Brief Overview About Role of Laparoscopy in Ovarian Cancer

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Abstract
Minimally invasive surgery (MIS) includes several different approaches, such as standard laparoscopy, robotics, mini-laparoscopy, and single-port laparoscopy. Surgeons choose the most appropriate method based on the availability of products, patient characteristics, tumor extension, and the type of surgery needed. The rate of serious complications associated with laparoscopy is low; complications are related mainly to the initial abdominal access and consist most often of vessel and bowel injuries. Proper patient selection, knowledge of surgical anatomy, and attention to appropriate abdominal access techniques may help prevent these complications. Laparoscopy may offer advantages in terms of a shorter hospital stay, decreased perioperative morbidity, lower wound infection and incisional hernia rates, less postoperative pain, and fast healing. Moreover, optical magnification of the abdominal vessels and structures, together with the availability of modern devices such as advanced bipolar, ultrasound instruments and topical hemostatic agents, increases the feasibility of laparoscopy procedures. Specific advantages exist in performing laparoscopy in ovarian cancer: Adjuvant chemotherapy can start sooner because of the minimal time needed for smaller incisions to heal, the risk of adhesion development is lower, it is useful in fertility-sparing cases, and it provides easier access to the retroperitoneum

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Introduction:

Minimally invasive surgery (MIS) includes several different approaches, such as standard laparoscopy, robotics, mini-laparoscopy, and single-port laparoscopy. Surgeons choose the most

appropriate method based on the availability of products, characteristics of patients, extension of the tumor, and the type of surgery needed. **(Fagotti et al., 2016)**

The rate of serious complications associated with laparoscopy is low; complications are related mainly to the initial abdominal access and consist most often of vessel and bowel injuries. Proper patient selection, knowledge of surgical anatomy, and attention to appropriate abdominal access methods may help in prevention of these complications. **(Ahmad et al., 2015)**

The rate of injuries during abdominal access varies from 5 to 30 per 10,000 procedures: 4.4 per 10,000 for bowel injuries, 3.1 per 10,000 for vascular injuries, and 3 per 1000 for injuries related to umbilical trocar insertion. **(Ahmad et al., 2015)**

The most common causes for laparoscopy failure are prior abdominal surgery, previous pelvic inflammatory disease or diverticulitis, diaphragmatic hernia, very large abdominal or pelvic masses, and severe obesity. **(Fagotti et al., 2016)**

The advantages of Laparoscopy are a shorter hospital stay, decreased perioperative morbidity, lower wound infection and incisional hernia rates, less postoperative pain, and fast healing. **(Rabinovich A, 2015)**

Moreover, optical magnification of the abdominal vessels and organs, together with the availability of modern devices such as advanced bipolar, ultrasound instruments and topical hemostatic agents, increases the feasibility of laparoscopy procedures. **(Gabay & Boucher, 2013)**

Specific advantages exist in performing laparoscopy in ovarian cancer: Adjuvant chemotherapy can start sooner because of the minimal time needed for healing of the smaller incisions, lower risk of adhesion development, it is useful in fertility-sparing patients, and it provides easier access to the retroperitoneum. **(Lin and Chen, 2013)**

Specific risks also have been reported for laparoscopy, such as port site metastases; however, this risk seems very low (0.97 %) and should not preclude laparoscopy in women with gynecologic malignancies managed by gynecologic oncologists. Indeed, this complication does not affect overall survival and may be treated by excisional surgery if it occurs. **(Fagotti et al., 2016)**

In this context, some preventive measures have been recommended to reduce port site metastases, such as peritoneal closure of port sites, port site excision at the time of debulking surgery, rinsing of the trocar, trocar fixation, reduction of the number of instrument transfers, suction of ascites before trocar removal. **(Fagotti et al., 2016)**

Laparoscopy has been incorporated in ovarian cancer treatment to manage early stage disease, advanced stage disease at primary diagnosis and after neoadjuvant chemotherapy (NACT), and recurrent disease. **(Fagotti et al., 2016)**

In the following sections, we present the current recommendations for laparoscopy based on the different stages of ovarian cancer.

☒ **Early stage ovarian cancer:**

Patients with localized tumors have longer 5-year survival rates than those in the advanced stages of disease, even though these tumors represent only 20 of 25% of all ovarian cancer cases **(Siegel et al., 2014)**

A review by the Cochrane Collaboration found no good-quality evidence to quantify the risks and benefits linked to laparoscopy for the management of early-stage ovarian cancer (ESOC), mainly because of the lack of randomized controlled trials (RCTs). **(Falcetta et al., 2016)**

However, available data from retro/ prospective series of epithelial serous ovarian cancer patients treated by laparoscopy show that laparoscopic surgical staging is a safe and technically feasible procedure. **(Fagotti et al., 2016)**

The careful selection of patients eligible for a laparoscopic approach is mandatory to reduce the complication rate and to minimize the risk of conversion to laparotomy, which is estimated to be around 3.7 % for patients affected by presumed ESOC. **(Park et al., 2013)**

☒ **Advanced ovarian cancer**

1. **Staging:**

Because of the absence of screening program for early detection and the vague symptoms in the early stages, about 75 to 80 % of ovarian cancer patients present with advanced disease. **(Fagotti et al., 2016)**

Primary debulking surgery (PDS) followed by paclitaxel/platinum-based chemotherapy is the gold standard for treating these patients. To achieve complete cytoreduction, a multidisciplinary approach is recommended. Neoadjuvant chemotherapy may be used in specific cases. **(Fagotti et al., 2016)**

The rationale for a laparoscopic evaluation before cytoreductive surgery includes the following points:

(1) Intraperitoneal diffusion of disease may be assessed easily with laparoscopy, and the surgeon may be more confident having direct visualization of the cancer spread.

(2) This approach might spare patients an unnecessary laparotomy resulting in suboptimal cytoreduction.

(3) Patients deemed not to be candidates for cytoreduction may proceed immediately to neoadjuvant chemotherapy without having to recover from laparotomy-related complications.

(4) Laparoscopy allows collection of tissue for definitive diagnosis and molecular analysis.

Fagotti et al. proposed a simple scoring system based on a laparoscopic predictive index value (PIV) to estimate the chances of achieving optimal cytoreduction based on the presence of an omental cake, peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric retraction, bowel infiltration, stomach infiltration, and liver metastases. **(Fagotti et al., 2006)**

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 %. **(Fagotti et al., 2006)**

This system was validated in an external cohort of 55 French patients with stage III–IV ovarian cancer, and the model then was prospectively validated. **(Fagotti et al., 2008)**

A potential concern regarding the implementation of preoperative laparoscopic assessment as part of standard practice is whether this approach is feasible at sites other than major academic institutions.

To answer this question, **Fagotti et al.** performed a prospective, multicenter trial (Olympia-MITO 13) evaluating the application of the laparoscopy based PIV in 120 patients at four satellite centers. The most difficult feature to assess was mesenteric retraction; however, an accuracy rate of 80 % or greater was reached in three of the four satellite centers. **(Fagotti et al., 2013)**

To determine the role of staging laparoscopy (S-LPS) in advanced ovarian cancer definitively, a last step was needed: to investigate whether the introduction of such management would have a negative impact on prognosis in these patients. To this end, a retrospective survival analysis of 300 women with International Federation of Gynecology and Obstetrics (FIGO) stages IIIC and IV ovarian, fallopian tube, or primary peritoneal carcinoma was published in 2013. **(Fagotti et al., 2013)**

The authors of this study reported no complications related to the laparoscopic procedure. The median progression-free survival (PFS) in women with R0 resection at PDS was 25 months (95 % CI, 15.1–34.8 months). **(Fagotti et al., 2013)**

Vizzielli et al. [23] demonstrated that tumor burden, as assessed by laparoscopic PIV, was an independent prognostic factor, together with residual tumor (RT) at primary surgery, in 348 patients who underwent laparoscopy before primary cytoreductive surgery or neoadjuvant chemotherapy. **(Vizzielli et al., 2014)**

A recent Cochrane review summarized the accuracy of the staging laparoscopy findings in determining disease resectability in patients with suspected advanced epithelial ovarian cancer. **(Van de Vrie et al., 2019)**

A total of 18 studies on 14 patient-cohorts were analyzed. Staging laparoscopy had overall a good accuracy compared to standard laparotomy except from the assessment of specific anatomical areas (e.g., retro-hepatic areas. The authors concluded that staging laparoscopy could be of benefit and should be adopted as a standard procedure in clinical practice. **(Van de Vrie R et al., 2019)**

The **National Comprehensive Cancer Network (NCCN)** guidelines include staging laparoscopy as a tool to determine whether advanced ovarian cancer patients should undergo primary cytoreductive surgery or neoadjuvant chemotherapy, with a category 2B level of evidence.

In conclusion, staging laparoscopy represent an easy and relatively low-morbid approach for the pre-operative assessment of advanced epithelial ovarian cancer patients. It can accurately predict

which patients will likely have a suboptimal cytoreduction at the time of primary cytoreductive surgery and would, therefore, benefit from neoadjuvant chemotherapy. **(Morotti et al., 2022)**

The utilization of staging laparoscopy 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 epithelial ovarian cancer, which is particularly relevant in those patients with poor performance status or "high-volume" stage IIIC or stage IV disease. **(Morotti et al., 2022)**

However, future high level evidence is warranted to confirm whether staging laparoscopy could be incorporated as standard clinical practice in the management of primary epithelial ovarian cancer. **(Morotti et al., 2022)**

2. **Primary debulking**

Only a few articles have been published describing primary laparoscopic cytoreduction.

Nezhat et al. reported an optimal cytoreduction rate of 88 % in a study series of 17 of 32 patients with advanced ovarian cancer who underwent MIS and had their tumors successfully debulked at laparoscopy. Patients undergoing laparoscopy had less blood loss and a shorter hospital stay compared with the laparotomy group, and no port-site metastases. DFS in the laparoscopic group was not inferior to that in the laparotomy patients. **(Nezhat et al., 2010)**

Fanning et al. published a study of 25 patients who underwent primary laparoscopic debulking and reported a cytoreduction rate of 92 %, with only two procedures converted to laparotomy. However, this case series had several limitations: The authors concluded that only 36 % of the patients had no residual disease, and they registered a postoperative complication rate of 24 %. **(Fanning et al., 2011)**

Based on a literature review by **Rabinovich**, robotic surgery appears to be adequate for debulking, exploring the abdomen and pelvis, and performing advanced procedures such as lymphadenectomy and omentectomy. **(Rabinovich, 2015)**

The author reported that the main advantage of laparoscopy is faster postoperative recovery compared with laparotomy. However, this study has several limitations, including its retrospective nature, evidence of biases in patient selection, and the lack of long-term follow-up to assess overall survival and PFS. **(Rabinovich, 2015)**

To date, minimally invasive surgery is not recommended for primary cytoreduction in advanced ovarian cancer patients. Large prospective trials are needed to assess the feasibility of primary laparoscopic-assisted cytoreduction, considering the real implications on the oncologic and surgical outcome and quality of life of these patients (LE IIIB). **(Fagotti et al., 2016)**

3. **Interval debulking surgery**

Current guidelines suggest administering neoadjuvant chemotherapy followed by interval debulking surgery in specific cases to reduce tumor size and increase the chances of optimal

cytoreduction. Laparoscopy may be performed at the time of interval debulking surgery to assess the response to chemotherapy and complete surgery. **(Fagotti et al., 2016)**

The current literature contains only a few studies, with a very low number of patients, on the role of minimally invasive surgery at the time of IDS, and no RCTs exist to clarify the oncologic impact of minimally invasive IDS (MI-IDS) in terms of survival rate. **(Favero et al., 2015)**

A retrospective review of data from 30 patients undergoing laparoscopic cytoreduction after neoadjuvant chemotherapy shows better perioperative outcomes, including median blood loss, median hospital stay, and intraoperative complications, than those from laparotomy series. **(Corrado et al., 2015)**

The use of S-LPS at the time of interval debulking surgery may be useful in planning the correct management of patients with partial or stable response to neoadjuvant chemotherapy. Future RCTs are needed to assess whether LPS-IDS may be performed safely in these patients. **(Fagotti et al., 2016)**

☒ **Recurrent ovarian cancer**

Patients with recurrent ovarian cancer may benefit from laparoscopy, which has several applications in this group, namely **(Fagotti et al., 2016)**:

1. To assess the extent of disease (especially peritoneal carcinomatosis).
2. To assess potential cytoreduction.
3. To reduce morbidity and mortality in cases of surgical treatment.
4. To reduce the length of time before starting systemic chemotherapy.
5. To integrate different treatments, such as hyperthermic intraperitoneal chemotherapy (HIPEC).

More importantly, it allows tumor biopsies for molecular analysis to individualize biologic therapy for each patient.

1. **Staging**

The integration of S-LPS with fluorodeoxyglucose positron emission tomography (FDG-PET)/CT can identify patients with peritoneal miliary carcinomatosis and extension of disease to the peritoneum or small bowel (S-LPS), and/or the presence of extra-abdominal disease and parenchymal/ lymph node metastases (FDG-PET/CT**). (Fanfani et al., 2014)**

2. **Treatment**

Considering the poor prognosis of most patients with recurrent ovarian cancer, laparoscopy may have not only a clinical and cost-effective advantage with respect to laparotomy but also a better physical and psychological impact on this subset of patients, improving their quality of life without compromising their survival. **(Fagotti et al., 2016)**

In the past years, several case series showed the feasibility of laparoscopy in debulking recurrent ovarian cancer. **(Escobar et al., 2014)**

These studies demonstrated that laparoscopy is feasible and safe for achieving cytoreduction in cases of localized recurrent ovarian cancer when used in tertiary referral centers by well-trained surgeons. **(Fagotti et al., 2016)**

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