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Feasibility and ability of laparoscopy to predict respectability in ovarian cancer: Review article

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Abstract--Background: Epithelial ovarian cancer is one of the leading causes of death in gynecological malignancies and the seventh most common cancer in the world among women. Aim and objectives: The main aim of this study was to study the feasibility and ability of laparoscopy in predicting optimum respectability in cases of ovarian cancer. Conclusion: Laparoscopy has an effective feasibility and ability in predicting optimum respectability in cases of ovarian cancer. As laparoscopy before starting treatment was a reliable additional diagnostic tool in predicting result of PDS, this can prevent laparotomies. This will optimize treatment for the individual patient.

Keywords--Laparoscopy, Chemotherapy, Adjuvant, Laparoscopes, Neoplasm

Introduction

Around the world, each year more than 225,000 women are diagnosed, and 140,000 women die from ovarian cancer. Ovarian cancer remains the fifth leading cause of cancer-related death (**Siegel, 2015**).

In Egypt cancer ovary is the 4th most common type of cancer affecting females representing 4.5% of all types. Epithelial ovarian carcinomas make up 90 to 95 percent of all types, (**Quirk, 2005**).

Approximately, two thirds of patients will have stage III-IV disease and sequenced multimodality therapy offers the most successful outcomes (**Earle, 2006**).

So primary surgical cytoreduction is generally performed whenever an optimal result is clinically feasible. The success rate of primary optimal cytoreduction for advanced ovarian cancers is highly variable, depending upon individual and institutional treatment philosophies and experiences. In centers with a particular interest and experience in cytoreductive surgery, rates of optimal resection are reported in 60-90% of cases (**Vergote et al 2010**).

However for the women with advanced ovarian cancer whom surgery might be suboptimum will have better prognosis if they have neoadjuvant chemotherapy and interval debulking. As a result, preoperative laparoscopic evaluation is being studied as a method for patient triage (**Morgan, 2014**).

Until now, the use of laparoscopic evaluation of resectability for advanced ovarian cancer still not well established and research is needed to evaluate the feasibility, risks, and usefulness of this approach.

The aim of this work was to study the feasibility and ability of laparoscopy in prediction of optimum resectability in cases of ovarian cancer.

Ovarian Cancer

Ovarian cancer (OC) is the leading cause of death in women diagnosed with gynecological cancers. It is also the fifth most frequent cause of death in women, in general. Most of the cases are diagnosed at an advanced stage, which leads to poor outcomes of this disease. The existing screening tests have a low predictive value contributing further to this misery. (**PDQ Adult Treatment Editorial Board, 2021**).

The standard line of care includes surgery and platinum-based chemotherapy. However, anti-angiogenic bevacizumab and Poly (ADP-ribose) polymerase (PARP) inhibitors have gained momentum in the management of this gynecological malignancy in the past decade (**Mancari et al., 2020**).

Predisposing factors

There are various risk factors associated with ovarian cancer. It mostly affects postmenopausal women, where increasing age is associated with an increased

incidence, advanced stage of this disease, and lower reported survival rates. The strongest risk factor of ovarian cancer is a positive family history of breast or ovarian cancer, where a personal history of breast cancer also augments the risk. Several studies have shown an increased risk of smoking, especially the risk of mucinous epithelial tumors (**Momenimovahed et al., 2019**).

Epidemiology

In 2020, there were approximately 21,750 new ovarian cancer cases all over the world, which comprise 1.2% of all cancer cases. The estimated number of deaths related to it is 13,940. The 5-year relative survival rate is expected to be 48.6%. Around 58% of cases presented at metastasized stage, where the 5-year survival dips down to 30.2% instead of 92.6% if detected at an early stage of local spread (**Siegel et al., 2020**).

In Egypt, **Ibrahim et al (2007)** showed that ovarian cancer represented 2.2 % of all incident cancers and accounted for 4.4% of all newly diagnosed female cancers. Another important regional registry in Egypt is the Aswan regional registry, in which thirty-five cases of ovarian cancer were registered in 2008, representing 5.6% of all female cancers cases (**Gharib et al., 2018**).

Mostafa et al (2012) evaluated ovarian cancer cases referred to and presented at the Alexandria Clinical Oncology Department (ACOD). They concluded that the age incidence of ovarian cancer in patients is 10 years younger than that seen in Western countries.

Histopathology and Molecular pathology

The four most common histological types of epithelial ovarian cancer are serous, endometrioid, clear cell, and mucinous tumor. They have further subtypes based on their peculiar biology and treatment responses. The uncommon subtypes are Brenner and seromucinous (**Arora et al., 2022**).

Ovarian cancer can be further classified into two subtypes- Type I or Type II tumors, the latter being a more fatal variant. Type I tumor includes low-grade serous, endometrioid, clear-cell, and mucinous carcinomas, with the rare subtypes being seromucinous and Brenner tumors (**Kurman et al., 2016**).

In contrast, the high-grade subtype (HGSC) shows significant nuclear atypia and mitosis (>12 per 10 high-power fields) with more copies of molecular abnormalities as seen by cytogenetic analysis. LGSCs are usually diagnosed at a young age and carry a better prognosis than HGSCs, which tend to present at an older age with a 10-year mortality rate of 70%. Further analysis revealed that a high frequency of KRAS and BRAF mutations are found in low-grade serous carcinoma, whereas high-grade serous carcinoma shows a high frequency of p53 and BRCA 1 and 2 genes mutations with an absence of KRAS/BRAF mutations (**Stewart et al., 2019**).

Ovarian mucinous carcinoma (MOC) is often heterogeneous, where a mixture of elements, including benign and malignant tumors, is found in a single specimen.

KRAS mutations are common in these tumors. There are two subtypes, endometrial and intestinal. As commonly associated with metastases from the gastrointestinal tract (GI), the intestinal subtype will show the presence of glands with architectural and cytology clinical features of adenocarcinoma; however, it may lack stromal invasion. Invasive mucinous carcinoma is uncommon, and the prognosis is found to be favorable compared to serous subtype, considering the mostly diagnosed at stage I itself, about 80%. The molecular alterations responsible for malignant conversion of the benign mucinous tumor are still unknown (**Babaier and Ghatage, 2020**).

Cytokeratin-7 (CK7) shows diffuse and strong staining in all serous ovarian tumors. It is positive in 80% to 100% of mucinous ovarian tumors, and other ovarian epithelial tumors also show positivity for CK7, while colorectal metastases are positive to CK20. About 96% of ovarian adenocarcinomas were positive for CK7 compared to metastatic colorectal, which shows about a 25% positivity (**Arora et al., 2022**).

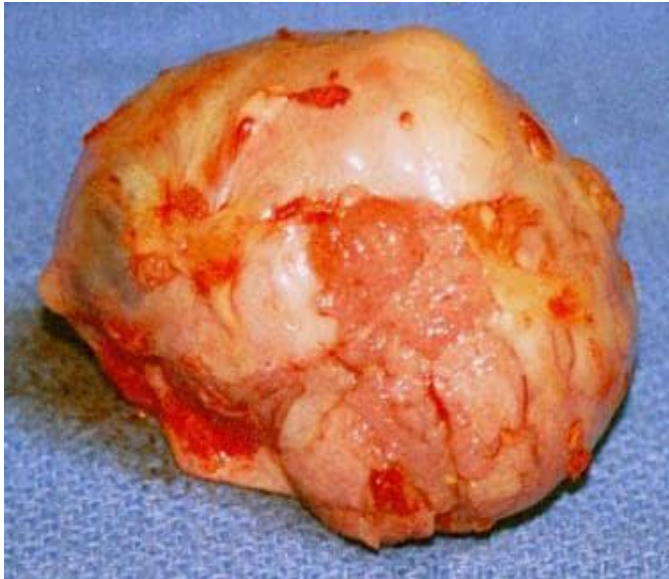


Figure 1: An enlarged ovary with a papillary serous carcinoma on the surface. From <https://emedicine.medscape.com/article/255771-overview>

A thorough physical examination should be done, including rectovaginal examination on an empty bladder to look for pelvic and abdominal masses in clinical cases of high suspicion. In advanced cases, a palpable pelvic mass or ascites or diminished breath sounds due to the presence of pleural effusions can also be found. As a result of metastases to the umbilicus, a sister Mary Joseph nodule will rarely be seen. Sign of Lesar-Trélat, which refers to a sudden increase in the finding of seborrheic keratosis, also gives a clinical clue indicating the presence of occult cancer (**Smith, 2017**).

Investigations

In patients with a high degree of clinical suspicion, radiological imaging including transvaginal ultrasonography (TVUS, highly sensitive and preferred) and/or transabdominal ultrasonography are done. Imaging gives a fair idea about the size, location, and complexity of the ovarian mass. For defining tumor extension, further imaging with chest and abdomen/pelvis CT scan, pelvic MRI, and/or PET scan can be done (**Arora et al., 2022**).

CA-125 levels can also be used to calculate the risk of malignancy index (RMI), which also utilizes TVUS findings and menopausal status. RMI above 200 is associated with a high risk of malignancy, with greater than 96 % specificity (**Dochez et al., 2019**).

The risk of malignancy algorithm (ROMA) utilizes a mathematical formula that incorporates HE-4 and CA 125 levels adjusted for pre and post-menopausal status to determine the risk of malignancy. The ROMA is a valuable screening test that takes advantage of the high specificity of HE4 and high-sensitivity of CA-125 to detect more patients of ovarian cancer overall, especially in the early stages (**Whitwell et al., 2020**).

It is followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) with para-aortic and pelvic lymph node dissection and omentum. The tissue biopsies evaluated by a pathologist help provide the final diagnosis concerning the histological type, grade, and staging (**Stewart et al., 2019**).

Management

Debulking Surgery

Treatment of ovarian cancer conventionally includes a combination of chemotherapy and surgery. For advanced-stage ovarian cancer, a debulking surgery comprising hysterectomy/bilateral salpingo-oophorectomy (BSO) has shown better outcomes. It is imperative to determine whether resectability would be beneficial for a patient by initially performing exploratory laparoscopic surgery (**Arora et al., 2022**).

Primary Debulking Surgery versus Neoadjuvant Chemotherapy

A gynecologic oncologist initially evaluates patients with suspected advanced stage IIIc or IV ovarian cancer to determine if they are appropriate surgical candidates or not. Neoadjuvant chemotherapy is recommended to decompress the tumor burden for the ones deemed poor surgical candidates with a low likelihood of optimal cytoreduction. According to the Society of Gynecologic Oncology (SGO) and American Society of clinical oncology (ASCO), clinical practice guidelines state that women with a favorable surgical profile can receive either neoadjuvant chemotherapy or undergo cytoreduction surgery (**Wright et al., 2016**).

In a pooled analysis of individual patient data from these two trials, EORTC 55971 and CHORUS trials, women with stage IV disease had better survival outcomes with neoadjuvant chemotherapy followed by cytoreductive surgery. An exploratory analysis of the EORTC 55971 randomized trial found that patients with stage IIIC (<4.5 cm) and less invasive metastatic tumors had better survival outcomes with primary cytoreductive surgery. In contrast, patients with stage IV disease (>4.5cm) and more invasive metastatic tumors had better survival outcomes with neoadjuvant chemotherapy (**van Meurs et al., 2013**).

Maximal Cytoreductive Surgery

One of the most powerful independent determinants of improved median survival among patients with stage III or IV ovarian carcinoma is to achieve maximal cytoreduction. Hence, irrespective of the surgery sequence, before or after neoadjuvant chemotherapy, optimal cytoreduction is strongly recommended to achieve ideally no residual disease.

Chemotherapy in Elderly

Elderly patients aged over 70 years or older with comorbidities who have stage III-IV ovarian cancer were studied in a randomized control trial, which showed worse survival outcomes with carboplatin monotherapy versus carboplatin-paclitaxel three weekly/weekly. But when combination therapy is being used, a modified dose-dense regimen of weekly carboplatin plus paclitaxel has shown to be better tolerated with a lower toxicity profile than the conventional dosing (three week's schedule) (**Pignata et al., 2014**).

An ongoing prospective trial of older women of age equal to or greater than 70 on different chemotherapy regimen combinations will help us predict chemotherapy tolerance. (**von Gruenigen et al., 2017**).

Maintenance Therapy

Maintenance therapy is conceptualized to ensure the effective killing of residual slowly dividing cells by decelerating the cell turnover so that the dormant population of cancer cells does not progress to grow enough to be detected by either elevation of biomarkers or clinical evidence of recurrent disease. Several randomized trials have been done to compare maintenance therapy versus observation (**Arora et al., 2022**).

A three-arm phase III trial following standard chemotherapy, GOG 0212, compared observation without immediate therapy to 12 months of paclitaxel or polyglutamated paclitaxel but showed disappointing results. To conclude, the results of maintenance, chemotherapy trials have been discouraging (**Khalique et al., 2014**).

Recurrent Ovarian Cancer

About 80% of women with advanced-stage ovarian cancer more commonly have tumor progression or recurrence. Platinum free interval (PFI) is one of the most

reliable predictors indicating the response of recurrent ovarian cancer to subsequent chemotherapy. PFI refers to the interval between the completion of the last platinum-based chemotherapy and the occurrence of relapse (**Luvero et al., 2014**).

Staging and assessment of Respectability in Ovarian Cancer.

Staging

Ovarian cancer is staged according to the 8th edition American Joint Committee of Cancer (AJCC), International Federation of Gynecology and Obstetrics (FIGO) staging system and corresponding Tumor, Node, Metastasis (TNM) classification (**Arora et al., 2022**).

Surgical Staging of Ovarian Cancer

Staging surgery for suspected early stage ovarian cancer includes the removal of all pelvic gynecologic organs: the uterus and cervix (total hysterectomy), both fallopian tubes and ovaries (bilateral salpingo-oophorectomy), a pelvic and para-aortic lymph node dissection (lymphadenectomy), removal of the omentum (omentectomy), peritoneal biopsies, and collection of pelvic fluid or washings. For mucinous carcinoma of the ovary, the rate of lymph node metastases is low and routine lymphadenectomy may be omitted (**Schmeler et al., 2010**).

Tumor markers

Carbohydrate antigen 125

Serum carbohydrate antigen 125, also called cancer antigen (CA-125), is the referent biomarker of ovarian cancer. Data on its utility in predicting resectability has been compiled in a meta-analysis. A preoperative serum level >500 U/mL showed a strong association with a risk of suboptimal cytoreduction, with an odds ratio of 3.69 (95% confidence interval (CI) = 2.02–6.73).(**Bendifallah et al., 2019**).

Human epididymis protein 4

Human epididymis protein 4 (HE4) has been proposed as a highly specific tumoral marker of ovarian malignancy. The preoperative serum level of HE4 has been shown to be predictive of optimal cytoreduction. **Paunovic et al., 2017**).

Predictive models based on tumor markers

Serum levels of CA-125 have been associated with other tumor markers in a mathematical model. Its association with serum HE4 levels in the risk of ovarian malignancy algorithm (ROMA) appears to be usable for diagnosis. The same mathematical model approach has been used to predict respectability. However, the limited number of studies, small sample size and poor sensitivity and specificity did not allow the demonstration of true efficacy (**Cui et al., 2019**).

Computed tomography

After clinical examination, imaging techniques are the first steps for assessing the spread of ovarian cancer and staging of the disease. Such mapping plays a major role in determining the treatment strategy. CT is the recommended imaging technique for the staging of ovarian cancer. CTs of the chest, abdomen, and pelvis with contrast-enhancement are recommended as standard procedures. **(American College of Radiology, 2018):**

The American College of Radiology (ACR) has listed the following items for assessing the resectability of ovarian cancer **(American College of Radiology, 2018):**

- lesions (>2 cm) at the root of the mesentery, gastrosplenic ligament, omentum of the lesser sac, porta hepatis, intersegmental fissure of the liver, diaphragm, liver dome and lung parenchyma
- lymphadenopathy at or above the celiac axis, presacral extraperitoneal disease,
- pelvic sidewall invasion. **(Roze et al., 2018).**

Positron emission tomography

Positron emission tomography (PET), using fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) as a tracer, combined with CT, has also been evaluated for the staging and prediction of resectability. This technique appears to be at least as accurate and probably more so in detecting lymph-node and distant metastases **(Khiewvan et al., 2017).**

Composite predictive model

Predictive models, other than that already discussed based on CA-125 levels, that combine several criteria have been tested. These models have various designs and can include tumor markers, imaging and clinical criteria, and imaging and biological criteria, such as platelet counts or CA-125 **(Suidan et al., 2017).**

The weakness of available scores and the technical progress in clinical practice have led to several successive updated versions of the PVI score. Although an improvement was reported, the negative predictive value was still poor, especially for parameters related to bowel infiltration. In addition, these new models have been included in the last Cochran review and are too recent to provide any data on survival outcome **(Petrillo et al., 2015).**

Laparotomy predictive scoring of resectability

None of previously cited strategies can predict resectability to no residual disease with a negligible margin of error. Consequently, evaluating the extent of the disease at the beginning of cytoreductive surgery is the ultimate step of the prediction of resectability process. The PCI was first described for assessing

gastrointestinal cancers and then used for ovarian cancers (**Kadhel et al., 2019**). There is also the Eisenkop score and that of **Aletti et al (2007)**.

Role of laparoscopy in ovarian cancer

It provides better treatment opportunities, improves the quality of life of patients, increases the survival rate of patients, and provides good living conditions. The treatment of early ovarian cancer is mainly carried out through surgery. Through the development of laparoscopic technology, more and more gynecological oncologists have also begun to apply laparoscopic technology to the treatment of ovarian cancer and found that they can reduce surgical trauma while treating diseases (**Hirabayashi et al., 2016**).

The role of laparoscopy in ovarian cancer surgery may be divided into the following categories (Vermeulen et al., 2021):

- 1- laparoscopic staging of apparent early ovarian cancer
- 2- laparoscopic assessment of disease extent and potential for resectability
- 3- hand-assisted laparoscopy for resection of selected cases of advanced ovarian cancer
- 4- Laparoscopic reassessment, or second-look operation, or rule out recurrence.

Laparoscopy to predict the result of primary cytoreductive surgery in advanced ovarian cancer patients

Selecting patients who benefit from primary debulking surgery, i.e. in whom complete surgery results are possible, should be optimized. In several institutes diagnostic laparoscopy is already standard of care to determine further treatment in ovarian cancer patients. Prospective and retrospective studies showed that predictability of surgical outcome with laparoscopy is better than that of standard diagnostic staging (**Brun et al., 2008**).

One strength of diagnostic laparoscopy is that initial evaluation can be performed, allowing the surgeon to directly visualize the tumor burden prior to making a decision on how to proceed. A 2005 study by **Fagotti et al (2005)** sought to determine the accuracy of laparoscopic assessment in a randomized clinical trial of 95 patients, 64 of whom met the inclusion criteria. (**Rutten et al., 2017**).

Kong et al (2021) concluded that laparoscopy and laparotomy appear to provide comparable survival outcomes, and laparoscopy might be an efficient and safe procedure for patients with eEOC.

Conclusion

Laparoscopy has an effective feasibility and ability in predicting optimum resectability in cases of ovarian cancer. Recurrence occurred in 26.3% of cases.

As laparoscopy before starting treatment was a reliable additional diagnostic tool in predicting result of PDS, this can prevent laparotomies. This will optimize treatment for the individual patient.

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