UNIVERSITÀ DEGLI STUDI DI PADOVA

CORSO DI LAUREA IN MEDICINA E CHIRURGIA

Dipartimento di Salute della Donna e del Bambino

Direttore: Prof. Eugenio Baraldi

U.O.C. Clinica Ginecologica Ostetrica

Direttore: Prof. Roberto Tozzi

TESI DI LAUREA

Prognostic factors for survival in patients with stage IV B ovarian cancer

Relatore: Prof. Roberto Tozzi

Correlatrice: Dott.ssa Meriem Koual

Laureanda: Margherita Picci

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SUMMARY

RIASSUNTO

Presupposti dello studio: Nel carcinoma ovarico di stadio IVB, i linfonodi dell'addome superiore e quelli sovradiaframmatici sono frequentemente sede di metastasi, perciò l'asportazione chirurgica di tali linfonodi metastatici sovramesenterici può favorire una citoriduzione ottimale e, potenzialmente, migliorare i tassi di sopravvivenza. Nonostante ciò, tale intervento non è stato ampiamente studiato e i dati disponibili riguardanti la sua sicurezza sono ancora limitati; di conseguenza, costituisce un approccio chirurgico attualmente dibattuto.

Scopo dello studio: Studiare l'impatto sulla sopravvivenza di diverse localizzazioni anatomiche delle metastasi, nelle pazienti con carcinoma ovarico di stadio IVB sottoposte a citoriduzione chirurgica. Inoltre, confrontare, all'interno di tale popolazione, le implicazioni prognostiche dell'asportazione chirurgica dei linfonodi metastatici sovramesenterici e inframesenterici.

Materiali e metodi: Abbiamo condotto uno studio retrospettivo internazionale e multicentrico, reclutando pazienti con tumore ovarico epiteliale di stadio IVB sottoposte a citoriduzione chirurgica tra Febbraio 2005 e Aprile 2023.

Risultati: Nel nostro studio sono state incluse 143 pazienti. La numerosità delle pazienti aventi metastasi a livello di un solo distretto anatomico al momento della diagnosi era troppo limitata (12.59%) per ottenere dei risultati significativi dal confronto dei tassi di sopravvivenza in base alla localizzazione delle metastasi. Tra le 55 pazienti aventi linfonodi sovramesenterici metastatici, nonostante le differenze tra i tassi di sopravvivenza non siano statisticamente significative, le 9 (16.36%) pazienti in cui tali linfonodi sono stati asportati chirurgicamente presentavano un OS e un DFS peggiore rispetto a coloro che non erano state sottoposte a tale intervento: l'OS era 13.3 contro 29.8 mesi ($p=0.064$) e il DFS era 10.0 contro 15.9 mesi ($p=0.386$). Inoltre, le pazienti andate incontro alla citoriduzione dei linfonodi sovramesenterici metastatici sono state soggette a un maggiore tasso di complicazioni, rispettivamente il 66.67% contro il 40.06%.

Conclusioni: Nonostante non vi siano differenze statisticamente significative tra i due gruppi, il nostro studio ha mostrato che le pazienti sottoposte a citoriduzione dei linfonodi sovramesenterici metastatici hanno dei tassi di sopravvivenza peggiori rispetto a coloro che non hanno affrontato tale intervento. Questi risultati sono in

linea con quanto evinto relativamente al tasso di complicanze, il quale risulta maggiore nella popolazione sottoposta a citoriduzione sovramesenterica. Infine, i nostri risultati non propendono per un approccio sovramesenterico, tuttavia riteniamo che dei nuovi studi su ampia scala siano fondamentali per definire l'effettivo vantaggio, in termini di sopravvivenza e di sicurezza, di tale intervento.

ABSTRACT

Background: In stage IVB ovarian cancer, upper abdominal and intrathoracic supradiaphragmatic lymph nodes can serve as common sites for metastases. In this setting, supramesenteric bulky lymph node cytoreductive surgery may contribute to minimize the volume of residual disease and to potentially improve survival rates. However, it has not been widely studied and available data on its safety are still limited; as a result, it remains a very controversial area.

Materials and methods: We conducted an international multicentric retrospective study including patients with stage IVB epithelial ovarian cancer that underwent visceral peritoneal debulking between February 2005 and April 2023.

Objective: To investigate the impact on survival of different anatomical localisations of metastases in stage IVB epithelial ovarian cancer patients who underwent a visceral peritoneal debulking. To compare, within this population, prognostic implications of supramesenteric and inframesenteric bulky lymph node removal.

Results: We included 143 patients in our study. The number of patients presenting metastases affecting one anatomical district only at diagnosis was too limited (12.59%) to obtain statistically significant results by analysing the impact on survival rates according to the localisation of metastasis. Within the subpopulation of 55 patients presenting metastatic supramesenteric lymph nodes, even though differences in survival rates were not statistically significant, the 9 (16.36%) patients who had such lymph nodes surgically removed had a poorer OS and DFS than those who did not, OS were 13.3 versus 29.8 months (p=0.064) and DFS were 10.0 versus 15.9 months (p=0.386). Moreover, patients who underwent supramesenteric metastatic lymph node debulking experienced a higher rate of complications, 66.67% versus 40.06%, respectively.

Conclusions: Although our results did not reveal statistically significant differences between the two groups, our study showed that patients who had supramesenteric bulky lymph nodes surgically removed had poorer survival rates than those who did not undergo such surgery. These findings are in line with those relative to complication rates, which are higher in the subpopulation that underwent the aforementioned procedure. Finally, our results do not lean towards

supramesenteric bulky lymph node removal, nevertheless we believe that further large-scale studies are essential to assess the effective benefit and safety profile of this procedure.

1 INTRODUCTION

1.1 Epidemiology

Ovarian cancer (OC) is the third most frequent gynaecological cancer worldwide, with 313 959 new cases and 207 252 deaths in 2020. Its incidence has the highest rate in the US and Europe and the lowest in Africa, South America and South-Central Asia (1).

OC is most frequently diagnosed among women aged 55-64, with a median age at diagnosis of 63.

Diagnosis is often late, in fact approximately 75% of patients are diagnosed at an advanced stage.

Despite age-adjusted death rates have been falling on average 2.8% each year over 2011-2020, survival rate remains at only 50.8% 5 years after diagnosis (2).

1.2 Histological classification

There are three main types of OC: *epithelial*, which is the most common, *germ cell* and *sex cord-stromal*, with the latter two accounting for approximately 5% of all OC. They all have significant differences in terms of epidemiology, risk factors, dissemination patterns, genetic alterations, chemotherapy response and prognosis. In this study we will focus our interest on epithelial ovarian cancer only.

According to morphologic, immunohistochemical and molecular features, epithelial ovarian cancer (EOC) subtypes are *serous* (77%), *endometrioid* (10%), *clear cell* (10%) and *mucinous* (3%).

Serous tumours can be classified into *high-grade serous carcinomas* (HGSCs), which account for approximately 80% of all subtypes of EOC, or *low-grade serious carcinomas* (LGSCs), which account for less than 5%. HGSCs carry a high frequency of mutations in p53 and BRCA1/2 and originate in the fallopian tubes with ensuing spread to the ovaries or peritoneum. Instead, LGSCs often present mutations in BRAF and KRAS; they usually occur at a younger age and have a considerably better prognosis than HGSCs. LGSCs usually originate in the ovaries and may derive from a *borderline* serous tumour; the neoplastic progression from a borderline tumour to a LGSC affects only 6-7% of patients and is a late occurrence (3–5).

Every patient diagnosed with OC, even in the absence of a family history, is recommended to undergo a sequencing-based genetic test to examine the presence of somatic and/or germline BRCA mutations and other homologous recombination deficiency (HRD). In fact, according to their genetic profile, tumours may have different clinical behaviours and responses to treatment.

In particular, up to 30% of HGSCs harbour germline or somatic homologous recombination mutations. Of note, 13%-21% harbour germline BRCA1/2 mutations (gBRCAm) and an additional 6% harbour somatic BRCA1/2 mutations (sBRCAm). Hereditary EOC in gBRCAm carriers is characterized by younger age, high-grade serous histology, high response to cytotoxic platinum-based agents and Poly ADP-ribose polymerase inhibitors (PARPi) and better clinical outcome. Sporadic EOC with HRD but no gBRCAm have the same biological and clinical behaviour as EOC in gBRCAm carriers ("BRCAness" phenotype). In general, patients with sBRCAm and gBRCAm showed a more favourable OS compared to patients with wild-type BRCA (6,7).

1.3 Etiopathology

The main carcinogenesis model is based on the STIC, the *serous tubal intraepithelial carcinoma*. The STIC, predominantly located in the distal portion of the fallopian tube, is most likely the earliest morphologically recognizable precursor lesion of HGSCs, carcinosarcomas and undifferentiated carcinomas (8).

The elevate cell turnover of the Fallopian tubes' epithelium, especially within the fimbriae, and the oxidative stress to whom it is exposed facilitate the appearance of several mutations, including p53, BRCA1 and BRCA2 (9,10). However, the exact mechanism by which the STIC develops into invasive pelvic serous carcinoma is not well understood nor described in the current literature (8).

Histological, molecular and genetic evidence shows that about 80% of tumours that were classified as high-grade serous carcinomas of the ovary or peritoneum may have originated in the fimbrial end of the fallopian tube. For this reason, high-grade serous ovarian, fallopian tube and peritoneal cancers should be all considered collectively. In fact, in 2014 the Gynaecologic Oncology Committee of FIGO (International Federation of Gynaecology and Obstetrics) revised the staging incorporating them in the same system (11).

1.4 Risk and protective factors

Non-modifiable risk factors for OC are age (in women under 40 years of age OC is considerably rare), uninterrupted ovarian cycles (birth control use, early onset of menses, pregnancy, breastfeeding and early menopause may decrease the risk of OC), endometriosis (malignant transformation of endometriosis affects only 0.7-2.5% of cases and endometriosis-associated epithelial OC tend to have a better prognosis) and ethnicity (specifically Jewish, French Canadian and Dutch) (2,12,13). Recently it has been shown that hormonal replacement therapy, which has been considered a risk factor for a long time, is not associated with an increased risk of OC overall (14).

The strongest risk factor of developing OC is genetics, in particular a positive family history of breast or ovarian cancer, which is most commonly associated with germline mutations in the BRCA1 or BRCA2 genes. Mutation carriers are estimated to have a cumulative lifetime risk of OC of 20-50% for BRCA1 and 10-20% for BRCA2. Despite family history being the strongest risk factor, among patients with OC and germline mutations in BRCA1/2, almost 40% of them do not have a family history. Therefore, all women, even in the absence of a family history, should be offered genetic testing at the time of diagnosis (11). Other genes whose mutations increase the risk of OC are the DNA mismatch repair (MMR) genes, that are responsible for Lynch syndrome, or hereditary nonpolyposis colorectal cancer, type II. It is an autosomal genetic disorder that is associated primarily with colorectal cancer and other malignancies, such as ovarian and endometrial cancers. Inherited MMR genes mutations are estimated to confer cumulative lifetime risks of OC in the range of 6.7% to 12% by age 70 (15).

Concerning protective factors, several studies demonstrated that multiparity, breastfeeding and oral contraceptives reduce the risk of OC. In particular, oral contraceptives' protective effect lasts for more than 20 years after the end of treatment. Moreover, its protective role has been demonstrated in women with BRCA mutations as well (16,17).

1.5 Staging

Table 1 summarises the revised FIGO staging system for cancer of the ovary, fallopian tubes and peritoneum together with its equivalents in the TNM classification (18).

Stage I: Tumor confined to ovaries or fallopian tube(s)	**T1-N0-M0**
IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	**T1a-N0-M0**
IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	**T1b-N0-M0**
IC: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:	
IC1: Surgical spill	**T1c1-N0-M0**
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface	**T1c2-N0-M0**
IC3: Malignant cells in the ascites or peritoneal washings	**T1c3-N0-M0**
Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer	**T2-N0-M0**
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	**T2a-N0-M0**
IIB: Extension to other pelvic intraperitoneal tissues	**T2b-N0-M0**
Stage III: Tumor involves 1 or both ovaries or 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	**T1-3/N0-1/M0**
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):	**T1/T2-N1-M0**
IIIA1(i) Metastasis up to 10 mm in greatest dimension	
IIIA1(ii) Metastasis more than 10 mm in greatest dimension	
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	**T3a2-N0/N1-M0**
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	**T3b-N0/N1-M0**
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)	**T3c-N0/N1-M0**
Stage IV: Distant metastasis excluding peritoneal metastases	**Any T, any N, M1**
Stage IVA: Pleural effusion with positive cytology	
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

***Table I**. FIGO staging classification for cancer of the ovary, fallopian tubes and peritoneum.*

1.6 Prognosis

Five-year overall survival of patients with OC is approximately 50.8%, however it is dependent on staging.

Localized tumours (confined to primary site) are associated with a 5-year relative survival of 92,4%, tumours that have spread to regional lymph nodes of 72,9% and metastatic tumours of 31,5% (2).

The main prognostic factors in early-stage disease are neoplastic grading, disease extension, patient's age and histological type. Instead, advanced-stage disease's prognostic factors are mucinous or clear-cell subtypes (which have a lower chemosensitivity), volume of residual tumour after surgery and BRCA status (19).

1.7 Screening and prevention

The main reason of EOC high mortality rate is the delayed diagnosis in advanced-stage disease: approximately 75% of patients are diagnosed at stage III or IV (20). Indeed, pelvic examination, levels of CA125 and transvaginal and transabdominal ultrasounds (US) as screening methods have not shown acceptable levels of sensitivity or specificity, both in the general and in the high-risk population (21,22). None of these screening methods have been shown to lead to an early detection or to reduce the mortality of EOC (11).

Regarding prevention, since BRCA1/2 mutation is a significant risk factor for EOC, women with a documented germline mutation of BRCA1/2 should be advised to have a prophylactic bilateral salpingo-oophorectomy after the completion of childbearing and an appropriate counselling (11).

1.8 Clinical presentation and diagnosis

The diagnostic delay that characterises EOC is caused by, besides the absence of effective screening methods, also by the lack and vagueness of symptoms (23). In fact, most patients remain asymptomatic until the tumour spreads. This silent process allows the progression of the disease which follows a typical pattern: EOC usually spreads via local shedding into the peritoneal cavity followed by implantation on the peritoneum, via local invasion of the bowel and, more broadly, in the abdominal cavity.

Symptoms include abdominal bloating and pain, pelvic pain, menstrual irregularities, fatigue, loss of weight, dyspepsia, urinary and intestinal disorders (20). As the disease progresses, abdominal distention and discomfort from ascites generally worsen and may be associated with respiratory symptoms because of the increased intraabdominal pressure or the transudation of fluid into pleural cavities (11).

Initial investigation includes a detailed medical history (with a focus on risk factors, personal and family history of other cancers) and a physical examination of the patient. They are followed by the measurement of CA125 (Carbohydrate Antigen 125) serum concentration and a transvaginal and transabdominal ultrasound (20).

OC may initially be detected as an adnexal mass through ultrasonography. HGSCs usually appear as complex cystic and solid masses at imaging, often with evidence

of peritoneal spread at the time of presentation. Most adnexal masses are benign (the frequency of malignancy is below 10%) and can be accurately categorized as benign or malignant on US. However, approximately 25% of adnexal masses remain indeterminate following ultrasonography and it is in these circumstances that magnetic resonance imaging (MRI) may be used, as it has a high negative predictive value for malignancy.

Percutaneous biopsy of a suspicious adnexal mass is not advised because of the risk of potentially upstaging a confined early-stage OC or because of the risk of sampling error, resulting in a missed cancer diagnosis.

In 2015 the American College of Radiology created the Ovarian-Adnexal Reporting and Data System (O-RADS) for both US and MRI, a risk stratification and management system developed to improve characterization of ovarian pathology. It provides standardized algorithms to decrease ambiguity in imaging reports and improve accuracy in determining malignancy risk. The O-RADS MRI score is summarized in table II (24,25).

O-RADS MRI score	Risk of malignancy	Descriptors
0	N/A	Incomplete evaluation (non-applicable)
1	0%	Physiologic findings including follicles, hemorrhagic cysts and corpora lutea ≤ 3 cm in premenopausal women
2	< 0.5%	Unilocular smooth-walled ovarian or paraovarian cysts containing simple or endometriotic fluid; no enhancing solid tissue Simple hydrosalpinx Cyst with lipid (mature teratoma) and no enhancing solid tissue Smooth solid mass with low signal at T2WI and DWI
3	~ 5%	Unilocular smooth-walled ovarian cysts containing proteinaceous, hemorrhagic, or mucinous fluid; no enhancing solid tissue Hydrosalpinx with non-simple fluid or mural thickening Multilocular cyst with smooth walls and septations Solid tissue components (excluding T2 dark/DWI dark), low-risk DCE curve
4	~ 50%	Solid tissue components (excluding T2 dark/DWI dark) with intermediate-risk DCE curve OR enhancement less than or equal to myometrium at 30–40 s (if no DCE)
5	~ 90%	Solid tissue components (excluding T2 dark/DWI dark) with high-risk DCE curve OR enhancement greater than myometrium at 30–40 s (if no DCE) Peritoneal findings (ascites or nodules)

Table I. *Abbreviated O-RADS MRI risk stratification scheme (24).*

High levels of CA125 (upper limit: 35 U/ml) are consistent with a diagnosis of epithelial ovarian, fallopian tube or peritoneal cancer. However, serum CA125 assay has low sensitivity in early stages and CA125 concentration may be increased also in case of menstruation, endometriosis, pregnancy and inflammatory diseases of the peritoneum. Moreover, recently it has been proven that the combined measure of CA125 and HE4 (Human Epididymis Protein 4, a new biomarker which

is currently being evaluated for OC early detection) has a better specificity than the two markers taken separately, therefore the association of CA125 and HE4 may be a useful diagnostic tool (26).

A contrast-enhanced CT scan of the pelvis, abdomen and chest is mandatory to assess the extent of the disease before surgery. In fact, although CT scans can delineate the intra-abdominal spread of disease to a certain extent, EOC should be diagnosed and staged surgically, in order to determine the precise histological diagnosis, peritoneal stadification and prognosis.

Every case must be discussed in a multidisciplinary team meeting (19).

1.9 Surgery

In case of suspected EOC, an initial surgical approach is fundamental. It consists of a two-step procedure: firstly, a diagnostic surgery to stage the tumour, evaluate its resectability and take biopsies. If resectability may be achieved, a primary surgery is performed. In case of extended disease non accessible to a primary surgery, a neoadjuvant chemotherapy followed by interval debulking surgery is proposed.

Surgery usually consists of a laparotomy through a midline incision, a full exploration of the abdomen and the pelvis of the patient and the resection of all macroscopic lesions in order to achieve complete resection (CC0). It must be performed under the care of an experienced gynaecologic oncologist surgeon (27).

1.9.1 Surgical approach for stage I-II

The main goal of early-stage tumours surgery is to remove the disease situated in the pelvis and evaluate potentially concealed metastases in the upper abdomen and retroperitoneum.

Aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations. According to the FIGO Cancer Committee, the procedure should include total hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy. In the absence of macroscopically visible peritoneal nodules, multiple biopsies in the peritoneal surfaces that are more likely to become neoplastic sites should be performed, such as bilateral paracolic gutters, the peritoneal reflection of the bladder, cul-de-sac, the undersurface of the right hemidiaphragm and both pelvic sidewalls (27).

Systematic aortic and pelvic lymphadenectomy is currently recommended for the initial management or for a re-staging of early-stage EOC (except for effusive mucinous subtypes) as it allows to correct staging to IIIA1 in case of lymph node involvement from 8,5% to 13% of patients (28). However, this procedure still represents an area of controversy in the literature. In fact, a prospective randomised study in patients with presumed early stage showed that systematic aortic and pelvic lymphadenectomy improved detection of metastatic lymph nodes compared with node sampling but was not associated with improved progression-free survival (PFS) or overall survival (OS) (29). Whereas, another study and a meta-analysis reported that it improved OS in patients with early-stage disease, even though it did not improve PFS (27,30,31).

1.9.2 Surgical approach for stage III-IV

The recommended therapeutic approach for advanced-stage EOC integrates cytoreductive surgery and systemic therapy (figure 1). The most important prognostic factor for survival, in fact, is the *volume of residual disease after surgical debulking (R0)*; cytoreduction is defined optimal if R0 is macroscopically absent (32).

In most cases, a laparoscopic evaluation should be performed to assess whether optimal cytoreduction is likely to be achieved by primary PDS or to determine whether NACT may be a better initial treatment option (27). In particular, it has been shown that the combination of exploratory laparoscopy and CT scan has a higher diagnostic power than CT alone, decreasing the rate of unnecessary laparotomy by almost 60% (33).

Primary debulking surgery (PDS) includes total extra fascial hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, pelvic and aortic bulky lymph node removal and removal of every macroscopically visible part of the tumour. In order to attempt optimal cytoreduction, bowel resection and partial or complete resection of other organs, such as spleen and diaphragm, may be performed (19). In standard practice, PDS is considered as standard of care in patients where R0 may be reasonably expected, while IDS may be performed when R0 is not reasonably achievable because of the extent of the disease, patient's poor performance status, comorbidities or logistic reasons (11,27).

In case of extended disease non accessible to a primary surgery, a neoadjuvant chemotherapy (NACT) followed by *interval debulking surgery* (IDS) (usually after 3-4 cycles) is proposed.

A recent Cochrane metanalysis, whose objective was to assess whether there was any advantage in treating resectable advanced EOC patients with NACT before IDS or with PDS followed by chemotherapy showed that there is no statistically significant difference in OS and PFS in the two analysed groups. However, adverse events, surgical morbidity and quality of life outcomes were poorly and incompletely reported across studies. Data suggest that NACT followed by surgery compared with PDS followed by adjuvant chemotherapy may reduce infections, venous thromboembolism, the need for blood transfusion, stoma formation and bowel resection, as well as postoperative mortality (34).

Some intra-abdominal localizations of the disease may be resectable, such as spleen metastases, metastases involving Glisson's capsule and isolated segmental hepatic metastases depending on where they are located. The criteria against abdominal cytoreduction are deep and widespread infiltration in the root of the mesentery, extended small bowel carcinomatosis, infiltration of the hepatic hilum, diffuse intraparenchymal neoplastic involvements of liver, stomach or pancreas (19).

In advanced EOC, the rate of pelvic and para-aortic lymph nodes metastases has been reported between 43% and 56% (35); nonetheless, the use of systematic pelvic and para-aortic lymphadenectomy in advanced EOC is currently an area of controversy (27). Some retrospective analyses suggested its potential survival benefit in patients with macroscopically completely resected advanced EOC (36,37). However, a recent study (LION, Lymphadenectomy in Ovarian Neoplasms) showed that systematic pelvic and para-aortic lymphadenectomy of radiologically (initial CT scan) and clinically (per operative palpation) negative lymph nodes in patients with advanced stage EOC and intra-abdominal complete resection does not improve OS or PFS and is associated with a higher incidence of postoperative complications, therefore it may be omitted (38).

In general, NCCN and ESMO guidelines recommend performing pelvic and para-aortic lymph node dissection in patients whose disease is confined to affected ovaries or to the pelvis and in patients with metastatic nodules beyond the pelvis that are 2 cm or less (presumed stage IIIB). Instead, in case of extensive disease

outside the pelvis (nodules >2 cm), suspicious and/or enlarged lymph nodes should be resected. Systematic lymph node dissection and resection of clinically negative nodes is not required (27,39).

Regarding IVB patients, extra-abdominal metastases are usually a contraindication of cytoreduction, however, in selected patients, they may be resected in case of involvement of inguinal, retrocrural, pericardial or axillary lymph nodes, parietal pleura and isolated parenchymal pulmonary metastases. A recent study investigated the prognostic value of pulmonary metastases resection with promising results, however patients that fulfil eligibility criteria for pulmonary metastasectomy are rare and the cohort of the study was very limited (40). In general, resection of extra-abdominal metastases, especially regarding lymph nodes, has not been widely studied in literature, therefore it remains a controversial topic, as discussed later on in this thesis.

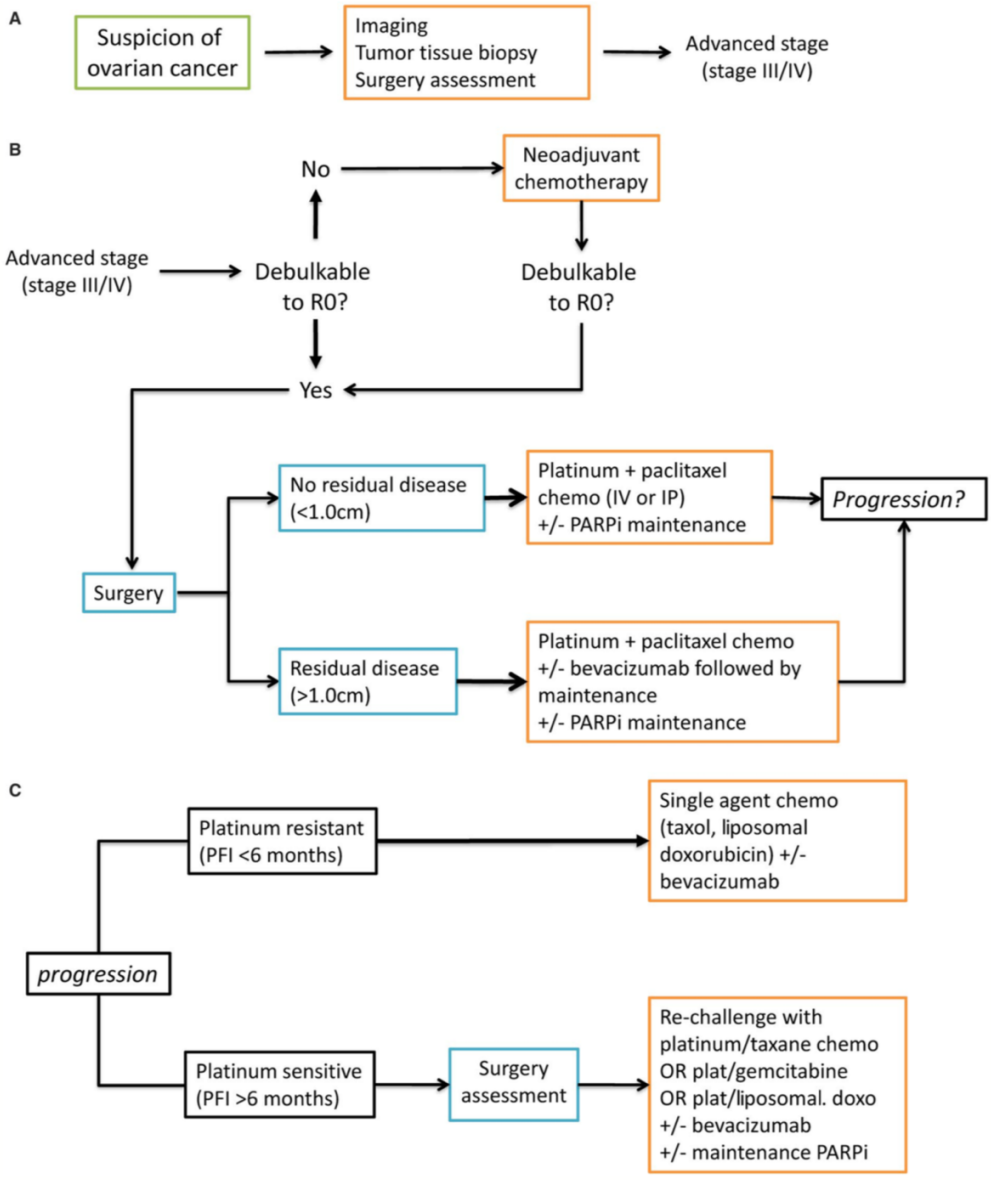

Figure 1. *Advanced Ovarian Cancer Treatment Guidelines. (A) Diagnosis, (B) frontline management, and (C) treatment upon recurrence.*

1.10 Systemic therapy

1.10.1 Chemotherapy

1.10.1.1 Chemotherapy for stage I-IIA

Low-risk patients (stage IA-IB G1) have a very good prognosis and surgery is sufficient in 95% of the cases. Adjuvant chemotherapy does not provide additional benefits; therefore, it is not indicated.

In intermediate-risk patients (stage IA-IB G2 and IC G1), instead, chemotherapy is optional and may be considered after appropriate counselling. In high-risk patients (stage IA-IB G3, IC G2/3 and IIA) adjuvant chemotherapy is indicated.

The standard treatment consists of either 6 cycles of Carboplatin AUC (area under the concentration-time curve) 5-6 or 3-6 cycles of a combination of Carboplatin AUC 5 and Paclitaxel 175 mg/m^2 (19).

1.10.1.2 Chemotherapy for stage IIB-IV

Regarding advanced-stage EOC, the current gold standard of chemotherapy is an intravenous combination of a platinum (Carboplatin or Cisplatin) and a taxane (Paclitaxel or Docetaxel).

The target dose for Carboplatin is an area under the concentration-time curve (AUC) of 5-6, while for Paclitaxel it is 175 mg/m^2 over 3 hours. The standard administration is every 21 days for 6 cycles (11). Common side effects of the Carboplatin-Paclitaxel combination are nausea and vomiting, myelosuppression, neuropathy and alopecia (41). It has been shown that administrating a dose-dense regimen of chemotherapy (both Carboplatin and Paclitaxel every week or Carboplatin every 3 weeks and weekly Paclitaxel) is associated with fewer toxic effects and a better quality of life, even if there is not a significant improvement in PFS and OS, compared with the standard regimen. Therefore, it may be a valid therapeutic alternative, particularly for elderly patients (42,43). Moreover, it has been demonstrated by several randomised clinical trials that doublet chemotherapy is optimal; in fact, adding a third drug has not shown an improvement in the outcome (44). Carboplatin is usually preferred to Cisplatin as it is as effective but has a better tolerability. Docetaxel has a similar efficacy to Paclitaxel, therefore it is an option in patients with an allergic reaction to the latter or an early sensory

neuropathy as it has less neurotoxicity, but it is more myelosuppressive than Paclitaxel (11,45). Carboplatin-Pegylated liposomal doxorubicin (PLD) combination is another valid alternative for patients presenting contraindication for Paclitaxel since it has a similar response rate but different toxicity (less neurotoxicity but more hematologic adverse effects) (46).

In advanced-stage EOC, chemotherapy may also be administrated directly in the peritoneum (*intraperitoneal chemotherapy*, IP), since in most cases the distribution of the disease is initially limited to the intra-abdominal cavity. IP chemotherapy has shown an improved PFS and OS in selected patients with optimally debulked (R0<1cm after PDS) stage III EOC (47–49). However, European guidelines are leaning away from IP chemotherapy, which is not widely used outside the US, because of the ongoing debate on its benefits and concerns regarding increased toxicity and catheter-related problems (11). IP chemotherapy may also be heated and instilled in the cavity during surgery (*hyperthermic intraperitoneal chemotherapy*, HIPEC). HIPEC has shown additional benefits in the outcome (improved PFS and OS in stage III EOC), nonetheless, there still remains a debate and its use is limited to experimental protocols (50). Several prospective studies are currently under recruitment to evaluate IP and HIPEC benefits in advanced-stage EOC in front-line treatment and recurrence, such as the CHIPPI trial, which is evaluating the efficacy in terms of disease-free survival (DFS) between HIPEC combined with standard care (PDS or IDS) and standard care alone (PDS or IDS alone) (51).

1.10.2 Targeted therapy

1.10.2.1 Bevacizumab

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF).

It has been demonstrated to improve PFS in patients receiving it as maintenance therapy following Carboplatin, Paclitaxel and concurrent Bevacizumab. The benefits with respect to both PFS and OS are greater among those at high risk for disease progression.

Moreover, the presence of mutations in BRCA genes or non-BRCA homologous recombination repair genes is associated with longer PFS and OS compared with non-carrier patients (52–55).

These findings led to the validation of the addition of Bevacizumab in combination with Carboplatin and Paclitaxel with a dose of 7.5-15 mg/kg every 3 weeks for 6 cycles and then as maintenance therapy (27). However, the role, optimal dose (7.5 mg/kg or 15 mg/kg), timing (primary or recurrent disease) and duration of treatment are still debatable (11).

Its adverse effects are hypertension, proteinuria, bleeding, delayed wound healing, propensity for bowel perforation or fistulisation and thromboembolic events, but they rarely lead to Bevacizumab discontinuation (56,57).

1.10.2.2 PARP inhibitors

Poly ADP-ribose polymerase (PARP) enzymes play a key role in the repair of single-strand breaks of the DNA. PARP inhibitors (PARPi), such as Niraparib, Olaparib and Rucaparib, especially in BRCA mutations and other HRD, lead to the accumulation of unrepaired DNA breaks that entails cellular death (58).

PARPi have shown a significant improvement in PFS as maintenance therapy in BRCA-mutated or HRD platinum-sensitive relapsed high-grade serous OC. Therefore, they are currently the standard of care as maintenance therapy following the Carboplatin and Paclitaxel chemotherapy (59–62).

Patients with BRCA mutations (both somatic and germline) have the greatest clinical benefit, followed by patients whose tumour presents other homologous recombination deficiency (63). However, there are indications for the use of Niraparib also in patients that do not carry BRCA mutations or other HRD.

All PARPi are associated with mainly low-grade adverse effects, such as nausea, fatigue and myelosuppression, which can mostly be managed with dose reductions and brief interruptions of the treatment (11).

A very recent trial studied the combination of Bevacizumab and Olaparib as maintenance therapy in advanced EOC patients in clinical response after first-line platinum-based chemotherapy plus Bevacizumab, irrespective of surgical status. The study demonstrated that the aforementioned combination has a statistically

significant increase in PFS and OS in patients with BRCA mutations and HRD compared with Bevacizumab alone, confirming the PARPi-Bevacizumab combination as one of the standards of care in HRD-positive tumours (64).

The FDA-approved indications for the use of Bevacizumab, Niraparib, Olaparib and Rucaparib are shown in table III.

Agent USPI Date	First-Line Chemotherapy	Maintenance After First-Line Chemotherapy	Recurrence Therapy	Maintenance After Recurrence Therapy
Bevacizumab September 2020[227]	For epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease following initial surgical resection.		For epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with paclitaxel, PLD, or topotecan, for platinum-resistant recurrent disease who received ≤2 prior chemotherapy regimens.	
			For epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum-sensitive recurrent disease.	
Niraparib April 2020[261]	None	For the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy.	For the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥3 prior chemotherapy regimens and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation[a], or • genomic instability[a] and who have progressed >6 months after response to the last platinum-based chemotherapy.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy.
Olaparib May 2020[262]	None	For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated[b] advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy. In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation[b], and/or • genomic instability[b]	For the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated[b] advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in CR or PR to platinum-based chemotherapy.
Rucaparib October 2020[263]	None	None	For the treatment of adult patients with deleterious *BRCA* mutation[c] (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥2 prior lines of chemotherapies.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy.

Abbreviations: CR, complete response; HRD, homologous recombination deficiency; PLD, pegylated liposomal doxorubicin; PR, partial response; USPI, US prescribing information.
[a]Select patients for therapy based on an FDA-approved companion diagnostic for niraparib.
[b]Select patients for therapy based on an FDA-approved companion diagnostic for olaparib.
[c]Select patients for therapy based on an FDA-approved companion diagnostic for rucaparib.

Table III*. FDA-approved indications for Bevacizumab and PARP inhibitors in ovarian cancer (27).*

1.11 Follow-up

Regarding EOC's follow-up, there are currently no clear guidelines on type and schedule (11).

In standard practice, patients are usually seen every 3 months during the first year of follow-up, then with a gradual increase in intervals to every 4-6 months after two years and annually after 5 years; however, it should be planned according to the

tumour's stage, histological type and biomolecular features, availability of effective treatments and treatments taken in the past.

During each follow-up, patients should have their history retaken and a physical and pelvic examination should be performed.

CA125 is usually checked at regular intervals during the follow-up in order to identify a potential recurrence early. Its levels might be pathological 2 to 5 months before clinical or radiological diagnosis of recurrence (19). In case of neither radiological nor clinical evidence of disease, some authors suggest that recurrence may be defined by the doubling of the upper limit of normal levels of CA125 for patients with normal baseline levels or by the doubling of the nadir value for patients whose CA125 have not normalized (20). However, a large study showed that treating patients with recurrent EOC with chemotherapy on the basis of CA125 progression alone does not improve survival rates and has a negative impact on the quality of life. In fact, asymptomatic patients with no radiological evidence of recurrence should be kept under close observation or in an appropriate trial. The decision to treat (with chemotherapy) should be based on symptoms as well as clinical and radiological findings (65).

According to the American College of Radiology's appropriateness criteria for the follow-up of EOC, contrast-enhanced CT scan is the modality of choice for detecting recurrence, with a sensitivity in the range of 58-84% and a specificity in the range of 60-100%. FDG-PET/CT is also usually appropriate as it can provide management-changing information about unresectable sites of tumour or small lymph nodes. CT and FDG-PET/CT are considered equivalent alternatives. Recurring abdomen ultrasounds are also recommended, despite their limited diagnostic accuracy (66).

Follow-up plays a key role in the identification of treatment-related complications and late toxicity too, which, if present, should lead to an endocrinological-reproductive evaluation.

In particular, it is important to pay close attention to early onset menopause induced by chemotherapy in younger patients (19). In that case, even though data is lacking and is often controversial, hormonal replacement therapy (HRT) may a valid option in young patients with early-stage serous EOC. HRT is not recommended in

advanced stages and in tumours that present oestrogen receptors (67).

1.12 Recurrence and second-line treatments

Approximately 80% of patients respond very well to first-line chemotherapy, however EOC relapses with a median time to recurrence of 16 months and recurrence rate is 75-80% 3 years after the completion of chemotherapy (11,68).

Recurrences are usually treated with chemotherapy, however in selected cases a secondary debulking surgery may be performed. A recent randomized trial studied 407 patients that had recurrent OC with a first relapse after at least a 6 months platinum-free interval (an interval during which no platinum-based chemotherapy is administered) and that were randomly assigned to undergo secondary cytoreductive surgery and then receive platinum-based chemotherapy or to receive platinum-based chemotherapy alone. Results showed that the median OS in the surgery group was significantly longer than in the no-surgery group (53.7 and 46 months, respectively) (69).

The most widely used clinical surrogate for predicting response to subsequent chemotherapy and prognosis is the *treatment-free interval*, which is the time from cessation of primary platinum-based chemotherapy to disease recurrence or progression.

Patients with a treatment-free interval of less than 6 months are defined *platinum-resistant.* Patients who have a disease progression while on treatment or within 4 weeks of stopping chemotherapy are defined as *platinum-refractory*. Platinum-resistant and platinum-refractory patients should be treated with nonplatinum-based chemotherapy (in that case, reported response rates are low, with a median survival of 9-12 months) or enrolled in an available clinical trial. Instead, *platinum-sensitive* patients (whose treatment-free interval is more than 6 months) are generally treated with another platinum-based chemotherapy (11).

In patients that are eligible for a second-line platinum-based therapy, the standard of care is a combination between Carboplatin and either Paclitaxel or Gemcitabine or PLD. If patient's performance status is mediocre, Carboplatin in monotherapy is a valid option (19). In addition to the second-line platinum-based doublet, a PARPi maintenance therapy is recommended, particularly in case of BRCA mutations (59–62). Instead, in case of patients with wildtype BRCA, with extent disease and highly

symptomatic, a combination of Carboplatin, Gemcitabine and Bevacizumab, followed by Bevacizumab alone as maintenance therapy is recommended until progression of the disease or intolerable toxicity (70).

Moreover, in case of recurrent low-grade stage II-IV serous OC, anti-oestrogen hormonal therapy, such as Aromatase inhibitors, Tamoxifene and Leuprolide acetate, may be used as maintenance therapy in patients who underwent PDS and a first-line platinum-based chemotherapy. In these cases, hormonal maintenance therapy has been shown to improve OS and PFS and to have a low impact of toxicity (71,72).

Recently, immune-checkpoints inhibitors have been used as monotherapy in platinum-resistant recurrences but have not shown any efficacy so far (73).

1.13 Complications

The most common complication of EOC recurrences is malignant bowel obstruction (MBO).

The criteria to define MBO are the following: clinical evidence of bowel obstruction (history, physical and radiological examination), bowel obstruction beyond the ligament of Treitz, diagnosis of intra-abdominal cancer with incurable disease or diagnosis of non-intra-abdominal primary cancer with clear intraperitoneal disease. Its symptoms include vomiting, abdominal pain and nutrient deprivation. At this moment its clinical management has not been defined properly, which makes it a major clinical challenge, with a median survival after diagnosis of less than 5 months. Surgical intervention may be successful in selected cases and consists of diverting stoma but is associated with significant morbidity and risk of perforation and death; therefore, it should not be performed in patients with poor performance status, intra-abdominal carcinomatosis and massive ascites (74).

In conclusion, EOC is a chronic disease, which may relapse several times and may have an important impact on quality of life, particularly because of treatment-related adverse events. Therefore, in case of recurrence, it is important to provide patients with control of the disease together with preservation of their quality of life, balancing therapies benefits and adverse events. In these circumstances, early intervention of palliative care plays a key role for patients and their families (20).

2 OBJECTIVE OF THE STUDY

2.1 Preface on stage IV ovarian cancer

2.1.1 Definition and prognosis

Stage IV EOC represent approximately 75% of diagnosed EOC. Despite a significant increase of OS over the last decades in early-stage disease, survival for stage IV patients did not grossly change, still remaining between 8% and 39% for sub optimally and optimally debulked patients, respectively. Nonetheless, literature regarding specifically stage IV EOC is lacking and only a few authors have addressed the question of its management and prognosis (75).

The staging of EOC was revised in 2014 and 2018 by the FIGO, which established that patients with cytologically proven pleural effusion and/or metastases are classified as stage IVA, whereas those with extra-abdominal parenchymal and/or lymph node metastases are classified as stage IVB. Patients with inguinal lymph node metastases or transmural digestive involvement with mucosal involvement, previously classified as stage III, became stage IVB.

The FIGO classification aims to group together patients with similar prognosis, however the prognostic value of the dichotomization into FIGO stages IVA and IVB remains controversial. Some recent studies showed that patients with stage IVA had significantly lower 5-year OS and PFS than those with stage IVB. In particular, initial pleural involvement (stage IVA) was a poor prognostic factor. Moreover, postoperative volume of residual tumour and recurrence rate were higher in stage IVA than in stage IVB (76,77).

In this study we took into consideration patients with stage IVB ovarian cancer, namely patients with parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity), as defined by the FIGO staging classification (18).

The most common sites of metastases in stage IVB EOC patients include peritoneum, liver, lymph nodes, lung, bone and brain. Distant sites where primary OC metastasizes may have different effect on prognosis and knowing that relationship may be crucial in designing effective treatment strategies for patients. At this moment, most studies have focused on single distant metastatic sites (78–

80), but few have investigated the association between different site-specific metastases and prognosis of ovarian cancer.

In particular, Deng et al. analyzed 1481 metastatic EOC patients and found that the prognosis of patients with distant metastases differs according to the site of metastasis. In particular, distant metastases to lymph nodes were associated with better OS compared to liver, lung (which were associated with the worst OS), bone and brain metastases. Furthermore, the number of metastatic sites did not affect OS. They also found that surgery and chemotherapy can greatly improve the prognosis of patients with distant lymph nodes metastases only (they had the best OS among the other 5 sites taken into account) (81).

Hjerpe et al. drew the same conclusions in their study: in a cohort of 551 stage IV EOC patients they showed that those with non-regional lymph nodes as only distant metastasis had a significantly longer OS than those with pleural metastases only or those with other/multiple metastases. These results suggest that disease disseminating predominately through the lymphatics would have a less aggressive nature than that directly invading the pleura or hematogenous spreading (82).

2.1.2 Interest in supramesenteric lymph nodes

In stage IVB OC, upper abdominal and intrathoracic supradiaphragmatic lymph nodes, such as hepatoceliac, splenic and cardiophrenic, can serve as a common site for metastases. In this setting, there may be two possible surgical approaches: supramesenteric and inframesenteric bulky lymph node removal. In the first one, upper abdominal and supradiaphragmatic bulky lymph nodes are resected, whereas in the latter one bulky lymph nodes are removed only if they are located just above the left renal vein but not further up (hepatoceliac, splenic and cardiophrenic bulky lymph node removal is not performed).

Multiple studies have consistently demonstrated that optimal debulking (R0) improves OC survival outcomes (32). In this perspective, performing a surgical resection of enlarged upper abdominal and supradiaphragmatic lymph nodes may contribute to minimize the volume of residual disease and, therefore, to improve survival rates. However, upper abdominal and supradiaphragmatic cytoreductive surgery (including, besides bulky lymph nodes resection, also diaphragmatic peritonectomy with or without pleurectomy, partial liver resection,

cholecystectomy, splenectomy with or without distal pancreatectomy and resection of the tumor at the porta hepatis) in stage IVB EOC patients has not been widely studied and remains a controversial area.

2.1.2.1 Cardiophrenic lymph nodes

Cowan et al. studied the feasibility and safety of cardiophrenic lymph nodes (CPLN) resection via video-assisted thoracic surgery (VATS) or via a transdiaphragmatic or subxiphoid approach in a cohort of 54 patients. They found that CPLN resection rendered all cases amenable to optimal debulking (to <1 cm), with over 50% obtaining complete gross resection, without delaying adjuvant treatment and with a low and acceptable morbidity rate. Median PFS was 17.2 months and median OS 70.1 months (83).

Lee et al. studied the prognostic significance of CPLN resection in a cohort of 50 patients with confirmed CPLN metastases that underwent CPLN resection via VATS or transdiaphragmatic excision during PDS. Among these patients, those who had undergone thoracic debulking did not have improved PFS or OS compared with patients who had not undergone debulking (84). However, according to a recent review, although this study failed to show a survival benefit for CPLN resection, the low complete gross resection rate of 27.8%, the more frequent intraperitoneal recurrence rate and the lower median OS of the entire cohort and subsets precluded adequate evaluation of the survival impact of CPLN resection as part of a comprehensive debulking strategy (85).

2.1.2.2 Hepatoceliac lymphnodes

Regarding hepato-celiac lymph nodes (HCLN), Tozzi et al. studied a cohort of 216 patients with stage IIIC-IV OC. Besides highlighting the role of the combination of CT scan and exploratory laparoscopy in detecting metastases in the porta hepatis (PH) and HCLN (CT scan alone failed to identify disease in 25.8% of patients), it was showed that PH/HCLN surgery was required in 15% patients with stage IIIC-IV in order to aim to complete resection. Median disease-free survival was 19 months and median OS was 42 months, no complication was specifically related to the PH/HCLN surgery, which resulted feasible and safe (86).

Gallotta et al. drew the same conclusions as the aforementioned authors. Moreover, despite the limits of the relatively low number of patients undergoing para-aortic

and mesenteric lymphadenectomy, patients with metastatic para-aortic and mesenteric lymph nodes showed metastatic involvement of HCLN in 62.8 and 70% of cases, respectively. This may encourage systematic intraoperative exploration of the HCLN area even in the absence of any suspicious lesion at preoperative imaging if metastatic para-aortic and mesenteric lymph nodes are documented (87).

In conclusion, studies on stage IVB EOC prognosis and surgical management are insufficient. Although the adoption of these procedures is increasingly propagated in specialized cancer centers, data on its safety and morbidity profile are still limited. Indeed, survival benefit from resection of these macroscopically involved areas in the upper abdomen and in the supradiaphragmatic space has not been established yet. Therefore, careful weighing of risks and benefits of increased radicality in these gray areas is essential to the achievement of a balance between unnecessary radicality with unclear benefit and surgical undertreatment with the risk of precluding a life-lengthening procedure (88).

We present an international multicentric retrospective study on stage IVB prognosis and factors for survival.

2.2 Objectives of the study

The primary objective of the study is to investigate the impact on survival of different anatomic localisations of metastases in stage IVB epithelial ovarian cancer patients who underwent a visceral peritoneal debulking.

The secondary objective is to study within this population the impact on survival of upper abdominal and intrathoracic supradiaphragmatic lymph node metastases surgical resection and identify prognostic factors for survival. In particular, the aim is to compare prognostic implications of two different surgical approaches: inframesenteric and supramesenteric bulky lymph node removal.

3 MATERIALS AND METHODS

3.1 Study design and data collection

We conducted an international multicentric retrospective population-based study recruiting patients from 3 institutions: Breast and gynaecologic oncology surgery, Georges Pompidou European Hospital (Paris, France), Department of Gynaecologic Oncology, Oxford Cancer Centre, Churchill Oxford University Hospital (Oxford, UK) and Unit of Gynaecology and Obstetrics, Department of Women and Children's Health, University of Padua (Padua, Italy).

Inclusion period was between February 2005 and April 2023. All patients who underwent visceral peritoneal debulking (VPD) for epithelial ovarian cancer in one of these 3 academic surgery departments were eligible.

Inclusion criteria were:

- Histology proven or suspected stage IVB cancer of the ovary, fallopian tube or peritoneum
- Performance status scored as ASA score ≤ 3 at pre-operative assessment
- Post chemotherapy patients: stable disease or any response

Exclusion criteria were:

- Preoperative: CT scan: presence of pulmonary metastases, 3 or more liver segments involvement, disease progression following chemotherapy
- Intraoperative: diffuse small bowel miliary serosal deposits.
- Evidence of other advanced neoplastic disease
- Current pregnancy

Pre-operative evaluation included gynaecological and physical evaluation, CA125, CT-scan of chest, abdomen and pelvis. All patients were discussed in a local multidisciplinary team meeting.

The American Society of Anesthesiologists (ASA) score was used to assess the preoperative health status of patients. Patients were assigned a score ranging from 1 to 6 if they were in good general condition (ASA 1), had moderate (ASA 2), severe (ASA 3) or life-threatening (ASA 4) organ dysfunction, with a life

expectancy of less than 24 hours (ASA 5) or in a state of encephalic death (ASA 6).

All VPD were performed under the care of different board-certified Gynaecologic Oncologists.

Data concerning patients' status, histological and molecular features of the tumour, surgical procedure, complications and follow up have been collected.

Three departmental databases were used to record, monitor and audit patients' data.

All patients who met the inclusion/exclusion criteria entered the study.

After approval of the local ethics committees, informed consent forms from the patients were obtained.

3.2 Primary and secondary outcomes

The primary outcome was to study the impact on survival of upper abdominal and intrathoracic supradiaphragmatic lymph nodes metastases and identify prognostic factors for survival.

For the need of the study, we sorted lymph nodes according to their anatomical district, 4 different anatomical areas were formed:

- Area1 made of pelvic, lomboaortic and inguinal lymph nodes
- Area 2 of pericolic and mesenteric lymph nodes
- Area 3 of suprarenal, gastric and porta hepatis lymph nodes
- Area 4 of mediastinal, cardiophrenic, pulmonary, axillary, supraclavicular, infraclavicular and cervical lymph nodes.

The secondary outcome was to compare two different surgical approaches on survival: inframesenteric and supramesenteric bulky lymph node removal.

For the need of the study, a new subpopulation of 55 patients presenting metastatic supramesenteric lymph nodes was defined by putting together patients with metastatic mediastinal, cardiophrenic and upper abdominal (including suprarenal, gastric and porta hepatis) lymph nodes.

3.3 Statistical analysis

Overall survival was defined as the time from the date of cytoreductive surgery to the date of last news or death from any cause. Disease-free survival (DFS) was defined as the time from cytoreductive surgery to tumor recurrence.

Continuous variables were expressed using the mean ± standard deviation. They were compared using the Student's *t*-test or the Wilcoxon test in the case of a non-parametric distribution. Categorical values were expressed using an absolute number and a percentage. They were compared using a Chi^2 test or a Fischer exact test. Kaplan–Meier curves were used to graphically express the differences in OS and PFS.

A p value <0.05 was considered statistically significant.

All statistical analyses were performed using an Excel database and a statistical calculator program (Jamovi version 2.3.28.0).

4 RESULTS

4.1 Descriptive analysis of the population

Between 2005 and 2023, 963 patients with diagnosed epithelial ovarian cancer, all FIGO stages combined, were treated at one of the 3 abovementioned institutions (712 patients in Paris from February 2005 to June 2021, 129 patients in Oxford from September 2007 to August 2016 and 122 patients in Padua from June 2021 to May 2023).

Among these patients, 178 (18.48%) were diagnosed with stage IVB; of these, 35 (3.63%) were excluded due to missing data or because they did not meet the inclusion criteria and 143 (14.85%) were included in our study. In particular, 39 patients were treated in Oxford, 25 in Padua and 79 in Paris.

Mean age of the population was 62.7 ± 11.9 years and mean levels of preoperative CA125 were 1631 ± 2636 U/ml.

Characteristics of patients and their tumour are detailed in table IV.

One hundred and twenty (83.9%) patients had primary ovarian cancer, followed by primary peritoneal (7.7%) and recurrent ovarian (4.9%). The great majority of our cohort, specifically 128 patients (90.8%) out of 143, was diagnosed with an epithelial serous OC. Moreover, 87.2% of tumours were diagnosed grade 3.

Characteristics regarding metastases' localisation and frequency are detailed in table V.

Most metastatic lymph nodes were in the pelvic and lomboaortic districts, in particular 53 (37.1%) patients had metastatic pelvic lymph nodes and 47 (32.9%) patients had metastatic lomboaortic lymph nodes. Other lymph nodes that were frequently the site of metastases were suprarenal (defined as lymph nodes above the left renal vein) and mediastinal, in 22 (15.4%) and 19 (13.3%) patients, respectively.

Regarding metastases to other organs (metastatic lymph nodes excluded), 57 (40.1%) patients had metastases in the large bowel, 133 (93.7%) in the omentum and 77 (53.8%) in the diaphragm.

	Frequency	Total	Percentage (%)
ASA			
1	16	86	18.6
2	43	86	50
3	26	86	30.2
4	1	86	1.2
Origin			
Primary ovarian	120	143	83.9
Recurrent ovarian	7	143	4.9
Primary peritoneal	11	143	7.7
Other	5	143	3.5
Pathology			
Serous	128	141	90.8
Endometroid	3	141	2.1
Mucinous	1	141	0.07
Clear cell	1	141	0.07
Undifferentiated	4	141	2.8
Other	4	141	2.8
Grade			
1	7	109	6.4
2	7	109	6.4
3	95	109	87.2

***Table IV**. Characteristics of patients and their tumour. ASA score: American Society of Anaesthesiologists score, 1: good general condition, 2: moderate organ dysfunction, 3: severe organ dysfunction, 4: life-threatening organ dysfunction.*

Metastases	Frequency	Total	Percentage (%)
To lymph nodes			
Inguinal	5	143	3.5
Pelvic	53	143	37.1
Lomboaortic	47	143	32.9
Pericolic	2	143	1.4
Mesenteric	4	143	2.8
Suprarenal	22	143	15.4
Gastric	4	143	2.8
Porta hepatis	2	143	1.4
Mediastinal	19	143	13.3
Pulmonary	2	143	1.4
Cardiophrenic	8	143	5.6
Axillary	4	143	2.8
Supraclavicular	7	143	4.9
Infraclavicular	1	143	0.7
Cervical	2	143	1.4
To other organs			
Small bowel	7	143	4.9
Large bowel	57	143	40.1
Liver	23	143	16.3
Spleen	32	143	22.5
Stomach	7	143	6
Omentum	133	143	93.7
Diaphragm	77	143	53.8
Pleurae	24	143	16.8

***Table V**. Characteristics of metastases' localisation and frequency.*

4.2 Descriptive analysis of cytoreductive surgery

The main characteristics of cytoreductive surgery are detailed in tables VI-1 and VI-2.

Out of the 143 patients in our cohort, 111 (77.6%) underwent interval debulking surgery, while 32 patients (22.4%) primary debulking surgery. One hundred and two (71.3%) patients were treated with neoadjuvant chemotherapy, while 33 (23.1%) had no treatment before cytoreductive surgery.

Before debulking surgery, an exploratory laparoscopy was performed in 120 (85.1%) patients.

Cytoreductive surgery had a mean duration of 434 ± 165 minutes, while hospitalisation lasted on average 15.4 ± 14.1 days.

During debulking surgery, 135 (95.1%) patients had a small bowel resection and 85 (59.9%) had a large bowel resection. Omentectomy was performed in 133 (93.7%) patients and liver resection in 124 (88.6%) patients. Diaphragm stripping was performed in 77 (53.8%) patients, while pleurectomy in 24 (16.8%).

Regarding surgical removal of bulky lymph nodes (table VII), every metastatic inguinal, pelvic, lomboaortic, pericolic, gastric and hepatic bulky lymph node was removed during cytoreductive surgery. Out of four metastatic mesenteric lymph nodes, 3 (75%) were resected. Out of 8 metastatic cardiophrenic lymph nodes, 3 (37.5%) were resected.

Metastatic suprarenal, mediastinal, pulmonary, axillary, infraclavicular, supraclavicular and cervical lymph nodes were not surgically removed.

At the end of the procedure, 114 (82%) patients had no residual disease (CC0); in 8 (5.8%) patients residual disease was less than 2.5mm, in 10 (7.2%) it was between 2.5mm and 2.5cm and in 2 (1.4%) there was a miliary extension of the disease.

Furthermore, 95 (70.4%) patients out of 135 had at least one recurrence, that, in most cases (35 out of 81, 43.2%), was treated with chemotherapy (table VIII).

	Frequency	Total	Percentage (%)
Surgical timing			
Primary debulking	32	143	22.4
Interval debulking	111	143	77.6
Previous management			
None	33	143	23.1
Noeadjuvant chemotherapy	102	143	71.3
Previous surgery and adjuvant chemotherapy	3	143	2.1
Unspecified	5	143	3.5
Explorative laparoscopy			
No	21	141	14.9
Yes	120	141	85.1
Presence of ascites			
No	71	120	59.2
Yes	49	120	40.8
Residual disease			
CC0	114	139	82
CC1 (<2.5mm)	8	139	5.8
CC2 (2.5mm<x<2.5cm)	10	139	7.2
CC3 (military)	2	139	1.4
Unspecified complete resection	5	139	3.6

Table VI-1*. Characteristics of cytoreductive surgery.*

	Frequency	Total	Percentage (%)
Hysterectomy			
No	8	142	5.6
Yes	128	142	90.1
Previously	6	142	4.2
BSO/MSO			
No	7	142	4.9
Yes	129	142	90.8
Previously	6	142	4.2
Small bowel resection			
No	135	142	95.1
Yes	7	142	4.9
Large bowel resection			
No	85	142	59.9
Yes	57	142	40.1
Omentectomy			
No	9	142	6.3
Yes	133	142	93.7
Liver resection			
No	124	140	88.6
Yes	16	140	11.4
Splenectomy			
No	104	140	74.3
Yes	36	140	25.7
Gastric resection			
No	60	63	95.2
Yes	3	63	4.8
Diaphragm stripping/pleurectomy			
No	42	143	29.4
Diaphragm stripping	77	143	53.8
Pleurectomy	24	143	16.8

Table VI-2*. Characteristics of cytoreductive surgery.*

Removed bulky lymph nodes	Frequency	Total	Percentage (%)
Inguinal	5	5	100
Pelvic	53	53	100
Lomboaortic	47	47	100
Pericolic	2	2	100
Mesenteric	3	4	75
Suprarenal	0	22	0
Gastric	4	4	100
Porta hepatis	2	2	100
Mediastinal	0	19	0
Pulmonary	0	2	0
Cardiophrenic	3	8	50
Axillary	0	4	0
Supraclavicular	0	7	0
Infraclavicular	0	1	0
Cervical	0	2	0

***Table VII**. Characteristics of surgically removed bulky lymph nodes.*

	Frequency	Total	Percentage (%)
Recurrence			
No	40	135	29.6
Yes	95	135	70.4
Treatment of recurrence			
None	27	81	33.3
Chemotherapy	35	81	43.2
Surgery	1	81	1.2
Target therapy	1	81	1.2
Chemotherapy and surgery	6	81	7.4
Chemotherapy and target therapy	8	81	9.9
Chemotherapy, surgery and target therapy	3	81	3.7

Table VIII*. Characteristics of recurrences and their treatment.*

4.1 Descriptive analysis of complications

Characteristics of complications in patients who underwent inframesenteric and supramesenteric bulky lymph node removal are detailed in tables IX-1 and IX-2.

Between the two subpopulations of patients who underwent inframesenteric and supramesenteric bulky lymph node removal, the latter experienced a higher rate of complications, 66.67% versus 40.06%, respectively. In particular, among patients who underwent such surgery, 16.67% deceased after the procedure, compared to the 1.55% of the other subpopulation.

Within patients who underwent inframesenteric metastatic lymph nodes debulking, medical, surgical and medical+surgical complications were equally distributed, while in the supramesenteric subpopulation, 50% of complications were medical rather than surgical.

Characteristics of complications in patients who underwent supramesenteric bulky lymph node removal are detailed in table X.

Lymph node removal	Patients with complication (%)	Intraoperative complications (%)	Post-operative complications (%)
Inframesenteric	62 (40.06)	20 (15.50)	56 (43.41)
Supramesenteric	6 (66.67)	0 (0)	6 (66.67)

***Table IX-1**. Characteristics of complications in patients who underwent inframesenteric and supramesenteric bulky lymph node removal.*

Lymph node removal	Medical complications (%)	Surgical complications (%)	Medical and surgical complications (%)	Death (%)
Inframesenteric	21 (16.28)	24 (18.6)	14 (10.85)	2 (1.55)
Supramesenteric	3 (50)	1 (16.67)	2 (33.33)	1 (16.67)

***Table IX-2**. Characteristics of complications in patients who underwent inframesenteric and supramesenteric bulky lymph node removal.*

Supramesenteric bulky lymph nodes removed	Complications	Intra-operative	Early (<15 days)	Late (>15 days)
Porta hepatis	Yes		Pleural effusion + wound dehiscence	
Gastric	Yes		Postoperative ileus due to stomach dilatation	
Porta hepatis	No			
Cardiophrenic + porta hepatis	No			
Cardiophrenic	Yes			Surgical wound infection
Gastric	Yes		Pleural effusion + gastric and duodenal fistualae + stoma necrosis + melena	Death
Gastric	No			
Cardiophrenic	Yes		Pleural effusion + anemia	
Cardiophrenic + gastric	Yes		Pleural effusion + anemia	

Table X. *Characteristics of complications in patients who underwent supramesenteric bulky lymph node removal.*

4.2 Descriptive analysis of overall and disease-free survival

Mean overall survival of patients in our cohort was 29.04 ± 24.55 months, while mean disease-free survival was 15.73 ± 13.28 months.

Kaplan-Meier survival curves are shown in figures 2 and 3.

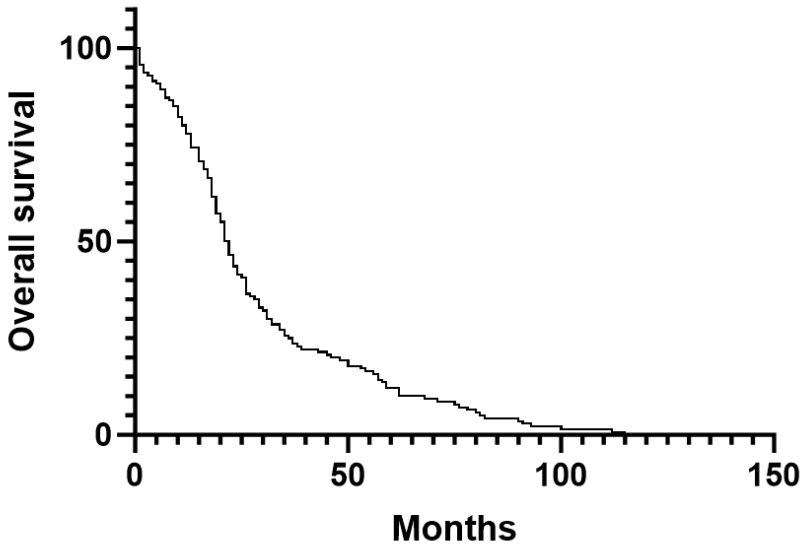

***Figure 2**. Kaplan-Meier overall survival curve.*

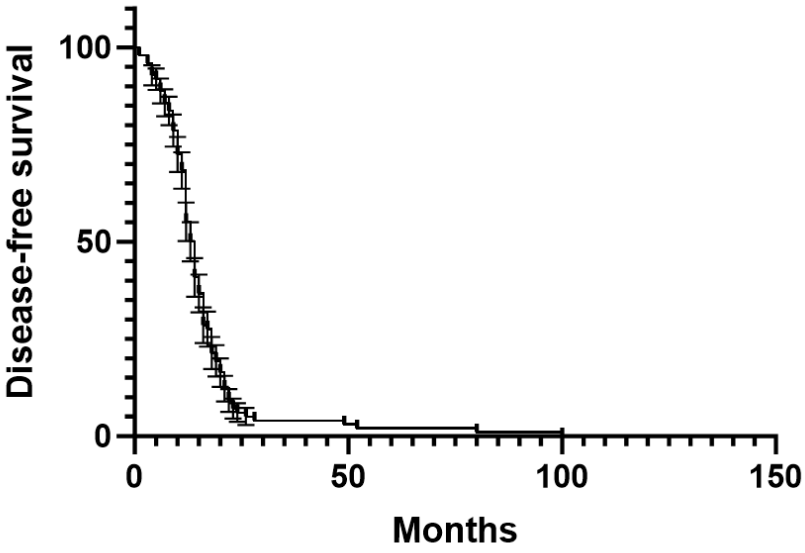

***Figure 3**. Kaplan-Meier disease-free survival curve.*

4.3 Survival analysis by site of metastases

Characteristics regarding survival of patients with abdominal and thoracic metastases, excluding metastatic lymph nodes, are detailed in tables XI and XII.

Analysing our cohort of patients according to the presence of site-specific metastases, allowed us to extrapolate their different impact on survival.

OS (months)	Non-metastatic	Metastatic	*p*
Other organs			
Small bowel	28.9	28.7	0.986
Large bowel	33.6	22.2	0.006
Liver	29.9	22.3	0.173
Spleen	31.3	20.7	0.031
Stomach	29.5	22.4	0.454
Omentum	42.6	27.9	0.084
Diaphragm	22.6	31.8	0.039
Pleurae	30.7	21.1	0.081

Table XI. *Overall survival of patients according to the presence of abdominal and thoracic metastases (metastatic lymph nodes excluded).*

DFS (months)	Non-metastatic	Metastatic	*p*
Other organs			
Small bowel	15.9	13.6	0.663
Large bowel	16.5	14.8	0.531
Liver	15.6	15.7	0.979
Spleen	15.7	15.7	0.996
Stomach	14.7	15.2	0.906
Omentum	31.8	14.6	0.002
Diaphragm	17.7	15	0.359
Pleurae	16.4	13.2	0.341

Table XII. *Disease-free survival of patients according to the presence of abdominal and thoracic metastases (metastatic lymph nodes excluded).*

Characteristics regarding survival of patients with metastases to lymph nodes are detailed in tables XIII and XIV.

Analogously to abdominal and thoracic metastases, we analysed our cohort of patients according to the presence of site-specific lymph node metastases, extrapolating their different impact on survival.

In addition, we sorted lymph nodes according to their anatomical district in 4 different subpopulations: Area 1 made of pelvic, lomboaortic and inguinal lymph nodes, Area 2 of pericolic and mesenteric lymph nodes, Area 3 of suprarenal, gastric and porta hepatis lymph nodes and Area 4 of mediastinal, cardiophrenic, pulmonary, axillary, supraclavicular, infraclavicular and cervical lymph nodes. Then, we selected patients with one or more metastases in one area only and we compared in pairs their survival by area in order to see if there was a statistically significant difference (table XV).

Areas	1st OS	2nd OS	p
1 vs 2	37.5	4.0	0.103
1 vs 3	37.5	43.0	0.785
1 vs 4	37.5	32.0	0.627
2 vs 3	4.00	43.0	0.139
2 vs 4	4.00	32.0	0.321
3 vs 4	43.0	32.0	0.550

Table XIII. *Comparison of overall survival of patients with metastatic lymph nodes in different anatomical areas. Area 1: pelvic, lomboaortic and inguinal lymph nodes, Area 2: pericolic and mesenteric lymph nodes, Area 3: suprarenal, gastric and porta hepatis lymph nodes, Area 4: mediastinal, cardiophrenic, pulmonary, axillary, supraclavicular, infraclavicular and cervical lymph nodes.*

OS (months)	Non-metastatic	Metastatic	*p*
Lymph nodes			
Inguinal	29.1	27.4	0.88
Pelvic	25.7	34.8	0.032
Lomboaortic	26.1	35.3	0.036
Pericolic	29.4	5	0.164
Mesenteric	29.7	5.25	0.049
Suprarenal	28.8	30.7	0.744
Gastric	29.7	6.75	0.065
Porta hepatis	29	31	0.91
Mediastinal	26.8	44.4	0.004
Pulmonary	29.3	14	0.385
Cardiophrenic	29.1	28.1	0.914
Axillary	29.4	16.5	0.302
Supraclavicular	29.3	23.4	0.537
Infraclavicular	29	28	0.966
Cervical	29.3	10.5	0.284
Area			
1	26.1	33.3	0.086
2	30.1	5.17	0.014
3	29.7	14.8	0.148
4	27.3	34.5	0.131

Table XIV. *Overall survival of patients according to the presence of site-specific lymph nodes. Area 1: pelvic, lomboaortic and inguinal lymph nodes, Area 2: pericolic and mesenteric lymph nodes, Area 3: suprarenal, gastric and porta hepatis lymph nodes, Area 4: mediastinal, cardiophrenic, pulmonary, axillary, supraclavicular, infraclavicular and cervical lymph nodes.*

DFS (months)	Non-metastatic	Metastatic	*p*
Lymph nodes			
Inguinal	15.9	11.7	0.593
Pelvic	15	17.2	0.455
Lomboaortic	15.9	15.4	0.873
Pericolic	15.9	1	0.267
Mesenteric	15.8	7	0.511
Suprarenal	15.8	14.7	0.802
Gastric	15.8	7	0.511
Porta hepatis	15.8	11.5	0.651
Mediastinal	15	21.8	0.107
Pulmonary	15.7	/	/
Cardiophrenic	15.5	22	0.338
Axillary	15.8	7	0.511
Supraclavicular	15.8	12.5	0.730
Infraclavicular	15.8	7	0.511
Cervical	15.7	16	0.984
Area			
1	15.2	16.6	0.620
2	16	4	0.208
3	15.9	10	0.450
4	14.5	22	0.038

Table XV. *Disease-free survival of patients according to the presence of site-specific lymph nodes. Area 1: pelvic, lomboaortic and inguinal lymph nodes, Area 2: pericolic and mesenteric lymph nodes, Area 3: suprarenal, gastric and porta hepatis lymph nodes, Area 4: mediastinal, cardiophrenic, pulmonary, axillary, supraclavicular, infraclavicular and cervical lymph nodes.*

4.4 Survival analysis by supramesenteric bulky lymph node removal

By putting together patients with metastatic mediastinal, cardiophrenic and upper abdominal (including suprarenal, gastric and porta hepatis) lymph nodes, a new subpopulation of 55 patients presenting metastatic supramesenteric lymph nodes was defined.

Within this subpopulation, 3 (37.5%) out of 8 patients with bulky cardiophrenic lymph nodes, 6 (21.43%) out of 28 patients with upper abdominal lymph nodes and 0 (0%) out of 19 patients with mediastinal lymph nodes underwent supramesenteric bulky lymph node removal. In total, in our subpopulation, 9 (16.36%) out of 55 patients underwent the aforementioned procedure.

Characteristics regarding survival of patients with mestastatic supramesenteric lymph nodes according to bulky lymph node surgical resection are detailed in tables XVI and XVII.

Even though differences in survival rates were not statistically significant, patients who had their metastatic supramesenteric lymph nodes surgically removed had a poorer OS and DFS than those whose lymph nodes were not resected: OS were 29.8 versus 13.3 months (p=0.064) (figure 4), while DFS were 15.9 versus 10.0 months (p=0.386) (figure 5).

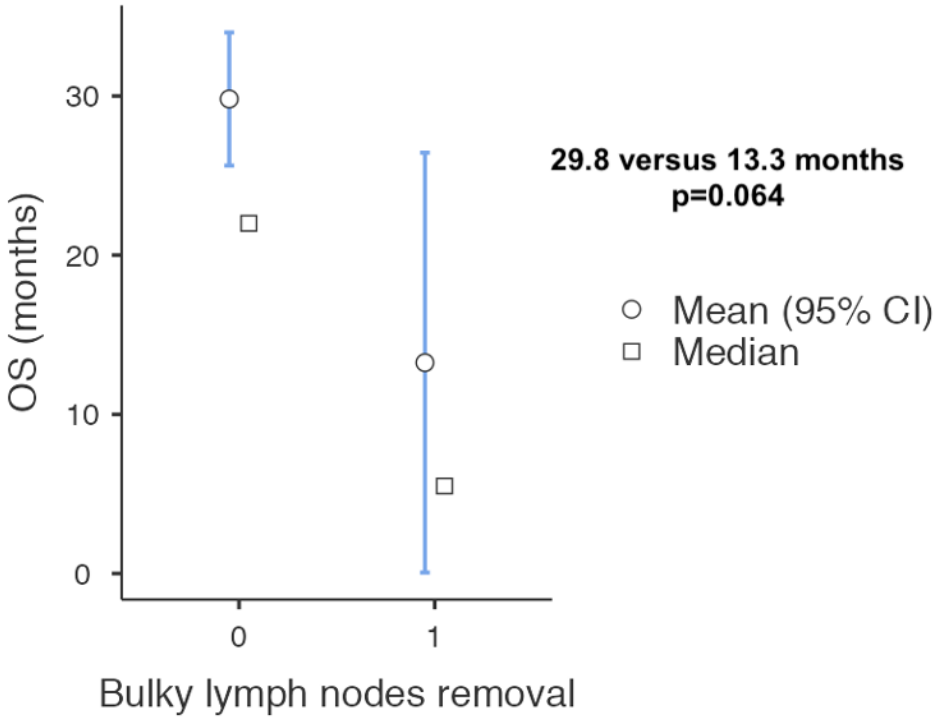

Figure 4. *Overall survival of patients with metastatic supramesenteric lymph nodes according to bulky lymph node removal.*

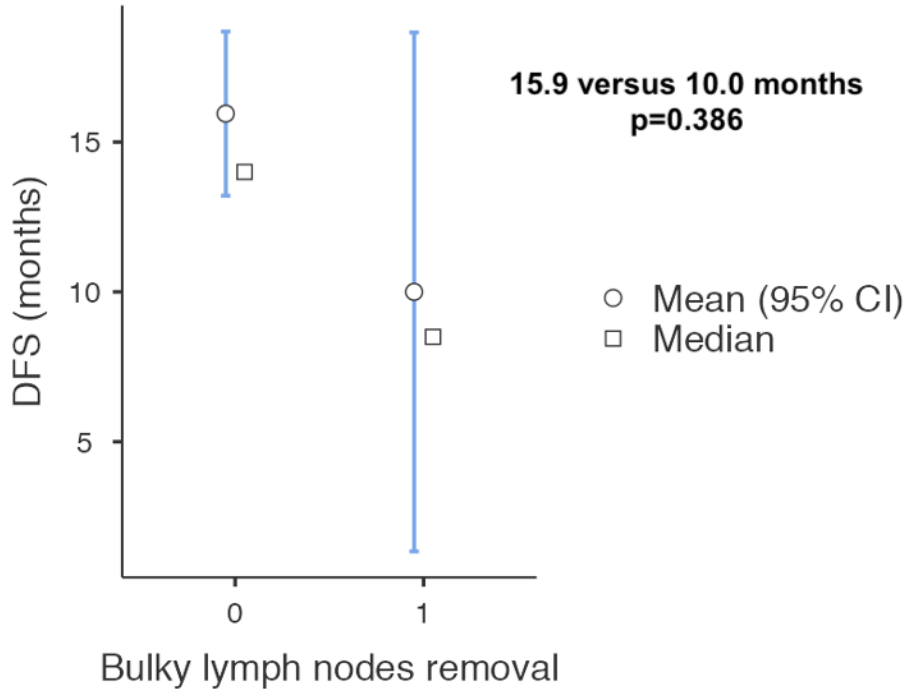

Figure 5. *Disease-free survival of patients with metastatic supramesenteric lymph nodes according to bulky lymph node removal.*

OS (months)	No surgical resection	Surgical resection	*p*
Lymph nodes			
Cardiophrenic	29.5	6.33	0.106
Upper abdominal	29.7	14.8	0.148

Table XVI. *Overall survival of patients with metastatic supramesenteric lymph nodes according to bulky lymph node surgical removal. Upper abdominal lymph nodes: suprarenal, gastric and hepatic lymph nodes. Supradiaphragmatic lymph nodes: mediastinal and cardiophrenic lymph nodes.*

DFS (months)	No surgical resection	Surgical resection	*p*
Lymph nodes			
Cardiophrenic	15.8	10.0	0.666
Upper abdominal	15.9	10.0	0.450

Table XVII. *Disease-free survival of patients with metastatic supramesenteric lymph nodes according to bulky lymph node surgical removal. Upper abdominal lymph nodes: suprarenal, gastric and hepatic lymph nodes. Supradiaphragmatic lymph nodes: mediastinal and cardiophrenic lymph nodes.*

5 DISCUSSION

5.1 Impact on survival of site-specific metastases

Our primary objective was to investigate the impact on survival of different anatomical localisations of metastases in stage IVB patients who underwent a visceral peritoneal debulking. To our knowledge, we present one of the largest cohorts in literature comparing survival rates of stage IVB patients according to multiple site-specific abdominal and thoracic metastases.

Advanced-stage patients are usually multimetastatic in the thoracoabdominal area and the number of patients with only one anatomical site of metastasis is very rare. In our cohort, the number of patients presenting metastases affecting one anatomical district only at diagnosis (and therefore patients whose survival rates could have been compared) was too limited (18 out of 143, 12.59%) to obtain statistically significant results for independent metastases' location.

However, the subgroup analysis by areas showed that patients with metastatic lymph nodes affecting the pelvic area (Area 1: pelvic, lomboaortic and inguinal lymph nodes) had better prognosis compared to those affecting Area 4 (mediastinal, cardiophrenic, pulmonary, axillary, supraclavicular, infraclavicular and cervical lymph nodes) with a higher OS of 37.5 and 32.0 months (p=0.627), respectively. These findings are consistent with the fact that pelvic, lomboaortic and inguinal metastatic lymph nodes (belonging to Area 1) are resected in most of the cases during cytoreductive surgery. Indeed, most of our patients were included before the Lion study's results and systematic pelvic and paraaortic lymphadenectomy were the guidelines in advanced OC, contributing to minimize residual disease. Conversely, lymph nodes located in Area 4 undergo debulking in selected cases only and could participate to disease progression.

5.2 Implications on survival of supramesenteric bulky lymph node removal

The secondary objective of our study was to compare prognostic implications of two different surgical approaches: inframesenteric and supramesenteric bulky lymph node removal. The supramesenteric approach consists in the surgical resection of metastatic lymph node situated in the upper abdomen and supradiaphragmatic area, such as hepatoceliac, splenic and cardiophrenic, whereas in the inframesenteric approach metastatic lymph nodes situated above the left renal vein are not removed.

Multiple studies have consistently demonstrated that optimal debulking (R0) improves survival outcomes (32). In this perspective, performing a surgical resection of upper abdominal and supradiaphragmatic bulky lymph nodes may contribute to minimize the volume of residual disease and, therefore, to potentially improve survival rates. However, upper abdominal and supradiaphragmatic lymph node cytoreductive surgery in stage IVB EOC patients has not been widely studied, literature on this matter is very limited and, as a result, it remains a very controversial area. Although the adoption of this procedure is increasingly propagated in specialized cancer centers, data on its safety are still limited and its survival benefit has not been established yet. In this setting, our study tried to delineate the impact on survival of upper abdominal and supradiaphragmatic bulky lymph node removal.

Even though differences in survival rates were not statistically significant between the two groups, our results showed that patients who had supramesenteric bulky lymph nodes surgically removed had poorer survival rates than those who did not undergo surgery. Overall survival was 29.8 versus 13.3 months (p=0.064), while DFS was 15.9 versus 10.0 months (p=0.386), respectively. In other words, in our limited cohort of patients with metastatic supramesenteric lymph nodes, performing cytoreduction of such lymph nodes seemed to have a negative prognostic impact on survival. This finding may suggest the benefit of performing cytoreductive surgery without removal of upper abdominal and cardiophrenic bulky lymph nodes. However, our cohort of patients with metastatic supramesenteric lymph nodes is limited (N=55), with only 9 (16.36%) patients who underwent debulking surgery.

Park et al. drew different conclusions in a very recent retrospective study of 120 patients with stage IVB OC undergoing PDS or IDS, including supradiaphragmatic debulking of metastatic cardiophrenic, parasternal, anterior mediastinal or supraclavicular lymph nodes (89). They found that, specifically in the subpopulation of patients with HGSCs that underwent PDS, the size of residual tumor in the supradiaphragmatic area ≥5 mm was a factor associated with decreased PFS and OS. In fact, mean PFS of patients with residual disease <5 mm was higher compared to that of patients with residual disease ≥5 mm with marginal statistical significance: 43.8 months versus 26.3 months (p=0.05), respectively. This finding suggests that supradiaphragmatic lymphadenectomy may be important during PDS to complete resection in stage IVB disease with thoracic lymph node metastases. The therapeutic effect of supradiaphragmatic lymphadenectomy, however, was not apparent in patients who underwent IDS. Authors hypothesis is that NACT has the potential to decrease the size of enlarged lymph nodes but does not eliminate hidden lymph node metastases, which cannot be resected due to size less than 5 mm on pre-operative CT.

However, it must be considered that Park et al. excluded from their study patients with middle and posterior mediastinal metastatic lymph nodes because their surgical resection was not facilitated by video-assisted thoracic surgery (VATS). Moreover, differently from our study, for the analysis they included the cardiophrenic area within the abdominal region, introducing a potential bias.

Nonetheless, Lee et al. retrospectively studied the prognostic significance of cardiophrenic lymph node resection in a cohort of 50 patients with confirmed metastases (84). They found that those who had undergone thoracic debulking did not have improved PFS or OS compared with patients who had not undergone debulking. Although this study showed that there was no survival benefit in performing a supradiaphragmatic cytoreduction, a recent review pointed out that adequate evaluation of the survival impact of CPLN resection was precluded due to several factors. Among these factors, there were the low complete gross resection rate of 27.8%, the more frequent intraperitoneal recurrence rate and the lower median OS of the entire cohort and subsets (85).

The benefit of cardiophrenic bulky lymph node resection was also retrospectively studied by Cowan et al. (83) in a cohort of 54 patients. They found that this

procedure (via video-assisted thoracic surgery or via a transdiaphragmatic or subxiphoid approach) rendered all cases amenable to optimal debulking (to <1 cm), with over 50% obtaining complete gross resection, without delaying adjuvant treatment and with a low and acceptable morbidity rate, suggesting the feasibility of the supradiaphragmatic approach. Median PFS of patients with surgically removed cardiophrenic metastatic lymph nodes were consistent in the study by Cowan et al. and in ours, 17.2 and 10.0 months, respectively; whereas the mean OS found in our study was significantly poorer than that of Cowan et al., 6.33 and 70.1 months, respectively. This discordance is likely due to our limited cohort of patients, as described above, and to different durations of the follow up in the two studies. In particular, in Cowan et al. study, follow up lasted a minimum of 3 years, while in ours, in some cases it had a much shorter duration, since some patients underwent debulking surgery very recently.

The abovementioned studies focus on supradiaphragmatic bulky lymph node removal only, however the supramesenteric approach consists of upper abdominal metastatic lymph node debulking too; therefore, we compared our results to those of studies regarding upper abdominal cytoreduction as well.

The role of upper abdominal cytoreduction was retrospectively studied by Tozzi et al. in a cohort of 216 stage IIIC-IV OC patients with metastatic hepato-celiac lymph nodes (86). Besides highlighting the role of the combination of CT scan and exploratory laparoscopy in detecting such metastases (CT scan alone failed to identify disease in 25.8% of patients), it was showed that surgical resection of porta hepatis and hepato-celiac bulky lymph nodes was required in 15% of patients with stage IIIC-IV in order to aim to complete resection. No complication was specifically related to the procedure, which resulted feasible and safe. Mean OS was 42 months and mean DFS was 19 months. These results significantly deviate from ours, however, as described above, these discrepancies may be due to our limited cohort and to a discordance between the two studies in the duration of follow up.

On the other hand, our results are consistent with those found by Gallotta et al. in their retrospective study, where DFS of patients with metastatic hepato-celiac lymph nodes surgically removed was 16 months, while ours was 10.0 months (87). Despite the limit of the relatively low number of patients undergoing para-aortic

and mesenteric lymphadenectomy, patients with metastatic para-aortic and mesenteric lymph nodes showed metastatic involvement of hepato-celiac lymph nodes in 62.8 and 70% of the cases, respectively. These findings may encourage systematic intraoperative exploration and eventual cytoreduction of the upper abdominal area, even in the absence of any suspicious lesion at preoperative imaging, if metastatic para-aortic and mesenteric lymph nodes are documented.

In terms of safety of the procedure, between the two subpopulations of patients who underwent supramesenteric bulky lymph node removal and those who did not, the first one experienced a higher rate of complications, 66.67% versus 40.06%, respectively. In particular, among patients who underwent such surgery, 16.67% deceased, compared to 1.55% of the other subpopulation. These findings are in line with the results obtained analyzing survival rates, which were notably higher in patients in whom supramesenteric metastatic lymph node debulking was not performed.

However, it must be considered that all the complications that occurred in the subpopulation that underwent the procedure were postoperative, with 50% being categorized as medical complications rather than surgical. Therefore, it cannot be definitely proven that all of these complications are directly associated with supramesenteric bulky lymph node removal itself.

Our study has some limitations. First, a retrospective study design is associated with an inherent bias for evaluating the effect of supramesenteric lymphadenectomy. That applies for multicentric design as well, in fact this type of study may be associated to centre-specific bias and errors. Second, the limited number of stage IVB patients with only supramesenteric metastatic lymph nodes act as a bias to evaluate the surgical effect. Lastly, an important limitation consisted in missing data of several patients, affecting especially disease-free survival rates.

In conclusion, our work underlines the disparities of metastases' characteristics and management in stage IVB OC patients. It also highlights some significant questions regarding surgical management of these patients that need to be answered and for whom further large-scale prospective studies are needed.

6 CONCLUSIONS

Surgical management of stage IVB ovarian cancer patients has evolved over the years, transitioning from primarily offering palliative treatments to striving for complete surgical resection in order to significantly improve survival rates. In this perspective, upper abdominal and supradiaphragmatic lymph node cytoreductive surgery may contribute to minimize the volume of residual disease with a benefit in survival rates. However, in stage IVB patients, it has not been widely studied and available data on its safety are still limited; as a result, it remains a very controversial area.

In this setting, our international multicentric retrospective study aimed to delineate the impact on survival of supramesenteric metastatic lymph node debulking. Although our results did not reveal statistically significant differences between the two groups, they showed that patients who had supramesenteric bulky lymph nodes surgically removed had poorer survival rates than those who did not undergo such surgery. These findings are in line with those relative to complication rates, which are higher in the subpopulation that underwent the aforementioned procedure. However, being postoperative complications, and mostly medical rather than surgical, it cannot be definitely proven that they are associated with supramesenteric metastatic lymph node debulking itself.

In conclusion, our results do not lean towards supramesenteric bulky lymph node removal, nevertheless we believe that further large-scale studies are essential to assess the effective benefit and safety profile of this procedure.

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LIST OF ABBREVIATIONS

OC	Ovarian Cancer
EOC	Epithelial Ovarian Cancer
HGSC	High-Grade Serous Carcinomas
LGSC	Low-Grade Serious Carcinomas
HRD	Homologous Recombination Deficiency
gBRCAm	Germline BRCA Mutation
sBRCAm	Somatic BRCA Mutation
STIC	Serous Tubal Intraepithelial Carcinoma
MMR	Mismatch Repair
US	Ultrasound
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PFS	Progression-Free Survival
PDS	Primary Debulking Surgery
NACT	Neoadjuvant Chemotherapy
IDS	Interval Debulking Surgery
AUC	Area Under the Concentration-time Curve
PLD	Pegylated Liposomal Doxorubicin
IP	Intraperitoneal Chemotherapy
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
VEGF	Vascular Endothelial Growth Factor
PARPi	Poly ADP-Ribose Polymerase Inhibitors
HRT	Hormonal Replacement Therapy
MBO	Malignant Bowel Obstruction

CPLN	Cardiophrenic Lymph Nodes
VATS	Video-Assisted Thoracic Surgery
PH	Porta Hepatis
HCLN	Hepatoceliac Lymph Nodes
DFS	Disease-Free Survival

LIST OF FIGURES AND TABLES