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TESI DI LAUREA

ULTRA-LAP TRIAL: LAPAROSCOPIC MULTI-VISCERAL SURGERY IN PATIENTS WITH STAGE IIIC-IV OVARIAN CANCER.

SAFETY AND FEASIBILITY TRIAL.

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INDEX

INDEX OF ACRONYMS

OC ..... *Ovarian Cancer*

AEOC ..... *Advanced Epithelial Ovarian Cancer*

VPD ..... *Laparotomic (traditional)Viscero Peritoneal Debulking*

L-VPD ..... *Laparoscopic Viscero-Peritoneal Debulking*

- uL-VPD ..... *up-front L-VPD*

- iL-VPD ..... *interval L-VPD*

EXL ..... *Exploratory Laparoscopy*

CR ..... *Complete Resection*

CRT ..... *Complete Response to Treatment*

GCIG ..... *Gynaecologic Cancer InterGroup*

MDT ..... *Multi Disciplinar Team*

OS ..... *Overall Survival*

PFS ..... *Progression Free Survival*

MI-IDS ..... *Minimally Invasive - Interval debulking surgery*

HGSC ..... *High Grade Serous Carcinoma*

HR ..... *Homologous Recombination*

GWBS ..... *General Well-Being Schedule*

RECIST ..... Response Evaluation Criteria In Solid Tumors

Alla mia famiglia.

RIASSUNTO

BACKGROUND

Il tumore dell'ovaio è una patologia aggressiva. Globalmente sono stimate 200 000 nuove diagnosi all'anno, e più del 75% di queste sono in stadio FIGO III-IV (OC) [6-26]. Per queste pazienti, il trattamento standard è una combinazione di chirurgia e chemioterapia. [43-7]. Negli ultimi tempi si è ottenuto un progresso significativo in termini di sopravvivenza dovuto all' introduzione di nuovi farmaci [8]. Per quanto concerne la parte chirurgica, una resezione complete (CR) di tutta la malattia visibile è unanimemente associata al migliore tasso di sopravvivenza [9-12]. Negli ultimi 20 anni, la ricerca chirurgica in ginecologia oncologica ha espanso enormemente il portfolio di procedure possibili per raggiungere il livello più alto di CR. Oggigiorno è molto comune performare chirurgia dell'alto addome [11-13], resezioni intestinali singole/multiple [40-37], chirurgia diaframmatica e cardio toracica. [1-27]. Il contributo della chirurgia nel OC è testimoniato dall' indisputato significato prognostico della CR, indipendentemente dall' iniziale modalità di trattamento. È quindi giustificato che gli oncologi ginecologici si impegnino a aumentare il numero di CR al livello più alto possibile. Con esso viene l'impegno a ridurre la morbidità chirurgica.

In questo scenario, il tentativo finale è stato, negli ultimi anni, l'uso della laparoscopia per completare l'intera operazione di debulking. [25-23]. Ad oggi sono stati pubblicati due studi sul trattamento laparoscopico di OC: gli studi MISSION e CILOVE [28-17]. Entrambi gli studi erano svolti su pazienti trattate con chemioterapia neoadiuvante. Lo studio MISSION trial includeva pazienti con una risposta complete alla chemioterapia, mentre lo CILOVE aveva dei criteri di inclusione per la chirurgia molto ristretti. Nel 2016, all' Ospedale Universitario di Oxford veniva registrato una valutazione di servizio sulla fattibilità del Visceral-Peritoneal Debulking (VPD) per via laparoscopica sull' OC con malattia residua post chemio nulla o grande. Più tardi, incoraggiati dai primi dati si registrava la fase I-II del trial clinico aperto a tutti i pazienti con OC: l'ULTRA-LAP trial. Qui viene riportata la parte della fattibilità e i risultati iniziali dell'ULTRA-LAP.

SCOPO DELLO STUDIO

Studio clinico non randomizzato (ULTRA-LAP) registrato per testare la sicurezza, effetti indesiderati e efficacia della chirurgia multi-viscerale laparoscopica (L-VPD) in pazienti con tumore dell'ovaio in stadio IIIC-IV. Qui presentiamo i risultati dello studio pilota condotto per la identificazione delle pazienti con AEOC più idonee al trattamento L-VPD.

MATERIALI E METODI

Fra marzo 2016 e ottobre 2021 tutte le pazienti con diagnosi clinica e radiologica di OC venivano discusse al meeting multidisciplinare ed erano sottoposte a laparoscopia esplorativa (EXL). Dopo revisione dell'imaging (tomografia assiale computerizzata) e del reperto della EXL, tutte le pazienti candidabili a resezione completa (CR) erano sottoposte a VPD. Alle pazienti reclutate in questo studio veniva offerto un tentativo di esecuzione della L-VPD. Il principale obiettivo dello studio era di testare la fattibilità e al sicurezza di questo approccio. Per comprendere quali pazienti fossero candidabili a questo studio si conduceva uno studio pilota con analisi delle operazioni concluse in laparoscopia e quelle convertita a laparotomia.

RISULTATI

Durante lo studio duecento otto pazienti con AEOC erano sottoposte a EXL. Cento ventuno erano poi sottoposte a VPD di intervallo dopo chemioterapia neoadiuvante e ottantasette a VPD up-front. Sul totale, centocinquantotto pazienti hanno ricevuto VPD tramite laparotomia (75.9%) e cinquanta (24.1%) tramite laparoscopia. Di quest' ultime trentaquattro pazienti secondo il protocollo d'intervallo (iL-VPD) e sedici seguendo il trattamento standard up-front (uL-VPD). I motivi più comuni di conversione sono stati: malattia con coinvolgimento diaframmatico con estensione dorsale, malattia spleno-pancreatica disomogenea, coinvolgimento di multipli segmenti intestinali, e malattia omentale invadente il colon trasverso. La morbidità intra e post- operatoria è stata molto bassa nel gruppo L-VPD. Il tasso di risposta completa al trattamento (CRt) è stato del 100% nel gruppo L-VPD e del 94% nel VPD. A una media di 20 mesi di follow il PFS era del 78% e OS del 92% per tutta la popolazione.

CONCLUSIONI

Nella parte della fattibilità dell'ULTRA-LAP abbiamo identificato le pazienti con AEOC più idonee per L-VPD. I risultati dello studio pilota supportano la fattibilità e la sicurezza dell' L-VPD in due gruppi di pazienti con OC: quelle con risposta completa di malattia dopo chemioterapia neo-adiuvante e quelle con malattia diffusa visibile (indipendentemente se a chirurgia up-front o d'intervallo) limitata a: pelvi (non escludendo il coinvolgimento del retto sigma), omento gastro colico, peritoneo parietale e diaframma, escludendo le pazienti con malattia che richiedesse la mobilizzazione della parte dorsale del fegato. Per entrambi i gruppi si è registrata una fattibilità del 100% e sono quindi stati conseguentemente reclutati all' ULTRA-LAP.

ABSTRACT

BACKGROUND

Ovarian cancer is an aggressive disease. It is estimated that 200 000 women are diagnosed globally every year and over 75% of them are FIGO stage III-IV ovarian cancer patients (OC) [6-26]. For these patients, the standard of treatment is the combination of surgery and chemotherapy [43-7]. Lately significant progress in survival has been achieved owing to the introduction of new drugs [8]. From the surgical perspective, a complete resection (CR) of all visible disease is unanimously associated with the best survival rate [9-12]. In the last 20 years, the surgical research in Gynecologic Oncology has vastly expanded the portfolio of procedures to achieve the highest rate of CR. It is now very common to perform upper abdominal surgery [11-13], single/multiple bowel resections [40-37], diaphragmatic and cardio-thoracic surgery [1-27]. The contribution of surgery to OC is witnessed by the undisputed prognostic significance of the CR, irrespective of the initial modality treatment. It is therefore justified that Gynecologic Oncologists strive to increase CR rate to the highest possible. Alongside comes the effort to reduce the

surgical morbidity. In this scenario, the ultimate attempt has been, in recent years, the use of laparoscopy to complete the entire surgical debulking [25-23]. Two studies have been published so far on the laparoscopic treatment of OC: the MISSION and CILOVE trials [28-17]. Both trials focused on patients who underwent neoadjuvant chemotherapy. The MISSION trial included patients with a complete response to chemotherapy and the CILOVE trial had very restrictive inclusion criteria for surgery. In 2016, we registered at the Oxford University Hospital, a service evaluation on the feasibility of Visceral-Peritoneal Debulking (VPD) by laparoscopy on OC with no or gross residual disease after chemo. Later on, encouraged by the early data, we registered a phase I-II clinical trial open to all patients with OC: the ULTRA-LAP trial. Here we report the feasibility part of the trial and the initial results of the ULTRA-LAP.

AIM OF THE STUDY

A non-randomized phase I-II clinical trial (ULTRA-LAP) was registered to test safety, side effects and efficacy of laparoscopic Visceral-Peritoneal Debulking (L-VPD) in patients with stage III-IV ovarian cancer (OC). A miniature, feasibility part of the trial aimed at identifying which OC patients are suitable to undergo L-VPD.

MATERIALS AND METHODS

Between March 2016 and October 2021, all consecutive patients with OC fit for surgery, underwent exploratory laparoscopy (EXL). All patients whose disease was deemed amenable for a complete resection (CR) at imaging review and EXL, underwent VPD. In all patients a consistent attempt was made at completing L-VPD. Primary endpoint of the initial feasibility part of the trial was to identify which OC patients could safely and effectively undergo L-VPD.

RESULTS

Two hundred and eight OC patients had EXL in the study period. One hundred and twenty-one underwent interval VPD and eighty seven up-front VPD. Overall, one hundred and fifty eight patients had VPD by laparotomy (75.9%) and fifty (24.1%) had L-VPD, of which thirty four patients as interval (iL-VPD) and 16 as up-front (uL-VPD). Most common reasons for conversion were: diaphragmatic disease extending dorsally, matted spleno-pancreatic disease, multiple bowel segments involvement and omental disease invading the transverse colon. Intra- and post-operative morbidity was very low in the L-VPD group. CR (complete response) rate was 100% in L-VPD group and 94% in VPD. At twenty months median follow-up, disease-free and overall survival were 78% and 92% for the whole population.

CONCLUSIONS

In the feasibility part of ULTRA-LAP, we identified the most suitable OC patients for L-VPD. The results of the pilot study support the feasibility of L-VPD in two groups of OC: those with no gross disease at interval surgery and those with gross visible disease at upfront or interval surgery, but limited to: pelvis (including recto-sigmoid), gastro colic omentum, peritoneum and diaphragm, the latter not requiring dorsal liver mobilization. Both groups had 100% feasibility and has been thus forth recruited to ULTRA-LAP.

1 INTRODUCTION

1.1 OVARIAN CANCER

Ovarian cancer is a heterogeneous, rapidly progressive, highly lethal disease of low prevalence.[32] Its lethality is also due to its delayed time to diagnosis. The tumor originates from altered ovarian cells, but some ovarian cancers originate from sites outside of the ovary; for example, many ovarian HGSCs probably originate in the fallopian tube and some subsets of ovarian cancer have been shown to arise from the peritoneum. In addition, clear-cell and endometrioid carcinomas can originate from endometrial tissue located outside the uterus (endometriosis). On the basis of the new WHO classification, most of these types of ovarian cancer will now be redefined as “ovarian or tubal cancers”. [24]

1.2 EPIDEMIOLOGY AND RISK FACTORS

In 2020, there are approximately 21,750 new ovarian cancer cases, representing 1.2% of all cancer cases. The estimated number of deaths related to it are 13,940. The 5-year relative survival rate is expected to be 48.6%. Around 15.7% of the ovarian cancer cases are diagnosed at the local stage, and about 58% at the metastasized stage, where the 5-year survival drops down to 30.2% instead of 92.6% if detected at an early stage of local spread. Ninety percent of ovarian cancers are epithelial, with the serous subtype being the most common. Age-adjusted rates of new ovarian cancer cases are on a reducing trend based on statistical models of analysis. [24]

The main risk factors associated with ovarian cancer are: [4]

1- Age: Ovarian cancer is more common in postmenopausal women, and increasing age is associated with a higher incidence of the disease.

2- Parity and use of contraceptives: women having given birth, oral contraceptive use, and lactation have a protective role towards all OC subtypes. Contrarily others such as older age at menopause and hormone replacement therapy confer increased risks. Besides some case-control studies have proven that a higher age at childbirth could decrease the risk of ovarian cancer.

3- Family history: Having a positive family history of breast or ovarian cancer (brca1/2) increases the risk of developing ovarian cancer. In particular, if close relatives such as a mother, sister, or daughter have had breast or ovarian cancer, the risk is higher. Additionally, a personal history of breast cancer also increases the risk. Besides *BRCA1* and *BRCA2*, other germline mutations in genes involved in DNA repair can increase the risk of developing ovarian cancer, including genes that are part of the Fanconi anemia–BRCA pathway, such as RAD51C, *RAD51D,* BRIP1, BARD1 and *PALB2*. Inherited mutations in other genes involved in DNA repair, such as *CHEK2*, *MRE11A*, *RAD50*, *ATM* and *TP53*, might also increase the risk of developing ovarian cancer. [40]

4- Endometriosis.

5- Smoking: Smoking has been associated with an increased risk of ovarian cancer, particularly mucinous epithelial tumors.

6- Environmental and lifestyle factors such as asbestos and talc powder exposures.

7- Lynch Syndrome

1.3 CLASSIFICATION

1.3.1 Histological classification

For many years OC has been referred to as a single entity, but has recently been subdivided into at least 5 different histological subtypes each with different identifiable risk factors, cells of origin, molecular compositions, clinical features and treatments. This classification includes epithelial cancers, that represent approximately 90% of ovarian cancers, serous, endometrioid, clear-cell and mucinous carcinomas. [32] As coherent with our era of personalized cancer medicine, reconducting diagnosis to a histopathological criteria is a *sine qua non* for successful treatment. Each tumor histotype will respond differently to chemotherapy. The International Federation of Gynecology and Obstetrics (FIGO) Committee on Gynecologic Oncology unanimously agreed that histologic type should be designated at staging.
In Figure 1 we can see the histological characteristics of the 6 main types of OC.

As shown in Figure 1 we can subdivide the disease in: **a** | **High-grade serous carcinoma** (HGSC): nuclear atypia, increased nuclear-to-cytoplasmic ratio and high number of mitoses characterize the disease. The arrow is pointing a portion characterized by the papillary architecture, often present. **b** | **Serous tubal intraepithelial carcinoma** (STIC) Similar morphological features as HGSC can be noticed, with severe atypia, mitoses and lack of cellular polarity. STIC lesions are thought to be precursors for HGSC. **c** | **Low-grade serous carcinoma** (LGSC) Is surprisingly characterized by mild nuclear atypia and a lower nuclear-to-cytoplasmic ratio. It is though characterized by a predominant papillary architecture. **d** | **Clear-cell carcinoma** is characterized by large atypical tumor cells. Most of its cells show a clear cytoplasm due to its stromal hyalinization, as indicated by the arrow. **e** | **Endometrioid adenocarcinoma** is characterized by gland formation that recapitulates endometrial glands. Its grading is based on cellular architecture and nuclear atypia. **f** | **Mucinous adenocarcinoma** shows mucin-filled tumor cells. As pointed by the arrow we can notice frequent goblet cell forms. [24]

Information about precursor sites of ovarian cancer has enabled the research of new prevention strategies, such as risk-reducing and opportunistic salpingectomy. This increased understanding of the biology underlying ovarian cancer has also led to changes in clinical research; clinical trials are now increasingly focusing eligibility requirements on the basis of ovarian cancer histology. In Table 1 are shown the characteristics of ovarian cancer by histology, genomic characteristics and active therapies, showing how the determination of the precise histological typology of tumor can influence the possible therapeutical strategies.

1.3.2 Genomic Classification

In Table 2 are shown some of the most frequent mutations involved in the development of OC.

Functions of commonly mutated inherited genes associated with increased risk of ovarian cancer*

1.3.3 FIGO staging

The primary site of the disease should be the first thing to be defined. On some patients, it cannot be possible to identify the primary site clearly; these cases should be listed as "undesignated". The histologic type must always be recorded.

Our focus during this study will be on the advanced stages of the disease.

Most ovarian cancers are HGSCs that usually present in stage III, of which the vast majority (84%) in stage IIIC. These tumors characteristically diffuse through the peritoneal membranes involving both pelvic and abdominal peritoneum. A minority of OC (less than 1 on 10) reach stations beyond the pelvis with exclusively retroperitoneal lymph node involvement and according to the literature these cases have a better prognosis than that of tumors with abdominal peritoneal involvement. The new FIGO staging includes a modification of stage III patients and assignment to stage IIIA1 based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination. Stage IIIA1 is further subdivided into IIIA1

(dimension of greatest metastasis ≤10 mm) and IIIA1 (dimension of greatest metastasis >10 mm). [29]

Stage IV corresponds to distant metastasis and includes patients with parenchymal liver/splenic involvement and extra-abdominal metastasis; 12% to 21% of patients present with stage IV disease. Extension of tumor from omentum to spleen or liver (stage IIIC) should be differentiated from isolated parenchymal metastases (stage IVB). [29]

1.4 CLINICAL PRESENTATION, SCREENING, DIAGNOSIS

Clinical presentation

When localized in the ovary the disease causes very few specific symptoms. It is due to his pattern of presentation THAT ovarian cancer has historically been called the “silent killer.” It is infact estimated that only 15% of ovarian cancers are localized to the ovary, with 17% being placed regionally, and 62% occurring as distant disease. With tumor spread into the pelvis and upper abdomen, the main symptoms consist of pelvic or abdominal pain or pressure, abdominal swelling, dyspepsia, and early satiety. As the disease progresses, patients can note weight loss, and develop bowel or ureteral obstruction. In retrospect, many patients will note a longer (usually months) history of unclear abdominal discomfort that is generally very aspecific and is initially not believed to represent relevant underlying pathology.

Although screening of asymptomatic women for ovarian cancer is not effective currently, knowledge of ovarian cancer symptoms may help identify patients at an earlier stage. Symptoms suggestive of ovarian cancer include pelvic/abdominal pain, urinary urgency/frequency, bloating, and early satiety, especially if symptoms are new (present for less than 1year) and frequent (occurring more than 12 days per month). A positive symptom index (any of those 6 symptoms that occurred more than 12 times per month in less than 1 year) had a sensitivity of 56.7% for early

stage disease and 79.5% for advanced disease. Specificity was 90% for patients older than 50 years and 86.7% for patients younger than 50 years. The presence of these symptoms should prompt consideration of ovarian cancer in the differential diagnosis and testing for the disease should be included in the workup. [22]

Screening

Ovarian cancer is an aggressive disease. It is estimated that 200 000 women are diagnosed globally every year and over 75% of them are FIGO stage III-IV ovarian cancer patients (OC) [6-26]. An effective screening strategy would represent a huge factor to lower the stage at diagnosis. At the moment there aren't any screening programs proven to work for the early detection of OC.
It has become possible to identify individuals at high risk of developing OC, such as those with germline mutations in *BRCA1* or *BRCA2* (which encode proteins involved in the repair of DNA damage via HR) or other genes associated with a high risk of developing OC. For these individuals, strategies to reduce the risk of ovarian cancer have been implemented through risk-reducing surgery, such as bilateral salpingo-oophorectomy. For women with an average risk of developing OC screening strategies are primarily focused on the biomarker CA125 (also known as mucin 16) and the use of transvaginal ultrasonography. It must be pointed that the detection of CA125 is not an effective screening test when used alone, given that CA125 levels are only increased in 50% of stage I ovarian cancers and can also be increased in benign disorders, such as uterine fibroids, ovarian cysts and other conditions such as liver disease and infections. The combination of the CA125 blood test and radiographic imaging, such as transvaginal ultrasonography, has been evaluated for use as a screening strategy. Combinations of these screening modalities have shown success in detecting early-stage cancers, but have not yet demonstrated definitive improvements in patient mortality, it cannot therefore be considered as an efficient screening strategy.

A new biomarker, HE4, Human epididymis protein 4 (also known as WFDC2) has recently been tested as a potential help in ovarian cancer screening. A systematic review reported better sensitivity, specificity and likelihood ratios for HE4

compared with CA125, but this has not yet been analysed within a screening strategy. The use of other novel markers for ovarian cancer screening are under investigation, including, for example, DNA analysis of uterine lavages or Pap smears for *TP53* mutations. [24]

Diagnosis

Like for many other abdominal diseases, diagnostic evaluation commonly initiates with palpation of an adnexal mass during a pelvic examination. Noninvasive diagnostic tests such as ultrasound examination offer a useful help to better define the disorder. Although most diseases prove to be benign, between 13% and 21% of women undergoing exploratory surgery for a suspicious adnexal mass will have an ovarian malignancy. Recommendation for surgery depends on the degree of suspicion that this mass may be malignant; factors that should be considered include age, menopausal status, family history, size and complexity of the mass, associated symptoms, CA 125, unilaterality versus bilaterality, and characteristics on ultrasound. Management may include observation with repeat examination, further radiographic imaging, and laparoscopy or laparotomy depending on the clinical circumstances. [22]

The preoperative evaluation of a woman with suspected ovarian cancer includes measurement of CA 125, which turns out to be elevated in more than 80% of patients with advanced EOC. Sensitivity is lower for stage I disease (50%). It also varies according to histology: it is highest in serous and lowest in mucinous EOC. Moreover, CA 125 is not specific for EOC, and it can be elevated in nonmalignant conditions such as endometriosis and pelvic inflammatory disease, as well as in other malignancies including endometrial and pancreatic cancers.

To better identify the diagnosis, staging, and treatment of EOC surgical exploration remains necessary. Ovarian cancer can spread ematogenously or via the lymphatic system, but in the greatest of cases the bulk of the tumor will be found on peritoneal surfaces. The mechanism behind the spreading is determined by the shedding of OC cells into the peritoneal cavity, determining his peritoneal disease, followed by possible circulation of these cells throughout the abdomen and pelvis, and eventual implantation onto peritoneal surfaces. The viability of these cells and successful

tumor growth is further dependent upon the development of sufficient neovascular scaffoldings to support cell survival and tumor growth.

OC's peculiar pattern of spread within the relatively accessible peritoneal cavity has led to attempts at surgical cytoreduction before the administration of chemotherapy. More than 30 years ago, a statistically significant number of studies has demonstrated an inverse association between the volume of the residual tumoral mass remaining at the end of surgery and overall survival (OS). These evidences have led to the goal of "optimal" tumor cytoreduction consisting of no macroscopic visible disease with initial diagnostic surgery. Regarding these ambition two terms have been introduced: "optimal" referring to a diameter inferior to 1cm and "suboptimal" as to a diameter greater that 1cm of the largest residual tumor nodule remaining after debulking surgery. The goal of debulking surgery is to render the patient completely debulked and visibly with no trace of disease. Patients who have their initial diagnostic surgery performed by a gynecologic oncology surgeon are more likely to be optimally cytoreduced. Patients who have had only a biopsy, paracentesis, or incomplete debulking should be referred to an experienced gynecologic oncologist for consideration for reoperation given the impact of initial surgery on clinical outcome. It should be recognized that it is unique among patients with solid tumors to attempt maximal surgical cytoreduction in the presence of widespread disease outside of the organ of origin.

The initial surgery is an exploratory laparoscopy (EXL) to diagnose and stage disease and to provide therapeutic benefit with cytoreduction. Determining the precise histological subtyping and surgical staging are necessary to determine the exact following systemic treatment, as well as prognosis.

Ovarian malignancies are surgically staged according to International Federation of Gynecology and Obstetrics (FIGO) staging system, which is outlined in Table 3.

Staging laparotomy requires a thorough inspection of the peritoneal cavity, including the paracolic gutters, pelvis, and domes of the diaphragm; total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO); liver palpation and biopsy (if indicated); lymph node sampling; omentectomy; and peritoneal

washings. The degree of surgical debulking should be reported, and if incomplete, the surgeon should describe the size, location, and extent of residual disease.

1.5 TREATMENT

The standard of treatment is the combination of surgery and chemotherapy [43-30]. Lately significant progress in survival has been achieved owing to the introduction of new drugs [5]. From the surgical perspective, a complete resection (CR) of all visible disease is unanimously associated with the best survival rate [9-12]. In the last 20 years, the surgical research in Gynaecologic Oncology has vastly expanded the portfolio of procedures to achieve the highest rate of CRt. It is now very common to perform upper abdominal surgery [11-13], single/multiple bowel resections [40,37], diaphragmatic and cardio-thoracic surgery [9-27]. The contribution of surgery to OC is witnessed by the undisputed prognostic significance of the CR, irrespective of the initial modality treatment. It is therefore justified that Gynaecologic Oncologists strive to increase CR rate to the highest possible. Alongside comes the effort to reduce the surgical morbidity.

1.6 ADVANTAGES OF LAPAROSCOPY

From the day the first laparoscopy was performed for a cholecystectomy, many more operations have been included into this surgical strategy, making it a successful alternative to laparotomy. The range of operations now extends from simple procedures such as herniorrhaphy and ovarian cystectomy to complex operations including radical prostatectomy, nephrectomy, and adrenalectomy.
The practical aspects in which this consists are:

1) less direct contact between the surgeon and the patient—and consequently less risk to acquire an infection for both the patient and the surgeon.
2) The loss of tactile clues can be disadvantageous. Images from three-dimensional structures are transmitted via the laparoscope onto a two-dimensional screen, making it difficult to judge depth and reducing the perceptual cues for

identification of anatomical structures. An added difficulty is that the visual field is smaller than with open surgery, and the necessity to work with screen images demands special mental as well as physical skills.

3) In laparoscopic dissection the limited range of motion from six to four degrees of freedom can hamper the ability to manipulate instruments and structures. After the trocar is inserted, the trocar site serves as both a fulcrum and a steadying point. A small movement at the proximal end gives a large movement at the distal end. The normal axis is inverted: The surgeon is effectively operating in a mirror.
4) Procedures performed laparoscopically are generally slower.

What are its advantages?

For the patient laparoscopic surgery has the advantages of avoiding large open wounds or incisions and therefore decreasing blood loss, pain and discomfort. Patients experience fewer undesired effects from analgesia because less antalgic therapy is required. Given the thinness of the tools, they' re less likely to cause tissue trauma and blood loss. The rate of postoperative complications is generally lower, especially those related to the wound such as dehiscence, infection, cellulitis and incisional hernia. Performance of the operation within the body cavity avoids the cooling, drying, excessive handling and retraction of internal organs associated with conventional 'open' techniques—possibly reducing postoperative peritoneal adhesions with their hazard of later bowel obstruction.

These benefits help to decrease the recovery period, and reduce the risks of bone loss, muscle atrophy and urinary retention associated with lengthy bed rest and inactivity. Other benefits of early mobilization are lower rates of chest infection and deep vein thrombosis. Finally, patients prefer small scars to large ones, and laparoscopic surgery is likely to generate less postoperative anxiety related to self-image. [44]

In the specific case of AEOC patients there are some additional advantages shown in Figure 4.

1.7 BACKGROUND TO THE METHODS

The standard of care for patients with advanced OC is surgery by laparotomy. Lately 2 studies have been published on the laparoscopic treatment of advanced OC: the MISSION and CILOVE trials [28,17]. Both trials focused on patients who underwent neoadjuvant chemotherapy. The MISSION trial included patients with a complete response to chemotherapy and the CILOVE trial had very restrictive inclusion criteria for surgery.

2. METHODS

2.2 DESIGN OF THE STUDY

This study is based on the data registered in 2016 at the Oxford University Hospital, where a service evaluation on the feasibility of Visceral-Peritoneal Debulking (VPD) by laparoscopy on OC patients with no or gross residual disease after chemo was initiated. Later on, encouraged by the early data, a phase I-II clinical trial was opened to all patients with OC: the ULTRA-LAP trial. Here is reported the feasibility part of the trial and the initial results of the ULTRA-LAP.

ULTRA-LAP is a phase I-II clinical trial designed to investigate the safety, morbidity and efficacy of laparoscopic surgery in OC. To test the feasibility of laparoscopic VPD (L-VPD), a database was elaborated including data taken from 2016 to 2021 by a service evaluation project that obtained Oxford University Hospital Trust approval (number 3267). Data were collected prospectively. The aim is to identify the most suitable OC candidates to undergo L-VPD to later recruit in ULTRA-LAP. The study was initially offered to all consecutive OC who had any response or stable disease after neoadjuvant chemotherapy. Later on, the study was expanded to include patients who were candidates to up-front surgery. The study was approved as a prospective phase I-II clinical trial at the University of Padua Hospital (ID 5497/AO/22). All OC underwent imaging review at the gynecologic oncology Multidisciplinary Team Meeting (MDT). The general policy on the initial treatment of OC was to offer neoadjuvant chemotherapy in Oxford (due to a Trust enforced decision) followed by interval VPD (i-VPD) and to offer up-front VPD (u-VPD) to all suitable patients in Padua. Once patients were discussed at the MDT with review of the imaging, an exploratory laparoscopy (EXL) would follow to confirm eligibility for VPD. The single accepted goal for VPD was CR of all visible disease. Inclusion and exclusion criteria for VPD have been previously published [39] and are reported in table 4.

2.3 PATIENTS SELECTION CRITERIA

The AEOC patients included are stage IIIC (positive lymph nodes and/or abdominal implants larger than 2cm) and IV (disease spread to liver parenchyma, lung, pleura, or other extra-abdominal sites).

Patients with disease precluding CR were not offered VPD. Response to chemotherapy was measured by the GCIG and RECIST criteria (Response Evaluation Criteria In Solid Tumors criteria) [33]. Based on CT scan review, we classified response as: complete (no visible disease), good partial (>50% reduction), partial (<50% reduction), or stable disease. Details of the VPD protocol have been previously reported [39]. The feasibility part of the study is designed as a miniature anticipation of ULTRA-LAP. All consecutive OC in the study period underwent EXL and a consistent attempt was made to accomplish the whole surgery by laparoscopy. Timing and reason for conversion to laparotomy were accurately recorded for each patient. Conversion rate, short- and long-term morbidity was also documented. Likewise, we recorded stage, histology, response to neoadjuvant chemotherapy (in patients who underwent interval VPD), disease load at time of surgery (defined with the peritoneal index and the Fagotti score), procedures performed and residual disease if any. For patients in the L-VPD group, data analysis was broken down in Up-front L-VPD (uL-VPD) and Interval L-VPD (iL-VPD). The final data collected included tumor stage, initial treatment and anatomic site of disease, to identify a group of OC that had the highest chance of having the whole VPD completed by laparoscopy.

2.4 AIM OF THE STUDY

The endpoint of the initial part of the trial was the feasibility (rate of surgery completed by laparoscopy). Because this part of the study was preparatory to ULTRA-LAP, safety (rate of complications specifically caused by the technique and rate of patients with an early recurrence compared to the laparotomy group) and efficacy (rate of surgery ended with CR) were also measured. The principal aim was to identify the most suitable sub-group of patients to include in ULTRA-LAP.

We recorded the surgical outcomes of patients whose surgery was completed by laparoscopy and the one who needed a conversion to laparotomy. Following VPD or L-VPD, a CT scan preceded the initiation of chemotherapy to confirm the surgical result with regards to residual disease. In case of questionable radiologic findings, the patient was discussed at the MDT meeting again.

2.5 STATISTICAL ANALYSIS

Although not considered strictly necessary, a sample size calculation was made for the feasibility part of ULTRA-LAP based on the Julious method [20]. The aim of the calculation was to determine the smallest number of patients to significantly test safety, so as to avoid futility or unnecessary danger to patients. If 4 patients had displayed early recurrence following a CR (defined as <4 months from completion of treatment) a first warrant was being issued. Had 2 further patients displayed early recurrence, the study would be interrupted. At the same time the sample size needed to be large enough to support feasibility. With this calculation we identified 24 patients as the number that would test safety (surgical and oncologic) and feasibility with a sufficient confidence interval. For the ULTRA-LAP trial, the Simon method [15] was used. In OC patients with gross disease, we anticipated a conversion rate of 80%, morbidity <20% and superimposable survival to the traditional surgery group. We calculated 62 patients to be a sufficient number to achieve a 90% power with a 5% significance. Once the data were collected, we used the chi-square test or Fisher's exact test to compare categorical variables, and the Student's t-test for continuous variables. A p value of 0.05 or < was considered statistically significant. The comparison was necessary within the L-VPD group to identify patients eligible to ULTRA-LAP, but had limited significance between VPD and L-VPD groups since the former had more complex surgery.

2.6 SURGICAL TECHNIQUE OF LAPAROSCOPIC VPD

The operation started by EXL. Exclusion criteria are reported in table 1 and were checked first. We used 2 x 10 mm (in the umbilicus and the Palmer's point) and 3 x 5 mm trocars (in the lower abdomen) which were placed in the usual positions (Figure 2). Only atraumatic instruments, bipolar scissors and graspers (Karl Storz, Tuttlingen Germany) were used for the diagnostic part including adhesiolysis and dissection.

Once exclusion criteria were checked through direct vision, the extension of the disease was examined thoroughly by pursuing dissection and mobilization to finally elect patients to L-VPD. Since the pelvis was never a cause of conversion to laparotomy, we always started from the upper abdomen. In patients where the diaphragmatic disease was evident, a proper liver mobilization was completed until the extent of disease could be fully assessed [11]. Same approach was used to assess gastro-splenic and gastro-colic omental disease. The lesser sac was entered through the gastro-epiploic arcade to separate, if possible, the meso-colon and the omoentum, and to identify the stomach and the pancreas. Additional ports were placed, if necessary, below the subcostal margin either in the pararectal line, the anterior axillary line or the posterior axillary line. The gastro-colic disease was assessed, particularly if adherent to the transverse colon. The concomitance of a transverse colon resection and a sigmoid-rectum resection was considered challenging at laparoscopy. The pelvis was assessed for the need of a sigmoid rectum resection. Once concluded that CR (complete resection) was achievable the actual resection started. Surgical techniques for diaphragmatic surgery [38] and en-bloc resection of the pelvis including sigmoid rectum resection [41] have already been reported.

3. RESULTS

A flowchart of the study is in Figure 4. Patient demographics and tumor characteristics are reported in Table 2. Two hundred eight OC patients were suitable for VPD in the study period (03.2016 to 11.2021) and underwent EXL. One hundred fifty-six were stage IIIC and fifty-two were stage IV. One hundred twenty-one patients entered the neo-adjuvant pathway and eighty-seven underwent up-front surgery. After three cycles of treatment, response to chemotherapy was complete in ten patients, good partial in thirty-eight, partial in fifty-one and stable disease was found in twenty-two patients. At time of surgery, disease load was a Fagotti score of eight or higher in all u-VPD patients and in eighty-four patients out of one hundred and twenty-one (69%) in the i-VPD group. Overall, one hundred and fifty-eight patients (76%) had the surgery converted to laparotomy to complete VPD: eighty-seven had i-VPD and 71 u-VPD. Fifty patients (24%) had L-VPD: thirty-four as iL-VPD and sixteen as uL-VPD. In patients whose surgery was converted to laparotomy, EXL lasted on average 38 minutes (range 7-113). Reasons for conversion to laparotomy in one hundred and fifty-eight patients are reported in table 3 and included: diaphragmatic disease extending dorsally (42%), matted spleno-pancreatic disease (17%), gastro-splenic omental disease (14%) multiple bowel segments involvement (12%) omental disease invading/inseparable from the transverse colon (10%).

In the i-VPD group, ten patients out of overall one hundred and twenty-one (8.2%) were found with no gross visible disease at time of surgery. In these 10 patients, laparoscopic surgery was consistent with hysterectomy, bilateral salpingo-oophorectomy, omentectomy and peritoneal biopsies. No conversion occurred and all patients went home within 48 hours.

Five out of ten had microscopic residual disease in the final histology. In table 4 all surgical procedures performed divided by groups are reported.

Excluding 10 patients with no gross visible disease at i-VPD after chemotherapy, the rate of sigmoid-rectum resection, diaphragmatic surgery, omentectomy and peritonectomy was not significantly different between VPD group and L-VPD. Rate of pleurectomy, splenectomy, tail pancreas resection, hepato-celiac lymphadenectomy was significantly higher in the VPD group.

Average surgical time was not significantly different (326' vs. 341', p=0.3), mean hospitalization time was significantly shorter in the L-VPD group (4 days vs. 11, p=0.02). Overall complications rate was significantly higher in the VPD group (21% vs. 8%, p=0.03). Grade 3 and 4 complications were also significantly higher in the VPD group (7% vs. 1.8%, p=0.017). Complete resection of all visible disease was accomplished in 100% of the L-VPD patients and in 94% of the VPD group. Patients in the L-VPD group started or re-started chemotherapy averagely twelve days before the VPD group (27 vs. 42 days). The breakdown of the L-VPD group patients allowed to stratify for the probability of a successful completion of the procedure. In patients with no gross visible disease after chemotherapy 100% success rate was achieved. Overall, patients in the i-VPD group had a significantly higher chance than the u-VPD to have the procedure completed by laparoscopy (28% vs. 18.3%, p=.02). Excluding patients with a complete clinical response to chemotherapy, twenty-four out of one hundred and eleven (21.6%) patients with gross visible disease had their interval surgery completed by laparoscopy. Likewise, patients with stage IIIC also had significantly higher chances then patients with stage IV.

Finally based on the disease load and dissemination, we identified a group of patients who had the highest chance of a complete L-VPD. They had disease confined to the pelvis (not excluding sigmoid-rectum and peritoneal invasion), gastro-colic omoentum not invading the meso-colon, peritoneum and diaphragmatic disease, the latter not requiring a dorsal liver mobilization. In these group of patients, irrespective of initial treatment, we recorded a 100% feasibility. The results of this pilot study have been incorporated in the ULTRA-LAP trial to select the most suitable candidates to be recruited in the trial.

4 DISCUSSION

The treatment of OC is a combination of surgery and chemotherapy.
None of the two is sufficient and both can be preparatory for the other.
While the advent of new drugs has significantly improved disease-free interval with maintenance therapy [2-16], surgery is increasing the rate of patients left with no residual disease by accomplishing more complex resection of disease. The ideal goal is to do the latter by reducing the morbidity of the procedures.
As it occurred in other branches of surgical oncology and in Gynecologic Oncology, the advent of laparoscopy was associated with extraordinary advantages for the patients. Shorter hospitalization, decreased rate of infection, thrombo-embolic events and need for analgesia were some of the features that made laparoscopy being the standard of care for most patients with malignancies. In patients with ovarian cancer, the use of laparoscopy was limited to women with early disease. Lately the use of laparoscopy was extended to patients with advanced disease to help identify women with disease amenable to complete resection [41,42]. As previously mentioned, two recent studies, the CILOVE and MISSION trials [28,17], have been published. From the latter a subsequent international multi-centric trial stemmed [13]. Both trials recruited OC patients in the neo-adjuvant chemotherapy pathway. The MISSION trial included patients with a complete clinical response to chemotherapy and the CILOVE adopted very restrictive criteria on the type of disease present. Indeed, peritoneal supra-meso-colic disease, pelvic mass >10 cm and supra-centimetric lymphadenopathy were exclusion criteria. Summing the patients in all 3 publications, the trials include around 150 patients. As a result of the selection process, the surgical procedures included in these trials very rarely exceeded a hysterectomy, bilateral salpingo-ophorectomy and omentectomy. Overall, bowel resection occurred in 3 patients and diaphragmatic peritonectomy in 6 patients out of 150. The rate of complete clinical response to chemotherapy is around 10%. Likewise, the chance that OC do not have any upper abdominal disease at interval surgery is scarce. It is fair to say that the study population included in these trials only represent a niche of OC patients. In centers with high patient's volume, most women will undergo up-front surgery. Those who enter the neo-adjuvant chemotherapy will most likely still need upper abdominal

surgery and procedures beyond the ones included in these trials. Therefore, irrespective of initial treatment modality, the most common surgical treatment for OC is multi-visceral debulking. In this scenario, ULTRA-LAP is currently the only trial addressing the feasibility of multi-visceral debulking surgery in OC. Current data sourcing from the feasibility part of the study confirm the feasibility of laparoscopic interval surgery in patients recruited in the neo-adjuvant chemotherapy who had a complete response. New data from this study support the feasibility of L-VPD in patients with gross disease after a partial response or stable disease to neo-adjuvant chemotherapy. Also, this study supports feasibility of L-VPD in a minority of patients at up-front surgery. Overall, this study identified patients whose disease was amenable for laparoscopic surgery based on the anatomic location of disease and irrespective of their initial treatment.

In OC with any pelvic disease, gastro-colic omental and diaphragmatic disease not requiring hepato-caval dissection a 100% success rate was achieved.

In the latter study group, the data were extremely encouraging in terms of safety and efficacy. Complications rate was significantly lower than standard surgery and efficacy was unaltered, reaching 100% CRt rate. These data reflect an initial effort on the use of laparoscopic surgery in completing multi-visceral in OC. It is a pioneering experience with all the limits of a ground breaking investigation. It is inherently depending on the surgical expertise and it can most certainly be improved.

The most relevant information is that the laparoscopic approach did not cause worse prognosis or higher morbidity. Quite to the contrary, it offered a significantly better surgical outcome to OC patients.

The prosecution of ULTRA-LAP will provide larger data on the feasibility, safety and efficacy of multi-visceral debulking in OC selected through the feasibility trial. Hopefully it may enlarge the study population. Considering the heterogeneity of ovarian cancer, there is a great attention to the role played by inflammation and immunity in tumor progression and resistance. Laparotomy is traditionally associated with a significant level of post-operative inflammation and immune depression [18]. In that respect, there are sufficient data to show that laparoscopy is associated to a lower level of immunodepression and less inflammation. The immediate outcome is a faster restoration of bowel movements for example, but also a faster return to normal levels of C-reactive protein and white cell count.

If this translates in a better oncologic outcome it needs proving, but surely it conveys a faster recovery time.

The last but not less relevant fact that needs to be added are the results obtained by the wellness mission trial: there's evidence of a better psychological condition for patients treated with L-VPD, as proven by the General Well Being Scale results. The data report is that the mean GWBS was 64.17 in the patients treated with laparotomy and 54.15 in the AEOC patients that underwent laparoscopy, with a statistically significant difference between the two groups ($p=0.004$) [19].

The results of this pilot study confirm the well known benefits of laparoscopy to these new cohort of patients. The results of the phase II prospective trial are awaited to include more patients and validate the role of laparoscopic multi-visceral debulking.

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TABLES

Table 1. Characteristics of ovarian cancer by histology, genomic characteristics and active therapies, showing how the determination of the precise histological typology of tumor can influence the possible therapeutical strategies. [40].

Histological subtype	Clinical findings	Genetic characteristics	Treatment options
High-grade serous carcinoma and high-grade endometrioid carcinoma	• Can present with peritoneal carcinomatosis, ascites and/or pelvic mass • Typically advanced stage at presentation	• Deficiencies in homologous recombination (50% of tumours) • Associated with *BRCA* and *TP53* mutations	• Platinum-based chemotherapy and poly(ADP-ribose) polymerase inhibitors • Tumours are initially sensitive to platinum-based chemotherapy, but most patients with advanced-stage cancer will recur
Low-grade serous carcinoma	• Presents in younger patients (median reported age: 43–55 years[81]) • Can be early or late stage at presentation	• Associated with *KRAS* and *BRAF* mutations • Tumours have genomic stability	• MEK inhibitors (currently being tested in clinical trials) and hormonal therapies
Low-grade endometrioid carcinoma	• Can be associated with endometriosis	• Associated with *PTEN, ARID1A* and *PIK3CA* mutations • Can have microsatellite instability	• Possible hormonal therapies (not yet established)
Clear-cell carcinoma	• Can present with parenchymal metastases (in the liver and the lungs) • Can be associated with hypercoagulability and hypercalcaemia	• Associated with *ARID1A* and *PI K3CA* mutations	• Immunotherpy agents • Can be resistant to platinum-based chemotherapy
Mucinous carcinoma	• Presents in younger patients and is typically early stage at presentation	1. Associated with *KRAS* mutations	• Tends to be insensitive to chemotherapy but is still treated initially with cytotoxic chemotherapy

Table 2. Some of the most frequently mutations involved in the development of OC.

Gene	Protein	Protein function
BRCA1	Breast cancer type 1 susceptibility protein	• Crucially involved in the repair of double-strand breaks by homologous recombination • Serves as a scaffold for other proteins involved in double-strand DNA repair, mostly through defective homologous recombination • Stabilizes RAD51-ssDNA complexes
BRCA2	Breast cancer type 2 susceptibility protein	
BARD1	BRCA1-associated RING domain protein 1	• Forms a heterodimer with BRCA1 • The BRCA1-BARD1 complex is essential for mutual stability
BRIP1	BRCA1-interacting protein 1 (also known as Fanconi anaemia group J protein)	• Binds to BRCA1 • The BRCA1-BRIP1 complex is required for S phase checkpoint activation
PALB2	Partner and localizer of BRCA2	• A bridging protein that connects BRCA1 and BRCA2 at sites of DNA damage • Helps load RAD51 onto ssDNA
RAD51C	DNA repair protein RAD51 homologue 3	• Strand exchange proteins that bind to ssDNA breaks to form nucleoprotein filaments and initiate DNA repair
RAD51D	DNA repair protein RAD51 homologue 4	
MSH2	MutS protein homologue 2	• Mismatch repair proteins that recognize and repair base-pairing errors occurring during DNA replication • Mutations in mismatch repair genes are associated with Lynch syndrome
MLH1	MutL protein homologue 1	
MSH6	MutS protein homologue 6	
PMS2	Mismatch repair endonuclease PMS2	

Table 3. Figo staging.

FIGO STAGE	CHARACTERISTICS	STAGE DISTRIBUTION	10-YEAR SURVIVAL RATE
I	Disease confined to the ovaries	20%	73%
IA	One ovary, capsule intact, no ascites		
IB	Both ovaries, capsule intact, no ascites		
IC	Stage IA or IB plus ascites or washings, capsule ruptures, tumor on ovarian surface		
II	Disease spread confined to the pelvis	5%	45%
III	Disease confined to the abdominal cavity, including surface of the liver; pelvic, inguinal, or para-aortic lymph nodes; omentum or bowel	58%	21%
IIIA	Negative lymph nodes, plus microscopic seeding of peritoneal surface		
IIIB	Negative lymph nodes, peritoneal implants <2 cm		
IIIC	Positive lymph nodes and/or abdominal implants >2 cm		
IV	Spread to liver parenchyma, lung, pleura, or other extra-abdominal sites	17%	<5%

Table 4. Criteria for Visceral-Peritoneal Debulking (VPD)

Inclusion criteria	Exclusion criteria
Pre-operative: • Histology proven or suspected stage IIIC-IV ovarian cancer • Performance status b2 • Any response or stable disease to chemotherapy in neo-adjuvant patients	*Pre-operative:* • Lung metastases • 3 or more liver segments involvement • Disease progression on chemotherapy *Intra-operative:* • Diffuse small bowel serosal deposits • Porta hepatis encasement

Table 5. Patient demographics and tumor characteristics. (n= 208)

Characteristics	VPD (n= 158)	L-VPD (n= 50)
Patients, n./tot, (%)	158/208 (76)	50/208 (24)
Age, mean yr (range)	68 (54-78)	62 (51-74)
CA-125, U/mL (range)	819 (129-3670)	645 (112-1187)
VPD		
Up-front VPD, n (%)	71 (45)	16 (32)
Interval VPD, n (%)	87 (55)	34 (68)
FIGO stage		
IIIC, n (%)	120 (76%)	44 (88%)
IV, n (%)	38 (24%)	6 (12%)

Legenda: VPD, Visceral Peritoneal Debulking; **L-VPD,** laparoscopic VPD; **CA-125,** cancer antigen 125.

Table 6. Reasons for conversion to laparotomy (n=158)

Schematic reasons	%
Diaphragmatic disease extended dorsally	42%
Matted spleno-pancreatic disease	17%
Gastro-splenic omental disease	14%
Multiple bowel segments involvement	12%
Omental disease invading/inseparable from the transverse colon	10%
Others	5%

Table 7. Surgical procedures and outcomes (n=208)

	VPD (n= 158)	L-VPD (n= 50)	p value
Average surgical time, minutes	341	326	NS
Mean hospitalization, days	11	4	**<0.05**
Complete resection (R=0)	149 (94.3)	50 (100)	NS
Procedures:			>0.05
S-R resection, n (%)	102 (64.5)	32 (64)	>0.05
Diaphragmatic surgery, n (%)	126 (79.7)	36 (72)	>0.05
Omentectomy, n (%)	158 (100)	50 (100)	>0.05
Peritonectomy, n (%)	140 (88.6)	36 (72)	>0.05
Pleurectomy, n (%)	32 (20.2)	-	
Splenectomy, n (%)	29 (18.3)	2 (4)	
Tail-P resection, n (%)	12 (7.6)	-	
H-C lymphadenectomy, n (%)	18 (11.3)	-	
Complete response to chemotherapy n/tot (%)	-	10/34 (29.4)	
Begin/Restart chemotherapy, mean days (range)	42 (38-59)	27 (18-41)	**<0.05**
Complications:			
Overall, n (%)	33 (20.8)	4 (8.0)	**<0.05**
G3-G4, n (%)	11 (6.9)	1 (1.8)	**<0.01**

Legenda: VPD, Visceral Peritoneal Debulking; **CHT**, chemotherapy; **L-VPD,** laparoscopic VPD; **i-VPD,** interval VPD; **S-R**, sigmoid-rectum; **H-C**, hepato-celiac.

FIGURES

Figure 1. . Histological subtypes of ovarian cancer

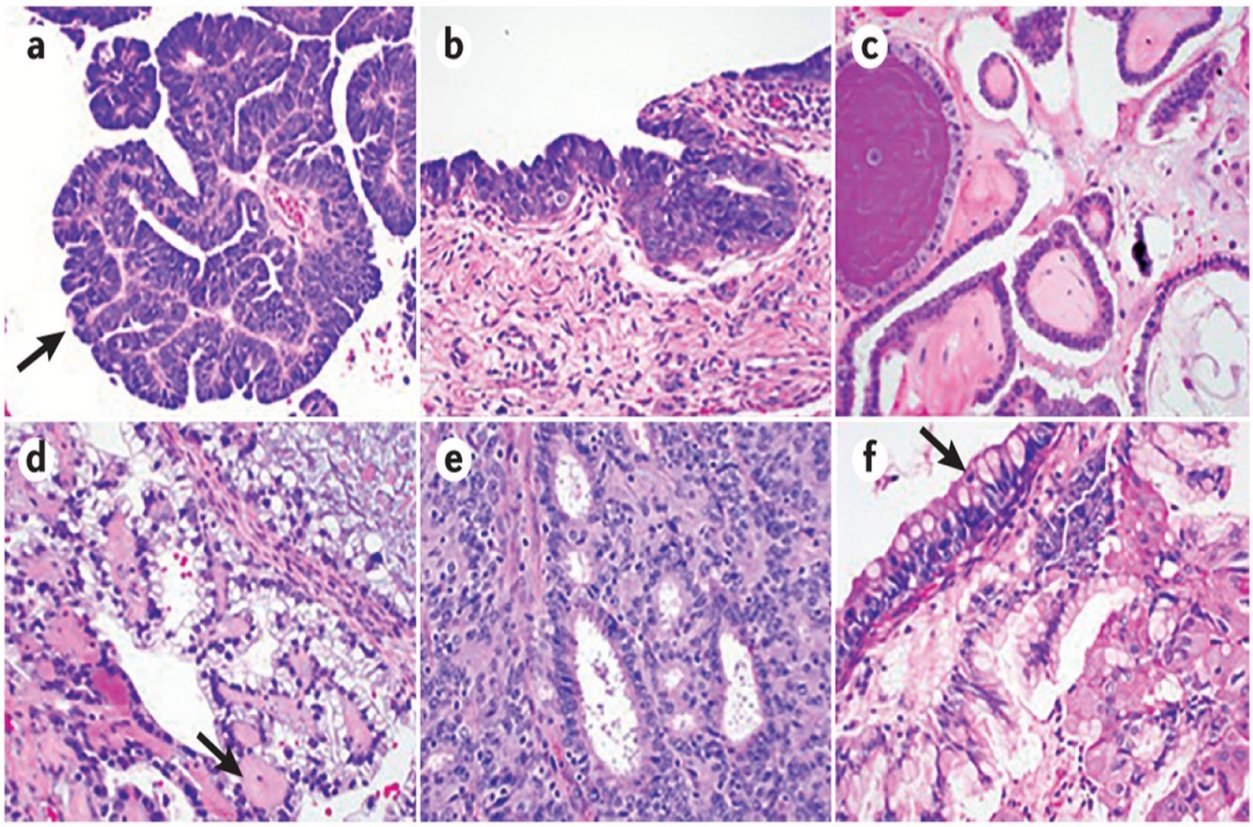
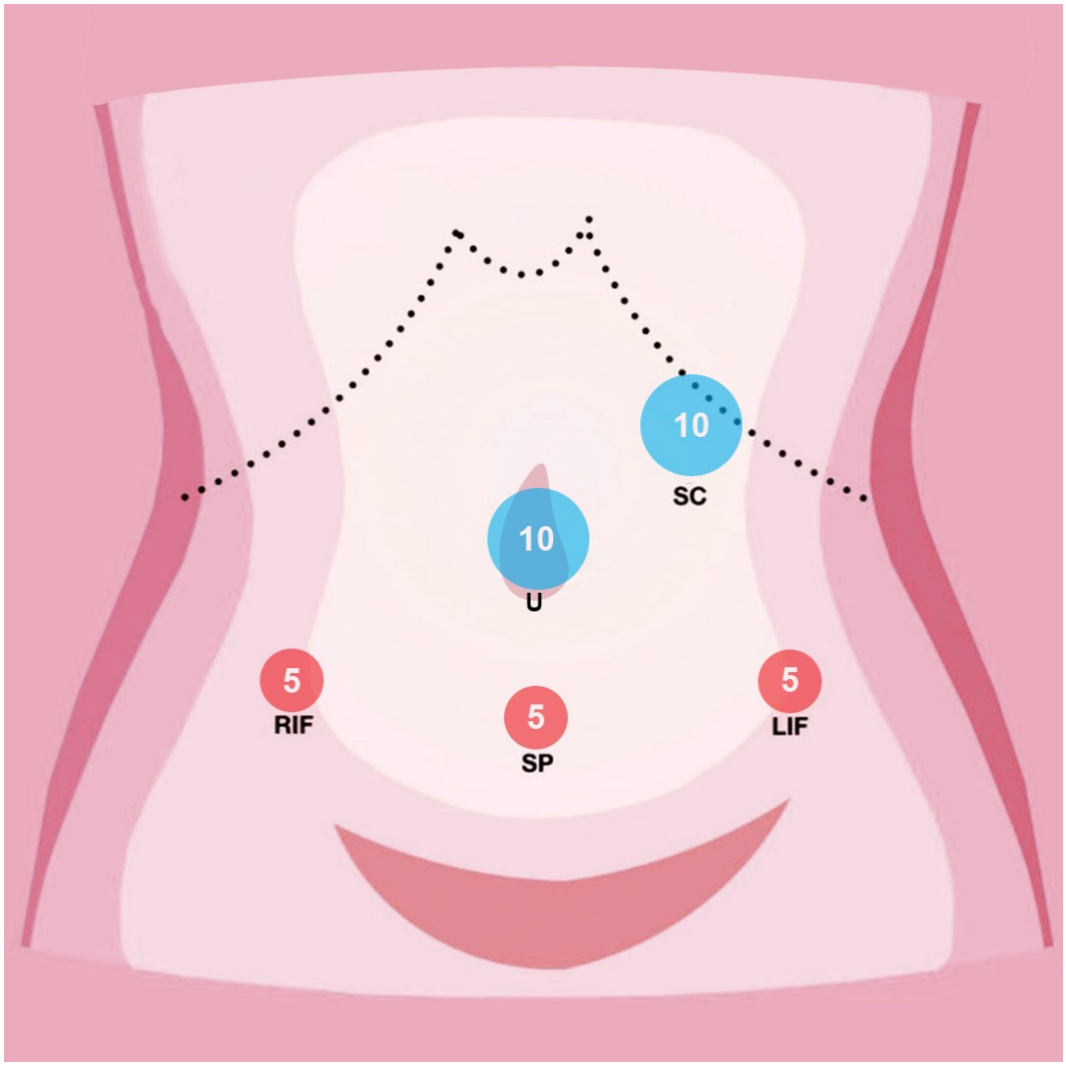
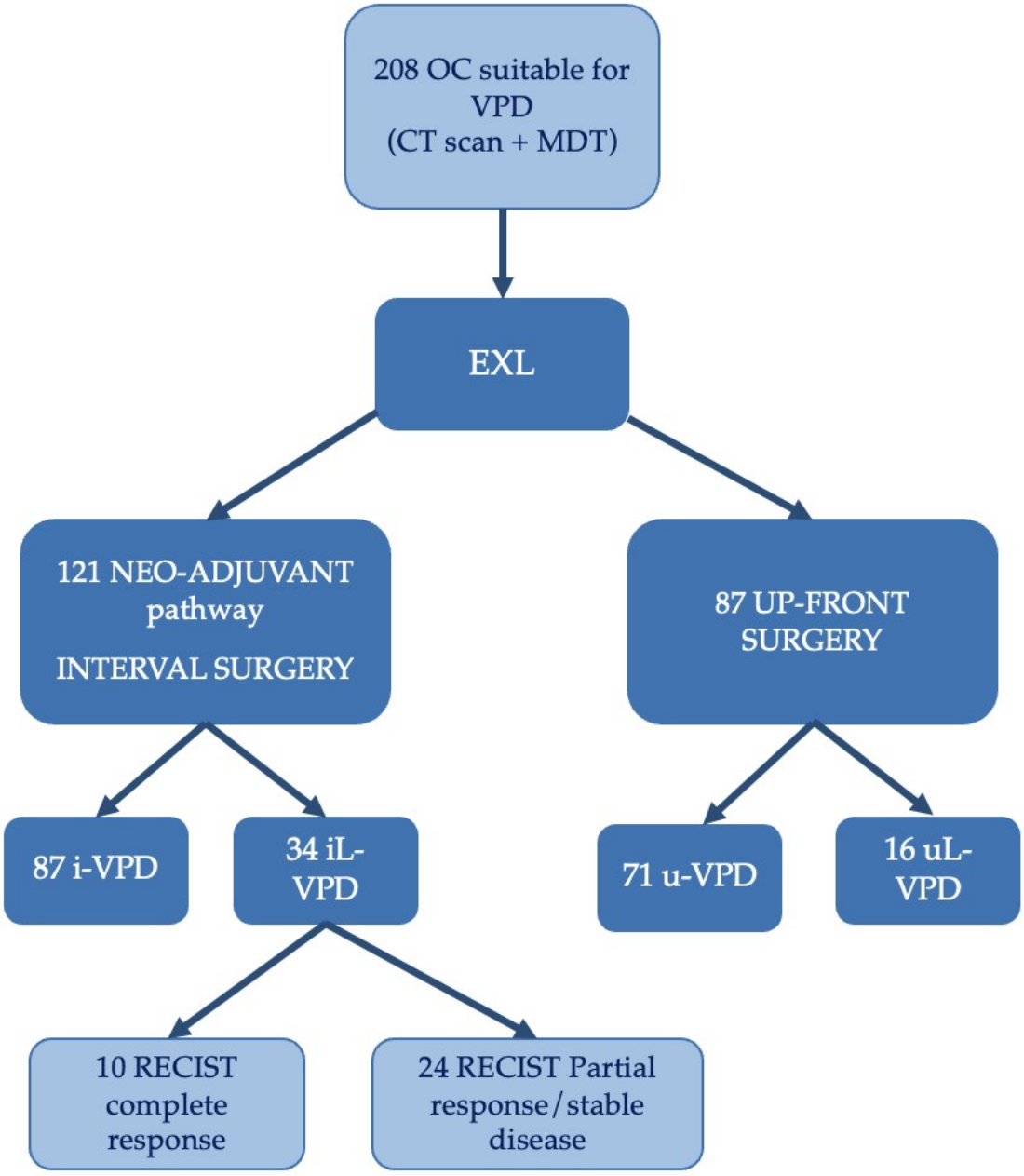


Figure 2. Trocars positioning for L-VPD. Port site position for laparoscopy using 10 mm-optic and 5 mm-ancillary trocars. SP: suprapubic; RIF: right iliac fossa; LIF: left iliac fossa; U: umbilicus; SC: subchondral.



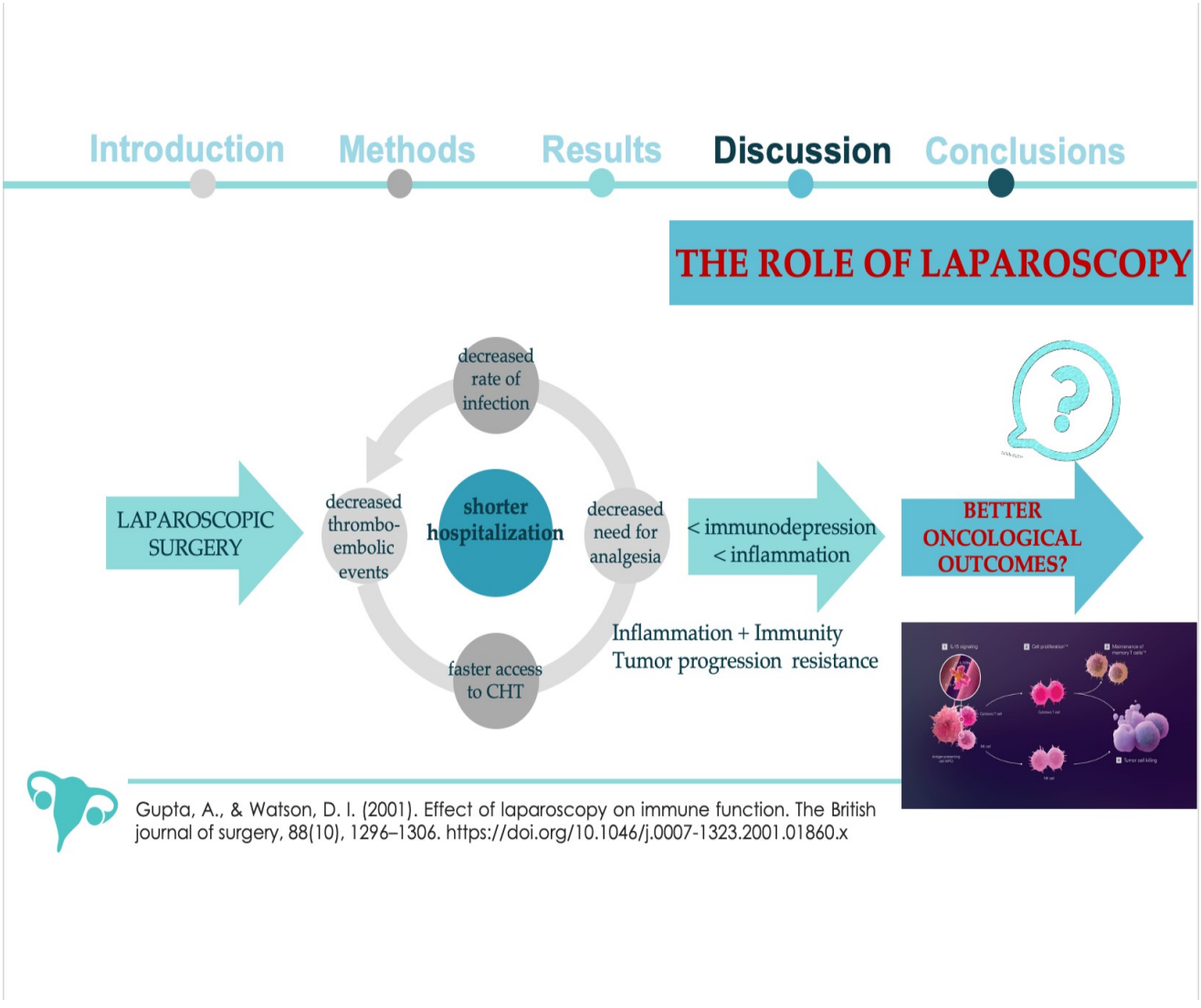
Legenda: SP: suprapubic; RIF: right iliac fossa; LIF: left iliac fossa; U: umbilicus; SC: subchondral.

Figure 3. Patient's flow-chart ULTRA-LAP trial



Legenda: VPD, Visceral Peritoneal Debulking; **CT**, computed tomography; **MDT**, multidisciplinary team; **EXL**, exploratory laparoscopy; **i-VPD,** interval VPD; **iL-VPD,** interval laparoscopic VPD; **uL-VPD,** up-front laparoscopic

Figure 4. potential advantages of laparoscopy in the treatment of OC patients.



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