The role of exploratory laparoscopy in surgical planning for ultra-radical surgery for ovarian cancer: a narrative review

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Contributions: (I) Conception and design: M Morotti, T Shi; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: M Morotti, G Valenti; (V) Data analysis and interpretation: M Morotti, VK Mavroeidis, T Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Objectives: The aim of this narrative review is to summarise the available evidence on the use of staging laparoscopy (S-LPS) in the pre-operative management of advanced epithelial ovarian cancer (EOC).

Background: EOC presents at an advanced stage in most women and is often characterised by extensive intraperitoneal spread. One of the main treatment goals in these patients is to determine the best therapeutic strategy: primary debulking surgery (PDS) versus neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). Identifying who can benefit from NACT can help optimise oncological management and avoid inappropriate upfront laparotomies. The role of S-LPS in clinical practice has increased significantly worldwide as a pre-operative tool for the management of advanced EOC.

Methods: An electronic database search was performed on PubMed, Medline, and Google Scholar for relevant studies from inception to February 2021.

Conclusions: S-LPS represents a safe and adequate procedure for the staging of advanced EOC in combination with CT imaging, and is associated with a shorter length of hospital stay and time to start systemic therapy. Particularly in centres with a high cytoreduction rate, S-LPS, in conjunction with CT-scan, could represent a useful diagnostic combination for the pre-operative surgical planning, along with allied multidisciplinary teams. The main concerns relate to inadequate retroperitoneal staging. However, it is a cost-effective procedure that also reduces the complications associated with futile laparotomies.

Keywords: Advanced ovarian cancer; cytoreduction; laparoscopy; staging; surgery

Received: 23 March 2021; Accepted: 04 June 2021; Published: 25 March 2022.
doi: 10.21037/gpm-21-25
View this article at: https://dx.doi.org/10.21037/gpm-21-25

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynaecological cancers in western countries (1). Two-thirds of patients with EOC are diagnosed at an advanced stage of disease (FIGO IIIC-IV). Conventional pre-operative assessment in advanced EOC consists of medical history, physical examination, CA125 and CEA serum levels, chest X-ray and contrast-enhanced

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abdominopelvic computed tomography (CT) scan (1).

Primary debulking surgery (PDS) is the standard of care for the treatment of EOC (2). Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is an alternative strategy which has gained popularity in recent years (3-6). Despite that, there is still controversy about whether NACT can be a valuable option in the treatment of EOC (7). IDS after NACT is increasingly applied worldwide as the primary treatment strategy in patients with EOC (8). This strategy has been shown to reduce surgical complexity and postoperative complications, compared with PDS (3-5), particularly in patients with worse performance status and/or high-volume disease (2,9-12).

In both PDS and IDS, removing all visible disease (R <1 cm, optimal debulking) is the most important prognostic factor associated with increased survival (13,14).

Therefore, identifying patients with extensive disease who are likely to have >1 cm of residual tumour after surgery is of paramount importance. When this is the case, the most appropriate management is to offer NACT or palliative chemotherapy, the latter in the case of six previous cycles of NACT.

It is also plausible that futile laparotomies should be prevented in women with EOC. Staging laparotomies are indeed associated with the risk of intraoperative and postoperative complications, which can delay the start of chemotherapy, along with an increased length of hospital stay, with the associated financial implications (15).

Unfortunately, the available non-invasive diagnostic methods such as CT, PET-CT, and serum tumour markers do not accurately predict the performance of optimal debulking (16). Although numerous investigators have tried to create prediction models by integrating various imaging techniques and clinical features, none of these models have proven to be useful in preventing futile laparotomies in the context of management of advanced EOC (17).

Staging laparoscopy (S-LPS) is increasingly incorporated into the management of advanced EOC as an important surgical planning tool before ultra-radical surgery (18) and has been shown to reduce the rate of futile laparotomies (19).

In this narrative review, we assess available up-to-date data on the use of S-LPS as part of the initial diagnostic work-up in women with advanced EOC.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-25/rc).

Material and methods

An electronic database search (PubMed, MEDLINE, Google Scholar) was performed with the objective of identifying all studies assessing the usefulness of S-LPS in the management of advanced EOC, published up to February 2021. Combinations of medical subject heading terms including "diagnostic laparoscopy", "diagnosis", "ovarian cancer", "ovarian cancer staging" were used. Two authors (MM, GV) independently examined the full texts of all articles. In case of disagreements in this selection, a final decision was taken upon discussion with the other two authors (VKM, TS). All pertinent articles written in English were retrieved, and the relative reference lists were reviewed in order to identify additional studies that could potentially be included.

Surgical technique of S-LPS

With the patient under general anaesthesia in a supine position, a 1.5–2 cm skin incision is made in the periumbilical region (above or below the umbilicus), according to the presence of a mass or previous scars on the abdominal wall. Another type of entry could be through the Palmer's point (3 cm below the left costal margin in the mid-clavicular line) (20).

Entrance in the peritoneal cavity is ensured via an open approach. Large volume ascites, if present, is firstly drained by open suction and sent for cytology. A primary exploration of the abdominal cavity by palpation could be performed to identify adhesions or bowel loops that could be an obstacle to the introduction of the trocar. The pneumoperitoneum is induced after introducing the trocar and the optics. One or two ancillary 5-mm trocars are then inserted in the iliac fossae or where it is technically possible. A careful, complete pelvic and abdominal examination is carried out to assess the spread of disease and any possible cause impeding optimal cytoreduction. All peritoneal surfaces are closely examined; the liver and spleen are evaluated by rotating the laparoscope 360° through the umbilical port. The small bowel loops and mesentery are exposed and evaluated by careful grasping. The pelvis is then assessed, when possible, after retraction of the bowel loops in the upper abdomen. An assessment of the sigmoid mobility to predict large bowel involvement can be done. Biopsies are usually taken. At the end of S-LPS, the abdomen is deflated with the trocars in place. The trocar

Table 1 Summary of studies evaluating S-LPS in advanced EOC

Author	Year	Type	FIGO stage	Patients (n)	PDS (n)	CR PDS (%)	Futile laparotomies (%)
Vergote *et al.*	1998	Retrospective	IIIc/IV	87	53	96	9
Fagotti *et al.*	2005	Prospective	IIIc/IV (18 % I–II)	95	64	50	27
Angioli *et al.*	2006	Prospective	IIIc/IV	15	11	91	2
Deffieux *et al.*	2006	Prospective	IIIc/IV	778	592	50	7
Fagotti *et al.*	2008	Prospective	IIIc/IV	113	113	69	50
Brun *et al.*	2008	Retrospective	IIIc/IV	55	26	75	15
Brun *et al.*	2009	Retrospective	IIIc/IV	52	28	91	2–50
Petrillo *et al.*	2015	Retrospective	IIIc/IV	234	234	59	19
Rutten *et al.*	2017	RCT	>IIb	102	63	81	10

EOC, epithelial ovarian cancer; PDS, primary debulking surgery, RCT, randomized controlled trial; S-LPS, staging laparoscopy.

sites are irrigated with 5% povidone-iodine to minimise the risk of port-site metastases, and are subsequently closed.

Qualitative LPS as a triage for resectability

Vergote *et al.* in 1998 firstly reported the clinical outcome of a sub-cohort of 77 patients subjected to S-LPS who had obvious metastatic EOC on radiological examination. The S-LPS findings drove the decision to perform or not PDS and eventually refer patients to NACT (21) (*Table 1*). The median duration of the S-LPS was 25 minutes, and the length of hospital stay was two days. PDS was performed in a subgroup of 28 patients (36%). Seventy-nine percent of these patients were cytoreduced to less than 0.5 cm largest residual disease. Six patients (7.7%) developed subcutaneous metastasis at the site of trocar insertion. The median duration between S-LPS and PDS was seven days.

Subsequently, a prospective study of 64 patients with suspected advanced EOC investigated the role of S-LPS and imaging in predicting the likelihood of optimal cytoreductive surgery (22). All patients were subjected to both S-LPS and standard laparotomy. S-LPS predicted suboptimal debulking in 100% of cases, while the conventional staging predicted it in only 73% of cases. In this first report from the Gemelli group, the rate of unnecessary laparotomies due to suboptimal debulking was 13% for both the conventional evaluation and the S-LPS (22).

In 2006, Deffieux *et al.* reported the use of S-LPS in 15 patients with advanced EOC whose pre-operative clinical and radiologic evaluations were reviewed and deemed unsatisfactory in terms of the likelihood of achieving complete cytoreduction (23). In comparison, a complete cytoreduction was achieved in nine of the ten patients considered resectable at S-LPS. Criteria of inoperability were: extensive involvement of the liver pedicle, infiltration of the diaphragmatic muscle near the sub-hepatic vessels, extensive involvement of the bowel or mesentery.

Angioli *et al.* reported a cytoreduction rate of 96% in a cohort of advanced EOC patients, which were deemed resectable at pre-operative S-LPS (24). Before the introduction of staging S-LPS, this group had an optimal cytoreduction rate of 46%. However, in a cohort of 55 advanced EOC patients, Brun *et al.* (25) reported a lower percentage (54%) of complete cytoreduction after S-LPS assessment. Another retrospective study by Nezhat *et al.* (26) assessed the value of S-LPS in selected patients with advanced EOC who were deemed eligible by imaging techniques. Of the 32 patients who underwent LPS, eleven (34.3%) had cytoreductive surgery, with an optimal cytoreduction rate of 72.7%.

S-LPS-based predictive model

Fagotti *et al.* re-analysed the same population published in 2005 to develop an S-LPS-based quantitative model, which could be further validated and used by other research groups. They proposed a simple scoring system based on an S-LPS predictive index value (PIV) that could estimate the chances of achieving an optimal cytoreduction based on the presence of (I) omental cake, (II) peritoneal carcinomatosis, (III) diaphragmatic carcinomatosis, (IV) mesenteric retraction, (V) bowel and/or (VI) stomach infiltration and (VII) liver metastases (27). Each parameter was assigned two points if present. A score greater than 8 predicted suboptimal surgery with a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 70%. They found that with a PIV cut-off of 8, the probability of complete cytoreduction was 0%, while the rate of performing unnecessary laparotomy was 40.5% (22).

This PIV was externally validated in a French cohort of 55 patients with possible advanced EOC (28) and then prospectively validated by the same Rome Gemelli group (29,30).

To assess whether the PIV assessment was feasible and reproducible in external centres, Fagotti *et al.* performed a prospective multicentre trial (Olympia-MITO 13) aiming to evaluate the application of the LPS-based PIV in 120 patients at four Italian satellite centres. The procedures were recorded and then blindly reviewed at a coordinator centre. An accuracy rate of 80% or greater was reached in three of the four satellite centres (31). The assessment of mesenteric retraction was the single site showing less concordance between different centres, suggesting that this PIV (Fagotti score) could be reproduced in different centres with different expertise.

To determine the safety of the S-LPS approach in advanced EOC, a retrospective survival analysis of 300 women with stage IIIC-IV EOC was performed (32). No S-LPS-related complications were reported, and no impact was noted on median progression-free survival (PFS). Moreover, Vizzielli *et al.* demonstrated that the overall tumour burden, as assessed by high S-LPS PIV, was an independent prognostic factor, together with residual tumour at primary surgery, in 348 patients who underwent S-LPS before PDS or NACT (33).

A recent randomised study evaluated the cost-effectiveness of S-LPS prior to PDS in preventing futile surgeries in 201 patients with suspected advanced EOC. Although the S-LPS cost was around 1,400€ per intervention, S-LPS reduced the proportion of futile laparotomies from 39% to 10%. Thus, the overall costs of both strategies appeared to be comparable. There was no significant difference in quality-adjusted life years (QALYs) between patients undergoing or not S-LPS (utility=0.01; 95% CI: 0.006–0.02) (34).

The value of peritoneal cancer index (PCI) assessment with S-LPS compared to laparotomy staging was confirmed by a large French retrospective review of 543 patients who underwent S-LPS for advanced EOC (35). Laparoscopic PCI showed an area under the curve (AUC) of 0.90 in predicting complete cytoreduction.

S-LPS is cost-effective

A recent cost-effectiveness analysis from a healthcare payer perspective was performed on S-LPS (36). Although the S-LPS strategy led to additional costs, which increased over the years (average additional cost of $7,034 in the US), it remains cost-effective. In fact, the benefit of S-LPS was influenced by the mitigation of serious complications and their associated costs.

A recent Cochrane review summarised the accuracy of the S-LPS findings in determining disease resectability in patients with suspected advanced EOC (37). A total of 18 studies on 14 patient-cohorts were analysed. S-LPS had overall a good accuracy compared to standard laparotomy except from the assessment of specific anatomical areas (e.g., retro-hepatic areas). However, despite the utilisation of S-LPS, there were still women who had suboptimally resected disease (i.e., >1 cm residual tumour) at PDS, probably due to the inherent inability of S-LPS to assess specific areas associated with sub-optimal debulking (retroperitoneal, mesenteric or retro-hepatic and peri-pancreatic area). However, it has to be acknowledged that what is considered resectable and which procedures are performed during PDS may differ between different centres. Nevertheless, the study estimated a reduction in suboptimal PDS (>1 cm residual tumour) from 39% to 10% (34). The authors concluded that S-LPS could be of benefit and should be adopted as a standard procedure in clinical practice.

Limitation of S-LPS and possible surrogate of imaging

As mentioned, although S-LPS seems promising in predicting complete tumour resection, it has limited or no value for the assessment of specific areas (as above) or extra-abdominal deposits. Imaging such as CT, MRI, PET-CT or whole-body MRI might be a necessary complement to S-LPS. CT scan is used extensively as an integral part of the pre-operative diagnostic assessment of EOC patients. The capability of CT-scan to predict optimal cytoreduction has been proven for decades (38,39). However, data are inconclusive with regards to its predictive ability of optimal cytoreduction. Some retrospective studies support the high diagnostic reliability of CT-scan in predicting optimal or suboptimal cytoreduction (39-42). Conversely, two multicentre studies did not confirm these data (43,44). Not surprisingly, several attempts were made to create a CT scoring system to predict disease resectability (41,45,46). However, these models have shown an inadequate predictive ability and a questionable reproducibility (47). Although there is extensive literature comparing the CT scan performance against S-LPS, few authors have considered combining the retrievable information from both evaluations. Tozzi *et al.* have recently compared the diagnostic power of CT scan alone with the combination of CT scan and S-LPS, considering eleven anatomical areas. The aim was to assess if the combination of both diagnostic tools could improve the pre-operative evaluation power of CT-scan alone and reduce unnecessary laparotomies. The authors have highlighted that S-LPS should not be used as a surrogate of the CT scan. However, the combination of the two techniques showed a better diagnostic power than CT-scan alone, particularly in detecting bowel, diaphragmatic, and mesenteric lesions (48,49). This information reduced the rate of futile laparotomies by better pre-operative planning together with allied specialist teams (48,49). FDG-PET/CT has been shown to be superior to conventional CT scan for the detection of carcinomatosis in the subdiaphragmatic peritoneal surfaces, bowel mesentery, and the detection of extra-abdominal disease (50), and it has been used in OC clinical trials (51). Also, whole-body MRI with diffusion-weighted sequence has been shown to be superior to CT and provided similar accuracy to PET/CT in the characterisation of primary lesions and distant metastases, but it had significantly better sensitivity and specificity in overall peritoneal staging (50). The predictive performance of S-LPS in conjunction with PET-CT and whole-body MRI has not been investigated yet".

On a separate note, it can be mentioned that in the present setting, the ongoing dynamic changes relating to the Covid-19 pandemic are expected to potentially further influence the ability to perform laparoscopic procedures, including S-LPS for advanced OC, in line with national and international guidelines.

Risks of S-LPS in the management in OC

The complication rate after S-LPS is low (reported between 1–5%), but this procedure still represents an additional surgical intervention requiring general anaesthesia with some complications reported as severe, potentially delaying the primary treatment (surgery or NACT) (52). During S-LPS, vessel and bowel injuries have been reported. Moreover, grasping of bowel loops may lead to unnecessary injuries if not handled properly (12).

Some concerns have also been raised regarding potential cancer dissemination with the induced carbon dioxide (CO_2) pneumoperitoneum and consequent port-site metastases. Most of these studies assessing potential S-LPS-induced metastatic spread were either conducted *in vitro* or were animal studies. Carbon dioxide was shown to promote *in vitro* growth of SKOV-3 ovarian cancer cell line. However, other animal studies showed no deleterious effect of CO_2 in EOC cell spread when compared with laparotomy or gasless LPS (53). Moreover, as advanced EOC has macro- and micrometastases, it is not clear what the clinical impact of such potential spread would be, also in view of adjuvant chemotherapy. However, due to the recent data on the risks associated with LPS for cervical cancer (54), further studies on the effect of pneumoperitoneum in OC cells might be useful.

Port-site metastases were also reported in 2–3% of cases after S-LPS. The risk of port-site metastases was reported higher in patients with recurrence of ovarian or primary peritoneal malignancies undergoing procedures in the presence of ascites (55,56). The overall prognosis did not seem to be affected by these port-site lesions. Several techniques have been reported to minimise port-site metastases, such as removing an intact specimen, layered closure of the trocar sites, irrigation of the trocar sites and potential trocar site excision (57,58).

Conclusions

S-LPS represents an easy and relatively low-morbid approach for the pre-operative assessment of advanced EOC patients. It can accurately predict which patients will likely have a suboptimal cytoreduction at the time of PDS and would, therefore, benefit from NACT. The utilisation of S-LPS in conjunction with other pre-operative tools (radiological imaging and serum CA125) has an accuracy of up to 96% in predicting suboptimal surgery.

This might be important in guiding the best treatment in advanced EOC, which is particularly relevant in those patients with poor performance status or "high-volume" stage IIIC or stage IV disease. However, future high-level evidence is warranted to confirm whether S-LPS could be incorporated as standard clinical practice in the management of primary EOC.

Although available evidence suggests that S-LPS is mostly equivalent to explorative laparotomy for staging the extent of intraperitoneal spread in EOC, a significant number of women cannot be evaluated by S-LPS. For instance, adhesions can prevent access to the abdomen or impair complete exploration of the peritoneal cavity. Moreover, the PIV score is focused on assessing the intraperitoneal diffusion of the disease without evaluating the extent of spread in the retroperitoneal space and extra-abdominal surfaces, which might prevent a complete resection in some cases.

In some institutions, S-LPS is already included in the standard diagnostic work-up, in some centres, it is only performed when there is doubt about resectability, while in other centres it is not used (59).

Indeed, it could be argued that S-LPS in advanced EOC may be of limited value for surgeons achieving a very high percentage of optimal cytoreductive surgery. In contrast, it could represent a more valuable opportunity for groups that sustain a less aggressive approach. However, also in centres with high cytoreduction rates, S-LPS could provide a more accurate mapping of the extension and resectability of the disease. Thus, surgery could be scheduled according to the S-LPS results with the appropriate involvement of allied specialist teams, as necessary. This could also help in estimating the expected surgical procedures and potential morbidity, informing the consent process accordingly, and planning the peri-operative care as required.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Hooman Soleymani Majd) for the series “Evolutions in the Management of Advanced Ovarian Cancer” published in *Gynecology and Pelvic Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-25/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-25/coif). The series “Evolutions in the Management of Advanced Ovarian Cancer” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/gpm-21-25
Cite this article as: Morotti M, Valenti G, Mavroeidis VK, Shi T. The role of exploratory laparoscopy in surgical planning for ultra-radical surgery for ovarian cancer: a narrative review. Gynecol Pelvic Med 2022;5:10.