Local-Regional Staging of Endometrial Carcinoma: Role of MR Imaging in Surgical Planning

PURPOSE: To assess magnetic resonance (MR) imaging in depicting the depth of myometrial infiltration, cervical invasion, and presence of enlarged lymph nodes in patients with endometrial adenocarcinoma compared with surgicopathologic findings.

MATERIALS AND METHODS: Thirty-seven consecutive patients with endometrial carcinoma were included in this prospective study. All patients underwent MR imaging and surgery. Qualitative image analysis included the depth of myometrial infiltration, infiltration of the uterine cervix, and presence of enlarged lymph nodes. Quantitative image analysis included tumor and myometrium contrast-to-noise ratios during different phases of dynamic imaging. MR imaging findings were compared with surgicopathologic findings. Sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values of MR imaging in depicting myometrial and cervical infiltration and in lymph node assessment were calculated.

RESULTS: Respective sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values in assessing myometrial infiltration were 87%, 91%, 89%, 87%, and 91%; those for cervical infiltration, 80%, 96%, 92%, 89%, and 93%; and those for lymph node assessment, 50%, 95%, 90%, 50%, and 95%. There was significant agreement between MR imaging and surgicopathologic findings in assessment of myometrial invasion ($P < .001$). Myometrial and cervical invasion and lymph node enlargement were correctly assessed with MR imaging in 28 (76%) of 37 patients. Quantitative analysis showed a significant improvement in tumor and myometrium contrast-to-noise ratios during the equilibrium phase compared with the arterial and precontrast phases ($P < .001$).

CONCLUSION: MR imaging coupled with contrast material–enhanced dynamic MR imaging is highly accurate in local-regional staging of endometrial carcinoma; more challenging is the assessment of pelvic and lumboaortic lymph nodes.

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Adenocarcinoma of the endometrium is the fourth most frequent cancer in women, with an estimated 34,000 cases and 6,000 deaths in the United States in 1996 (1).

Surgery is the treatment of choice in patients with noninvasive or locally advanced disease (2). The surgical technique consists of an exploratory laparotomy, with total hysterectomy, bilateral oophorectomy, peritoneal washing, and, in selected high-risk patients, omental and peritoneal biopsies and lymphadenectomy.

Therefore, preoperative clinical and instrumental staging of the local spread of disease, as well as local and distant lymph node involvement, represent a critical step in tailoring the extent and the radicalness of surgery (3). This issue becomes even more relevant considering that, besides the traditional approach, less-invasive surgical techniques have been recently attempted to achieve standard recommendations for the management of endometrial cancer, with the advantage of an excellent surgical outcome of hospitalization, morbidity, and quality of life (4,5).

In particular, laparoscopy and minilaparotomy have been emerging as alternatives for patients with early endometrial cancer (4,5). In addition, it has to be taken into account...
that patients with endometrial cancer, who are often elderly, obese, and have cardiovascular and metabolic comorbidities, which increase the risks of complications from abdominal surgery, are the best candidates for a vaginal approach to total hysterectomy (6). In this setting, a thorough clinical work-up is mandatory to minimize the risk of understaging the disease and jeopardize the entire therapeutic plan.

Magnetic resonance (MR) imaging has proved accurate in the assessment of the depth of myometrial infiltration by endometrial carcinoma (7–11) and has higher accuracy than other imaging modalities, such as sonography and computed tomography (CT) (12,13). MR imaging is also helpful in the assessment of the extent of cervical invasion (14) and in identification of enlarged pelvic and lumboaortic lymph nodes (15,16). Such capabilities could be of great help to the gynecologic oncologist in planning surgery, especially less-invasive surgical approaches.

The aim of our study was to prospectively assess MR imaging in depicting the presence of endometrial adenocarcinoma compared with surgicopathologic findings.

MATERIALS AND METHODS

Study Population

Between June 1997 and February 2001, a total of 46 consecutive patients with untreated endometrial carcinoma were considered for inclusion in this prospective study. The study was approved by the hospital review board, and informed consent was obtained from all patients.

Inclusion criteria for the study were the presence of endometrial adenocarcinoma histologically documented by means of endometrial biopsy and surgical candidates for staging with lymph node sampling based on clinical results.

Six patients were excluded from the study because the definitive histologic diagnosis was different than adenocarcinoma: carcinosarcoma in five patients and leiomyosarcoma in one patient. Three patients were also excluded because they subsequently underwent surgery at a different institution (two patients) or because they refused surgery (one patient). Therefore, our study population included 37 patients (mean age, 58.8 years; range, 36–79 years). Thirty-one (84%) patients were postmenopausal and six (16%) patients were premenopausal; none of the patients underwent exogenous hormonal replacement therapy or tamoxifen treatment.

At histologic examination, 31 (84%) of 37 tumors were endometrioid adenocarcinomas, five (13%) were papillary serous adenocarcinomas, and one (3%) was an adenocarcinoma with squamous differentiation. In regard to tumor grades, six (16%) patients had grade 1 tumors (well-differentiated tumor glands), 19 (51%) had grade 2 tumors, and 12 (32%) had grade 3 tumors (anaplastic carcinomas).

All patients underwent surgery. Thirty-four (92%) patients underwent type 2 radical hysterectomy, two (5%) underwent type 3 hysterectomy, and one (3%) underwent type 1 hysterectomy according to the classification of Piver et al (17). Eleven (30%) patients underwent pelvic lymph node sampling, and 10 (27%) patients underwent systematic pelvic and lumboaortic lymphadenectomy. In 16 of 37 patients, surgical observation and palpation demonstrated normal lymph nodes; lymph node status was determined histologically in 21 (57%) patients. The mean interval between MR imaging and surgery was 9.3 days (range, 1–49 days).

MR Imaging

MR imaging studies were performed with a 1.5-T superconducting magnet (Echospeed; GE Medical System, Milwaukee, Wis). The pelvic phased-array coil was used in all patients. To reduce bowel peristalsis, 1 mg of butylscopolamine (Buscopan; Schering, Ingelheim am Rhein, Germany) was administered intramuscularly in all patients before the examination.

Transverse T1-weighted spin-echo images were obtained with the following imaging parameters: 500/14 (repetition time msec/echo time msec), 4-mm section thickness, 1-mm intersection gap, 256 × 256 matrix, and an acquisition time of 4.24 minutes.

Transverse T2-weighted spin-echo images were obtained with the following imaging parameters: 2500/85, echo train length of 12, 4-mm section thickness, 1-mm intersection gap, 256 × 256 matrix, and an acquisition time of 4.24 minutes.

Sagittal T1-weighted RARE images were obtained with 4000/85, echo train length of 12, 4-mm section thickness, 1-mm intersection gap, 256 × 256 matrix, and an acquisition time of 4.24 minutes.

Sagittal T2-weighted RARE images were obtained with 3500–4000/90, echo train length of 12, 3-mm section thickness, 1-mm intersection gap, 256 × 256 matrix, and an acquisition time of 5.52 minutes.

Furthermore, oblique coronal (parallel to the main axis of the body of the uterus) and short-axis (perpendicular to the main axis of the body of the uterus) T2-weighted RARE images of the uterus were obtained in 32 (86%) and nine (24%) patients, respectively, with the same parameters as were used for the sagittal T2-weighted images, with an acquisition time of 4.24 minutes.

Dynamic MR imaging, after the administration of 0.1 mmol gadolinium per kilogram of body weight, was performed by using a quadruphasic technique, which enables acquisition of images at four phases (precontrast, arterial, venous, and equilibrium) relative to the injection of the contrast material. Dynamic imaging was performed by using a fast multiplanar spoiled gradient-echo (FMSPGR) pulse sequence with chemically selective fat-saturation pulse along the sagittal plane in 25 (68%) of 37 patients and along the short axis in 12 (32%) patients. The parameters were 160/2.5, 3-mm section thickness, 1-mm intersection gap, 256 × 256 matrix, and an acquisition time of 1.08 minutes.

Transverse T2-weighted RARE images with use of a body coil were then acquired up to the renal hila to assess the presence of lumboaortic lymphadenopathy. The parameters were 4000/90, 8-mm section thickness, 1-mm intersection gap, 256 × 192 matrix, and an acquisition time of 4.16 minutes.

Image Analysis

Qualitative image analysis.—MR images were independently analyzed by two radiologists (R.M., P. Mirk) with experience in gynecologic imaging (over 10 years), and the reports were made without knowledge of the clinical findings. Interpretation discrepancies were resolved by consensus.

MR images were analyzed for the following parameters: (a) tumor signal intensity on T1- and T2-weighted images compared with that of adjacent myometrium; (b) visibility of the junctional zone on T2-weighted images as a band of low signal intensity immediately subjacent to the endometrial stripe; (c) the pattern of uterine enhancement at dynamic imaging, categorized as subendometrial enhancement (type 1), thick enhancement layer corresponding to the junctional zone (type 2), and enhancement of the whole myometrium (type 3) (18); (d) myometrial infiltration detected on T2-weighted images on the basis of disruption or discontinuity of the junctional zone and/or irregular myometrial enhancement at the endometrium/myometrium interface in all three types of myometrial enhancement—furthermore, the
depth of infiltration was classified as absent, less than 50%, and greater than 50%; (e) infiltration of the uterine cervix, detected as a high-signal-intensity mass within the endocervical canal and/or disruption of the normal low-signal-intensity cervical stroma on T2-weighted images; and (f) presence of enlarged pelvic and/or lumboaortic lymph nodes (cutoff value, 10 mm along the minimal transverse diameter).

Quantitative image analysis.—The analysis included the signal-to-noise ratio in the tumor and myometrium during all phases of the dynamic study: precontrast, arterial, venous, and equilibrium phases. The contrast-to-noise ratio in the tumor and myometrium was subsequently calculated during each phase of the dynamic study. Quantitative image analysis was performed on a workstation by using an operator-defined region of interest on pre- and postcontrast MR images.

Furthermore, tumor volume was calculated with the ellipsoid formula by measuring the three diameters of the tumor (19). All measurements were performed on a workstation with an electronic caliper by a radiologist (G.M.) who did not perform the qualitative analysis.

Histopathologic Analysis

Surgical specimens were sectioned along the longitudinal plane of the uterus. The depth of myometrial invasion was estimated grossly, was confirmed microscopically without knowledge of MR findings, and was classified according to International Federation of Gynecology and Obstetrics classification as stage IA, tumor confined to the endometrium; stage IB, tumor infiltrating less than 50% of myometrial thickness; or IC, tumor infiltrating 50% or more of myometrial thickness.

Lymph node dissection was performed with anatomic labeling into common, internal and external iliac, internal obturator, and lumboaortic node groups by surgeons (G.S., P.A.M.) in the operating room. The total number of lymph nodes, their site, and the number of metastatic lymph nodes were subsequently docu-
Figure 2. Endometrial carcinoma infiltrating whole thickness of myometrium (stage IC). (a) Sagittal RARE T2-weighted (3,800/90) image shows hyperintense endometrial neoplasm (arrows) infiltrating adjacent myometrium to more than 50% of its thickness. (b) Sagittal dynamic equilibrium phase FMSGPR T1-weighted (160/4.2, 90° flip angle) image shows hypointense lesion infiltrating (arrowheads) whole thickness of subjacent myometrium.

Statistical Analysis

MR imaging findings were compared with surgicopathologic findings, and sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy were calculated for cervical invasion and myometrial infiltration (assessed as <50% or ≥50%) by endometrial carcinoma and lymph node metastases. A Fisher exact test was used to analyze the correlation between MR imaging findings and surgicopathologic specimens in assessing myometrial infiltration. In this setting, only two classes for both MR imaging and surgicopathologic specimens were considered: depth of myometrial infiltration either absent or less than 50% (stages IA and IB, respectively) and depth of myometrial infiltration ≥50% or greater (stage IC).

Furthermore, a repeated-measures analysis of variance, with one “within” factor, was applied to assess the tumor and myometrium contrast-to-noise ratio during each phase of the dynamic study for each subject. A P value less than .05 was considered to indicate a statistically significant difference.

RESULTS
Qualitative Analysis

On T1-weighted images, endometrial carcinoma appeared isointense to the adjacent myometrium in all 37 (100%) patients. On T2-weighted images, the tumor appeared hyperintense compared with the adjacent myometrium in 32 (86%) patients, isointense in four (11%) patients, and hypointense in one (3%) patient (Fig 1). On T2-weighted images, the junctional zone was visualized in 29 (78%) patients; whereas in eight (22%) patients, all in postmenopausal status, the junctional zone was not visible (Figs 1, 2).

Uterine enhancement was categorized as type 1, thin layer between the endometrium and myometrium (subendometrial enhancement), in 15 (40%) patients; type 2, thick enhancement layer corresponding to the junctional zone, in eight (22%) patients; and type 3, enhancement of the whole myometrium, in 14 (38%) patients (Fig 1).

According to surgicopathologic data, myometrial infiltration was correctly assessed in 31 (84%) patients, was underestimated in four (11%) patients, and was overestimated in two (5%) patients (Figs 1, 2). The results of MR imaging assessment of the depth of myometrial infiltration are reported in Table 1. Consensus among readers in assessing myometrial infiltration was requested in six (16%) patients.

Furthermore, when only two classes of myometrial invasion, less than 50% and 50% or greater, were considered, MR imaging helped make the correct assessment in 91% of patients with myometrial infiltration of less than 50% and in 87% of patients with myometrial infiltration of 50% or greater. Overall, MR imaging sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values in assessing myometrial infiltration were 87%, 91%, 89%, 87%, and 91%, respectively (Table 2). This resulted in a statistically significant correlation.
between MR imaging findings and surgicopathologic specimen in assessing the depth of myometrial invasion in our series ($P < .001$).

MR imaging assessment of cervical infiltration by endometrial carcinoma resulted in eight (22%) of 37 patients with true-positive, 26 (70%) patients with true-negative, two (5%) patients with false-negative, and one (3%) patient with false-positive results (Fig 3). Overall MR imaging sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values in the assessment of cervical infiltration were 80%, 96%, 92%, 89%, and 93%, respectively (Table 2).

MR imaging assessment of lymph node status resulted in one (5%) of 21 patients with true-positive, 18 (85%) of 21 patients with true-negative, one (5%) of 21 patients with false-positive, and one (5%) of 21 patients with false-negative findings (Fig 4).

At histopathologic examination, 338 lymph nodes were examined. When the site of the lymph nodes was taken into consideration, the patient with true-positive findings had a left external iliac node, the one with false-positive findings had a left internal iliac node, and the one with false-negative findings had seven positive lymph nodes (four left internal obturator and three left external iliac nodes).

Overall, MR imaging sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values in the detection of lymph node metastases were correctly preoperatively assessed at MR imaging in 28 (76%) of 37 patients, were overstaged in four (11%) patients, and were downstaged in five (13%) patients (Table 2). Causes of downstaging were cervical infiltration in two patients, myometrial infiltration in two patients, and lymph node invasion in one patient. Causes of overstaging were myometrial infiltration in two patients and cervical infiltration and lymph node invasion in one patient each.

**Quantitative Analysis**

The signal-to-noise ratios of the tumor and myometrium during all phases of the dynamic study are reported in Figure 5. The contrast-to-noise ratio of the tumor and myometrium progressively improves from the precontrast phase to the equilibrium phase (Figs 5, 6), with significant improvement during the equilibrium phase compared with the other phases of the dynamic study ($P < .001$).

The mean tumor volume, calculated according to the ellipsoid formula by measuring the three tumor diameters, was 56.2 cm$^3$ (range, 0.2–403.8 cm$^3$).

**DISCUSSION**

Surgery is the treatment of choice in patients with noninvasive or locally advanced endometrial carcinoma. The recent introduction of less-invasive surgical techniques requires a more accurate preoperative work-up to prevent the risk of understaging the disease and impair the therapeutic plan.

**Figure 3.** (a) Coronal oblique RARE T2-weighted (3,500/90) image shows hyperintense neoplasm (arrows) extending down to uterine cervix infiltrating hypointense cervical stroma (stage IIIB). The cervical infiltration was missed in another patient on both (b) sagittal RARE T2-weighted (3,800/90) and (c) sagittal dynamic equilibrium phase FMSPGR T1-weighted (160/4.2, 90° flip angle) images.

**Figure 4.** Endometrial carcinoma with pelvic lymph nodes (stage IIIC). (a) Transverse RARE T2-weighted (4,000/90) image shows endometrial carcinoma (arrows) infiltrating myometrium for more than 50% of its thickness and internal obturator lymph node with minimal transverse diameter of less than 10 mm. (b) Histologic specimen shows metastatic tissue within lymph node; neoplastic emboli (arrows) can also be detected. (Hematoxylin-eosin stain; original magnification, ×2.)
In this setting, MR imaging has proved accurate in the preoperative assessment of the depth of myometrial invasion (7–11), the extent of cervical invasion (14), and identification of enlarged pelvic and lumboaortic lymph nodes (15,16) separately. In this study, we evaluated the capability of MR imaging in helping to predict all factors requested by the gynecologic oncologist to plan surgical treatment.

Endometrial carcinoma could be easily detected on T2-weighted MR images, where it appeared hyperintense in 32 of 37 (86%) patients; whereas on T1-weighted images, the detection of endometrial carcinoma was more difficult since the T1 relaxation time is equivalent to that of adjacent myometrium, and therefore the two tissues appeared iso¬intense on T1-weighted images.

Dynamic MR imaging performed during the injection of gadolinium chelates is useful in depicting endometrial carcinoma, owing to different vascularity of the tumor and myometrium, and in helping to differentiate it from fluid filling the endometrial cavity. In our series, lesion detection is more easily achieved during the equilibrium phase, which demonstrated a significantly better tumor and myometrium contrast-to-noise ratio than did the other phases of the dynamic study (P < .001).

Determining the presence and depth of myometrial invasion is a highly critical factor, as is used in most institutions to predict nodal metastases, since patients with 50% or greater myometrial invasion have a six- to sevenfold increased prevalence of pelvic and lumboaortic lymph node metastases compared with patients with myometrial invasion that is absent or less than 50% (20). Therefore, the preoperative determination of myometrial invasion helps in planning the extent of lymphadenectomy.

The presence and depth of myometrial infiltration can be assessed on T2-weighted images as an interruption of the junctional zone, which appears hypointense, contrary to endometrial adenocarcinoma, which appears hyperintense. In postmenopausal women, however, the junctional zone may be poorly visible and the myometrium may be thinned due to uterine involution, making the presence and depth of myometrial infiltration more difficult to assess. In fact, in our series, the junctional zone was poorly visible in eight (22%) of 37 patients. To overcome this limitation, dynamic MR imaging should be performed, because it can depict different enhancement times of the adenocarcinoma compared with those of the adja¬cent myometrium, which improves in this manner the contrast resolution of the tumor and myometrium. In our series, by combining T2-weighted and dy¬namic MR imaging, there was a significant correlation between MR imaging and histopathologic findings in the assessment of myometrial infiltration (P < .001).

Preoperative assessment of cervical infiltration in endometrial carcinoma is im¬portant in planning treatment and predicting prognosis. Several investigators have reported that macroscopic cervical involvement seems to impart a worse prognosis than does microscopic involvement (21,22). Therefore, preopera¬tive assessment of cervical infiltration may help in planning radical surgery or additional radiation therapy (21,22). T2-weighted imaging is well suited for de¬tecting cervical infiltration by endome¬trial carcinoma, since normal cervical stroma appears hypointense on T2-weighted images, because of the high content of fibrous tissue, and endome¬trial carcinoma appears hyperintense, leading therefore to high contrast resolution. Some authors reported that dy¬namic MR imaging during injection of gadolinium chelate improves detection of cervical infiltration by endometrial carcinoma (23). Despite this, in our series we missed cervical infiltration in two pa¬tients and overstaged cervical infiltration in one patient. Notwithstanding such er¬rors, we report a 92% accuracy in detecting cervical involvement.

Although not included in the Interna¬tional Federation of Gynecology and Ob¬stetrics clinical staging, pelvic lymph node status is one of the most important prognostic factors in endometrial carcino¬ma. MR imaging has the capability to directly depict lymph nodes without any need for contrast medium. This is be¬cause vessels show the physiologic “flow void” phenomenon, appearing deeply hypointense when the phenomenon oc¬curs and differently from lymph nodes, which appear of intermediate signal in¬tensity with all pulse sequences, because of their parenchymal structure.

Similarly to all other noninvasive imaging methods, however, MR imaging has a limitation in the assessment of the lymph node status, the most important being the difficulty in enabling differen¬tiation between metastatic and nonmeta¬static lymph nodes of similar size. The presence of central necrosis, detected as high signal intensity on T2-weighted im¬ages, has a 100% positive predictive value in the diagnosis of metastasis (16). How¬
ever, central necrosis occurs most frequently when the maximal transverse diameter of the lymph nodes is 2 cm or greater (16).

When necrosis is absent, the criterion used in oncologic patients for differentiating metastatic from normal lymph nodes is size, with a cutoff value of 1 cm along the minimal diameter of the lymph node. In our series, in one patient along the minimal diameter of the nodes is size, with a cutoff value of 1 cm

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ameter of the lymph nodes is 2 cm or
diameter of cervical lymph nodes seems more difficult. The size criterion may indeed be misleading, and even the most refined MR pulse sequences or dynamic techniques cannot improve the diagnostic accuracy in this setting. The future introduction of lymph node–specific contrast agents may help in this difficult task.

References