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Review

The impact of pleural disease on the management of advanced ovarian cancer

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HIGHLIGHTS

- Malignant pleural effusion is the most common site of stage IV EOC.
- PET/CT is able to identify stage IV EOC patients.
- VATS can alter the therapeutic management.

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ABSTRACT

Malignant pleural effusion is the most common site of stage IV ovarian cancer. A positive cytology is required for a stage IVA diagnosis. Unfortunately, the accuracy rate of pleural cytology remains low. A number of factors have been identified as prognostic for clinical outcomes in patients with epithelial ovarian cancer (EOC), the International Federation of Gynaecology and Obstetrics (FIGO) stage and residual tumor after debulking surgery being the most widely reported. Thereby careful selection of patients is crucially important, yet no preoperative predictor has proven sufficiently reliable to predict surgical outcome. The authors present a review of the literature on stage IV ovarian cancer specifically focusing on prognostic value of FIGO stage, preoperative workup, role of video-assisted thoracic surgery and maximal cytoreductive surgery.

Contents

1. Introduction

Ovarian cancer is the seventh most common cancer in women worldwide and their fifth leading cause of death. Every year, more than 225,000 women are globally diagnosed with ovarian cancer, with

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a lifetime risk of around 1:50. Despite continuous progress in imaging, more than 70% of patients was diagnosed at an advanced stage and will die of their disease with an overall five-year survival of less than 40%. Despite modern maximum surgical efforts and platinum based chemotherapy introduced over 30 years ago, survival rates of women with EOC has nevertheless changed very little.

The cornerstone of treatment of ovarian cancer is debulking surgery followed by combination taxane and platinum chemotherapy. Numerous factors have been identified as prognostic for clinical outcomes in patients with EOC, with the FIGO stage and residual volume of tumor after primary surgery being the most widely reported. In the last decade, the objective of EOC debulking surgery has evolved from residual tumor of <1 cm to no visible tumor. Whether this target is obtained in a primary debulking surgery or in an interval debulking surgery is still controversial. Vergote et al. in 2013 [1] proved in a randomized trial that neoadjuvant chemotherapy (3 cycles–interval debulking surgery–3 cycles) offered the same survival results as primary debulking surgery in stage IIIC and IV EOC patients. However, this study has received several criticisms mainly related to the heterogeneity of the surgeries performed. Looking into detail, this study showed that patients with peritoneal nodules of >5 cm may benefit from interval debulking surgery. It is common practice that neoadjuvant surgery is offered when an experienced and specialized surgical team deems that the amount and location of disease will not allow the optimal target of "no macroscopic disease" to be reached or if the patient is unfit for a major surgery. Thereby careful selection of patients is crucially important. However, no preoperative predictor has yet proven sufficiently reliable to predict surgical outcome. The presumed benefit of cytoreduction in stage IV patients is controversial.

In this study we review the literature on stage IV ovarian cancer specifically focusing on FIGO prognostic value, preoperative imaging techniques, maximal cytoreductive surgery and the role of video-assisted thoracic surgery (VATS).

2. Prognostic value of pleural involvement

The International Federation of Gynaecology and Obstetrics (FIGO) has recently made some changes in the staging classification of ovarian cancer in order to improve prognostic discrimination. Unlike other solid tumors, gynecologic cancers in general and ovarian cancer in particular, constitute a surgically staged disease. However, ovarian cancer is not a unique disease and stage IV includes a broad spectrum of disease. The new staging considers as stage IV those patients with distant metastases excluding peritoneal or retroperitoneal nodal disease below the diaphragm and makes a distinction between IVA — pleural effusion with positive cytology — and IVB — parenchymal metastases and metastases to extra-abdominal organs. Pleural effusion with negative cytology has not been taken into account.

Patients diagnosed with pleural effusions are reported to have poorer prognosis. Eitan et al. [2] reported a decrease in survival when comparing optimally cytoreduced stage IIIC patients with stage IV ones based solely on malignant effusions. Mironov et al. [3] in a series of 203 patients found that the presence of moderate-to-large pleural effusions was independently associated with poorer overall survival (after controlling for cytoreductive status).

Nevertheless, the diagnostic value of pleural cytology in the context of ovarian cancer has been recently challenged in several studies. Using video-assisted thoracoscopy (VATS) as gold standard, Juretzka et al. [4] found that in a cohort of patients with moderate to large pleural effusions VATS demonstrated macroscopic disease in 65% of patients, with nodules greater than 1 cm in 73%, and nodules of <1 cm in 27%. Among patients with negative cytology, 40% were found to have macroscopic disease. Similar results were found by Diaz et al. [5]. In their study, VATS revealed macroscopic disease in 69% of patients, with nodules of >1 cm present in 62% of them. Among the 11 patients with negative cytology, 36% had macroscopic disease.

Although these studies are limited by the small sample size and the restrictive inclusion of patients with only moderate to large pleural effusions, one might consider that pleural cytology may not be a reliable indicator of the presence of macroscopic disease.

Porcel et al. [7] analyzed retrospectively the etiologies of pleural effusion in a cohort of 3077 patients. In order of frequency, the etiology was cancer, heart failure, pneumonia and tuberculosis. They reported an overall accuracy rate of pleural fluid cytology of 59%. Another retrospective study of 414 patients with pleural effusions found that they were malignant in 67.9% of the patients. The author demonstrated that pleural malignant disease was diagnosed by cytology in only 57.6% of the patients [8].

Another issue regarding pleural involvement is the respective prognostic impact of abdominal and pleural tumor burden. At the time of initial diagnosis, up to 70% of patients has peritoneal involvement. Güth et al. [9] showed in autopsy findings that among 166 patients with advanced EOC, only 2 had no peritoneal involvement of disease at the time of death and death from OC is associated with tumor dissemination to the peritoneum in nearly all patients.

In a retrospective study conducted by Winter et al. [6] data from 360 patients with stage IV showed that malignant pleural effusion was the most common site of stage IV disease. The authors showed that neither disease progression nor survival was different between patients with 0.1 to 1 cm and those with 1.1 to 5 cm of residual disease. No difference in outcomes if the remaining disease was located intra- and/or extra-peritoneal or intraparenchymal. In this study, stage IV patients had a median OS that was comparable with that of stage III patients.

Patients with pleural disease that is considered to be resectable to microscopic disease might therefore be good candidates for ultraradical cytoreductive surgery.

Aletti et al. [10] found in a retrospective study that for patients with positive pleural cytology the abdominal peritoneum was the most frequent site of disease recurrence and that three-fourths of patients presented malignant pleural effusion at the time of death when it was present at initial diagnosis. They concluded that the initial site of stage IV disease is strongly predictive of disease site at the time of initial failure and death. Whether these patterns of spreading would change due to targeted therapy is an interesting question. Tanner et al. [11] found that patients receiving adjuvant IP chemotherapy are less likely to first recur in the lower abdomen or pelvis and more likely to recur outside the abdominal cavity. Likewise, Rauh-Hain et al. [12] demonstrated in a cohort of 292 patients that those who received bevacizumab as part of primary treatment had a higher rate of lung and/or pleural recurrence and a lower rate of liver recurrence.

3. Preoperative workup

According to FIGO guidelines [13] any imaging tool can be used to diagnose distant metastases. The recommended preoperative workup comprises abdominal computed tomography (CT) and chest X-ray to detect pleural disease.

The differential diagnosis of pleural effusion may be very difficult although symptoms may prove very helpful for evaluating the different causes of the pleural effusions, like fever, weight loss or hemoptysis. A chest radiograph remains the most common tool used for the diagnosis of pleural effusions. Useful radiological signs in pleural effusions are blunting of the costophrenic angle, density of the hemithorax and loss of the hemidiaphragm [14]. However, most of these signs do not appear until the pleural fluid is over 200 mL. In a prospective study of 36 pleural effusions [15], 24 were correctly identified in anteroposterior supine radiographs (sensitivity of 67%, specificity of 70%). Another prospective study including 320 pleural cavities showed that pleural effusion was correctly identified by supine chest radiograph in only 55% of cases [16]. A normal supine radiograph does not exclude a pleural effusion.

CT has showed high accuracy ranging from 60 to 90% in staging the extent of disease but low sensitivity in the small-bowel mesentery and