Anatomical, Imagistic and Structural Study of Pharamagnetic Substances in Cervical Tumors

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Along with the findings of recent years in medical imaging, a wide range of contrast agents have been developed and used in order to improve the quality of the images acquired and to get a diagnosis with the highest accuracy. Modern substances used in nuclear magnetic resonance imaging contain ions with one or more free electrons, which have fewer side effects and are eliminated by the kidney in a short time. This is used in MRI practice in T1 section, where these substances reduce relaxation time and increase signal strength. Our study included a group of 17 patients diagnosed with cervical cancer, who were also investigated by MRI technique with paramagnetic contrast agents. We followed the cervix-related aspects in the T1 and T2 sections and applied the EMM score criteria to determine the level of extramural invasion of the blood vessels. The results are conclusive in the advanced stages of the disease when EMM staging criteria are similar to those of TNM.

Keywords: extramural vascular invasion (EMM), cervical cancer, MRI with paramagnetic substances

Staging of gynecological cancers is based on surgical pathological findings, with the exception of cervical cancer, which is clinically diagnosed, as it is stipulated by International Federation of Gynecology and Obstetricians (FIGO). This is currently the most commonly used staging system [1].

MRI (magnetic resonance imaging) is the most accurate method of examining the female pelvis, being considered superior to computed tomography in tumor extension evaluation and capable of appreciating ganglionic lymphatic system. Nuclear magnetic resonance provides the most accurate data on cancer extensibility and allows perfect anatomical delimitation, eventually enhanced by MRI contrast products [2,3]. Nuclear magnetic resonance investigation may be associated with contrast agents. The evolution of these substances over time is critical, there are nowadays as few adverse effects and are eliminated from the body by the kidneys within 90 minutes.

Among the most popular contrast agents are those called paramagnetic and based on several ions with one or more free electrons. In the category of these most commonly used ions is gadolinium, subject to chelation because it induces the most powerful relaxing effect [4]. Also, T1 sections are commonly used because there is an increase in signal intensity and a positive contrast signal with the magnetic dipole of neighboring protons.

The aim of this study is to investigate the possibility of using these substances in early diagnosis and cervical cancer staging [5], following a protocol that correlates the extramural blood vessel aspects (EMM score) with the TNM staging. This protocol has been previously used by us, but only in patients diagnosed with colorectal cancer.

Experimnetal part

Materials and methods

The study was performed in a group of 17 patients admitted to the Cuza Voda Clinical Obstetrics and Gynecology Hospital, diagnosed with cervical cancer with various localizations. Patients were investigated by: clinical examination, cervico-vaginal test, colposcopy with biopsy, anatomopathological examination, CT and MRI in order to perform a preoperative imaging evaluation and to provide information about tumoral location, tumoral staging with depth of invasion, and their correspondence to fascies, adjacent organs and blood and lymphatic vessels.

The MRI exam was performed on a 0.23T (low field) PICKER OUTLOOK PROVIEW, accessible especially to claustrophobic, anxious and obese patients. The sequences used were T2TSE, T1TSE native and postcontrast, spectral suppression with inversion recovery (STIR) to suppress the signal from the adipose layer.

T2 sequences were purchased in at least 2 planes - axial and sagital (most useful for cervical pathology), optionally coronal, with small FOV (field of view), respectively increased resolution for evaluation of uterus, cervix, vagina and parametryum. Paraaxial T2 sequence (perpendicular to the long axis of the cervix) is preferred especially for the evaluation of the parametryum invasion.

The T1 axially-sequence with large FOV were used for scanning the entire pelvis, with particular attention to the detection of low paraaortic and inguinal adenopathies, respectively the assessment of bone structures in the examination field for the detection of possible secondary determinations. The examination protocol provides sections in multiple sequences - T2 TSE, T1 TSE, with sections of 1.5 mm thickness and 2 mm interval. The STIR examination involved sections of 5 mm and 5 mm thick.

Results and discussions

Cervical cancer has an intermediate signal in T2 (hyponormal to normal cervical mucosa and hypernormal to fibromuscular internal stroma). Crucial for diagnosis is the appreciation of irrigation of the cervical fibrous stroma [6]. The low signal differentiates stage IB from IIB [7].

Searching for tumor extension in the vagina (best appreciated on axial and sagittal sections), it were performed sections in sequences - T2 and T1 postcontrast (differentiates stage IIA from IIB). The parametryum for extracervical tumor extension, T1 sequences without fat saturation and T2 and T1 postcontrast with fat saturation are inspected. They are very sensitive for the extent of disease - stage IIIB parametryum.

We followed the imprecisely delimited sequences that infiltrate the adipose tissue of parametryum, respectively the signal intensity of invaded parameters of fat. MRI appreciates the status of ureters in axial and/or sagittal sections in T2 sequences for abnormal dilation following neoplastic invasion - stage IIIB. In axial and sagittal T2 and T1 sections, with contrast paramagnetic agents, we followed the occupation and invasion of the tissue plans that separate the cervix from the bladder or rectum - stage IVA [8, 9].

The inspection of the pelvic lateral walls is done not only to indicate the direct tumor extension but also to indicate adenopathies. It is essential to highlight the invasion of parametryum and the damage to the fibrous stroma [10,11]. The accuracy of MRI staging is between 76-92% (fig. 1).
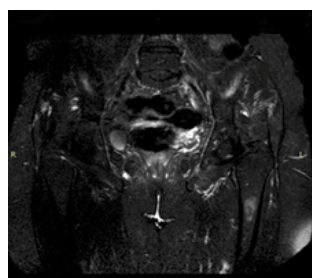

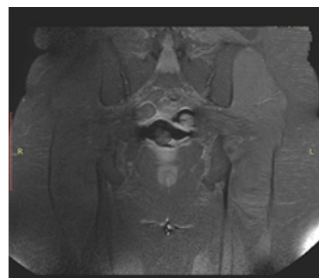Fig. 1 Long-distance tortuosities and nodosities specific to IV EMM score in stage IIB of cervical neoplasm

Fig. 2 Tumor formed with an anular effect at the level of homolateral intramural vessels

MRI T2 sections can be used to demonstrate a number of prognostic factors for local disease recurrence and survival rate in cervical cancer patients who were initially listed for histopathological studies. These include the tumoral extension to the lateral resection margin, the depth of the extramural tumoral extension and the presence of the extramural venous invasion (fig. 2).

The normal uterine cervix is perforated by numerous small venules that appear on MRI-T2 sections with a intensity signal from weak to intermediate. Extramural venous invasion is recognized on MRI-T2 sections by the expansion and irregularity of venules adjacent to the primary cervical tumor due to contiguous tumor extension. The involved vein generally appears by intermediate intensity signal and loss of normal vascular flow.

The lymphatic vessels accompanying the blood vessels are much smaller than these and therefore can not be viewed on the MRI-T2 sections. However, there is evidence from specialized literature that tumoral invasion of extramural veins acts as a surrogate marker for lymphatic tumoral permeability. Therefore, patients with apparent extramural venous invasion at MRI have theoretically a greater risk and incidence of lymphatic invasion.

From a practical point of view, the recognition of MRI features that are associated with increased risk of lymphatic invasion may alert the treating physician to enhance the assessment of lymphatic status and also to increase the arguments for neoadjuvant radio-chimioterapies in order to reduce the recurrence of local invasion.

Extramural vascular invasion (EMM) is defined as the presence of tumoral cells in the vasculature beyond the *muscularis propria*. It is produced by small tumors that penetrate deeper and beyond the parametryum and is known to be a poor marker for survival and recurrence of the disease. On MRI images, EMM score gives a serpentine appearance of tumor extension within a vascular structure (fig. 3).

Fig. 3 Sagittal MRI, EMM II-III score with intramural vessels in cervical neoplasm in TNM stage II
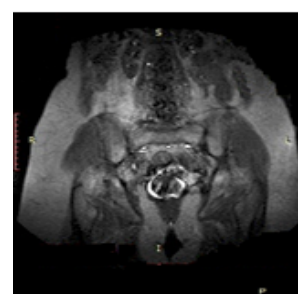
Fig. 4 Transverse IRM, EMM I score in cervical neoplasm in TNM stage I, intramural vessels

MRI correlation with histopathological evaluation gives a much more accurate estimate of EMM scoring. MRI may be superior to histopathological analysis of resection specimens in EMM identification, especially if surgical technique is limited [12,13]. MRI has the advantage of in vivo demonstration of vascular anatomy and therefore, tumor invasion can be immediately identified. For these reasons, the evaluation of the presence or absence of EMM scoring should be a routine in our hospitals. Stage I EMM can be diagnosed if correlated with the histopathological examination (fig. 4).

Extrauterine venous invasion can also have a role in evaluation of preoperative risk, reconsidering decisions about chemotherapy or intensifying neoadjuvant treatment. A good EMM regression of fibrosis (> 50%) is associated with a significantly better survival rate, independent of final staging. MRI is more accurate associated with EMM identification for large vessels compared to small calibers ones. Although EMM identification of small vessels is more difficult to achieve from a radiological and histo-pathological point of view, this would seem to have reduced clinical consequences.

Using preoperative acquired images we applied diagnose staging by using the EMM score. We correlated our results with the usual staging of TNM. The most important anatomical surgical aspects are the sacral rectal genital pubic fibrous fascicles and the relationships with the surrounding organs.

Histopathologically, extramural venous invasion demonstrated that cervical cancer was associated with a lower survival rate and increased risk of lymphatic invasion and remote metastases.

An EMM score higher than 2 in MRI T2 sections has a high sensitivity and specificity for venous invasion of more than 3 mm in diameter, as it was histopathologically demonstrated. However, the EMM score has a moderate sensitivity in predicting lymphatic nodes involvement.

Weaknesses identified in the protocol:
-sensitivity of the method in the early stages;

-mode of differentiation of pre-operative T2 and T3 stages (which requires the need for neoadjuvant therapy);

-establishing a new protocol by integrating existing knowledge with the aspects obtained by angiographies performed on the resection specimens, anatomo-pathological results, immunohistochemical preparations and specific neurohormonal markers.

Criteria for Improving the EMV Score:

-the appearance of the margins of the tumor - the tumoral invasion in the small veins can produce nodosities of their wall, distinct from desmoplasia;

-localization of the tumor against large vessels - the presence of the tumoral signal in the vascular structures

-calibrate affected vessels - these increase in volume, the signal inside them is a medium gray;

-the margin of the blood vessels - the tumor can be expanded inside the vessels and can give a look from smooth to irregular or nodular.

Following the correlation of the investigations carried out in the cervical neoplasia with the pre-existing rectal studies, in the case of uterine cervix, approx. 46% of the cases studied had specificity and diagnostic accuracy and prognosis. For the most part, these cases are in advanced stages - IIB and IIIA and B [14,15]. The data obtained in the study could reveale aspects of extramural invasion in Stages IIB and IIIA and IIIB corresponding to confirmed data in colorectal cancer, which promises the accuracy of this new method in cervical neoplasia.

Conclusions

MRI is a widely used method of investigation, with very good acuity in most cases of colorectal neoplasms that might be attempted to be extended to cervical cancers. The current tendencies towards minimally invasive techniques but with very high accuracy are achieved by the correct multidisciplinary interpretation of the aspects related to the paraneoplastic vascular invasion. The advanced stages of the EMV score correlates with those of the classic TNM stadium. The tumoral invasion of the extramural veins surrounding the primary lesion in cervical cancer acts as a surrogate marker for lymphatic permeation of the tumor. Therefore, patients with obvious venous extrauterine invasion at MRI have theoretically a greater risk and incidence of lymphatic invasion.

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