2] 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%.[3] 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.[4]

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[4]

Surface epithelial-stromal tumors

Serous tumors: Benign (cystadenoma), borderline tumors (serous borderline tumor) and malignant (serous adenocarcinoma)

Mucinous tumors, endocervical-like and intestinal type

Benign (cystadenoma), borderline tumors (mucinous borderline tumor), malignant (mucinous adenocarcinoma)

Endometrioid tumors

Benign (cystadenoma), borderline tumors (endometrioid borderline tumor) and malignant (endometrioid adenocarcinoma).

Clear cell tumors

Benign, borderline tumors and malignant (clear cell adenocarcinoma).

Transitional cell tumors

Brenner tumor, brenner tumor of borderline malignancy, malignant Brenner tumor and transitional cell carcinoma (non-Brenner type).

Epithelial-stromal

Adenosarcoma and carcinosarcoma (formerly mixed Müllerian tumors)

Sex cord-stromal tumors

Granulosa tumors: Fibromas, fibrothecomas and thecomas

Sertoli cell tumors: Leydig cell tumors

Sex cord tumor with annular tubules

Gynandroblastoma and steroid (lipid) cell tumors

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.

Malignant, not otherwise specified

Metastatic cancer from non-ovarian primary

Colonic, appendiceal, gastric and breast.

The benign ovarian masses can be divided into neoplastic and nonneoplastic tumors (Table 1).

Table 1: Classification of benign masses of ovary.[5]

Benign masses of ovary	
Non-neoplastic masses	**Neoplastic tumors derived from coelomic epithelium**
Germinal inclusion cyst	Cystic tumors
Pregnancy luteoma	Serous cystoma
Endometrioma	Mucinous cystoma
Theca lutein cyst	Mixed forms
	Fibroma, adenofibroma
	Brenner tumor
	Tumors derived from germ cells
	Dermoid (benign cystic teratoma)

NON-NEOPLASTIC OVARIAN MASSES

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 haemorrhage 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 or septations. A haemorrhagic 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 involve over time, but they do need to be included in the differential diagnosis.

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-sac 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.[5]

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 cystadenomas and cystic teratomas (dermoids). Benign cystadenomas 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.[6]

Serous cystadenoma

Serous cystadenomas 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, frondlike solid projections or nodules or areas of necrosis are seen in malignancy. On microscopic examination, psammoma bodies are characteristic feature of this tumour. Psammoma bodies are calcified granules arising as a result of degeneration of the papillary implants.

Mucinous cystadenoma

Mucinous cystadenomas 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 secretory 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.

Dermoid cyst (Benign cystic teratoma)

These neoplasms are thought to arise from early ova that have been triggered by some type of parthenogenetic 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]

Fibroma

These are benign solid tumour 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]

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 hyperplastic 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 Brenner 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.[9]

MALIGNANT OVARIAN TUMORS

Ovarian neoplasms consist of various histologic subtypes. Epithelial ovarian cancers are the most common subtype and is present in 90% of cases. The incidence of ovarian tumor increases with age 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, intraoperatively and postoperatively. 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.

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 10. 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 is a risk factor.[12] 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 polyembryoma produce a-fetoprotein and b-hCG.[13] Depending on the component present, mixed germ cell tumors may secrete b-hCG, a-fetoprotein. Dysgerminoma is the ovarian counterpart to testicular seminoma.[14] 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.[15]

EVALUATION OF OVARIAN TUMOR

Clinical presentation

Patient with ovarian tumour 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.[17] They can also get detected during routine gynaecological examination.

IMAGING MODALITIES

Pelvic ultrasonography

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 [Grade B].[18] Many tools have been designed to increase the sensitivity and specificity of ultrasonography to recognize malignant ovarian lesion and to avoid unnecessary staging laparotomy.

Transabdominal ultrasound is preferred for lesions extending out of pelvis. Transvaginal 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.[19] 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%.[20]

IOTA SIMPLE RULES AND SIMPLE RULES RISK CALCULATION[21]

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, M1: Irregular solid tumor, M2: Presence of ascites, M3: At least 4 papillary structures, M4: Irregular multilocular solid tumor with largest diameter >100 mm and 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 evaluation

Colour 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 (<1), low resistance index (<0.4), high time-averaged maximum velocity (>15 cm/s) and absence of diastolic notch.[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 significant 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.[23]

Risk of malignancy index (RMI)

It combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U). The RMI is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml). RMI=U×M×CA-125 level, where U=ultrasound score (higher-risk morphology=3, low-risk morphology=1), M=menopausal status (postmenopausal=3, premenopausal=1), and CA-125 level is the actual testing value. If score> 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 are other markers which are raised in germ cell tumors.[25]

The OVA1 test

It is a biomarker panel that measures five proteins (CA-125, β2-microglobulin, apolipoprotein A1, 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 ≥5.0 in premenopausal women and ≥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 recommend 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 operatively.[27]

Colonoscopy and endoscopy

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

Differential diagnosis

other nonovarian 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, nulliparity, 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.[28]

Familial ovarian cancer[29]

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 has maternal or paternal transmission and multiple family members are involved over several generations.

In hereditary breast-ovarian cancer syndrome, there is inherited germline mutation of BRCA1 and BRCA2. In BRCA1 mutations are located on long arm of chromosome 17q and BRCA2 are located on 13q12. There is estimated risk of ovarian cancer of 39% to 46% for carriers of the BRCA1 mutation but a lower rate of 10% to 20% for carriers of the BRCA2 mutation.[30] In Lynch II syndrome, there is inherited mutation in a family of DNA repair genes (MSH2, MLH1, 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.[31]

A 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 tumour 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 tumours (53.3%), followed by mucinous tumours (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).[33]

MANAGEMENT OF OVARIAN TUMOR

Complete evaluation of patient is done after analysing 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, 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 neoadjuvant 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 ascitic 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 hemidiaphragm 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 spatulaa. 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) who 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.[34]

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, IIB, and IIC

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.[34] 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 lesions or tumor tissue is reduced to <1 cm in greatest dimensions. Bulky tumors have large proportion of cells in the resting or G0 phase thus rendering them less sensitive to the chemotherapeutic agent. Cytoreduction produces smaller residual masses with a relatively higher growth fraction and this also reduces total no. of chemotherapy cycles and prevents acquired chemoresistance.

Table 2: Staging classification of ovarian carcinoma using the federation of international gynaecologists and obstetricians (FIGO) nomenclature.[17]

FIGO stage	Description
I	Tumor confined to ovaries or fallopian tube(s)
IA	Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
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
IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
IC1	Surgical spill
IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
IC3	Malignant cells in the ascites or peritoneal washings
II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic intraperitoneal tissues
III	Tumor involves one or both ovaries or fallopian tubes or primary peritoneal cancer with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIA1 (i)	Metastasis ≤10 mm in greatest dimension
IIA1 (ii)	Metastasis >10 mm in greatest dimension
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	Macroscopic peritoneal metastasis beyond the pelvis ≤2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC	Macroscopic peritoneal metastasis beyond the pelvis >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)
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)

Stage III-IV

Interval debulking surgery may be performed after 3-4 cycles of chemotherapy. As with primary debulking surgery, every effort is done to remove all visible metastatic tumors in abdomen, pelvis, retroperitoneum. In three randomized prospective clinical trials, AGO-OVAR 3, 5, and 7 the progression free survival (PFS) and overall survival was significantly improved in stage III and IV disease after optimal cytoreduction.[35] All peritoneal surfaces should be visualized and those suspicious should be biopsied. An omentectomy is performed. All suspicious and/or enlarged lymph nodes to be resected.Procedures that may be required for optimal debulking are bowel resection, appendecectomy, stripping of diaphragm, splenectomy, partial cystectomy, ureteroneosystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy and/or distal pancreatectomy.

Hyperthermic intraperitoneal cisplatin (HIPEC) can be considered during debulking surgery in stage III disease. HIPEC is delivering a cytotoxic drug in a hyperthermic solution at the end of cytoreductive surgery. HIPEC combat the microscopic residual disease remaining after complete cytoreduction, this microscopic disease eventually leads to cancer implant by tumor cell entrapment hypothesis. Cisplatin is the most frequently used drug for HIPEC.[36]

Metastatic tumors (Krukenberg tumor)

These are metastatic tumors of ovary where primary is from extraovarian site most likely gastrointestinal tract. World health organization's diagnostic criteria states that diagnosis is based on presence of stromal involvement, mucin-producing neoplastic Signet ring cells (SRCC) and ovarian stromal sarcomato proliferation.[37] Symptoms are

abdominal swelling and discomfort, weight loss, respiratory distress, chest pain, followed by nausea, vomiting or epigastric pain. The major signs of metastasis are: bilaterality (of 74% has bilateral ovarian cancer and 26% has unilateral tumour); size of the injury (less than 10 cm); surface involvement; extensive intra-abdominal spread and a widespread infiltrative pattern. Management and prognosis depend on primary tumor. therefore, it is essential to identify correctly.

SPECIAL CIRCUMSTANCES

Fertility sparing surgery (preserving uterus and contralateral 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, mucinous or malignant sex chord stromal tumors, low malignant potential) who wish to preserve fertility.[38]

Mucinous 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[17]

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.

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.

Paclitaxel and cisplatin (IV/IP)

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 intraperitoneal (IP) infused as rapidly as possible

via IP portd, 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 II-IV DISEASE[17]

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.

Cisplatin (for hyperthermic intraperitoneal chemotherapy [HIPEC])

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. Repeat cycle every 3 weeks. Or day 1: 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 and 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.[39]

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 and days 1, 8 and 15: Bleomycin 30 units IV over 10 minutes. Repeat cycle every 3 weeks for 3-4 cycles.

Etoposide and carboplatin (for patients with stage IB-III 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.[40]

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