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Review Article

The attributive value of comprehensive surgical staging in clinically early-stage epithelial ovarian carcinoma: A systematic review and meta-analysis

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HIGHLIGHTS

- 18.7% of the clinically early-stage EOC patients get upstaged based on surgical staging.
- Serous or poorly differentiated EOC tumors have the highest upstaging risk after surgical staging.
- The surgical staging steps are frequently tumor positive, but lead less often to upstaging.
- This meta-analysis gives insight in the contribution of each surgical staging step.

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ABSTRACT

Background. Tumor positivity and upstaging rates from various surgical staging steps performed in clinically early-stage epithelial ovarian carcinoma (EOC) vary widely in literature.

Aim. To quantify tumor positivity and upstaging rates for all staging surgery steps in EOC patients. Differences between subgroups based on their clinical and histological characteristics are explored.

Methods. A systematic search using synonyms of 'ovarian cancer', 'neoplasm staging', and 'neoplasm metastasis' was conducted in PubMed, Embase, and the Cochrane Library. Meta-analysis was performed on 23 included studies, comprising 5194 clinical stage I or II EOC patients who underwent comprehensive surgical staging. Studies were assessed using the Newcastle-Ottawa Scale risk-of-bias tool. Pooled proportions and 95% confidence intervals were calculated using an inverse variance weighted random-effects model.

Results. Overall upstaging rate of clinically early-stage EOC patients was 18.7% (95%CI: 14.1–23.4%). Serous histology or high grade EOC showed the highest upstaging rate at 35.3% (95%CI: 21.8–48.7%) and 40.9% (95% CI: 35.6–46.2%). Lymph node involvement resulted in an upstaging rate of 8.7% (95%CI: 6.2–11.3%). Tumor was identified in uterus, cytology, peritoneal biopsies, omentum and appendix in 6.2% (95%CI: 1.8–10.7%), 18.4% (95%CI: 13.8–22.9%), 9.7% (95%CI: 3.8–15.6%), 5.2% (95%CI: 1.7–8.8%) and 3.6% (95%CI: 0.0–7.5%) of EOC patients. The corresponding upstaging rates were 5.9% (95%CI: 1.4–10.4%), 8.5% (95%CI: 1.8–15.2%), 3.5% (95%CI: 1.0–6.0%), 3.9% (95%CI: 1.4–6.3%) and 1.6% (95%CI: 0.0–3.4%), respectively.

Conclusion. The attributive value of comprehensive surgical staging in clinically early-stage EOC patients remains substantial, particularly in serous and high grade tumors.

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Contents

1. Introduction

Epithelial ovarian carcinoma (EOC) has an annual incidence of 11.0 and a mortality rate of 7.3 cases per 100.000 women within the Netherlands [1]. Approximately 30% of the EOC patients present with clinically early-stage (i.e., FIGO stage I-II) disease at initial evaluation [2]. The treatment plan of clinically early-stage EOC is determined by comprehensive surgical staging, enabling valid prognosis estimates and, more importantly, determines adjuvant treatment.

The ten-year follow-up data from the European Organization for Research and Treatment of Cancer – Adjuvant ChemoTherapy in Ovarian Neoplasm (EORTC-ACTION) – trial demonstrated complete staging surgery was significantly associated with a superior recurrence-free and overall survival. Adjuvant chemotherapy appeared only beneficial in clinically early-stage EOC patients with possible unidentified residual disease due to absent or incomplete staging surgery [3,4].

As recommended by the International Federation of Gynecology and Obstetrics (FIGO), a comprehensive staging surgery should include a hysterectomy, bilateral salpingo-oophorectomy, cytology of ascites or peritoneal washings, peritoneal biopsies, infracolic omentectomy, and pelvic- and para-aortic lymphadenectomy [5,6]. Up to one-third of these clinically early-stage EOC patients are reported to be upstaged following staging surgery. However, exact upstaging rates vary widely between individual studies, mainly due to case-mix differences [7,8].

With this systematic review and meta-analysis, we aim to determine the upstaging rate after comprehensive surgical staging in patients with clinically early-stage EOC. The influence of clinical factors, such as histological type, differentiation grade, and lymph node assessment method, will be studied. Furthermore, we aim to clarify the difference between tumor positivity and upstaging rate for each surgical staging step performed in patients.

2. Material & methods

2.1. Systematic search

This systematic review was developed and completed in compliance with the PRISMA and MOOSE guidelines (Appendix Table A1 and A2). PubMed (MEDLINE), Embase, and the Cochrane Library databases were systematically searched between 6 April 2020 and 15 April 2020. The search was limited to studies published between 1975 and 2020. The following terms were used: "ovarian neoplasm", "ovarian cancer", "neoplasm metastasis", "tumor spread", "pattern", "neoplasm staging", "TNM" and "neoplasm grading", including their synonyms and alternative spellings (Appendix Table A3). Separate searches were performed with the MeSH terms in PubMed and the Emtree terms in Embase. Additional literature was searched through cross-examining the references of the retrieved articles.

2.2. Selection and eligibility

Rayyan software (Qatar Computing Research Institute, HBKU, Doha, Qatar) was used for title and abstract screening for eligibility (R.V.), and subsequent duplicate removal [9]. A second reviewer (J.H.) double-checked study eligibility with discrepancies solved by consensus discussion. Studies were included in our meta-analysis if they met the following predefined criteria: (1) randomized controlled trial, prospective or retrospective cohort study; (2) patients with clinically FIGO stage I or II EOC defined according to the FIGO guidelines. The majority (20/27) of the studies did not include a definition of clinical stage. The other (7/27) studies described clinical stage as 'tumor confined to 1 or 2 ovaries', and used CT, MRI and/or ultrasound in the preoperative workup to detect or exclude metastatic disease; (3) serous, mucinous, endometrioid or clear cell histological subtype EOC on final pathology; (4) comprehensive surgical staging adhering to the FIGO guideline at the time of surgery, completed in all included patients and with full description of the performed surgical steps in staging (i.e., hysterectomy, peritoneal washings, peritoneal biopsies, omentectomy, appendectomy and/or lymph node dissection); (5) results presented on tumor status and upstaging rate for the various steps of the staging surgery.

Studies were excluded when they were: (1) not written in English, non-human, or if the full-text version was not available; (2) patients with other malignancies in present or past.

2.3. Quality assessment and data collection

Two independent reviewers (R.V. and J.H.) performed a systematic quality assessment for all eligible studies using the Newcastle-Ottawa

Scale (NOS), and data collection of the included studies [10]. Discrepancies were resolved by discussion and consensus between the reviewers.

The NOS evaluates the study's quality based on three perspectives (i.e., selection, comparability, and outcome), with three domains each. A maximum overall score of 9 points could be obtained, indicating that the study is comparable to a well-designed double-arm cohort study. Studies assessed with an overall score of 5 or lower, indicating a high risk of bias, were excluded from the review as decided during the protocol stage.

2.4. Statistical analysis

This meta-analysis' primary outcomes are the rate of identifying tumor and upstaging rate of the individual steps encompassing a staging surgery in clinically early-stage EOC patients. As a secondary analysis, we will study the effect of histological type, differentiation grade, and lymph node assessment method on the tumor and the upstaging rate.

The analysis was performed with the statistical software R version 4.0.0 (2020-04-24, R Foundation for Statistical Computing, Vienna, Austria) with the 'meta' package version 4.3–0, created by G. Schwarzer, attached. For all studies, individual proportions and 95% confidence intervals were calculated. Because of the interstudy statistical heterogeneity, a random-effects meta-analytical model was used to pool the calculated proportions. Studies were weighted on their inverse variance. The statistical heterogeneity was quantified by the I2-statistics and the between-study variance by the tau2-statistic. The corresponding forest plots were created to summarize the ascertained result visually. A metaregression analysis was used to study the association between covariates (e.g., number of resected lymph nodes) and their relevant pooled proportions (e.g., upstaging due to lymph node assessment). A *P*-value <0.05 is deemed significant.

3. Results

3.1. Systematic search and quality assessment

The systematic search resulted in 4017 unique articles. After title and abstract screening and full-text assessment, 27 studies met the predefined inclusion criteria (see Appendix Fig. A1). Quality assessment yielded one article [11] within an overall judgment of 8 points (i.e., low risk of bias) and 22 studies [7,8,12–31] with 6–7 points (i.e., moderate risk of bias) (see Appendix Fig. A2). Four articles had an overall score of 5 or lower (i.e., high risk of bias) and were excluded from further analysis [32–35]. The predominant quality issues within the included studies were unexplained missing or unreported data, lack of reproducible method description, or unspecified study population. The characteristics of the included 23 studies are shown in Table 1.

3.2. Overall upstaging rate

From the 23 studies, a total of 5194 EOC patients between 1975 and 2020 with clinically stage I or II were identified, of which 931 were upstaged based on surgical-pathological findings. The upstaging rate within the individual studies varied from 4.3% to 38.5%. The pooled meta-analytical estimate was 18.7% (95%CI: 14.1–23.4%) (see Appendix Fig. A3). A metaregression analysis on the year of inclusion did not provide a significant association ($p = 0.188$) with the overall upstaging rate (−0.4% per year; 95%CI: −0.9-;0.2%) (data not shown). Eleven studies investigated 3627 patients with clinically stage I EOC only, which resulted in an upstaging rate of 23.0% (95%CI: 15.5–30.5%). The other twelve studies included a mix of patients with clinically FIGO stage I and II EOC in which 14.5% (95%CI: 9.6–19.4%) out of 1567 patients were upstaged (see Appendix Fig. A4). This difference between subgroups is not statistically significant ($p = 0.771$).

3.3. Surgical steps

Three studies ($n = 1230$) reported the uterus's tumor positivity and four the upstaging rate ($n = 1326$). The uterus was positive for a tumor in 6.2% (95%CI: 1.8–10.7%) of the cases, with a corresponding upstaging rate of 5.9% (95%CI: 1.4–10.4%) (Fig. 1; see Appendix Fig. A5 and A6).

Five studies ($n = 1753$) reported the tumor positivity of cytology from ascites or peritoneal washings and seven ($n = 1986$) on its upstaging rate. Cytology was positive for tumor cells in 18.4% (95%CI: 13.8–22.9%) (Fig. 1; see Appendix Fig. A7). Patients get upstaged due to positive cytology in 8.5% of the cases (95%CI: 1.8–15.2%) (Fig. 1: see Appendix Fig. A8).

Four studies ($n = 415$) investigated the tumor positivity of the peritoneum, whereas 7 ($n = 928$) reported the contribution of peritoneal

Table 1
Characteristics of included studies.

Author	Year	Country	Inclusion period	Study Design	Clinical Stage	Histotype	N total	N upstaged (overall)
Young et al.	1983	USA	1976 – Not mentioned	Prospective	I-II	Not mentioned	100[a]	31
Onda et al.	1996	JPN	1987–1995	Prospective	I-II	SMEC	59[a]	13
Cass et al.	2000	USA	1986–1998	Retrospective	I	SMEC	96[a]	37
Le et al.	2001	CAN	1975–1999	Retrospective	I	SMEC	94[a]	34
Faught et al.	2003	CAN	1985–2000	Retrospective	I	SMEC	128	43
Negishi et al.	2004	JPN	1987–2002	Prospective	I-III	SMEC	150	19
Ayhan et al.	2005	TUR	1981–2001	Retrospective	I-II	SME	102[a]	7
Ayhan et al.	2007	TUR	1984–2001	Retrospective	I	SME	169	53
Powless et al.	2009	USA	1994–2003	Retrospective	I-II	SMEC	211	9
Mujezinović et al.	2010	SVN	1994–2008	Retrospective	I-II	SMEC	48	3
Ditto et al.	2012	ITA	2003–2011	Prospective	I-II	SMEC	111	16
Garcia-Soto et al.	2012	USA	1993–2009	Retrospective	I	SMEC	86	25
Mahdi et al.	2013	USA	1988–2007	Retrospective	I	C	1359[a]	61
Bachmann et al.	2014	DEU	Not mentioned	Retrospective	I-II	SMEC	75	6
Lee et al.	2014	KOR	1991–2010	Retrospective	I-II	SMEC	324	45
Mueller et al.	2016	USA	1994–2011	Retrospective	I	C	145[a]	32
Gouy et al.	2017	FRA	1976–2016	Retrospective	I	M	68	7
Naru et al.	2017	IND	2014–2015	Prospective	I-II	SME	38[a]	8
Minig et al.	2017	ESP	2000–2006	Retrospective	I	SME	163[a]	25
Bogani et al.	2017	USA	1975–2016	Retrospective	I-II	SEC	290	42
Babayeva et al.	2018	DEU	2000–2014	Retrospective	I-II	SMEC	59[a]	18
Padhy et al.	2018	USA	1998–2016	Retrospective	I	EC	85	4
Hengeveld et al.	2019	NLD/DNK	2005–2017	Retrospective	I	SMEC	1234	393

S: serous, M: mucinous, E: endometrioid, C: clear cell. a = number of patients of required study population within larger cohort.

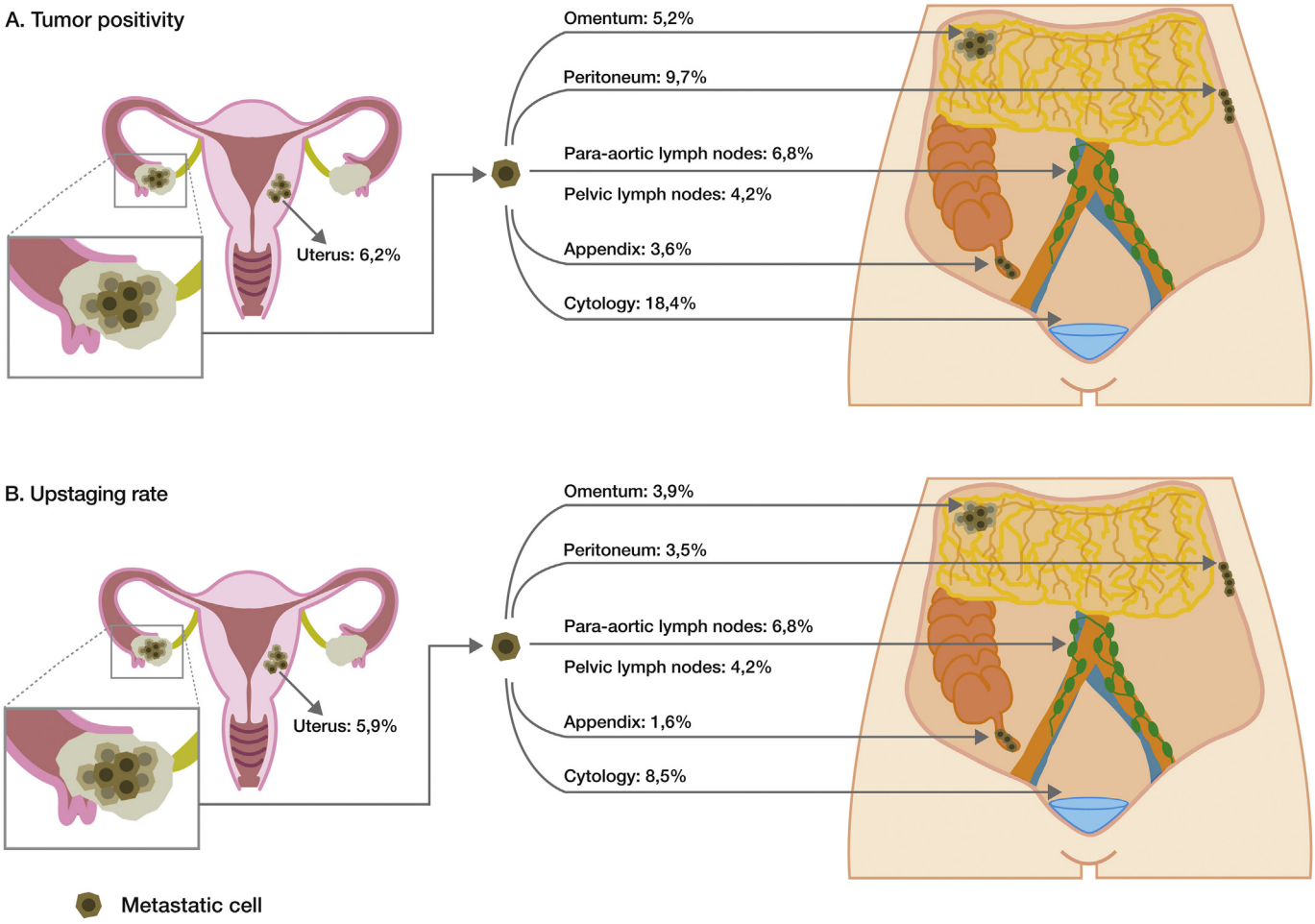

Fig. 1. Tumor positivity (A) and upstaging rate (B) of the individual surgical components of the comprehensive staging surgery of clinically early-stage epithelial ovarian carcinoma.

biopsies in the upstaging rate (Fig. 1: see Appendix Fig. A9 and A10). Positive peritoneal biopsies were found in 9.7% (95%CI: 3.8–15.6%) of the patients, but in 3.5% (95%CI: 1.0–6.0%) did this led to upstaging.

From 8 studies ($n = 2085$), the omentum was tumor positive in 5.2% (95%CI: 1.7–8.8%) of the patients, with an upstaging rate of 3.9% (95%CI: 1.4–6.3%) derived from 11 studies ($n = 2412$) (Fig. 1; see Appendix Fig. A11 and A12).

Three studies ($n = 407$) reported a tumor positive appendix in 3.6% (95%CI: 0.0–7.5%) of patients (Fig. 1; see Appendix Fig. A13). One study, Gouy et al., reported no appendiceal involvement was observed among their 24 included clinically stage I mucinous EOC patients who had undergone an appendectomy. No data specifically on the mucinous subgroup is available from the other included studies. Four ($n = 507$) evaluated the upstaging rate of early-stage EOC patients due to appendiceal involvement (Fig. 1; see Appendix Fig. A14), with a pooled result of 1.6% (95%CI: 0.0–3.4%).

3.4. Lymph node assessment

Sixteen studies on 3251 cases reported surgical lymph node status assessment, yielding an upstaging rate of 8.7% (95%CI: 6.2–11.3%) (see Appendix Fig. A15). We decided to exclude the mucinous EOC patients in this analysis, since nodal metastasis rarely occur in this subgroup [36–38]. After excluding mucinous EOC patients, the rate becomes 12.0% (95%CI: 8.2–15.8%) (see Appendix Fig. A16). Nine studies ($n = 2142$) reported which lymph nodes were positive (i.e., pelvic vs. para-aortic). Upstaging due to positive pelvic lymph nodes occurred in 4.2% (95%CI: 2.8–5.6%), whereas only positive para-aortic lymph nodes led to an upstaging rate of 6.8% (95%CI: 3.5–10.2%) (see Appendix Fig. A17 and A18).

In 10 studies, without mucinous histology, the number of removed lymph nodes was reported. A metaregression analysis found no significant association ($p = 0.069$) between upstaging and the number of removed lymph nodes (0.2% higher upstaging rate per extra node resected; 95%CI: 0.0–0.4%) (data not shown). Multivariate adjusting for the mean year of inclusion did not alter this result ($p = 0.169$) (data not shown).

3.5. Histology and differentiation grade

Ten studies ($n = 352$) reported an overall upstaging rate of 35.3% (95%CI: 21.8–48.7%) for patients with a serous EOC. Endometrioid EOC was evaluated in 11 studies ($n = 270$) and showed an upstaging rate of 19.7% (95%CI: 9.5–29.9%). A total of 7 studies ($n = 167$) reported the upstaging in clear cell EOC at 11.2% (95%CI: 3.1–19.4%). The lowest risk of upstaging was found in mucinous EOC (10 articles, $n = 248$) at 7.4% (95%CI: 3.6–11.2%) following comprehensive surgical staging (Fig. 2). The differences between the subgroups are statistically significant ($p < 0.001$).

Six studies evaluated the upstaging in low grade ($n = 242$) and high grade EOC ($n = 326$) with upstaging in 17.6% (95%CI: 12.8–22.3) and 40.9% (95%CI: 35.6–46.2%) of cases, respectively. The difference between the subgroups is statistically significant ($p < 0.001$) (Fig. 3). The included studies' data did not permit analysis on the upstaging

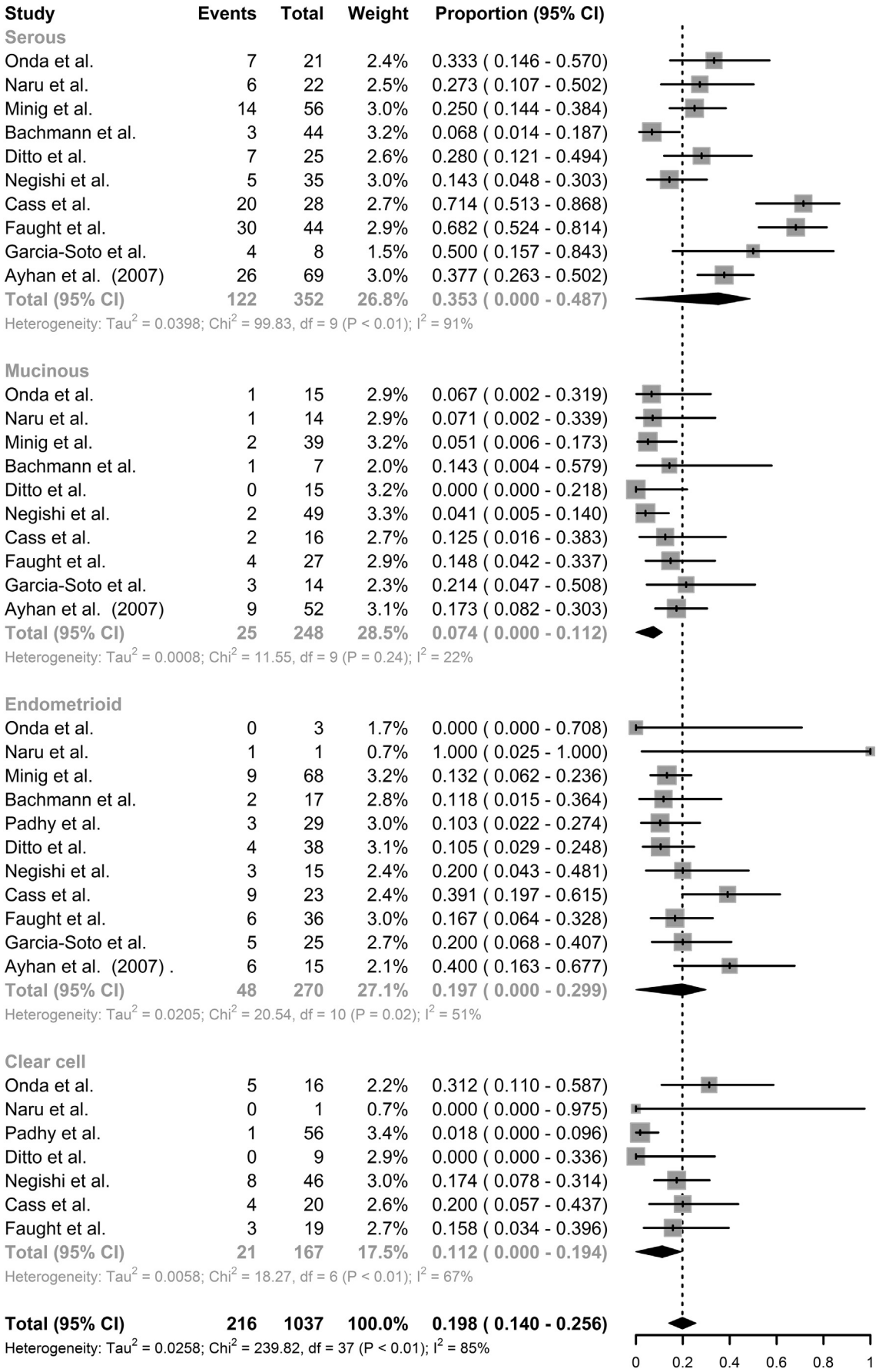

Fig. 2. Forest plot showing the overall upstaging rate in clinically early-stage epithelial ovarian carcinoma patients with subgroup analysis for histological subtype.

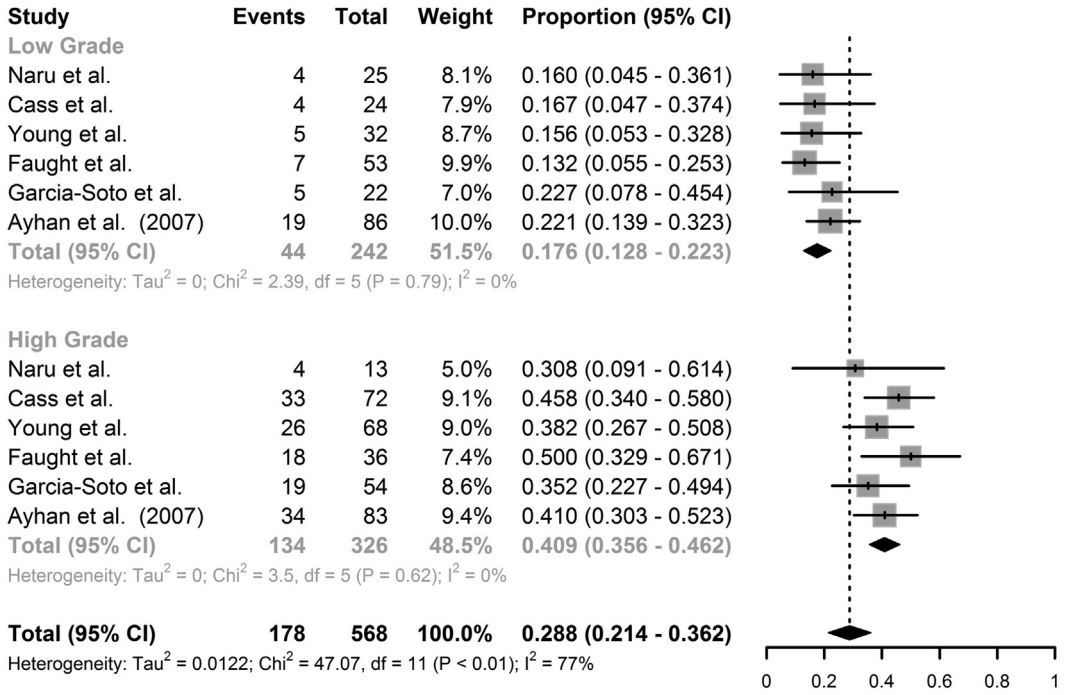

Fig. 3. Forest plot showing the overall upstaging rate in clinically early-stage epithelial ovarian carcinoma patients with subgroup analysis for differentiation grade.

results of the various surgical steps stratified for the histological types or differentiation grade.

4. Discussion

4.1. Main findings

We found that 18.7% of clinically FIGO stage I-II EOC patients are upstaged based on comprehensive surgical staging. The individual estimates from the included 23 studies varied widely, ranging from 4.5% up to 38.5%, highlighting the need for a pooled approach to increase accuracy. The result of this study enables clinicians to more accurately inform patients on the staging utility and clinical consequences of their planned surgery. This can be further stratified according to individual patient characteristics in FIGO stage, histology and tumor differentiation. The upstaging rate increases to 23.0% in those patients suspected of stage I EOC. The stage II EOC patients seem to reduce the overall risk, however, in this subgroup less tumor positive sites (e.g., uterus involvement) will lead to upstaging than in stage I. Notably, those with a high grade tumor (40.9%), and serous EOC (35.3%), yielded a high probability of upstaging. We have pooled the data of grade II and III tumors into high grade tumors to ensure translation to the clinical practice. In contrast to what we expected, and based on a limited number of cases, clear cell carcinoma of the ovary was not associated with a substantial upstaging risk (11.2%) relative to the overall risk of 18.7%. While certain low-risk groups exist, we could not identify any subgroup in which a staging surgery can be safely omitted based on an absent benefit.

This meta-analysis provides insight into the tumor positivity rate, and the upstaging contribution of each component encompassing surgical staging. The tumor positivity was identified in uterus, cytology, peritoneal biopsies, omentum, and the appendix in 6.2%, 18.4%, 9.7%, 5.2%, and 3.6% of EOC patients, respectively, with corresponding upstaging rates of 5.9%, 8.5%, 3.5%, 3.9%, and 1.6%. Remarkably, results on tumor involvement of the uterus, and the contralateral ovary are only scarcely reported in the included studies. This is a limitation across the retrieved studies, and particularly restricts the ability to preoperatively assess the understaging risks in young women where fertility-sparing surgery is considered.

Lymph node assessment resulted in 8.7% upstaging, whereas this increased to 12.0% when mucinous EOC cases were excluded. This was decided based on previous reports on the rare lymphatic metastatic dissemination of mucinous EOC, at approximately 0.8% found at staging [38]. When specified upon lymph node level, para-aortic lymph nodes are more often affected with 6.8% upstaging, than pelvic lymph nodes with 4.2%. The impression might be given that the combined upstaging risk for both positive pelvic and para-aortic lymph nodes is higher relative to the calculated overall risk of 8.7%. However, a subgroup of patients (2.3%) had metastases in both their pelvic and para-aortic lymph nodes. Furthermore, the included studies differed between the data analyses, possibly contributing to a variation in results.

Unfortunately, the terms lymph node sampling, dissection, and lymphadenectomy were used interchangeably within the included literature. A metaregression was used to study whether an association between the number of resected lymph nodes – regardless of the name used for the type of structured nodal assessment – and the upstaging rate. This did not yield a significant association, though this can possibly be attributed to insufficient statistical power as it was based on ten included studies. When multivariately adjusted for the study period of each individual study, assuming that recent studies would routinely use a CT based nodal assessment preoperatively, the results remained not significant.

4.2. Strengths and limitations

The strength of this study is its methodology conducted with adherence to the relevant PRISMA and MOOSE guidelines. We performed a rigorous literature search within PubMed, Embase, and Cochrane Library and assessed studies with two independent reviewers. Nevertheless, our findings should always be interpreted within the limits of the original studies. We attempted to control this issue by excluding high risk of bias studies and the adoptation of strict inclusion criteria. The

latter was emphasized on the definition (i.e., adhering to guidelines) and clear description of what comprehensive surgical staging entailed in each study, thus ensuring comparability between studies with this regard.

A limitation is that the Newcastle-Ottawa Scale is a tool originally designed to assess the risk of bias in double-arm (i.e. two sample comparative) cohort studies. However, the majority of studies within our meta-analysis consists of single sample cohort studies. Its adaptation here may have reduced its designed utilty as a risk of bias tool.

Furthermore, the use of published aggregate data inherent to a review and meta-analysis, precluded a detailed subgroup analysis to a quality level comparable to a design with individual patient data. An analysis on the tumor positivity and staging value of the various surgical steps stratified on histology and differentiation was not reliably possible. Nor did the studies report the frequency, or clinical consequences, of preoperative imaging in sufficient detail to multivariately adjust our analysis for this potential confounder. Also, for certain analyses only a very limited number of the total of 23 studies (5194 cases) included in this review reported relevant data (e.g., 1 study had data on the contralateral ovary).

4.3. Interpretation

This meta-analysis justifies comprehensive staging surgery in early-stage EOC patients, given that 18.7% will ultimately be upstaged, consequently influencing adjuvant treatment and prognosis. Although the clinical benefits and implications regarding comprehensive staging or restaging surgeries are well defined, it should be clear that these procedures also carry significant risks for complications. Intra- and postoperative complications occur in up to 15.8% of the patients, including internal bleeding, injuries to the urinary tract or intestines, infections, and complications of wound healing [39]. Its long-term sequelae, such as lymphedema caused by lymphadenectomy, manifest in over 30% of the patients, and negatively influence the quality of life [40,41]. A laparoscopic approach could reduce some of the surgical morbidity, though further trials would be required before a definitive statement can be made about the clinical value of laparoscopic staging [42–44].

While all staging surgery steps were found to have upstaging value, some contributed only in a limited amount. Conceptually, the benefits have to outweigh the associated disadvantages of each component. Kleppe et al. suggest omitting a systematic lymphadenectomy in grade I mucinous EOC since the incidence of positive lymph nodes is low, and the morbidity as a direct consequence of lymphadenectomy high [45]. We could not perform an analysis in this specific subgroup, as insufficient data of this patient group could be extracted. Therefore, we were unable to corroborate this statement with the group level data retrieved from the included studies. Previous reports have estimated the lymphadenopathy risk in apparent stage I-II mucinous EOC at 0.8%. In the Netherlands, lymph node assessment is currently no longer a required part of the staging surgery in patients with mucinous histology.

5. Conclusions

This meta-analysis demonstrated that 18.7% of the clinically early-stage EOC patients are upstaged based on comprehensive surgical staging. Patients with serous and high grade EOC have the highest risk of being upstaged. Tumor positive uterus, cytology, peritoneal, omentum, and appendix samples do occur frequently, but lead substantially less frequent to a higher stage (1.6–8.5%) due to their overlap. This meta-analysis provides a better insight to both patient and clinician into the individual contribution of each component in surgical staging.

Author's contribution

The research question was formulated by RV and CG. Methods were designed by RV, JH, and CG. The search, risk of bias assessment, and data collection were performed by RV and JH. The statistical analysis was conducted by JH. Results were interpreted by all authors. The manuscript was drafted by RV and JH and critically revised by CG, RZ, PW and MA.

Ethical approval

Not applicable.

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Not applicable.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.04.007.

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