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Diffusion MRI: technical principles and application to uterine cervical cancer

IRM de diffusion : bases techniques et application au cancer du col utérin

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Conflit d'intérêt

aucun

Abstract

Imaging is involved in the management of uterine cervical cancer with several objectives: 1/ to assess local and lymph node extension of the initial disease; 2/ evaluate treatment response to conservative therapy; 3/ detect recurrences. Pelvic MRI is the first-line examination in all these indications. It is the key element for delineation after image fusion when the indication of chemoradiation therapy is made. It is also essential for guiding the placement of applicators and optimising the dosimetry of brachytherapy. The diffusion-weighted acquisition is a sequence sensitive to the motion of water molecules. It allows distinguishing water molecules with free diffusion from water molecules with diffusion restricted by obstacles such as cell membranes or the cytoskeleton. The diffusion is thus connected to the cellularity of the explored tissue, and the cancers, being hypercellular, will present a

high signal. It thus provides additional information thanks to a high contrast between the tumour and the surrounding tissues, facilitating detection, evaluation of the volume and extent of the disease.

Keywords

Cervix uteri; Cancer; Magnetic resonance; Imaging; Diffusion-weighted imaging; Chemoradiation; Treatment; Planning

Résumé

L'imagerie intervient dans la prise en charge du cancer du col utérin avec plusieurs objectifs : 1/ faire le bilan d'extension locale et ganglionnaire de la maladie initiale ; 2/ évaluer la réponse au traitement conservateur ; 3/ détecter les récurrences. L'IRM pelvienne est l'examen de première intention dans toutes ces indications. C'est l'élément clef de la délinéation après fusion d'image lorsque l'indication d'une chimioradiothérapie est posée. Elle est aussi indispensable pour guider la mise en place des applicateurs et optimiser la dosimétrie de la curiethérapie. L'acquisition pondérée en diffusion est une séquence sensible aux mouvements des molécules d'eau. Elle permet de distinguer les molécules d'eau en mouvement dont la diffusion est libre des molécules d'eau dont la diffusion est restreinte par des obstacles tels que les membranes cellulaires ou le cytosquelette. La diffusion est donc reliée à la cellularité du tissu exploré, et les cancers, hypercellulaires, seront en franc hypersignal. Elle apporte ainsi des informations supplémentaires grâce à un contraste élevé entre la tumeur et les tissus environnants, facilite la détection, l'évaluation du volume et de l'extension de la maladie.

Mots clé

Cancer ; col utérin ; Imagerie ; Résonance magnétique ; Pondération diffusion ; Chimioradiothérapie, Planification ; Traitement

1. Introduction: Importance of imaging for radiation therapy in the management of cervical cancer

The majority of cervical cancers are squamous cell carcinomas (80-90 %) or adenocarcinomas (10-20 %). Positive diagnosis of cervical cancer will be made by histological examination on a cervical biopsy or conization and not by imaging. Imaging will be used in the management of the initial disease with several objectives: 1/ to assess the local and lymph node extension of the initial disease; 2/ to evaluate response to conservative therapy; 3/ to detect recurrence. Pelvic MRI is the first-line examination in all these indications, and the diffusion-weighted acquisition provides essential information that will be useful to both the radiologist and the radiation oncologist.

The initial spread of cervical cancer is determined by the International Federation of Gynaecology and Obstetrics (FIGO) classification which was revised in 2018 (Table) (1). Until 2018, the FIGO staging did not take into account imaging or node status. These changes gave imaging a more prominent place

in the initial assessment closer to the practices of expert centres. Briefly, stage I cancers are limited to the cervix; stage II cancers expand beyond the cervix without reaching the lower third of the vagina or the pelvic wall; stage III cancers present invasion of the lower third of the vagina or pelvic wall, present hydronephrosis or a non-functional kidney, have pelvic or retroperitoneal lymph nodes; stage IV cancers present invasion of pelvic organs or extrapelvic extension.

The challenge at the diagnostic stage is to make the right decision during the multidisciplinary tumour board between surgery or chemoradiation therapy (2). For stages IA, IB1 et IB2, patients will undergo surgical treatment. Starting at stage IA2, a complementary pelvic lymphadenectomy is indicated. For IB2 stages, initial uterine and vaginal brachytherapy can be proposed. If the patient has lymph node involvement, additional concomitant chemoradiation is administered.

For stages IB3- IVA, the reference treatment is concomitant chemoradiation. The irradiation fields are pelvic and retroperitoneal or not, followed by a uterovaginal brachytherapy. Irradiation volumes are based on imaging (MRI, [^{18}F]-fluorodeoxyglucose [FDG] positron emission tomography combined with computed tomography [PET-CT]) and/or the results of a laparoscopic retroperitoneal lymphadenectomy.

Stages IVB are rare and management will be discussed on a case-by-case basis depending on the extent of the disease and the patient's general condition. Treatment relies on chemotherapy and eventually complementary radiation.

2. Technical bases of diffusion MRI

2.1. Principle of diffusion-weighted imaging

The MRI signal is due to the dephasing of protons in water molecules. The contrast depends on the difference in proton dephasing rate between different tissues.

The principle behind diffusion weighted magnetic resonance imaging (DW-MRI) is the exploration of microscopic movements of water. It allows distinguishing between mobile water molecules in which diffusion is free (as in cerebrospinal fluid), and water molecules whose diffusion is restricted (by cell membranes fibres macromolecules, etc.). Diffusion is therefore dependent on the cellularity of the explored tissue (3), which makes this technique particularly interesting in cancers which are hypercellular and therefore present many obstacles restricting diffusion.

2.2. Image acquisition

The diffusion-weighted sequence is first and foremost a T2-weighted MRI sequence (4). Two intense, symmetrical, and opposite gradients are applied separated by a latency time during which the water molecules will diffuse more or less according to the intra- and extracellular obstacles they may

encounter. These gradients will result in a dephasing and then rephasing of the protons in the voxel. The mobile diffusing water molecules will move out of the voxel during the latency time and therefore be in completely rephased. They will thus see their contribution to this signal fall. On the contrary, static water molecules will be dephased and rephased completely and will have a signal that will not be affected by these gradients. They will therefore emit a high signal intensity. Water molecules inside cells have a much more limited degree of movement than water molecules in the extracellular space, due in particular to the existence of cell membranes and the cytoskeleton. A highly cellular tissue such as tumours will thus have a low diffusion coefficient, emitting a high signal on the MRI image, appearing brighter than normal tissues in which water molecules will diffuse much more (5).

The diffusion sequence was developed initially in brain imaging for the early diagnosis of stroke. Its use has been extended to whole body imaging thanks to technical developments allowing faster acquisition with fewer motion artefacts for use in oncology (6).

Quantification of the diffusion of water molecules can be performed using the apparent diffusion coefficient (ADC), expressed in square millimetres per second (4). This quantitative parameter has been used in many studies to characterise tumours or assess their response to treatment(7). Its use in clinical practice has yet to be defined.

Diffusion images suffer from low spatial resolution, but they can be merged with a morphological sequence providing anatomical information to compensate this drawback (figure 1).

3. Role of imaging in cervical cancer

3.1. Imaging for the initial staging of cervical cancer

3.1.1. Definition of the target volume

Two target volumes are important for patient management: the volume of tumour extent (gross tumour volume, GTV T et clinical target volume, CTV T) and the lymph node volume (GTV N et CTV N).

The imaging assessment will consist of a pelvic MRI exploring the lymph node regions up to the renal veins and including a diffusion-weighted sequence (8).

Elements on imaging that may compromise surgical management:

- largest diameter greater than or equal to 4 cm (measured in all three planes);
- extent to the parameters, the lower third of the vagina or the pelvic wall;
- extent to adjacent organs.

MRI is considered the reference examination to define location, size and invasion of parameters, pelvic wall or adjacent organs (7,9).

The accuracy of the definition of the lesion boundaries is improved by the contrast between normal and tumour tissues on the diffusion sequence (figure 2), thus contributing to the definition of the cervical volume. Diffusion-weighted imaging has an added value in particular for the detection of an extent to the parameters compared to the morphological T2-weighted sequence (diagnostic accuracy greater than 90% vs. 80 to 85% respectively), and more specifically by reducing false positives (10-12). MRI also has a high negative predictive value to eliminate bladder or rectal involvement (13).

Beyond the definition of volume and local extent spread imaging has an important role in detecting lymph node involvement particularly retroperitoneal lymph nodes. This is important in order to discuss whether to perform a staging lymphadenectomy, and determine whether these areas should be treated surgically or with radiation (14). MRI is highly specific when the size (small axis) of the lymph nodes is increased (greater than 10 mm). Its sensitivity ranges from 37 to 71% for the morphological sequences, to 86% when adding the diffusion-weighted sequence (15). However it is not very sensitive nor specific for detecting lymph node metastasis in subcentimetric lymph nodes (16). Of note, even normal lymph nodes show a high signal on the diffusion-weighted sequence which decreases its specificity (figure 3b). In these cases (normal- sized lymph nodes, ¹⁸FDG PET-CT has a much better sensitivity (75%–100%) and specificity (87%–100%) particularly in patients with advanced stage disease (17,18). It could therefore be proposed during the multidisciplinary tumour board for the assessment of distant spread, particularly for tumours over 4 cm size (stage IB3 and higher) (2).

3.1.2. Identification of non-target organs

A lesser known application of diffusion MRI is the identification of normal organs, some of these appearing with a moderately high signal (figure 3). This is the case with ovaries, which are sometimes difficult to identify on morphological sequences especially if they are paucifollicular. The diffusion sequence thus makes it possible to improve the delineation for dosimetry after image fusion.

3.1.3. Evaluation of treatment response

MRI is the reference examination to assess the efficacy of chemoradiation, and to detect possible complications such as infection or fistulas (19). MRI is thus routinely used to evaluate response to chemoradiation and guide uterovaginal brachytherapy and should be performed 7 to 8 weeks after the end of treatment (20). It allows evaluating whether complete remission has been achieved and detects possible residual disease, which may then be treated by surgery (Fig. 4) (8). If the response is considered complete on imaging with *ad integrum* restitution of the cervical signal (and in particular of the fibrous low signal), there is no need to perform further exploration (21). Indeed, this sign has a high negative predictive value (97%). If, on the contrary, an anomaly is detected, a PET-CT can be proposed to exclude distant spread before surgery is considered.

Diffusion MRI has been used in several studies to predict the final efficacy of therapy. The pretreatment value of apparent diffusion coefficient, as well its early changes from the pretreatment value were predictive of the observed MRI response at the end of therapy (22,23).

3.2. Detection of recurrences

Recurrences of cervical cancer usually occur early i.e. within 2 years of starting treatment (60 to 70% of cases). Recurrence can be local (cervicovaginal), in lymph nodes or distant. They present similarly to the initial tumour with an intermediate signal on the T2-weighted sequence, but it may be difficult to distinguish between post therapeutic changes and tumour recurrence (24). Diffusion MRI is then useful because a high signal anomaly (other than infection or fistula) will be in favour of recurrence (25). For lymph node recurrence, the diffusion-weighted sequence is useful due to its ease of detection of pelvic or retroperitoneal lymph adenopathy due to their high signal (figure 5).

4. Conclusion

Pelvic MRI is the reference examination for initial assessment of cervical cancer. It is the key element for delineation of target volumes after image fusion when there is an indication for chemoradiation. It is also in central to guide the implementation of applicators and optimise the dosimetry of brachytherapy. In combination with the clinical examination, it allows evaluating the efficacy of treatment and detecting recurrences. Overall, the diffusion sequence, with the additional information it provides through a high contrast between tumour and surrounding tissues, facilitates the detection of cancer, evaluation of the volume and spread of the disease.

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Figure legends

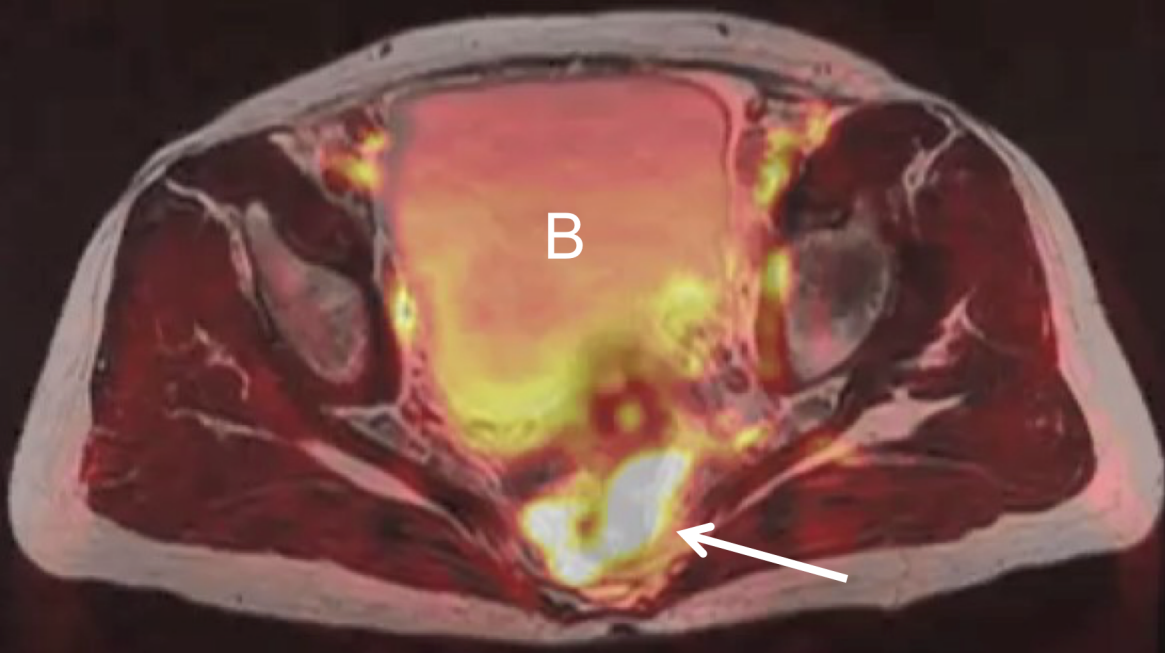
Figure 1. Diffusion MRI: application to uterine cervical cancer. Fused T2-weighted images (greyscale) and diffusion-weighted images (colour) combining spatial resolution of the morphological sequence with the contrast of the functional sequence. The arrow indicates the cervical cancer extending in the posterior pelvic cavity. B: bladder.

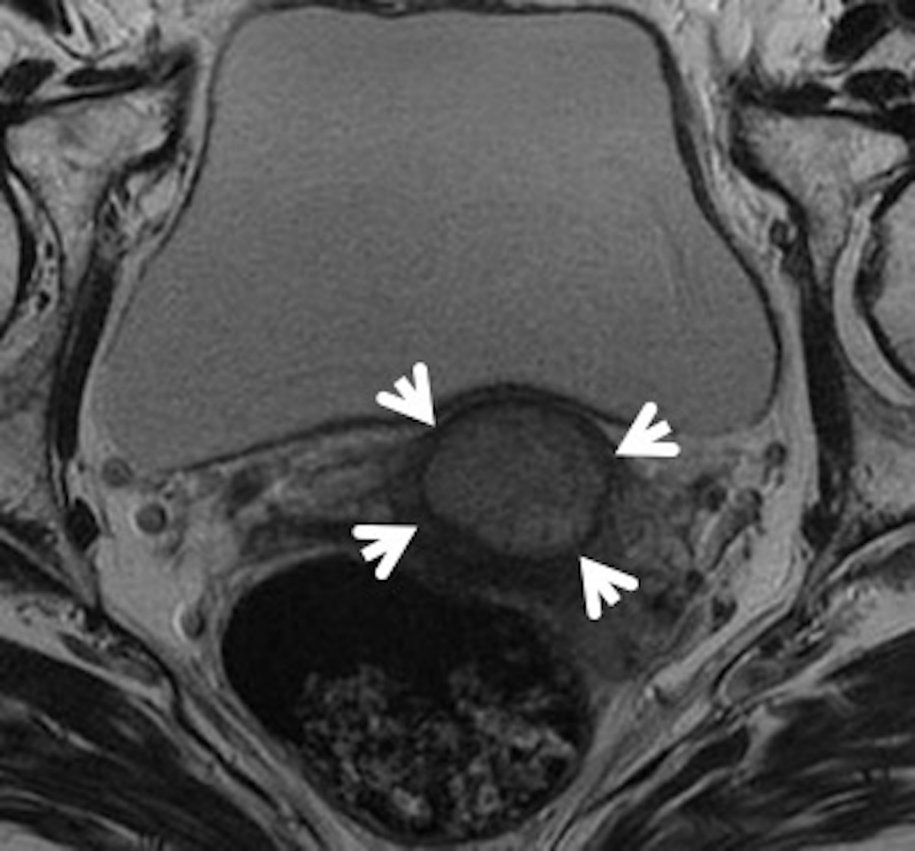
Figure 2. Diffusion MRI: application to uterine cervical cancer. a-d: images in two patients with cervical cancer; a,c: T2-weighted images; b,d: diffusion-weighted images. a, b: the cancer is limited to the cervix, with no extent to parametria; on the T2-weighted image (a), the cervical stromal ring is intact, seen as a circumferential low intensity line around the tumour (arrowheads); on the diffusion-weighted image (b), the cancer is seen as a high intensity lesion; c,d: there is an extent to parametria left and right (arrows) seen as nodular or irregular hyperintense signal extending to the parametrium. Note the presence of large left iliac adenopathies.

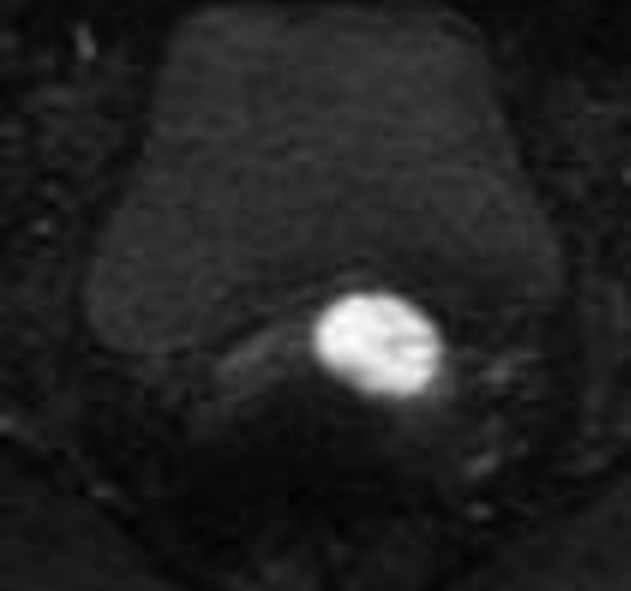
Figure 3. MRI of a 46 year-old patient with cervical cancer. a: T2-weighted image; b: diffusion-weighted image. The ovaries (arrows), paucifollicular, are hard to detect on the T2-weighted sequence, but easily identifiable on the diffusion-weighted sequence. Note also the visible infracentimetric left external iliac lymph node on the diffusion-weighted sequence (arrowhead).

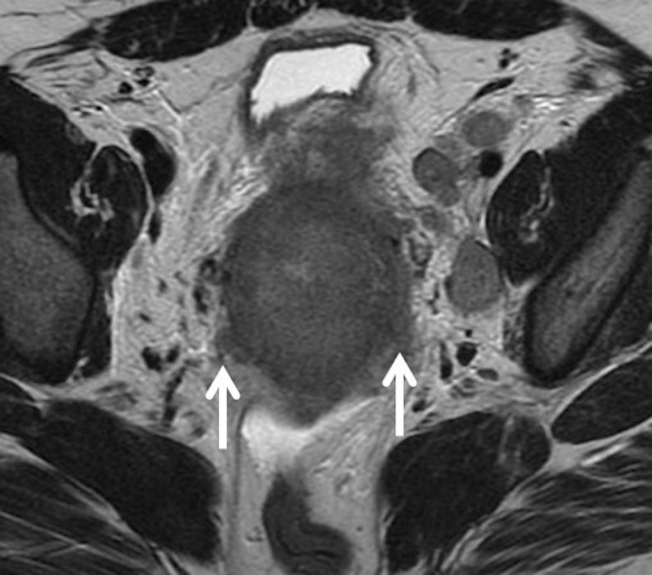
Figure 4. T2-weighted pelvic MRI of two patients with cervical cancer. a: for patient 1, the initial tumour (FIGO stage IB3) presents as a mass with an intermediate T2 signal (arrow), i.e. less high than fluids such as the urine in the bladder, but higher than muscles; b: after therapy, the cervix returns to its normal appearance, with a circumferential low signal similar to muscles (arrow) corresponding to the fibrous ring, spiculated retractions (arrowhead) can be observed that are not related to residual disease. c: for patient 2, the initial tumour extended into the right parametrium (arrow) (FIGO stage IIB); d: after therapy, though the tumour has decreased in size, residual tumour persists identified by its intermediate T2 signal. FIGO: International Federation of Gynaecology and Obstetrics.

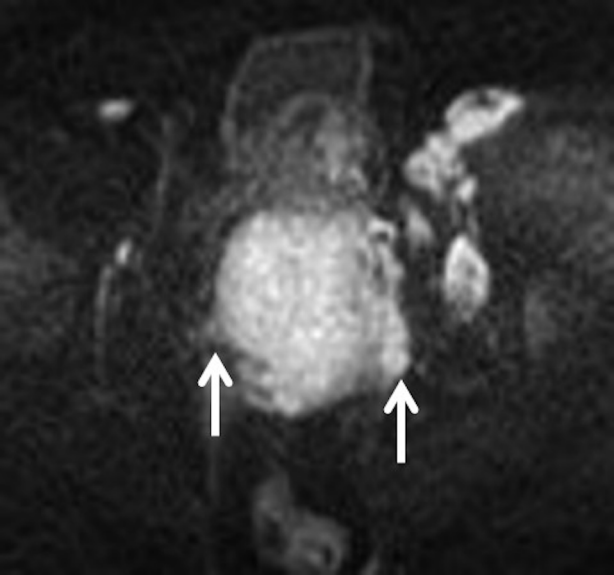
Figure 5. MRI for the detection of vaginal and lymph node recurrence of a cervical cancer treated by surgery and brachytherapy. a: the vaginal recurrence presents as an asymmetrical thickening of the vaginal stump (arrows) with an intermediate signal on T2-weighted image ; b: clear high signal of the vaginal recurrence on the diffusion-weighted image; c: the lymph node recurrence (arrows) presents as a lymph node with high signal on the T2-weighted image, which can easily be missed amid the high signal of the surrounding fatty tissue or be taken for a lymphocele secondary to staging lymphadenectomy; d: the high signal on the diffusion-weighted sequences improves sensitivity for detection of lymph node metastasis.

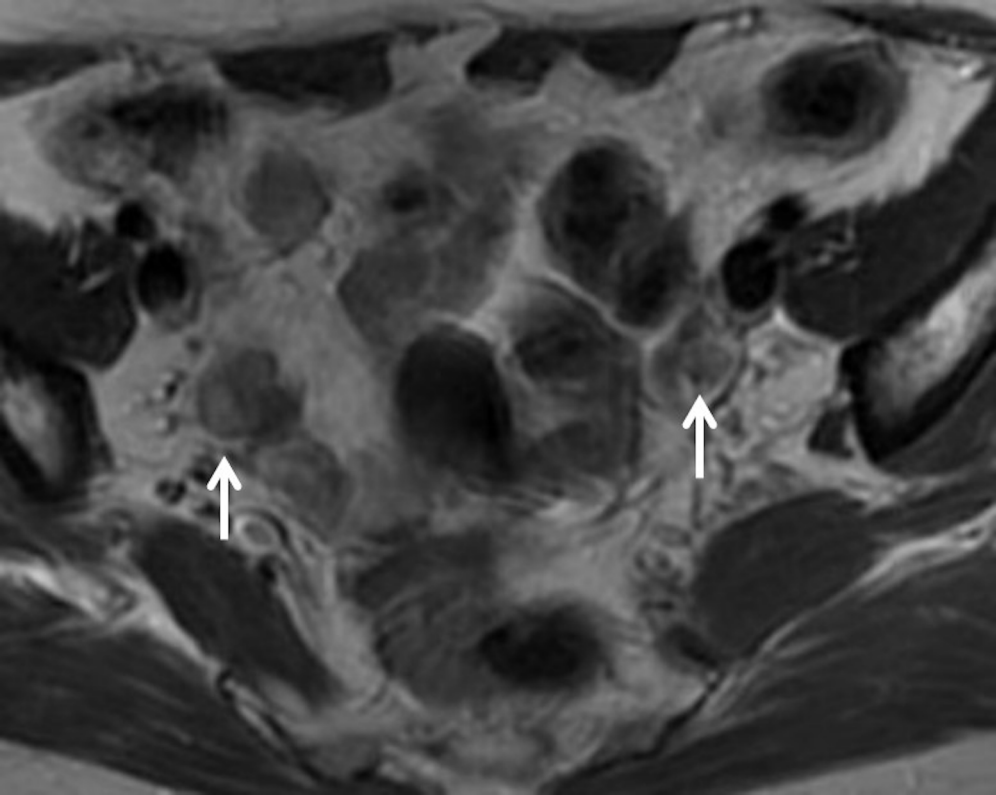


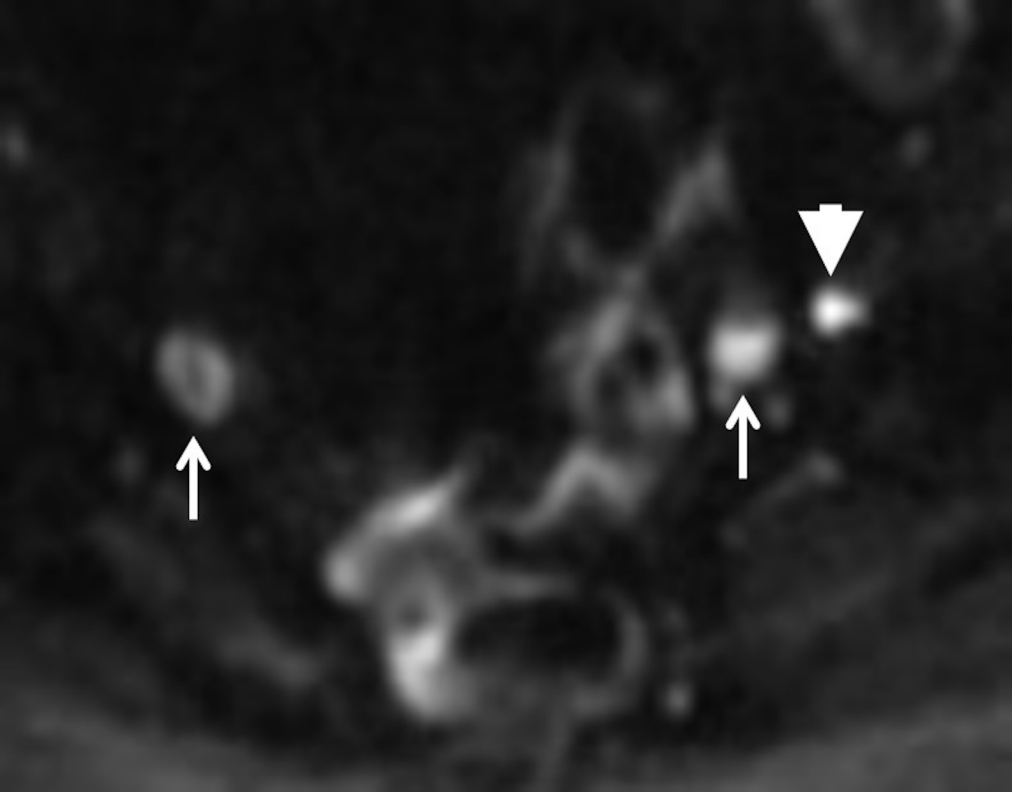


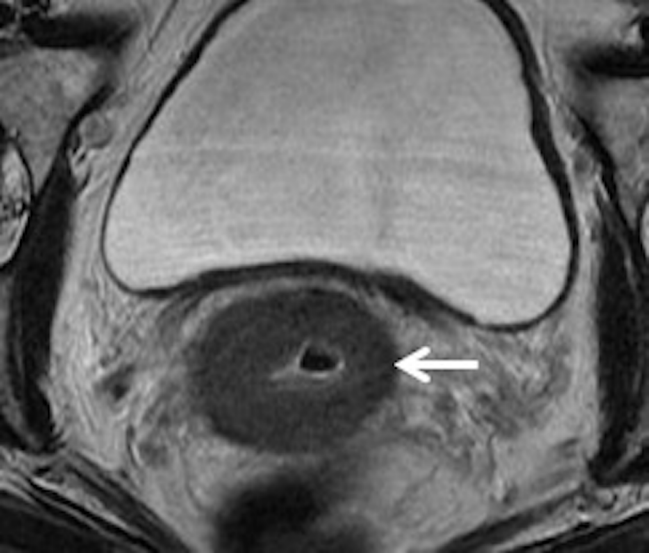


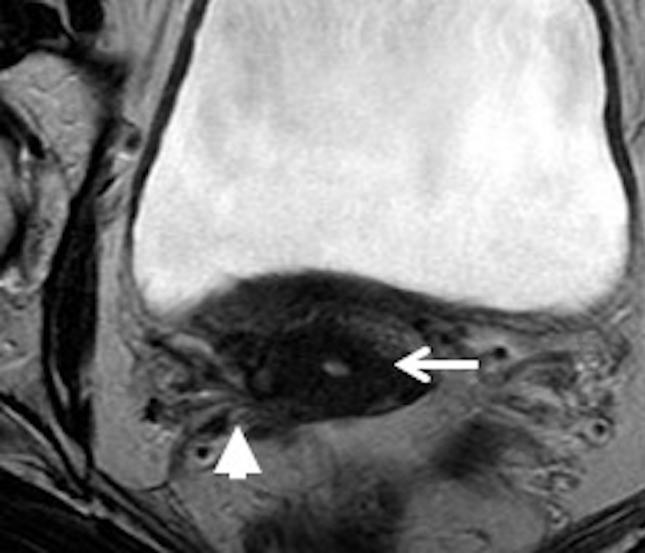


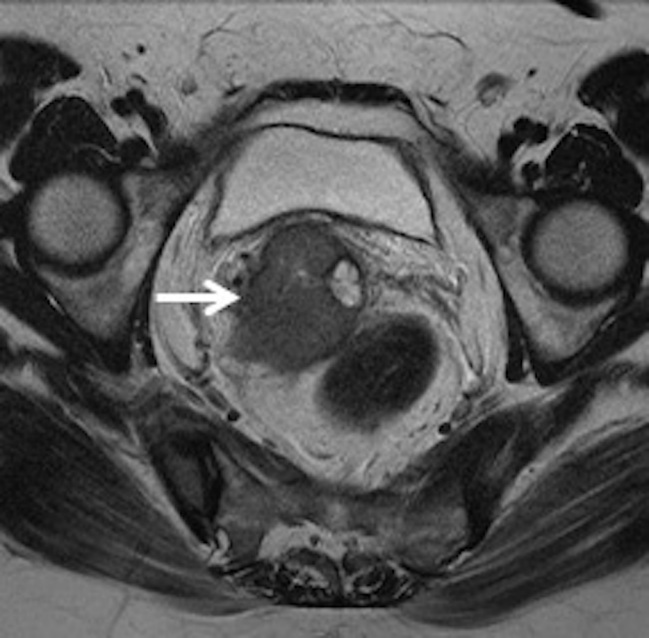


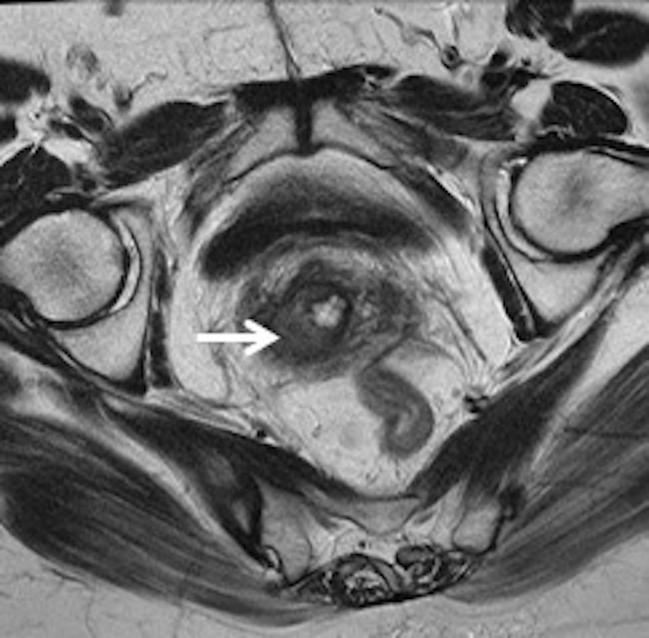






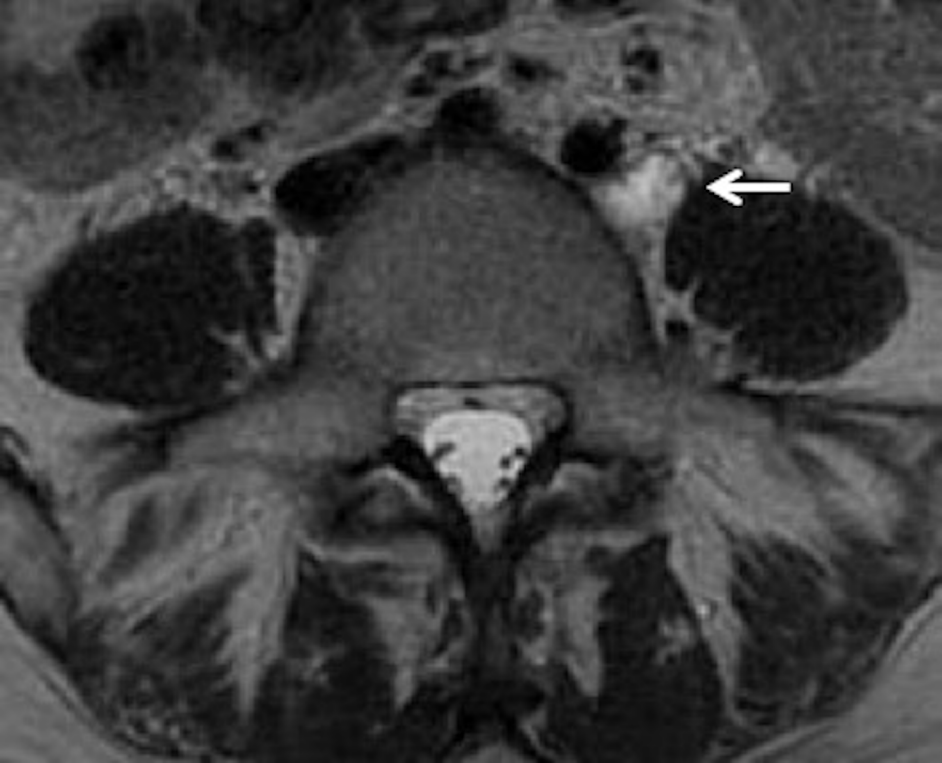












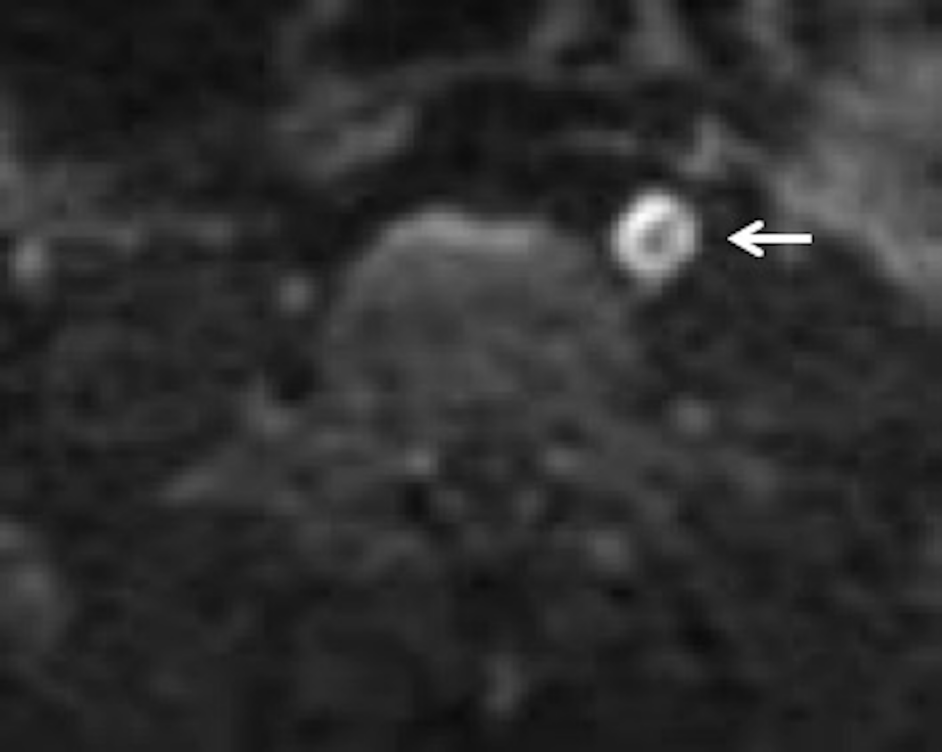


Table 1. Uterine cervical cancer stages classification according to the International Federation of Gynaecology and Obstetrics (FIGO), revised in 2018 (adapted from [1]).

Stages	Criteria
<i>Stage I</i>	Lesion limited to the cervix (whether there is an extent to the corpus or not)
IA	Invasion of stroma < 5 mm depth
IA1	Invasion of stroma < 3 mm depth
IA2	Invasion of stroma \geq 3 mm et < 5 mm depth
IB	Lesion limited to the cervix, invasion \geq 5 mm depth
IB1	Size < 2 cm
IB2	Size \geq 2 cm and < 4 cm
IB3	Size \geq 4 cm
<i>Stage II</i>	Lesion extending beyond the cervix without spread to lower third of vagina or pelvic wall
IIA	Extent to higher two thirds of vagina, but no extent to parameters
IIA1	Size < 4 cm
IIA2	Size \geq 4 cm
IIB	Extent to parameters but not pelvic wall
<i>Stage III</i>	Extent to lower third of vagina and/or pelvic wall and/or hydronephrose or non functional kidney and/or pelvic and/or retroperitoneal lymph node metastasis
IIIA	Extent to lower third of vagina but no extent to pelvic wall
IIIB	Extent to pelvic wall and/or hydronephrose or non functional kidney
IIIC	Pelvic and/or retroperitoneal lymph node metastasis (r if on imaging, p if pathology)
IIIC1	Pelvic lymph nodes only
IIIC2	Retroperitoneal lymph nodes
<i>Stage IV</i>	Extrapelvic extension or spread to adjacent organs
IVA	Extent to adjacent organs (biopsy-proven extent to bladder or rectum mucosa)
IVB	Distant metastasis