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The value of surgical staging in patients with apparent early stage epithelial ovarian carcinoma

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HIGHLIGHTS

- One third of apparent stage I epithelial ovarian carcinoma are upstaged.
- On third of upstaged patients have an altered treatment plan.
- Performing every step of the complete staging process does not lead to finding more metastases.
- Not performing biopsies from the abdominal peritoneum (para-colic gutters and right diaphragmatic surface) is justifiable.

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ABSTRACT

Objective. The value of surgical staging of apparent early stage epithelial ovarian carcinoma (EOC) is unclear. The aim of this study was to evaluate the importance of surgical staging on the stage of disease and treatment plan.

Material and methods. All patients with apparent stage I EOC undergoing staging from 01/01/2005 to 30/06/2017 in all Danish hospitals and in the Radboud University Hospital Nijmegen, the Netherlands, were evaluated to identify the pathological findings responsible for upstaging and changes in treatment plans.

Results. We included 1234 patients with apparent stage I EOC. The staging steps often missed were the biopsy from the right diaphragmatic surface (missed in 96.9% of all patients) and lymph node (LN) sampling or lymphadenectomy (missed in 65.5% of all patients). Upstaging occurred in 393 patients (31.8%) due to microscopic spread to both ovaries (0.8%); ovarian surface (5.8%); positive cytology (10.0%); fallopian tubes (3.1%), ovary (1.5%) and/or uterus serosa (1.2%); pelvic peritoneum (4.3%); LNs (4.7%); omentum (3.7%); abdominal peritoneum (0.6%) and right diaphragmatic surface (2.6%). Of the 393 upstaged patients, 138 (35.1%) had an altered treatment plan due to metastases found by surgical staging.

Conclusion. Staging was incomplete in most patients, mainly because a biopsy of the diaphragm was omitted. However, surgical staging led to adjuvant treatment in 35.1% of the upstaged patients. Peritoneal biopsies (paracolic gutters and right diaphragm) were of little value, since few patients had an adjustment of treatment plan due to these biopsies. Omitting these biopsies, in the absence of peritoneal abnormalities, is justifiable.

1. Introduction

In apparent early stage epithelial ovarian carcinoma (EOC) the standard treatment is comprehensive surgical staging. Accurate staging is one of the most critical steps in the treatment of EOC and is important for adjuvant treatment and prognosis. Biopsies or tissue specimens obtained during a staging procedure are of great clinical value as occult metastases may result in a change in treatment plan.

Since the 1970s, more insight has been gained into the behaviour of ovarian carcinoma. Based on the knowledge obtained from research, independent guidelines are developed for staging ovarian carcinoma [1]. These guidelines are broadly similar but differ in their recommendation regarding lymph node (LN) sampling or lymphadenectomy and the number of biopsies that needs to be taken [2,3]. Over time, the guidelines have undergone minor changes according to new findings [4]. Present consensus includes hysterectomy, bilateral salpingo-oophorectomy (BSO), cytology of peritoneal washing or ascites, careful inspection and palpation of all peritoneal surfaces, biopsies from macroscopic suspected lesions and random peritoneal biopsies of the pelvic peritoneum (anterior and posterior cul-de-sac and pelvic side-walls),

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abdominal peritoneum (para-colic gutters and right diaphragmatic surface), excision of the infracolic omentum and pelvic and para-aortic LN sampling or dissection. In women who want to retain their fertility, a fertility preserving approach with only unilateral salpingo-oophorectomy, biopsy of the contralateral ovary and without hysterectomy is an acceptable treatment.

The Danish and Dutch guidelines are slightly different concerning what is needed for a complete staging (CS). The Dutch guideline prefers LN sampling of pelvic and para-aortic lymph nodes with a requirement of at least 10 LNs whereas the Danish guideline recommends pelvic and para-aortic lymphadenectomy but does not require a minimum amount of LNs. Both agree on the remainder of the staging process [5,6].

Evidence shows that the full staging operation as described above is rarely completely executed [7–9]. Further questions exist about the pathological value, in terms of upstaging, and the clinical value, in terms of therapeutic benefit and prognosis, of the staging process [9–15].

Studies show conflicting information with regards to the staging procedure. Some conclude that complete surgical staging is highly important whereas others cautiously conclude that parts of the staging process could be omitted, such as leaving out the random peritoneal biopsies if no abnormalities are seen [7,9,11,12]. If this last statement is true, then it is of high importance to evaluate the individual steps (washing, extensive examination of the abdomen and tissue sampling) taken in the staging procedure. By using one of the largest data sets yet gathered, the aim of this study was not only to assess the importance of a complete staging procedure, but also to investigate the influence of the different steps of the staging protocol on staging and plan of treatment, in women with apparent stage I EOC.

2. Materials and methods

All patients who underwent staging and treatment for a first episode of an apparent early stage EOC, between 01-01-2005 and 31-06-2017 from all Danish hospitals and from one of the largest university hospital in The Netherlands (Radboudumc), were included. Patients were excluded when (1) full file or documentation was not available; (2) macroscopic spread was seen during surgery; (3) other malignancies were documented in the file at the time of surgery; (4) final pathology showed a type of non-epithelial ovarian histology; (5) or final pathology showed a tumour of low malignant potential (borderline).

Danish data were obtained from the Danish Gynaecologic Cancer Database (DGCD), the Danish National Pathology Registry and the Danish Civil Registration System [16]. These Danish national databases register clinical, surgical, as well as histology details for all Danish cancer patients. A study on the completeness of the data on pathology and surgery of EOC, reported to the DGCD, has previously been published and found a completeness of 97.3% and an agreement of 88.3% [17]. Dutch data were collected through a search by the hospital database and the patient medical records were queried for relevant clinical and pathologic data including demographics, history, surgical reports and pathologic data that included tumour histology grade and final stage.

The apparent and final stage of disease was automatically updated into the Danish database and for the Dutch data it was generated according to findings during surgery and pathology. All the patients, treated prior to 2014, were restaged to the 2014 Federation of Gynecology and Obstetrics (FIGO) staging for ovarian, fallopian tube and peritoneal cancer based on the findings during operation and pathology. Stage IIIA1(i) and IIIA1(ii) were taken together in stage IIIA1, since the size of the metastases was unavailable in the dataset. Surgery was performed by an experienced gynaecological oncologist in all cases.

The various steps of the staging protocol were assessed to determine: (1) how many patients underwent each step; (2) in how many patients was the collected tissue collected positive; (3) the pathological and clinical value of the histological results.

Numbers and percentages displayed in the study were calculated based on the patients who had undergone this specific staging step. The number of biopsies taken was calculated based on the locations of where the surgeon reported tissue was taken. A comparison of the biopsies taken from the peritoneum pelvic sidewalls for Danish and Dutch patients was not performed since in the Danish database biopsies of the pelvic sidewalls were not registered. For this reason, complete pelvic staging in this study included biopsies from the posterior and anterior cul-de-sac.

Patients received adjuvant chemotherapy when they were finally staged at stage IC or higher, had a grade III tumour, had a specific histological tumour type or where not completely staged. [5]

The study was approved by the RKKP (The Danish Clinical Registries), the DGCD and the Danish Data Protection Agency (File no: VD-2018-317).

2.1. Statistical analysis

Data analysis was performed using IBM SPSS version 22. A two-sided p-value < 0.05 was considered statistically significant. Independent-samples *t*-test was used for comparison of means. Danish and Dutch data were combined in this study to find out if the percentage of patients receiving complete staging surgery was unique to the country. Only remarkable differences between the cohorts were described in this paper.

3. Results

3.1. Population

In total 8282 patients underwent an operation for a tumour of the ovaries. Of those 1234 cases fulfilled the criteria: apparent early stage EOC who underwent surgical staging, including 60 patients from Holland and 1174 from Denmark. Fig. 1 shows the flowchart and the reasons for exclusion. Demographic, surgical and tumour characteristics are shown in Table 1 for the Danish and Dutch data, respectively. The patient characteristics between the Danish and Dutch data were non-significant for all criteria but age and grade.

3.2. Comprehensive staging-procedure

Table 2 shows the comprehensive staging procedure, the tissues taken and the amounts of patients who received this specific step of the procedure.

The CS process according to the Danish or Dutch guideline as described was performed in 37/1234 patients (3.0%) and the median number of biopsies sampled per patient was 2.0 (range: 0 to 8). Dutch patients were significantly more often staged completely according to the guidelines than the Danish patients (23.3% versus 2.0%). Upstaging was not more often found in women who were completely staged as compared to women who were incompletely staged (24.3% versus 32.1%, $p = 0.31$).

The biopsy that was most frequently missed was the biopsy of the right diaphragmatic surface, which was not taken in 96.9% of the cases ($N = 1196$). Complete staging without biopsy of the right diaphragm was executed in 174 patients (14.1%).

Pelvic and para-aortic lymphadenectomy or LN sampling were correctly performed in 426 patients (34.5%).

Significant differences between Danish and Dutch data were found in the execution of the biopsies of the posterior and anterior cul-de-sac (for posterior cul-de-sac 38.9% in Danish versus 75.0% in Dutch patients, $p = 0.001$; and for anterior cul-de-sac 37.4% in Danish patients versus 8.3% in Dutch patients, $p = 0.001$), the right diaphragmatic surface (8.3% Danish versus 33.3% Dutch patients, $p = 0.001$) and the fulfilment of the and para-aortic LN sampling or lymphadenectomy (45.3% in

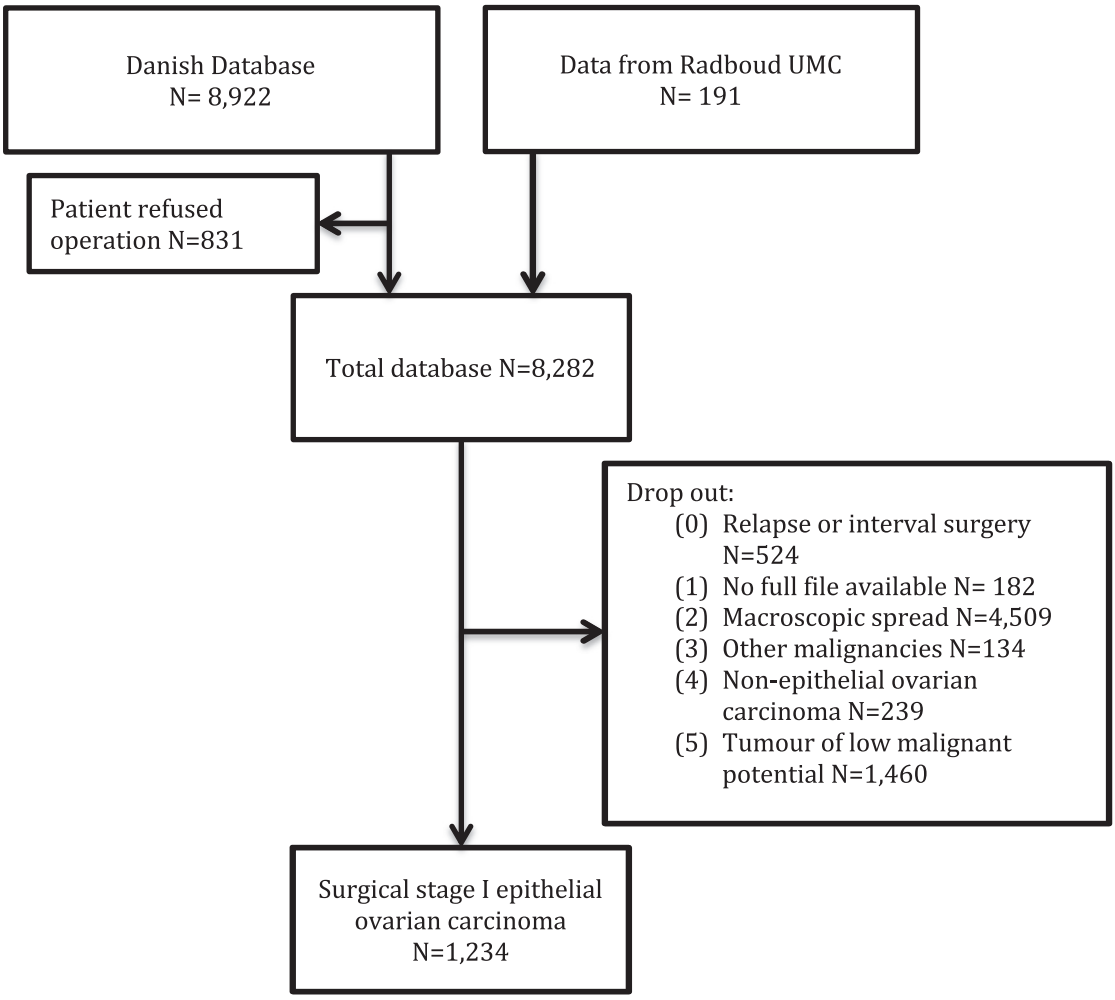

Fig. 1. Flowchart.

Danish versus 73.3% in Dutch patient, p = 0.001), and hysterectomy (34.5% versus 71.1%, p = 0.001).

The surgical characteristics between the group who underwent at least staging of the LNs versus patients who did not undergo LN staging were only significant on operation time (154 versus 115 min, p < 0.01), but not on blood loss.

3.3. Pathological and clinical value

Overall, 393 of 1234 patients (31.8%) were upstaged secondary to pathological findings, of whom 17 patients (28.3%) were from the Dutch cohort. In these 393 upstaged patients a median number of 2.0 biopsies (range: 0–6) per patient were taken.

Table 3 shows an overview of the apparent stage and defined end stage of the disease. Of the 37 patients who received a CS eight (21.6%) got upstaged and of the patients who received CS but no diaphragm biopsy, 46 of the 172 patients (26.7%) were upstaged. These differences were not significant.

The pathological findings and the number of patients who underwent a specific staging step are shown in Table 4. Below is shown which biopsy caused the upstaging.

Of the patients that were upstaged nine patients (0.7%) were upstaged to IB due to spread to both ovaries; 71 (5.8%) to stage IC2 due to pathological findings on the surface of the ipsilateral ovary; 105/1047 (10.0%) to stage IC3 due to malignant cells in the ascites or peritoneal washing. Upstaging to stage IIA was due to spread to the fallopian tubes in 38 ovarian cancer cases (3.1%), the ovaries in 19 fallopian tube cancer cases or in case of spread on the surface of the contralateral ovarian surface (1.5%) and/or the uterus serosa in 12 (1.2%). Of the 443 patients that underwent a biopsy of at least the anterior and posterior cul-de-sac 19 patients (4.3%) were upstaged to a stage IIB. Of the 426 patients who underwent complete LN staging 20 patients (4.7%) were upstaged to stage IIIA1 due to spread to pelvic LNs (N = 7), para-aortic LNs (N = 12) or both (N = 1). Of the 1148 patients who underwent an infracolic omentectomy or omentum biopsy 43 patients (3.7%) were upstaged, whereas of the 783 patients who underwent random biopsies of the abdominal peritoneum four (0.5%) were upstaged to a stage IIIA2. Another seven patients had spread to the omentum and abdominal peritoneum. One patient (2.6%) had spread to the right diaphragmatic surface that caused upstaging to stage IIIA2. Eight patients were upstaged to stage IVB due to parenchymal metastases (N = 1), metastases to the thorax (N = 6) or both (N = 1). Spread to the thorax and/or liver in these eight patients was only found with computed tomography after the staging procedure.

A total of 207 patients (16.8%) were upstaged due to spread to a non-gynaecological organ (omentum, LNs, cytology or peritoneum).

Down staging happened in 50 patients (4.1%) as the pathological examination did not confirm the clinical suspicion of metastases or surface lesions. This happened to 16 patients (1.3%) with clinical metastases to both ovaries and 34 (2.8%) with clinical suspicion of spread on the ovarian surface.

Grade of histology was an important factor for upstaging. The higher the grade of histology, the higher the chance of upstaging (p < 0.01). Patients with high-grade serous were more frequently upstaged than

Table 1
Patient characteristics.

	Danish n (%)	Dutch n (%)	p-Value
Total patients	1174	60	
Age, median (range), y	61.9 (13.8–93.2)	55.5 (22.5–87.4)	0.00
Menopausal status			NS
Postmenopausal	836 (71.2%)	34 (56.7%)	
Premenopausal	259 (22.1%)	24 (40.0%)	
Previous hysterectomy	65 (5.5%)	2 (3.3%)	
Unknown	14 (1.2%)		
Parity			NS
Nulliparous	240 (20.4%)	19 (31.7%)	
Multipara	845 (72.0%)	37 (61.7%)	
Missing	89 (7.6%)	4 (6.7%)	
BMI, mean (range)	25.6 (13.3–51.5)	25.7 (16.5–42.3)	NS
Missing	51 (4.3%)	–	
CA-125 (at time of diagnosis), mean (range)	325 (3–33,634)	799 (4–39,000)	NS
Missing	484 (41.2%)	5 (8.3%)	
RMI, mean (range)	2260 (3–100,902)	865 (18–6570)	NS
Missing	605 (51.5%)	49 (81.7%)	
Technique			NS
Laparotomy	1101 (93.8%)	42 (70.0%)	
Laparoscopy	49 (4.2%)	3 (5.0%)	
Robot-assisted	24 (2.0%)	15 (25.0%)	
Histology			NS
Serous	410 (34.9%)	15 (25.0%)	
Mucinous	299 (25.5%)	27 (45.0%)	
Endometrioid	255 (21.7%)	6 (10.0%)	
Seromucinous	17 (1.4%)	–	
Clear cell	146 (12.4%)	11 (18.3%)	
Brenner	10 (0.9%)	–	
Other	37 (3.2%)	1 (1.7%)	
Grade			0.00
1	522 (44.5%)	12 (20.0%)	
2	252 (21.5%)	9 (15.0%)	
3	239 (20.2%)	21 (35.0%)	
Missing	161 (13.7%)	18 (30.0%)	

other histological subtypes with grade 3 disease ($p < 0.05$). Histology type was another significant factor for upstaging as both serous and endometrioid ovarian cancer were more frequently upstaged than other histological subtypes ($p < 0.01$). Upstaged patients had a significantly higher age (mean 63.0 versus 60.1, $p < 0.05$) and were more often post-menopausal ($p < 0.01$).

A total of 1216 patients (98.5%) met the criteria for adjuvant treatment according to national guidelines, but just 828 patients of them (68.1%) received chemotherapy. Most patients received chemotherapy based on histological type and tumour grade. Five-hundred-and-nineteen of these patients (71.3%) had stage IC or higher and 57 patients (6.9%) had stage IA or IB with a grade 3 tumour. Of the 181 patients (21.9%) left, only six underwent full staging. Of these six patients three had a histological tumour type whereby chemotherapy was always given. The three patients left still received chemotherapy without a documented reason. 386 of the 1216 patients (31.7%) did not receive chemotherapy where they had to according to the guideline. Of these patients five (1.3%) were stage IIIA; eight (2.1%) stage IIB; seven (1.8%) stage IIA; 85 (22.0%) stage IC; nine (2.3%) stage IB and 274 (71.0%) stage IA. Of the patients with stage IA and stage IB only one patient (stage IA) was fully staged but had a grade 3 endometrioid carcinoma.

Table 3
The apparent stage and defined end stage of patients with EOC who underwent a staging operation.

		Defined end stage										
		IA	IB	IC1	IC2	IC3	IIA	IIB	IIIA1	IIIA2	IVB	Total
Apparent stage	IA	463	9	0	31	30	16	9	10	15	1	584
	IB	16	13	0	12	5	8	7	5	13	3	82
	IC1	0	0	152	28	17	13	18	6	8	2	244
	IC2	30	4	0	163	53	26	19	7	20	2	324
	Total	509	26	152	234	105	63	53	28	56	8	1234

Of the 393 upstaged patients 138 (35.1%) had a change in their treatment plan due to a solitary metastasis. Twenty-four patients (1.9%) had a change in their treatment plan due to positive cells on the ovarian surface (ipsilateral); 18 (1.7%) due to positive cytology; one patient (0.1%) due to spread on the ovarian surface of the contralateral ovary; 42 patients to the pelvic peritoneum, of whom 16 (3.6%) completely staged; 22 with LN metastases, of whom 15 (3.5%) with complete LN staging with spread to pelvic ($N = 4$), para-aortic ($N = 10$) or both ($N = 1$); 25 (2.2%) with spread to the omentum; three (0.4%) to the abdominal peritoneum and an additional three (0.4%) with spread to the omentum and abdominal peritoneum. Seven patients were found to have distant metastases that changed their treatment plan.

4. Discussion

Accurate staging is one of the most critical steps in the treatment of EOC. It is the key to prognosis, treatment recommendations and it is crucial to avoid under- and over-treatment.

Table 2
Comprehensive staging protocol.

Staging procedure	Tissue	All patients (N = 1234) (%)	Danish (N = 1174)	Dutch (N = 60)
Cytology	Ascites/washing	1047 (84.8%)	84.4%	93.3%
Hysterectomy	Hysterectomy	999 (81.0%)	81.2%	76.7%
	Previous hysterectomy	164 (13.3%)	13.7%	5.0%
Oophorectomy	Unilateral	61 (4.9%)	3.9%	23.3%
	Bilateral	1173 (95.1%)	96.4%	76.7%
	Biopsy	6 (0.6%)	–	10.0%
Salpingectomy	Unilateral	49 (4.0%)	3.2%	18.3%
	Bilateral	1181 (95.7%)	96.4%	81.7%
Infracolic omentectomy	Infracolic	1129 (91.5%)	93.5%	68.3%
	Biopsy	19 (1.5%)	–	31.7%
	Previous omentectomy	13 (1.1%)	1.1%	–
Adhesions ovary		99 (8.0%)	7.9%	10.0%
Macroscopic suspected lesions		–	–	–
Peritoneum posterior cul-de-sac (Douglas)		502 (40.7%)	38.9%	75.0%
Peritoneum anterior cul-de-sac		486 (39.4%)	37.4%	78.3%
Peritoneum pelvic side-walls		6 (0.5%)		10.0%
Peritoneum right diaphragmatic surface		38 (3.1%)	1.5%	33.3%
Peritoneum min. 2 (not further specified)		783 (63.5%)	62.3%	86.7%
Lymph node sampling (at least 10 LN) or lymphadenectomy	Para-aortic LN sampling		–	66.7%
	Pelvic LN sampling		–	66.7%
	Para-aortic lymphadenectomy		34.5%	–
	Pelvic lymphadenectomy		45.2%	–

Table 4
Pathological findings.

Site of microscopic spread	Positive (%)[a]	Negative (%)[a]	Missing (%)
Spread to both ovaries	168 (14.3%/13.6%)	1005 (85.7%/81.4%)	61 (4.9%)
Ovarian surface	309 (25.0%/25.0%)	925 (75.0%/75.0%)	–
Cytology	165 (15.8%/13.3%)	882 (84.2%/71.5%)	187 (15.1%)
Fallopian tubes	63 (5.1%/5.1%)	1164 (94.9%/94.3%)	7 (0.6%)
Ovary	26 (2.1%/2.1%)	1208 (97.9%/97.9%)	–
Uterus serosa	27 (2.7%/2.2%)	972 (97.3%/78.8%)	71 (5.8%)
Peritoneum pelvis[b]	27 (6.0%/5.7%)	416 (93.9%/33.7%)	791 (64.1%)
LN pelvis	19 (3.3%/1.5%)	556 (96.7%/45.1%)	659 (53.4%)
LN para-aorta	20 (4.5%/1.6%)	429 (95.5%/34.8%)	785 (63.6%)
Peritoneum abdomen	13 (1.7%/1.0%)	770 (98.3%/62.4%)	451 (36.5%)
Peritoneum diaphragm	1 (2.6%/0.1%)	37 (97.4%/3.0%)	1196 (96.9%)
Omentum	50 (4.4%/4.1%)	1098 (95.7%/89.0%)	73 (5.9%)

[a] % of the total amount of patients from whom tissues were taken/% of the total population.
[b] In total 443 patients (35.9%) had a biopsy of the posterior and anterior cul-de-sac.

It is a common issue that the CS procedure is only performed in the minority of cases. This study confirms that a complete staging is executed in just a small number of patients eligible for surgical staging. This large dataset adds to several smaller studies about the lack of CS in apparent early stage EOC [7–9]. Whereas this study showed a CS procedure in just 3% of all patients, Cho et al. and Timmers et al. found complete staging in 23.5% and 33.5%, respectively [5–8]. A reason for this is not found. Reasons for not performing a full staging procedure were only registered for the Dutch patients: no curative goal; benign or tumour of low malignant potential in frozen section (but malignant in final pathology) or fertility preserving treatment. A possible explanation for the difference in complete staging between the Dutch and Danish data found in this study is that the data from the Netherlands is single-centred, so guidelines might be more uniform and only few doctors are performing the operation.

Upstaging occurred in 31.8% (N = 393) of our patients, which was comparable to what was found in previous studies [14]. Upstaging was not more often found in women who were completely staged as compared to women who were incompletely staged. Importantly, there was no difference in the median number of biopsies taken between the patients who were upstaged as compared to patients who remained stage I disease. The biopsy most often missed, the biopsy of the right diaphragm, was seldom positive for metastasis – and when it was positive had no further contribution to adjuvant therapy. These findings suggested that performing every step of the CS process does not lead to finding more metastases and both biopsies of the diaphragm as well as peritoneal biopsies of the abdomen could likely be left out.

Previous research has been conducted into the various steps of the staging process. Our study supported the outcomes of other studies conducted in the field of fertility preserving treatment of EOC, in terms of the safety of this treatment in young women with stage I disease [18–22].

A review, performed in 2016, showed that in patients with early stage EOC, with macroscopic healthy peritoneum, microscopic peritoneal metastases were found in 1.2%–9.3% [23]. In our study, this percentage was within these limits and supports earlier findings, that microscopic peritoneal metastases are mainly found in the pelvic peritoneum, where it also shows clinical value. However, a point of discussion is the scarce sampling (3.1%) of the abdominal peritoneum and right diaphragm in our study population which is insufficient for strong conclusions [9,11].

Our finding of micro-metastases in apparent normal omentum in 4.4% of the cases also backs the literature. In a review performed by Arie et al. in 2013 omental involvement has been found in 2% to 7% of all cases [14]. Although, previous studies were uncertain about the clinical value of an infracolic omentectomy, in our study 2.2% had a change in treatment plan according to positive findings in the omentum [9,10,14].

The results from our study showed that it was of pathological and clinical value to perform a LN sampling or lymphadenectomy, as it led to upstaging in 3.5%. These findings are supported by the literature and previous research has shown furthermore that patients who underwent LN sampling or lymphadenectomy showed better survival [8,24–26].

Our results showed that especially in grade 3 tumours staging is of importance, in particular in tumours with serous histology. Furthermore, tumours of endometrioid subtype, despite the grade, also were more frequently upstaged. The fact that just a minority of the patients were completely staged, may have influenced the results. However, as high-grade tumours are more prone to develop LN metastases and are more often diagnosed at an advanced stage, our findings were in line of expectation.

The strength of the present study was its large sample size and that Dutch and Danish data were compared. Combining these data makes the present study the biggest in this field to date. Differences between the Danish and Dutch data could all be explained. We assumed that the population should be similar in both countries considered the geographic, lifestyle and age distribution of the countries.

The study was based on a database and on patient reports, which may contain bias. The data in the Danish system and the Dutch patient records were prospectively collected by the surgeon to make the chance on recall bias as small as possible.

Dutch patients were more often completely staged. However, the limited number of Dutch data may have caused some bias. This bias is expected to be of limited impact as we only found differences in age and grade in the Danish and Dutch patients.

In conclusion, this study showed that complete surgical staging is not often performed in Denmark nor Holland. Clinical relevance of the biopsies of the abdominal peritoneum (para-colic gutters and right diaphragmatic surface) is low and choosing not to perform these biopsies on macroscopic healthy abdominal peritoneum is justifiable. Staging is of most important value in patients with grade 3 tumours, especially serous or endometrioid subtypes.

Author contribution section

Dr. Zusterzeel came up with the research topic together with Dr. Lajer and MSc Hengeveld. Prof. Dr. Høgdall, Dr. Rosendahl and MSc Hengeveld have been collecting and analysing the data. MSc Hengeveld has done the manuscript preparation. Dr. Zusterzeel, Dr. Lajer, Prof. Dr. Høgdall and Dr. Rosendahl have been reading and correcting the manuscript.

Declaration of Competing Interest

There are no conflicts of interest to report.

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