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Can preoperative magnetic resonance imaging replace intraoperative frozen sectioning in the evaluation of myometrial invasion for early-stage endometrial carcinoma?

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ABSTRACT

Objectives: To examine the performance of preoperative magnetic resonance imaging (MRI) and intraoperative frozen sectioning in the assessment of myometrial invasion during the early stages of endometrial cancer.

Material and methods: This retrospective study employed data from patients with endometrial cancer who were operated on between January 2013 and November 2018. Patients who underwent preoperative MRI and were of FIGO 2009 stage I were included in the study. Radiological staging and intraoperative staging by frozen sectioning were carried out. The data were analyzed to assess agreement of the overall results concerning myometrial invasion.

Results: In total, 222 patients were enrolled. Their mean age was 58.3 ± 8.5 years. The accuracy of MRI for the detection of myometrial invasion was 88.7% and its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 91.6%, 82.1%, 92.2%, and 80.9%, respectively, with a kappa coefficient of 0.734 (95% confidence interval [CI], 0.684–0.784; $p < 0.001$). The accuracy of intraoperative frozen sectioning was 94.4%, and its sensitivity, specificity, PPV, and NPV were 97.7%, 85.7%, 94.7%, and 93.4%, respectively, with a kappa coefficient of 0.856 (95% CI, 0.812–0.900; $p < 0.001$). No significant difference in accuracy was observed between MRI and frozen sectioning ($p = 0.057$). MRI and frozen sectioning were sensitive for the detection of myometrial invasion, according to receiver operating curve analyses (areas under the curve, 0.869 and 0.917, respectively; $p < 0.001$).

Conclusions: The assessment of myometrial invasion by preoperative MRI and intraoperative frozen sectioning during the early stages of endometrial carcinoma was highly accurate.

Key words: endometrial cancer; myometrial invasion; magnetic resonance imaging; MRI; frozen sectioning

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INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the United States and other developed countries [1]. As the majority of patients present with abnormal vaginal bleeding, particularly during the postmenopausal period, most cases are diagnosed in the early stages [2]. The prognosis for early-stage disease is generally excellent [3].

Surgical staging of endometrial cancer is necessary [2]. Disease staging provides insight about prognosis and adjuvant treatment [2]. The FIGO 2009 stage I subgroup is defined according to the depth of myometrial invasion (stage IA, no invasion or invasion < 50% of the myometrial thickness; stage IB, invasion ≥ 50% of the myometrial thickness) [4]. In addition, myometrial invasion determines the risks of extrauterine disease and lymph node metastasis [5]. Lymph node metastasis occurs in 30% of cases of deep myometrial invasion, but only 5% of cases with superficial myometrial invasion [5]. Systematic lymphadenectomy is advised as part of surgical staging for high-risk patients [2]. In contrast, previous reports indicate that systematic lymphadenectomy does not improve disease-free or overall survival during the early stages of the disease [6, 7]. Lymphadenectomy may

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cause complications, such as lymphedema and lymphocysts; thus, it should be avoided in low-risk patients [2]. The risk of recurrence can be estimated by assessing the depth of myometrial invasion during preoperative radiological evaluation or by intraoperative frozen sectioning.

Preoperative radiological examination has been used to assess endometrial cancer, and magnetic resonance imaging (MRI) is the recommended diagnostic imaging method [8]. The updated guidelines of European Society of Urogenital Radiology recommend MRI as the imaging modality of choice for the evaluation of disease extent in patients with newly diagnosed endometrial cancer [9]. The European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO), and European Society of Gynaecological Oncology (ESGO) recommend preoperative MRI for the evaluation of myometrial invasion in patients with stage 1 endometrial cancer [2]. Thus, MRI can be used to assess myometrial invasion during the early disease stage [8, 10, 11]. However, several studies have shown that the prediction of myometrial invasion using MRI alone can be difficult [12, 13].

Intraoperative examination modalities for endometrial tumors have been evaluated previously [14]. Tumor assessment by frozen sectioning has been found to have greater importance than gross examination [15]. However, the accuracy of frozen sectioning can be low [16]. Furthermore, some patients cannot be evaluated preoperatively by MRI, and low image quality may affect the ability to estimate disease extent preoperatively. In such situations, intraoperative frozen sectioning may play an important role. In addition, older patients and those with medical comorbidities, and younger patients who want to preserve their fertility, are not eligible for the operation [17]. Thus, preoperative evaluation is more important in these patients. Additionally, systematic lymphadenectomy and optimal staging cannot be performed in some patients because of the morbidity of lymphadenectomy and the extent of surgery [2, 18]. Preoperative clinical staging gains importance in these patient groups.

Unnecessary lymphadenectomy with complications and morbidity can be prevented by the preoperative and intraoperative evaluation of myometrial invasion during the early stages of the disease [10]. Under-staging can be avoided in high-risk patients [10], and inoperable cases can be staged clinically [2].

Objectives

The aim of this study was to examine the performance of preoperative MRI and intraoperative frozen sectioning in the assessment of myometrial invasion before surgical staging in patients with early-stage endometrial cancer in a high-volume tertiary cancer center employing experienced radiologists and pathologists in a gynecological oncology department.

MATERIAL AND METHODS

This retrospective study employed data from 337 patients with endometrial cancer who were diagnosed and operated on between January 2013 and November 2018 in a high-volume cancer center in western Turkey. Patients with advanced stages (≥ II) of the disease and those with synchronous tumors were excluded. Patients who did not undergo pelvic MRI and were scanned with abdominal computed tomography or positron emission tomography/computed tomography, cases that were diagnosed incidentally after hysterectomy and patients who were not performed frozen sectioning were excluded. In total, 222 patients who were diagnosed preoperatively by biopsy, underwent MRI in our center, and were optimally staged by gynecological oncologists, and performed frozen sectioning in our department were included in the study. This study was approved by the local institutional ethic committee.

All biopsy samples were obtained preoperatively by dilatation and curettage or pipelle sampling. Pelvic MRI was carried out with a 1.5 Tesla system (Siemens Avanto, Siemens Aera, GE Optima 360; Erlangen, Germany) and a six-channel body coil. The imaging protocol involved sagittal, axial, coronal, and oblique axial T2-weighted images without fat saturation, as well as precontrast and postcontrast (gadoteric acid, 0.1 mmol/kg) T1-weighted fat saturated images in the axial plane. One radiologist with 8 years of experience with pelvic MRI evaluated the images before surgery. The degree of myometrial invasion was interpreted as superficial or deep (≥ 50% of the myometrium). Radiological stages were assigned according to the imaging findings.

After a multidisciplinary tumor board examined the preoperative results, the patients underwent surgical staging by gynecological oncologists. Explorative laparotomy or laparoscopy was performed, followed by hysterectomy and bilateral salpingoophorectomy. The specimens were taken to the pathology department for frozen sectioning, according to the preoperative risk stratification of the endometrial cancer [2]. The lymph nodes were dissected according to the frozen sectioning results and preoperative risk group. Pathologists examined hysterectomy specimens using a longitudinal section of the endometrial cavity and uterine cervix, and a horizontal section from the uterine fundus, in each case. After placing the specimen over a film of optimal cutting temperature medium on a cryostat, the tumor was frozen, cut into 5-µm slices using a microtome, and then prepared for staining with hematoxylin and eosin for microscopic evaluation. Tumor histology, grade, and diameter, and depth of myometrial invasion (superficial or deep), were examined. The same pathologists with experience in gynecological oncology examined the slides used for the final pathological report. In cases of diagnostic discrepancy, another pathologist examined the slides. The tumor board evaluated the

Table 1. Clinical characteristics of the patients

Variables n [%]	N = 222
Age, mean ± SD	58.3 ± 8.5
Parity, median [range]	3 (0–10)
Menopausal Status Premenopausal Postmenopausal	 37 (16.7%) 185 (83.3%)
BMI, mean ± SD (kg/m^2) > 30 kg/m2 [n, %]	34.3 ± 6.0 169 (76.1%)
CA125, median (range) > 35 U/mL [n, %]	17 (2–800) 27 (12.2%)

SD — standard deviation; BMI — body mass index, kg/m2; CA 125 — cancer antigen 125, U/mL

postoperative results and final stages according to the FIGO 2009 classification to determine the optimal treatment [13]. No or < 50% myometrial invasion was considered to reflect stage IA, and ≥ 50% invasion was classified as stage IB, according to the FIGO 2009 classification [4].

The accuracy, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the results of preoperative MRI and intraoperative frozen sectioning according to the final pathology results. The Cohen kappa statistic was used to examine the agreement of the overall results concerning myometrial invasion. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of the tests. SPSS software (ver. 21; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses, and p-values < 0.05 were considered to be significant.

RESULTS

In total, 222 patients with stage 1 endometrial carcinoma were enrolled in this study. The clinical characteristics of the patients are shown in Table 1. The mean age of the patients was 58.3 ± 8.5 years. Most of the patients were postmenopausal (83.3%) and obese (body mass index > 30 kg/m^2; 76.1%). Twenty-seven (12.2%) patients had high (> 35 U/mL) preoperative levels of serum cancer antigen (CA) 125.

The surgical and histopathological results are summarized in Table 2. Approximately 64% of the patients were treated by laparotomy, and the majority (86.1%) of them underwent pelvic ± para-aortic lymphadenectomy. The most common tumor histological type was endometrioid, and 58.1% of the tumors were of grade 2. In total, 172 of 222 (77.5%) patients had tumor sizes > 2 cm. Lymphovascular space involvement (LVSI) was detected in 20.7% of the pathological specimens. The median sizes of tumors without and with LVSI were 3.5 (0.2–9) cm and 4.5 (2–8) cm, respectively (p = 0.001). According to the final pathological reports, 155 (69.8%) patients had stage IA and 67 (30.2%) had stage IB disease. The median dissected pelvic lymph node count was 12 (0–53).

Table 2. Surgical and histopathological characteristics of the patients

	n [%]
Surgery TAH + BS ± O TLH/ Robotic Hysterectomy + BS ± O TAH + BSO + Pelvic LND TLH/ Robotic Hysterectomy + BSO + Pelvic LND TAH + BSO + Pelvic LND + Para-aortic LND TLH + BSO + Pelvic LND + Para-aortic LND	 17 (7.7) 36 (16.2) 41 (18.5) 34 (15.3) 85 (38.3) 9 (4.0)
Tumor Histological Type Endometrioid Serous/Clear Cell Mixed* Others (Carcinosarcoma, Adenosarcoma, ESS)	 193 (86.9) 8 (3.6) 14 (6.3) 7 (3.2)
Tumor Grade 1 2 3	 65 (29.3) 129 (58.1) 28 (12.6)
Tumor Size, cm, median [range] ≤ 2 cm > 2 cm	3,5 (0.2–9) 50 (22.5) 172 (77.5)
LVSI None Present	 176 (79.3) 46 (20.7)
FIGO Stage IA IB	 155 (69.8) 67 (30.2)
Pelvic LN Count, median	15 (2–53)
Para-aortic LN Count, median, [range]	9 (1–41)

TAH + BS ± O — total abdominal hysterectomy and bilateral salpingectomy with or without oophorectomy; TLH + BS ± O — total laparoscopic hysterectomy and bilateral salpingectomy with or without oophorectomy; TAH + BSO + Pelvic LND — total abdominal hysterectomy and bilateral salpingoophorectomy plus pelvic lymphadenectomy; TLH + BSO + Pelvic LND — total laparoscopic hysterectomy and bilateral salpingoophorectomy plus pelvic lymphadenectomy; TAH + BSO + Pelvic LND + Para-aortic LND — total abdominal hysterectomy and bilateral salpingoophorectomy plus pelvic and para-aortic lymphadenectomy; TLH + BSO Pelvic LND + Para-aortic LND — total laparoscopic hysterectomy and bilateral salpingoophorectomy plus pelvic and para-aortic lymphadenectomy; LN — lymph node
*endometrioid + mucinous, endometrioid + serous, endometrioid + clear cell
ESS — endometrial stromal sarcoma
LVSI — lymphovascular space invasion

The median time between MRI and operation was 21 (7–52) days. Tables 3 and 4 define the relationships of radiological staging and frozen sectioning to the final pathological results. Table 5 shows the results for combined consideration of MRI and frozen sectioning. The correlation of MRI

Table 3: Magnetic resonance imaging (MRI) and final pathological results[a]

		Stage		Total
		IA	IB	
MRI	IA	142 (64.0)	12 (5.4)	154 (69.4)
	IB	13 (5.9)	55 (2.8)	68 (30.6)
Total		155 (69.8)	67 (30.2)	222 (100)

[a] n, %

Table 4. Frozen sectioning and the final pathological results[a]

		Stage		Total
		IA	IB	
Frozen section	IA	126 (70.8)	7 (3.9)	133 (74.7)
	IB	3 (1.7)	42 (23.6)	45 (25.3)
Total		129 (72.5)	49 (27.5)	178 (100)

[a] n, %

Table 5. Preoperative magnetic resonance imaging (MRI) and additional intraoperative frozen sectioning and final pathological results[a]

		Stage		Total
		IA	IB	
MRI + Frozen section	IA	127 (71.4)	2 (1.1)	129 (72.4)
	IB	2 (1.1)	47 (26.4)	49 (27.5)
Total		129 (72.5)	49 (27.5)	178 (100)

[a] n, %

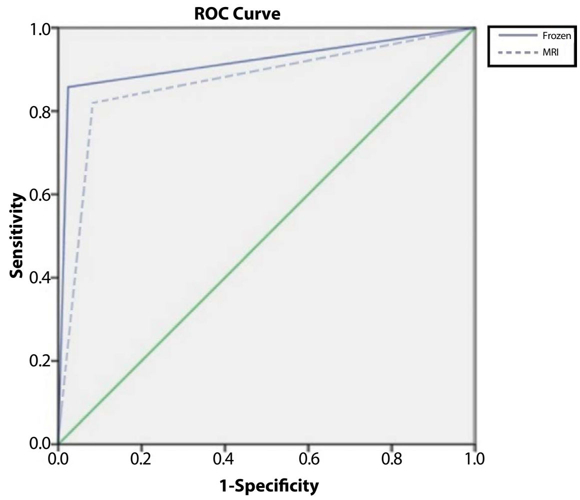

Figure 1. Receiver operating characteristic (ROC) curve for intraoperative frozen sectioning and magnetic resonance imaging (MRI) for the assessment of deep myometrial invasion (areas under the curve, 0.917 and 0.869, respectively; $p < 0.001$)

and frozen sectioning with the final pathological findings is shown in Table 6. The accuracy of MRI for the detection of myometrial invasion was 88.7%, and its sensitivity, specificity, PPV, and NPV were 91.6%, 82.1%, 92.2%, and 80.9%, respectively, with a kappa coefficient of 0.734 (95% confidence interval [CI], 0.684–0.784; $p < 0.001$). The accuracy of intraoperative frozen sectioning was 94.4%, and its sensitivity, specificity, PPV, and NPV were 97.7%, 85.7%, 94.7%, and 93.4%, respectively, with a kappa coefficient of 0.856 (95% CI, 0.812–0.900; $p < 0.001$). The rates of overdiagnosis were 8.4% for MRI and 2.3% for frozen sectioning. The rates of underdiagnosis were 17.9% for MRI and 14.3% for frozen sectioning. Preoperative MRI yielded 5.4% false-negative and 5.9% false-positive results for the prediction of deep myometrial invasion. The false-negative and false-positive ratios for frozen sectioning were 3.9% and 1.7%, respectively. No significant difference in accuracy was observed between MRI and frozen sectioning, according to McNemar's test ($p = 0.057$). When MRI and frozen sectioning were considered together, the accuracy was 97.8% and the sensitivity, specificity, PPV, and NPV were 98.5%, 95.9%, 98.5%, and 95.9%, respectively, with a kappa coefficient of 0.944 (95% CI, 0.916–0.972; $p = 0.028$).

The ROC curves for the assessment of deep myometrial invasion are shown in Figure 1 for MRI and frozen sectioning. MRI and the frozen sectioning significantly detected myometrial invasion, according to the ROC curve analyses (areas under the curve, 0.869 and 0.917, respectively; $p < 0.001$).

DISCUSSION

Endometrial cancer is commonly diagnosed in postmenopausal women; the average age of patients in the United States is 63 years [3]. Most cases in our study group were postmenopausal and > 50 years of age, consistent with the literature. Obesity is an important risk factor for endometrial carcinoma [19]. The majority of the patients in our study group were obese, and the morbid obesity rate was high. Preoperative elevated serum CA 125 levels (> 35 U/mL) are associated with extrauterine disease [20]. Although the patients had early-stage disease, CA 125 levels were above the limit in 12.2% of cases in this study. Elevated CA 125 levels are correlated with increasing depth of myometrial invasion [20]. The median CA 125 level was higher in the deep myometrial invasion group, consistent with previous studies [20, 21].

Table 6: Correlation between preoperative magnetic resonance imaging (MRI) and intraoperative frozen sectioning and final pathological results

	Accuracy	Kappa Coefficient	Sensitivity	Specificity	PPV	NPV	Over-Diagnosis	Under-Diagnosis
MRI	88.7 %	0.734	91.6%	82.1%	92.2%	80.9%	8.4%	17.9%
Frozen Section	94.4 %	0.856	97.7%	85.7%	94.7%	93.4%	2.3%	14.3%
MRI + Frozen Section	97.8 %	0.944	98.5%	95.9%	98.5%	95.9%	1.6%	4.1%

PPV — positive predictive value; NPV— negative predictive value

Surgery for endometrial cancer can be performed with laparotomy or laparoscopy [22]. As minimally invasive surgery is recommended because of its lesser morbidity, the laparoscopic surgery rate is increasing with increases in minimally invasive surgical skills and facilities [22]. Only patients at high risk of recurrence should undergo lymphadenectomy [2]. This procedure can cause lower extremity lymphedema, lymphocysts, and surgical morbidities [4]. In this study, the risk classification was estimated using age, tumor histology, grade, and radiological and frozen sectioning findings. Although the patients in this study group had early-stage disease, pelvic or para-aortic lymphadenectomy was applied in the majority of cases. This pattern can be explained by the change in our approach since the January 2016 ESMO/ESTRO/ESGO consensus conference report, with no lymphadenectomy performed in a low-risk patient [2]. The majority of patients with endometrial cancer are diagnosed at the early stage [3]. All patients in this study were diagnosed at an early stage, and most cases were diagnosed as stage IA.

MRI is an appropriate imaging modality for the detection of myometrial invasion, extrauterine disease, and lymph node metastasis in patients with endometrial cancer [8]. Clinical staging can be estimated according to the radiological evaluation. Lin et al. [23] reported high sensitivity and specificity levels for MRI and an accuracy of 94%. However, other authors reported that the accuracy of MRI can be as low as 65% [24]. The sensitivity and accuracy levels obtained in this study were higher than in previous reports. The kappa coefficients also showed good correlations; thus, radiologists' experience is important for the interpretation of imaging results.

The intraoperative pathological examination of frozen-sectioned specimens is convenient for the detection of myometrial invasion [14, 15, 25]. However, Case et al. [16] reported that the accuracy of frozen sectioning is low (67%), posing a risk for under-staging, which can lead to suboptimal treatment, so they advised surgical staging for all patients with endometrial cancer. In our study, the accuracy of frozen sectioning was high, which is thought to be related to the skill level of the pathologists at our center, who have more than 10 years of experience in gyneco-pathology. In addition, a high correlation was observed between frozen sectioning findings and the final pathological results for deep myometrial invasion.

Tanaka et al. [26] and Kisu et al. [27] reported that frozen sectioning has a higher correlation rate than does MRI. They mentioned that diffusion-weighted MRI can have the same diagnostic precision as frozen sectioning [11]. In our study, the accuracies of MRI and frozen sectioning were similar. Additional frozen sectionings are recommended when MRI is positive or negative for the presence of myometrial invasion [27]. In our study, the correlation ratios were high when MRI and additional frozen sectioning results were interpreted together. In addition, over-diagnosis and under-diagnosis rates were lower with this approach.

Some patients cannot be operated on due to advanced age, morbid obesity, and/or medical comorbidities [2, 17]. In addition, some young patients wish to preserve their fertility [2, 28]. Thus, surgical staging cannot be performed and intra-abdominal or extrauterine spread of the disease cannot be seen in these cases. Clinical evaluation and preoperative MRI may be more important for these non-surgical patient groups.

A limitation of this study is its retrospective design. However, the high accuracy and correlation rates from a high-volume center, as well as the involvement of experienced radiologists and pathologists, support the importance of radiological and intraoperative evaluation. As diffusion-weighted MRI can increase the correlation rate, diffusion-weighted images have also been used recently.

CONCLUSIONS

The detection of myometrial invasion before surgery and the final pathology results reveal the need for lymphadenectomy to predict the prognosis, and are also thought to be very important for non-surgical patients. The assessment of myometrial invasion by preoperative MRI and intraoperative frozen sectioning during the early stages of endometrial carcinoma was highly accurate. Preoperative MRI can have the same diagnostic precision as frozen sectioning. The assessment of myometrial invasion by preoperative MRI and additional intraoperative frozen sectionings provided the most accurate results. So over-diagnosis and under-diagnosis rates were lower with this approach.

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