Incomplete surgical staging in clinical early-stage ovarian cancer: guidelines versus daily practice

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A R T I C L E   I N F O
Article history:
Received 25 May 2021
Received in revised form 8 September 2021
Accepted 16 September 2021
Available online 14 October 2021

Keywords:
Ovarian cancer
Surgical oncology
Staging
Lymph nodes

A B S T R A C T

Background: Incomplete surgical staging of patients with early-stage epithelial ovarian cancer (EOC) has been reported in up to 98% of cases, when based on the International Federation of Obstetrics and Gynecology (FIGO) staging procedure. The aim of the present retrospective study was to clarify the reasons for incomplete staging.

Methods: The PRISMA (Prevention Recovery Information System for Monitoring and Analysis) technique was used to evaluate cases with FIGO I-IIa EOC based on incomplete staging from five gynecologic oncologic center hospitals in the Netherlands in the period 2010–2014.

Results: Fifty cases with an incomplete surgical staging of EOC according to national guidelines were included. The most common reasons for incomplete staging were insufficient random biopsies of the peritoneum (n = 34, 68%), and less than ten lymph nodes being resected and/or found at pathology (n = 16, 32%). The most mentioned reason for not performing biopsies was, besides forgetting to do so, believing that after careful inspection and palpation, taking biopsies is irrelevant and/or already are being taken while performing a hysterectomy (peritoneum of cul-de-sac, bladder). The value of contralateral pelvic lymph node dissection in case of a unilateral ovarian malignancy was also doubted, influencing the number of lymph nodes resected.

Conclusions: The most important reasons for incomplete staging in EOC are, besides omitting elements by accident, questioning the importance of obligatory elements of the staging procedure. A structured list of staging steps during surgery and more evidence-based consensus concerning these obligatory elements might increase the number of complete staging procedures in EOC.

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Introduction

In newly diagnosed clinical early-stage epithelial ovarian cancer (EOC), the aim of surgery is to resect the tumor combined with an adequate staging procedure. This will provide prognostic information by means of the definite stage and will define whether adjuvant chemotherapy is needed or can be safely omitted [11]. According to the International Federation of Obstetrics and Gynecology (FIGO) a staging procedure should include a peritoneal washing or a sample of ascites, hysterectomy and bilateral oophorectomy, infracolic omentectomy (complete, partial or biopsies), numerous peritoneal biopsies from several locations at risk for tumor implantation, pelvic and para-aortic lymphadenectomy and biopsies of suspected lesions and adhesions.
subsequently classification can be used to provide a more realistic view of daily practice [10]. In considering with the PRISMA-Medical method, the results of this analysis indicate that active failures (human error) and latent conditions (technical and organizational failures) surrounding incidents are systematically analyzed and discussed with the gynecologists of each participating hospital, seven patients (12%) appeared to have had a complete staging after all, but were interpreted differently during selection by the NCR data managers. In two of these cases the location of the aorto caval lymph node dissection was not well described, and in five cases the gynecologist used anatomical terms describing the location that were unfamiliar to the data managers. Therewith, 50 cases remained for inclusion in this study.

Most patients (n = 34, 68%) underwent one operation, all laparotomies with frozen section. In 15 patients (30%) a second operation was performed (of which laparoscopic in 10 patients), and in one patient (2%) despite three surgical procedures (two laparotomies and one laparoscopy) the staging procedure still was incomplete. Nineteen patients (38%) received adjuvant chemotherapy. In two cases, it was unknown whether adjuvant chemotherapy was given (4%) and one patient refused chemotherapy. For the remaining 29 patients (58%), according to the gynecologic oncologist, there was no indication for adjuvant chemotherapy because the FIGO stage was based on a complete staging procedure.

Incomplete staging.

The number of missing elements was one in 12 patients (24%), two in 17 patients (34%), three in eight patients (16%), four in four patients (8%), five in four patients (8%), and six or more in the remaining five patients (10%).

Table 1 shows incompleteness of the staging procedure with respect to the different elements. The most frequent reason for incomplete staging was insufficient peritoneal biopsies of the different locations (n = 34; 68%). Reasons for not performing certain biopsies were 1) simply forgetting to do so (n = 11, 2) presumption that the biopsy (cul-de-sac and bladder peritoneum) is already part of the hysterectomy (n = 5), 3) the opinion of the surgeon that after careful inspection taking biopsies of macroscopically normal peritoneum is irrelevant (n = 6), 4) chemotherapy already being indicated (i.e. based on peroperative findings such as rigid adhesions of the ovarian tumor to the pelvic wall), hence complete staging would not be contributory (n = 6), 5) technical problems (n = 3),
6) comorbidity or malignancy elsewhere (n = 2), and 7) the wish of the patient to not receive adjuvant therapy (n = 1) (Fig. 2).

In eight patients (16%) no lymph nodes were resected, either because it was technically impossible (n = 4) or because the outcome of the lymph nodes, according to the gynecologist, had no therapeutic consequences (n = 4, Fig. 2). In 25 patients (50%) no contralateral pelvic lymph nodes were resected. In eight patients (16%) the number of resected lymph nodes was less than ten. This could be partly explained by the fact that in five of these patients only lymph nodes were resected on the ipsilateral pelvic region. Furthermore, although according to the gynecologist enough tissue was resected from the para-aortic region, the pathologist did not identify any lymph nodes in one patient (2%). Taking ascites or peritoneal washing was omitted by accident in 12 patients (24%), taking biopsies from adhesions surrounding the tumor was omitted in 14%, an omentum biopsy or omentectomy in 2%, and a biopsy was not performed in three patients (6%), but one patient refused. The second patient, 25 years of age with a mucinous subtype carcinoma, underwent a second surgical procedure to complete the staging process in which, except leaving uterus and other normal-looking adenx in situ (fertility wish), no high para-aortal / paracaval lymph nodes were resected, and less than 5 peritoneal biopsies were taken. In this case, the surgeon took retroperitoneal tissue in the upper para-aortic and para-caval region, in which the pathologist however did not identify any lymph nodes.

**Discussion**

In this retrospective analysis we found that incomplete staging in EOC, performed by gynecologic oncologists, is most often due to insufficient biopsies of different locations of the peritoneum (n = 34; 68%), and less than ten lymph nodes being resected and/or found at pathology (n = 16; 32%). The most mentioned reason for not performing biopsies was, besides forgetting to do so, believing that after careful inspection and palpation, taking blind biopsies is irrelevant and/or biopsies already are being taken while performing a hysterectomy (peritoneum of the cul-de-sac, broad ligament and bladder). Forgetting to take blind biopsies was registered in 11 cases and there can be little excuse to justify such negligence. Ten patients died within five years. Seven of these patients obtained adjuvant chemotherapy in addition to the staging procedure, and one patient refused adjuvant chemotherapy offered. The remaining two patients were young of age (both 25 years), and despite an incomplete staging with respect to both peritoneal biopsies and lymph nodes, no adjuvant chemotherapy was offered.

Previous studies report incidences of incomplete staging up to 98% [3,5–8]. In the majority of these patients no or inadequate lymph node resection was performed, but also no or an insufficient number of random peritoneal biopsies was frequently found [3,8]. Studies reporting on treated patients before 2000 conclude that lack of specialized skills and/or knowledge of the gynecologist might be a possible explanation for incomplete staging [3,5,6,12]. However, in the present study only gynecologic oncological center hospitals were included of which one can assume that they do have the skills and knowledge that is required. Nevertheless, taking blind biopsies was simply forgotten in about one third (11/34) of the incomplete biopsy cases. A standardized surgical report, and check lists with all parts of the staging procedure according to the FIGO guidelines available in the operation rooms, might be a solution to forgetting parts of the procedure.

It has been argued that upstaging of EOC on the basis of solely positive blind biopsies is low and therefore that taking blind biopsies is unnecessary. [8]. But this would be true for most of the different staging steps. In two reviews on surgical staging of EOC the average yield of positive blind biopsies of the peritoneum in a number of studies were found in 1.2 up to 9.3% [13,14]. From a more general perspective, it can be said that random peritoneal biopsies are recommended at an early stage of the disease, because it takes little extra time, entails almost no extra morbidity, and may result in a higher FIGO stage with thus therapeutic consequences. Furthermore, systematic peritoneal biopsies ensure careful palpation and examination of all surfaces. The latter notion is the more important in view of the recent trend to perform staging of EOC laparoscopically, therewith losing the contribution of palpating subperitoneal abnormalities [15].

Adequate lymph node sampling appears to be an essential part of the staging procedure in clinical early stage EOC. In a review on lymph node metastases, the overall incidence varied from 6.1% to 29.6% (mean 14.2%) [16]. Despite its importance, the reported incidence of lymph node staging worldwide varies between 10% and 30% [17]. In a recent report on lymph node staging in The Netherlands, the incidence of lymph node dissection improved from 26% in 2000 to 67% in 2012. Moreover, the percentage of patients from whom 10 or more lymph nodes were removed also increased during the study period (from 2.3% to 47.6%) [18]. In the present study, in 16 patients with an incomplete staging procedure (32%), either no lymph nodes were resected or the number of lymph nodes identified was below ten. Various reasons for this were mentioned by the gynecologists. First of all, in five patients no lymph nodes were resected because it had no therapeutic

### Table 1

| Part of staging procedure | n (%) | Complete | Incomplete | Inapplicable |
|---------------------------|-------|----------|------------|--------------|
| Ascites                   | 39 (78%) | 12 (24%) | 25 (52%) |
| Ovary and uterus          | 45 (90%) | 5 (10%) | 30 (60%) |
| Omentum                  | 48 (96%) | 2 (4%) | 46 (96%) |
| Biopsies (> 4)            | 16 (32%) | 34 (68%) | 0 (0%) |
| Douglas                   | 23 (46%) | 27 (54%) | 0 (0%) |
| Bladder peritoneum        | 32 (64%) | 18 (36%) | 0 (0%) |
| Fossa ovarica right       | 9 (18%) | 41 (82%) | 0 (0%) |
| Fossa ovarica left        | 11 (22%) | 32 (68%) | 0 (0%) |
| Paracolic right           | 37 (74%) | 13 (26%) | 0 (0%) |
| Paracolic left            | 37 (74%) | 13 (26%) | 0 (0%) |
| Diaphragm                 | 25 (50%) | 25 (50%) | 0 (0%) |
| Lymph nodes (≥ 10)        | 34 (68%) | 16 (32%) | 0 (0%) |
| Lymph nodes location      |       |          |            |
| - Aortocaval high         | 25 (50%) | 25 (50%) | 0 (0%) |
| - Pelvic isilateral       | 41 (82%) | 9 (18%) | 0 (0%) |
| - Pelvic contralateral    | 25 (50%) | 25 (50%) | 0 (0%) |
| Suspicious lesions        | 30 (60%) | 1 (2%) | 19 (38%) |
| Adhesions with tumor      | 31 (62%) | 7 (14%) | 12 (24%) |
consequences according to the gynecologist (already indication for adjuvant chemotherapy, i.e. the presence of rigid adhesions of the ovarian tumor to the pelvic wall clinically appropriate for FIGO stage IIB). In another four patients it was mentioned that the procedure was technically impossible, mainly related to intense intra-abdominal adhesions, extensive blood loss and/or obesity. Secondly, although according to the gynecologist enough tissue at the different pelvic and para-aortal locations were sampled, the number of lymph nodes identified by the
pathologist were less than ten, hence insufficient according to the Dutch guideline. This could be partly explained by the fact that in five patients, pelvic lymph nodes were obtained only at the ipsilateral side. In 25 patients (50%), including these five patients, the value of a contralateral pelvic lymphadenectomy in case of a unilateral ovarian tumor was questioned and therefore omitted. In the already mentioned review examining the incidence and locations of lymph node metastases in early stage EOC, 20% of all lymph node metastases were located at the pelvic regions only. Only contralateral lymph node metastases of a unilateral tumor were found in 16% of positive pelvic nodes and 11% of positive paraaortic nodes [16]. These findings provide a strong argument against an ipsilateral node dissection only. Current research into the feasibility of sentinel node detection in ovarian cancer would be a welcome alternative [19].

Besides the resection of not enough fatty tissue containing the lymph nodes by the gynecologist, the pathologist examining the tissue resected may influence the definite number of lymph nodes recognized. In a study observing the impact of nodal retrieval after educating the pathologist, it was found that extra education about the importance of nodal count significantly increased the nodal count at pathology [20]. New pathological methods are being investigated and have shown promising results. Svec et al. showed that re-fixing in a lymph node revealing solution containing ethanol, diethyl ether, glacial acetic acid and formalin, increased the number of revealed lymph nodes in colorectal resection specimens [21]. In another study comparing standard formalin fixation with fat-clearing by acetone in specimens after gastrectomy, more lymph nodes were found using acetone, though this was not statistically significant. More high-quality trials are needed to study the optimal technique for retrieving lymph nodes at pathology.

Complete staging has been proven to be an important prognostic factor in EOC [4,18]. There is evidence that, in contrast to incompletely staged patients, adjuvant chemotherapy in completely staged patients does not improve survival and should be omitted [4,18,22,23]. This argument makes a comprehensive and complete surgical staging the most important. We have analyzed the reasons for this and these data might serve to improve the staging performance of EOC. It should be said that the low percentages of complete surgical staging of EOC according to the existing guidelines might be flattered. In our study we found some reasons of the gynecologic oncologists for deliberately omitting certain staging steps in the individual clinical situation, perfectly plausible. In 34 patients the taking of blind peritoneal biopsies was incomplete. Of these, taking the biopsies was considered to have no therapeutic consequences in six patients, there were technical problems in two patients and comorbidity problems or a second malignancy in five patients, the value of a contralateral pelvic lymph node dissection in case of a unilateral ovarian malignancy was also doubted, influencing the number of lymph nodes resected. Introducing a third staging category (considered adjustment of staging procedure) might give a more realistic picture of the actual staging performance. A structured list of staging steps to be used during surgery and evidence-based consensus of obligatory staging steps might help in achieving a higher rate of complete staging procedures.

Conclusion

The most common reasons for incomplete staging were insufficient random biopsies of the peritoneum, and less than ten lymph nodes being resected and/or found at pathology. The most mentioned reasons for not performing biopsies were forgetting to do so, or believing that, after careful inspection and palpation, taking biopsies is irrelevant and/or already are being taken while performing a hysterectomy (cul-de-sac, bladder). The value of contralateral pelvic lymph node dissection in case of a unilateral ovarian malignancy was also doubted, influencing the number of lymph nodes resected. Introducing a third staging category (considered adjustment of staging procedure) might give a more realistic picture of the actual staging performance. A structured list of staging steps to be used during surgery and evidence-based consensus of obligatory staging steps might help in achieving a higher rate of complete staging procedures.

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DECLARATIONS

Author contributions. JJB, PL, JB, MA, MV, DB, HA, NR and JBT analyzing, reviewing and co-writing. MA selection of cases, analyzing and reviewing. RK design of study, analyzing, co-writing and reviewing. All authors have read and approved the manuscript.

Conflict of interest. The authors declare that they have no conflict of interest.

Funding. There was no funding for this study.

Ethics approval and consent to participate. The PRISMA commission consisted of eight gynecologists, a member of the NCR (MA), and a medical researcher. All included cases were analyzed and discussed with the gynecologic oncologists of each of the 5 participating hospitals. All members participating in the commission signed a non-disclosure agreement. Ethical approval was obtained in all regional hospitals (Commission of Medical Ethics, May 2015, reference number 15–4–044).
