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Accuracy of frozen section at early clinical stage of endometrioid endometrial cancer: a retrospective analysis in Germany

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Abstract

Purpose The aim of this study was to estimate the accuracy of intra-operative frozen section (FS) diagnosis during hysterectomy for early-stage endometrial cancer (EC).

Methods At the Department of Obstetrics and Gynecology, University of Luebeck, between 2009 and 2014, the intra-operative FS pathology of 164 patients with pre-operative endometrial curettage, showing G1 or G2 endometrioid EC at an early clinical stage (FIGO I–II), was compared retrospectively with the final paraffin section reports. The accuracy of myometrial invasion (MI) in all patients and separately in stage FIGO I patients was calculated and the under- or overtreatment of the patients was analyzed. A subgroup analysis was performed focusing on the percentage of inadequate staging by FS with clinical consequences.

Results Concordance of FS and final pathology results in terms of FIGO stage was 85.2%, with an under-diagnosis rate of 14% and an over-diagnosis rate of 0.8%. The subgroup analysis rate of patients who were inappropriately operated using FS was 6.6%, while 3.3% underwent a secondary operation. The overall accuracy of FS in predicting MI was 93.3% and in patients with stage FIGO I, 92.7%. Sensitivity, specificity, PPV and NPV were 98.25%, 89.06%, 88.89% and 98.28%, respectively, and in stage FIGO I, 98.25%, 84.62%, 90.32% and 97.06%, respectively.

Conclusion The authors consider that intra-operative FS is a reliable diagnostic method to identify the clinical stage of EC and especially MI, to determine the necessity of lymphadenectomy. Further development of diagnostic techniques is essential to maximize diagnostic accuracy.

Keywords Endometrial cancer · Intra-operative frozen section · Myometrial invasion · Intra-operative cancer evaluation

Introduction

Endometrial cancer is the eighth most common cancer and the most common type of cancer of the female reproductive tract in developed countries. It accounts for 4.8% of all women's cancer types [1]. Worldwide, 320,000 women suffered from endometrial cancer in 2012 and it caused 76,000 deaths, making it the third most common cause of death in gynecological cancers [2].

In 1988, the Federation of Gynecology and Obstetrics introduced a surgical staging procedure for endometrial cancer including total hysterectomy, bilateral salpingectomy, cytologic washings, and pelvic and para-aortic lymphadenectomy [3]. The value of pelvic and para-aortic lymphadenectomy in early-stage endometrial cancer, with regard to the therapeutic value and benefits in terms of survival, is still a matter of debate [4]. The risk of lymph node metastasis is low in G1 or G2 endometrioid carcinoma, with less than 50% myometrial invasion. On the other hand, patients with any type of G3 endometrium cancer or non-endometrioid adenocarcinoma (serous, clear cell carcinoma, etc.), independent of grade status, are considered as high risk and an extended operative staging with lymphadenectomy is obligatory during hysterectomy [5]. The histological type and grade of cancer can be diagnosed pre-operatively by

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endometrial biopsy or curettage. However, this pre-operative evaluation of myometrial invasion is an inaccurate method. Thus, most gynecological centers perform intra-operative evaluation of myometrial invasion to clarify the need for lymphadenectomy [6].

The most common usage of intra-operative frozen section in gynecological oncology is associated with endometrial and ovarian tumors [7]. Until now, it seems to be the most reliable criterion for extending the surgical staging procedure or not. Deferred diagnosis of frozen section could be caused by errors in block selection, artifacts or lesions which require formal mitotic count and extensive sampling [8].

The German guidelines for endometrial carcinoma recommend intra-operative frozen section to determine the depth of myometrial invasion. This allows operative procedures to be minimized to reduce peri-operative morbidity and to ameliorate healthcare cost effectiveness.

This retrospective analysis presents the experience of a single university center with frozen section diagnosis of patients with low-risk endometrial cancer.

Material and methods

This is a retrospective study carried out on patients who underwent surgery for endometrioid endometrial carcinoma at the Department of Obstetrics and Gynecology, University of Luebeck, from 2009 until 2014. The medical history, intra- and post-operative histological results of all patients were recorded; patients without documented histopathological results were excluded.

All cases were diagnosed by curettage. Patients with high-risk cancer, such as serous or clear cell carcinoma, and with clinically advanced tumor grade (FIGO III–IV) were not included in the study. Intra-operative frozen section pathology was performed in patients with low (G1)- or medium (G2)-grade endometrioid endometrial carcinoma. Frozen section pathology was then compared with the final paraffin section pathology report. Frozen section is used to estimate intra-operatively the depth of myometrial invasion and decide subsequently whether to proceed to pelvic and para-aortal lymphadenectomy (myometrial invasion equal to or more than 50%) or not (MI less than 50%).

These findings were analyzed to clarify the diagnostic accuracy of frozen section compared with the final histology in terms of grade and myometrial invasion. In addition, a subgroup analysis was performed to evaluate the percentage of inadequate lymphadenectomy due to false frozen section results.

The FIGO system was used to categorize the specimens of endometrial cancer. Regarding the surgical techniques, laparoscopic total hysterectomy or vertical midline abdominal incision was performed in all cases. The specimen was intra-operatively delivered to an experienced pathologist, opened along both lateral walls, sliced transversely from the mucosa to the serosa and evaluated both macroscopically and microscopically. In most cases, the pathologist took two slices from the deepest invasion site of the tumor. Post-operatively, the same pathologist who evaluated the frozen section examined the specimens and generated the final histological results after 5–6 days. Histological subtype, grade, depth of myometrial invasion, tumor size, cervical and adnexal involvement, based on FIGO staging and weight of uterus, were documented.

The term ‘underestimated’ was used when the frozen section result referring to tumor stage was lower than the final histological result. In this instance, the patient had to undergo lymphadenectomy or additional operative measures. Similarly, the term ‘overestimated’ was used if unnecessary lymphadenectomy or another radical operation was performed due to false frozen section diagnosis.

During the research, the authors came across a shortcoming, the absence of the tumor grade’s description in some of the frozen section reports. Consequently, in this relatively small number of patients, it was not possible to conduct an additional analysis with statistically valid results, concerning the correlation of tumor grade in frozen section and paraffin histology.

Statistical analysis was performed by utilizing the SPSS 19.0 software (IBM SPSS Statistics for Windows Armonk, NY: IBM Corporation, 2010). Odds ratio with 95% of confidence intervals was generated. Cross-tables were used to estimate the accuracy, sensitivity, specificity, PPV and NPV of the frozen section in predicting myometrial invasion and FIGO stage.

The study is in compliance with the Helsinki declaration, and it was approved by the Medical Ethical Committee of the University of Luebeck.

Results

Of the 164 patients included in this study, 43 were excluded because of insufficient documentation. The mean age of patients (n: 121) at initial diagnosis was 64.6 years (for patients’ characteristics, see Table 1). The concordance between final paraffin histology and frozen sections amounted to 85.2% (103/121). A univariate statistical analysis shows that the accuracy of histopathological results comparing frozen section and paraffin histology is not dependent on FIGO stage ($p = 0.97$) (for FIGO stages and histological accuracy, see Table 1). Patient characteristics are not associated with accuracy of frozen section (Table 1).

The percentage of false results referring to frozen sections came to 14.8% (18/121). In 17/18 patients, the depth

Table 1 Characteristics of the study population and validity of histopathogical result dependent on FIGO stage, with analysis of the accuracy and necessity of re-operation

Characteristics	*n* (%)	Concordant FS *n* (%)	Discordant FS
FIGO stage			
1a	57 (47.1%)	49 (47.6%)	8 (44.4%)
1b	38 (31.4%)	32 (31.1%)	6 (33.3%)
2	14 (11.6%)	12 (11.6%)	2 (11.1%)
3a	8 (6.7%)	6 (5.8%)	2 (11.1%)
3b	1 (0.8%)	1 (0.9%)	0 (0%)
3c1	2 (1.6%)	2 (1.9%)	0 (0%)
3c2	1 (0.8%)	1 (0.9%)	0 (0%)
Histological-type Endometrioid	121 (100%)	103 (85.2%) 113 (93.4%) with clinical relevance	18 (14.8%) 8 (6.6%) necessity of re-operation
Myometrial invasion at final histology			
< 50%	57 (47.1%)	49 (47.6%)	8 (44.5%)
≥ 50%	39 (32.2%)	33 (32.0%)	6 (33.3%)
≥ 50% (with and without infiltration of the serosa or the cervix)	65 (52.9%)	54 (52.4%)	10 (55.5%)
Median age	64.1	63.5	69
Median BMI	30.1	30.3	29.1
Premenopausal	19 (16%)	16 (15.5%)	3 (16.6%)
Postmenopausal	102 (84%)	87 (84.5%)	15 (83.4%)
Total number	121	103	18

As shown, the clinical parameters of patients with discordant histopathological result do not differ from those with concordant results (compare median age, BMI, menopausal status)

of myometrial invasion was underestimated and in only 1/18 was it overestimated (Table 2).

The majority of patients in the underestimated group (5/17) was evaluated by frozen section as pT1a but the final histology showed myometrial invasion equal to or more than 50% (pT1b). Secondary lymphadenectomy was indicated in only three cases and not for the remaining two patients because of the advanced age of these patients.

Furthermore, in one case the frozen section analysis diagnosed less than 50% myometrial invasion (pT1a) and in another case more than 50% (pT1b). In both these cases, the paraffin histology revealed infiltration of the serosa pT3a. A re-operation was not indicated, in one patient because of advanced age and unsuspicious intra-operative situs and in the other patient due to histologically negative lymph nodes. In another case, no cancer was found at the frozen section analysis but the final histology revealed myometrial invasion of more than 50% (pT1b). This patient underwent an appropriate staging re-operation (Table 2).

According to the subgroup analysis, 93.4% (113/121) of patients underwent the appropriate operative therapy, based on the frozen section results, without the need for re-operation. As mentioned above, in 8.1% of patients the false diagnosis of frozen section pathology did not negatively

Table 2 Pre-operative and post-operative histological results of 121 patients with endometrioid endometrial cancer compared with tumor stage and analysis of the underestimated and overestimated cases

Frozen section report	Paraffin section report					Total
	No tumor	T1a	T1b	T2	T3a	
No tumor (T1a)	*1*	**7**	**1**	0	0	9
T1a	0	*48*	**5**	0	**1**	54
T1b	0	**1**	*33*	**2**	**1**	37
T2	0	0	0	*13*	0	13
T3a	0	0	0	0	*8*	8
Total	1	56	39	15	10	121 (17 underestimated and 1 overestimated)

The italic numbers show the concordance between frozen section and paraffin section reports

influence their treatment. Nevertheless, 6.6% of patients were inappropriately operated due to frozen section reports, but only 3.3% (4/121) underwent a secondary surgical operation (Table 1).

The accuracy of frozen section in predicting myometrial invasion < 50% and ≥ 50% amounted to 93.3% (113/121). The sensitivity, specificity, PPV and NPV were 98.25%, 89.06%, 88.89% and 98.28%, respectively (Table 3).

Additionally, another subgroup analysis was performed to analyze the accuracy of the frozen section with regard to myometrial invasion in tumor stage FIGO I, excluding the presence of cervical invasion, the absence of tumor in stage pT1a and the infiltration of serosa in stage pT1b (Table 3). The accuracy was 92.7% (89/96).

Discussion

The histopathological risk factors (deep endometrial invasion, large size of tumor and poor differentiation) for the suspicion of lymph node metastasis were published in 1987 by the Gynecologic Oncology Group (GOG) study [9], GOC 33. Nowadays, these histopathological factors remain the most essential parameters for the prediction of lymph node metastasis [10]. However, in the current study, tumor size and its differentiation were not routinely reported by the pathologist in the frozen section results and thus, the absence of these data did not lead to study exclusion. Furthermore, the small number of patients with lymph node metastasis (three) did not permit an extensive and combined statistical analysis concerning histopathological risk factors and lymph node metastasis. Although the above-mentioned risk factors are taken into consideration, the indication to proceed to pelvic and para-aortic lymphadenectomy, the extent of lymphadenectomy and its therapeutic role still remain controversial [4]. For instance, the results of a large ASTEC study [11] did not support routine use of lymphadenectomy in all early stages of endometrial cancer because there was no evidence of benefit in terms of overall survival and recurrence. However, information about the need for post-operative adjuvant therapy and the prognosis of patients with endometrial cancer is collected by surgical staging. There is an ongoing enquiry into the evaluation of the risk factors which determine the need for lymphadenectomy. Potential complications of lymphadenectomy, such as lymphedema, nerve and vascular injuries, could increase the risk of morbidity and decrease the quality of life, underlining the clinical benefits for the patients of an accurate staging and its necessity [12]. The authors proceeded directly to pelvic and para-aortic lymphadenectomy, without performing intra-operative frozen section of the uterus, only in cases of G3 endometrioid endometrium cancer.

In this study, frozen section accuracy in the determination of myometrial invasion (< 50% or ≥ 50%) was high. The concordance between final histology and frozen section amounted to 93.3% for all patients and 92.7% in the subgroup analysis for patients with stage FIGO I. Overall, the FIGO stage does not influence the accuracy of the frozen section result ($p = 0.97$, Table 1). Sensitivity and specificity for all patients were 98.25% and 89.06%, and for patients with stage FIGO I, 98.25% and 84.62%, respectively (Table 3). In other studies, the accuracy of frozen section for myometrial invasion ranged from 54 to 95% [13–17]. Turan et al. [18], in a retrospective analysis of 816 patients with endometrial cancer, reported an 85.4% accuracy of frozen section in the evaluation of MI, with sensitivity and specificity at 88.8% and 98.3%, respectively. Furthermore, Quinlivan et al. [19] in a study with 460 patients reported an accurate detection rate of depth of MI in 88% of cases. However, there are other studies which show a poor accuracy in 72% [20] or less [21, 22] of patients.

In the current study, the accuracy of frozen section concerning FIGO stage pT1a, pT1b, pT2 and pT3a amounted to 85.2%. Most of the discordant cases (8/18) were focally presented as cancers with no or minimal myometrial invasion which were not detected by frozen section. However, surgery was performed successfully and further staging was not necessary. On the contrary, 6.6% (8/121) of patients were inappropriately operated according to the frozen section, but only half of them finally underwent a re-operation because of advanced age and the consequent increased risk of morbidity (Table 1). In another study [19], the percentage of

Table 3 Sensitivity, specificity, positive predictive value and negative predictive value of myometrial invasion in all patients, independent of tumor stage, and in patients with endometrial cancer tumor stage FIGO I, determined by intra-operative frozen section versus final histology

All patients/FIGO I	Frozen section		Diagnostic indices of myometrial invasion			
Final histology	< 50%	≥ 50%	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
< 50%	56 (46.3%)/56 (58.3%)	7 (5.7%)/6 (6.3%)	98.25/98.25	89.06/84.62	88.89/90.32	98.28/97.06
≥ 50%	1 (0.8%)/1 (1.1%)	57 (47.1%)/33 (34.3%)				
Total	57 (47.1%)/57 (59.4%)	64 (52.9%)/39 (40.6%)				

patients receiving sub-optimal surgical management due to frozen section errors was 5.3% and in a prospective study [10] with 784 patients from Mayo Clinic the percentage amounted to 1.3%. In the authors' study, the main reason for inappropriate operation was the inaccuracy of frozen section to determine the exact extent of myometrial invasion (7/8). Additionally, in six of eight cases myometrial invasion was underestimated < 50% and in one case it was overestimated ≥ 50% (Table 2). This problem has also been recorded in the literature [19]. The percentage of patients who were underestimated or overestimated was 5.7% (7/121) and 0.8% (1/121), respectively. In the subgroup analysis of patients with stage FIGO I, the percentages amounted to 6.3% (6/96) and 1.1% (1/96), respectively. In another large study [18] with endometrial carcinoma stage IA-IVB, the percentages were 10.6% and 4%, respectively. This study included cases without carcinoma in frozen section, thus the percentage of the underestimation was high. Although there are many studies on the accuracy of FS in endometrial cancer, it is not easy to compare the results with those of the current study because they include different parameters and different methods for the use of frozen section at staging.

Nowadays, magnetic resonance imaging (MRI), transvaginal sonography (TVS), three-dimensional transvaginal sonography (3D TVS) and intra-operative gross visual assessment (GVA) are well-known alternative techniques to frozen section for the evaluation of myometrial invasion of endometrial carcinoma. Two reviews [22, 23] reported an accuracy of 83–86% in detecting the depth of endometrial invasion using radiologic assessment (e.g. MRI). Overall, the literature reports inconsistent results [24, 25] with sensitivity for myometrial invasion ranging from 33 to 88% and specificity from 74 to 100%. A head-to-head comparison [26] between frozen section and pre-operative MRI with 201 patients revealed that frozen sections are more accurate in diagnosing endometrial invasion than MRI. Similar data were obtained using TVS as a diagnostic tool for endometrial invasion [27, 28, 29, 30]. A prospective blinded study [31] that included 155 patients showed significantly better results for the frozen section group compared to the TVS group. Furthermore, two studies [32, 33] with a small sample size of 40 patients suffering from endometrial cancer showed a higher accuracy (sensitivity 100%) and a better performance of 3D TVS in detecting myometrial invasion than MRI. Nevertheless, more research with larger studies is essential to achieve more valid results. The technique of GVA is a very economical method compared to frozen section. However, it is widely known that frozen section has a higher accuracy than GVA [34, 35]. Until now, there exists no better diagnostic method than frozen section pathology. Frozen section remains the surgical gold standard since, according to international guidelines, sentinel node biopsy is still not part of the surgical treatment of endometrial carcinoma. Our study emphasizes the outstanding relevance of frozen section and its accuracy.

The fact that the current study is a retrospective analysis might be seen as a disadvantage. However, in this case prospective studies do not have important advantages except perhaps better documentation possibilities. The pathologic analysis may not differ in a prospective setting from the retrospective setting chosen in this study. Thus, the authors consider retrospective studies with well-documented data, analyzing frozen section accuracy, are not inferior to prospective studies. Furthermore, a meta-analysis from Alcazar et al. [36] reported that retrospective studies tend to demonstrate higher accuracy of frozen section than prospective studies.

In conclusion, frozen section is effective for intra-operative staging of endometrial cancer and it provides high potential for selecting the appropriate operative treatment. The development and combination of diagnostic methods could further improve the accuracy of endometrial cancer staging, minimizing overtreatment and its potential complications. This development should be further supported by large cohorts and multicentric studies.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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