MAGNETIC RESONANCE IMAGING IN THE STAGING OF CERVICAL CANCER*

Claudia C. Camisão[1], Sylvia M.F. Brenna[2], Karen V.P. Lombardelli[3], Maria Célia R. Djahjah[4], Luiz Carlos Zeferino[5]

Abstract **Cervical cancer is the worldwide leading cause of cancer-related death of women, especially in developing countries. The International Federation of Gynecology and Obstetrics recommends staging during surgery, however, surgical-pathologic staging would not be feasible in cases of more advanced cancers. Generally, in these cases, the staging is performed by means of clinical and gynecological examination and basic imaging studies. However, such an approach fails to demonstrate the actual extent of the disease, and does not include significant prognostic factors such as tumor volume, stromal invasion and lymph node involvement. Magnetic resonance imaging has increasingly been utilized in cervical cancer staging, since at early stages of the disease its performance may be compared to intraoperative findings and, at advanced stages, it shows to be superior to the clinical evaluation. Additionally, magnetic resonance imaging presents an excellent imaging resolution for the different densities of pelvic structures, does not require ionizing radiation, is comfortable for the patient, improves de staging, allowing the early detection of recurrence and the identification of reliable prognostic factors which contribute to the therapeutic decision making process and results prediction with an excellent cost-effectiveness. The present article is aimed at reviewing the most significant aspects of magnetic resonance imaging in the cervical cancer staging.**
Keywords: Cervical cancer; Staging; Magnetic resonance imaging.

Resumo *Ressonância magnética no estadiamento dos tumores de colo uterino.*
O câncer de colo uterino é a maior causa de morte entre mulheres em todo o mundo, notadamente nos países em desenvolvimento. A Federação Internacional de Ginecologia e Obstetrícia preconiza o estadiamento durante o ato operatório, porém nos casos mais avançados a abordagem terapêutica não é cirúrgica. Nestes casos, o estadiamento, em geral, é feito com o exame clínico ginecológico e exames básicos de imagem. Entretanto, essa forma de abordagem não expressa a real extensão da doença e não inclui importantes fatores prognósticos como volume tumoral, invasão estromal e acometimento linfonodal. A ressonância magnética está sendo cada vez mais utilizada para este fim, pois nos estádios iniciais seu desempenho pode ser comparado aos achados intra-operatórios e nos estádios avançados se mostra superior em relação à avaliação clínica. A ressonância magnética apresenta excelente resolução para diversas densidades das estruturas pélvicas, não utiliza radiação ionizante, é confortável, melhora o estadiamento, permite a detecção precoce de recidiva e a identificação de fatores prognósticos fidedignos que contribuem na decisão e predição dos resultados terapêuticos, com excelente custo-efetividade. Este artigo tem como objetivo revisar os aspectos da ressonância magnética mais importantes no estadiamento desta doença.
Unitermos: Câncer de colo uterino; Estadiamento; Ressonância magnética.

INTRODUCTION

Presently, uterine cervix carcinoma represents a significant public health problem. Despite the longer survival of patients because of earlier diagnoses and more effective therapies, this disease still remains as the leading cause of cancer-related death of women in the majority of developing countries[1]. Cervical carcinoma is a slow-growing disease, usually invading the vagina and the paracervical space along the parametrium and uterosacral ligaments. Also, bladder, rectum, pelvic and paraaortic lymph nodes may be invaded[2]. The pattern of pelvic dissemination of cervical carcinoma restricts the utilization of surgical treatment for early stages of the disease, given the lack of a safety margin in the resection of tumors which may have already affected the paracervical space.

The staging recommended by International Federation of Gynecology and Obstetrics (FIGO) is widely adopted both for therapy planning and post-therapy follow-up, however it has shown to be inaccurate in the estimation of the actual tumor extent. Additionally, the FIGO staging system does

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not take into consideration relevant prognostic factors such as the tumor volume, vascularization, endophytic or exophytic growth, stromal invasion and lymph nodes involvement[3,4]. Considering this flaw, the FIGO Committee on Gynecologic Oncology started recommending that the definite staging is based on the surgeon's and pathologist´s intraoperative findings (Figure 1)[5].

In cases where cervical carcinoma is locally advanced (above IIb), the majority of specialized centers have opted for exclusive radiotherapy or radiotherapy in association with chemotherapy. Therefore, the clinical finding that could not be intraoperatively confirmed should be based predominantly on highly accurate studies. However, in developing countries, basic imaging equipment is not always widely available in health services; so the gynecological examination ends up being the main alternative for staging of cervical carcinomas. The involvement of the parametrium evaluated by rectal examination is a parameter which frequently characterizes a locally advanced carcinoma[6]. Mistakes may occur, especially due to underestimation of the disease extent as a consequence of limitations of the clinical-gynecological examination[7].

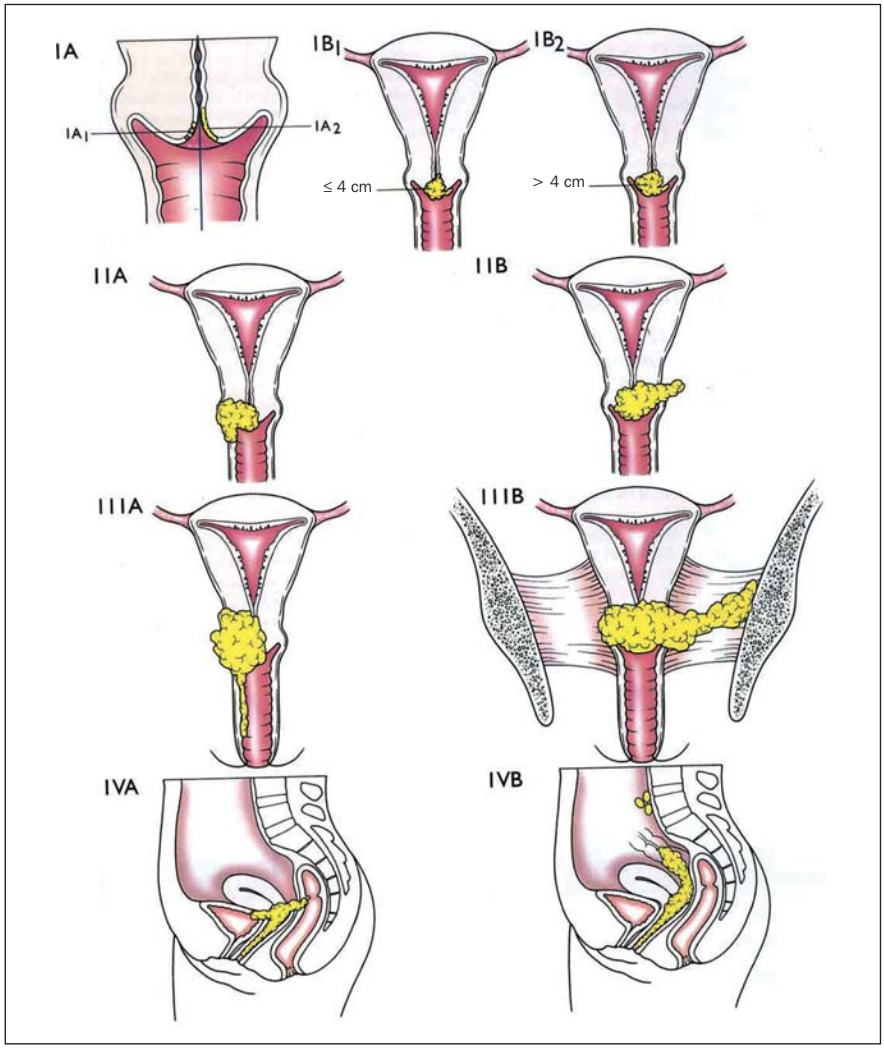

Figure 1. Staging of uterine cervix carcinoma according to FIGO[3].

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) can evaluate the actual extent of the disease because of its high spatial and contrast resolution for pelvic tissues and organs. Some advantages of MRI are short acquisition time with multiplanar images, comfort for the patient, absence of ionizing radiation, and, mainly, the high reproducibility in the evaluation of musculotendinous structures in the pelvis which are of great relevance in the parametrium evaluation[8].

T2-weighted images provide excellent details of the cervical anatomy and normal uterus, besides identifying the primary tumor and its extent. The normal cervical stroma presents a low density signal on this sequence, and about 95% of tumors of uterine cervix appear as slightly hyperintense masses in relation to the surrounding stroma[9] (Figure 2). Pre-invasive lesions of uterine cervix carcinoma cannot be identified on T2-weighted images, but may be described as an area of marked early impregnation in the arterial phase of MRI dynamic studies[10].

Prognostic parameters influencing in an appropriate therapy choice, and which may be evaluated by means of gynecological examination, can be evaluated by MRI with a good cost-effectiveness ratio, considering that patients with cervical cancer submitted to MRI as the initial staging method, require less tests or procedures in comparison with those submitted to a traditional staging method[11,12].

As a matter of fact, MRI has shown a better accuracy than the clinical examination and computed tomography (CT) as staging methods, particularly in the parametrial evaluation. Comparative studies of the three methods (MRI, CT and clinical examination) have demonstrated 92% accuracy for MRI compared with 78% for clinical examination, and 70% for CT[13]. With the arrival of new turbo sequences and phased-array coils, sensitivity reported for parametrial invasion was 100%[14]. Other authors highlight a 98% negative predictive value for parametrial invasion in T2-weighted turbo spin-echo (TSE) and short tau inversion recovery (STIR) sequences[15,16].

The correlation between uterine cervix carcinoma staging proposed by FIGO and MRI findings is described in Table 1[17].

Examination technique

MRI for staging of uterine cervix tumors should cover from the plane passing

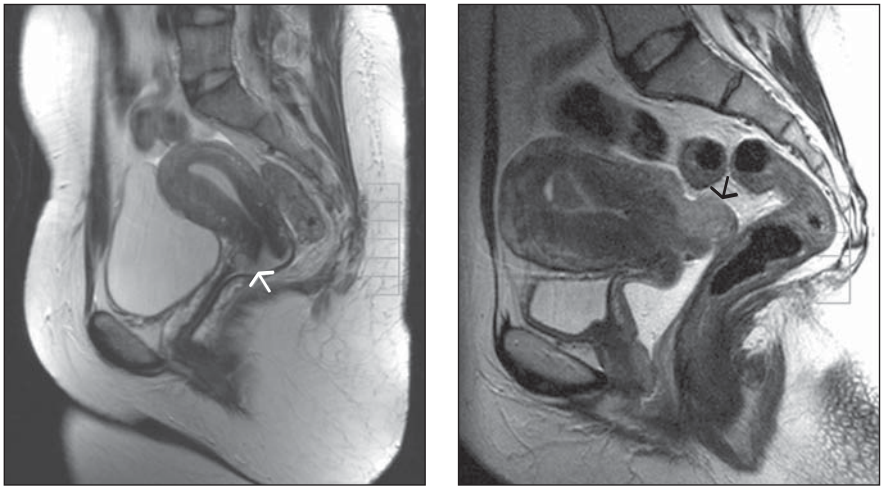

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Figure 2. A: Sagittal T2-weighted TSE sequence, hyperintense uterine cervix tumor. Part of the (hypointense) cervical stroma is intact. Preserved vaginal canal (stage Ib). **B:** Sagittal T2-weighted TSE sequence, slightly hyperintense tumor in the posterior portion of the uterine cervix, extending to the upper vaginal third (stage IIa).

Table 1 Correlation between FIGO staging of uterine cervix cancer and MRI findings[17].

Stage		MRI T2-weighted sequence
Ia	Microinvasor	No tumor evidence
Ib	Invasive, confined to the cervix	Hyperintense tumor on T2-weighted sequence in contrast with hypointense signal from cervical stroma
Ib1	Clinically visible lesion ≤ 4 cm	Tumor partially or completely replacing the hypointense cervical stroma, not surpassing the parametrial interface represented by a hypointense halo
Ib2	Clinically visible lesion > 4 cm	
IIa	Tumor invades the upper vaginal third, but does not affect the lower vaginal third	Segmental interruption of hypointense signal on the upper third of the vaginal wall
IIb	Tumor invades the parametrium, but not the pelvic wall neither the lower vaginal third	Hyperintense tumor interrupting hypointense halo of the interface between cervical stroma and parametrium
IIIa	Involvement of the lower vaginal third, without affecting the pelvic wall	Segmental interruption of the hypointense signal of the lower vaginal third
IIIb	Pelvic wall involvement or hydronefrosis	Tumor extending to the musculature (internal obturator muscle, piriform muscle or levator ani muscle) or causing hydroureter
IVa	Tumor invades the bladder or rectum mucosa	Loss of hypointense signal of the internal wall (mucosa) of the bladder or rectum
IVb	Distant metastasis	Distant metastasis

through the inferior renal pole to the vulva, including the paraaortic and pelvic regions. The anterior saturation band should be utilized as a routine to reduce respiratory and peristaltic artifacts. On the other hand, the posterior saturation band is dispensable. The use of antiperistaltic agents four to six hours before the examination also is recommended to reduce artifacts resulting from intestinal peristalsis[3,10]. The phased-array coil improves the signal-noise ratio, allowing the acquisition of more detailed images than the formerly utilized body coils, and, consequently improving the imaging resolution. However, body coils may be useful for obese patients with a very protuberant abdomen, or for retroperitoneal evaluation[18]. The utilization of endorectal and endovaginal coils has been described as means to produce high-signal images, but, despite the high degree of definition, their use is limited because of the lack of consensus about their advantages over the phased-array coils[19].

The staging of uterine cervix tumors requires three planes in the T2-weighted TSE sequence in high resolution, i.e., 512 matrix, small field-of-view (FOV), sections always < 5 mm (preferably 3–4 mm), with gap of zero, all of them obtained in the axial plane. Additionally, a T1-weighted TSE sequence in the true axial plane of the pelvis with large FOV is essential for acquisition of a global pelvic view[17].

Sagittal images are useful for demonstrating the relation between tumor and cervix, uterine body, vagina and adjacent organs such as bladder and rectum. On the other hand, axial images are relevant for detection of parametrial and pelvic wall invasion, ureteral and lymph nodes involvement. The coronal plane, in conjunction with the sagittal and axial planes, is useful in the parametrial evaluation, and particularly necessary for measurement of the tumor volume (Figure 3).

T2-weighted TSE is the sequence of choice in the evaluation of lymph nodes involvement, since in this sequence, muscles and vessels appear hyperintense, differently from lymph nodes. Fat suppression improves even more the identification of structures or lesions surrounded by adipose tissues like parametrium and lymph nodes[15,20] (Figure 4).

Many times, the use of contrast is not necessary in the staging, since, in most of cases, precontrast sequences provide the necessary information. Besides, dynamic sequences frequently underestimate the tumor volume and the depth of the stromal invasion, and should not be utilized for these purposes[21]. However, the use of contrast agent may be useful for facilitating the identification of fistulous tracts in advanced diseases or in the post-therapy follow-up[10].

TUMOR GROWTH PATTERNS

The tumor arises in the cervical canal and extends peripherally towards the cervical stroma, progressively replacing it. A full-thickness stromal invasion may occur, and, by contiguity, a parametrial invasion (IIb). Cervical canal obstruction is usual, and frequently causes the endometrial cavity to be distended with blood, serous fluid or purulent material[22] (Figure 5).

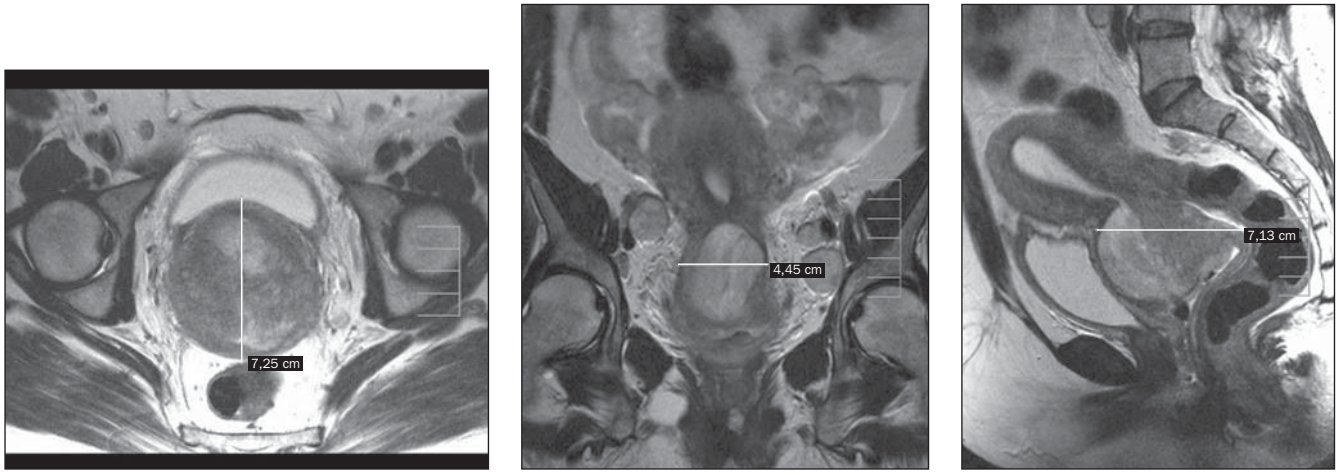

Figure 3. A: Axial T2-weighted TSE sequence, tumor completely replacing the cervical stroma in its largest anteroposterior diameter**. B:** Coronal T2-weighted TSE sequence of the same patient showing the largest latero-lateral diameter of the tumor. Note the bilateral adenomegalies. **C:** Sagittal T2-weighted TSE sequence, largest craniocaudal diameter of the tumor. Preserved signal of the bladder mucosa.

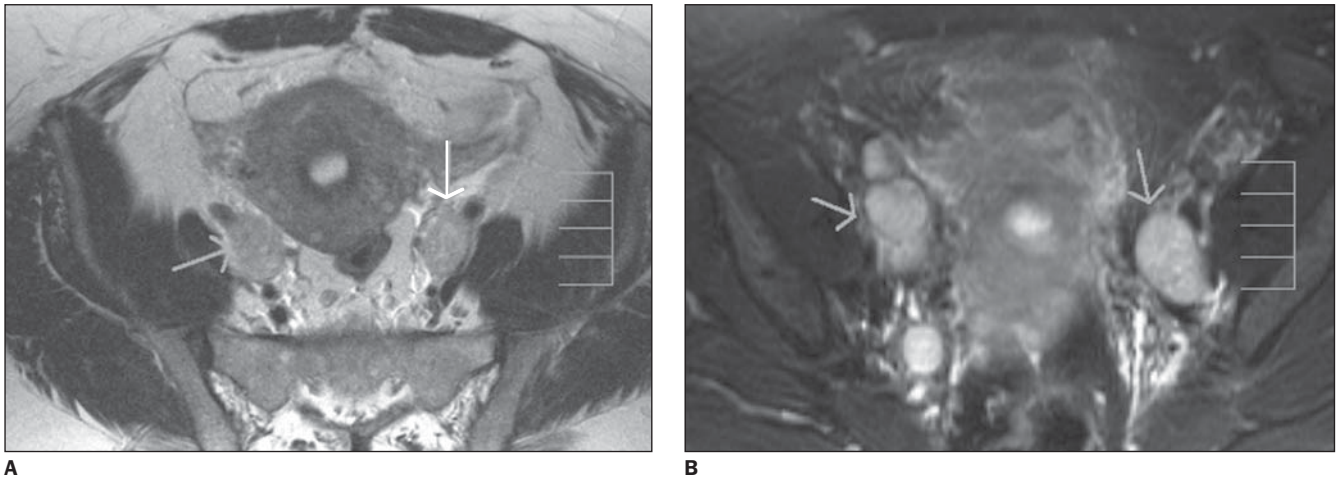

Figure 4. A: Axial T2-weighted TSE sequence, the same patient in Figure 3 in an uppermost plane. The arrows indicate bilateral adenomegalies, with a slightly hyperintense signal similar to the cervical tumor. **B:** Axial T2-weighted TSE sequence with fat suppression. The arrows indicate the same adenomegalies as **a**, more evident in this sequence.

Tumors extending into the uterine cavity are associated with a worst prognosis and higher prevalence of distant metastases[2]. Clinically, tumors with endophytic growth are difficult to be measured, since the largest component cannot be directly visualized and evaluated in a gynecological examination. The clinical evaluation of exophytic tumors is easier, but MRI facilitates the identification of a possible vaginal invasion.

Evaluation of parametrium and pelvic wall

The parametrium is the connective tissue between the layers of the broad ligament. Medially it is contiguous with the uterus, cervix and proximal vagina; extending laterally to the pelvic wall. Inferiorly, it is nearly the cardinal ligament. It is predominantly consisted of fat through which run uterine vessels, nerves and lymphatic vessels[11].

Parametrial invasion (above IIb) is a significant prognostic factor influencing in the diagnosis and therapeutic choice. On T2-weighted sequences, the interface between the normal cervical stroma and the parametrium appears like a hypointense ring or halo surrounding the cervix. A preserved hypointense halo represents a high negative predictive value for parametrial invasion[15,17]. The indicator of parametrial invasion is the segmental interruption or complete absence of this halo in the interface between the cervical stroma and the parametrial fat, or yet, the clear protrusion of the tumor into the parametrium[13,23]. Some authors correlate the complete replacement of the cervical stroma and the tumor extension into the uterine body with the parametrial invasion. In these cases, 94% of the parametrium is invaded, with direct relation between the size of the tumor and the parametrial involvement[15,22]. Loss of parametrial fat may be an indicator of invasion, but this is a non-specific sign, since peritumoral inflammation also

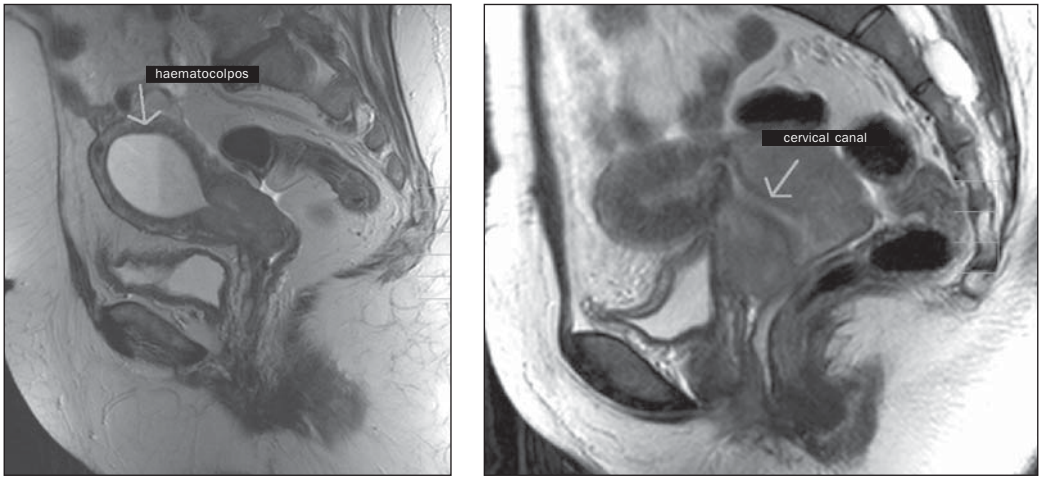

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Figure 5. A: Sagittal T2-weighted TSE sequence, hyperintense tumor completely replacing the uterine cervix stroma and obstructing the cervical canal, causing distension of the endometrial cavity filled with a highly hyperintense fluid. **B:** Sagittal T2-weighted TSE sequence, tumor completely replacing the uterine cervix stroma; so there is no accumulation of fluid inside the endometrial cavity.

may result in loss of fat simulating invasion.

Contrast-enhanced T1-weighted sequences have demonstrated higher accuracy than the T2-weighted in parametrial evaluation[10] (Figure 6). In cases where the tumor extends into the parametrium it may reach the ureter, causing hydronephrosis (IIIb). Hydronephrosis associated with mass in the uterine cervix are specific signs of parametrial invasion[12].

Parametrial invasion up to the pelvic wall (IIIb) is diagnosed when the tumor cannot be separated from the pelvic wall at clinical examination. At MRI, this diagnosis is made when the distance between the tumor and the pelvic wall is < 3 mm, or when T2-weighted sequences show partial or complete loss of a normal hyposignal of the pelvic wall musculature (piriform muscle, internal obturator muscle, levator ani muscle or coccygeal muscle) (Figure 7). In these cases, iliac vessels become compressed and narrowed by the tumor, and the bone destruction may occur by direct extension of a diffusely infiltrated tumor[25].

Vaginal involvement

MRI is highly sensitive in the detection of vaginal invasion, with 93% accuracy[11]. The sign of vaginal involvement is better characterized on high-resolution T2-weighted sequences, showing the segmental interruption of the normal hypointense signal of the vaginal wall, or yet a hyperintense vaginal thickening (tumor), or the mass itself in contiguity with the vaginal wall (Figure 8). Vaginal invasion corresponds to stage IIa; when this invasion extends up to the lower vaginal third, corresponds to stage IIIa[25]. Additionally, the use of intravaginal ultrasonographic gel during the MRI acquisition is recommended to distend and fill the cavity with a highly hyperintense material on T2-

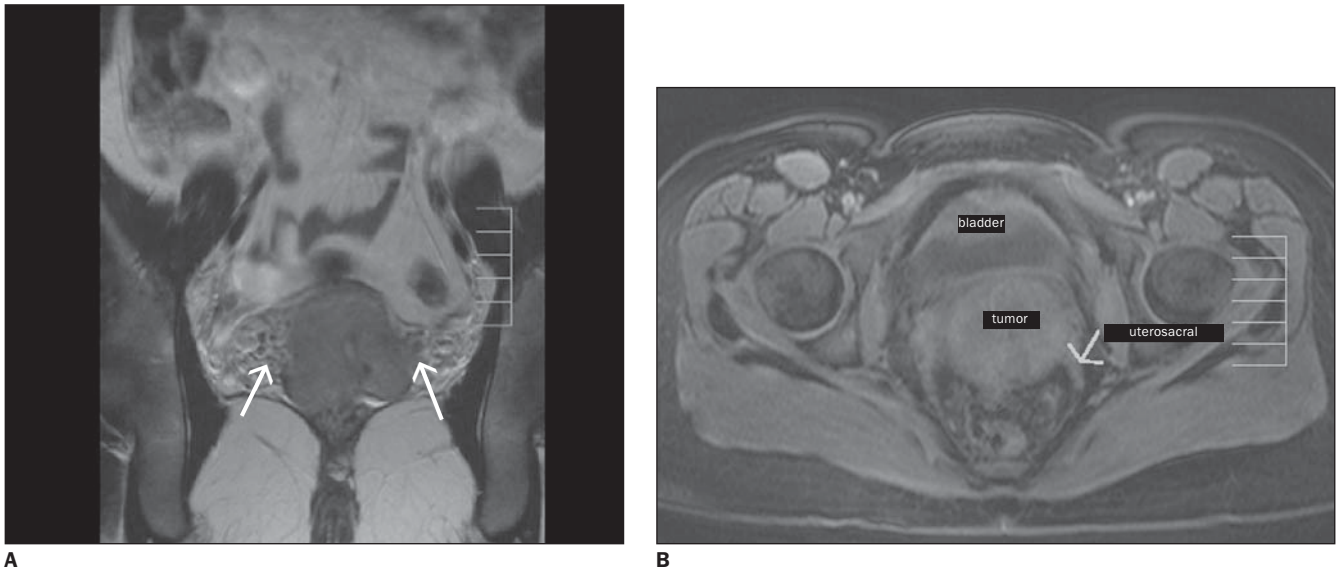

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Figure 6. A: Coronal T2-weighted TSE sequence showing bilateral parametrial invasion, loss of hypointense halo separating the interface between the cervical stroma and the parametrial fat. Note the fimbrias laterally along the parametrium which also represent indirect signs of parametrial invasion (stage IIb). **B:** Axial T1-weighted sequence with fat suppression of the same patients, showing the bilateral involvement of uterosacral involvement.

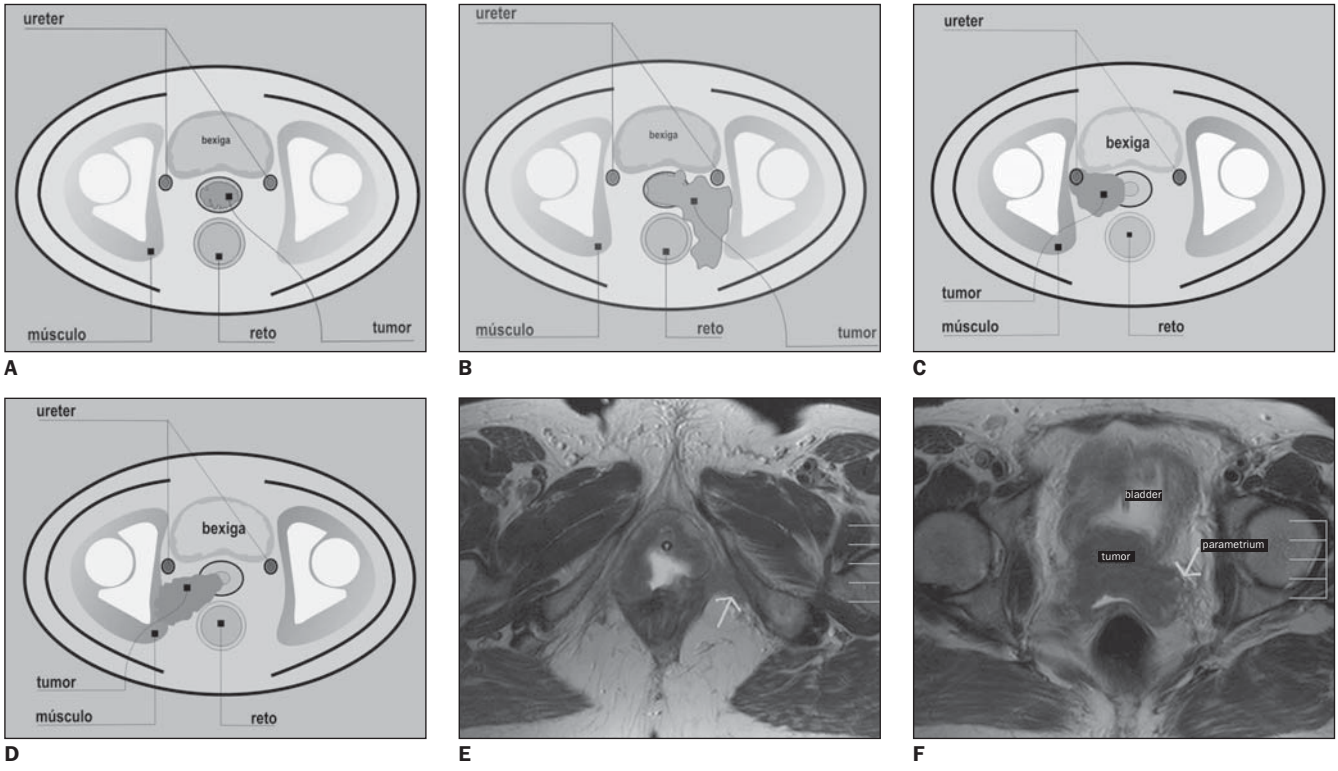


Figure 7. A: Axial illustration of the pelvis showing a tumor restricted to the cervix, with no sign of parametrial invasion (stage I). **B:** Axial illustration of the pelvis showing a tumor invading the parametrium, without reaching the pelvic wall or right ureter (stage IIb). **C:** Axial illustration showing cervical tumor invading the parametrium and reaching the right ureter (stage IIIb). **D:** Axial illustration showing cervical tumor invading the parametrium and reaching the pelvic wall (stage IIIb). **E:** Axial T2-weighted TSE sequence showing a cervical tumor involving the urethra, and extending up to the pelvic wall with alteration of the ischium signal (arrow). **F:** An uppermost image of the same sequence clearly showing parametrial invasion (arrow).

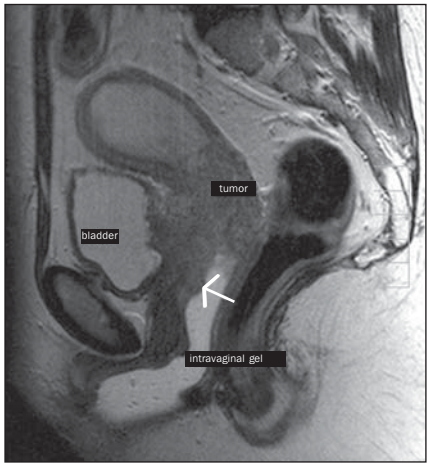


Figure 8. Sagittal T2-weighted TSE sequence showing uterine cervix tumor invading the upper vaginal third. Observe that the introduction of the intravaginal ultrasonographic gel (highly hyperintense on T2-weighted sequences) distends the vaginal wall and improves de assessment of the invasion.

weighted sequences in order to improve the tumor contrast (slightly hyperintense on T2-weighted sequences) and the vaginal wall contrast ((hypointense on T2-weighted sequences). This procedure improves the sensitivity in the evaluation of the vaginal invasion. About 20 ml of gel applied at the moment of the examination are sufficient[10].

Lymph node involvement

Several studies have demonstrated the significance of the lymph node involvement as a factor of worsening in the survival prognosis of women affected by uterine cervix tumor[3,26]. There are three drainage routes from the cervical lymph nodes through which the tumor propagates (Figure 9): the lateral route, along the external iliac vessels; the hypogastric route, along the internal iliac vessels; and the presacral route, along the uterosacral ligament. All of the three routes drain into the common iliac lymph nodes, through which the tumor may reach the paraaortic lymph nodes. Generally, the paracervical and parametrial lymph nodes are the first to be affected, followed by the obturator lymph nodes and, subsequently, the external and internal iliac lymph nodes[27].

T2-weighted are the sequences of choice for evaluation of pelvic lymph nodes, since in these sequences vessels and musculature become hypointense, facilitating the differentiation from lymph nodes which are slightly hyperintense on T2-weighted sequences (Figure 10). T2-weighted TSE fat suppressed sequences allow the suppression of the adipose tissue surrounding the lymphatic vessels, improving the accuracy in the detection of pelvic adenomegalies[12] (Figure 11). Up to the present moment, the suspicion of lymph node metastasis by means of MRI is limited to the increase in the size of the lymph node. Lymph nodes > 10 mm in axial diameter are considered as abnormal. Also, some higher limits are suggested for determined specific sites, as follows: for lymph nodes in the internal iliac chain, 7 mm; for common iliac lymph nodes, 9 mm; and for external iliac lymph nodes, 10 mm. Positron emission tomography with fluorodeoxy-D-glucose (PET-FDG) seems to offer higher specificity than MRI for enlarged

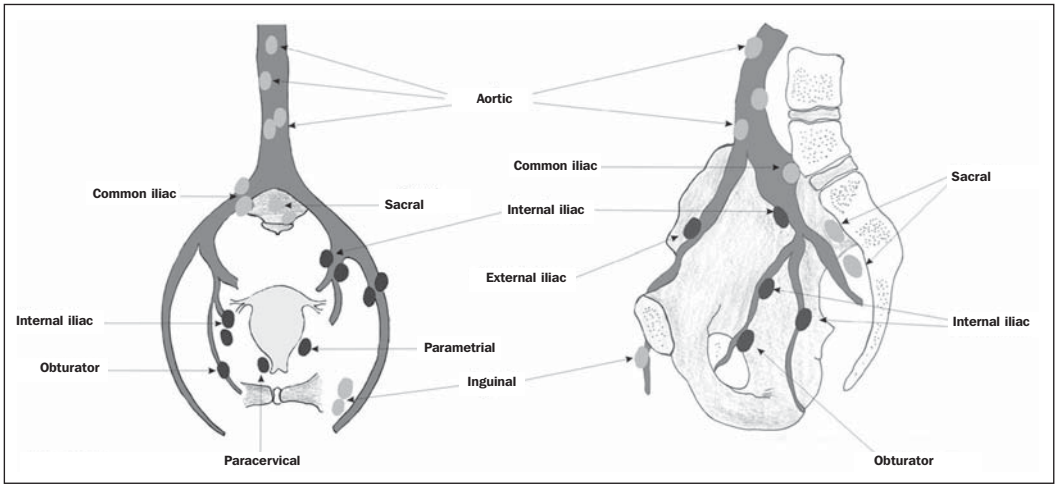


Figure 9. Lymphatic drainage route of uterine cervix tumor. Coronal (left) and sagittal (right) illustrations showing, in black, primarily affected lymph nodes, and, in gray, those secondarily affected.

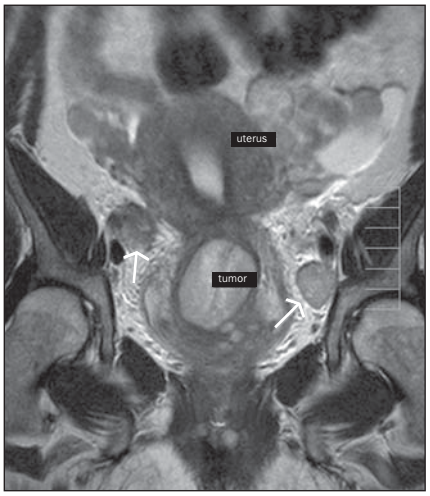


Figure 10. Coronal T2-weighted TSE sequence showing uterine cervix tumor and bilaterally enlarged lymph nodes (arrows).

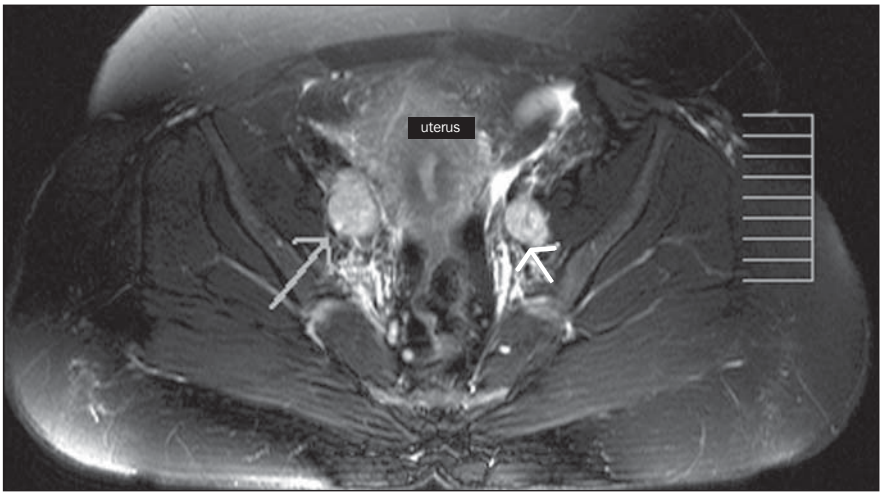


Figure 11. Axial T2-weighted sequence with fat-suppression on the same plane as Figure 10, showing enlarged and hyperintense lymph nodes in this sequence.

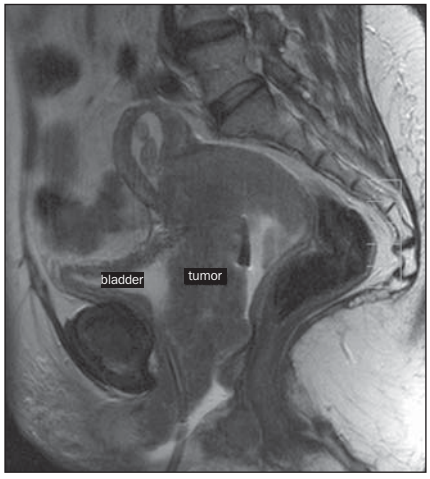
pelvic lymph nodes[3]. When lymph node central necrosis is identified, the positive predictive value for malignancy is 100%. It has been already demonstrated that lymph nodes with necrosis or signal intensity similar to the tumor presented worst prognosis. The diagnosis of lymph node necrosis may improve with the use of endovenous contrast [25,28].

Most recently, improvement has been demonstrated in the MRI sensitivity for detection of metastatic lymph nodes in uterine cervix tumors, utilizing a new type of lymph node-specific contrast agent called ferumoxtran-10, with nanoparticles of iron oxide (USPIO). However the utilization of this contrast agent is not a consensus yet[29]. Considering that the FIGO staging system does not take the lymph nodes involvement into consideration, the detection of enlarged pelvic lymph nodes on MRI corresponds to stage IIIb, as well as the diagnosis of enlarged paraaortic lymph node corresponds to stage IVb[12].

Invasion of bladder and rectum

Invasion of bladder or rectum (IVa) may be difficult to be detected only by a physical examination. MRI has shown to be a reliable method for detection of bladder invasion with 83% sensitivity, specificity near 100%, and 99% accuracy. When the bladder presents invaded by the tumor, its wall, which normally is hypointense, shows a focal or diffuse area with increase in the signal intensity on T2-weighted sequences, or simply a vegetating mass into the lumen is observed[10,30]. For defining the bladder invasion, it is important to observe that signal alteration is present both for the bladder muscle and mucosa, otherwise the tumor may be just contiguous to the bladder[4]. Other indicative signs of invasion are hyperintensity on the internal surface of the posterior wall, nodularity or irregularity in the bladder wall (Figure 12). On the other hand, the vesico-ureteral junction is poorly evaluated because of the difficult visualization of a non-dilated ureter on MRI.

Direct invasion of the ureter is not frequent, however, in the setting of ureter invasion, a tumor extension is observed along the uterosacral ligaments. Findings, usu-



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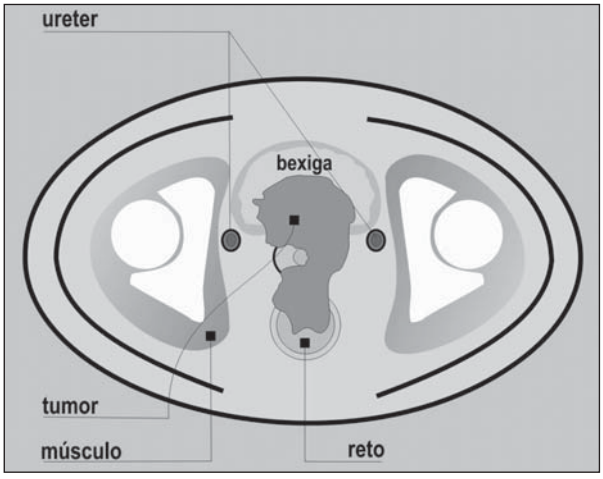

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Figure 12. A: Sagittal T2-weighted TSE sequence showing uterine cervix tumor invading the bladder mucosa (stage IVa). **B:** Axial illustration showing the tumor invading the bladder and rectum mucosas.

ally, are: focal thickening or segmental interruption of the hypointense signal on the anterior rectal wall[10].

FINAL CONSIDERATIONS

Even though MRI is not utilized by the majority of oncology services for staging uterine cervix tumors, and, up to this moment, it has not been officially approved by FIGO yet, it is the best imaging method in terms of accuracy for assessment of tumors, and plays an essential role in the therapeutic planning and follow-up[31].

MRI has shown to be better than the clinical examination, and, when utilized as the initial staging method, reduces the number of invasive procedures and radiological studies such as urography, cytoscopy and rectosigmoidoscopy, with lower cost for the management of the disease. Additionally, the correct assessment of the tumor extent and volume allows optimizing the planning of the fields for external pelvic radiotherapy and brachytherapy.

A recent study has demonstrated that the MRI-aided radiotherapy planning may reduce the possibility of geographic errors as compared with the conventional radiotherapy planning[32]. It is important that the radiologist interpreting a pelvic MRI for uterine cervix tumor, is familiarized with the findings and, mainly, provides information regarding tumor volume, invasion of parametrium, vagina and adjacent organs, besides indicating the tumor growth type and lymph nodes involvement.

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