OVARIAN TUMORS

Ovarian cancer is the ninth most common cancer in women, and the fifth leading cause of female cancer death. Detection of ovarian cancer while it is in its early stages significantly improves prognosis. Unfortunately, most cases of ovarian cancer are discovered when the cancer is already advanced **(ACOG, 2011).**

The overall global mortality attributed to ovarian cancer exceeds that of any other gynecological cancer with over 50% of the more than 200,000 women newly diagnosed each year expected to perish from the disease **(Altekruse et al., 2010).**

Risk factors

Most of the risk factors for ovarian cancer are hormonal in nature. Nulliparity is a risk factor for ovarian cancer, likely because ovulation is not suppressed due to pregnancy. Both obesity and hormone replacement therapy raise the risk for ovarian cancer **(Seiden and Michael, 2012).**

1-Age

Malignant neoplasm of the ovaries occur at all ages, including infancy and childhood **(VanNagell, 2003; Jacobs and Omram, 2001)**.However, the strongest patient-related risk factor for ovarian cancer is increasing age **(Change and Risch, 1997).** Malignant germ cell tumors are most commonly seen in females younger than 20years, whereas epithelial-cancer of the ovary is an age related disease. The mean age at diagnosis of epithelial ovarian cancer is 53years and that of border line tumors is 45 years. However, may be diagnosed 10 years earlier in women with family history of ovarian and breast cancer **(Whittemore, 1992; Jemal et al., 2008).**

2-Genetics

The major genetic risk factor for ovarian cancer is a mutation in BRCA1 or BRCA2, DNA mismatch repair genes. This occurs in 10% of ovarian cancer cases. Only mutation in one allele is needed to be at high risk for ovarian cancer, because the risk is autosomal dominant. The gene can be inherited through either the maternal or paternal line. Though mutations in these genes are usually associated with increased risk of breast cancer, they also carry a 30-50% lifetime risk of ovarian cancer, a risk that peaks in a woman's 40s-50s. This risk is also cited as 40-60% for BRCA1 mutations **(Jayson et al., 2014).** Mutations in BRCA2 are less risky than those with BRCA1, with a lifetime risk of 20-40% **(Seiden and Michael, 2012).**

A strong family history of endometrial cancer, non polyposis colonic cancer, or other gastrointestinal cancers may indicate the presence of a syndrome known as hereditary non polyposis colorectal cancer (HNPCC, also known as Lynch syndrome), which confers a higher risk for developing ovarian cancer, among many other types of cancer. Lynch syndrome is caused

by mutations in mismatch repair genes, including MSH2, MLH1, MLH6, PMS1, and PMS2 **(Seiden and Michael, 2012).**

Three distinct hereditary patterns have been identified

a. The site specific familial ovarian cancer syndrome, in which only ovarian cancer is seen, accounts for 10-15% of hereditary ovarian cancers.

b. The hereditary breast/ovarian cancer syndrome is associated with 65-75% of hereditary ovarian cancer. Women with this syndrome have an increased incidence of breast and ovarian carcinomas alone or in combination.

c. Hereditary non polyposis colo- rectal cancer syndrome (HNPCC). The affected individuals may have colonic, endometrial, breast, ovarian, or other cancers. Members of HNPCC account for an additional 10-15% of hereditary ovarian cancer.

All the three syndromes have a pattern of early onset cancer and vertical transmission and hence 50% risk can be predicted in the off springs and siblings of affected individuals **(Jacobs, 1994; Carlson et al., 1994**).

3- Ethnicity

The incidence of ovarian cancer is higher among white women than African-American women in the USA. Overall rates of ovarian cancer are higher in North America than in Japan. These differences may be related to genetics, diet, or environmental exposure, or a combination of these potential influences **(Gohagan et al., 1995).**

4-Reproductive factors

Women who are nulliparous, who have their child birth after age 35 or who have late menopause and early menarche have an increased risk of epithelial ovarian cancer. Nulligravidae are 2.45 times more likely to develop ovarian tumors than those women who have been pregnant three or more times **(Pardie et al., 2004).**

One possible explanation could be that the endocrinological status of pregnancy protects against ovarian cancer and the underlying hormonal imbalance in infertile women put them at higher risk for ovarian cancer **(Beral et al., 1999).**

A second view suggests that the repeated ovulatory activity is a factor in malignant transformation of the ovarian surface epithelium, since ovulation cause minor trauma to this epithelium, which can act as a promoting factor in the carcinogenic process, this referred as theory of "incessant ovulation" **(Risch et al.,2006).**

Decreased risk of epithelial ovarian cancer is associated with breast feeding due to inhibition of ovulation **(Beral et al., 1999).**

5- Hormones

Hormonal conditions such as polycystic ovary syndrome and endometriosis are associated with ovarian cancer, but the link is not completely confirmed **(Jayson et al., 2014).**

a. Oral contraceptives

The use of oral contraceptives has been associated with a decreased risk of epithelial ovarian cancer, particularly among long term users **(Goff et al., 2007).**

In multiple case-control studies, the protective effect persists for some years following discontinuation of the pill use. The relative risk of ovarian cancer is approximately 0.5 among women with 5 or more years use, compared with women who never used pills **(Seiden, 2000).**

b. Fertility drugs

Two different studies suggested that the prolonged use of fertility drugs as clomiphene citrate may increase the risk of borderline and invasive ovarian neoplasm however this information has limited application in programs of selected screening studies **(Pardie et al., 2004; Risch et al., 2006; Jayson et al., 2014).**

c. Hormonal replacement therapy

No increased risk of ovarian cancer has been observed among postmenopausal women who use hormonal replacement therapy **(Pardie et al., 2004).**

6- Chemical carcinogens

It has been suggested that ovarian cancer may be initiated by chemical carcinogens via the vagina, uterus and fallopian tubes. There is a clinical evidence of the migration of chemical substances from the vagina to the peritoneal cavity and ovaries. A significantly higher incidence of epithelial cancer is demonstrated in patients who regularly use talc either as dusting powder on the perineum or on sanitary napkins. Talc powder placed on the perineum may gain access to the ovary by ascending through the genital tract, acting as co-carcinogen **(Change and Risch, 1997; Cramer et al., 1999).**

A number of studies have reported an increased mortality from ovarian cancer among women who experienced occupational exposure to amphibole forms of asbestos. Associations were also found between alcohol consumption and cancers of the ovary **(Wong et al., 1999).**

7- Dietary factors

The major dietary differences between industrialized and non-industrialized nations primarily involve the intake of meat and animal fats and explain the increased age-adjusted annual ovarian cancer among industrialized countries. A significant dose response relationship between the intake of fat from animal sources and risk of developing ovarian cancer has been reported. Also increased the risk with saturated fat and decrease with vegetables fiber consumption has been reported. Studies of dietary factors have been inconclusive **(Goff et al., 2007).**

8- Viruses

No epidemiologic or experimental evidence exists to incriminate viruses in the development human ovarian cancer. Mumps virus because of its gonadotropic properties is an obvious candidate among known viruses for oncogenic activity in the ovary. Ovarian cancer patients tend to have lower persistent mumps complement-fixing antibody titers and it has been indicated that immunologic incompetence enables development of ovarian cancer, possibly through a direct etiologic role of mumps virus. At present however, the evidence for mumps as an etiologic agent in ovarian cancer remains speculative **(West, 2005).**

Protective factors

Suppression of ovulation, which damages the ovarian epithelium, and its associated inflammation, is generally protective. Multiparty, taking oral contraceptives, and breast-feeding, all of which are protective factors. Tubal ligation is protective because carcinogens are unable to reach the ovary and fimbriae via the vagina, uterus, and fallopian tubes **(Seiden and Michael,**

2012). Hysterectomy with (bilateral salpingo-oophorectomy) dramatically reduces the risk of not only ovarian cancer but breast cancer also **(Jayson et al., 2014).**

Pathology

Ovarian cancers are classified according to the microscopic appearance of their structures (histology or histopathology). Histology dictates many aspects of clinical treatment, management, and prognosis **(Hoffman et al., 2012; Kosary and Carol, 2007).**

Ovarian carcinomas are heterogeneous and are primarily classified by cell type into serous, mucinous, endometrioid, clear cell, and Brenner (transitional) tumors corresponding to different types of epithelia in the organs of the female reproductive tract **(Seidman et al., 2002).**

The tumors in each of the categories are further subdivided into three groups: benign, malignant and intermediate (borderline tumor or low-malignant-potential) based on their clinical behavior **(Scully, 1999).**

Table (1): WHO histological classification of ovarian tumors (Scully, 1999).

1) epithelial ovarian tumors

I. Serous tumors

A. Benign (cystadenoma)
B. Borderline tumors (serous borderline tumor)
C. Malignant (serous adenocarcinoma)

***II. Mucinous tumours*, endocervical-like and intestinal type:**

A. Benign (cystadenoma)
B. Borderline tumors (mucinous borderline tumor)
C. Malignant (mucinous adenocarcinoma)

III. Endometrioid tumours

A. Benign (cystadenoma)
B. Borderline tumors (endometrioid borderline tumor)
C. Malignant (endometrioid adenocarcinoma)

IV. Clear-cell tumours

A. Benign
B. Borderline
C. Malignant (clear cell adenocarcinoma)

V. Transitional cell tumors

A. Brenner tumor
B. Brenner tumor of borderline malignancy
C. Malignant Brenner tumor
D. Transitional cell carcinoma (non-Brenner type)

VI. Squamous cell carcinomas

VII. Undifferentiated carcinoma

2)Sex cord-stromal tumor

I. Granulosa tumors (adult and juvenile)

II. Tumors in the thecoma-fibroma group

A. Fibromas
B. Fibrothecomas
C. Thecomas
D. Sclerosing stromal tumor

III. Virilizing Sertoli-Leydig cell tumor

A. Sertoli cell tumors **B.** Sertoli-leydig cell tumors

IV. Sex cord tumor with annular tubules

V. Gynandroblastoma

VI. Steroid (lipid) cell tumors

A. stromal luteoma
B. leydig cell tumor
C. steroid cell tumor, not otherwise specified

3)Germ cell tumor

I. Teratoma:

A. Immature **B.** Mature

II. Monodermal (e.g., struma ovarii, carcinoid)

III. Dysgerminoma

IV. Yolk sac tumor (endodermal sinus tumor)

V. Embryonal carcinoma

VI. Polyembryoma

VII. Nongestational choriocarcinoma

VIII. Mixed germ cell tumors

4) Malignant, not otherwise specified

- ***Metastatic cancer from non ovarian primary:***

A. Colonic, appendiceal
B. Gastric
C. Breast

- **Epithelial carcinoma**

Surface epithelial-stromal tumor, also known as ovarian epithelial carcinoma, is the most common type of ovarian cancer. It includes serous tumor, endometrioid tumor, and mucinous cystadenocarcinoma. Less common tumors are malignant Brenner tumor.

1. Low-grade serous carcinoma(type 1)

Low-grade serous carcinoma is less aggressive than high-grade serous carcinomas, though it does not typically respond well to chemotherapy or hormonal treatment **(Jayson et al., 2014).**

2. High-grade serous carcinoma(type 2)

Most people with epithelial ovarian carcinoma have a high-grade serous carcinoma **(Jayson et al., 2014).**

3. Mucinous carcinomas (MCs)

Mucinous tumors account for 10%–15% of all primary ovarian tumors; however 80% are benign and most of the remainder is borderline tumors. If metastases to the ovary, particularly from the gastrointestinal tract, are carefully excluded, only 3%–4% of ovarian carcinomas are of mucinous type. The cells of MCs may resemble those of the gastric pylorus, intestine, or endocervix **(Prat, 2004; Lee et al., 2003).**

Nevertheless, the vast majority of these tumors show gastrointestinal differentiation. The origin of these tumors is unknown. Large size (>13 cm) and unilaterality are features suggestive of a primary MC, while metastases are typically smaller and bilateral. Primary MCs of the ovary are usually

confined to the ovary, without ovarian surface involvement or pseudomyxoma peritonei **(Lee et al., 2003).**

4. Endometrioid carcinomas (ECs)

Endometrioid tumors of the ovary closely mimic their uterine counterparts. ECs account for 10% of all ovarian carcinomas, occur most frequently in women of perimenopausal age, and most are found at an early stage **(Prat, 2004).**

The ovarian tumors are bilateral in 28% of cases and are associated in 15%–20% of cases with carcinoma of the endometrium **(Lee et al., 2003; Irving et al., 2005).**

Most ECs are low-grade adenocarcinomas and seem to arise from endometriotic cysts. Up to 42% of cases have evidence of ipsilateral ovarian or pelvic endometriosis **(Prat, 2004; Lee et al., 2003).** Squamous differentiation occurs in 50% of cases **(Prat, 2004).**

5. Clear-cell carcinoma

Typically, they are cystic neoplasm with polypoid masses that protrude into the cyst. On microscopic pathological examination, they are composed of cells with clear cytoplasm (that contains glycogen) and hob nail cells (from which the glycogen has been secreted). The pattern may be glandular, papillary or solid.

Benign and borderline variants of this neoplasm are rare, and most cases are malignant. These tumors may have a worse prognosis than serous tumors **(Chan et al., 2008).**

Clear-cell ovarian carcinomas do not typically respond well to chemotherapy and may be related to endometriosis **(Jayson et al., 2014).**

6. Transitional cell (Brenner) tumors

Transitional cell tumors are epithelial ovarian tumors formed by cells that resemble those of the internal lining of the urinary bladder (the transitional epithelium or urothelium). These tumors presumably are derived from surface ovarian epithelium that undergoes urothelium like transformation (e.g., urothelial metaplasia, Walthard nests). They may occur in association with similar tumors in the urinary bladder. Transitional cell tumors rarely occur and are often reported within the category of other specified epithelial-stromal tumors. Most benign transitional cell ovarian tumors are very small, asymptomatic, incidentally discovered, and clinically irrelevant. They are solid and nodular, and most are unilateral. Benign transitional cell ovarian tumors often arise in association with endocervical-type mucinous and serous tumors, and they most frequently occur between the fifth and sixth decades of life **(Scully, 1999; Scully et al., 1998; Kurman , 1994).**

- **Sex cord stromal tumor**

Sex cord-stromal tumor, including estrogen-producing granulosa cell tumor, the benign thecoma and virilizing Sertoli-Leydig cell tumor or arrhenoblastoma, accounts for 8% of ovarian cancers **(Seiden and Michael, 2012).**

- **Germ cell tumor**

Germ cell tumor accounts for approximately 30% of ovarian tumors but only 5% of ovarian cancers; because most germ cell tumors are teratomas and

most teratomas are benign. Germ cell tumors tend to occur in young women (20's-30) and girls. Whilst overall the prognosis of germ cell tumors tends to be favorable, it can vary substantially with specific histology: for instance, the prognosis of the most common germ cell tumor (dysgerminomas) tends to be good, whilst the second most common (endodermal sinus tumor) tends to have a poor prognosis. In addition, the cancer markers used vary with tumor type: choriocarcinomas are monitored with beta-HCG; dysgerminomas with LDH; and endodermal sinus tumors with alpha-fetoprotein **(Seiden and Michael, 2012).**

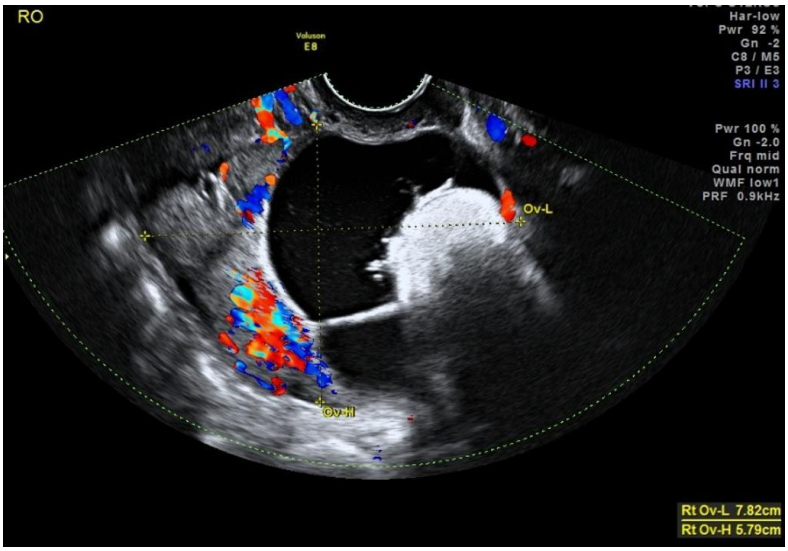

Figure (1): Ultrasound picture of dermoid cyst showing the "tip of the iceberg" sign **(Beller, 1998).**

- **<u>Other Carcinomas</u>**

They are mixed tumors containing elements of more than one of the above classes of tumor histology.

- **Secondary ovarian cancer**

7% of ovarian cancers are due to metastases while the rest are primary cancers. Common primary sites are breast cancer, colon cancer, appendiceal cancer, and stomach cancer **(Seiden and Michael, 2012).**

Krukenberg tumor is one of the secondary ovarian carcinoma that metastasizes from gastro-intestinal tract malignancy, or- to a lesser extent- from other primary as breast cancer. Surface epithelial-stromal tumor can originate in the peritoneum, in which case the ovarian cancer is secondary to primary peritoneal cancer, but treatment is basically the same as for primary surface epithelial-stromal tumor involving the peritoneum **(Seiden and Michael, 2012).**

Staging:

The stage of a cancer is a term used to describe its size and whether it's spread beyond its original area of the body. It’s often not possible to tell exactly what the stage of an ovarian cancer is until an operation has been done to remove it.

Suspected or confirmed ovarian cancer is staged surgically. Based upon the findings during exploratory surgery, the tumor is formally "staged" according to the size, extent, and location of the cancer. Accurate staging during surgery is very important in determining a woman's long-term outcome (prognosis) and choosing the appropriate treatment regimen after surgery **(Jayson, 2014).**

Microscopic examination is critical for predicting tumor behavior and deciding the best therapeutic approach. Such examination includes the

assessment of specific histological type and extent of disease and the grading of tumor differentiation **(Fleming et al., 1997).**

Table (2): The FIGO stages (2014) are as follows (Jayson, 2014; Society for Gynecologic Oncology, 2014).

Description				Stage
Cancer is completely limited to the ovary				I
involves one ovary, capsule intact, no tumor on ovarian surface, negative washings			IA	
involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings			IB	
Tumor involves one or both ovaries			IC	
surgical spill			IC1	
capsule has ruptured or tumor on ovarian surface			IC2	
positive ascites or washings			IC3	
Pelvic extension of the tumor (must be confined to the pelvis) or primary peritoneal tumor, involves one or both ovaries				II
Tumor found on uterus or fallopian tubes			IIA	
Tumor elsewhere in the pelvis			IIB	
cancer found outside the pelvis or in the retroperitoneal lymph nodes, involves one or both ovaries				III
metastasis in retroperitoneal lymph nodes or microscopic extra pelvic metastasis			IIIA	
metastasis in retroperitoneal lymph nodes		IIIA1		
the metastasis is less than 10 mm in diameter	IIIA1(i)			
the metastasis is greater than 10 mm in diameter	IIIA1(ii)			
microscopic metastasis in the peritoneum, regardless of retroperitoneal lymph node status		IIIA2		
metastasis in the peritoneum less than or equal to 2 cm in diameter, regardless of retroperitoneal lymph node status; or metastasis to liver or spleen capsule			IIIB	
metastasis in the peritoneum greater than 2 cm in diameter, regardless of retroperitoneal lymph node status; or metastasis to liver or spleen capsule			IIIC	
distant metastasis (i.e. outside of the peritoneum)				IV
pleural effusion containing cancer cells			IVA	
metastasis to distant organs (including the parenchyma of the spleen or liver), or metastasis to the inguinal and extra-abdominal lymph nodes			IVB	

Origin of adnexal masses

- The Ovaries
- GIT structures:
  - Crohn's disease
  - Diverticulitis
  - GIT neoplasm
- Pelvic kidney
- PID with tubo-ovarian abscess
- Ectopic pregnancy
- Fallopian tubes; as pyosalpinx and hydrosalpinx.
- Other pelvic structures **(Canis et al., 2000).**

Clinical features helpful in evaluation of adnexal masses:

Adnexal masses are common clinical findings involving the reproductive organs or non-gynecologic structures. Although most adnexal masses are acquired lesions, a few arise as congenital anomalies.

They may be identified in asymptomatic women during routine pelvic examination or may cause symptoms. Typical complaints include pain, pressure sensations, dysmenorrhea, or abnormal uterine bleeding **(Goff et al., 2004).**

Epidemiologic factors associated with ovarian cancer include nulliparity, a personal history of breast cancer, the number of affected first degree relative(s) with ovarian or breast cancer, a family history of a BRCA mutation, or membership within a recognized inherited malignancy syndrome. Approximately 5% of all epithelial ovarian carcinomas are attributable to the inheritance of highly penetrant mutations in the breast/ovarian cancer susceptibility genes BRCA-1 and -2 **(Seiden and Michael, 2012).**

Signs and symptoms

Signs and symptoms of ovarian cancer are frequently absent in early stages and when they exist they may be subtle. In most cases, the symptoms persist for several months before being recognized and diagnosed, or they may be misdiagnosed as a condition like irritable bowel syndrome **(Jayson, 2014).**

Most typical symptoms include bloating, abdominal or pelvic pain or discomfort, difficulty eating, indigestion, heartburn, nausea, early satiety, and possibly urinary symptoms. If these symptoms start to occur more than 12 times per month after no history of such symptoms, the diagnosis should be considered **(Seiden and Michael, 2012; Goff, 2012).**

These symptoms are caused by a mass pressing on the other abdomino-pelvic organs or from metastases **(Seiden and Michael, 2012**).

Clinical examination

Ovarian cancer is considered one of the hardest to diagnose diseases in gynecological pathology, often being referred as the silent killer. This "name" was attributed because of the lack of precursor lesions and a specific set of symptoms, the disease being diagnosed in most cases during a routine examination and even then in a late stage. The medical history is very important, and should be carefully not excluded. Family history is in most cases very meaningful of ovarian or breast cancer.

Diagnosis of ovarian cancer starts with physical examination (including abdominal& pelvic examination).Physical examination may reveal increased abdominal girth and/or ascites. Pelvic or pelvi-abdominal mass may be also felt **(Seiden and Michael, 2012**).

Clinical criteria stated by **Cohen et al., 2001** for diagnosis of ovarian masses include:

- Premenopausal women (<50 years):
  - Family history of breast or ovarian cancer (in a first-degree relative).
  - Evidence of abdominal or distant metastases (by examination or imaging study).
  - Ascites
  - CA125 >200 U/ml.
- Postmenopausal women (>50 years):
  - Family history of breast or ovarian cancer (in a first degree relative).
  - Evidence of abdominal or distance metastasis (by examination or imaging study).
  - Nodular or fixed pelvic mass.
  - Ascites
  - CA125 >25 U/ml.

Laboratory investigations

When an ovarian malignancy is included in the list of diagnostic possibilities, a limited number of laboratory tests are indicated. A complete blood count (CBC) and serum electrolyte test should be obtained in all patients **(Miller and Ueland, 2012).**

A CA-125 test is useful in differential diagnosis and in follow up of the disease, but it by itself has not been shown to be an effective method to screen for early-stage ovarian cancer due to its unacceptable low sensitivity and specificity.

Measurement of serum CA 125 is routinely used to aid diagnosis. However, its utility to detect early disease is questionable as it is elevated

only in about 50% of patients with the International Federation of Gynecology and Obstetrics (FIGO) stage I disease. In advanced disease, CA 125 is elevated in about 85% of patients. It is not specific for ovarian cancer and raised CA 125 levels may be found in non-gynecological malignancies (e.g. breast, lung, colon and pancreatic cancer) and benign disease (e.g. endometriosis, pelvic inflammatory disease and ovarian cysts) **(Miller and Ueland, 2012).**

Serum carcinoembryonic antigen (CEA) and CA 19–9 levels are sometimes measured in situations where it is unclear whether an ovarian mass is of gastrointestinal origin, or a primary mucinous ovarian tumor. Similarly, in these situations, colonoscopy and/or gastro copy are sometimes considered, particularly when CA 125/CEA ratio is ≤25 **(Lerner et al., 1994).**

Ovarian cancer at its early stages (I/II) is difficult to diagnose until it spreads and advances to later stages (III/IV). This is because most symptoms are non-specific and thus of little use in diagnosis **(Rossing et al., 2010).**

The serum β HCG level should be measured in any female in whom pregnancy is a possibility. In addition, serum alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) should be measured in young girls and adolescents with suspected ovarian tumors because the younger the patient, the greater the likelihood of a malignant germ cell tumor **(Seiden and Michael, 2012; Nossov et al., 2008)**.

Several preliminary studies examining multiple novel biomarkers in addition to CA125 have led to initial enthusiasm. These include the OvaSure serum test, which includes examination of leptin, prolactin, osteopontin, insulin-like growth factor-II, macrophage inhibitory factor, and CA125, as well as the OvaCheck test, which involves proteomic profile analysis of

serum proteins. Unfortunately, the lack of validation studies has precluded their effectiveness as screening tests for ovarian cancer in otherwise asymptomatic women **(Visintin et al., 2008; Mor et al., 2005; Petricoin et al., 2002).**

In addition, recent studies using proteomics-based methods have shown that Haptoglobin levels were elevated in the sera of patients with ovarian cancer. The evaluation of Haptoglobin on survival rates and the outcome of patients with ovarian cancer have not been examined as yet. Haptoglobin levels could provide a useful measure in the prognostic evaluation of ovarian cancer **(Society of Gynecologic Oncology, 2014; Smith et al., 2012).**

The Roles of Imaging in Ovarian Cancer

Imaging is an integral part of ovarian cancer detection, diagnosis, management, and treatment follow-up.

Briefly, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are established imaging modalities in the evaluation of ovarian cancer, and positron emission tomography (PET) is an emerging modality.

1-Ultrasonography and Doppler studies:

Transvaginal ultrasound has consistently been the most promising imaging modality for routine screening for ovarian cancer among the imaging modalities that have been tested **(Rieber et al., 2001).**

Ultrasonography is the most common imaging test to evaluate adnexal masses **(Cotran et al., 2010).**

Trans-abdominal examinations require a full urinary bladder as an acoustic window for optimal visualization of the adnexae. In contradistinction, a transvaginal examination does not have this requirement but may not be as useful for the assessment of large adnexal masses **(Baak et al., 2005; Cotran et al., 2010).**

The addition of color flow Doppler study which evaluates the vascular patterns of adnexal masses, might improve the sensitivity and specificity of the ultrasonic diagnosis of benign and malignant lesions **(Kurjak et al., 2010; Ahmed et al., 2005).**

The appearance of any ovarian mass by ultrasound can be described in terms of the following:

1. Size or volume of lesion.
2. Locules and septa.
3. Papillary projection.
4. Cyst wall thickness and septal thickness.
5. Echogenicity of the lesion.
6. Echo-dense foci and acoustic shadowing.
7. Finally the presence or absence of ascites.

The presence of hydronephrosis, intra hepatic lesions, or other intra abdominal masses is clearly relevant.

The goals are to differentiate benign and malignant disease and to discriminate between epithelial ovarian carcinoma and other primary or secondary ovarian malignant tumors **(Silverberg, 2005; Baak et al., 2005).**

The features suggestive of ovarian malignancy on ultrasound include septations greater than 3 mm, mural nodularity, and papillary projections, ascites or bilateral adnexal masses.

Unilocular or multilocular ovarian cystic lesions without solid parts are more likely to be benign **(Valentin, 1997; Mironov et al., 2007).**

In other words, the most significant feature predictive of ovarian malignancy is the presence of solid components within the mass **(Brown et al., 1998).**

Ultrasound and Doppler waves remain the main diagnostic tools for diagnosis of various adnexal masses. Several scoring systems and mathematical models using ultrasound variables have been developed for the preoperative prediction of probability of malignancy **(Aslam et al., 2000).**

2- Computed Tomography (CT) of abdomen and pelvis:

CT scanning is preferred to assess the extent of the tumor in the abdominopelvic cavity, The advent of multislice CT, which allows faster acquisition times and higher spatial resolution, has led to a great increase in the number of CT examinations performed.

Although CT has been shown to be the modality of choice in staging and preoperative planning for ovarian cancer, it is generally not considered helpful for primary characterization of adnexal masses **(Tempany et al., 2000; Byrom et al., 2002).**

CT is one of the most important tools used in evaluation of the pathology of the lower abdomen and the pelvis. Optimal bowel opacification is essential for the detection and staging of gynecologic diseases on CT. Also optimal vascular enhancement can be achieved by administering 120 to 150 mL of

iodinated contrast material via the peripheral vein **(Urban and Fishman, 1995).**

Ovarian cancer is usually in an advanced stage at diagnosis due to the presence of peritoneal carcinomatosis, which develops as a result of peritoneal fluid circulation. Tumor implants of varying size can occur anywhere from the diaphragm to the pelvis. Computed tomography (CT) can be used to detect these metastatic lesions, which can be miliary or large and appear as soft-tissue or low-attenuation masses. Recent advances in CT technology have increased the flexibility of image acquisition, thereby allowing the use of thin sections and multiplanar reformatting (**Pannu et al., 2003).**

With multidetector CT, thin-section images of the abdomen and pelvis can be obtained to assess for sub centimeter implants and to create three-dimensional images with reduced artifact. Multiplanar reformatting can be used to confirm the presence of implants. Structures such as the diaphragm, paracolic gutters, bowel, and cul-de-sac can be evaluated in multiple planes for surface nodularity and small implants (**Pannu et al., 2003).**

3- Positron Emission Tomography, PET-CT:

It is a new imaging modality, helpful in the diagnosis of recurrent ovarian cancer which can be difficult on cross-sectional imaging; variable sensitivities and specificities have been reported for positron emission tomography (PET). Positron is injected intravenous to have a high affinity to rapidly dividing cells then detected radiological. Combined functional and anatomic imaging with PET plus computed tomography (CT) potentially allows for improved detection of tumor masses. A trial involving a larger

number of patients with a spectrum of disease volumes is necessary to determine the impact of PET-CT in clinical practice **(Kim et al., 2009).**

4- Magnetic resonance imaging (MRI) of abdomen and pelvis:

When an adnexal mass is detected on CT, it is common practice not to characterize the mass based on its appearance on CT, but to refer patients to ultrasound or MRI for further characterization of the mass and management guidance.

MRI is considered a problem-solving technique in the assessment of adnexal masses **(Rieber et al., 2001).**

Owing to multiplanar capability and excellent tissue contrast, MRI imaging is one of the preferred imaging modalities of the female pelvis in many instances, particularly for the staging of malignant gynecologic diseases **(Walsh, 1992).**

MRI is non invasive, and imaging of pelvis is practically advantageous due to the natural contrast of the pelvic fat, bowel gas, and urine in urinary bladder. A major advantage of MRI is its multiplanner capability**.** Multiplanner of the pelvis is especially useful in evaluation of the base and dome of bladder, uterus, and rectum despite their close proximity. MRI causes no known harmful effects on the fetus, embryo, on reproductive organs, and is apparently safe in pregnancy **(Outwater and Schiebler, 1994).**

MRI differentiates vessels from solid structures without the use of intravenous contrast since moving blood in general produces no signal (signal void) **(Hricak et al., 2000).**

Although that, MRI is expensive, and has limited availability compared to ultrasonograghy. Also it dose not visualize adhesions, and can not always

distinguish between malignant and inflammatory changes, which decrease specificity. In addition, a long scanning time is usually required **(Hricak et al., 2000).**

Gadolinium-enhanced MRI further improves characterization of the internal architecture of ovarian lesions and has been shown to be more accurate than ultrasound in the assessment of adnexal masses.

Gadolinium-enhanced MRI has been shown to have sensitivity, specificity, and accuracy up to 100%, 98%, and 99%, respectively, in the identification of solid components within an adnexal mass, and just as on ultrasound the presence of enhancing solid tissue on MRI is highly sensitive and specific in predicting malignancy **(Kurtz et al., 1999).**

Cytological and pathological investigations:

➢ U/S guided aspiration:

Fluid collections in the pelvic cavity can be aspirated by using a fine needle if the collected fluid is uncomplicated and small in amount. To perform transvaginal aspiration, the vaginal vault and cervix are prepared with povidone-iodine. An endovaginal US transducer, with a sterile rubber sheath and a needle guide; is applied firmly against the vaginal fornix. A sharp thrust of the needle can help traverse the elastic vaginal tissue.

When multiple fluid collections are identified, each locule should be aspirated. It is recommended that aspirates from all collections should be obtained through separate sterile procedures to ensure optimal antimicrobial coverage and avoid cross-contamination **(Heneghan et al., 1999).**

The problems of US-guided aspiration of ovarian cysts are high recurrence rate, potential risk for seeding malignant cells along the needle track, and the risk of sampling error that could delay diagnosis of an occult malignancy. Therefore, only ovarian cysts with clearly benign US appearance should be managed with this technique **(caspi et al., 1996).**

➢ Percutaneous Catheter Drainage:

PCD is a well-accepted technique for draining abdominal and pelvic fluid collections such as abscesses, hematomas, lymphoceles, and peritoneal pseudocysts. Infected tumors also can be drained percutaneously to relieve debilitating symptoms. Basic techniques of puncture, guide wire insertion, tract dilation, and catheter placement are identical to those used in other parts of the body. Puncture for transvaginal or transrectal PCD is done under the guidance of endoluminal US **(Laopaiboon et al., 2010).**

➢ U/S guided biopsy:

Biopsy of the masses in the female pelvis can be performed by using various types of the needles and biopsy guns. Biopsy guns are preferred for solid pelvic masses, whereas fine needle aspiration biopsy is commonly used for cystic masses. Injury to the bladder, intestine, or vessels can be avoided by US monitoring during the biopsy **(O'Neill et al., 2001).**

Exploratory laparotomy:

Pelvic mass represents a number of different benign and malignant conditions. The traditional strategy for establishing a final diagnosis was to perform an exploratory laparotomy. Many unfortunate women with advanced ovarian cancer undergo suboptimal primary surgery at local hospitals. The

suboptimal intervention affects prognosis and increases patient morbidity and mortality **(Obeidat et al., 2004).**

Risk scoring

A widely recognized method of estimating the risk of malignant ovarian cancer based on initial workup is the risk of malignancy index (RMI) **(NICE clinical Guideline, 2011)** generally, a RMI score of over 200 is considered to indicate high risk for ovarian cancer **(Jayson, 2014).**

The RMI is calculated as follows:

RMI = ultrasound score x menopausal score x CA-125 level in U/ml **(Jayson, 2014).**

There are two methods to determine the ultrasound score and menopausal score, with the resultant RMI being called RMI 1 and RMI 2, respectively, depending on what method is used as shown in table (3) **(Nossov et al., 2008; Sasaroli et al., 2009).**

Table (3): The risk of malignancy index (RMI): RMI 1 and RMI 2, respectively, depending on what method used.

RMI 2	RMI 1	Feature
• 0 = none. • 1 = one abnormality. • 4 = two or more abnormalities.	• 0 = no abnormality. • 1 = one abnormality. • 3= two or more abnormalities.	Ultrasound abnormalities: including: • Multilocular cyst. • Solid areas. • Ascites. • Intra-abdominal metastases.
• 1 = premenopausal. • 4 = postmenopausal.	• 1 = premenopausal. • 3 = postmenopausal.	Menopausal score.
Quantity in U/ml	Quantity in U/ml	CA-125

IOTA Criteria: (The International Ovarian Tumor Analysis)

The IOTA Group has published the largest study to date investigating the use of ultrasound in differentiating benign and malignant ovarian masses. Using data derived from the IOTA Group, simple ultrasound rules were developed to help classify masses as benign (B-rules) or malignant (M-rules). Using these rules the reported sensitivity was 95%, specificity 91%, positive likelihood ratio of 10.37 and negative likelihood ratio of 0.06. Women with an ovarian mass with any of the M-rules ultrasound findings should be referred to a gynecological oncological service **(Timmerman et al., 2005).**

The IOTA Simple Rules for Identifying a Benign or Malignant Tumor

Rules for predicting a malignant tumor (M-rules)

- M1 Irregular solid tumor
- M2 Presence of ascites
- M3 At least four papillary structures
- M4 Irregular multilocular solid tumor with largest diameter ≥100 mm
- M5 Very strong blood flow (color score 4)

Rules for predicting a benign tumor (B-rules)

- B1 Unilocular
- B2 Presence of solid components with the largest diameter <7mm
- B3 Presence of acoustic shadows
- B4 Smooth multilocular tumor with largest diameter<100 mm
- B5 No blood flow (color score 1)

Screening

Screening for any type of cancer must be accurate and reliable—it needs to accurately detect the disease and it must not give false positive results in people who do not have cancer.

The purpose of screening is to diagnose ovarian cancer at an early stage, when it is more likely to be treated successfully **(Seiden and Michael, 2012; Croswell et al., 2012).**

Ovarian cancer screening is of high clinical interest because the disease is not typically detectable at its early stages, when it is the most curable.

Women with mutations in the BRCA genes who wish to preserve their fertility may choose annual pelvic ultrasound screening to detect ovarian cancer, instead of having a prophylactic salpingo-oophorectomy and hysterectomy **(Hoffman et al., 2012).**

Screening is the application of a test to detect a potential cancer when no signs or symptoms of the cancer are present **(Clark, 2003).**

Ideally, the cancer is detected before it is clinically apparent, when treatment may be more effective, less expensive, or both.

If a screening test result is abnormal, a diagnostic test should be ordered and treatment pursued if cancer is discovered.

The value of a screening test is compromised if symptomatic individuals are included in the target population, since those with symptoms may already have advanced disease that warrants a diagnostic evaluation.

The gold standard for screening is the ability to decrease mortality from cancer.

Therefore, the goal of ovarian cancer screening is to reduce mortality by detecting the cancer in earlier stages, when survival rates are improved **(Clark, 2003; Chu and Rubin, 2006).**

The ideal outcome is for the cancer to be detected early enough to be cured.

For ovarian cancer, the first and last principles apply: the disease incurs a high mortality rate, and effective treatment for early stage disease exists.

However, the challenges of ovarian cancer screening lie in the remaining principles: knowledge of the natural history and biology is evolving, the disease incidence is low in the general population, and the preclinical phase can be estimated but is not definitively known **(Jacobs et al., 1992; Mok et al., 1992; Shridhar et al., 2001).**

Investigators have also shown that up to 1.9 years may exist between the development of ovarian cancer and its clinical detection **(Skates et al., 1999).**

General Population Screening

Transvaginal Ultrasound

Transvaginal ultrasound (TVUS) has been evaluated for use in ovarian cancer screening in the general population.

Because of the close proximity of the probe to the ovaries, TVUS offers excellent resolution of ovarian morphology. Volume, outline, papillations, and complexity of ovarian masses can be used to raise suspicion of cancer.

Benign ovarian lesions are common, however, resulting in false-positives that may necessitate invasive surgery for asymptomatic women **(VanNagell et al., 2000).**

CA-125

CA-125 is the most extensively studied tumor marker for ovarian cancer.

Several issues limit the usefulness of CA-125 as a screening tool for ovarian cancer.

First, although over 90% of advanced-stage patients display CA-125 elevations, only 50% to 60% of patients with stage I disease display elevations.

Second, tumors with mucinous histologies are less likely to be associated with a CA-125 elevation **(Jacobs et al., 1996).**

Third, CA-125 has inadequate specificity, particularly in pre- and perimenopausal women.

False-positive elevations are seen with benign ovarian cysts, endometriosis, adenomyosis, fibroids, diverticulitis, and liver cirrhosis, in addition to other benign and malignant conditions.

Conventional pelvic examination is being compared with annual TVUS and with annual CA-125 followed by TVUS only if the CA-125 is rising.

Whatever the outcome of trials based on CA-125 as an initial step, a screening strategy with greater sensitivity is required because 20% of ovarian cancers fail to express CA-125.

Over the past decade, novel markers have been discovered using monoclonal antibodies raised against ovarian cancer tissue, lipid analysis, gene expression arrays, and proteomic techniques.

Proteomic techniques have been used for early detection of ovarian cancer in two ways: to identify a distinctive pattern of peptide and protein expression in serum from healthy women and from patients with ovarian cancer **(Zhang et al., 2006).**

Ovarian Cancer Screening in High-Risk Women

Women with a BRCA1 mutation have a 39% to 46% lifetime risk of ovarian cancer, and women with a BRCA2 mutation have a 12% to 20% lifetime risk of ovarian cancer **(Antoniou et al., 2003; King et al., 2003).**

Although prophylactic bilateral salpingo-oophorectomy (BSO) remains the mainstay of ovarian cancer prevention in these high-risk individuals, strategies for screening and early detection are important for high-risk women who have not yet chosen to undergo the surgical procedure or who are unwilling to do so.

CA-125 and TVUS every six months in women with known BRCA1 or BRCA2 mutations, starting at age 35 or 5 to 10 years earlier than the age at first diagnosis of ovarian cancer in the family **(King et al., 2003).**

Management

Surgical management of early primary disease

The aim of surgery for early ovarian cancer is to resect the tumor and to undertake adequate staging. This will provide prognostic information and will

define whether chemotherapy is needed. The diagnosis may be made preoperatively, but sometimes a tumor is an incidental finding.

Accurate surgical staging is important as it may unmask occult advanced disease. Depending on the histological grade and subtype, ≤30% of the patients with apparently early epithelial ovarian cancer will be upstaged after comprehensive surgical staging **(Garcia et al., 2012; Timmers et al., 2010).**

Bulky lymph nodes should be resected in an effort to remove all visible residual disease. Adequate, non-fertility-sparing surgery should consist of peritoneal washings, ideally taken before manipulation of the tumor, bilateral salpingo-oophorectomy, hysterectomy, multiple peritoneal biopsies of all abdominal fields, at least infracolic omentectomy, appendectomy in case of mucinous histology and pelvic and para-aortic lymph node dissection up to the renal veins **(Maggioni et al., 2006).**

When young women are affected, fertility-sparing surgery could be considered in early-stage disease, but always after thoroughly informing the patient about the potential risks. Patients with stage IA or stage IC with unilateral ovarian involvement and favorable histology, which is mucinous, serous, endometrioid or mixed histology and grade 1 or 2, would be amenable to organ-preserving surgery, but only in combination with complete surgical staging. This would include a lymphadenectomy to exclude more advanced disease **(Fruscio et al., 2013).**

Surgical management of primary advanced ovarian cancer

Advanced epithelial ovarian cancer, the aim is complete cytoreduction of all macroscopic visible disease, since this has been shown to be associated

with a significantly increased overall survival **(Dubois et al., 2009; vanderBurg et al., 1995; Vergote et al., 2010).**

In order to achieve this, a maximal surgical effort is required, including intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph nodes and splenectomy **(Aletti et al., 2009).**

Optimal cytoreduction is defined as total macroscopic tumor clearance with no residual visible disease **(Dubois et al., 2009).**

In advanced bulky stage IIIC or IV disease, three cycles of platinum-based neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy.

The use of primary chemotherapy with interval surgery is becoming more widely accepted and is offered to patients with poor performance status at presentation, low albumin levels and in those with very extensive tumor dissemination **(Vergote et al., 2010).**

The value of surgical cytoreduction in relapsed epithelial ovarian cancer remains controversial and is not regarded as a standard of care.

Surgery at first relapse appears to be associated with a survival benefit only when a complete tumor resection can be obtained **(Harter et al., 2009; Zang et al., 2011).**

Patients with two of three of the following criteria: complete resection at first surgery, good performance status and absence of ascites had the best survival.

Adjuvant chemotherapy for early-stage disease

Chemotherapy is more beneficial than observation in patients with early-stage ovarian cancer Patients who received platinum-based adjuvant chemotherapy had better overall survival than patients who did not receive adjuvant treatment **(Winter-Roach et al., 2009)**.

Therefore, adjuvant chemotherapy should be offered not only to sub optimally staged patients but also to those optimally staged at higher risk of recurrence **(Swart, 2007).**

Chemotherapy

Chemotherapy has been a general standard of care for ovarian cancer for decades, although with highly variable protocols. Chemotherapy is used after surgery to treat any residual disease, if appropriate. In some cases, there may be reason to perform neoadjuvant chemotherapy, and is common when a tumor cannot be completely removed or optimally debulked via surgery. If a unilateral salpingo-oophorectomy is performed, adjuvant chemotherapy can be given **(Jayson, 2014).**

Chemotherapy in ovarian cancer typically consists of platins, a group of platinum-based drugs. Carboplatin is given in combination with either paclitaxel or docetaxel; the typical combination is carboplatin with paclitaxel **(Jayson, 2014).**

If ovarian cancer recurs, it is considered partially platinum-sensitive or platinum-resistant, based on the time since the last recurrence treated with platins: partially platinum-sensitive cancers recur 6–12 months after last treatment, and platinum-resistant cancers have an interval of less than 6

months. Second-line chemotherapy should be given only after the cancer becomes symptomatic, because there is no difference in survival between treating asymptomatic (elevated CA-125) and symptomatic recurrences. For platinum-sensitive tumors, platins are the drugs of choice for second-line chemotherapy, in combination with other cytotoxic agents. Regimens include carboplatin combined with pegylated liposomal doxorubicin, gemcitabine, or paclitaxel. For platinum-resistant tumors, there are no high-efficacy chemotherapy options. Single-drug regimens (doxorubicin or topotecan) do not have high response rates **(Jayson, 2014).**

In people with BRCA mutations, platinum chemotherapy is more effective **(Jayson, 2014).**

Radiation therapy

Radiation therapy is not effective for advanced stages because when vital organs are in the radiation field, a high dose cannot be safely delivered. Radiation therapy is then commonly avoided in such stages of ovarian cancer treatments **(Hruby et al., 1997).**

Hormonal therapy

Despite the fact that 60% of ovarian tumors have estrogen receptors, ovarian cancer is only rarely responsive to hormonal treatments. Estrogen alone does not have an effect on the cancer, and Clomiphene Citrate and Aromatase Inhibitor are rarely effective **(Jayson, 2014).**

Palliative care

Palliative care is a holistic treatment with a focus on relieving symptoms and increasing or maintaining quality of life. It has been recommended as part of the treatment plan in patients with advanced ovarian cancer or with significant symptoms.

Palliative care can entail medical& surgical treatment of symptoms and complications of the cancer, including pain, nausea, constipation, ascites, bowel obstruction, edema and mucositis. Especially if the cancer advances and becomes incurable, treatment of symptoms becomes one of the main goals of therapy **(ASCO, 2014).**

Follow-up

Specific follow-up depends on, for example, the type and stage of ovarian cancer, the treatment, as well as the presence of any symptoms. There is usually a check-up appointment approximately every 2 to 3 months initially, followed by twice per year for up to 5 years. For epithelial ovarian cancers, the most common test upon follow-up is CA-125 level. However, treatment based only on elevated CA-125 levels and not any symptoms can increase side effects without any prolongation of life, so the implication of the outcome of a CA-125 test should be discussed before taking it **(American Cancer Society, 2014).** The recommendation as of 2014 is that there may be recurrent cancer if the CA-125 level is twice normal **(Jayson, 2014).**

For women with germ cell tumors, follow-up tests generally include alpha-fetoprotein (AFP) and Human Chorionic Gonadotropin (HCG). For women with stromal cancers, tests including hormones

like estrogen, testosterone, and inhibin are sometimes helpful **(American Cancer Society, 2014).**

PET-CT scans may reveal sites of disease not visible on CT scans. The principal role of this imaging modality is to help the selection of patients for secondary debulking surgery, by excluding additional sites of disease not seen on CT scans and not amenable to cytoreduction **(Rustin et al., 2009).**

Using conventional two-dimensional gel electrophoresis, it was noted that a decreased intensity of staining for serum haptoglobin was observed in samples from patients undergoing chemotherapy, this change also correlated well with the profile of CA-125 levels before and after chemotherapy **(Ahmed et al., 2005).**

Recurrence rates

Ovarian cancer frequently recurs after treatment. If a recurrence occurs in advanced disease, it typically occurs within 18 months of initial treatment (18 months progression-free survival). Recurrences can be treated but the disease-free interval tends to shorten and chemo resistance increases with each recurrence **(Jayson, 2014).**

Prognosis

Ovarian cancer usually has a relatively poor prognosis. It is disproportionately deadly because it lacks any clear early detection or screening test, meaning that most cases are not diagnosed until they have reached advanced stages **(Society of Gynecologic Oncology, 2014; Smith et al., 2012; Rezk et al.,2011).**

Ovarian cancer metastasizes early, often before it has been diagnosed. High-grade tumors metastasize more readily than low-grade tumors. Typically, tumor cells begin to metastasize by growing in the peritoneal cavity. More than 60% of women presenting with ovarian cancer have stage III or stage IV cancer, when it has already spread beyond the ovaries **(Seiden and Michael, 2012).**

The five-year survival rate for all stages of ovarian cancer is 46%.For cases where a diagnosis is made early in the disease, (stage 1), the five-year survival rate is 92.7% **(Seiden and Michael, 2012).**

Studies have shown that haptoglobin levels are significantly higher in patients with advanced disease and those with poor survival indicating that the pre-operative haptoglobin level could serve as an independent prognostic factor in patients presenting with EOC.Similarly to CA-125, haptoglobin also reflects response to treatment **(Ahmed et al., 2005; Ye et al., 2003; Zhao et al., 2007).**

Prognostic factors of ovarian cancer

1. Age

Ovarian cancer may occur at any age, including infancy and childhood. The incidence rate however increases with age with the greatest number of new cases in the fifth and sixth decade **(ACOG, 2011).**The predominant type of ovarian lesion in young women is benign or of low malignant potential. High grade aggressive carcinomas on the other hand are more frequently seen in postmenopausal women with associated poor prognosis **(Ewertz et al., 1988).**

2. Presence and extent of tumor spread

The staging classification of ovarian cancer was revised by the International Federation of Gynecology and Obstetrics (FIGO) in 2014 **(Jayson, 2014; Society for Gynecologic Oncology, 2014)**. It is considered a surgical staging style. The diagnosis of advanced disease is often made on the basis of preoperative diagnostic evaluation and less frequently during surgical exploration **(Auersperg et al., 1995).** Early ovarian tumors that are apparently confined to the ovaries or the pelvis (stage I, II) require meticulous surgical staging **(Auersperg et al., 1994).**

3. Ascites

This clinical finding constitutes by itself an unfavorable prognostic sign **(Yancik, 1993).**

4. Tumor grading and degree of differentiation

The morphology and histological pattern, including the architecture and grade of the lesion, are important prognostic variables. The value of histological grade as an independent prognostic factor has not been clearly established **(Auersperg et al., 1995).**

5. CA-125

Is a tumor-associated antigen that has been used clinically to monitor patient with epithelial ovarian carcinomas. Elevated CA-125 levels are not specific to ovarian cancer and have been observed in patients with non gynecological cancers and in other benign conditions as first trimester pregnancy or endometriosis. The available evidence suggests that using CA-125 alone, particularly at reference value of 35U/ml, does not have a

sufficiently high sensitivity to be recommended for routine screening of ovarian cancer **(Jacobs et al., 1992).**

6. Oncogene expression

More than 60 pro-oncogens have been identified, and studies have focused on the amplification or expression of these genetic loci and their relationship to the development and progression of cancer **(Berchuck et al., 1990).**

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Prof.Dr. Samir Khalf

samiraiz@hotmail.com


ArabicOBGYN.net