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Original Article

Comparison of preoperative myometrial invasion on MRI with intraoperative frozen section in predicting adverse prognostic factors and survival in endometrioid endometrial cancer

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Abstract

Aim: There are no studies that have evaluated the accuracy of the finding of myometrial invasion in each modality in predicting adverse prognostic factors and survival. We compared the association of myometrial invasion on MRI and frozen section with presence of adverse prognostic factors and decreased disease-specific survival (DSS) in endometrioid endometrial cance.

Material and Methods: A total of 149 patients diagnosed and treated surgically for endometrioid endometrial cancer at a single institution between 2010 and 2017 were included in the study. Accuracies of radiological myometrial invasion and frozen section myometrial invasion in predicting the histopathological myometrial invasion, other adverse prognostic factors and DSS were compared.

Results: Frozen section had an accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 89.2%, 100.0%, 84.7%, 72.8% and 100.0%, respectively in diagnosing histopathological deep (≥50%) myometrial invasion with a kappa value of 0.876 ($p<0.001$). MRI had an accuracy, sensitivity, specificity, PPV and NPV of 71.3%, 55.8%, 80.6%, 63.2%, 75.3%, respectively with a kappa value of 0.392 ($p<0.001$) in predicting deep myometrial invasion. The accuracy of the finding of deep myometrial invasion on frozen section was higher than the finding of deep myometrial invasion on MRI in predicting the presence of adverse prognostic factors. However, the specificities and NPV's were higher than their respective sensitivity and PPV values overall for both modalitiesd.

Conclusion: Although MRI is frequently used in the preoperative evaluation of patients with endometrial cancer, the finding of deep myometrial invasion on MRI was not as accurate as that of frozen section in predicting the presence of adverse prognostic factors and poor survival. However, both test modalities demonstrated high specificity and NPV. As such both tests may provide higher efficacy in identifying patients without advanced disease who may not require complete lymph node dissection.

Keywords: Endometrioid endometrial cancer; MRI; frozen section; myometrial invasion; prognostic factors; prognosis; survival.

INTRODUCTION

In parts of the world with the successful implementation of cervical cancer screening programs, endometrial cancer is the most common gynecological malignancy (1). Preoperative assessment of the extent of disease is critical for evaluating the need for surgical procedures such as lymph node dissection in patients with endometrial cancer. Magnetic Resonance Imaging (MRI) is increasingly used in the preoperative work-up of patients with endometrial cancer (2). Among the most commonly assessed findings on MRI is myometrial invasion (3). Despite the prevalent preoperative use of MRI, intraoperative frozen sectioning is also employed in many institutions to guide surgical management.

Although a number of studies have compared the accuracy of MRI and frozen sections in predicting histopathological

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myometrial invasion (4-6), there are limited studies that have evaluated the association of myometrial invasion in each modality with adverse prognostic factors and poor survival. Herein, we sought to compare the association of myometrial invasion on MRI and frozen section with the presence of adverse prognostic factors such as the presence of lymphovascular space invasion (LVSI), lymph node metastasis (LNM), high tumor grade, advanced stage and decreased disease-specific survival (DSS) in endometrioid endometrial cancer. The preoperative and intraoperative findings of myometrial invasion can be used to predict the definitive histopathological patient characteristics.

MATERIAL and METHODS

This was a retrospective cohort study. A total of 149 patients diagnosed and treated surgically for endometrioid endometrial cancer at a single institution between 2010 and 2017 were included in the study. Patients who met the following criteria were included in the study: a. undergoing preoperative MRI within one month before the operation at the same institution where the surgeries took place b. diagnosed with endometrioid endometrial cancer c. was followed-up at the same institution d. underwent surgical treatment including hysterectomy, comprehensive lymphadenectomy e. received frozen sectioning intraoperatively for the endometrial tumor. Patients who received radiotherapy or chemotherapy prior to surgical treatment were excluded from the study. Patients underwent hysterectomy and bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy as well as adjuvant therapy as indicated. A comprehensive lymph node dissection was performed for all patients. Age, preoperative MRI myometrial invasion findings, myometrial invasion on frozen sections, histopathological diagnoses, and clinicopathological patient characteristics were retrieved and reviewed from patient records. Disease-specific survival (DSS) as the interval from the date of diagnosis to the time of death due to disease, was calculated from follow-up records and National Death Registry, last checked on June 6, 2019. The study was approved by the Institutional Ethics Committee (#13, 27 June 2019).

Accuracy of myometrial invasion on MRI in predicting deep (≥50%) histopathological myometrial invasion was compared to frozen sectioning. Also, the accuracy of the finding of deep myometrial invasion on MRI was compared to the finding of deep myometrial invasion on frozen sectioning in predicting the presence of adverse prognostic factors (advanced stage, higher grade, LVSI, LNM) and DSS.

Pelvic MRI protocol

Pelvic MRI was obtained by a 1.5-T MR imaging unit (MagnetomAera, Siemens Medical Systems, Germany) within one month before surgery. The imaging protocol consisted of sagittal, axial, coronal and oblique axial T2-weighted images and T1-weighted images in the axial plane before and after administration of contrast in the axial plane. Dynamic contrast material-enhanced (DCE) imaging of the pelvis was performed after the administration of 0.1 mmol/kg of body weight gadolinium chelate (Gadovist; Bayer, Mississauga, Ontario, Canada). The extent of myometrial invasion was noted as superficial (<50% of the myometrium) or deep (≥ 50% of the myometrium). MRI findings were interpreted by a radiologist experienced in gynecological oncology.

Frozen section analysis

Immediately after hysterectomy, the specimen was sent to the Department of Pathology to be evaluated by an experienced pathologist in the field of Gynecological Oncology. The specimen was sliced longitudinally along the lateral walls enabling the gross inspection of the endometrial cavity. The specimen was then cut transversely from the mucosa to the serosa and examined microscopically and macroscopically. Two full-thickness samples were sliced from what was deemed to be the deepest point of the myometrial invasion of the tumor, macroscopically. The specimen block was frozen in a film of Optimal Cutting Temperature Compound and sliced at 5 µm by a microtome on a cryostat. Several levels of sliced specimen spaced out at a distance of 25-50 µm were stained with hematoxylin and eosin and microscopically assessed for the extent of myometrial invasion. The location, depth of myometrial invasion, the histological subtype and the grade of the tumor and its possible extension to the cervix were reported following the frozen sectioning. Several sections including the remnants of the frozen section were used for paraffin embedding and fixation for a definitive histopathological diagnosis made by a different pathologist experienced in the field of Gynecological Oncology.

Statistical Analysis

The prognostic significance of myometrial invasion on MRI was compared to that on frozen sectioning in terms of histopathological myometrial invasion and other prognostic factors using the Chi-Square test and post-hoc test with Bonferroni adjustments. Kaplan-Meier analysis was used to investigate the potential association between outer half myometrial invasion on MRI and frozen sectioning with survival outcomes and the Log-rank test was used to determine statistical significance. Accuracy, sensitivity, specificity, positive predictive value, and negative predictive values were calculated for the finding of deep myometrial invasion on frozen section and MRI in predicting adverse prognostic factors. Wilcoxon signed-rank test was used to compare the accuracies of MRI and frozen section. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 25.0 statistical software package (SPSS Inc., Chicago, IL).

RESULTS

A total of 149 patients diagnosed with endometrioid endometrial cancer were included in the study. The average age of patients was 60±10.8 (34-88). The distribution of clinicopathological and radiological patient characteristics are presented in Table 1.

Table 1. Distribution of clinicopathological characteristics of patients with endometrioid endometrial cancer.

Patient characteristics		N (%)
Stage	I or II	86%
	III or IV	14%
MI	Absent	60%
	Present	40%
Grade	1	70%
	2	24%
	3	6%
LVSI	Absent	83%
	Present	17%
LNM	Absent	89%
	Present	11%
MI on frozen section	<50%	75%
	≥50%	25%
MI on MRI	<50%	67%
	≥50%	33%

MI: myometrial invasion

The associations of myometrial invasion on MRI and frozen section with definitive tumor stage, myometrial invasion, tumor grade, LNM, and LVSI are shown in Tables 2 and 3, respectively. Frozen section had an accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 89.2%, 100.0%, 84.7%, 72.8% and 100.0%, respectively in diagnosing histopathological deep myometrial invasion with a kappa value of 0.876 (p<0.001). MRI had an accuracy, sensitivity, specificity, PPV and NPV of 71.3%, 55.8%, 80.6%, 63.2%, 75.3%, respectively with a kappa value of 0.392 (p<0.001) in predicting definitive deep myometrial invasion.

Table 2. Association of myometrial invasion on frozen section with prognostic factors in endometrioid endometrial cancer.

		Myometrial Invasion on Frozen Section		
		<50% (%)	≥50%	P
Stage	I or II	89%	65%	0.006
	III or IV	11%	35%	
Definitive MI	<50%	85	0	<0.001
	≥50%	15	100%	
Grade	1 or 2	96%	86%	0.002
	3	4%	14%	
LNM	Absent	93%	86%	0.016
	Present	7%	14%	
LVSI	Absent	90%	71%	0.004
	Present	10%	29%	

Table 3. Association of myometrial invasion on MRI with prognostic factors in endometrioid endometrial cancer.

		Myometrial Invasion on MRI		
		<50% (%)	≥50%	P
Stage	I or II	92%	76%	0.022
	III or IV	8%	24%	
Definitive MI	<50%	75%	37%	<0.001
	≥50%	25%	63%	
Grade	1 or 2	96%	84%	0.068
	3	4%	16%	
LNM	Absent	93%	81%	0.068
	Present	7%	19%	
LVSI	Absent	90%	67%	0.002
	Present	10%	33%	

The accuracy, sensitivity, specificity, PPV and NPV values for diagnosing the presence of adverse prognostic factors based on the finding of deep myometrial invasion on frozen section and MRI are given in Table 4. The accuracy, sensitivity, specificity, PPV and NPV of deep myometrial invasion on frozen section for predicting advanced stage were 72.4%, 25.5%, 92.2%, 57.8% and 74.6%, respectively. The accuracy, sensitivity, specificity, PPV and NPV of deep myometrial invasion on frozen section for predicting grade 3 tumors were 73.5%, 71.4%, 73.5%, 11.9% and 98%, respectively. The accuracy, sensitivity, specificity, PPV and NPV of deep myometrial invasion on frozen section for predicting the presence of LNM were 72.1%, 56.3%, 74.1%, 21.9% and 92.9%, respectively. The accuracy, sensitivity, specificity, PPV and NPV of deep myometrial invasion on frozen section for predicting the presence of LVSI were 72.3%, 51.8%, 76.5%, 33.3% and 87.7%, respectively.

The accuracy, sensitivity, specificity, PPV and NPV of deep myometrial invasion on MRI for predicting advanced stage were 69.3%, 60.0%, 70.7%, 23.6% and 92.1%, respectively. The accuracy, sensitivity, specificity, PPV and NPV of deep myometrial invasion on MRI for predicting grade 3 tumors were 69.8%, 66.7%, 70.0%, 15.7% and 96.1%, respectively. These values for predicting the presence of LNM based on the finding of deep myometrial invasion on MRI were 67.3%, 58.3%, 68.3%, 18.4% and 93.1%, respectively. The values for predicting the presence of LVSI based on the presence of deep myometrial invasion on MRI were 72.3%, 60.0%, 70.7%, 23.7% and 92.1%, respectively.

Table 4. Accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the finding of deep myometrial invasion on frozen section and MRI in predicting the presence of certain adverse prognostic factors in endometrioid endometrial cancer.

		Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p-value*
Myometrial Invasion	Frozen	89.2	100.0	84.7	72.8	100.0	<0.001
	MRI	71.3	55.8	80.6	63.2	75.3	
Advanced Stage	Frozen	72.4	25.5	92.2	57.8	74.6	0.038
	MRI	69.3	60.0	70.7	23.6	92.1	
High Grade	Frozen	73.5	71.4	73.5	11.9	98.0	0.022
	MRI	69.8	66.7	70.0	15.7	96.1	
LVSI	Frozen	72.3	51.8	76.5	33.3	87.7	0.10
	MRI	72.3	60.0	70.7	23.7	92.1	
LNM	Frozen	72.1	56.3	74.1	21.9	92.9	0.013
	MRI	67.3	58.3	68.3	18.4	93.1	

*Comparison of accuracy

Patients with definitive histopathological superficial myometrial invasion had a mean DSS of 97.1 [95% Confidence Interval (CI), 93.6-100.6] months, which was significantly higher than DSS of patients with histopathological deep myometrial invasion – 79.9 (95% CI, 71.0-88.8) months (p=0.001) (Figure 1). Patients with superficial myometrial invasion on frozen sections had a mean DSS of 96.3 (95% CI, 92.5-100.1) months, which was significantly higher than DSS of patients with deep myometrial invasion on frozen section – 75.3 (95% CI, 62.0-88.6) months (p=0.009) (Figure 1). Patients with superficial myometrial invasion on MRI had a mean DSS of 96.0 (95% CI, 91.9-100.1) months, compared to patients with deep myometrial invasion on MRI with a DSS of 80.6 (95% CI, 71.8-89.3) months (p=0.05) (Figure 1).

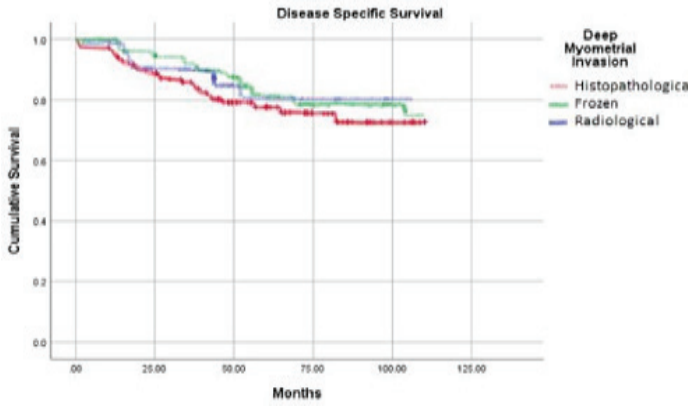

Figure 1. Comparison of survival in months according to histopathological (p=0.001), frozen section (p=0.009) and radiological (p=0.05) deep myometrial invasion

DISCUSSION

Endometrioid endometrial cancer is the most common histological subtype of endometrial cancer (1). The 5-year survival for endometrial cancer is over 90% (7,8). Most patients with endometrial cancer are diagnosed at an early stage (7,8). Although the first choice of treatment is a hysterectomy, there is controversy surrounding the performance of routine systematic lymphadenectomy for all patients (9,10). Several studies have reported of a survival benefit in patients with myometrial invasion who undergo lymphadenectomy (11). Deep myometrial invasion has been associated with the presence of lymph node metastasis (12) and therefore, preoperative MRI and intraoperative frozen sections are being frequently used to predict the presence of deep myometrial invasion. The most common positive finding on preoperative MRI is myometrial invasion (3). Histopathological myometrial invasion, higher grade, LVSI and extrauterine disease spread are associated with the presence of metastatic lymph nodes (13,14). Various studies have attempted to investigate the association between findings on different imaging modalities and definitive histopathological tumor characteristics. For example, Gulseren et al. have reported that increased SUV max on PET-CT was associated with high grade, deep myometrial invasion, advanced stage and larger tumor size in patients with endometrioid endometrial cancer (15).

Herein, we sought to compare the accuracy of the finding of myometrial invasion on MRI with that of frozen section in predicting the final histopathological presence of LVSI, deep myometrial invasion, metastatic lymph nodes, advanced stage as well as DSS. In this study, the finding of deep myometrial invasion on frozen sections was significantly associated with the presence of all adverse

prognostic factors. In contrast, the finding of deep myometrial invasion on MRI was significantly associated with a definitive diagnosis of deep myometrial invasion, advanced stage, presence of LVSI but not high tumor grade or LNM. In this study, the finding of deep myometrial invasion on frozen section demonstrated higher accuracy in predicting the presence of adverse prognostic factors compared to the finding of deep myometrial invasion on MRI. The presence of deep myometrial invasion on frozen section was significantly associated with poor survival. However, both modalities displayed higher specificities and NPVs than their respective sensitivities and PPVs in terms of predicting the presence of adverse prognostic factors. As such, both modalities may enable the identification of patients who are at low risk of having metastatic lymph nodes. Therefore, lymph node dissection can be avoided in patients who demonstrate superficial myometrial invasion on frozen section and MRI.

A number of studies have compared the accuracy of MRI in predicting deep myometrial invasion to the accuracy of frozen sections (4-6). In their cross-sectional study, Sanchez et al. reported that intraoperative frozen section was slightly better in predicting definitive deep myometrial invasion but both modalities were useful overall (4). Similarly, Kisu et al. found that frozen section was significantly more accurate in predicting the histopathological presence of deep myometrial invasion than MRI (5). In their study, the sensitivity and specificity of MRI for detection of deep myometrial invasion were 74.2% and 89.6%, and these values for frozen sections were 73.1% and 100%, respectively. Tanaka et al. conducted a study in which the diagnostic accuracy of MRI was compared to that of frozen sections in predicting deep myometrial invasion (6). In a total of 378 patients with different subtypes of endometrial cancer, the sensitivity, specificity, PPV and NPV for deep myometrial invasion on MRI were 57.8%, 92.0%, 69.3%, and 87.5%, respectively, with a kappa value of 0.53. These values for frozen sections were 66.7%, 97.9%, 90.9%, and 90.4%, respectively with a kappa value of 0.71 (6). Lastly, Haldorsen et al. found the accuracy of MRI in predicting the presence of deep myometrial invasion to be as low as 65% (16). Our results are consistent with previous studies that have found frozen section to be superior to MRI in predicting histopathological deep myometrial invasion with similar values of accuracy, sensitivity and specificity.

Although studies have sought to compare the diagnostic accuracy of MRI and frozen section in predicting deep myometrial invasion, there are limited studies comparing the accuracy of the finding of deep myometrial invasion on MRI and frozen section in predicting the presence of risk factors associated with advanced disease and presence of metastatic lymph nodes. Hahn et al. have investigated the significance of presence of myometrial invasion and cervical invasion for predicting the presence of risk factors associated with metastatic lymph nodes (17). They found that both MRI and intraoperative frozen section had a high specificity and high NPV for predicting myometrial and cervical invasion. Their findings demonstrated that both modalities could be used to identify low-risk patients who would not require lymph node dissection. Similar to the study by Hahn et al, in this study, the finding of deep myometrial invasion on frozen sections and MRI had high specificity and NPVs for predicting the presence of risk factors associated with the presence of metastatic lymph nodes and advanced disease. Deep histopathological myometrial invasion offered the highest predictive value of poor DSS. Additionally, the presence of deep myometrial invasion on frozen section was significant in predicting DSS compared to myometrial invasion on MRI.

Although studies have suggested that the accuracy of frozen section can be low (18), we have found that the finding of deep myometrial invasion on frozen section was highly accurate in predicting histopathological deep myometrial invasion and it was more accurate than MRI. In contrast to our findings, Karataşlı et al. reported that MRI and frozen section had accuracies of 88.7 and 94.4%, respectively. They noted that preoperative MRI could carry similar precision in diagnosing myometrial invasion as frozen section (19). Additionally, they also demonstrated that when used together, preoperative MRI and intraoperative frozen sections yielded the highest diagnostic accuracy than either modality alone (19).

Although MRI is frequently used in the preoperative evaluation of patients with endometrial cancer, the finding of deep myometrial invasion on MRI was not as accurate as frozen section in predicting the presence of adverse prognostic factors and poor survival. However, both test modalities demonstrated high specificity and NPV. As such, both tests may provide higher efficacy in identifying patients without advanced disease who may not require complete lymph node dissection

CONCLUSION

Although MRI is frequently used in the preoperative evaluation of patients with endometrial cancer, the finding of deep myometrial invasion on MRI was not as accurate as frozen section in predicting the presence of adverse prognostic factors and poor survival. However, both test modalities demonstrated high specificity and NPV. As such, both tests may provide higher efficacy in identifying patients without advanced disease who may not require complete lymph node dissection.

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