Impact of Open Laparoscopy in Patients Under Suspicion of Ovarian Cancer

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Abstract. *Background/Aim: Feasibility and value of diagnostic open laparoscopy (DOL) was assessed in patients presenting under suspicion of advanced ovarian cancer (AOC) mostly with large-volume ascites. Patients and Methods: This retrospective study analyzed 143 consecutive patients who underwent DOL for histopathological verification of AOC performed from 2002 to 2012. Results: Out of the 143 patients presenting at our Center with an ovarian mass and mostly with ascites under suspicion of ovarian cancer, we diagnosed 125 AOCs, three AOCs with three concomitant tumors of other origin, and 15 other diseases causing an ovarian mass and ascites mimicking AOC (e.g. gastrointestinal malignancies, tuberculosis, mesothelioma, endometrial cancer and benign conditions). Conclusion: DOL can be considered a valid and safe diagnostic tool for histopathologically verifying epithetlial ovarian cancer and preventing patients with other diagnoses undergoing the wrong course of therapy.*

Worldwide, epithelial ovarian cancer (EOC) is one of the leading causes of death due to gynecological malignancy and the seventh most common cancer among women with an annual incidence of 239,000 (1). Diagnosis is most commonly made at advanced stages, when cancer already has spread to the whole abdominal cavity and other compartments (2).

Having set the tentative diagnosis of ovarian cancer for a patient, standard work-up includes a clinical examination, gynecological workup consisting of a vaginal palpation, transvaginal and abdominal ultrasonography, and measurement of the tumor markers [*e.g.* cancer antigen 125 (CA 125) and carcinoembryonic antigen (CEA) (3, 4). To generate further information, additional radiological studies such as a computed-tomography (CT) (5, 6) a magnetic resonance imaging (MRI) (7) or positron-emission tomography (PET/CT) can be performed (8).

Therapeutic strategies include optimal cytoreductive surgery ("no residual tumor") and a platinum- and taxane-based chemotherapy. Chronological sequence of surgery and chemotherapy can vary (adjuvant or neoadjuvant regimen). For patients who are thought to have operable disease, lack of ascites and a good performance status primary debulking surgery (PDS should be attempted). All other patients may benefit from neoadjuvant chemotherapy followed by interval debulking surgery (IDS) and afterwards the completion of chemotherapy, which has been shown by several investigations such as the EORTC 55971 trial, and more recently by the CHORUS trial (9-11). Yet the ability of the standard diagnostic work-up to predict which patients might benefit from primary surgery is low, resulting in 25% to 62% of patients undergoing primary surgery with residual tumor more than 1 cm in diameter (10, 12, 13). The neoadjuvant concept uses ascites as a biomarker for resectability and prognosis. The presence of malignant ascites is an established independent prognostic factor in retrospective and prospective analyses (14). A large amount of ascites (>500 ml) is consistent with diffuse peritoneal carcinomatosis and correlates with a low probability of achieving optimal tumor resection (9). Diagnostic open laparoscopy (DOL) is a safe procedure that allows visualization of the contents of the patients abdomen and pelvis transcutaneously using a camera system. In our cohort, DOL is performed to visualize the tumor burden, measure or estimate the amount of ascites and histologically prove the diagnosis.

An important aspect of DOL but one neglected in literature is the fact that in patients finally diagnosed with other diseases, invasive laparotomy can be prevented. No source of literature was found dealing with this topic.

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Key Words: Advanced ovarian cancer, ascites, diagnostic open laparoscopy, epithelial ovarian cancer, neoadjuvant chemotherapy, primary debulking surgery, sampling.

This study was explicitly conducted to evaluate the number of patients who can be spared PDS due to diagnosis other than EOC when histopathological proof has not been obtained, rather than to examine or validate any scores of resectability of AOC.

Patients and Methods

We conducted a retrospective analysis of 143 consecutive patients who underwent DOL before neoadjuvant treatment or with inconclusive findings during workup, without ascites, under suspicion of suffering from advanced ovarian cancer between 2002 and 2012.

DOL was performed after clinical and gynecological examination, laboratory testing (blood count, CA 125, CEA), abdominal and transvaginal ultrasound and computed tomography or magnetic resonance imaging if results altogether suggested the diagnosis of AOC verified by our interdisciplinary tumor conference. After DOL, patients then were treated according to the neoadjuvant treatment concept or in the case of other diagnosis to the therapy of the national guidelines.

Patient records and surgical statistics were retrospectively screened for relevant data and documented in Microsoft Excel 2013 strictly anonymously.

Surgical technique. A horizontal incision of approximately 12-15 mm was made in the lower umbilical plica. The rectus sheath was then identified and incised horizontally. Afterwards, the peritoneum was opened and fascia and peritoneum secured with two Vicryl 2-0 sutures at the upper and the lower aspect of the incision. Under visual control, a 11-mm trocar was introduced into the abdominal cavity. Once the trocar was positioned correctly, and fixed by the two Vicryl 2-0 sutures previously set. Next carbon dioxide was insufflated to create a pneumoperitoneum. A 6-mm trocar was then inserted under direct view medially of the anterior iliac spine on the surgeon's site. An attempt was made to inspect the entire abdominal cavity systematically by using atraumatic forceps; the ovaries, fallopian tubes, uterus, pelvic peritoneum, serosa and mesentery of the large and small bowel, liver surface, paracolic gutters and diaphragm were visualized accurately. If necessary, an additional 6 mm trocar was introduced contralaterally to allow better dissection of adhesions with scissors and better manipulation of the bowel. Ascites was removed and preserved for later use in diagnosis. Biopsy specimens of the ovaries, metastatic nodules or peritoneal surface were taken and sent to the pathologist. At the end of the procedure, all abdominal layers were closed separately. Monocryl 2-0 was used for the subcutaneous closure and nylon 3-0 for the skin with a subcuticular suture. The 5 mm port site incisions were closed with a subcuticular suture only.

Ethical Approval. The protocol of this study was submitted to the Ethics Committee of the University of Bonn for consideration. Because of the strictly anonymous collection of data, the commission saw no reason to analyze the protocol in detail. No restrictions or objections were raised.

Results

One hundred and forty-three (n=143) patients with an ovarian mass and ascites or inconclusive findings during the examination, suspected as having AOC underwent DOL between 2002 and 2012.

Table I. *Patient data*.

Variable	Max	Min	Mean	Median
Age, years	81.4	27.4	59.4	59.7
CA 125 (at admission), U/ml	17,990	17.9	1,986.4	906
Duration of surgery, min	70	15	42.6	45
Amount of ascites, ml	15,000	20	1,898.7	1,300

Basic patient data are summarized in Table I. Reasons for presentation were abdominal discomfort (56.64%, n=81), pain (20.98%, n=30), constipation (0.7%, n=1), other reasons (including weakness, weight loss, dyspnea, urinary stasis and gastrointestinal discomfort (nausea, vomitus, heartburn, biliary colic; 9.79%, n=14) or a general checkup (11.89%, n=17). The median age of the patients was 59.7 years (range=27.4-81.4 years). All patients underwent transvaginal and abdominal ultrasonography examinations before surgery (100%, n=143). Clinical examination suggested ascites under 500 ml in 19.58% (n=28) and more than 500 ml in 80.42% (n=115) of cases.

The median CA 125 level was 906 U/ml (range=17.9-17,990 U/ml). All cases had CEA values within established physiological reference ranges.

DOL lasted between 15 and 70 min (median=45 minutes, n=143). The median amount of ascites extracted during DOL was 1,300 ml (range: 20-15,000 ml). Surgery was performed without complications in 97.2% (n=139) of cases, whereas in 2.8% (n=4), complications occurred. In one patient, a bowel lesion due to distinct adhesions and adhesiolysis occurred and was managed by serosal suturing. Two intra-abdominal bleedings due to massive adhesions and one subcutaneous bleeding on the trocar-insertion site were managed by coagulation, there was no need for secondary surgery.

Cytological specimens were taken during all surgeries (100%, n=143). A total of 78.32% (n=112) of specimens showed malignant cells, whereas no malignant cells were detectable in 20.28% (n=29) and in 1.4% (n=2), cells in the specimens could not be determined.

Histopathology reports obtained during DOLs revealed 125 AOCs (87.4%), three AOCs with three concomitant tumors of other origin (2.1%), and 15 cases of other disease (10.5%) (Figure 1). The three AOCs with concomitant tumors were associated with pseudomyxoma peritonei, rectal cancer and endometrial cancer. The 15 other diseases mimicking AOCs were two cases of peritoneal tuberculosis, two of colonic cancer, two of gastric cancer, two of metastasized breast cancer, one of sclerosing peritonitis, one of esophageal cancer, one of Krukenberg tumor (signet ring cell carcinoma), one of pancreatic cancer, one of peritoneal mesothelioma, one with intestinal carcinoma of unknown origin and one of Meigs syndrome.

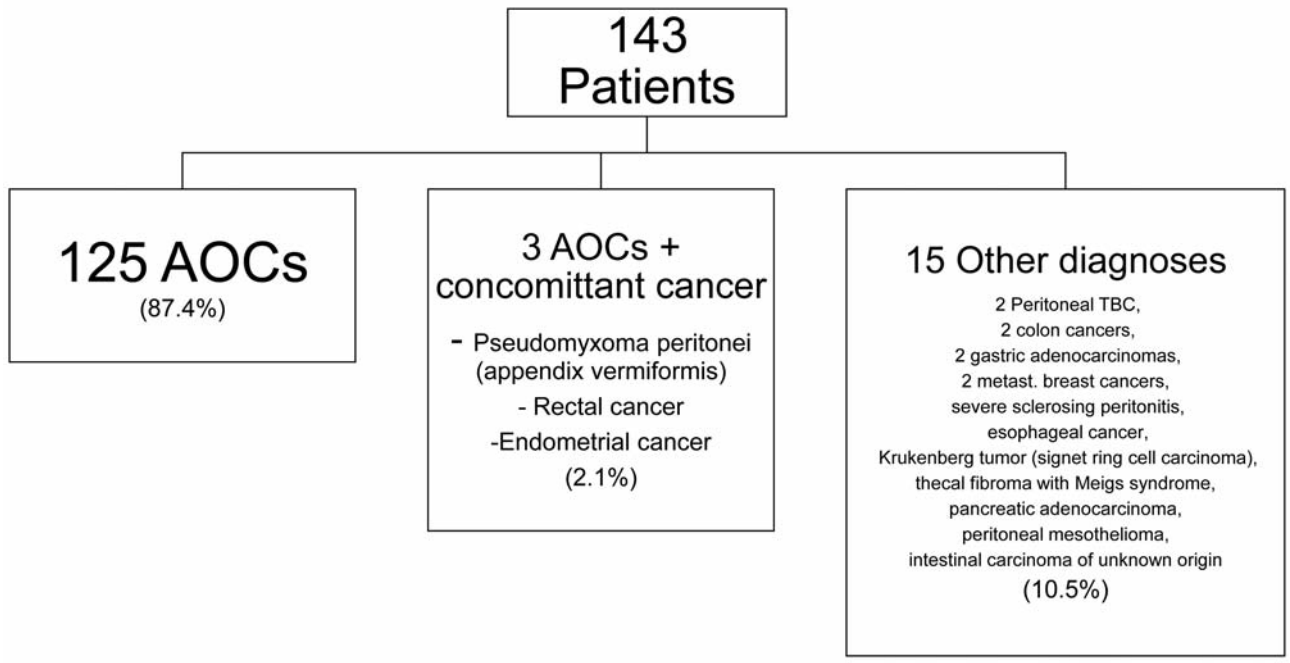

Figure 1. *Distribution of diagnoses in the investigated cohort of 143 women mostly presenting with ascites and under suspicion of advanced ovarian cancer (AOC). TBC: Tuberculosis.*

Discussion

Complete resection of all macroscopic disease at primary debulking surgery has definitely been established to be the single most important independent prognostic factor in advanced ovarian carcinoma (15-17). Current discussions on the implementation of DOL in the general workup of patients with AOC focus on the question whether determination of complete resectability of disease is better predictable by DOL (18-20).

Yet it is not clear if DOL is an adequate tool to forecast complete resection (18). This article does not deal with this aspect but focuses on DOL within the concept of neoadjuvant treatment or primary debulking in AOC and the diagnosis of diseases other than AOC.

Over the past couple of years there seems to be a change of paradigm. Neoadjuvant chemotherapy has been introduced as one appropriate option in AOC.

Overall survival (OS) has been described as being similar in patients treated with neoadjuvant chemotherapy and IDS compared with the standard approach of primary surgery followed by chemotherapy [AOC International Federation of Gynecology and Obstetrics (FIGO) stage III and IV with stage III meaning that the tumor involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis/metastasis to the retroperitoneal lymph nodes, or in the case of stage IV, distant metastasis excluding peritoneal metastasis). Moreover, peri- and postoperative morbidity seems to be lower in patients treated with IDS after neoadjuvant chemotherapy (10, 21). Our group demonstrated that patients with AOC (FIGO III, FIGO IVa) with diffuse peritoneal carcinosis detectable by large ascites volume (>500 ml) as surrogate marker benefit from neoadjuvant chemotherapy in terms of survival time and less perioperative morbidity (9, 13, 21). DOL is, as shown, an important first step to identify patients for or exclude them from the neoadjuvant treatment concept by measuring or estimating the ascites volume and especially delivering histopathological samples.

CT-guided biopsy might be an alternative approach to obtaining a histological specimen of detected tumorous lesions. Our experience shows that such an approach is suitable for only a small percentage of patients due to several burdens. For CT-guided biopsy, tumors have to be at least 1 cm in diameter or larger, which excludes the frequent miliar peritoneal manifestations. Furthermore, lesions which are surrounded by fatty tissue often do not allow the tumor to be punctured, which precludes biopsy. The access to the abdominal cavity *via* CT-guided puncture using a ventral approach is often impractical due to anatomical reasons (*e.g.* bladder, bowel, bowel movements and adhesions). Other approaches for obtaining histological specimens by CT-guided puncture used access through the transpiriform-muscle, transgluteal, the posterior oblique approach in prone position, the iliopsoas muscle, or a direct transosseous

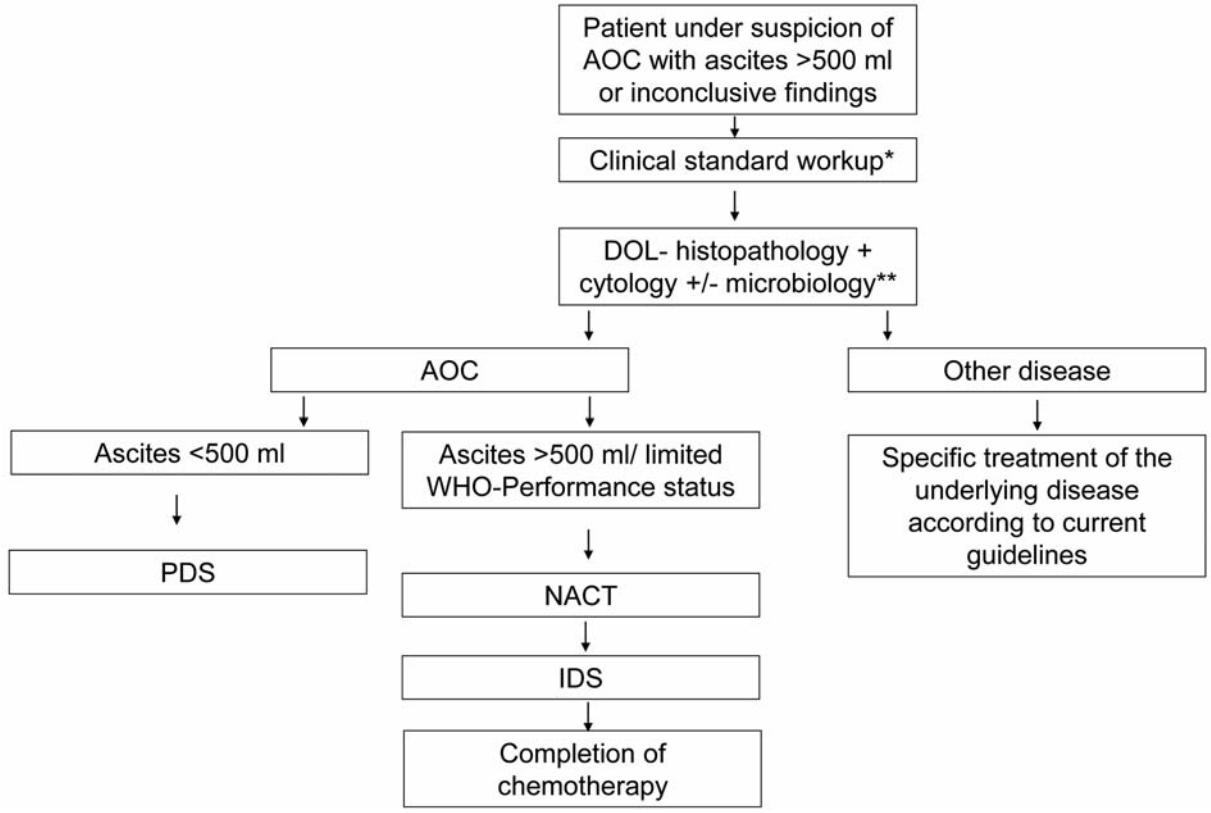

Figure 2. *Suggestion for the workup of patients under suspicion of advanced ovarian cancer (AOC). Laparoscopy is used as a triage test. Diagnostic open laparoscopy (DOL) is performed in patients with ovarian masses mostly with ascites under suspicion of AOC when computed tomography (CT)-guided biopsy is not possible/available. If laparoscopy histopathologically diagnoses AOC and ascites >500 ml, patients can avoid undergoing primary debulking and will be treated according to the neoadjuvant treatment concept [patients <500 ml ascites underwent primary debulking surgery (PDS)]. Patients with other diseases will be spared laparotomy and undergo standard treatment for their specific disease. CA 125; Cancer antigen 125; CEA: carcinoembryonic antigen; MRI: magnetic resonance imaging; NACT: neoadjuvant chemotherapy; IDS: interval debulking surgery. *Clinical examination, gynecological examination, transvaginal and abdominal ultrasonography, laboratory testings (blood count, CA 125, CEA, creatinine), additional radiological study (CT or MRI abdomen/pelvis). **In some cases CT-guided biopsy may be favorable.*

approach are not common, lack experience and data, and may be associated with transient pelvic pain (22).

Within the presented selection procedure by performing DOL, the exclusion of other primary tumors, especially those of gastrointestinal origin, is possible. Diseases that are known to mimic AOC, such as Krukenberg tumors (23), peritoneal tuberculosis (24-26), peritoneal mesotheliomas (27) and abdominal lymphomas (28), have been described.

This study clearly shows that this is another beneficial aspect associated with DOL: 10.5% of patients under suspicion of AOC suffered from diseases other than AOC, and 2.1% (Figure 1) suffered from a concomitant disease which complicates the choice of therapy and they, therefore, would not have been treated appropriately and be harmed by the performance of an unnecessary laparotomy. Thus, treatment for this cohort of patients is different from those of patients with AOC, most not demanding radical debulking procedures but therapy such as hyperthermic intraperitoneal chemotherapy (mesothelioma), neoadjuvant radiochemotherapy (rectal cancer, esophageal cancer), neoadjuvant chemotherapy (gastric cancer), less invasive surgeries than large debulking-laparotomies or basic regimens of combined antibiotics (tuberculosis), or other medications (sclerosing peritonitis).

Although DOL remains an invasive procedure under general anesthesia, surgical complication rates, as described in this evaluation, are few and comparable with those in literature (29-31). Therefore, DOL seems to be a safe and feasible diagnostic procedure. Figure 2 shows our suggestion for the workup in patients under suspicion of suffering from AOC, not yet histopathologically verified. The suggested workup is tailored to patients in evaluation of ovarian masses and ascites under suspicion of AOC and includes the positive side-effect of diagnosing diseases other than AOC, which therefore do not undergo laparotomy.

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Conflicts of Interest

The Authors declare that they have no conflict of interest.

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