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# Overdiagnosis of Endometrium Cancer: A Retrospective Study

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## ABSTRACT

**Objective:** The deep myometrial invasion (MI) is a risk factor for lymph node metastases in endometrial cancer (EC). There is no consensus regarding which diagnostic method should be preferred for evaluating deep MI. Preoperative magnetic resonance imaging (MRI) and intraoperative frozen section (FS) examinations are the most definitive two diagnostic methods for evaluating deep MI. This study was designed to compare the diagnostic accuracy of preoperative MRI and intraoperative FS examinations in predicting deep MI and review their impact on clinical management and cost on health care.

**Methods:** MRI and FS findings of 65 patients with surgically staged EC between 2016 and 2019 were evaluated for deep MI. A definitive diagnosis of paraffin sections was used as the gold standard diagnosis.

**Results:** For detection of deep MI, accuracy, sensitivity, and specificity of MRI were 53.06%, 61.9%, and 65.9% respectively and significantly low consistency was observed between the final pathology results (p=0.034). Significant strong consistency was observed between the FS and the final pathology results for the detection of deep MI. Accuracy, sensitivity, and specificity were 77.18%, 85.7%, and 95.5%, respectively (p=0.000). Laparotomy rate (p=0.026), operation time (p=0.047), total days of hospitalization (p=0.004), rate of intensive care administration (p=0.027), and the total health-care cost were significantly higher in the MRI inconsistent group (p=0.015).

**Conclusion:** For the diagnostic approach and staging algorithm of EC, each clinic should take into account the accuracy of their diagnostic tests and individualize on a patient and clinical basis.

**Keywords:** Cost and cost analysis, endometrial neoplasms, frozen sections, magnetic resonance imaging, overdiagnosis, overtreatment

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## INTRODUCTION

The World Health Organization reported 380,000 new cases of endometrial cancer (EC) diagnosed in 2018 worldwide. Overall, EC is the sixth most common cancer in women after breast, colon, lung, cervical, and thyroid cancer. On the other hand, among the gynecological malignancies in women, EC is the most common cancer in developed countries and the second most common cancer in developing countries after cervix carcinoma (1). Pathologically, the most common type of EC is the endometrioid type with a better prognosis (2). Clinically the cancer is divided into two types. Type I tumors are low-grade [Federation of Gynecology and Obstetrics (FIGO) grade 1 and 2] endometrioid type ECs and have a better prognosis. Type II tumors include FIGO grade 3 endometroid and non-endometrioid EC and are associated with a poor prognosis. Poor prognostic factors showing high risk of lymph node metastasis are type II tumors, deep myometrial invasion (MI) ≥50%, lymphovascular space invasion (LVSI), and cervical stromal invasion (3). Tumor size greater than 2 cm is associated with an increased risk of lymph node metastasis in endometrioid-type EC regardless of the stage (4). According to the 2009 FIGO guidelines; EC staging is performed surgically and every patient should be operated unless there is a contraindication for surgery. Despite technological developments today, no imaging method can replace surgical staging with histological tissue diagnosis confirmation (3,5). Today, during surgical staging, complete lymphadenectomy, which was performed routinely, is now accepted as a treatment option for high-risk patients. In the MRC ASTEC study, it was shown that lymphadenectomy has no therapeutic benefit in early-stage EC (3,6,7). Preoperative magnetic resonance imaging (MRI) and intraoperative frozen section (FS) examinations are the most definitive diagnostic methods, often used together, in the evaluation of deep MI and cervical stromal invasion (8). The primary aim of this study was to compare the diagnostic accuracy of preoperative MRI and intraoperative FS examinations in predicting deep MI. Our secondary aim is to investigate the accuracy of existing diagnostic tests in the detection of low-risk patients and their impact on clinical management and cost on health care in our clinic.

## METHODS

### Study Design

The study was planned retrospectively and cross-sectionally. The study population consisted of 68 patients who were surgically staged for EC between 2015 and 2019 in our clinic. Three patients whose MRI reports could not be obtained were excluded from the study. Ethics approval with thesis subjects number E.9224 was obtained from Taksim Training and Research Hospital Clinical Research Ethics Committee on 27.02.2019 (decision no: 3). The diagnosis of EC was made by pathological examinations obtained from Pipelle biopsy, dilation curettage, or hysteroscopic biopsy materials. Final pathology results were determined by paraffin block results. Patients were staged according to the FIGO 2009 criteria. The demographic data of the patients and additional risk factors for EC, pathology reports, MRI reports, and final pathology reports were accessed from the clinical database of our hospital. The duration of the operation, the need for blood product replacement perioperative or postoperative period, the need for intensive care follow-up after the operation, the length of stay in the hospital, and the pre-operative and postoperative hemoglobin levels were obtained from the surgery and anesthesia reports. Total costs for patients were calculated by Turkish Lira (TL) and converted into US dollars ($) according to the exchange rate of the Central Bank of the Republic of Turkey on the discharge date of the patients and used in cost analysis.

### MRI Examination

All patients underwent preoperative routine contrast-enhanced pelvic MRI examinations before the operation in our hospital with a General Electric (GE signa HD Milwaukee, USA) 1.5 Tesla device. The imaging protocol was axial and sagittal T2-weighted fast-spin echo. MRI sequences were performed with slice thicknesses of 5 mm, intersectional gaps of 1.0 mm, and fields of 20-50 cm. Dynamic contrast-enhanced MRIs were obtained with axial fat-saturated T1-weighted GRE imaging before and 30, 60, and 120 seconds after intravenous administration of contrast agent using 0.1 mmol/kg meglumine gadoterate (Magnescope®; Guerbet Japan). MRI examination was reported by radiologists specialized in gynecologic oncology at our hospital. The MRI data of each patient was examined by at least two radiologists, and the final MRI diagnoses were determined through their discussion of observations.

### FS Examination

The hysterectomy and bilateral salpingo-oopherectomy material was perioperatively carefully examined and the endometrium was sliced at 3-5 mm intervals, and full-thickness endometrial tissue, which is the deepest visible macroscopic invasion area, was examined microscopically. After the entire specimen was fixed on the coverslip with a cryostat, it was placed in a pre-chilled Hystobath (Nesland Instruments Newington, NH). After 4-6 µm-thick tissue slices were cut with a acrotome (Leica CM 1900, Leica Microsystems, Numsloch, Germany), they were quickly stained with hematoxylin-eosin staining, and the stage of deep MI of the tumor was microscopically evaluated by the expert pathologists of our hospital.

### Surgical Staging for EC

The choice of abdominal surgery or endoscopic surgery was made by the patient, surgeon, and anesthesiologist, with the patient's informed consent, in a multidisciplinary manner, taking into account the patient's American Society of Anesthesiology (ASA) score and additional comorbidities. All procedures in our clinic were performed by gynecological oncology surgeons. As the operating procedure, after exploration by laparoscopy or laparotomy, hysterectomy and bilateral salpingo-opherectomy material were sent to the pathology department of our hospital for FS examination. In case of EC with suspicious lymph node

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involvement in preoperative MRI examinations, or with deep MI of the tumor above 50% in the pre-operative MRI or intraoperative FS examination, or in type II tumors, complete lymph node dissection was performed rather than suspicious lymph node sampling.

### Statistical Analysis

Mean, standard deviation, median, lowest, highest, frequency, and percentage values were used in the descriptive statistics. The distribution of variables was measured using the Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. Pearson's chi-square test was used in the analysis of qualitative independent data, and Cohen's kappa test was used for the consistency analysis. SPSS 22.0 (IBM Corporation, Armonk, NY, USA) program was used in the analysis. A p-value of <0.05 was considered significant.

## RESULTS

### Demographic Data

Demographic and pathological data of all patients (n=65) are given (Table 1a, b). The age range of the patients was between 42

**Table 1a. Demographic and pathological data of the patients**

| | Min-max | Median | Mean ± SD |
|---|---|---|---|
| Age | 42.0-80.0 | 61.0 | 61.1±8.1 |
| Gravida | 0.0-15.0 | 5.0 | 4.7±3.0 |
| Parity | 0.0-11.0 | 3.0 | 3.6±2.3 |
| Operation time (minutes) | 120-480 | 240 | 241±68 |
| Hospital stay (days) | 3.0-27.0 | 11.0 | 10.9±5.1 |
| Cost in TL | 1204-6194 | 2790 | 2953±1182 |
| Cost in $ | 207-2431 | 836 | 871±384 |
| Admission Hb | 9.3-15.0 | 12.0 | 12.1±1.3 |
| Discharge Hb | 7.2-14.0 | 11.0 | 10.9±1.3 |
| Tumor size | 0.2-12.0 | 4.0 | 4.7±2.8 |

TL: Turkish Lira, $: US Dollar, Hb: hemoglobin, SD: standard deviation

**Table 1b. Demographic and pathological data of the patients**

| | | Number | % |
|---|---|---|---|
| ASA score | I | 16 | 24.6% |
| | II | 37 | 56.9% |
| | III | 12 | 18.5% |
| Surgery type | Laparoscopy | 29 | 44.6% |
| | Laparotomy | 36 | 55.4% |
| ES Transfusion | (-) | 53 | 81.5% |
| | (+) | 12 | 18.5% |
| Post-op ICU | (-) | 45 | 69.2% |
| | (+) | 20 | 30.8% |
| Final pathology FIGO surgical stage | Ia | 40 | 61.5% |
| | Ib | 9 | 13.8% |
| | II | 9 | 13.8% |
| | IIIb | 1 | 1.5% |
| | IIIc1 | 4 | 6.2% |
| | IIIc2 | 1 | 1.5% |
| | IV | 1 | 1.5% |
| Tumor location | Fundus/corpus | 53 | 81.5% |
| | Lower segment | 12 | 18.5% |
| PB histopathological type | Grade I-II | 58 | 89.2% |
| | Grade III | 7 | 10.8% |

ASA: American Society of Anesthesiology, FIGO: Federation of Gynecology and Obstetrics, ES: erythrocyte suspension, ICU: intensive care unit, PB: pipelle biopsy

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and 80 years, and the mean age was 61.1±8.1 years. The number of patients with an ASA score of III was 12 (18.5%). The number of patients with previous abdominal surgery was 25 (38%). While laparoscopic intervention was preferred in 29 patients (44.6%), surgery was performed by laparotomy in 36 patients (55.4%). The mean operation time was 241±68 minutes [minimum-maximum (min-max): 120-480 minutes], while the mean hospital stay was 10.9±5.1 days (min-max: 3.0-27 days). While the total cost in TL was 2953±1182 TL on average (min-max: 1204-6194 TL), it was $871±$384 in $ (min-max: $207-$2431). While the mean hemoglobin values before the operation were 12.1±1.3 mg/dL (min-max: 9.3-15.0 mg/dL), the mean hemoglobin values after the operation were 10.9±1.3 mg/dL (min-max: 7.2-14.0 mg/dL). Erythrocyte suspension transfusion was administered to 12 (18.5%) patients preoperatively or postoperatively. Twenty patients (30.8%) were admitted to the intensive care unit (ICU) of our hospital after the operation. In the final postoperative pathological staging, 40 patients were FIGO stage Ia (61.5%), 9 patients were FIGO stage Ib (13.8%), 9 patients were FIGO stage II (13.8%), 1 patient was FIGO stage IIIb (1.5%), 4 patients were FIGO stage IIIc1 (6.1%), 1 patient was FIGO stage IIIc2 (1.6%), and 1 patient was FIGO stage IV (1.6%). The mean tumor size was 4.7±2.8 cm (min-max: 0.2-12.0 cm). The tumor was located in the fundus/corpus in 53 (81.5%) patients, while it was located in the lower segment in 12 (18.5%) patients.

## Deep MI Detection Results of MRI and FS Examinations

In our study, when the pre-operative MRI examinations and the final pathology results were compared in terms of deep MI of the tumor, a significantly low consistency was observed, accuracy, sensitivity, and specificity were 53.06%, 61.9%, and 65.9% respectively (p=0.034). When the intraoperative FS examinations and the final pathology results were compared in terms of the degree of deep MI of the tumor, a significant strong consistency was observed, accuracy, sensitivity, and specificity were 77.18%, 85.7%, and 95.5%, respectively (p=0.000) (Table 2).

In the literature, the presence of adenomyosis or uterine myoma is associated with low consistency of preoperative MRI examination with the final pathology results in detecting deep MI (9,10). In our study, when the pathologies that could increase the discordance between the pre-operative MRI examinations and final pathology results for detecting deep MI were compared; the presence of uterine fibroid or adenomyosis rate, tumor size, and location of the tumor did not differ significantly between the two groups; the preoperative MRI examinations and final pathology results were consistent or inconsistent in terms of detecting deep MI (p>0.05) (Table 3a, b).

## Impact on Clinical Management and Cost on Health Care for Patients

When the two groups of patients whose preoperative MRI examinations and final pathology results were consistent and inconsistent were compared; the two groups did not differ significantly in age or ASA score (p>0.05). In those with preoperative MRI examinations and the final pathology results are inconsistent; laparotomy rate (p=0.026), operation time (p=0.047), total days of hospitalization (p=0.004), need for ICU administration after the operation (p=0.027) and total cost for patients in TL (p=0.015)

**Table 2. Comparison of MRI and frozen examinations with final pathology results**

| | | Myometrial invasion based on final pathology | | Accuracy | Sensitivity | Specificity | Kappa | p-value |
|---|---|---|---|---|---|---|---|---|
| | | (-) | (+) | | | | | |
| MRI invasion | (-) | 29 | 8 | 53.06% | 61.9% | 65.9% | 0.256 | 0.034 |
| | (+) | 15 | 13 | | | | | |
| Frozen invasion | (-) | 42 | 3 | 77.18% | 85.7% | 95.5% | 0.822 | 0.000 |
| | (+) | 2 | 18 | | | | | |
| At least one of the MRI or frozen tests | (-) | 27 | 3 | 86.36% | 62.79% | 70.77% | 0.429 | 0.000 |
| | (+) | 16 | 19 | | | | | |

Cohen's kappa analysis; MRI: magnetic resonance imaging

**Table 3a. Comparison of demographic data of the groups whose MRI and final pathology results were compatible and inconsistent and their effects on patient management**

| | Pathology-MR consistent | | Pathology-MR inconsistent | | p-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median | Mean ± SD | Median | |
| Age | 61.1±8.4 | 62.0 | 61.0±7.8 | 60.0 | 0.964[t] |
| Operation time (minutes) | 233±72 | 210 | 256±60 | 240 | 0.047[m] |
| Total length of stay (days) | 9.5±4.5 | 8.0 | 13.3±5.4 | 11.0 | 0.004[m] |
| Cost (TL) | 2699±1108 | 2640 | 3418±1194 | 3170 | 0.015[m] |
| Cost ($) | 774±335 | 778 | 1048±410 | 952 | 0.005[m] |

[t]t-test, [m]Mann-Whitney U test. TL: Turkish Lira, $: US Dollar, SD: standard deviation, MRI: magnetic resonance imaging

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and $ (p=0.005) were significantly higher compared to the group whose preoperative MRI examinations and final pathology results were consistent (Table 4a, b).

## DISCUSSION

### Evaluating Each Diagnostic Test Separately

Investigating 65 patients who were surgically staged for EC within 4 years in our clinic, when each diagnostic test was considered separately; we performed advanced surgical staging in 15 patients (23%) with a low risk of EC due to the low specificity of the pre-operative MRI examinations we routinely requested. This number was two patients (3%) for the FS analysis. On the other hand, if we had planned the surgical staging without preoperative MRI examinations but only with intraoperative FS examinations, we would have underestimated the surgical staging of three patients (4.6%). The first case, total lymph node dissection was already planned preoperatively for the patient's operation since the endometrial biopsy result was reported as high-grade serous cancer. Our second patient, a 64-year-old FIGO stage I endometrioid type adenocarcinoma, was 4x2.5 cm in size and located in the fundus on ultrasound examination. In both pre-operative MRI, intraoperative FS, and postoperative paraffin section examinations, deep MI was <50%; however, in the pre-operative MRI examination, possible pelvic lymph node involvement was reported. Therefore, total lymph node dissection was performed. In the final pathology results of 25 pelvic and paraaortic lymph node examinations, one pelvic lymph node was reported as positive in the final pathology results, and the patient was surgically reported as FIGO stage IIIC1. In our last patient, who was 57 years old, with endometrioid adenocarcinoma FIGO stage I, there was a polypoid mass of 4x4.5 cm in the posterior fundus on ultrasound examination. Although the deep MI of the tumor was <50% in the pre-operative MRI and intraoperative FS examinations, the deep MI of the tumor was ≥50% in the final paraffin examinations. Because the tumoral involvement was not detected in the suspicious pelvic lymph node sampling of the patient, the patient was surgically reported as FIGO stage Ib.

### The Mayo Criteria

Grade I and II endometrioid type EC, size less than 2 cm in the pre-operative radiological examinations and deep MI <50% in

**Table 3b. Comparison of demographic data of the groups whose MRI and final pathology results were compatible and inconsistent and their effects on patient management**

| | | Pathology-MR consistent | | Pathology-MR inconsistent | | p-value |
|---|---|---|---|---|---|---|
| | | Number | (%) | Number | (%) | |
| ASA | I | 12 | 28.6% | 4 | 17.4% | 0.547[X²] |
| | II | 22 | 52.4% | 15 | 65.2% | |
| | III | 8 | 19.0% | 4 | 17.4% | |
| Surgical | Laparoscopy | 23 | 54.8% | 6 | 26.1% | 0.026[X²] |
| | Laparotomy | 19 | 45.2% | 17 | 73.9% | |
| Need for ICU after surgery | (-) | 33 | 78.6% | 12 | 52.2% | 0.027[X²] |
| | (+) | 9 | 21.4% | 11 | 47.8% | |

[X²]Pearson's chi-square test. ASA: American Society of Anesthesiology, MRI: magnetic resonance imaging, ICU: intensive care unit

**Table 4a. Comparison of pathologies that may increase the inconsistency of MRI examination with final pathology results**

| | | Pathology-MR consistent | | Pathology-MR inconsistent | | p-value |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| Presence of fibroid/ adenomyosis in the pathology report | (-) | 26 | 61.9% | 17 | 73.9% | 0.328[X²] |
| | (+) | 16 | 38.1% | 6 | 26.1% | |
| Tumor location in pathology report | Located in the fundus/corpus | 33 | 78.6% | 20 | 87.0% | 0.405[m] |
| | Located in the lower segment | 9 | 21.4% | 3 | 13.0% | |

[m]Mann-Whitney U test, [X²]Pearson's chi-square test. MRI: magnetic resonance imaging

**Table 4b. Comparison of pathologies that may increase the inconsistency of MRI examination with final pathology results**

| | Pathology-MR consistent | | Pathology-MR inconsistent | | p-value |
|---|---|---|---|---|---|
| | Mean ± SD | Median | Mean ± SD | Median | |
| Tumor size in pathology report | 4.4±2.8 | 4.0 | 5.1±2.8 | 4.5 | 0.454[m] |

[m]Mann-Whitney U test, MRI: magnetic resonance imaging, SD: standard deviation

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the intraoperative FS examinations, was defined as "low risk" by Mariani et al. (11). In this patient group, the risk of retroperitoneal lymph node metastasis was found to be 5% or lower. Therefore, routine lymph node dissection can be ignored in this patient group. Later, this idea was supported by a community-based study conducted by Vargas et al. (4). In this patient population, the risk of retroperitoneal lymph node metastasis was reported to be approximately 1%. When we evaluated our three patients who had false-negative intraoperative FS results, we considered the existing criteria because one of our patients had non-endometrioid-type EC on endometrial biopsy and the tumor size was greater than 2 cm in the pre-operative ultrasonographic examinations of our other two patients. We would have included these three patients in the high-risk group for lymph node metastasis. As a result, we could avoid any undertreatment for surgical staging using Mayo criteria.

### Patient Management and Cost Analysis

In our clinic, evaluating patients by a multidisciplinary team, surgical intervention is planned endoscopically if there are no contraindications. In the LAP2 randomized controlled study of the Gynecologic Oncology Group (12), 1696 patients between clinical stages I-IIA were randomized to the laparoscopy group and 920 patients to the laparotomy group. Similar rates of intraoperative complications were found in the laparoscopy group. In the laparoscopy group, a longer operative time (mean, 204 vs. 130 minutes) and a lower postoperative complication rate (14% vs. 21%) were found. In the same study, the >2-day length of hospital stay (52% vs. 94%) and the need for lymph node dissection (8% vs. 4%) were lower in the laparoscopy group; however, no significant difference was found in terms of the total number of lymph nodes removed between the two groups. In our study, although the rate of laparotomy was significantly higher in the group whose preoperative MRI examinations and final pathology results were inconsistent compared to the consistent group, the operation time was 30 minutes longer on average (210 vs. 240 minutes) and the total number of days of hospitalization was 3 days longer on average (8 days vs. 11 days). Likewise, the costs for patients in the group with inconsistent MRI examination results were significantly higher on average by 530 TL ($74) compared to the group with consistent preoperative MRI examination results in terms of deep MI of the tumor (p=0.015).

### The Possible Cause of Low Consistency of MRI According to the Current Literature

The role of FS examination as a diagnostic test in showing the degree of deep MI, shown as a limitation of selective lymph node dissection in the literature, is controversial due to variable sensitivity and specificity results (13,14). The meta-analysis by Andreano et al. (15) reported a sensitivity of 86% and specificity of 86% for dynamic MRI for the diagnosis of deep MI. In our retrospective analysis, the possible cause of our low consistency of preoperative MRI findings and the final pathology results in detecting the deep MI of the tumor is, the pre-operative MRI sequences were performed with slice thicknesses of 5 mm. On the other hand, in intraoperative FS examinations, the endometrium was sliced at 3-5 mm intervals. In the current literature review, reports with high sensitivity and specificity of preoperative MRI for detecting deep MI of the tumor, imaging technique was performed with 3-5 mm intervals.

The current guidelines of the European Society of Gynecological Oncology, the European Society for Radiotherapy and Oncology, and the European Society of Pathology recommend, for predicting deep MI of EC, preoperative MRI examinations are used but not intraoperative FS examination (16,17). However, these guidelines do not show sufficient evidence because there is no satisfactory data directly comparing both methods on the same subjects. We think that the Mayo criteria can be safely used in centers such as our clinic where intraoperative FS examination shows strong consistency in determining deep MI of the tumor. Without combining two diagnostic tests for detecting deep MI but keeping preoperative MRI examination for high-risk tumors for adjacent/distant organ involvement, high-risk patients for LVSI or cervical involvement.

### Study Limitations

The main limitation of this study is the relatively small study population and design retrospectively. Any further prospective large series will support our findings.

## CONCLUSION

Creation and implementation of ideal follow-up and treatment plans in EC emerges as a responsibility, not only a consideration of deontological perspective but also a need in health-care economics in the practice of medicine. Considering current scientific data, we think that our study is important in the EC diagnostic approach and patient management algorithm, as it emphasizes the need for treatment centers to individualize their current diagnostic tests on a patient and clinical basis, considering the accuracy of existing tests.

**Ethics Committee Approval:** Ethics approval with thesis subjects number E.9224 was obtained from Taksim Training and Research Hospital Clinical Research Ethics Committee on 27.02.2019 (decision no: 3).

**Informed Consent:** Retrospective study.

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