

SYSTEMATIC REVIEW

Frozen section diagnosis of borderline ovarian tumors with suspicious features of invasive cancer is a devil's dilemma for the surgeon: A systematic review and meta-analysis

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Abstract

Introduction: Frozen section diagnoses of borderline ovarian tumors are not always straightforward and a borderline frozen section diagnosis with suspicious features of invasive carcinoma (reported as “at least borderline” or synonymous descriptions) presents us with the dilemma of whether or not to perform a full surgical staging procedure. By performing a systematic review and meta-analysis, the prevalence of straightforward borderline and “at least borderline” frozen section diagnoses, as well as proportion of patients with a final diagnosis of invasive carcinoma in these cases, were assessed and compared, as quantification of this dilemma may help us with the issue of this clinical decision.

Material and methods: PubMed, EMBASE and Cochrane library databases were searched and studies discussing “at least borderline” frozen section diagnoses were included in the review. Numbers of specific frozen section diagnoses and subsequent final histological diagnoses were extracted and pooled analysis was performed to compare the proportion of patients diagnosed with invasive carcinoma following borderline and “at least borderline” frozen section diagnoses, presented as risk ratio and risk difference with 95% confidence intervals (95% CI).

Results: Of 4940 screened records, eight studies were considered eligible for quantitative analysis. A total of 921 women was identified and 230 (25.0%) of these women were diagnosed with “at least borderline” ovarian tumor at the time of frozen section. Final histological diagnoses were reported in five studies, including 61 women with an “at least borderline” diagnosis and 290 women with a straightforward borderline frozen section diagnosis. Twenty-five of 61 women (41.0%) of the “at least borderline” group had invasive cancer at final diagnosis, compared with 28 of 290 women (9.7%) of the straightforward borderline frozen section group (risk difference -0.34 , 95% CI -0.53 to -0.15 ; relative risk 0.25, 95% CI 0.13–0.50).

Conclusions: Women diagnosed with “at least borderline” frozen section diagnoses were found to have a higher chance of carcinoma upon final diagnosis when compared

Abbreviations: CI, confidence interval.

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with women with a straightforward borderline frozen section diagnosis (41.0% vs 9.7%). Especially in the serous subtype, and after preoperative consent, full staging during initial surgery might be considered in these cases to prevent a second surgical procedure.

KEYWORDS

borderline tumors of the ovary, frozen section, operative surgical procedure, ovarian cancer, ovarian neoplasm

1 | INTRODUCTION

Women with clinical early-stage ovarian cancer need a full surgical staging which involves taking samples from defined areas within the abdominal cavity, omentectomy, next to pelvic and para-aortic retroperitoneal lymph node dissection, to decide whether further (systemic) adjuvant treatment is required and to provide an indication of prognosis. In the case of borderline ovarian tumor diagnosis, adequate staging includes careful inspection of the peritoneum, peritoneal washing, peritoneal staging biopsies (pelvic peritoneum, paracolic gutters, diaphragm [4–6 biopsies]) and omentectomy (at least infracolic).¹ Surgeons will decide whether to perform a full surgical staging procedure based on the results of rapid histological analysis on the ovarian mass during surgery, known as ‘frozen section’. However, even for the well-trained gynecopathologist, this is often a real challenge, as is illustrated by the fact that 21% of borderline ovarian tumors (synonymous with “atypical proliferative tumor”) diagnosed at frozen section examination turned out to be invasive cancer at the final pathology.^{2,3} Borderline ovarian tumors are composed of mild to moderately atypical epithelial cells that show proliferation greater than that seen in benign tumors, but less than carcinomas. Although usually absent in borderline ovarian tumors, one or more foci of stromal invasion of <5 mm in the largest linear area might be present and should be classified and treated as borderline ovarian tumor. Serous borderline tumors account for approximately 50% of all borderline tumors and mucinous borderline tumors for approximately 40%.^{3,4}

In addition to a suboptimal accuracy rate of frozen section diagnosis of borderline ovarian tumors, another difficulty may be that it is not always possible for the pathologist to report a frozen section diagnosis as a borderline ovarian tumor or an invasive carcinoma according to the World Health Organization criteria.⁵ Therefore, an intermediate diagnosis, further denoted as “at least borderline”, is suggested in cases of borderline ovarian tumors showing equivocal or suspicious features for invasive carcinoma.⁶ This situation is a dilemma for the surgeon because one has to decide whether to await the final diagnosis on the paraffin section with the risk of a second procedure if the final diagnosis shows invasive cancer, or to perform a full staging procedure with a risk of overtreatment if the final diagnosis turns out to be a borderline ovarian tumor.

It may be important for the surgeon to know how many of the women with an “at least borderline” diagnosis have a final diagnosis of carcinoma in order to justify the decision of performing full

Key message

Just over 40% of women diagnosed with “at least borderline” at frozen section were found to have carcinomas upon final diagnosis; full staging at the time of initial surgery might be considered in these cases, especially in the serous subtype.

staging at the time of initial surgery. Although the accuracy of borderline ovarian tumor frozen section analysis has been the subject of many studies, only a few of these studies reported on the accuracy of “at least borderline” frozen section results. Therefore, the aim of this systematic review was (i) to assess the prevalence of “at least borderline” frozen section results and (ii) to investigate discordance rates between the frozen section and final histological diagnoses in women with borderline ovarian tumor diagnoses at frozen section, with special interest in the number of women diagnosed with invasive carcinoma at paraffin section analysis.

2 | MATERIAL AND METHODS

2.1 | Eligibility criteria

A protocol was defined prior to the search, including the population criteria, comparisons and the outcomes of interest. Our systematic review was carried out following the suggestions from the Preferred Reporting Items for Systematic Reviews and Meta-examinations (PRISMA) statement, during the process of evidence acquisition and synthesis.^{7,8} Irrespective of the study design, all studies that have discussed the use of qualifying terms in the case of frozen section results that could not rule out invasive carcinoma, were considered eligible for the systematic review. Studies involving frozen section evaluation of only non-ovarian tissue and studies not reported in English were not included in the review.

2.2 | Information sources and literature search

A comprehensive search of PubMed (MEDLINE, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations),

EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews was conducted from its earliest inception to 10 December 2020, by using a carefully composed search string: (“intraoperative” OR “intraoperative” OR “frozen section” OR “frozen sections” OR “fresh”) AND (“ovarian” OR “Ovary” OR “adnexal”) AND (“tumor” OR “tumour” OR “tumors” OR “tumours” OR “neoplasm” OR “adnexal mass”). Results from these databases were supplemented by hand-searching the reference lists of recent systematic reviews on similar topics.

2.3 | Study selection and data collection process

Two reviewers independently reviewed all citations for eligibility in two stages (titles/abstracts and full-text). Following selection of the eligible studies, data regarding study characteristics (author, year of publication, study design, study period, sample size, inclusion and exclusion criteria) and patient characteristics (age, histology), as well as data regarding the outcomes of interest, were extracted. As this definition might be used differently in the studies, articles were included for quantitative (meta-)analysis in case the prevalence of both borderline and “at least borderline” frozen section diagnoses were reported as separate categories (whether or not in relation to the final histological diagnosis), whereas it was likely in these studies that “at least borderline” was only reported in cases of borderline frozen sections showing equivocal or suspicious features for invasive carcinoma. Women with a “rule out borderline” (maximum borderline) frozen section diagnosis were counted as (straightforward) borderline frozen section diagnosis. Women with a benign or malignant frozen section diagnoses were not included in quantitative analysis.

2.4 | Methodological quality and risk of bias assessment

Assessment of methodological quality of observational studies was performed using the Newcastle-Ottawa Quality Assessment Scale and overall quality assessment of the included studies was conducted using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines.^{9,10}

2.5 | Synthesis of results and statistical analysis

For each of the studies included in the quantitative analysis, the numbers of borderline and “at least borderline” frozen section diagnoses and, if known, the numbers of invasive carcinomas as a final histopathologic diagnosis, were presented. The meta-analysis was performed using the Cochrane Review software (REVIEW MANAGER version 5.4 for Windows) and the data was pooled using the Der Simonian–Laird random-effects model. Risk

ratios and risk differences were calculated and presented together with 95% confidence intervals (95% CI) and the I^2 test was used to describe the percentage of variation across studies that is due to heterogeneity rather than chance (low level heterogeneity <50%, moderate 50%–75%, high >75%). Due to the inherent heterogeneity between the studies, the random-effects model was chosen.

3 | RESULTS

3.1 | Evidence acquisition

The Cochrane Library, PubMed (MEDLINE) and EMBASE search resulted in the identification of 4939 studies, and one study was identified using another source. Of these, 126 evaluated the use of frozen section technique in ovarian neoplasms (Figure 1). Twenty-one studies discussed the use of qualifying terms in the case of frozen section results that could not rule out invasive carcinoma.^{6,11–30} Eleven of these actually reported on numbers of women with such frozen section diagnoses, using “at least borderline”.^{11,12,14,16,22,23,25–28,30} The study by Robinson et al was excluded from quantitative analysis because it was unclear whether the qualifying terms used in 11 women indicated a suspicion of a borderline ovarian tumor or invasive carcinoma (eg “suggestive of”).¹¹ The studies by Nili et al²⁶ and Yoshida et al³⁰ were also excluded from quantitative analysis because only the number of women with an “at least borderline” frozen section diagnosis prior to a permanent diagnosis of invasive carcinoma were reported.

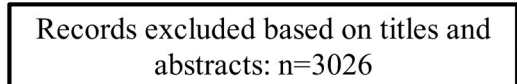
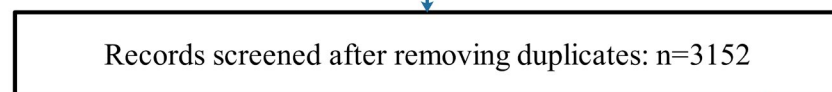
3.2 | Summary of included studies and patients

Characteristics of each of the studies that were included in the quantitative analysis are shown in Table 1 and the main results regarding the final study population are shown in Table 2 and Figure 2. In total, 921 women were identified, of which 691 (75.0%) were diagnosed with borderline and 230 (25.0%) with “at least borderline” on frozen section evaluation. Ismiil et al,¹⁶ Ureyen et al²³ and Gokcu et al²⁵ did not report on paraffin section diagnoses in relation to the frozen section diagnoses and were therefore not included in the pooled meta-analysis of the proportion of discordance (invasive carcinoma as final diagnosis). Overall, 15.1% of women (53/351) were diagnosed with invasive carcinoma on paraffin section evaluation. In each of the studies, proportions of women diagnosed with invasive carcinoma on paraffin section evaluation were higher in the “at least borderline” frozen section diagnosis group. Twenty-eight of 290 (9.7%) borderline frozen section diagnoses and 25 of 61 (41.0%) of “at least borderline” frozen section diagnoses were diagnosed with invasive carcinoma on paraffin section evaluation, which is a combined risk difference of -0.34 (95% CI -0.53 to -0.15) and a relative risk of 0.25 (95% CI 0.13–0.50) in favor of a borderline ovarian tumor diagnosis.

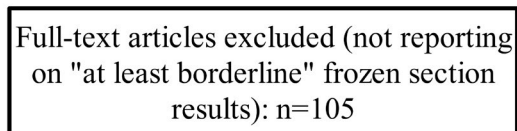
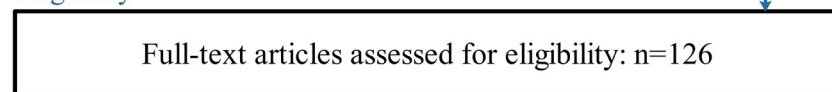
Identification



Screening



Eligibility



Included

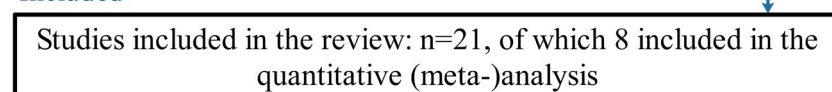


FIGURE 1 Study design

TABLE 1 Characteristics of the studies included in the quantitative meta-analysis

Study, year of publication	Study design	Study period	Hospital type	Pathologists' level	Handling of histology slides within study	Risk of bias
Menzin et al ¹²	Retrospective, single-center	1986–1993	University hospital	Junior, senior and senior gynecologic pathologists	Central review of all slides by gynecologic pathology team	Moderate
Kayikcioglu et al ¹⁴	Retrospective, single-center	1992–1997	Tertiary care teaching hospital	Level of pathologists not described	No central review of slides.	High
Ismiil et al ¹⁶	Retrospective, single-center	1999–2005	Tertiary care teaching hospital	Both gynecologic and surgical pathologists	No central review of slides.	High
Basaran et al ²²	Retrospective, single-center	2007–2012	Tertiary care teaching hospital	Senior pathologist (frozen section) and gynecologic pathologist (permanent diagnosis)	Slide review of discrepant cases.	Moderate
Ureyen et al ²³	Retrospective, single-center	1990–2012	Tertiary care teaching hospital	Pathologists experienced in gynecologic pathology (the same for both frozen section and final pathology)	No central review of slides.	Moderate/high
Gokcu et al ²⁵	Retrospective, multicenter	1998–2014	Secondary and tertiary care hospitals	Level of pathologist not described	No central review of slides	High
Huang et al ²⁷	Retrospective, systematic review and meta-analysis	2005–2015	University hospital	Frozen and paraffin section slides by two different senior pathologists (>5 years of experience)	No central review of slides	Moderate
Huang et al ²⁸	Retrospective, single-center	2003–2015	University hospital	Non-gynecologic and gynecologic pathologists	Re-review of discordant cases by a gynecologic pathologist	Moderate

TABLE 2 Results of the systematic review of literature. Distribution of borderline and “at least borderline” frozen section results and subsequent paraffin section diagnoses, as well as risk differences, risk ratios and pooled analysis

Study, year of publication	Total no. of patients ^a	Borderline frozen section diagnoses ^b	Of which carcinoma on paraffin section evaluation	At least borderline frozen section diagnoses	Of which carcinoma on paraffin section evaluation	Risk difference M-H, random	Confidence interval	Risk ratio M-H, random	Confidence interval
Menzin et al ¹²	48	31 (64.6%)	6 (19.4%)	17 (35.4%)	7 (41.2%)	-0.22	-0.49 to 0.05	0.47	0.19–1.17
Kayikcioglu et al ¹⁴	30	23 (76.7%)	3 (13.0%)	7 (23.3%)	4 (57.1%)	-0.44	-0.83 to -0.05	0.23	0.07–0.78
Ismil et al ¹⁶	76	40 (52.6%)	Unknown	36 (47.4%)	Unknown	Not estimable		Not estimable	
Basaran et al ²²	48	47 (97.9%)	6 (12.8%)	1 (2.1%)	1 (100.0%)	-0.87	-1.48 to -0.26	0.18	0.06–0.53
Ureyen et al ²³	126	110 (87.3%)	Unknown	16 (12.7%)	Unknown	Not estimable		Not estimable	
Gokcu et al ²⁵	368	251 (68.2%)	Unknown	117 (31.8%)	Unknown	Not estimable		Not estimable	
Huang et al ²⁷	145	131 (90.3%)	12 (9.2%)	14 (9.7%)	3 (21.4%)	-0.12	-0.34 to 0.10	0.43	0.14–1.34
Huang et al ²⁸	80	58 (72.5%)	1 (1.7%)	22 (27.5%)	10 (45.5%)	-0.44	-0.65 to -0.23	0.04	0.01–0.28
Total	921	691 (75.0%)	28/290 (9.7%)	230 (25.0%)	25/61 (41.0%)	-0.34	-0.53 to -0.15	0.25	0.13–0.50
Combined									
Heterogeneity						$I^2 = 52\%$; $P = 0.08$		$I^2 = 40\%$; $P = 0.16$	

^aWomen with a rule out borderline, borderline or at least borderline frozen section diagnosis.

^bRule out borderline were added to the borderline frozen section diagnoses.

3.3 | Methodological quality and risk of bias assessment

Using the Newcastle-Ottawa Quality Assessment Scale and GRADE criteria, the overall quality of existing evidence was considered “low”. There was a moderate to high risk of bias (selection, allocation/misclassification) within and across studies due to retrospective designs, incomplete reporting of outcome data (three studies not reporting on paraffin section diagnoses), absence of central review of pathology slides in most of the studies and because most of the studies did not specify the exact (cyto- and histologic) criteria for using “rule out borderline” or “at least borderline” as a frozen section result (Table 1). Heterogeneity of the studies was considered low to moderate (I^2 of 40% [risk ratio] and 52% [risk difference]).

4 | DISCUSSION

On a regular basis, it is hard for the pathologist to report a frozen section diagnosis as a borderline ovarian tumor or an invasive carcinoma according to the World Health Organization criteria because of features that are suspicious but not convincing enough to speak of invasive carcinoma, and sometimes “at least borderline” is used.^{5,6} To quantify this, and to explore the possible implications for clinical practice, we performed a systematic review and meta-analysis of the literature. First, it has been shown that 25% of borderline ovarian tumor frozen section diagnoses are reported as “at least borderline”. Secondly, in just over 40% of these women, permanent histology evaluation shows invasive carcinoma, which is considerably higher than in the case of both the straightforward borderline frozen section diagnoses in this study (approximately 10%) and borderline frozen section diagnoses in the Cochrane review by Ratnavelu et al² (21% invasive carcinoma).

Because of the considerable chance of a final diagnosis of carcinoma following a frozen section diagnosis of “at least borderline”, full surgical staging at the initial surgery in these cases might be considered. This strategy may avoid incomplete staging and the subsequent indication for adjuvant chemotherapy or a second surgical staging procedure with all its (possible) consequences when final diagnosis shows cancer.^{31,32} On the other hand, this might expose women to the risks of surgical overtreatment, which might lead to lymphocysts or lymphedema following a lymph node sampling, should the final diagnosis show a borderline ovarian tumor. Furthermore, it is important to point out that one should avoid unnecessary removal of a healthy ovary, as preservation of at least (a part of) one ovary is the standard management in young women with a borderline ovarian tumor, whereas bilateral salpingo-oophorectomy is the standard management of borderline ovarian tumors in menopausal women.¹ The aforementioned potential risks and benefits of performing additional staging procedures at the time of initial surgery should be discussed with the patient upfront as part of shared decision-making. Of course, other factors may influence the decision to perform a full

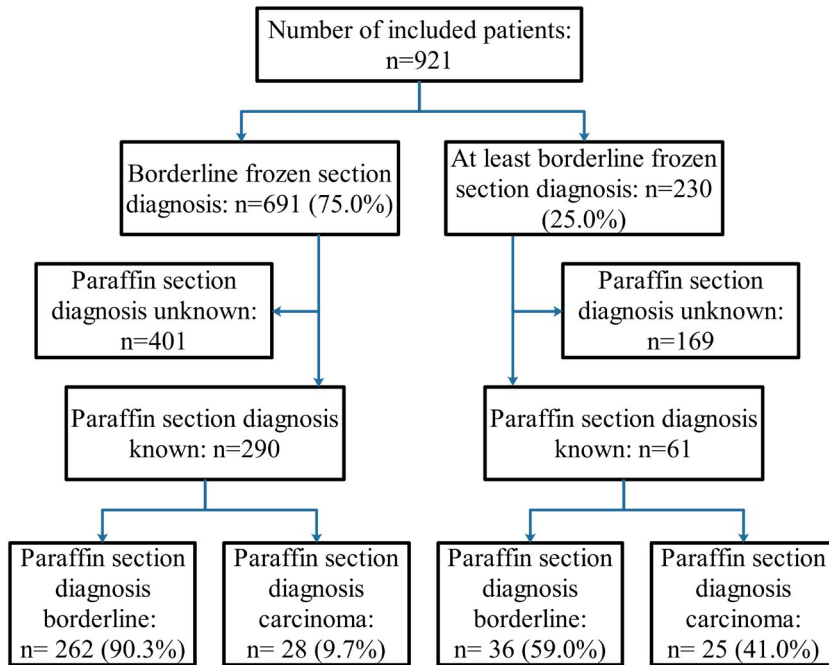


FIGURE 2 Representation of the final study population following quantitative meta-analysis

surgical staging procedure at the time of the initial surgery, such as patient characteristics (eg age or wish for fertility-sparing surgery), possibility for a second procedure with minimal invasive surgery paid by insurance, and other factors such as macroscopic appearance of the tumor and preoperative CA-125 levels.^{3,33}

A considerable number of surgeons do not perform a lymph node sampling in cases of suspected FIGO stage I mucinous carcinoma with an expansile growth pattern because the prevalence of positive lymph nodes is low (0.9%–2.6%). It is important to note that mucinous carcinomas with an infiltrative growth pattern present more frequently at an advanced stage, thus lymph node sampling for this subgroup should not be omitted. Mucinous carcinomas with an infiltrative growth pattern can be more easily distinguished from a mucinous borderline tumor at frozen section analysis than can those with an expansile growth pattern.^{31,34–38} Unfortunately, the included studies did not have information about the number of serous vs mucinous subtypes of the “at least borderline” cases, and consequently also not about infiltrative vs expansile growth pattern in the case of a mucinous carcinoma. However, one would expect that the majority of the mucinous “at least borderline” cases would be related to the mucinous expansile growth pattern carcinomas, as especially in this group it is difficult to distinguish a borderline ovarian tumor from invasive carcinoma. Thus, one should be reluctant to perform full surgical staging at the time of the initial surgery when frozen section evaluation shows a mucinous borderline tumor with features suspicious of mucinous carcinoma (with an expansile growth pattern).

The present study has some limitations. Given the nature of the included studies regarding the study designs, patient populations and definitions of when to use qualifying terms to specify a frozen section diagnosis, there is a high risk of bias within and across studies. In our meta-analysis we selected only those studies where both borderline and “at least borderline” diagnoses were included as

separate frozen section diagnostic categories, so that the latter category was only used in cases of tumors suspected of being invasive carcinoma, which made heterogeneity less likely. However, most of the studies did not specify the exact (cyto- and histologic) criteria for using “at least borderline” as a frozen section result, which might have contributed to the differences between the studies with respect to the proportion of women with borderline and “at least borderline” results at frozen section, as well as the proportion of women diagnosed with borderline ovarian tumor or invasive carcinoma on paraffin section evaluation. Furthermore, a large span of time was covered by the studies included in the pooled analysis, so diagnostic criteria might have changed over time, which also might have contributed to heterogeneity of the data. However, despite these factors, the heterogeneity with respect to the outcome of interest was not considered to be high, given the calculated I^2 percentages.

5 | CONCLUSION

In conclusion, just over 40% of women diagnosed with “at least borderline” at the time of frozen section were found to have carcinomas upon final diagnosis on paraffin sections. Full staging at the time of initial surgery might be considered in these cases after preoperative consent in order to prevent a second procedure in a considerable number of women, especially in the serous subtype. One should be reluctant to perform full surgical staging at the time of the initial surgery when frozen section evaluation shows a mucinous borderline tumor with features suspicious of mucinous carcinoma with an expansile growth pattern, as the prevalence of women with positive lymph nodes is low in the case of mucinous carcinoma with an expansile growth pattern. Future studies may provide more detailed information concerning the methodology of sampling by the

pathologist and also criteria that used qualifying terms such as 'at least borderline' or 'suggestive of', so that more studies could be included in future meta-analyses. Furthermore, it could be evaluated whether improvement of sampling protocols during frozen section examination, as well as finding more differentiating criteria, leading to specific training of pathologists with respect to discrimination of these tumor categories, could improve the reporting of frozen section diagnostics.

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CONFLICT OF INTEREST

None.

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