Overview of Ovarian Cancer: Pathology, Staging, Diagnosis and Risk Factor

Waheed Yousry Gareer [1] ; Alaa Mohamed Khalil [2] ; Mansour Mohamed Moursy[2], Mohamed Mahmoud Al kilany[2] ; Saad Nagy Salama[2]

[1] *Surgical oncology National cancer institute, Egypt.*
[2] *General Surgery Department, Faculty of Medicine, Zagazig University, Egypt.*

Corresponding author: Saad Nagy Salama, saaddnagy@gmail.com

ABSTRACT

Ovarian cancer (OC) is the seventh most common type of malignant neoplasm in women and the eighth cause of mortality in them worldwide. The classification of OC is made by the possible origin of one of the three main components of the ovary: epithelium, stroma, and germinal cells. The most clinical introduction of epithelial ovarian carcinoma (EOC) might be either intense or subacute. Several risk factors appear to influence the developing of OC. There are frequently few therapeutic choices available because of how quietly it manifests. Health care practitioners must have a fundamental understanding of the warning signs and symptoms of ovarian cancer, as well as the imaging techniques in order to give the patient the best care possible. The aim of this review to highlight the pathological condition of OC and the associated risk factors. Also, to review the suitable way to deal with assessment of women with suspected ovarian malignant growth.

Keywords: Ovarian Cancer; Staging, Diagnosis ; Risk Factors; Management

DOI: 10.48047/ecb/2023.12.8.584

Introduction

Ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women in the world, accounting for nearly 4 % of all female cancers. OC also represents the third leading gynecologic cancer, following cancer of the cervix and uterine corpus, and causes more deaths per year than any other cancer of the female reproductive system **(1)**.

On a worldwide basis, an estimated 239,000 new cases are diagnosed and 152,000 women die of OC annually **(2)**. Mortality is high because women typically present with late stage disease when the overall 5-year relative survival rate is 44%. Thus, the public health burden is significant **(3)**.

Ovarian cancer (OC) incidence exhibits wide geographic variation. The highest age adjusted incidence rates are observed in developed parts of the world, including North America and Western and Northern Europe, with rates in most of these areas exceeding 8 per 100,000 **(1).**While, the rates are lowest in Asia and Africa. The incidence rates in Northern Africa including Egypt are (5.6 per 100.000) **(4)**.

- **Pathology of Ovarian Cancer**

Epithelial ovarian tumors are heterogeneous neoplasms which are primarily classified according to cell type into serous, mucinous, endometrioid, clear-cell, transitional, and squamous cell tumors **(5)**. Parenthetically, none of these cells are found in the normal ovary and their development has long been attributed to mullerian 'neometaplasia' of the ovarian surface epithelium (mesothelium). More importantly, these tumors are further subdivided into

benign, borderline (intermediate), and carcinoma depending on the degree of cell proliferation and nuclear atypia, and the presence or absence of stromal invasion **(4,5)**.

Borderline tumors show epithelial proliferation greater than that seen in their benign counterparts and variable nuclear atypia; however, in contrast to carcinomas, there is absence of stromal invasion, and their prognosis is much better than that of carcinomas. Despite the lack of ovarian stromal invasion, serous borderline tumors, particularly those with exophytic growth, can implant on peritoneal surfaces and, 10% of peritoneal implants, progress to low-grade serous carcinoma (LGSC), and invade the underlying tissues. The biologic behavior of invasive peritoneal implants is similar to that of LGSC **(6)**.

Malignant epithelial tumors (carcinomas) are the most common ovarian cancers accounting for 90% of cases. Although traditionally referred to as a single entity, ovarian cancer is not a homogeneous disease but rather a group of diseases, each with different morphology and biologic behavior **(5,7)**.

Currently, based on histopathology, immunohistochemistry, and molecular genetic analysis, at least five main types of ovarian carcinomas are identified: high-grade serous carcinomas (HGSCs; 70%), endometrioid carcinomas (EC; 10%), clear-cell carcinomas (CCC; 10%), mucinous carcinomas (MC; 3%), and LGSC (<5%) **(Table 1)**. These tumors account for 98% of ovarian carcinomas, can be reproducibly diagnosed by light microscopy, and are inherently different diseases, as indicated by differences in epidemiological and genetic risk factors, precursor lesions, patterns of spread, molecular events during oncogenesis, response to chemotherapy, and prognosis **(5,6)**.

Table (1): Ovarian carcinoma: clinical and molecular features of the five most common types[(5)]

	HGSC	**LGSC**	**MC**	**EC**	**CCC**
Precursor lesions	Tubal intraepithelial carcinoma	Serous bordline carcinoma	Cystadenoma/ Bordline tumor	Atypical endometriosis	Atypical endometriosis
Pattern of spread	Very early transcoelomic	transcoelomic	Usually confined to ovary	Usually confined to pelvis	Usually confined to pelvis
Molecular abnormalities	*BRCA,P53*	*BRAF,KRAS*	*KRAS,HER2*	*PTEN,ARIDIA*	*HNFI,ARIDIA*
Chemosensivity	High	Intermediate	Low	High	Low
Prognosis	Poor	Intermediate	Favorable	Favorable	Intermediate

In the era of personalized cancer medicine, reproducible histopathological diagnosis of tumor cell type is a sine qua non condition for successful treatment. For instance, it has been found that different tumor types respond differently to chemotherapy. The poor response rate of CCC (15%) contrasts notably with that of HGSCs (80%), resulting in a lower 5-year survival for clear cell compared with HGSC in patients with advanced stage tumors (20% *vs* 30%) **(Figure 1)**. The clear cell and mucinous types, in particular, are candidates for clinical trials to identify more active therapy than what is presently used **(9,10)**.

The fact that one tumor type (HGSC) accounts for over two thirds of cases, does not justify classifying ovarian carcinomas into only two types, lumping together the other four

(endometrioid, clear cell, mucinous, & LGSCs) as type 1 carcinomas'**(11)**. In fact, the latter tumors are clinically, morphologically, and molecularly distinct diseases that individually bear resemblance neither to HGSC nor to each other. Thus, classifying ovarian carcinomas into just two types (I and II) is artificial and limits progress in understanding the biology or improving the management of the less common types of ovarian carcinomas **(12)**.

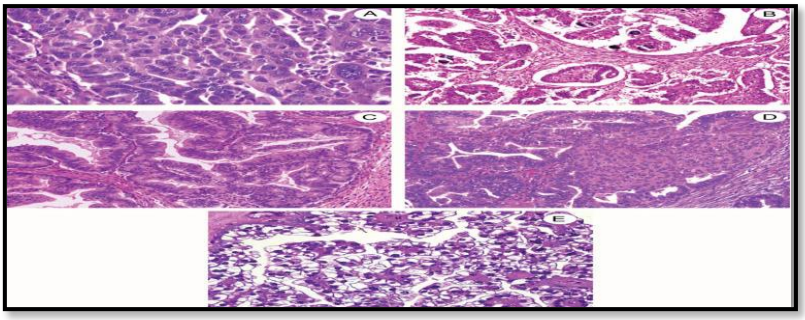

Figure (1): illustrated (A) high-grade serous carcinoma; (B) low-grade serous carcinoma; (C) mucinous carcinoma; (D) endometrioid carcinoma; and (E) clear-cell carcinoma [(5)].

In general, epithelial ovarian cancers (EOC) predominantly metastasize by exfoliation. Malignant cells are first released into the peritoneal cavity when the tumor penetrates through the ovarian surface. By following the normal circulation of peritoneal fluid, implants may then develop anywhere in the abdomen. A unique characteristic of ovarian cancer is that metastatic tumors do not usually infiltrate visceral organs, but exist as surface implants. As a result, aggressive debulking is possible with reasonable morbidity **(13)**.

Due to its marked vascularity, the omentum is the most frequent location for disease spread and is often extensively involved with tumor **(Figure 2)**. Nodules are also commonly present on the undersurface of the right hemidiaphragm and small bowel serosa, but all intraperitoneal surfaces are at risk **(13,14)**.

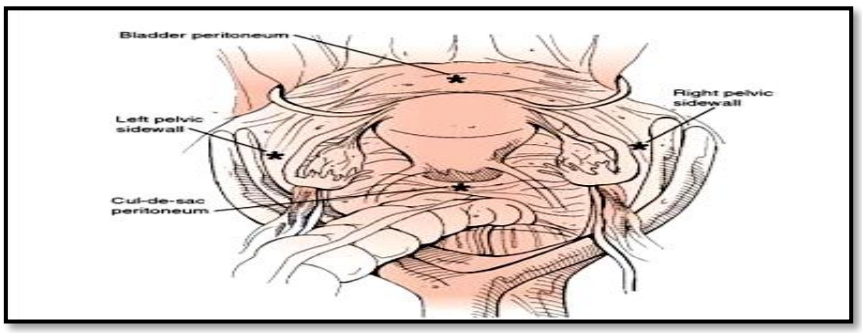

Figure (2): Pelvic spread of ovarian cancer can occur by direct extension to continguous organs or by noncontinguous peritoneal spread[(14)].

- **Staging of Ovarian Cancer**

The International Federation of Gynecologists and Obstetricians (FIGO) have revised the previous staging of ovarian cancer **(Figure 3)**. Stage I Tumor confined to ovaries including: IA (tumor limited to 1 ovary (capsule intact); no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings); IB (tumor limited to both ovaries (capsules intact) or; no tumor on ovarian surface; no malignant cells in the ascites or peritoneal washings). IC (tumor limited to 1 or both ovaries, with any of the following: "IC1" surgical spill; "IC2" capsule ruptured before surgery or tumor on ovarian surface, and "IC3" malignant cells in the ascites or peritoneal washings). Stage II Growth involving one or both ovaries with pelvic

extension (below pelvic brim) including: IIA (extension and/or implant on uterus and/or Fallopian tubes); and
IIB(Extension to other pelvic intraperitoneal tissues) **(15)**.

Stage III Tumor involves 1 or both ovaries, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes including IIIA1(Positive retroperitoneal lymph nodes only (cytologically or histologically proven); IIIA1(i) Metastasis ≤ 10mm in greatest dimension; IIIA1(ii) Metastasis >10mm 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 ≤ 2cm 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). Stage IV Distant metastasis excluding peritoneal metastases; Stage IVA (Pleural effusion with positive cytology); Stage IVB (Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity) **(15,16)**.

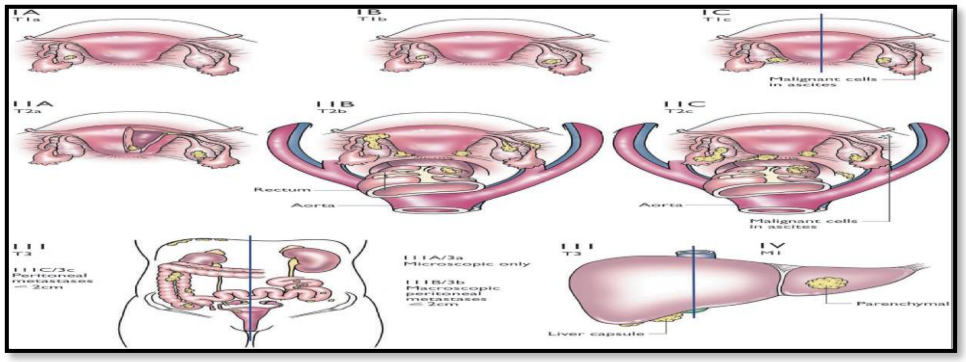

Figure (3): The previous Staging classification of ovarian cancer: primary tumor and metastases (FIGO and TNM) [(16)].

- **Risk factors of Ovarian Cancer**

1-Inherited susceptibility:

One of the most significant risk factors for OC is a family history of the disease, which occurs among approximately 7 % of women with OC. First degree relatives of OC probands have a three- to seven fold increased risk, especially if multiple relatives are affected and at early age at onset **(17)**. It is clear that a subset of OCs occurs as part of a hereditary cancer syndrome that is inherited in an autosomal dominant pattern. The majority of hereditary OCs can be attributed to mutations in the *BRCA1* and *BRCA2* genes **(18)**.

According to data from the Breast Cancer Linkage Consortium, the risk of OC through age 70 years is up to 44 % in *BRCA1* families and approaches 27 % in *BRCA2* families **(19)**. Mutation screening of population- based series of OC cases has shown that 10–15 % of epithelial OCs can be attributed to mutations in either *BRCA1* or *BRCA2* **(17)**. In addition, OC occurs in families with hereditary nonpolyposis colorectal cancer syndrome (HNPCC), also known as Lynch syndrome.The genetic defects underlying HNPCC (the mismatch repair genes *hMLH1, hMSH2, hPMS1, hPMS2,* and *hMSH6)* may account for at least 2 % of epithelial OC and confer up to a 20 % lifetime risk. Overall, mutations in highly penetrant genes account for 10–15 % of epithelial OCs **(18, 19)**.

2- Hormonal risk factors:

Hormones such as estrogen and progesterone are believed to be involved in promoting ovarian carcinogenesis. There are two, not necessarily mutually exclusive hypotheses that reflect what are currently known about the disease. The "incessant ovulation" hypothesis proposes that the number of ovulatory cycles increases the rate of cellular division associated with the repair of the surface epithelium after each ovulation, thereby increasing the likelihood of spontaneous mutations that may promote carcinogenesis **(20)**.

Indeed, positive correlations exist between increasing numbers of lifetime ovulations and OC risk. The second hypothesis, often referred to as the "gonadotropin hypothesis," posits that gonadotropins such as luteinizing hormone and follicle- stimulating hormone overstimulate the ovarian epithelium, causing increased proliferation and subsequent malignant transformation **(20,21)**. The epidemiology of OC does not help clearly distinguish between these two hypotheses.

3-Age at menarche and age at menopause:

According to the incessant ovulation hypothesis, early age at menarche and late age at menopause could increase the risk for OC through an increased number of ovulatory cycles. Conversely, according to the gonadotropin hypothesis, a late age at menopause delays the surge of postmenopausal gonadotropin hormones, possibly reducing OC risk. Numerous epidemiologic studies have examined the relation between lifetime menstrual history and OC risk. Results of studies that have examined the age at onset of menses are not terribly consistent **(22)**.

4-Pregnancy, parity, and infertility:

The association between pregnancy and OC risk has been studied extensively. Pregnancy causes anovulation and suppresses secretion of pituitary gonadotropins. Both the "incessant ovulation" and the "gonadotropin" hypotheses would predict that pregnancy reduces the risk of OC. Indeed, one of the most consistent findings is that parous women have a 30–60 % lower risk for OC than nulliparous women. Furthermore, each additional full-term pregnancy is estimated to lower risk by approximately 15 % **(23)**.

It is yet to be determined whether nulliparity and low parity per se, rather than difficulty becoming pregnant due to female infertility, is the relevant factor. Infertility appears to be associated with increased OC risk in most studies, but not all **(1)**. Possible reasons for the inconsistent results may include the failure to examine the various types of infertility separately. Furthermore, it has been reported that some factors such as a personal history of endometriosis or polycystic ovarian syndromemay influence both infertility and OC risk **(24)**.

A particular challenge is trying to distinguish an influence of infertility from an adverse effect of fertility drug exposure. Although some studies report that women with a prior history of fertility drug use who remain nulliparous are at an elevated risk for ovarian tumors, particularly tumors of low malignant potential the results are not consistent. Early detection bias may explain the discrepant findings, as early stage cancers may be overdiagnosed in infertile women due to the close medical surveillance **(25)**.

5-Lactation:

Lactation suppresses secretion of pituitary gonadotropins and leads to anovulation, particularly in the initial months after delivery **(22)**. If the incessant ovulation and gonadotropin hypotheses are true, lactation should reduce the risk of OC. Although the majority of studies have identified a slight decrease in OC risk with lactation , some have not.Despite the conflicting results, the overall impression is that lactation protects against epithelial OC, especially in the first few months following delivery **(23,26)**.

6-Benign gynecologic conditions and gynecologic surgery:

Several gynecologic conditions have been examined as risk factors for OC, including polycystic ovarian syndrome (PCOS), endometriosis, and pelvic inflammatory disease (PID). PCOS is a heterogeneous disease often characterized by obesity, hirsutism, infertility, and menstrual abnormalities. The association between PCOS and OC risk was investigated using data from the cancer and steroid hormone study **(27)**. Among 476 histologically confirmed epithelial OC cases and 4,081 controls, 7 cases (1.5 %) and 24 controls (0.06 %) reported a history of PCOS (OR = 2.5- fold, 95 % CI: 1.1–5.9). The association appeared to be stronger among women who never used oral contraceptives (OR = 10.5, 95 % CI: 2.5–44.2). Larger studies that adjust for potential confounders of the PCOS-OC association are needed before conclusions can be drawn regarding these findings **(28)**.

Endometriosis is one of the most common gynecologic disorders, affecting 10–15 % of women in reproductive years **(29)**. Even though endometriosis is considered a benign condition, it has been linked with OC. The risk of OC increased with effect sizes ranging from 1.3 to 1.9. The strongest associations were evident among endometrioid and clear cell histologies, consistent with molecular data that supports the uterus as the origin of these subtypes. However, the association between endometriosis and endometrioid and clear cell ovarian carcinomas may represent sharing of similar risk factors rather than a causal association, a topic that merits further research **(29)**.

PID causes inflammation of the endometrium, fallopian tubes, and ovaries. Previous studies that evaluated the association between PID and OC risk yielded inconsistent results. PID is a risk factor especially among subjects diagnosed with PID before the age of 35 and women who had at least five episodes of PID. Note, however, that the absolute rates of OC among women with PID are clearly low overall **(30)**.

It is well established that among high risk women, bilateral prophylactic oophorectomy decreases OC risk by at least 90 % **(31)**. Numerous studies have identified a reduced risk of OC associated with either a hysterectomy or tubal ligation (without oophorectomy), with the protective effect for each of these procedures ranging from 30 to 40 %. Although it is uncertain how these procedures reduce the risk of OC, removal of the uterus and/or blockage of the tubes may prevent potential carcinogens from ascending the genital tract and decreases blood flow to the ovaries **(31,32)**. Also, retrograde menstruation may promote iron-induced oxidative stress and subsequent cancer development in the fallopian tubes and ovaries **(30)**.

7-Oral contraceptives:

The 30-40 % lower risk of ovarian cancer among women who ever used oral contraceptives is firmly established. The findings are consistent over the past several decades. The risk reduction increases with duration of use by at least 5 % per year, with about a 50 % reduction in risk for long-term use of 10 years or greater, and persists long after use has ceased **(33)**.

8-Hormone replacement therapy (HRT):

The benefit of oral contraceptives on OC risk is well established; however, the data on another exogenous hormone, HRT, is less clear. It has been postulated that HRT may reduce OC risk by decreasing the secretion of gonadotropins. However, the reduced levels are still above those of premenopausal women. Conversely, postmenopausal HRT may increase OC risk due to increased estrogen-induced proliferation of ovarian cells **(34)**. Furthermore,

several prospective studies have found that longer durations of HRT use are associated with OC risk **(34-36)**.

9-Anthropometric factors:

One area of great interest is body mass index (BMI). In postmenopausal women the predominant source of circulating estrogens is aromatization of androgens in adipose tissue **(30)**. The association between BMI and OC risk remains unresolved. The findings to date suggest BMI may confer a slight increased risk of OC, but considering adiposity is a modifiable risk factor **(1)**.

10-Diet and nutrition:

Ecological studies have generated a number of hypotheses about the association between diet and OC risk **(35)**. Despite numerous analytical epidemiologic studies on various aspects of diet, the findings for most exposures remain inconsistent. The notable exception is intake of vegetables, for which the evidence that higher intakes are associated with lower risk is emerging **(35)**.

11-Exercise and physical activity:

The potential general health benefits of exercise are well established, and a specific effect on OC might be expected, at least indirectly, through exercise effects on reduction of adipose tissue (and therefore estrogen levels), lower ovulation frequency, and reduced chronic inflammation **(36)**.

12-Other lifestyle and environmental factors:

The majority of early reports concluded that smoking was not associated with an increased risk of OC. Based on results from more contemporary studies, this may have been because analyses were not stratified by histologic subtype. In fact, smoking appears to increase the risk for invasive mucinous tumors in a dose-response manner, but not other subtypes **(36)**.

Alcohol consumption, a common and modifiable exposure, has been investigated as a possible cause of OC in numerous case-control and cohort studies with conflicting results. Most have observed null associations, but there is an equal number that have found increased and decreased Risk **(37)**.

Assessment of occupational risk factors for OC has been challenging due to a lack of studies to detect associations. There was some evidence for excess risk among women employed in dry cleaning, telecommunications, paper packaging, and textile industries implicating exposures to organic dusts, aromatic amines, and hydrocarbons **(38)**.

Both human and animal studies have found asbestos fibers in the ovaries. The link between asbestos exposure and OC is less firmly established, in part due to small numbers of women who have been exposed to asbestos and disease misclassification (i.e., peritoneal mesothelioma, an asbestos-related disease, is often misdiagnosed as OC on death certificates). Despite the lack of consistency, the International Agency for Research on Cancer (IARC) has declared that evidence is "sufficient" in humans that exposure to asbestos causes OC **(39)**.

Similar to asbestos, talcum powder is a silicate that has been studied extensively in relation to cancer risk. An approximately 30 % increase in risk of OC with regular genital exposure to talc, and more recent studies suggest that women with certain variants in glutathionine S-transferase M1 (*GSTM1*) and/or glutathionine S-transferase T1 (*GSTT1*) have a higher risk of OC associated with talc use **(39)**.

Several studies have investigated the association between many analgesic drugs and OC incidence. The regular use of aspirin and NSAIDs was associated with hazard ratios of 1.11 (95 % CI: 0.92–1.33) and 0.81 (95 % CI: 0.64–1.01), respectively **(40,41)**.

- **Diagnosis of Ovarian Cancer:**

All the more generally, infection displays in a subacute form in ladies with either early or propelled malady. These conditions are typically assessed in an outpatient setting. On the other hand, an adnexal mass might be found unexpectedly at the season of imaging performed for another sign. Rarely, EOC is found at the season of medical procedure performed for another sign **(42)**.

The assessment of ladies with highlights suggestive of EOC is normally a two-stage process including initial assessment and surgical assessment.

I.Initial assessment

Analysis of ovarian disease begins with a physical examination (counting a pelvic examination), lab tests (for CA-125 and again different markers), imaging (pelvic ultrasound and other imaging modalities) and hazard scoring **(43)**.

Physical examination including a pelvic examination is fundamental for determination: physical examination may uncover expanded stomach circumference and additionally ascites, while pelvic examination may uncover an ovarian or stomach mass. An adnexal mass is a huge finding that frequently shows ovarian malignant growth, particularly on the off chance that it is settled, nodular, sporadic, strong, and additionally two-sided. 13–21% of adnexal masses are brought about by threat; nonetheless, there are other amiable reasons for adnexal masses (e.g ovarian follicular growth). Ovaries that can be felt are additionally an indication of ovarian disease in postmenopausal women **(44)**.

Different parts of a physical examination for suspected ovarian malignant growth can incorporate a bosom examination and an advanced rectal test. Palpation of the supraclavicular, axillary and inguinal lymph hubs may uncover lymphadenopathy, which can be demonstrative of metastasis. Another marker might be the nearness of a pleural emission, which can be noted on auscultation **(44)**.

Utilization of serum biomarkers for the determination of epithelial ovarian malignant growth is a functioning territory of examination. Biomarkers are commonly utilized in blend with one another or with different discoveries (eg, ultrasound). Just a couple of biomarkers are monetarily accessible **(45)**.

Malignant growth antigen 125 (CA 125) as a biomarker for EOC was first portrayed in 1983. CA 125 is as of now the most generally utilized biomarker for EOC, and it is affirmed by the US Food and Drug Administration (FDA) for checking reaction to treatment in ladies with EOC. The CA 125 antigen is a transmembrane glycoprotein gotten from both coelomic and müllerian epithelia. The antigen complex contains two noteworthy areas (A & B). A segment of the extracellular area incorporates rehash arrangements that quandary the OC125 and M11 monoclonal antibodies. The first CA 125 test responds with OC125, and the more up to date CA 125 II test uses both the OC125 and M11 moieties. The two tests are regularly utilized in clinical practice. While CA 125 II might be progressively explicit, there is no information to help the predominance of one test over the other. The ordinary qualities for the two tests are: CA 125: ≤35 U/Ml -CA 125 II: <20 U/Ml **(46)**.

Carcinoembryonic antigen: (CEA) is a protein ordinarily found in embryonic or fetal tissue. Serum levels vanish totally after birth, however little sums might be available in the

colon (Menon and Jacobs, 2012). CEA may likewise be lifted in bosom, pancreas, thyroid and lung malignancies. The commonplace furthest limit of typical for CEA in non-smokers is 3.8 micrograms per liter (mcg/L). For smokers, the furthest reaches of ordinary is 5.5mcg/L **(47)**.

Malignant growth antigen 19-9 (CA 19-9) is a mucin protein that might be lifted in ovarian disease yet is utilized sparingly in ovarian malignant growth the executives. CA 19-9 is utilized essentially to screen sickness reaction to treatment or recognize malignant growth repeat in patients with an archived gastric disease, pancreatic disease, gallbladder malignant growth, cholangiocarcinoma and adenocarcinoma of the ampulla of Vater **(48)**.

Human epididymis protein 4 (HE4): HE4 gives off an impression of being overexpressed in EOC. HE4 is less inclined to be erroneously raised in kind ovarian masses than CA125. HE4 and CA125 seem to have parallel sensitivities in identifying threat in patients with pelvic masses, these tests may have predominant affectability when utilized together. As of now, the US FDA has affirmed the utilization of HE4 just for observation in patients with EOC but not as a strategy for early location **(49)**.

Mesothelin (MSLN) is an antigen found in ordinary mesothelium, and has been identified in patients with mesothelioma, ovarian malignant growth and some squamous cell carcinomas. A pee based MSLN measure is progressively powerful. It was likewise discovered that serum CA125 levels were reciprocal to MSLN levels: CA125 levels were lifted in 75% of beginning time malignant growth patients, and when patients experienced both CA125 and pee MSLN testing, 82% of beginning period diseases could be identified when one or the two markers were hoisted **(50)**.

Osteopontin (OPN) is a glycophosphoprotein emitted by enacted T- lymphocytes, macrophages and leukocytes as a reaction to irritation. OPN has been observed to be essentially lifted in patients with EOC when contrasted and sound controls, patients with amiable ovarian sicknesses and patients with other gynecologic malignancies **(51)**.

Many biomarkers for EOC are under scrutiny. The accompanying serum markers have been accounted for to be possibly valuable: lysophosphatidic corrosive (LPA), haptoglobin, transthyretin, apolipoprotein A1, serum C-receptive protein, and OVX1 **(50)**.

Pelvic ultrasound is ordinarily the primary line imaging study used to describe an adnexal mass **(51)**. The sonographic way to deal with adnexal mass portrayal can be abridged as a four-advance methodology:

(a) Stage one: asymptomatic straightforward pimples somewhere in the range of 5-7 cm ought to experience yearly sonographic assessment .When a straightforward blister surpasses 7 cm in size, the SRU recommends that attractive reverberation imaging be considered if the growth was not completely assessed **(51)**. In postmenopausal ladies, the SRU agreement may pick any limit from 1 to 3 cm as a reasonable cut-off for not following a basic sore in a postmenopausal lady . Rare ovarian sores more than 5 cm in distance across in postmenopausal ladies have been accounted for as straightforward on ultrasound however ended up being marginal tumors with nodularity noted terribly or histologically, Given the nearness of gross knobs at pathology, almost certainly, these blisters were not very much assessed on sonography **(51)**.

(b) Stage two the mass is anything but a straightforward blister, the following inquiry to consider is whether a physiologic procedure, for example, corpus luteal involution, drain into a growth, or abutting basic sores, could represent the sonographic highlights that make the pimple "not basic" **(51)**.

(c) Stage three: to assess the mass for any highlights that are normal for explicit substances, such as endometrioma , mature teratoma , pedunculated leiomyoma, hydrosalpinx و peritoneal incorporation pimple , and malignancy.

(d) Stage four: follow-up ultrasound or extra testing **(51)**.

Danger of harm record (RMI): RMI is a multimodality approach that joins serum CA 125, pelvic ultrasound, and menopausal status into a file score to anticipate the danger of ovarian malignant growth in ladies with an adnexal mass. RMI I is a result of the ultrasound check score (U), menopausal status (M), and serum CA 125 dimension (RMI I= U x M x CA 125). The NICE rules exhort that all ladies with a RMI I score of ≥ 200 ought to be alluded to a master. The ultrasound result is scored 1 point for every one of the accompanying qualities: multi-locular pimple, strong territories, metastases, ascites, and two-sided masses. U= 0 for a ultrasound score of 0 points, U= 1 for a ultrasound score of 1 point, and U= 3 for a ultrasound score of 2 to 5 points. Menopausal status is scored as 1= premenopausal and 3= postmenopausal **(52)**.

OVA1 is a test that incorporates five serum biomarkers. The OVA1 test fuses five proteins that are fluidly communicated in ovarian malignant growth. Two are up-directed (CA 125 II, beta 2 microglobulin) and three down-managed (transferrin, transthyretin, apolipoprotein A1). The OvaCalc programming joins the qualities for each examine and uses the OVA1 calculation to produce an ovarian danger chance list score. The numeric outcome ranges from 0.0 to 10.0 and is translated as pursues: In premenopausal ladies (Low likelihood of threat: OVA1 <5.0, High likelihood of harm: OVA1 ≥5.0) **(53)**.

Danger of Malignancy Algorithm (ROMA) to evaluate the probability of threat in ladies who are intending to have medical procedure for an adnexal mass. ROMA utilizes CA 125 and HE4 testing and translates the outcomes utilizing two separate strategic relapse calculations, contingent upon menopausal status. In premenopausal ladies: High danger of harm ≥13.1 percent. In postmenopausal ladies: High danger of harm ≥ 27.7 percent **(54)**.

II. Surgical Evaluation

The preoperative assessment guides careful arranging and incorporates the accompanying segments. Assess the capacity to endure medical procedure Patients who are older or have therapeutic comorbidities not contender for medical procedure, a picture guided biopsy of the ovary (or on the other hand, paracentesis or picture guided biopsy of intraabdominal infection) is performed to affirm the nearness of EOC preceding treatment with chemotherapy **(55, 56)**.

Imaging studies can survey for the degree of ailment in ladies with associated intraabdominal spread with EOC. Stomach and pelvic modernized tomography (CT) or attractive reverberation imaging (MRI) is the most usually utilized modalities. CT belly and pelvis is more affordable and more agreeable for the patient than MRI. Chest radiography is performed in many patients to assess for pleural radiation, pneumonic metastases, and mediastinal lymphadenopathy.. Liver-spleen filters, bone outputs, and cerebrum checks are pointless except if side effects or signs recommend metastases to these locales **(57)**.

Picture guided omental biopsy can be performed under US or CT direction in patients regarded unsatisfactory for medical procedure clinically or dependent on imaging to histologicaly affirm ovarian danger preceding beginning of neoadjuvant chemotherapy. Biopsy is likewise basic before debulking medical procedure if there is clinical worry that the stomach and pelvic sickness might be auxiliary to an essential sore other than the ovary, for example from a bosom or stomach danger, or contamination **(58)**.

Upper and lower GIT endoscopy for patients with anomalous side effects or imaging discoveries suggestive of GIT association **(59)**.

Synchronous essential malignant growths of the ovary and endometrium have been accounted for in around 10 percent of ladies with OC and 5 percent of ladies with endometrial disease. Ladies at an expanded hazard for both ovarian and endometrial malignancy are those with Lynch disorder and those with an estrogen-emitting tumor (in spite of the fact that these are sex rope stromal tumors as opposed to epithelial carcinoma **(60)**.

CONCLUSION:

Ovarian Cancer is one of the gynecological neoplasms with worse prognosis in late stage. A list of established factors that have been shown to increase the risk of ovarian cancer including age, family history, nulliparity, increased number of life time ovulatory cycles, hormone replacement therapy, infertility, obesity, sedentary lifestyle, cigarette smoking, alcohol consumption, and dietary fat. In addition, a protective factors including oral contraceptive use oophorectomy; hystrectomy, tubal ligation, lactation and high vegetable intake.

The final diagnosis must be confirmed with medical procedure to assess the stomach cavity, biopsies; marker tests, and evaluate for malignant growth cells in the stomach liquid if there is sufficient doubt of EOC according to physical examination, malignant markers, imaging, and Hazard scoring. Early OC may be successfully treated with surgery alone; advanced disease may require complex management and treatment.

No conflict of interest.

References:

1- **Gaona-Luviano, P., Medina-Gaona, L. A., Magaña-Pérez, K. (2020)**. Epidemiology of ovarian cancer. Chin Clin Oncol, 9(4), 47.
2- **Kurnit, K. C., Fleming, G. F., & Lengyel, E. (2021)**. Updates and new options in advanced epithelial ovarian cancer treatment. Obstetrics and gynecology, 137(1), 108.
3- **Menon, U., Gentry-Maharaj, A., Burnell, M., Singh, N., Ryan, A., Karpinskyj, C., Parmar, M. (2021)**. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. The Lancet, 397(10290), 2182-2193.
4- **Kuroki, L., & Guntupalli, S. R. (2020)**. Treatment of epithelial ovarian cancer. Bmj, 371.
5- **Žilovič, D., Čiurlienė, R., Sabaliauskaitė, R., & Jarmalaitė, S. (2021).** Future screening prospects for ovarian cancer. Cancers, 13(15), 3840.
6- **Cheung, A., Shah, S., Parker, J., Soor, P., Limbu, A., Sheriff, M., & Boussios, S. (2022)**. Non-epithelial ovarian cancers: how much do we really know?. International Journal of Environmental Research and Public Health, 19(3), 1106.
7- **Martins, F. C., Couturier, D. L., Paterson, A., Karnezis, A. N., Chow, C., Nazeran, T. M., ... & Brenton, J. D. (2020)**. Clinical and pathological associations of PTEN expression in ovarian cancer: a multicentre study from the Ovarian Tumour Tissue Analysis Consortium. British journal of cancer, 123(5), 793-802.
8- **Desbois, M., Udyavar, A. R., Ryner, L., Kozlowski, C., Guan, Y., Dürrbaum, M., Wang, Y. (2020)**. Integrated digital pathology and transcriptome analysis identifies molecular mediators of T-cell exclusion in ovarian cancer. Nature communications, 11(1), 5583.

9- **Hodgson, A., & Turashvili, G. (2020)**. Pathology of hereditary breast and ovarian cancer. Frontiers in Oncology, 10, 531790.
10- **Falzone, L., Scandurra, G., Lombardo, V., Gattuso, G., Lavoro, A., Distefano, A. B., Scollo, P. (2021).** A multidisciplinary approach remains the best strategy to improve and strengthen the management of ovarian cancer. International Journal of Oncology, 59(1), 1-14.
11- **Akazawa, M., & Hashimoto, K. (2020).** Artificial intelligence in ovarian cancer diagnosis. Anticancer research, 40(8), 4795-4800.
12- **Zong, L., Zhou, Y., Zhang, M., Chen, J., & Xiang, Y. (2020).** VISTA expression is associated with a favorable prognosis in patients with high-grade serous ovarian cancer. Cancer Immunology, Immunotherapy, 69, 33-42.
13- **Lõhmussaar, K., Kopper, O., Korving, J., Begthel, H., Vreuls, C. P., van Es, J. H., & Clevers, H. (2020).** Assessing the origin of high-grade serous ovarian cancer using CRISPR-modification of mouse organoids. Nature communications, 11(1), 2660.
14- **Ismail, A., Abulsoud, A. I., Fathi, D., Elshafei, A., El-Mahdy, H. A., Elsakka, E. G., Doghish, A. S. (2022)**. The role of miRNAs in ovarian cancer pathogenesis and therapeutic resistance-A focus on signaling pathways interplay. Pathology-Research and Practice, 154222.
15- **Bast Jr, R. C., Lu, Z., Han, C. Y., Lu, K. H., Anderson, K. S., Drescher, C. W., & Skates, S. J. (2020).** Biomarkers and strategies for early detection of ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention, 29(12), 2504-2512.
16- **Atallah, G. A., Abd. Aziz, N. H., Teik, C. K., Shafiee, M. N., & Kampan, N. C. (2021).** New predictive biomarkers for ovarian cancer. Diagnostics, 11(3), 465.
17- **Manchanda, R., Lieberman, S., Gaba, F., Lahad, A., & Levy-Lahad, E. (2020).** Population screening for inherited predisposition to breast and ovarian cancer. Annual review of genomics and human genetics, 21, 373-412.
18- **Baroutsou, V., Underhill-Blazey, M. L., Appenzeller-Herzog, C., & Katapodi, M. C. (2021)**. Interventions facilitating family communication of genetic testing results and cascade screening in hereditary breast/ovarian cancer or lynch syndrome: A systematic review and meta-analysis. Cancers, 13(4), 925.
19- **Feng, Z., Zuo, K., Ju, X., Chen, X., Yang, W., Wen, H., Wu, X. (2023).** Risk-reducing salpingo-oophorectomy among Chinese women at increased risk of breast and ovarian cancer. Journal of Ovarian Research, 16(1), 125.
20- **Li, H., Liu, Y., Wang, Y., Zhao, X., & Qi, X. (2021).** Hormone therapy for ovarian cancer: Emphasis on mechanisms and applications. Oncology reports, 46(4), 1-27.
21- **Huang, J., Chan, W. C., Ngai, C. H., Lok, V., Zhang, L., Lucero-Prisno III, D. E., NCD Global Health Research Group of Association of Pacific Rim Universities (APRU). (2022).** Worldwide burden, risk factors, and temporal trends of ovarian cancer: A global study. Cancers, 14(9), 2230.
22- **Azizah, F., Mulawardhana, P., & Sandhika, W. (2021).** Association of age at menarche, parity, and hormonal contraceptive use with the histologic type of ovarian cancer. Gynecology Obstetrics Magazine, 29(3), 18-123.
23- **Sandvei, M. S., Pinborg, A., Gissler, M., Bergh, C., Romundstad, L. B., van Leeuwen, F. E., ... & Opdahl, S. (2023)**. Risk of ovarian cancer in women who give birth after assisted reproductive technology (ART)—a registry-based Nordic cohort study with follow-up from first pregnancy. British Journal of Cancer, 128(5), 825-832.
24- **Stewart, L. M., Stewart, C. J. R., Spilsbury, K., Cohen, P. A., & Jordan, S. (2020).** Association between pelvic inflammatory disease, infertility, ectopic pregnancy and the

development of ovarian serous borderline tumor, mucinous borderline tumor and low-grade serous carcinoma. Gynecologic Oncology, 156(3), 611-615.

25- **Nitecki, R., Clapp, M. A., Fu, S., Lamiman, K., Melamed, A., Brady, P. C., ... & Rauh-Hain, J. A. (2021).** Outcomes of the first pregnancy after fertility-sparing surgery for early-stage ovarian cancer. Obstetrics and gynecology, 137(6), 1109.

26- **Scadden, J. (2022).** Breastfeeding and Lactation Consulting. Fay W. Whitney School of Nursing, University of Wyoming, Honors Capstone Project, 9-15.

27- **Brennan, A., & Rees, M. (2021).** Menopausal hormone therapy in women with benign gynaecological conditions and cancer. Best Practice & Research Clinical Endocrinology & Metabolism, 35(6), 101575.

28- **Mandelbaum, R. S., Adams, C. L., Yoshihara, K., Nusbaum, D. J., Matsuzaki, S., Matsushima, K., ... & Matsuo, K. (2020).** The rapid adoption of opportunistic salpingectomy at the time of hysterectomy for benign gynecologic disease in the United States. American journal of obstetrics and gynecology, 223(5), 721-e1.

29- **Aiura, R., Nakayama, S., Yamaga, H., Kato, Y., & Fujishima, H. (2021).** Systemic thromboembolism including multiple cerebral infarctions with middle cerebral artery occlusion caused by the progression of adenomyosis with benign gynecological tumor: a case report. BMC neurology, 21(1), 1-8.

30- **Piek, J. M., van Lieshout, L. A., Hermens, R. P., Gelderblom, M. E., & de Hullu, J. A. (2020).** The rapid adoption of opportunistic salpingectomy at the time of hysterectomy for benign gynecological disease in the United States. American Journal of Obstetrics & Gynecology, 223(6), 948-949.

31- **Sunde, J., Wasickanin, M., Katz, T. A., Wickersham, E. L., Steed, D. E., & Simper, N. (2020).** Prevalence of endosalpingiosis and other benign gynecologic lesions. PLoS One, 15(5), e0232487.

32- **Kotsopoulos, J., & Narod, S. A. (2020).** Prophylactic salpingectomy for the prevention of ovarian cancer: who should we target?. International journal of cancer, 147(5), 1245-1251.

33- **Park, J., Huang, D., Chang, Y. J., Lim, M. C., & Myung, S. K. (2022).** Oral contraceptives and risk of breast cancer and ovarian cancer in women with a BRCA1 or BRCA2 mutation: a meta-analysis of observational studies. Carcinogenesis, 43(3), 231-242.

34- **Achimaș-Cadariu, P. A., Păun, D. L., & Pașca, A. (2023).** Impact of Hormone Replacement Therapy on the Overall Survival and Progression Free Survival of Ovarian Cancer Patients: A Systematic Review and Meta-Analysis. Cancers, 15(2), 356.

35- **Ji, E., Kim, K., Lee, B., Hwang, S. O., Lee, H. J., Lee, K., Kim, Y. B. (2022).** Postoperative Hormone Replacement Therapy and Survival in Women with Ovarian Cancer. Cancers, 14(13), 3090.

36- **Lee, H. J., Lee, B., Choi, H., Kim, T., Kim, Y., & Kim, Y. B. (2023).** Impact of Hormone Replacement Therapy on Risk of Ovarian Cancer in Postmenopausal Women with De Novo Endometriosis or a History of Endometriosis. Cancers, 15(6), 1708.

37- **El-Sherif, A., El-Sherif, S., Taylor, A. H., & Ayakannu, T. (2021).** Ovarian cancer: lifestyle, diet and nutrition. Nutrition and Cancer, 73(7), 1092-1107.

38- **Leung, L., Lavoué, J., Siemiatycki, J., Guénel, P., & Koushik, A. (2023).** Occupational environment and ovarian cancer risk. Occupational and Environmental Medicine.

39- **Singh, T., Neal, A. S., Moatamed, N. A., & Memarzadeh, S. (2020).** Exploring the potential of drug response assays for precision medicine in ovarian cancer. International Journal of Molecular Sciences, 22(1), 305.

40- **Westrick, A. C., Bailey, Z. D., Schlumbrecht, M., Hlaing, W. M., Kobetz, E. E., Feaster, D. J., & Balise, R. R. (2020).** Residential segregation and overall survival of women with epithelial ovarian cancer. Cancer, 126(16), 3698-3707.
41- **Funston, G., Hamilton, W., Abel, G., Crosbie, E. J., Rous, B., & Walter, F. M. (2020).** The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study. PLoS medicine, 17(10), e1003295.
42- **Timmerman, D., Planchamp, F., Bourne, T., Landolfo, C., du Bois, A., Chiva, L., Fotopoulou, C. (2021).** ESGO/ISUOG/IOTA/ESGE Consensus Statement on pre-operative diagnosis of ovarian tumors. International Journal of Gynecologic Cancer, 31(7).
43- **Fortner, R. T., Poole, E. M., Wentzensen, N. A., Trabert, B., White, E., Arslan, A. A., Tworoger, S. S. (2019).** Ovarian cancer risk factors by tumor aggressiveness: an analysis from the Ovarian Cancer Cohort Consortium. International journal of cancer, 145(1), 58-69.
44- **Bast Jr, R. C., Lu, Z., Han, C. Y., Lu, K. H., Anderson, K. S., Drescher, C. W., & Skates, S. J. (2020).** Biomarkers and strategies for early detection of ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention, 29(12), 2504-2512.
45- **Whitwell, H. J., Worthington, J., Blyuss, O., Gentry-Maharaj, A., Ryan, A., Gunu, R., ... & Timms, J. F. (2020).** Improved early detection of ovarian cancer using longitudinal multimarker models. British journal of cancer, 122(6), 847-856.
46- **Charkhchi, P., Cybulski, C., Gronwald, J., Wong, F. O., Narod, S. A., & Akbari, M. R. (2020).** CA125 and ovarian cancer: a comprehensive review. Cancers, 12(12), 3730.
47- **Zhang, M., Cheng, S., Jin, Y., Zhao, Y., & Wang, Y. (2021).** Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 1875(2), 188503.
48- **Banerjee, S., Moore, K. N., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., DiSilvestro, P. (2021).** Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology, 22(12), 1721-1731.
49- **Kim, M., Chen, C., Wang, P., Mulvey, J. J., Yang, Y., Wun, C., ... & Heller, D. A. (2022).** Detection of ovarian cancer via the spectral fingerprinting of quantum-defect-modified carbon nanotubes in serum by machine learning. Nature Biomedical Engineering, 6(3), 267-275.
50- **Rizzo, S., De Piano, F., Buscarino, V., Pagan, E., Bagnardi, V., Zanagnolo, V., ... & Aletti, G. (2020).** Pre-operative evaluation of epithelial ovarian cancer patients: Role of whole body diffusion weighted imaging MR and CT scans in the selection of patients suitable for primary debulking surgery. A single-centre study. European Journal of Radiology, 123, 108786.
51- **Ghose, A., Gullapalli, S. V. N., Chohan, N., Bolina, A., Moschetta, M., Rassy, E., & Boussios, S. (2022).** Applications of proteomics in ovarian cancer: dawn of a new era. Proteomes, 10(2), 16.
52- **Vergote, I., González-Martín, A., Ray-Coquard, I., Harter, P., Colombo, N., Pujol, P., ... & Witteveen, E. (2022).** European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer. Annals of Oncology, 33(3), 276-287.
53- **Shih, I. M., Wang, Y., & Wang, T. L. (2021).** The origin of ovarian cancer species and precancerous landscape. The American journal of pathology, 191(1), 26-39.
54- **Stewart, C., Ralyea, C., & Lockwood, S. (2019, April).** Ovarian cancer: an integrated review. In *Seminars in oncology nursing* (Vol. 35, No. 2, pp. 151-156). WB Saunders.

55- **Bonifácio, V. D. (2020).** Ovarian cancer biomarkers: moving forward in early detection. Tumor Microenvironment: The Main Driver of Metabolic Adaptation, 355-363.
56- **Kurian, A. W., Ward, K. C., Abrahamse, P., Bondarenko, I., Hamilton, A. S., Deapen, D., Katz, S. J. (2021).** Time trends in receipt of germline genetic testing and results for women diagnosed with breast cancer or ovarian cancer, 2012-2019. Journal of Clinical Oncology, 39(15), 1631.
57- **Falzone, L., Scandurra, G., Lombardo, V., Gattuso, G., Lavoro, A., Distefano, A. B., ... & Scollo, P. (2021).** A multidisciplinary approach remains the best strategy to improve and strengthen the management of ovarian cancer. International Journal of Oncology, 59(1), 1-14.
58- **Rizzo, S., Del Grande, M., Manganaro, L., Papadia, A., & Del Grande, F. (2020).** Imaging before cytoreductive surgery in advanced ovarian cancer patients. International Journal of Gynecologic Cancer, 30(1).
59- **Du Bois, A., Sehouli, J., Vergote, I., Ferron, G., Reuss, A., Meier, W., ... & Harter, P. (2020).** Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: Final analysis of AGO DESKTOP III/ENGOT-ov20.
60- **Lei, Z., Wang, Y., Wang, J., Wang, K., Tian, J., Zhao, Y., ... & Chinese Peritoneal Oncology Study Group. (2020).** Evaluation of cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for stage III epithelial ovarian cancer. JAMA network open, 3(8), e2013940-e2013940.