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Comparison of frozen section accuracy with final pathology results in early clinical stage of endometrioid type endometrial cancer

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ABSTRACT

Objectives: We aimed to compare the accuracy of the depth of myometrial invasion determined by intraoperative frozen section in the early clinical stage of endometrioid type endometrial cancer, with the result of the final postoperative paraffin section.

Methods: The study was carried out with 102 patients who were diagnosed with type 1-2 endometrioid endometrial cancer in the gynecology clinic of the state hospital between January 2015 and 2019. Retrospective demographic data, clinical characteristics, and pathology results of the patients who underwent surgical staging were recorded.

Results: The mean age of the patients was 59.3 ± 9.1 years and 82.3% of the patients were in the postmenopausal period. The mean age of patients with a depth of myometrial invasion < ½ was lower than myometrial invasion > ½, which was statistically significant ($p < 0.001$). According to the final postoperative pathology results, 93.1% (n = 95) of the cases were diagnosed as FIGO stage 1. The subgroups were 66.7% stage 1a and 26.4% stage 1b. When the stage and grade distribution was made according to the final postoperative pathology result, stage 1a grade 2 endometrial cancer was the most common with a rate of 43.1%. Concordance of the intraoperative and postoperative pathology results for the depth of myometrial invasion was 84.3%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 86.76%.

Conclusions: The accuracy of the intraoperative frozen section in endometrial cancers is quite higher. For this reason, intraoperative pathological examination results are important in terms of minimizing the complications of unnecessary surgery.

Keywords: Endometrial cancer, frozen section, myometrial invasion

Endometrial cancer (EC), which is the most common gynecological cancer seen worldwide, usually occurs in women between the ages of 55-64. Most of the patients present with the complaint of vaginal bleeding at an early stage. As a result, 80% of the cases are diagnosed early at the initial stage and the 5-year survival is 95% [1, 2]. The most common and diagnosed histological type is Type 1 endometrioid adeno-

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carcinoma. They have a better prognosis and usually result from hyperplasia. Type 2 EC is seen at a rate of 10-20%. These tumors are usually high-grade estrogen nonresponsive tumors and, have a poor prognosis. Also, a precursor lesion is rarely detected [3, 4]. One of the biggest problems to be solved in the therapy of EC has been the high-accuracy prediction of preoperative risk. The potential to accurately detect the risk of metastasis and recurrence that may develop during the diagnosis and follow-up of cancer facilitates cancer management. In this way, side effects of unnecessary adjuvant therapy are minimized [5].

Frozen section is defined as intraoperative pathology consultation requested. Although it is generally performed to understand whether the sent tissue is malignant or benign, it is a rapid pathological evaluation method used in cases such as what the disease may be, determination of other necessary examinations for the disease, the size of the tumor, if any, the extent of the tumor, the extent to which the surgery will be expanded, and the determination of the surgical margin [6]. The accuracy rate of frozen examination, which is increasingly used today, in gynecological cancers is between 91.5%-97.4%. Frozen examination in gynecology is mostly used in tumors of ovarian origin, followed by cancers of the endometrium, cervix, and vulva, respectively [7]. Mayo Clinic defines those with low risk of lymph node metastasis as grade 1 histopathology, tumor diameter of 2 cm and below, superficial myometrial invasion (< 1/2), and grade 1-2, on the other hand, described low-risk patients as no myometrial invasion, any grade or superficial myometrial invasion grade 1 [8]. Lymph node dissection has side effects such as prolonging the operation time, increasing the risk of bleeding, impaired lymphatic return, and subsequent edema in the lower extremities [9, 10]. For these reasons, frozen examination becomes very important to be successful, the surgeon and pathologist must cooperate [7].

This work, we aimed to investigate the value and reliability of FS in surgical management by comparing the result of the depth of myometrial invasion (MI) in intraoperative EC with the final pathological outcome.

METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical confirmation was obtained by applying to the local commision (Date: 08/01/2020 Decision No: 2011-KAEK -25 2020/01-13). The study was carried out with 102 patients who undertake surgery with the identify of type 1-2 endometrioid EC as a result of endometrial biopsy in Bursa Ali Osman Sönmez Oncology Hospital Gynecology clinic between January 2015-2019. The study was designed retrospectively, no written informed consent form was obtained from patients. Grade 3 EC, no endometrioid type endometrial cancer, presence of extrauterine tumor, and chemotherapy were determined as exclusion criteria. Preoperative histopathological diagnosis in the cases included in the study; was obtained by pathological examination of endometrial material sampled with pipelle and dilation and curettage. Intraoperative frozen section results of cases with grade 1 and /or grade 2, Type 1 and /or Type 2 endometrioid EC as a result of endometrial biopsy were compared with the final postoperative definitive pathological diagnosis. In the operation, abdominal fluid sampling was performed for cytological examination, primarily following the abdominal exploration in all patients. After the hysterectomy was sent to the pathology department of our hospital, a full-thickness tissue sample, including the serosa, was taken from the area that was macroscopically thought to be the deepest of the tumor, and the tissue was frozen in the frozen device. Sections of 0.5-micron thickness were taken. The depth of myometrial invasion was evaluated microscopically by staining with H&E, and verbal and written information was given to the operating room team. The frozen section and PS examination of all materials were performed by two experienced pathologists and the staging system published by FIGO in 2009 was used [11]. All cases; mean age, menopausal status, body mass index, gravida-parities, histological grades, surgical stages, and depth of MI were evaluated. Intraoperative FS results and postoperative final pathology results (FPR) were compared.

Statistical Analysis

The IBM SPSS 22 program was used for data analysis. The conformity of quantitative variables to normal distribution was investigated using the Shapiro-Wilk test. Normal distribution was expressed as mean ± standard deviation, and abnormal distribution was expressed as the median (minimum-maxi-

mum). Qualitative variables are shown as frequency and percentage. During the comparison of independent groups, the sample t-test was used to analyze the normally distributed data, and the Mann-Whitney U test was used for abnormally distributed data. The relationship between qualitative variables was examined by Fisher Exact and Chi-Square analysis. The sensitivity and specificity values of the applications recommended as diagnostic tests were calculated according to the gold standard test. The results obtained as $p < 0.05$ were considered significant.

RESULTS

In this study, the ages of the patients were between 42 and 78 years. Of the cases with grade1 and/or grade 2 endometrioid type EC as a result of the endometrial biopsy, 82.3% (n = 84) patients were in menopause, while 17.7% (n = 18) patients were in the premenopausal period. The complaints of the women were postmenopausal bleeding (PMB) (82.5%), abnormal uterine bleeding (13.7%), and increased endometrial thickness (3.8%) respectively (Table 1). When the cases with endometrioid type EC were evaluated according to the preoperative grade; grade 2 endometrioid type EC was the most common with a rate of 66.6% (n = 68). Grade 1 endometrioid type EC was found to be 33.4 % (n = 34). When the stage and grade distribution of the cases according to the postoperative FPR was made, the most common EC was stage 1a grade 2 EC with a rate of 43.1% (Table 1).

The average age of patients with an MI depth less than ½ was lower than the MI depth > ½ patients (57 [51-62] vs 61 [59-73] years respectively, $p < 0.001$). There was no significant difference between the groups in terms of body mass index (BMI) and MI depth in the FPR. In terms of MI depth measurement, the FPR of 59.5 % (n = 50) of 84 postmenopausal patients was MI < ½, and the FPR of 40.5% (n = 34) patients was MI > ½. Premenopausal 17.7% (n = 18) patients did not have a FPR MI > ½. When the cases divided into 2 groups according to their menopausal status, a significant difference was found in terms of MI depth ($p = 0.012$). Among the cohort number of FIGO Stage 1a patients with an MI depth of < ½ in the frozen evaluation was higher than FIGO Stage 1b patients (66.7%, n = 68) vs (26.4%, n = 27). FIGO stage

Table 1. Clinical features, surgical stage and grade of endometrial cancer patients

Parameter	n	%
Menopause status		
Postmenopausal period	84	82.3
Premenopausal period	18	17.7
Application complaint		
Postmenopausal bleeding	84	82.5
Abnormal uterine bleeding	14	13.7
Endometrial thickness	4	3.8
Preoperative grade		
Grade 1	34	33.4
Grade 2	68	66.6
Postoperative stage and grade		
Stage 1a grade 1	24	23.5
Stage 1a grade 2	44	43.1
Stage 1b grade 1	24	23.5
Stage 1b grade 2	3	2.9
Stage > 1 grade > 2	7	6.9

1a and 1b early-stage patients total constituted 93.1% (n = 95) of the group. Since the final pathology result 6.9 % (n = 7) of the patients in the study was reported as FIGO Stage > 1 and grade > 2, they were not included in the comparison. Final pathology result was consistent with in 63 (92.6%) of 68 patients whose frozen section result was MI depth < ½, while FPR was reported as MI depth >½ 5 (7.4%) patients. At the same time, MI depth was found to be >½ in the FPR of all (100%, n = 27) patients whose MI depth was >½ in frozen examination ($p < 0.001$) (Table 2).

When frozen and final pathology results were compared in terms of accurately predicting the depth of MI, the sensitivity rate was 84.3%, the specificity rate was 100%, the positive predictive value was 100%, the negative predictive value was 92.6%, the false positive rate was 0%, and the false negative rate was 7.4% (Table 3).

DISCUSSION

In all patients with a diagnosis of endometrial cancer who do not have a high surgical risk, primary treat-

Table 2. The relationship of final pathology result with age, BMI, menopausal status and myometrial invasion depth result of frozen section

Parameter	Final pathology < ½ MI	Final pathology > ½ MI	*p* value
Age (year)	57 (51-62)	61 (59-73)	**< 0.001**
BMI (kg/m$^{2)}$	33.78 ± 8.12	33.61 ± 7.1	0.768
Menopause status			**0.012**
Postmenopausal	50 (59.5)	34 (40.5)	
Premenopausal	18 (17.7)	0 (100)	
Frozen section			
MI: no (n = 68)	63 (92.6)	5 (7.4)	**< 0.001**
MI: present (n = 27)	0 (0)	27 (100)	

Data are shown as mean ± standard deviation or median (minimum-maximum) or n (%). BMI = Body mass index, MI = Myometrial invasion

ment may be surgery followed by surgical staging. However, considering the increase in mortality and morbidity that surgical staging will bring to the patient, the benefits and harms of performing complete surgical staging for each patient have begun to be discussed [12, 13]. However, in patients at very high risk for surgery and in the early stages, treatment can be individualized. If primary radiotherapy is in advanced stages, neoadjuvant primary chemotherapy applications may be on the agenda. However, information about the need for postoperative adjuvant therapy and the prognosis of patients with endometrial cancer is only provided by surgical staging [14]. Although endometrial cancers are usually detected between the ages of 50-65, the average age is 60 years. [15, 16]. In our study, the mean age of the patients was 59, which was similar to the literature. The parity of these patients was calculated as 2.4 ± 1.3. In this respect, no data can be presented regarding the effect of nulliparity or infertility on the development of endometrial cancer. In the literature, the average age of incidence of endometrial cancers is over 40 years. In this current study, 82.3% of the cases at the time of diagnosis were in the postmenopausal period, and 17.7% of the cases were in the premenopausal period. Since endometrial cancer is most frequently seen in the postmenopausal period, the most common presenting complaint was also observed as postmenopausal bleeding in our study [6]. Studies have shown that approximately 75% of patients diagnosed with endometrial cancer are at stage 1 [17]. According to the post-operative final pathology results of the cases included in our study, 93.1% (n = 95) were found to be stage 1, 66.7% were reported as stage 1a, and 26.4% as stage 1b. Although full staging of EC is still used for standard surgery, the place of lymph node dissection (LND) for the early stage is controversial. Parameters with high risk for lymph node metastasis (LNM); type II histology has been reported as a deep myometrial invasion (≥ 1/2) and large tumor diameter (> 2 cm). The design of our study was based on early-stage and low-grade EC patients and based on the depth of myometrial invasion [18].

The pathologist has to give the result of intraop-

Table 3. The results obtained when the frozen and final pathology results were compared in terms of depth myometrial invasion

	Sensitivity	Specificity	PPV	NPV	False negative rate	False positive rate
Frozen section evaluation	84.3%	100%	100%	92.6%	7.4%	0%

PPV = Positive predictive value, NPV = Negative predictive value

erative FS within the specified time to minimize the duration of the surgery and possible complications, and therefore only a limited number of tissue sections are taken. At the same time, the pathologist's experience is very important because the location and number of sections taken from the gross examination determine the accuracy of the FS [19]. In the study of Fanning *et al*. [20], the accuracy rate was found to be 95% for myometrial invasion when at least four sections were taken in FS. In our study, at least three sections were taken and the accuracy rate was 84% for the depth of myometrial invasion in FS. Therefore, a learning curve and experience for the pathologist to be used in clinical practice are required to increase the diagnostic accuracy for FS. Furukawa *et al*. [21], reported the specificity of frozen examination in endometrial cancer as 95.9% and the sensitivity as 91.7% in endometrial cancer. In the study of Durdag *et al*. [22], the accuracy of FS in predicting final pathology results was 76.23% for histology, 75.45% for grade, and 85.31% for depth of myometrial invasion. These rates are similar to our study's comparative results for the depth of myometrial invasion. In another study by Mandoto *et al*. [23], the accuracy of FS in predicting the final pathology results was 76.23% for histology and 75.45% for grade. The 85.31% success rate of the frozen section results for myometrial invasion depth supported the 84.3% detection rate of myometrial invasion depth in our study [23].

In the study of Gitas *et al*. [24], with patients with early-stage (FIGO I-II) and low-grade EC, the correlation between the depth of myometrial invasion of FS and the final pathology result was found to be high. The concordance of the frozen section and final pathology results in terms of FIGO stage was 85.2%, the rate of underdiagnosis was 14% and the rate of overdiagnosis was 0.8%. In this current study, the concordance of the FS and final pathology results was found to be 84.3%, while the false positive rate was 0% and the false negative rate was 7.4%, which was significantly lower.

The disadvantage of frozen examination is that it prolongs the operation time by an average of 20-30 minutes depending on the number of sections taken. Apart from the prolongation of the operation time with the waiting time required for the FS result.

Limitations

The most important limitations of our study were that it was designed with a low number of cases, early-stage and low-grade patients, and evaluated only the depth of myometrial invasion. However, the evaluation of EC pathology results by two experienced pathologists in our study increased the accuracy and reliability of the study results.

CONCLUSION

In conclusion, frozen section enables the staging of endometrial cancer intraoperatively with a very high accuracy rate, increasing the surgeon's success in choosing the appropriate operative treatment. This high accuracy of results minimizes unnecessary surgery and potential complications in staging.

Authors' Contribution

Study Conception: LÖ; Study Design: LÖ; Supervision: N/A; Funding: N/A; Materials: N/A; Data Collection and/or Processing: LÖ; Statistical Analysis and/or Data Interpretation: GÖ; Literature Review: GÖ; Manuscript Preparation: LÖ and Critical Review: GÖ.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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