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«SURGICAL APPROACHES TO THE LESSER PELVIS AND THE PERINEUM»

MASTER'S THESIS

The role of systematic pelvic and para-aortic lymphadenectomy in the management of patients with advanced epithelial ovarian, tubal, or peritoneal cancer

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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Ο ρόλος της συστηματικής πυελικής και παραορτικής λεμφαδενεκτομής στην αντιμετώπιση ασθενών με προχωρημένο καρκίνο των ωοθηκών, των σαλπίγγων ή του περιτοναίου.

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ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

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Αφιερωμένο στη μνήμη της μητέρας μου, Φωτεινής.

ABSTRACT

Objective: To investigate whether systematic pelvic and para-aortic lymphadenectomy offers superior survival rates and less peri-operative complications in patients with advanced epithelial ovarian cancer (EOC), tubal, or peritoneal cancer.

Methods: We searched the electronic databases PubMed, Cochrane Central Register of Controlled trials, and Scopus from inception to September 2021. We considered randomised controlled trials (RCTs) comparing systematic pelvic and para-aortic lymphadenectomy with no lymphadenectomy in patients with advanced EOC. Primary outcomes were overall survival and progression-free survival. Secondary outcomes were peri-operative morbidity and post-operative mortality.

Results: 2 RCTs with a total of 1074 enrolled patients were included in our review. Meta-analysis demonstrated similar overall survival (HR = 1.03, 95% CI [0.85 – 1.24]) and progression-free survival (HR = 0.92, 95% CI [0.63 – 1.35]). Regarding peri-operative morbidity, systematic lymphadenectomy was associated with higher rates of lymphoedema and lymphocysts formation (HR = 7.31, 95% CI [1.89 – 28.20]) and need for blood transfusion (HR = 1.17, 95% CI [1.06 – 1.29]). No statistically significant differences were observed in regard to other peri-operative adverse events between the two arms.

Conclusions: Systematic pelvic and para-aortic lymphadenectomy is likely associated with similar overall survival and progression-free survival compared to no lymphadenectomy in optimally debulked patients with advanced EOC. Systematic lymphadenectomy is also associated with an increased risk for certain peri-operative adverse events. Further research needs to be conducted on whether we should abandon systematic lymphadenectomy in completely debulked patients during primary debulking surgery.

Keywords: *Ovarian neoplasms, epithelial ovarian cancer, systematic lymphadenectomy.*

ΠΕΡΙΛΗΨΗ

Σκοπός: Ο σκοπός της τρέχουσας εργασίας είναι να εξετάσει το ρόλο της συστηματικής πυελικής και παραορτικής λεμφαδενεκτομής σε ασθενείς με προχωρημένο καρκίνο των ωοθηκών, και πιο συγκεκριμένα να εξετάσει εάν η θεραπευτική αυτή μέθοδος προσφέρει μακρύτερη επιβίωση και λιγότερες μετεγχειρητικές επιπλοκές συγκριτικά με τη μη αφαίρεση της λεμφαδενικής αυτής αλυσίδας.

Μέθοδοι: Πραγματοποιήθηκε ανασκόπηση της υπάρχουσας βιβλιογραφίας με σκοπό την ανεύρεση τυχαιοποιημένων μελετών, οι οποίες συνέκριναν τη συστηματική λεμφαδενεκτομή με τη μη αφαίρεση των πυελικών και παραορτικών λεμφαδένων σε ασθενείς με προχωρημένο καρκίνο των ωοθηκών. Πρωτογενή αποτελέσματα της έρευνάς μας αποτέλεσαν η συνολική επιβίωση των ασθενών, καθώς και η άνευ νόσου επιβίωσή τους. Δευτερογενή αποτελέσματα αποτέλεσαν η μετεγχειρητική θνητότητα και θνησιμότητα.

Αποτελέσματα: Στην ανασκόπησή μας συμπεριελήφθησαν 2 τυχαιοποιημένες έρευνες, με συνολικό αριθμό συμμετάσχοντων ασθενών, 1.074 γυναίκες με προχωρημένο καρκίνο των ωοθηκών. Η μετα-ανάλυση των δεδομένων φανέρωσε ήσσονος σημασίας διαφορές, τόσο στη συνολική επιβίωση (HR = 1.03, 95% CI [0.85 – 1.24]), όσο και στην άνευ νόσου επιβίωση των ασθενών (HR = 0.92, 95% CI [0.63 – 1.35]), μεταξύ των δύο μεθόδων. Όσον αφορά τις μετεγχειρητικές επιπλοκές, η συστηματική λεμφαδενεκτομή φαίνεται να σχετίζεται με μεγαλύτερο ρίσκο για σχηματισμό λεμφοκυστών και λεμφοιδήματος (HR = 7.31, 95% CI [1.89 – 28.20]), καθώς και αυξημένο ρίσκο για ανάγκη μετάγγισης αίματος (HR = 1.17, 95% CI [1.06 – 1.29]). Δεν παρατηρήθηκαν σημαντικές διαφορές στις πιθανότητες για εμφάνιση λοιπών μετεγχειρητικών επιπλοκών μεταξύ των δύο μεθόδων.

Συμπεράσματα: Η συστηματική πυελική και παραορτική λεμφαδενεκτομή σχετίζεται με παρόμοια ποσοστά επιβίωσης και αυξημένο ρίσκο για ορισμένες μετεγχειρητικές επιπλοκές, συγκριτικά με τη μη συστηματική αφαίρεση λεμφαδένων σε γυναίκες με προχωρημένο καρκίνο των ωοθηκών.

GENERAL PART

Introduction

Ovarian cancer is a generic term that refers to any type of cancer that derives from the female ovary. Ovarian neoplasms are heterogenous and can resemble any type of cell lining of the normal adnexa, including germ cells, sex cord - stromal cells (e.g. granulosa cells, theca cells and Leydig cells) and epithelial cells. Neoplasms originating from the epithelial lining of the ovaries account for approximately 90% of all diagnosed cases of ovarian cancer[1].

Due to the lack of an effective screening method, the majority of ovarian cancer cases (~55%) are diagnosed at an advanced stage, at which the tumour has already metastasised to distant organs, more frequently to the peritoneum, the gastrointestinal tract, the liver or the spleen. Only 15% of patients are diagnosed at an early stage, while the tumour is confined to the ovary, thus making ovarian cancer a malignancy with poor overall prognosis. According to the National Cancer Institute of the United States, the overall 5-year survival of women with ovarian cancer is approximately 49%[2]. In patients with advanced disease, the 5-year survival is reduced to 30%[2].

Epithelial ovarian cancer (EOC) resembles a very complex genomic and histopathologic entity that requires a multi-disciplinary therapeutic approach. Consequently, this thesis project will focus on the pathogenesis, diagnosis, and treatment of EOC as it is responsible for the biggest fraction of ovarian cancer-related deaths.

Epidemiology

Ovarian cancer is the 2nd most common gynaecologic malignancy, yet the most lethal one, and is the 7th most common cancer affecting women worldwide[3]. According to the Global Cancer Observatory of the World Health Organization (WHO), in 2020 there were an estimated 313,959 new cases of ovarian cancer worldwide, as well as 207,252 ovarian cancer-related deaths[4]. Despite this relatively low incidence compared to other malignancies, ovarian cancer is the 5th leading cause of cancer deaths among women in the United States and the 8th leading cause of women's cancer deaths worldwide[5]. The incidence of ovarian cancer varies regionally and racially, with the highest incidence rates being observed in developed countries. Central and Eastern Europe encounter the highest incidence rates with 10.7 per 100,000 women, followed by Northern Europe and North America with 8.8 and 8.1 per 100,000 respectively. Intermediate incidence rates have been observed in Western Europe and Asia (6.2 to 7.1 per 100,000), while the lowest incidence rates can be found in Africa and the Caribbean (4.4 to 5.5 per 100,000) (Figure 1). Regarding the ethnic groups, Caucasian women hold the highest prevalence of ovarian cancer (12 per 100,000), followed by Hispanic (10.3 per 100,000), Asian (9.2 per 100,000) and African-American women (0.4 per 100,000)[6].

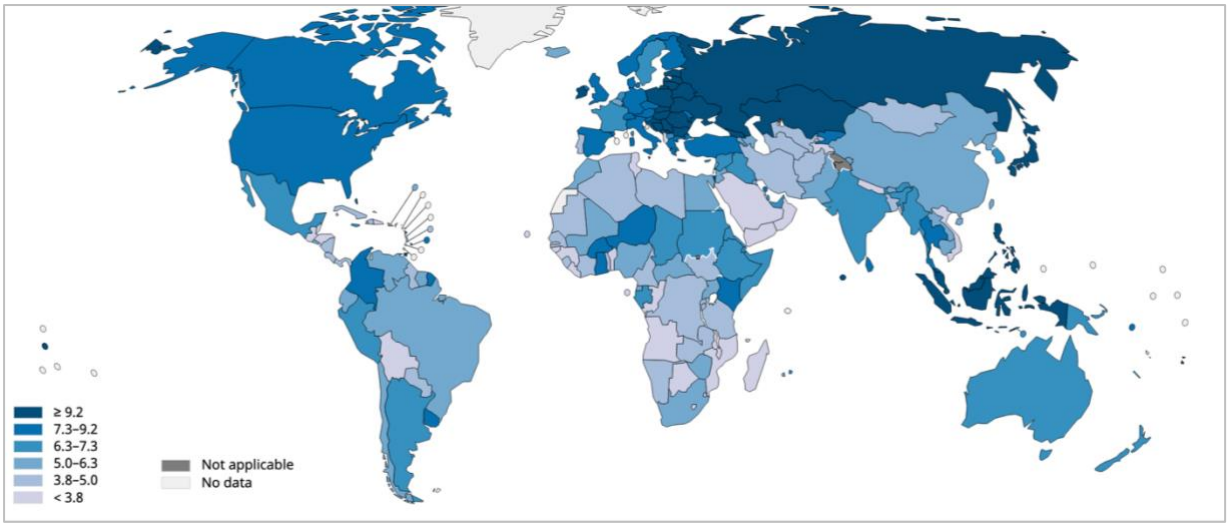


Figure 1. Age-standardised incidence rates by geographic region. Source: GLOBOCAN 2020.

Ovarian cancer incidence rates increase with age. The rates start to increase steadily by the age of 15 to 19 reaching a sharp increase at the mid-40s[7]. Women between the ages of 55 and 64 are in higher risk of developing the disease, with the median age at diagnosis being 63 years[8] (Figure 2). According to the National Cancer Institute of the United States, the percentage of deaths is higher among women of 65 to 74 years of age, while the median age at death is 70 years.

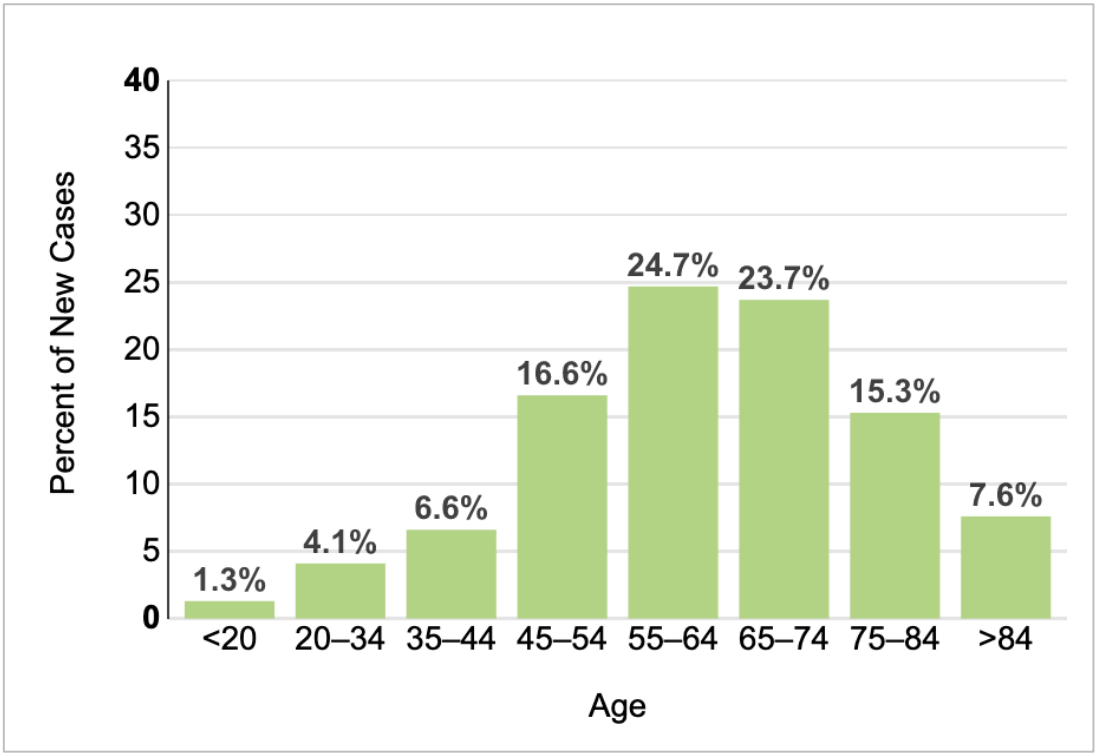


Figure 2. Percentage of new cases by age of diagnosis. Source: National Cancer Institute. Surveillance, Epidemiology and End Results Program (SEER).

EOC has the highest fatality/case ratio compared to all the gynaecologic malignancies, mainly because more than half of the patients are diagnosed at an advanced stage[9]. This could be attributed to tow main reasons; (1) the lack of an effective screening program in the general population, and (2) the lack of symptomatology of the disease at its early stages.

By comparison, ovarian cancer has a death/incidence ratio which is approximately 3 times higher than for breast cancer[10]. The 5-year survival rates are indicative of this fact, as they drop significantly in cases of women presenting with advanced stage disease (~30%). The overall 5-year survival for women diagnosed with ovarian cancer is approximately 49%, but this is highly influenced by the histological type, the age and the stage of the disease at the time of diagnosis[2]. Figures 3 and 4 present in detail the 5-year survival at each stage, as well as the percentage of case presentation by stage.

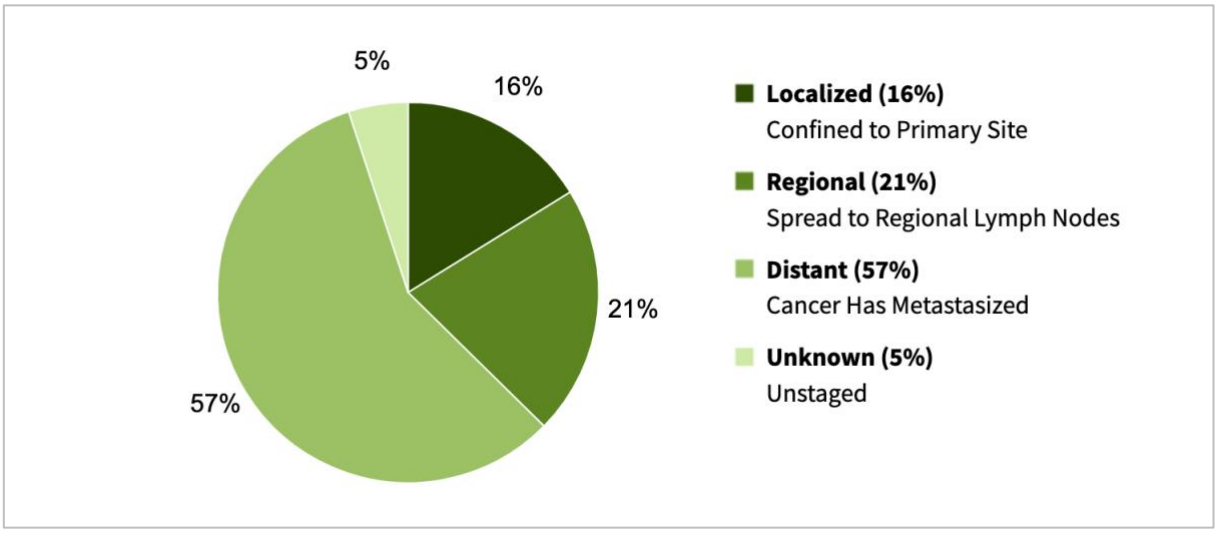


Figure 3. Extent of the disease at the time of diagnosis. Source: National Cancer Institute. Surveillance, Epidemiology and End Results Program (SEER).

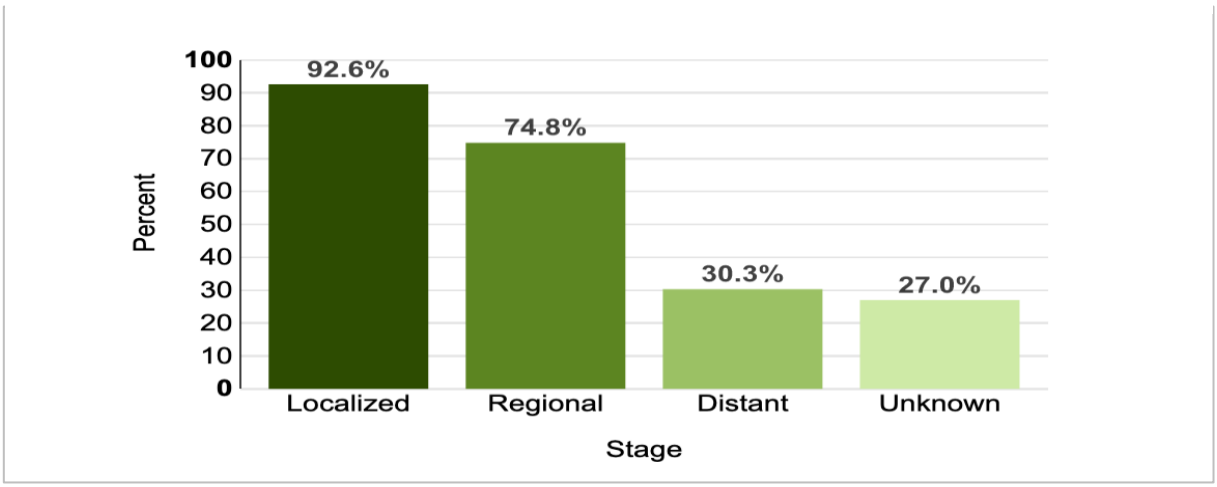


Figure 4. 5-year relative survival. Source: National Cancer Institute. Surveillance, Epidemiology and End Results Program (SEER).

Regarding the trends in the incidence rates of ovarian cancer, there has been a steady decrease in new cases observed every year for the last twenty years. The SEER program of the National Cancer Institute of the United States has reported an incidence rate of 9.3 per 100,000 women as for 2018, compared to 13 per 100,000 in 2008 and 14.4 per 100,000 in 1998. Mortality has also declined from 8.7 deaths per 100,000 in 1998 to 6 deaths per 100,000 in 2019[2]. However, the decline in mortality is quite small compared to other gynaecologic neoplasms in the last thirty years. For instance, mortality from breast cancer dropped by 1/3 and mortality from cervical cancer dropped by half at the same period[7]. Figure 5 summarizes the trends in incidence and mortality rates of ovarian cancer over the past years.

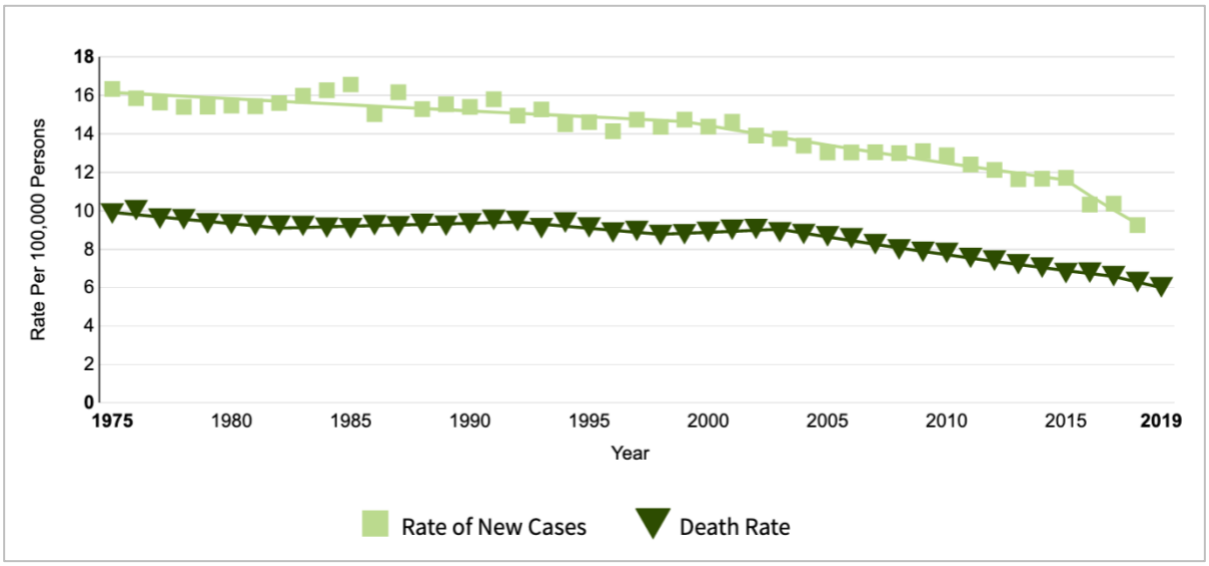


Figure 5. Incidence and mortality rates by year. Source: National Cancer Institute. Surveillance, Epidemiology and End Results Program (SEER).

Pathogenesis

Although the normal female adnexa is composed of various cell types, the majority of neoplasms arise from cells of the coelomic epithelium resulting in epithelial ovarian cancer (EOC)[11]. Neoplastic transformation of those cells may occur if they are genetically predisposed to oncogenesis or exposed to certain oncogenic agents.

Approximately 75-80% of EOCs are of serous histological type, the majority of which are high-grade cancers[8]. Less common subtypes include mucinous (10%), endometrioid (10%), clear cell (<1%), transitional cell carcinoma or Brenner's tumour (<1%) and undifferentiated tumours[11]. Each subtype resembles a different part of the epithelial structures of the female reproductive tract. For instance, serous EOC appears similar to the glandular epithelium of the fallopian tubes (endosalpinx). Mucinous tumours resemble the endocervical mucosa, while the endometrioid tumours mirror the endometrium.

Although it has been acknowledged that EOC is a multifactorial and complex entity, the specific events that lead to the transition of normal tissue to neoplasia have not yet been established, nor has a definite precursor lesion been identified[12]. Numerous theories exist regarding the origin of EOC. The predominant theory associates the repeated trauma and repair cycles of the ovarian epithelium during normal ovulation with subsequent genetic alterations that further progress to malignant transformation[12]. This is supported by evidence that suppression of ovulation leads to decreased risk for development of ovarian cancer[13].

A second theory assumes that EOCs originate from the fimbriated end of the fallopian tubes. In 2001, Piek et al. published a paper in which they reported the presence of dysplastic changes in

the fallopian tubes of women who went through prophylactic salpingo-oophorectomy due to genetic predisposition to ovarian cancer[14]. Those lesions, known as serous tubal intraepithelial carcinomas (STICs), resembled high-grade serous carcinoma (HGSC) of the ovaries, a common subtype of EOC. Later studies, in which the fimbriated end of the fallopian tubes of women diagnosed with EOC was extensively examined, identified STICs or small tubal high-grade serous carcinoma in 50-70% of cases, most of which had advanced-stage disease[15,16]. Collectively, those findings suggest that many cases of EOC might actually originate in the epithelium of the fallopian tube and later migrate and implant in the ovary giving the impression of a primary ovarian cancer[14]. HGSCs have also phenotypic characteristics similar to those of the fallopian tube mucosa, while they also share identical TP53 and other mutations[15]. Peritoneal serous carcinomas are also identical to serous EOC and fallopian carcinomas in terms of biologic behaviour, clinical characteristics, and response to chemotherapy. Thus, high-grade serous cancers of the ovaries, fallopian tube carcinomas and peritoneal carcinomas are now considered as a single entity[17]. Based on those data, patients with EOC, fallopian tube cancer and peritoneal cancer should be staged accordingly by the common International Federation of Gynaecology and Obstetrics (FIGO) system that was revised in 2014.

EOC is considered to be an invasive type of cancer. The biological features of EOC are unique, as they differ from the classic and well-studied pattern of hematogenous metastasis found in most types of cancers. The most common mode of dissemination is by exfoliation of cells that have already been formed in the primary site[12]. Once they have detached from the primary tumour, those cells metastasize via a passive mechanism, as they get carried along the circulatory pathway of the peritoneal fluid. As the peritoneal fluid moves with the force of respiration from the pelvis towards the diaphragm, passing through the paracolic gutters and the intestinal mesenteries, clusters of tumour cells are implanted within the peritoneal cavity[8].

Therefore, metastases are commonly located on the posterior cul-de-sac (Douglas pouch), paracolic gutters, right hemidiaphragm, liver capsule, peritoneal surface of the intestines and their mesenteries and the greater omentum, resulting in the characteristic omental cake.

Before ovarian tumour cells detach and start floating around the peritoneum, they often undergo an epithelial-to-mesenchymal transition, which facilitates their attachment to the basement membrane and loosens the intracellular adhesions between the cancer cells[18]. A crucial component for the adhesion of neighbouring cells is the glycoprotein E-cadherin, which is located at cell adherence junctions[19]. Loss of E-cadherin in EOC cells correlates with epithelial-to-mesenchymal transition and the acquisition of an invasive phenotype[20]. This process allows cancer cells' implantation to the peritoneum and facilitates their survival under crowded hypoxic conditions, through up-regulation of the fibronectin receptor $\alpha_5\beta_1$-integrin[21,22]. This adaptation to oxidative stress contributes to their high resistance in chemotherapy. Once the metastatic colony is established in the peritoneum, tumour cells undergo mesenchymal-to-epithelial transition once more into an epithelial phenotype, in order to sustain fast growth.

Hematogenous dissemination of EOC is rather uncommon. Only 2-3% of patients present with metastasis to vital organ parenchyma suggestive of hematogenous spread[8]. Systematic metastases are more frequently seen at the later stages in the course of the disease. Rather the lymphatic spread to the pelvic and para-aortic lymph nodes is the common behaviour of the tumour, particularly in advanced stages of EOC[23]. Further dissemination can occur via the diaphragmatic lymphatic channels, infiltrating the supraclavicular lymph nodes.

Prevention

Risk factors

The lifetime risk of ovarian cancer in the general population is approximately 1.2%. However, the risk increases with the presence of risk factors, the most significant of which is a positive family history of breast or ovarian cancer[12]. There has been identified a 3-fold increase in the overall risk of developing ovarian cancer in women with a first degree relative with ovarian cancer[24]. Certain hereditary cancer syndromes can be responsible for the development of ovarian cancer, raising the lifetime risk up to 50% depending on the syndrome[12]. Hereditary cancer syndromes that have been associated with the development of ovarian cancer to date are: hereditary breast and ovarian cancer syndrome (most commonly associated with BRCA1, BRCA2 germline mutations), Lynch's syndrome, and Peutz-Jeghers syndrome[25].

Most of the known risk factors are not accountable to change, with early menarche (prior to age 12), late menopause (after age 50) and age being the most notable. Other major risk factors include nulliparity, obesity, increased number of lifetime ovulatory cycles and the presence of hereditary cancer syndromes. Endometriosis is an independent risk factor of EOC, with malignant transformation occurring in approximately 2.5% of patients, who are typically of reproductive age, and is associated with 15-20% of clear cell and endometrioid ovarian cancer[26]. Ethnic differences confer variable risk. Caucasians have the highest age-adjusted annual incidence compared to Hispanics, African-Americans and Asians[2]. Finally, the results of a recent meta-analysis published in 2018 reported a consistent association between perineal talc use and development of ovarian cancer[27]. A recent pooled analysis of four large cohorts suggested a statistically significant association of perineal talc use with the development of ovarian cancer in women with patent reproductive tracts, compared with women that had

undergone tubal ligation or hysterectomy, suggesting a retrograde movement of the powder within healthy genital tracts[28]. Nonetheless, there has been a major controversy in regards with the significance of these results.

Protective factors

On the other hand, certain protective factors have been identified to reduce the risk of EOC. Oral contraceptive pills (OCPs) have been proven to exert duration-dependent reductions in ovarian cancer incidence in the general population[29]. Women who use OCPs for 5 or more years reduce their relative risk to 0.5, which accounts for a 50% reduction in the probability of developing ovarian cancer. Parity is also considered a major protective factor against EOC. In fact, having at least one child ensures a risk reduction of 0.3 to 0.4. Moreover, women who have had two children and have used OCPs for 5 or more years have a 70% reduction in the likelihood of developing ovarian cancer[30]. As a result, OCPs could be considered as a reliable and relatively safe means of chemoprevention, especially for women with a positive family history of ovarian cancer.

Prophylactic salpingo-oophorectomy is one of the few surgical measures for risk reduction mainly in high-risk patients with a strong family history or a known BRCA1 or BRCA2 mutation. Bilateral surgical removal of the fallopian tubes and the ovaries significantly reduce, but not eliminate the risk of ovarian cancer, since similar malignancies may arise from the peritoneum or the secondary mullerian system as discussed previously. Tubal ligation is also a broadly accepted risk-reducing surgery, which incorporates the benefit of a less invasive procedure in comparison with bilateral salpingo-oophorectomy. Tubal ligation seems to reduce the risk for ovarian cancer in both high genetic risk and average genetic risk populations[31]. This

risk reduction, which is up to 33%, mainly affects the endometrioid and clear cell histologic subtypes, while it is estimated to last for up to 14 years post-surgery[32].

In a study published by Pearce et al. in 2015, the distribution of lifetime risk of ovarian cancer in the general population of the U.S. was closely examined. The results associated the use of OCPs and tubal ligation with a reduced lifetime risk for the development of ovarian cancer. On the other hand, OCPs use and tubal ligation were absent among women with the higher lifetime risk[33]. More precisely, women with the lowest lifetime risk (0.35%) were those who had at least two children, had used OCPs for at least 5 years and had a prophylactic tubal ligation, with a negative family history. On the contrary, nulliparous women, who had never used OCPs and had a positive family history without having a prophylactic tubal ligation, were at higher risk of developing ovarian cancer (8.78%).

Screening

The most profound reason for the high mortality rates of EOC is the late stage at which most women are diagnosed. For this reason, researchers' interest has shifted towards strategies for early diagnosis using certain biomarkers combined with imaging techniques. Currently, there is no proven effective screening method for early detection of ovarian cancer. The use of cancer antigen 125 (CA-125), a biomarker that has been previously tested as a screening method, has not shown promising results mainly because of its low sensitivity and specificity[34]. CA-125 can be markedly elevated in patients with benign ovarian tumours, in non-gynaecologic malignancies and any other inflammatory condition of the pelvis. Furthermore, CA-125 serum levels are elevated above baseline in only half the women diagnosed with stage I or stage II ovarian cancer. However, data suggests that specificity of CA-125 is improved when its levels

are followed overtime[35]. Thirty years after its discovery, CA-125 is still FDA-recommended for monitoring of treatment response in patients with EOC.

Human epididymis 4 (HE-4) protein is a second biomarker that seems to be of some diagnostic value for ovarian cancer. Compared to CA-125, HE-4 has a similar sensitivity for detection of advanced-stage ovarian cancer, but a greater specificity in differentiating between malignant and benign tumours[36]. The combined use of HE-4 and CA-125 was incorporated in the risk of ovarian malignancy algorithm (ROMA), which was FDA-approved in 2011. ROMA combines the measurements of those biomarkers with the menopausal status of the patient in order to determine the risk for malignancy in any woman presenting with a pelvic mass[37]. However, as with CA-125, HE-4 levels are not specific for ovarian cancer, as they are also elevated in individuals with other gynaecologic malignancies as well as cancers of the respiratory tract[38]. Nevertheless, the remarkable increase in both biomarkers' serum levels in women with ovarian neoplasms support the need for further research on their practicality as tools for early detection.

In addition, imaging techniques have not been proven to effectively detect ovarian cancer at an early stage. Transvaginal sonography (TVS) has not shown any value as primary screening tool, as it is mostly used for diagnosis of benign masses, which are confined in the ovaries. Unfortunately, most cases of EOC would have already metastasised before being detectable under TVS. In support with that, current studies do not show a benefit in screening asymptomatic population with TVS[39]. Magnetic resonance imaging (MRI) and computed tomography (CT) are commonly used as staging tools[40]. Early stages of ovarian cancer development may be missed by both imaging modalities, with CT having an even lower sensitivity compared to MRI for distinguishing benign from malignant masses[41,42].

A recently published randomised trial conducted in the United Kingdom, the UKCTOCS trial, compared the existing modalities in an attempt to establish an ovarian cancer screening program that could potentially reduce ovarian-cancer related deaths[43]. Women were randomly assigned to annual multimodal screening (which incorporated CA-125 measurements by utilising the ROCA algorithm), annual TVS screening, or no screening. No significant reduction in ovarian and tubal cancer deaths was observed in the multimodal screening or the group screened by TVS compared to the no screening group. This was the most recent randomised trial of that scale that attempted to explore an effective screening program for the general populations. Unfortunately, screening for ovarian cancer cannot be recommended to date.

Clinical findings

Signs and symptoms

Early stage EOC is associated with poorly defined or vague symptoms, which are usually of minor severity to prompt a woman to seek medical advice. This is one of the two major reasons (the other being the lack of an effective screening method) why nearly 60% of women with ovarian cancer present with distal metastases at the time of diagnosis[2]. The most common symptoms of women with ovarian cancer include bloating, pelvic or abdominal pain or pressure, urinary frequency or urgency, difficulty eating and early satiety[44]. This non-specific nature of the symptoms renders early detection even harder, as they are not usually associated with gynaecologic issues even by healthcare practitioners. Yet, there are only minor differences in the symptoms reported by women with early-stage disease and those with late-stage ovarian cancer[45]. Occasionally, patients may present with anorexia and nausea secondary to ascites or bowel obstruction, while dyspnoea is also a common symptom due to pleural effusions. Ascites and pleural effusions are two entities that usually coexist in patients with advanced EOC.

The most significant finding on clinical examination of women with EOC is the presence of a pelvic mass[8]. A solid, fixed, irregular pelvic mass is highly suggestive for malignancy. If, in addition, an abdominal mass or ascites is present, the diagnosis of ovarian cancer is almost definite. A tympanic percussion noted over the lateral abdomen of the patient indicates the presence of a large mass that displaces the bowel to the periphery. On the contrary, a central tympanic percussion note is highly suggestive of ascetic fluid[12]. Women of reproductive age could present with menstrual abnormalities. Abnormal vaginal bleeding should raise concern for a synchronous endometrial carcinoma or metastasis to the lower genital tract.

Laboratory findings

CA-125 is the most widely used tumour marker yet is mainly used for follow-up purposes as its sensitivity and specificity is low. The accepted upper limit of normal is 35 IU/mL, but this is a rather arbitrary cut-off. Women with a disseminated EOC can appear with extremely high values of CA-125 (>200IU/mL). However, normal values do not rule out the diagnosis of EOC. HER-4 is less frequently used, but it seems to have greater specificity than CA-125 for the detection of ovarian cancer in premenopausal women and it may be used for excluding EOC in these patients[46]. Inflammatory markers (e.g. C-reactive protein) may be elevated.

Imaging studies

Transvaginal sonography can facilitate differentiation between a benign and a malignant adnexal mass. Typical characteristics of ovarian cancer under the ultrasound include a solid component, which is often nodular or papillary, septations, and ascites[12]. In addition, the use of colour flow Doppler can evaluate the vascular patters that may be suggestive of malignancy[47]. However, a definite diagnosis cannot be made unless malignancy is proven by histology.

CT and MRI are commonly used for staging purposes, in the case of the former, and for visualization of the retroperitoneal structures, in the case of the latter. MRI has also been beneficial in cases of ovarian cancer during pregnancy, as it does not emit radiation which is harmful to the foetus. Among other imaging modalities, a patient with suspected ovarian malignancy should undergo a chest radiograph in order to exclude any metastatic parenchymal disease, as well as to detect a possible pleural effusion.

Diagnosis

The accurate diagnosis of EOC can be challenging, especially in women presenting with advanced-stage disease, because many tumours of the gastrointestinal tract can imitate the pattern of dissemination of ovarian cancer at initial presentation[48]. The definite diagnosis of EOC requires histologic examination of the resected adnexa[8]. Generally, a detailed pathological and surgical report is necessary for both the characterization of the tumour and the planning of the treatment protocol.

Before surgical exploration, the patient should undergo detailed biochemical and haematologic assessments. The preoperative evaluation should also include a radiograph of the chest for detection of possible pleural effusion. It is of paramount importance to exclude the presence of other primary malignancies that could metastasize to the ovaries. A breast examination and mammography should be performed in order to rule out a primary breast cancer. Women with menstrual irregularities or metrorrhagia should undergo curettage and endometrial biopsy to exclude the presence of a metastatic or synchronous endometrial cancer. Finally, gastroscopy and colonoscopy may deem necessary in order to exclude a possible Krukenberg tumour or any other primary malignancy of the gastrointestinal tract. For the latter, the carcinoembryonic antigen (CEA) to CA-125 ratio can also be utilised.

Initial surgical staging for EOC can be performed either with laparotomy or laparoscopically, with the latter providing a minimally invasive and safe technique which is well researched and broadly accepted[49]. Important information that should be disclosed in every surgical report includes an accurate description of the biopsy sites and a comprehensive documentation of the

extent of any residual disease, in case a primary debulking surgery (PDS) is performed. According to the College of American Pathologists Protocol for the examination of specimens from patients with ovarian carcinomas, the pathological report of the collected tissue should describe in detail the following:

- Specimen site of collection
- Procedure followed during specimen collection
- Lymph node sampling present or absent
- Specimen integrity
- Primary tumour site
- Ovarian surface involvement
- Tumour dimensions
- Histologic type
- Histologic grade
- Presence of implants
- Extent of involvement of other tissues/organs
- Lymph/vascular invasion
- Pathologic staging stage
- Any additional pathologic findings

Once the diagnosis of epithelial ovarian cancer is established by pathological evaluation, the treatment plan decided by the multidisciplinary team (MDT) is initiated.

Differential diagnosis

The differential diagnosis of a pelvic mass is influenced by the age of the patient, the characteristics of the mass on pelvic examination, and its radiographic appearance. In general EOC must be differentiated from benign tumours and functional cysts of the ovaries[50]. In terms of the patient's age, prepubescent children as well as postmenopausal women are at greatest risk for a malignant ovarian neoplasm, whereas women of reproductive age are more likely to have a functional ovarian cyst or endometrioma[12]. Generally, a variety of benign gynaecologic conditions including pelvic inflammatory disease, endometriosis and pedunculated uterine leiomyomata can resemble EOC. Mature teratomas are an example of ovarian tumour primarily found in women of reproductive age (20-30 years of age). It is the most common neoplasm diagnosed during pregnancy and only 1% of them are malignant[51]. Another benign ovarian tumour that can imitate EOC is the ovarian fibroma, which is strongly associated with Meigs' syndrome[52]. The characteristic triad of the syndrome includes the presence of ovarian fibroma, ascites, and pleural effusion, which collectively resembles EOC.

One of the methods used to differentiate between a benign and a malignant ovarian tumour is the risk of malignancy index (RMI)[53]. The RMI incorporates the menopausal status, the sonographic characteristics of the tumour, the presence of metastasis and the serum CA-125 levels. In an analysis of 204 patients with an ovarian mass, an RMI<200 correctly identified 77% of benign tumours and 91% of invasive ovarian neoplasms. An RMI of > 200 had a sensitivity of 84%, specificity of 77%, positive predictive value of 76% and negative predictive value of 85% in detecting both borderline and invasive ovarian tumours, showing promising results[50].

Finally from an infectious diseases point of view, female peritoneal tuberculosis can be an excellent imitator of disseminated peritoneal carcinomatosis, a characteristic feature of EOC[54,55]. The differentiation between female peritoneal tuberculosis and peritoneal carcinomatosis with normal-sized ovaries by CT may raise a diagnostic challenge for physicians. In such cases, heterogeneous parenchymal hyper-attenuation and capsular changes of the ovary may raise the concern of ovarian cancer[56]. In all cases, non-gynaecologic malignancies should always be considered and closely investigated as they could alter the therapeutic plan and modify the prognosis.

Staging

Cancer staging can be either pathological or clinical. Pathological staging is usually considered more accurate as it allows a thorough examination of the tumour and its spread, in contrast with the clinical staging which is confined to indirect observation of the tumour in relation to its anatomical position in the body. However, clinical and pathological staging should complement each other, especially in the case of epithelial ovarian cancer, which is a malignancy with extensive metastases, thus accurate staging provides a better management of the patient.

Ovarian cancer is staged according to the AJCC/TNM or FIGO classification system. The first system describes the extent of the primary tumour (T), the presence of metastasis to adjacent lymph nodes (N) and the presence of distal metastases (M). The FIGO classification system is more commonly used for ovarian cancer and is based on findings during surgical exploration. The FIGO classification was last modified in 2014.

Surgical staging is of paramount importance in EOC, since the subsequent therapeutic scheme will be determined by the stage of the disease. According to the standard protocol, surgical exploration is performed through a laparotomy, which allows access to the upper abdomen. The ovarian tumour should be resected and removed intact, and a frozen histologic section obtained. The confirmation or not of ovarian malignancy determines the next steps of the operation.

Table 11.1 FIGO Staging Cancer of the Ovary, Fallopian Tube, and Peritoneum (2014)		
FIGO		*TNM*
Ov	**Primary tumor, ovary**	Tov
FT	**Primary tumor, fallopian tube**	Tft
P	**Primary tumor, peritoneum**	Tp
X	**Primary tumor cannot be assessed**	Tx
Designate histologic type:		
High-Grade Serous (HGS), Endometrioid (E), Clear Cell (CC), Mucinous (M), Low-Grade Serous (LG), Other or cannot be classified (O); Germ Cell (GC), Sex-Cord Stromal Cell Tumor (SC)		
Stage I	**Tumor confined to ovaries or fallopian tube(s)**	T1
IA	Tumor limited to one ovary (capsule intact) or fallopian tube	T1a
	No tumor on ovarian or fallopian tube surface	
	No malignant cells in the ascites or peritoneal washings	
IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes	T1b
	No tumor on ovarian or fallopian tube surface	
	No malignant cells in the ascites or peritoneal washings	
IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:	T1c
IC1	Surgical spill intraoperatively	
IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface	
IC3	Malignant cells in the ascites or peritoneal washings	
Stage II	**Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)**	T2
IIA	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries	T2a
IIB	Extension to other pelvic intraperitoneal tissues	T2b
Stage III	**Tumor involves one or both ovaries, fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**	T3
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis	T1, T2, T3aN1
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)	
IIIA1(i)	Metastasis ≤10 mm in greatest dimension	
IIIA1(ii)	Metastasis >10 mm in greatest dimension	
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a/T3aN1
IIIB	Macroscopic peritoneal metastases beyond the pelvic brim ≤2 cms in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b/T3bN1
IIIC	Macroscopic peritoneal metastases beyond the pelvic brim >2 cms in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1)	T3c/T3cN1
Stage IV	**Distant metastasis excluding peritoneal metastases**	Any T, Any N, M1
IVA	Pleural effusion with positive cytology	
IVB	Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity)	
Note 1: Includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ		
Note 2: Parenchymal metastases are stage IVB		

Figure 6. FIGO and respective TNM staging of ovarian, fallopian tube and peritoneal cancer. Source: Berek and Hacker's Gynecologic Oncology.

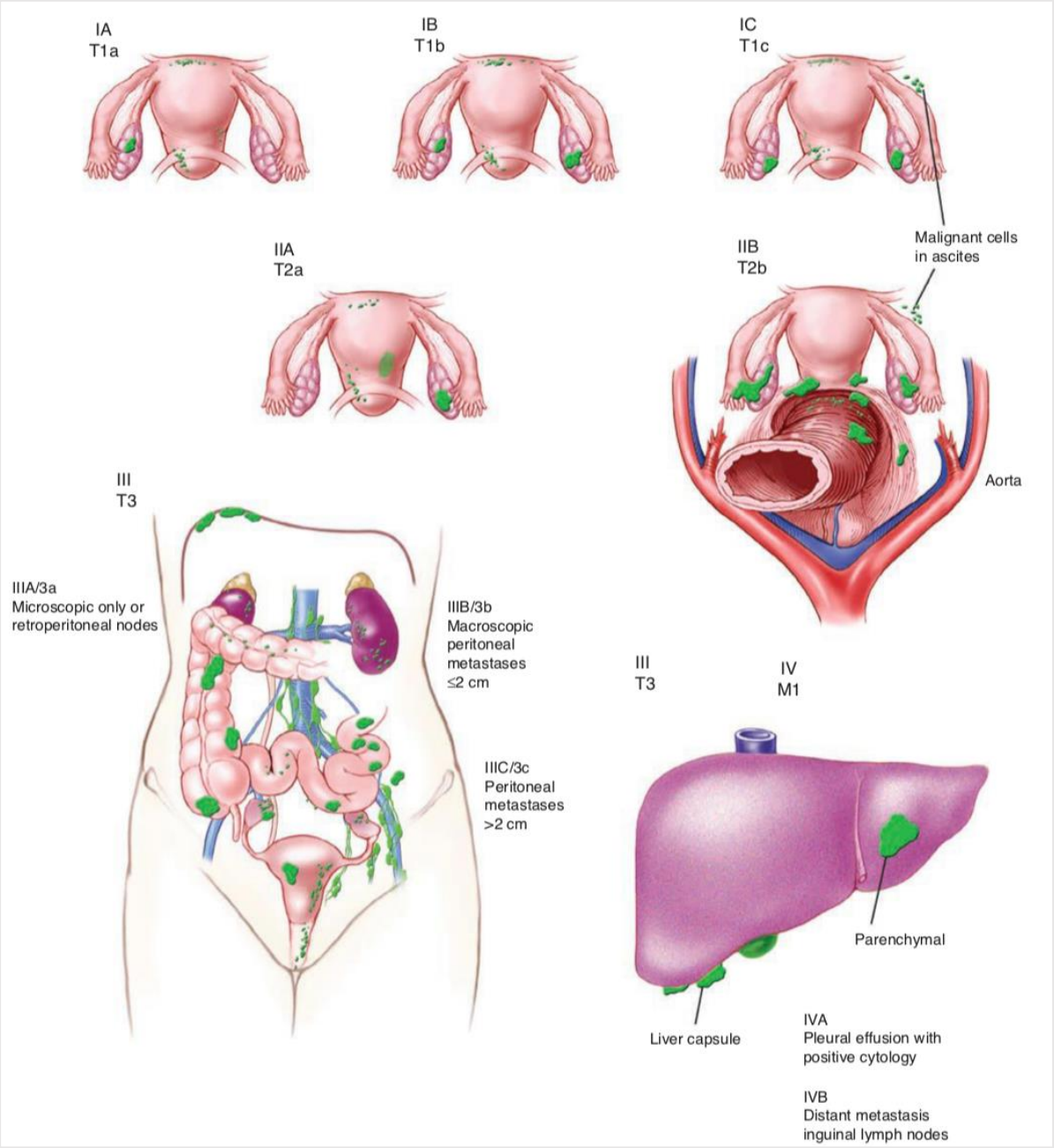


Figure 7. FIGO and TNM staging. Source: Berek and Hacker's Gynecologic Oncology.

The last years, minimally invasive surgery has gained ground in the field of surgical staging of ovarian cancer. Many studies report certain advantages of laparoscopic staging over the standard laparotomy[49,57]. Intraperitoneal diffusion of the disease may be assessed adequately with laparoscopy and the surgeon can have direct visualization of the cancer spread at excellent image quality and high magnification. Even more importantly, patients deemed not to be

candidates for cytoreduction may proceed immediately to neoadjuvant chemotherapy protocol without having to recover from laparotomy-related complications[49]. The Fagotti score can be utilised in order to predict the surgical outcome and divert patients to neoadjuvant chemotherapy or proceed with laparotomy and primary debulking surgery. Regardless the technique used, it is crucial that a complete and detail staging is performed in all women presenting with EOC by surgeons with expertise in the field, as this provides the best possible outcomes[58].

Treatment

The treatment plan in ovarian cancer is determined by the histologic type of the tumour, the grade and the FIGO stage of the patient at the time of diagnosis. As the current thesis project is dedicated to the treatment of choice in women with advanced stage EOC, the following text will focus on the standard therapeutic protocol in each stage.

Early stage epithelial ovarian cancer

The treatment of stage I EOC is primarily surgical. During surgery, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and surgical staging are performed[59]. Women of child-bearing age that have had a thorough surgical staging without any signs of spread beyond the ovary may undergo fertility-sparing surgery with unilateral salpingo-oophorectomy, in case they desire pregnancy. However, those women should be closely followed with routine transvaginal sonographies and serum CA-125 level measurements. The contralateral ovary and the uterus should be removed after completion of childbearing.

Patients with early-stage epithelial ovarian cancer of grade 1 or 2 are of no need of adjuvant therapy as confirmed by prospective studies. The 5-year survival of those patients according to a randomized trial published in 1990 without any treatment after initial surgery was 94%[60]. In patients with suspicious features, such as poorly differentiated carcinomas or presence of malignant cells either in ascitic fluid or in peritoneal washings, additional treatment is warranted. Adjuvant chemotherapy, which can either be single agent carboplatin or a platinum-taxane combination is the treatment of choice for those patients[60,61]. Carboplatin can be substituted for cisplatin as it is better tolerated, causes less side effects, and has similar

efficacy[62]. Even though radiotherapy is a therapeutic option that belongs to the past for epithelial ovarian cancer, a population-based study published by British Columbia in 2011, reported that patients with stage I and II non-serous EOC who received whole abdomen and pelvis radiotherapy exhibited a 43% reduction in overall mortality[63]. Report of a separate analysis including 241 patients with stage I and II clear cell ovarian cancer showed that adjuvant irradiation was associated with improved progression-free survival, while it reduced pelvic relapse rates from 62% to 76%[64]. Abdominal recurrence occurred in 42% with chemotherapy and only 13% with whole-abdominal and pelvic irradiation. Following those promising results, there has been renewed interest in the role of radiotherapy in early stage ovarian cancer.

Advanced stage epithelial ovarian cancer

- **Cytoreductive surgery**

The management of patients with advanced EOC, tubal, or peritoneal cancer is primarily surgical, with few modifications made according to the performance status of the patient. If the patient is deemed a suitable candidate, she should undergo an initial exploratory procedure - either by laparoscopy or laparotomy- followed by removal of as much disease as possible according to the standard treatment protocol. If the initial exploration was performed by laparoscopy, the gynaecologic oncologist should convert the procedure to laparotomy. The operation to remove the primary tumour as well as any associated metastases in referred as cytoreductive or debulking surgery[8]. The ultimate goal of cytoreductive surgery is to achieve complete cytoreduction; that is excision of the primary tumour with a bilateral salpingo-oophorectomy together with all macroscopically visible metastatic carcinomatosis. If complete cytoreduction is not possible, residual disease of <1cm is described as optimal cytoreduction. Of late, optimal cytoreduction was deemed acceptable or even the main goal of primary debulking surgery. In the last years there is a radical shift towards complete cytoreduction, while optimal debulking is abandoned, as there is enough evidence that zero residual disease is the most crucial prognostic factor[65]. Patients that raise concerns regarding the feasibility of complete debulking, should rather undergo neoadjuvant chemotherapy.

The respectability of the metastatic tumour is highly dependent on the location and the extent of the metastatic disease. For instance, complete cytoreduction may not be feasible in the presence of extensive disease on the diaphragm, in the liver parenchyma, in the lesser omentum and along the base of the small bowel mesentery[66]. Nonetheless, the goal of cytoreductive surgery should always remain complete cytoreduction, as patients with a completely resected

primary and metastatic disease have the best prognosis and approximately 60% of them will be free of disease at 5 years[65]. In cases where complete cytoreduction is not feasible, extensive bowel and urologic resections are not indicated, unless there are signs of potential bowel obstruction. Yet surgical excision of the primary tumour and omental cake in those patients is usually feasible and results in an improvement of symptoms.

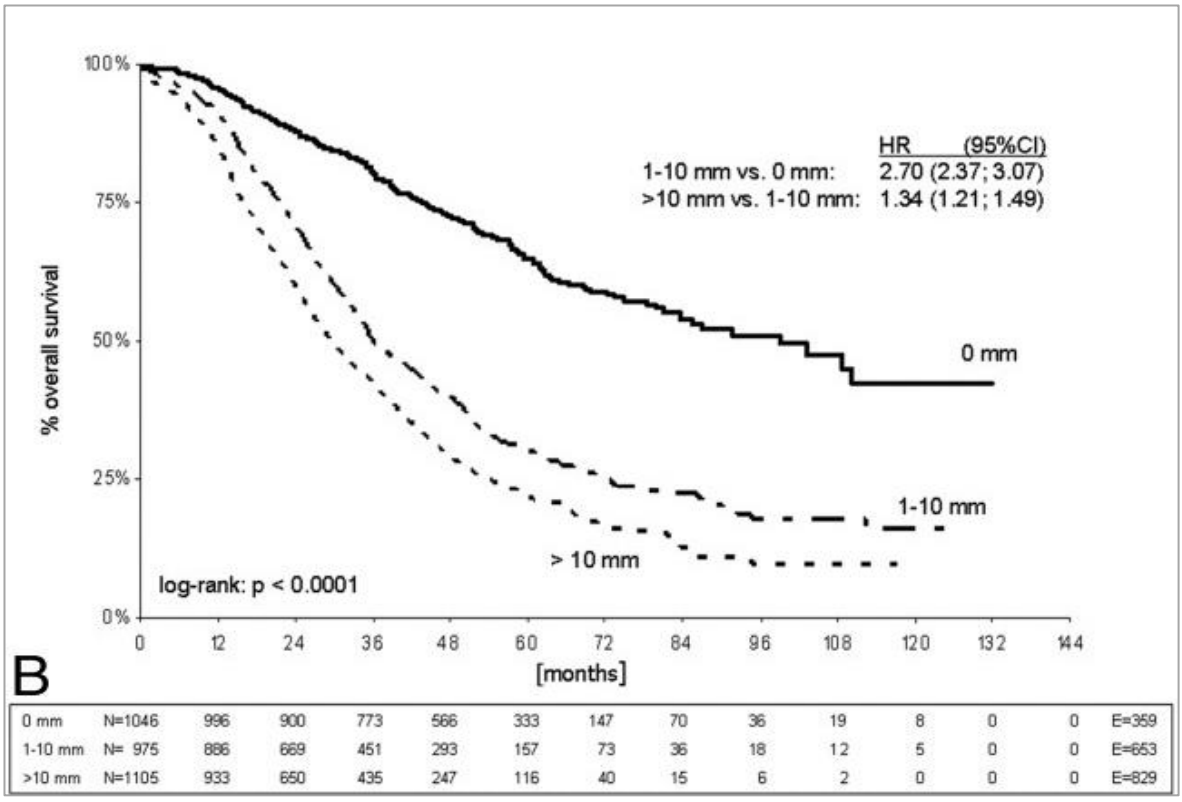


Figure 8. Overall survival by residual disease after cytoreductive surgery.
Source: duBois et al. 2009. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 trials. *Cancer.* 2009 Mar 15;115(6):1234-44.

The most characteristic feature of advanced EOC, tubal or peritoneal cancer is the omental cake caused by the dissemination of the disease in the greater omentum. Infracolic omentectomy is recommended in all cases of advanced-stage ovarian cancer, even in the absence of gross tumour involvement, because it is a common site of microscopic metastatic disease. Occasionally, a splenectomy might be necessary in order to resect all the omental carcinomatosis[67].

A hysterectomy is generally performed because the uterus is a common site for metastatic disease, while there is also a risk of synchronous endometrial cancer in patients with endometrioid carcinoma of the ovary. Some surgeons also perform appendectomy as a routine part of the staging procedure. Studies show that greater than 10% of these patients have microscopic metastases in normal-appearing appendixes[68]. However, routine appendectomy is controversial as many studies support that the appendix should only be removed in cases of mucinous tumours or an abnormally appearing appendix[69].

Finally, lymphadenectomy is the last crucial part of cytoreductive surgery, although controversial. Accounting for the prognostic importance of lymphatic metastasis, the FIGO staging classification was amended to include a sub-stage for nodal involvement. Although there have been reports that a systematic pelvic and para-aortic lymphadenectomy improves survival, there are no extensive studies to support this. All studies supporting the impact of systematic pelvic and para-aortic lymphadenectomy on survival of patients with EOC have been retrospective series, which are prone to a certain degree of selection bias. On the contrary, the first international randomised trial published in 2005 recruited 427 women with advanced epithelial ovarian carcinoma to undergo either systematic pelvic and para-aortic lymphadenectomy or resection of bulky nodes only. The results showed that there was no difference in 5-year overall survival (48.5% vs. 47%, respectively)[70]. Moreover, results from further studies have shown that systematic lymphadenectomy is associated with a risk of vascular injury, lymphocysts formation, lymphoedema, pulmonary embolism and post-operative mortality even when performed by experienced surgeons[71]. In any case, the controversy still exists and there is room for further research regarding the role of systematic lymphadenectomy in advanced-staged epithelial ovarian cancer. The specific part of this thesis project is dedicated to the potential harms and benefits of systematic pelvic and para-aortic

lymphadenectomy when treating women with advanced EOC and whether it should be established as standard of care during primary debulking surgery.

- **Chemotherapy**

After initial cytoreduction, adjuvant systemic chemotherapy is used as standard of treatment. Platinum and taxane-based combination is the standard chemotherapeutic regimen for women with advanced EOC[8]. Combination chemotherapy has been proven superior to any monotherapy treatment by most studies in patients with advanced EOC[72,73]. Agents shown to be effective include cisplatin, carboplatin, cyclophosphamide and paclitaxel, the most effective regimen being the combination of paclitaxel and carboplatin[74,75]. Typically, chemotherapy is started 4–6 weeks after surgical intervention and is administered at 6-8 cycles in 3-week intervals[12]. Earlier administration has not been shown to provide a benefit. Potential toxicities of this treatment include nausea, vomiting, diarrhoea, alopecia, nephrotoxicity, and myelosuppression. The chemotherapeutic agents are typically administered intravenously. However, newer studies have tried to investigate the value of intraperitoneal administration of chemotherapy. The results are controversial as some studies report better survival while other studies report worse perioperative outcomes and more complications without any survival benefits[76–78]. The ongoing OVHIPEC-2 international, randomised trial could probably add to our existing knowledge on the potential harms and benefits of hyperthermic intraperitoneal chemotherapy administration in patients with advanced EOC[79]. The results of this trial are expected within 2026.

The majority of patients develop resistance to platinum-based regimens during the course of treatment. Salvage therapy for ovarian cancer is rarely curative, although significant prolongation of survival may be achieved in some cases. The response to re-treatment with

platinum-based chemotherapy is influenced by the time interval between completion of the initial regimen and subsequent disease recurrence; the greater the interval, the greater is the probability of good response[12]. In 2019, a randomised phase III trial carried out by Coleman et al. examined the role of secondary surgical cytoreduction in patients with recurrent ovarian cancer[80]. Patients were randomly assigned to either undergo a secondary surgical resection of the recurrent tumour, followed by adjuvant chemotherapy, or to receive chemotherapy alone. The results showed that secondary cytoreduction did not offer any survival benefit over chemotherapy alone. However, this could be attributed to the arguably low rates of complete cytoreduction during surgery, as only 67% of women assigned to surgery arm achieved complete resection.

- **Neoadjuvant chemotherapy**

Neoadjuvant chemotherapy should be considered a viable alternative to primary debulking surgery in certain subpopulations. Typically, 3 or 4 cycles of platinum-based chemotherapy are initiated, followed by interval debulking surgery, concluding with 3 to 4 more cycles of systemic chemotherapy. Randomised trials have shown similar survival to the standard treatment, while it is also associated with fewer perioperative complications[81–84]. Conditions that seem to favour the initiation of neoadjuvant chemotherapy include patients with stage IV ovarian cancer, patients with large metastatic lesions, thoracic metastases and/or affected cardiophrenic lymph nodes, as well as patients with poor performance status who could not tolerate an extensive primary debulking surgery. A recent meta-analysis of randomised trials, carried out by Tzanis et al., aimed to identify the subgroup of patients that could potentially benefit more from neoadjuvant chemotherapy compared to the standard treatment[85]. The results, yet to be published, showed a trend towards neoadjuvant chemotherapy for patients

with stage IV disease (HR: 0.88, 95% CI [0.71 – 1.09]) and for patients with metastatic lesions 5 – 10 cm in diameter (HR: 0.86, 95% CI [0.69 – 1.08]). Neoadjuvant chemotherapy was also associated with statistically significant lower rates of peri-operative morbidity and post-operative mortality. Currently, guidelines from the European Society of Gynaecologic Oncology (ESGO) recommend neoadjuvant chemotherapy only for patients whose performance status is not compatible with a radical surgery and for patients with unresectable disease[86].

- **Supplementary treatment options**

To date, many supplementary treatment options have been studied, but only few of them have been proven to be of benefit for advanced EOC. Poly-ADP-ribose polymerase (PARP) inhibitors, targeting the vascular endothelial growth factor have been closely examined for their role as first-line treatment, as well as for maintenance treatment.

The ICON7 and GOG218 trials closely examined the role of adding bevacizumab, a PARP inhibitor, to the standard of treatment in women with EOC. The results showed that the addition of bevacizumab to the standard of treatment significantly prolonged the progression-free survival, although failed to impact the overall survival. A secondary analysis of the ICON7 trial including women in high risk of progression (inoperable patients and patients with residual disease >1cm after debulking surgery) showed that the addition of bevacizumab significantly increased both the median progression-free survival and the median overall survival in this subgroup of patients. Currently, the addition of bevacizumab has been adopted as a maintenance treatment for selected high-risk patients, for 15 months duration. The BOOST trial, designed to address the potential benefit of extending the maintenance treatment period to 30 months, did not demonstrate any improvement in the overall survival of patients with EOC, tubal or

peritoneal cancer[87]. The recommendation for a 15-moth maintenance treatment with bevacizumab for high-risk patients with EOC still remains to date.

In the recent years there has been an increasing interest in immunotherapy for various types of cancer. EOC is no exception, since it appears to be a highly immunogenic tumour, especially the high-grade serous histotype, which is the most common one. Tumour infiltrating lymphocytes (TIL) have been identified in approximately 55% of ovarian tumours, as well as peripheral blood and ascitic fluid, with BRCA and HRD (homologous recombination deficiency) positive tumours being the more immunogenic. In this context, the JAVELIN200 trial attempted to investigate the potential role of immunotherapy with avelumab, alone or in combination with chemotherapy in patients with platinum-resistant and platinum-refractory ovarian cancer[88]. Unfortunately, avelumab failed to exert a significant improvement on overall survival or progression-free survival, neither combined with chemotherapy, nor alone.

Many trials are being designed in order to investigate the potential role of immunotherapy in ovarian cancer, even though the results have not yet been promising. As a result, it is recommended to focus on the optimal combination of existing therapeutic options, until novel treatments are proven effective.

SPECIFIC PART

Introduction

Epithelial ovarian, tubal, or peritoneal cancer have been recognised as one neoplastic entity, mainly because of the common histopathologic characteristics that they share. They account for the most deaths from gynaecologic malignancies in women, as the majority of cases are diagnosed at an advanced stage, reducing the 5-year survival rate as low as 30%[2]. The only reliable therapeutic option for women with advanced ovarian cancer is primary debulking surgery followed by adjuvant platinum-based systemic chemotherapy. The goal of primary surgery is to resect all macroscopically visible tumour to zero residual disease (complete cytoreduction). Complete cytoreduction has been proven to be one of the most critical prognostic factors for advanced ovarian cancer.[65]

Lymphatic spread is a characteristic feature of epithelial ovarian cancer (EOC) even at early stages[89]. Studies aiming to assess nodal involvement in all stages, by performing systematic lymphadenectomy, have reported up to 55% rates of pelvic and para-aortic nodal metastases in patients with stage III and IV disease[90]. The results published by those series have led surgeons in recent years towards more radical primary debulking surgeries involving the complete resection of pelvic and para-aortic nodes. However, the results published by retrospective studies regarding the survival of women treated with systematic pelvic and para-aortic lymphadenectomy have been controversial[91–94]. As a result, there is still not enough data in order to establish systematic lymphadenectomy as a mainstay of primary debulking surgery.

In this study, we aim to investigate whether systematic pelvic and para-aortic lymphadenectomy offers superior survival rates and less peri-operative complications in patients with advanced EOC.

Methods

This systematic review is reported in accordance with the PRISMA guidelines[95].

Literature search strategy

We searched the electronic databases PubMed, Cochrane Central Register of Controlled trials and Scopus for articles published from inception to September 2021. The search terms were "ovarian neoplasms", "ovarian cancer", and "lymph node excision". We also searched the grey literature for relevant studies (Open Grey). Finally, we tried to identify any related articles in the literature, either by scrutinising the references of relevant studies or by manually searching other sources, including Google Scholar. Only studies published in English were eligible for our review.

Inclusion and exclusion criteria

We included studies following the PICOS model:

- Population: women over 18 years of age with newly diagnosed epithelial ovarian, tubal or peritoneal cancer, FIGO stages III and IV, confirmed by imaging and histological or cytological analysis.
- Intervention: systematic excision of pelvic and para-aortic lymph nodes.
- Comparison: no excision of pelvic and para-aortic lymph nodes.
- Outcomes: overall survival and progression-free survival were primary outcomes. Peri-operative adverse events and post-operative mortality were secondary outcomes.
- Study design: RCTs only.

Studies were excluded in the context of the following exclusion criteria: (1) patients diagnosed with recurrent disease (rather than newly diagnosed patients); (2) patients treated with interval debulking surgery after neoadjuvant chemotherapy administration; (3) lymphadenectomy performed at second-look surgery; (4) chemotherapy not administered only systemically, but also intraperitoneally; (5) non-RCT studies, and (6) studies not published in English.

Data extraction

Data were collected from abstract, main manuscript, graphs, tables, supplementary material and/or trial protocol. The following data were collected: (1) trial characteristics including study design, year of publication, first author's name, number of participating institutions, total number of participants enrolled, number of patients allocated in each arm, and duration of follow-up; (2) clinical information on patients' age, FIGO staging, histologic subtypes, chemotherapeutic agents used, route of administration and number of cycles, and surgical techniques used; and (3) outcome data including overall survival, progression-free survival, peri-operative complications and time period within which they were assessed.

Risk of bias assessment

We assessed the quality of the included studies per outcome using the revised version of the Cochrane risk-of-bias tool for randomised trials (RoB 2)[96]. We assessed the studies included in our review for potential risk of bias in each outcome arising from: the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Plots demonstrating the results of our assessment were created using the robvis tool[97].

Statistical synthesis

Time-to-event data meta-analyses were conducted for follow-up outcomes and the results were reported as summary hazard ratios (HRs) and associated 95% confidence intervals (CIs). Direct methods were applied to calculate individual study HR and standard error (SE) for specific outcome measures from reported HR with CIs on the research arm of each trial[98,99]. The inverse-variance method of meta-analysis was used. Dichotomous outcome data were summarized using the Mantel-Haenszel method by calculating the risk ratio (RR) and 95% CI. We created corresponding forest plots using the Review Manager software (RevMan 5.4)[100]. We applied fixed effect analyses in the absence of substantial conceptual, statistical, and visual heterogeneity, otherwise a random effects model was employed. We quantified the variability in effect estimates due to heterogeneity by calculating the I^2.

Assessment of the quality of evidence

The quality of evidence was assessed in line with the GRADE methodology[101]. We presented the overall certainty of evidence for each outcome and subgroup analyses using the GRADEpro GDT software[102].

Results

Study characteristics

Our search identified a total of 1973 articles. After initial screening and application of inclusion and exclusion criteria, we identified 2 eligible RCTs, that reported a total of 1074 patients[70,103]. The PRISMA flow diagram can be accessed at the supplementary appendix.

Panici et al. 2005 was a multi-centre randomised trial conducted in Australia, Germany, Italy, and United Kingdom. Sixteen participating institutions enrolled a total of 452 women from 1991 to 2003, with a median follow-up of 68.4 months. Patients optimally debulked (residual disease ≤1 cm) at primary debulking surgery, with histologically confirmed stage IIIB – IV epithelial ovarian cancer were randomised to undergo either systematic pelvic and aortic lymphadenectomy or resection of enlarged lymph nodes only (≥1 cm in diameter). Women in both arms received adjuvant treatment with platinum-based chemotherapy. The primary outcome was overall survival, while secondary endpoints included progression-free survival and peri-operative morbidity.

Harter et al. 2019 was a multi-centre randomised trial conducted in 59 institutions across Austria, Belgium, Czech Republic, Germany, Italy, and Korea. Participating centres had to qualify in order to participate in the trial. 650 women underwent randomisation between 2008 and 2012. The follow-up period was 6 years. Patients were randomised if they had histologically confirmed epithelial ovarian cancer stage IIB – IV, which was resected to zero residual disease (complete resection) during primary debulking surgery. Women with macroscopically enlarged lymph nodes were not included in the trial. Patients that fulfilled the inclusion criteria were

randomised to undergo either systematic pelvic and para-aortic lymphadenectomy or no lymphadenectomy. The primary endpoint was overall survival, while secondary endpoints included progression-free survival, quality of life, and number of resected lymph nodes. Even though peri-operative morbidity was not an endpoint of this study, data on adverse events were reported and were included in our quantitative synthesis.

Risk of bias assessment

Both trials reported data suitable for time-to-event analyses. The risk of bias was deemed low for both studies. Regarding peri-operative morbidity, the included studies were also judged to be at low risk for bias. The corresponding plots can be accessed at the supplementary appendix.

Outcome measures

1. **Overall survival and progression-free survival**

Meta-analysis of included studies revealed no difference in the overall survival between patients in the systematic lymphadenectomy arm and patients in the no lymphadenectomy arm (HR = 1.03, 95% CI [0.85 – 1.24]), i^2 = 0%, low certainty of evidence). No statistically significant difference was also observed in the progression-free survival between the two arms (HR = 0.92, 95% CI [0.63 – 1.35], i^2 = 84%, very low certainty of evidence).

2. **Peri-operative adverse events**

There were no data regarding cumulative peri-operative adverse events of grade 3 or 4, suitable for quantitative synthesis. Systematic lymphadenectomy was associated with increased risk for lymphocysts formation and lymphedema compared to no lymphadenectomy arm (RR = 7.31,

95% CI [1.89 – 28.2], i^2 = 28%, moderate certainty of evidence), as well as more frequent need for blood transfusion (RR = 1.17, 95% CI [1.06 – 1.29], i^2 = 0%, moderate certainty of evidence). No statistically significant difference was observed between the two arms regarding the formation of intestinal fistula (RR = 0.81, 95% CI [0.34 – 1.95], i^2 = 0%, low certainty of evidence).

3. Post-operative mortality

Meta-analysis regarding post-operative mortality could not pe performed, as one of the two included studies (Panici et al. 2005) reported 0 events in both arms. As a result, the risk ratio could not be calculated. Harter et al. 2019 reported 10 deaths in the systematic lymphadenectomy arm versus 3 deaths in the control arm (RR = 3.34, 95% CI [0.93 – 12.04]), which shows a trend towards no lymphadenectomy, although without being statistically significant.

All corresponding forest plots can be accessed at the supplementary appendix.

Discussion

This meta-analysis demonstrated no survival benefit of patients with advanced EOC treated with either therapeutic approach, both in terms of overall survival and progression-free survival. Regarding peri-operative morbidity, the "no lymphadenectomy" arm was associated with fewer events of lymphoedema or lymphocysts formation and lower rates of blood transfusion. No statistically significant difference was observed in the rates of fistula formation between the two arms. Finally, as far as post-operative mortality is concerned, a quantitative synthesis could not be performed because only one study provided data suitable for analysis (Panici et al. 2005 reported 0 events in both arms, as a result the risk ratio could not be calculated). Post-operative mortality data reported by the LION trial (Harter et al. 2019) demonstrated a non-statistically significant trend towards the "no lymphadenectomy" arm (3 deaths versus 10 deaths in the systematic lymphadenectomy arm).

To our knowledge, this is the only meta-analysis examining the role of systematic lymphadenectomy in patients with advanced EOC that included only RCTs. Previous meta-analyses published in the literature have based their results in retrospective studies, which are prone to a certain degree of bias. The main reason is the selection of patients and the rationale behind their potential assignment to each arm. Since systematic lymphadenectomy adds a profound burden to the overall treatment plan, patients with comorbidities and a poor performance status could find themselves assigned to the "no lymphadenectomy" arm regardless of the stage of disease or the histology of the tumour. On the other hand, younger patients, in good condition without any comorbidities might have been more prone to undergo systematic lymphadenectomy. By including only RCTs to our review, we managed to overcome this potential source of bias.

Nevertheless, our meta-analysis was still subject to certain limitations, the most profound of which was the heterogeneity observed in the recruited population between the two trials. While the control arm in the LION trial comprised of patients receiving primary debulking surgery without resection of any lymph nodes (patients with clinically positive lymph nodes were excluded), patients enrolled in the control arm of Panici et al. trial received resection of all macroscopic disease, including any affected lymph nodes. In other words, lymphadenectomy was performed to patients in both arms in Panici et al. trial. This could potentially mask the true effect of systematic lymphadenectomy on survival, while also add a significant treatment burden to the "no lymphadenectomy" arm.

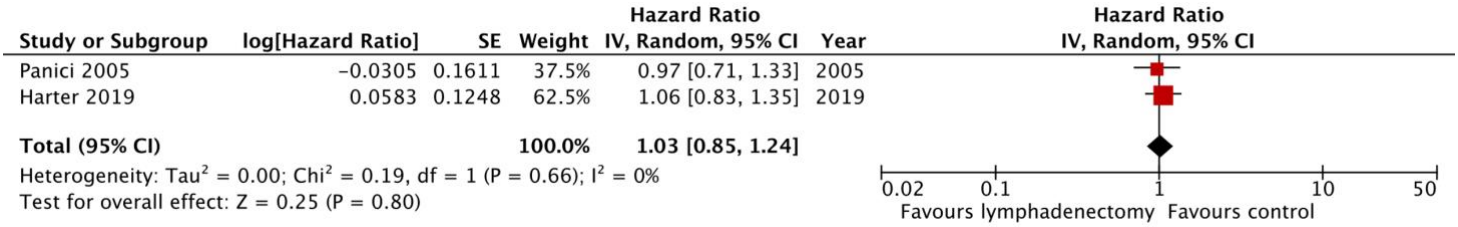
Another source of heterogeneity was the residual disease of patients recruited in both arms after debulking surgery. On the one hand, the LION trial only recruited women after complete resection of all visible intra-abdominal tumour, while on the other hand Panici et al. recruited patients after they were optimally debulked (residual disease <1 cm). As a result, the majority of patients enrolled by the latter trial had residual intra-abdominal tumour (<1 cm), which could affect their prognosis substantially, since complete resection has been proven to be a crucial prognostic factor in patients with advanced EOC.

An additional source of heterogeneity lied in the participating institutions and their evaluation for quality of surgery. All centres that participated and enrolled patients in the LION trial (Harter et al. 2019) had to qualify for surgical quality. Participating institutions were evaluated for their competence in performing complete debulking of intra-abdominal tumours as well as complete lymphadenectomy, within a time period of 12 months prior to their participation in

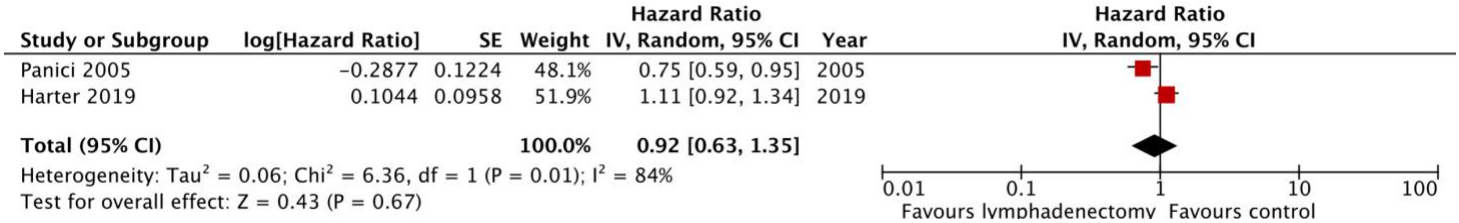
the trial. Quality of participating institutions has always been a major concern in trials focusing on patients with advanced EOC and our meta-analysis in no exception. As it is now proven that qualified centres offer superior survival outcomes to women with advanced stage disease, the quality control applied in the LION trial aimed to reduce heterogeneity that arises by different level of experience between centres within the same trial. Such an evaluation of the participating institutions was not performed by Panici et al. in their trial. This resulted in an additional source of heterogeneity for our study.

In conclusion, despite the aforementioned limitations, our study provides evidence regarding the direct comparison of systematic pelvic and para-aortic lymphadenectomy with primary debulking surgery alone in patients with advanced EOC. Our data suggest that systematic lymphadenectomy does not improve survival, while -in some cases- it is associated with higher rates of peri-operative adverse events compared to no systematic lymphadenectomy. In the context of high heterogeneity between the included trials, a future RCT enrolling patients only after complete debulking has been achieved, while excluding patients with clinically affected lymph nodes could provide data that could lead as a to a more definite conclusion regarding the role of systematic pelvic and para-aortic lymphadenectomy.

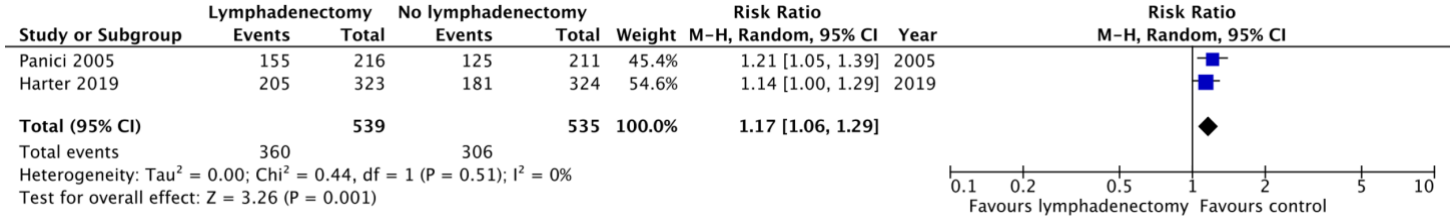
SUPPLEMENTARY APPENDIX



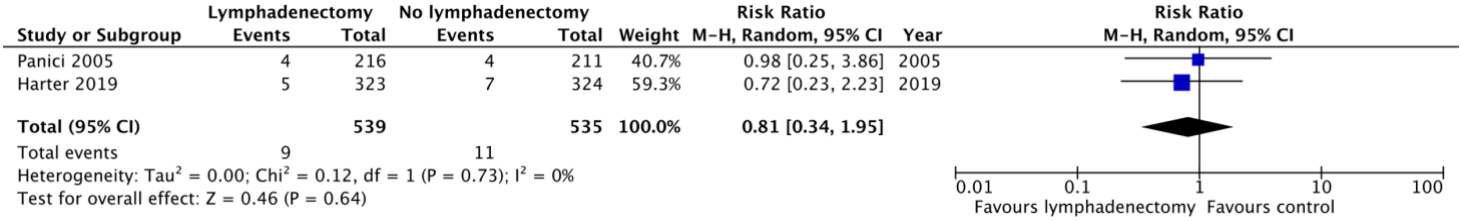
Graph 1. Forest plot for overall survival.



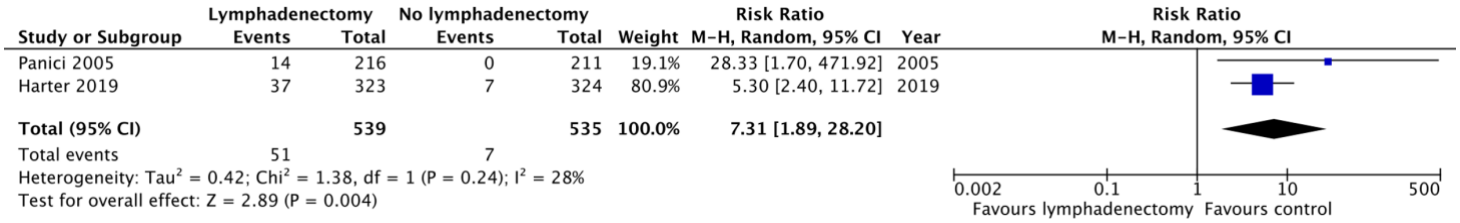
Graph 2. Forest plot for progression-free survival.



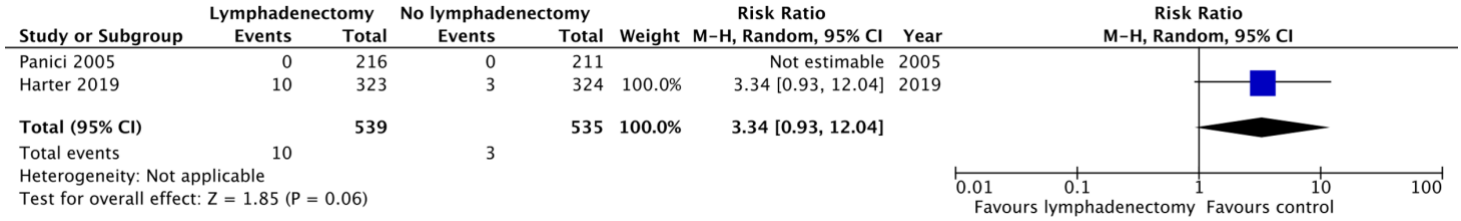
Graph 3. Forest plot for blood transfusion needs.



Graph 4. Forest plot for intestinal fistula formation.

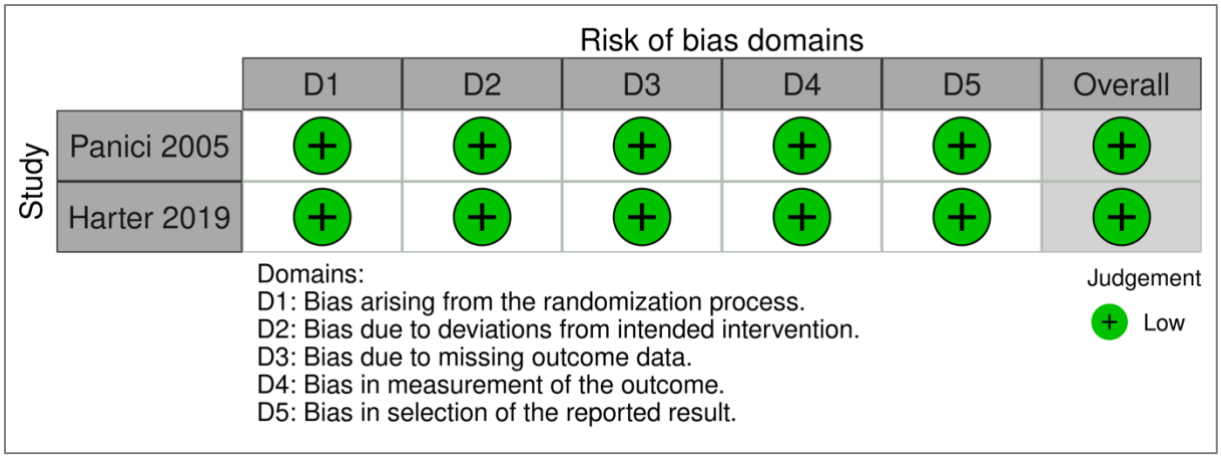


Graph 5. Forest plot for lymphoedema or lymphocysts formation.



Graph 6. Forest plot for post-operative mortality.

Note: Panici et al. reported 0 events in both arms. As a result, the risk ratio could not be calculated.



Supplementary Figure 1. Risk of bias assessment. Traffic-light plot.

REFERENCES

1. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. *Cancer Biol Med*. 2017;14(1):9-32. doi:10.20892/J.ISSN.2095-3941.2016.0084

2. Surveillance, Epidemiology, and End Results (SEER). National Cancer Institute. Accessed March 21, 2019. https://seer.cancer.gov/statfacts/html/ovary.html

3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29. doi:10.3322/caac.21208

4. Global Cancer Observatory. Accessed March 8, 2022. https://gco.iarc.fr/

5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E386. doi:10.1002/ijc.29210

6. Gaona-Luviano P, Adriana L, Medina-Gaona, Magaña-Pérez K. Epidemiology of ovarian cancer. *Chinese Clin Oncol*. 2020;9(4):47-47. doi:10.21037/CCO-20-34

7. *Ovarian Cancers: Evolving Paradigms in Research and Care*. National Academies Press; 2016. doi:10.17226/21841

8. Berek JS, Hacker NF. *Berek and Hacker's Gynecologic Oncology*. 6th ed. Wolters Kluwer

9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30. doi:10.3322/caac.21442

10. Howlader N, Altekruse SF, Li CI, et al. US Incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status. *JNCI J Natl Cancer Inst*. 2014;106(5). doi:10.1093/jnci/dju055

11. Scully RE (Robert E, Young RH (Robert H, Clement PB, Armed Forces Institute of Pathology (U.S.), Universities Associated for Research and Education in Pathology. *Tumors of the Ovary, Maldeveloped Gonads, Fallopian Tube, and Broad Ligament*. Armed Forces Institute of Pathology; 1998. Accessed May 16, 2019. https://archive.org/details/tumorsofovarymal00scul

12. DeCherney AH, Laufer N, Nathan L, Roman AS. *Current Diagnosis & Treatment : Obstetrics & Gynecology*. 12th ed. McGraw Hill Medical; 2019. http://search.ebscohost.com/login.aspx?direct=true&db=edsmgh&AN=edsmgh.scn00390037&site=eds-live&authtype=uid

13. Iversen L, Fielding S, Lidegaard Ø, Mørch LS, Skovlund CW, Hannaford PC. Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark: prospective, nationwide cohort study. *BMJ*. 2018;362:k3609. doi:10.1136/bmj.k3609

14. Piek JMJ, van Diest PJ, Zweemer RP, et al. Dysplastic changes in prophylactically

removed Fallopian tubes of women predisposed to developing ovarian cancer. *J Pathol*. 2001;195(4):451-456. doi:10.1002/path.1000

15. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial Carcinoma of the Fimbria and Pelvic Serous Carcinoma: Evidence for a Causal Relationship. *Am J Surg Pathol*. 2007;31(2):161-169. doi:10.1097/01.pas.0000213335.40358.47

16. Przybycin CG, Kurman RJ, Ronnett BM, Shih I-M, Vang R. Are All Pelvic (Nonuterine) Serous Carcinomas of Tubal Origin? *Am J Surg Pathol*. 2010;34(10):1407-1416. doi:10.1097/PAS.0b013e3181ef7b16

17. Dubeau L. The cell of origin of ovarian epithelial tumours. *Lancet Oncol*. 2008;9(12):1191-1197. doi:10.1016/S1470-2045(08)70308-5

18. Lengyel E. Ovarian cancer development and metastasis. *Am J Pathol*. 2010;177(3):1053-1064. doi:10.2353/ajpath.2010.100105

19. Huber MA, Kraut N, Beug H. Molecular requirements for epithelial–mesenchymal transition during tumor progression. *Curr Opin Cell Biol*. 2005;17(5):548-558. doi:10.1016/j.ceb.2005.08.001

20. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest*. 2009;119(6):1420-1428. doi:10.1172/JCI39104

21. Imai T, Horiuchi A, Wang C, et al. Hypoxia attenuates the expression of E-cadherin via up-regulation of SNAIL in ovarian carcinoma cells. *Am J Pathol*. 2003;163(4):1437-1447. doi:10.1016/S0002-9440(10)63501-8

22. Sawada K, Radjabi AR, Shinomiya N, et al. c-Met Overexpression Is a Prognostic Factor in Ovarian Cancer and an Effective Target for Inhibition of Peritoneal Dissemination and Invasion. *Cancer Res*. 2007;67(4):1670-1679. doi:10.1158/0008-5472.CAN-06-1147

23. Chen SS, Lee L. Incidence of para-aortic and pelvic lymph node metastases in epithelial carcinoma of the ovary. *Gynecol Oncol*. 1983;16(1):95-100. Accessed May 17, 2019. http://www.ncbi.nlm.nih.gov/pubmed/6884834

24. Stratton JF, Pharoah P, Smith SK, Easton D, Ponder BAJ. A systematic review and meta-analysis of family history and risk of ovarian cancer. *Br J Obstet Gynaecol*. 1998;105(5):493-499. doi:10.1111/J.1471-0528.1998.TB10148.X

25. Risch HA, McLaughlin JR, Cole DEC, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet*. 2001;68(3):700-710. doi:10.1086/318787

26. Pavone ME, Lyttle BM. Endometriosis and ovarian cancer: links, risks, and challenges faced. *Int J Womens Health*. 2015;7:663. doi:10.2147/IJWH.S66824

27. Penninkilampi R, Eslick GD. Perineal Talc Use and Ovarian Cancer. *Epidemiology*. 2018;29(1):41-49. doi:10.1097/EDE.0000000000000745

28. O'Brien KM, Tworoger SS, Harris HR, et al. Association of Powder Use in the Genital Area With Risk of Ovarian Cancer. *JAMA*. 2020;323(1):49-59. doi:10.1001/JAMA.2019.20079

29. Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral Contraceptive Pills as Primary Prevention for Ovarian Cancer. *Obstet Gynecol*. 2013;122(1):139-147. doi:10.1097/AOG.0b013e318291c235

30. Negri E, Franceschi S, Tzonou A, et al. Pooled analysis of 3 European case-control studies: I. Reproductive factors and risk of epithelial ovarian cancer. *Int J cancer*. 1991;49(1):50-56. Accessed May 17, 2019. http://www.ncbi.nlm.nih.gov/pubmed/1874569

31. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis. *J Ovarian Res*. 2012;5(1):13. doi:10.1186/1757-2215-5-13

32. Cibula D, Widschwendter M, Majek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. *Hum Reprod Update*. 2011;17(1):55-67. doi:10.1093/humupd/dmq030

33. Pearce CL, Stram DO, Ness RB, et al. Population Distribution of Lifetime Risk of Ovarian Cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 2015;24(4):671-676. doi:10.1158/1055-9965.EPI-14-1128

34. Lowry KP, Lee SI. Imaging and Screening of Ovarian Cancer. *Radiol Clin North Am*. 2017;55(6):1251-1259. doi:10.1016/j.rcl.2017.06.010

35. Yuan Q, Song J, Yang W, et al. The effect of CA125 on metastasis of ovarian cancer: old marker new function. *Oncotarget*. 2017;8(30):50015-50022. doi:10.18632/oncotarget.18388

36. BAST RC, BADGWELL D, LU Z, et al. New tumor markers: CA125 and beyond. *Int J Gynecol Cancer*. 2005;15(s3):274-281. doi:10.1111/j.1525-1438.2005.00441.x

37. Moore RG, Miller MC, Disilvestro P, et al. Evaluation of the diagnostic accuracy of the risk of ovarian malignancy algorithm in women with a pelvic mass. *Obstet Gynecol*. 2011;118(2 Pt 1):280-288. doi:10.1097/AOG.0b013e318224fce2

38. Karlsen MA, Sandhu N, Høgdall C, et al. Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. *Gynecol Oncol*. 2012;127(2):379-383. doi:10.1016/j.ygyno.2012.07.106

39. Buhling KJ, Lezon S, Eulenburg C, Schmalfeldt B. The role of transvaginal ultrasonography for detecting ovarian cancer in an asymptomatic screening population: a systematic review. *Arch Gynecol Obstet*. 2017;295(5):1259-1268. doi:10.1007/s00404-017-4346-4

40. Manegold-Brauer G, Bellin AK, Tercanli S, Lapaire O, Heinzelmann-Schwarz V. The special role of ultrasound for screening, staging and surveillance of malignant ovarian tumors: distinction from other methods of diagnostic imaging. *Arch Gynecol Obstet*. 2014;289(3):491-498. doi:10.1007/s00404-013-3081-8

41. Bharwani N, Reznek RH, Rockall AG. Ovarian Cancer Management: The role of imaging and diagnostic challenges. *Eur J Radiol*. 2011;78(1):41-51. doi:10.1016/j.ejrad.2010.11.039

42. Michielsen K, Dresen R, Vanslembrouck R, et al. Diagnostic value of whole body

diffusion-weighted MRI compared to computed tomography for pre-operative assessment of patients suspected for ovarian cancer. *Eur J Cancer*. 2017;83:88-98. doi:10.1016/j.ejca.2017.06.010

43. Menon U, Gentry-Maharaj A, Burnell M, et al. 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. *Lancet*. 2021;397(10290):2182-2193. doi:10.1016/S0140-6736(21)00731-5/ATTACHMENT/AB1EA4C1-0517-45E2-AA5B-B3603CD66800/MMC1.PDF

44. Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index. *Cancer*. 2007;109(2):221-227. doi:10.1002/cncr.22371

45. Olsen CM, Cnossen J, Green AC, Webb PM. Comparison of symptoms and presentation of women with benign, low malignant potential and invasive ovarian tumors. *Eur J Gynaecol Oncol*. 2007;28(5):376-380. Accessed May 17, 2019. http://www.ncbi.nlm.nih.gov/pubmed/17966216

46. Teh BH, Yong SL, Sim WW, Lau KB, Suharjono HN. Evaluation in the predictive value of serum human epididymal protein 4 (HE4), cancer antigen 125 (CA 125) and a combination of both in detecting ovarian malignancy. *Horm Mol Biol Clin Investig*. 2018;35(1). doi:10.1515/hmbci-2018-0029

47. Ueland FR, DePriest PD, Pavlik EJ, Kryscio RJ, van Nagell JR. Preoperative differentiation of malignant from benign ovarian tumors: the efficacy of morphology indexing and Doppler flow sonography. *Gynecol Oncol*. 2003;91(1):46-50. Accessed May 17, 2019. http://www.ncbi.nlm.nih.gov/pubmed/14529661

48. Muñoz M, Ramirez PT, Echeverri C, Álvarez LG, Palomino MA, Pareja LR. Gastrointestinal stromal tumors as an incidental finding in patients with a presumptive diagnosis of ovarian cancer. *J Gynecol Oncol*. 2012;23(1):48. doi:10.3802/jgo.2012.23.1.48

49. Fagotti A, Perelli F, Pedone L, Scambia G. Current Recommendations for Minimally Invasive Surgical Staging in Ovarian Cancer. *Curr Treat Options Oncol*. 2016;17(1):3. doi:10.1007/s11864-015-0379-8

50. CHIA YN, MARSDEN DE, ROBERTSON G, HACKER NF. Triage of ovarian masses. *Aust New Zeal J Obstet Gynaecol*. 2008;48(3):322-328. doi:10.1111/j.1479-828X.2008.00825.x

51. Sahin H, Abdullazade S, Sanci M. Mature cystic teratoma of the ovary: a cutting edge overview on imaging features. *Insights Imaging*. 2017;8(2):227-241. doi:10.1007/s13244-016-0539-9

52. Benjapibal M, Sangkarat S, Laiwejpithaya S, Viriyapak B, Chaopotong P, Jaishuen A. Meigs' Syndrome with Elevated Serum CA125: Case Report and Review of the Literature. *Case Rep Oncol*. 2009;2(1):61-66. doi:10.1159/000210441

53. Fagotti A, Ferrandina G, Vizzielli G, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. *Eur J Cancer*. 2016;59 CC-:22-33. doi:10.1016/j.ejca.2016.01.017

54. Ertas IE, Gungorduk K, Ozdemir A, et al. Pelvic tuberculosis, echinococcosis, and actinomycosis: Great imitators of ovarian cancer. *Aust New Zeal J Obstet Gynaecol*. 2014;54(2):166-171. doi:10.1111/ajo.12191

55. Bagga R, Muthyala T, Saha S, et al. Peri and post-menopausal women with complex adnexal masses, ascites, and raised CA-125: Is it ovarian cancer or tuberculosis? *J Midlife Health*. 2016;7(4):193. doi:10.4103/0976-7800.195700

56. Shim SW, Shin SH, Kwon WJ, Jeong YK, Lee JH. CT Differentiation of Female Peritoneal Tuberculosis and Peritoneal Carcinomatosis From Normal-Sized Ovarian Cancer. *J Comput Assist Tomogr*. 2017;41(1):32-38. doi:10.1097/RCT.0000000000000446

57. Nezhat FR, Pejovic T, Finger TN, Khalil SS. Role of Minimally Invasive Surgery in Ovarian Cancer. *J Minim Invasive Gynecol*. 2013;20(6):754-765. doi:10.1016/j.jmig.2013.04.027

58. Aletti GD, Peiretti M. Quality control in ovarian cancer surgery. *Best Pract Res Clin Obstet Gynaecol*. 2017;41:96-107. doi:10.1016/j.bpobgyn.2016.08.008

59. Young RC, Decker DG, Wharton JT, et al. Staging laparotomy in early ovarian cancer. *JAMA*. 1983;250(22):3072-3076. Accessed May 18, 2019. http://www.ncbi.nlm.nih.gov/pubmed/6358558

60. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant Therapy in Stage I and Stage II Epithelial Ovarian Cancer. *N Engl J Med*. 1990;322(15):1021-1027. doi:10.1056/NEJM199004123221501

61. Berek JS. Adjuvant Therapy for Early-Stage Ovarian Cancer. *N Engl J Med*. 1990;322(15):1076-1078. doi:10.1056/NEJM199004123221510

62. Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst*. 2003;95(2):105-112. Accessed May 19, 2019. http://www.ncbi.nlm.nih.gov/pubmed/12529343

63. Swenerton KD, Santos JL, Gilks CB, et al. Histotype predicts the curative potential of radiotherapy: the example of ovarian cancers. *Ann Oncol Off J Eur Soc Med Oncol*. 2011;22(2):341-347. doi:10.1093/annonc/mdq383

64. Hoskins PJ, Le N, Gilks B, et al. Low-Stage Ovarian Clear Cell Carcinoma: Population-Based Outcomes in British Columbia, Canada, With Evidence for a Survival Benefit As a Result of Irradiation. *J Clin Oncol*. 2012;30(14):1656-1662. doi:10.1200/JCO.2011.40.1646

65. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials. *Cancer*. 2009;115(6):1234-1244. doi:10.1002/cncr.24149

66. Crawford SC, Vasey PA, Paul J, Hay A, Davis JA, Kaye SB. Does Aggressive Surgery Only Benefit Patients With Less Advanced Ovarian Cancer? Results From an International Comparison Within the SCOTROC-1 Trial. *J Clin Oncol*.

2005;23(34):8802-8811. doi:10.1200/JCO.2005.02.1287

67. Eisenkop SM, Spirtos NM, Lin W-CM. Splenectomy in the context of primary cytoreductive operations for advanced epithelial ovarian cancer. *Gynecol Oncol*. 2006;100(2):344-348. doi:10.1016/j.ygyno.2005.08.036

68. Cosyns S, De Sutter P, Tournaye H, Polyzos NP. Necessity of appendectomy for mucinous borderline ovarian tumors. Systematic review. *Arch Gynecol Obstet*. 2016;294(6):1283-1289. doi:10.1007/s00404-016-4174-y

69. Cheng A, Li M, Kanis MJ, et al. Is it necessary to perform routine appendectomy for mucinous ovarian neoplasms? A retrospective study and meta-analysis. *Gynecol Oncol*. 2017;144(1):215-222. doi:10.1016/j.ygyno.2016.10.041

70. Panici PB, Maggioni A, Hacker N, et al. Systematic Aortic and Pelvic Lymphadenectomy Versus Resection of Bulky Nodes Only in Optimally Debulked Advanced Ovarian Cancer: A Randomized Clinical Trial. *JNCI J Natl Cancer Inst*. 2005;97(8):560-566. doi:10.1093/jnci/dji102

71. Trimbos JB. Lymphadenectomy in ovarian cancer. *Curr Opin Oncol*. 2011;23(5):507-511. doi:10.1097/CCO.0b013e32834847e7

72. Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials. Advanced Ovarian Cancer Trialists Group. *BMJ*. 1991;303(6807):884-893. doi:10.1136/bmj.303.6807.884

73. Muggia FM, Braly PS, Brady MF, et al. Phase III Randomized Study of Cisplatin Versus Paclitaxel Versus Cisplatin and Paclitaxel in Patients With Suboptimal Stage III or IV Ovarian Cancer: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2000;18(1):106-106. doi:10.1200/JCO.2000.18.1.106

74. Neijt JP, ten Bokkel Huinink WW, van der Burg ME, et al. Randomized trial comparing two combination chemotherapy regimens (CHAP-5 v CP) in advanced ovarian carcinoma. *J Clin Oncol*. 1987;5(8):1157-1168. doi:10.1200/JCO.1987.5.8.1157

75. Lambert HE, Berry RJ. High dose cisplatin compared with high dose cyclophosphamide in the management of advanced epithelial ovarian cancer (FIGO stages III and IV): report from the North Thames Cooperative Group. *Br Med J (Clin Res Ed)*. 1985;290(6472):889-893. doi:10.1136/bmj.290.6472.889

76. Cascales-Campos P, Gil J, Feliciangeli E, Parrilla P. HIPEC in ovarian cancer: Treatment of a new era or is it the end of the pipeline? *Gynecol Oncol*. 2015;139(2):363-368. doi:10.1016/j.ygyno.2015.06.012

77. Spiliotis J, Halkia E, Lianos E, et al. Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study. *Ann Surg Oncol*. 2015;22(5):1570-1575. doi:10.1245/s10434-014-4157-9

78. Sin EI-L, Chia CS, Tan GHC, Soo KC, Teo MC-C. Acute kidney injury in ovarian cancer patients undergoing cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy. *Int J Hyperth*. 2017;33(6):690-695. doi:10.1080/02656736.2017.1293304

79. Koole S, Van Stein R, Sikorska K, et al. Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for FIGO stage III epithelial ovarian cancer: OVHIPEC-2, a phase III randomized clinical trial. *Int J Gynecol Cancer*. 2020;30(6):888-892. doi:10.1136/IJGC-2020-001231

80. Coleman RL, Spirtos NM, Enserro D, et al. Secondary Surgical Cytoreduction for Recurrent Ovarian Cancer. *N Engl J Med*. 2019;381(20):1929-1939. doi:10.1056/NEJMOA1902626

81. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer. *N Engl J Med*. 2010;363(10):943-953. doi:10.1056/NEJMoa0908806

82. Onda T, Satoh T, Saito T, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. *Eur J Cancer*. 2016;64:22-31. doi:10.1016/j.ejca.2016.05.017

83. Fagotti A, Ferrandina G, Vizzielli G, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. *Eur J Cancer*. 2016;59:22-33. doi:10.1016/j.ejca.2016.01.017

84. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet*. 2015;386(9990):249-257. doi:10.1016/S0140-6736(14)62223-6

85. Tzanis, Alexander; Iavazzo, Christos; Tsouvali, Hara; Hadjivasilis, Alexandros; Antoniou GAS. Neoadjuvant chemotherapy versus primary debulking surgery in FIGO stages III and IV epithelial ovarian, tubal, or peritoneal cancer: a systeamtic review and meta-analysis. Published online 2021.

86. Querleu D, Planchamp F, Chiva L, et al. European society of Gynaecological Oncology (ESGO) guidelines for ovarian cancer surgery. *Int J Gynecol Cancer*. 2017;27(7):1534-1542. doi:10.1097/IGC.0000000000001041

87. Pfisterer J, Joly F, Kristensen G, et al. Optimal treatment duration of bevacizumab (BEV) combined with carboplatin and paclitaxel in patients (pts) with primary epithelial ovarian (EOC), fallopian tube (FTC) or peritoneal cancer (PPC): A multicenter open-label randomized 2-arm phase 3 ENGOT/GCIG trial of the AGO Study Group, GINECO, and NSGO (AGO-OVAR 17/BOOST, GINECO OV118, ENGOT Ov-15, NCT01462890). *https://doi.org/101200/JCO20213915_suppl5501*. 2021;39(15_suppl):5501-5501. doi:10.1200/JCO.2021.39.15_SUPPL.5501

88. Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. *Lancet Oncol*. 2021;22(7):1034-1046. doi:10.1016/S1470-2045(21)00216-3

89. Kleppe M, Wang T, Van Gorp T, Slangen BFM, Kruse AJ, Kruitwagen RFPM. Lymph

node metastasis in stages I and II ovarian cancer: a review. *Gynecol Oncol*. 2011;123(3):610-614. doi:10.1016/J.YGYNO.2011.09.013

90. Morice P, Joulie F, Camatte S, et al. Lymph node involvement in epithelial ovarian cancer: analysis of 276 pelvic and paraaortic lymphadenectomies and surgical implications. *J Am Coll Surg*. 2003;197(2):198-205. doi:10.1016/S1072-7515(03)00234-5

91. Chen SS. Survival of ovarian carcinoma with or without lymph node metastasis. *Gynecol Oncol*. 1987;27(3):368-372. doi:10.1016/0090-8258(87)90260-5

92. Scarabelli C, Gallo A, Visentin MC, Canzonieri V, Carbone A, Zarrelli A. Systematic pelvic and para-aortic lymphadenectomy in advanced ovarian cancer patients with no residual intraperitoneal disease. *Int J Gynecol Cancer*. 1997;7(1):18-26. doi:10.1046/J.1525-1438.1997.00418.X

93. Abe A, Furumoto H, Irahara M, et al. The impact of systematic para-aortic and pelvic lymphadenectomy on survival in patients with optimally debulked ovarian cancer. *J Obstet Gynaecol Res*. 2010;36(5):1023-1030. doi:10.1111/J.1447-0756.2010.01274.X

94. Fang C, Zhang Y, Zhao L, Chen X, Xia L, Zhang P. The relationship between retroperitoneal lymphadenectomy and survival in advanced ovarian cancer patients. *BMC Cancer*. 2020;20(1). doi:10.1186/S12885-020-07144-1

95. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg*. 2010;8(5):336-341. doi:10.1016/J.IJSU.2010.02.007

96. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366. doi:10.1136/bmj.l4898

97. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2021;12(1):55-61. doi:10.1002/jrsm.1411

98. Antoniou GA, Antoniou SA, Smith CT. A guide on meta-analysis of time-to-event outcomes using aggregate data in vascular and endovascular surgery. *J Vasc Surg*. 2020;71(3):1002-1005. doi:10.1016/j.jvs.2019.05.037

99. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8(1):16. doi:10.1186/1745-6215-8-16

100. Review Manager (RevMan). Published online 2020. revman.cochrane.org

101. Schunemann H, Brozek J, Guyatt G, Oxman A. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations.*; 2013. https://gdt.gradepro.org/app/handbook/handbook.html

102. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. Published online 2020.

103. Harter P, Sehouli J, Lorusso D, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. *N Engl J Med*. 2019;380(9):822-832.

doi:10.1056/NEJMOA1808424