Pelvic lymph nodes in cervical cancer: usefulness of diffusion-weighted magnetic resonance imaging in the correct diagnosis. Preliminary results

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Aims and objectives

Introduction

Uterine cervical carcinoma is the second most frequently diagnosed malignancy in women worldwide [1]. Cervical carcinoma is clinically staged according to the International Federation of Obstetrics and Gynecology (FIGO) recommendations. The presence of lymph node metastasis is the strongest prognostic factor in women with locally advanced cervical cancer (LACC, i.e. FIGO stage IB2 or higher), because it influences the survival rates and affects the treatment planning [2]. Chemoradiation therapy, combining external beam radiation therapy and cisplatin-based chemotherapy with intracavitary brachytherapy, is considered the standard treatment for these patients [3]. In our Center, an investigational approach including neoadjuvant chemoradiotherapy (nCRT) followed by radical surgery is currently applied [4].

It has been shown that functional imaging using \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG) PET-CT is more sensitive than morphological imaging techniques, such as CT and MRI, in detecting lymph node metastasis, as it enables to detect and localise even not enlarged metastatic nodes, thus overcoming the limitation of the size-based characterization [5, 6, 7]. A threshold diameter of 10 mm in the short axis is in fact the most accepted criterion applied in both CT and MRI for distinguishing metastatic from non-metastatic nodes. Previous studies have shown that, using size criteria, the sensitivity of MRI for detecting metastatic nodes in cervical carcinoma ranges from 24 to 73%, because of the inability to detect micrometastases in normal-sized lymph nodes [8].

More recently, the apparent diffusion coefficient (ADC), which is derived from diffusion-weighted imaging (DWI), has been shown to facilitate the non-invasive characterization of tissues on the basis of their water diffusion properties. ADC is lower in malignant than in non-cancerous tissues as cancer tissue presents high-cell densities and abundant intra- and extra-cellular membranes. Several studies have proven the feasibility of ADC as a diagnostic tool in differentiating metastatic from non-metastatic lymph nodes [9].

It is widely known that tumor ADC values increase following successful treatment, as a result of a reduction in cellular density and barriers to water motion [10-13], but until now, few studies have considered the usefulness of DWI in monitoring and predicting the response to nCRT in patients with cervical cancer [14-17]. Furthermore, to our knowledge, none of these studies investigated whether modifications of ADCs observed in metastatic nodes during treatment could represent a powerful tool to assess lymph node in vivo response to therapy and predict outcome and local disease control before surgery.
The purpose of our study was to prospectively investigate changes in ADCs and short-axis diameters in metastatic pelvic lymph nodes in patient with LACC receiving nCRT, and to assess the relationship between these changes and final response to therapy.

Methods and materials

Patients

Between November 2010 and November 2013, 74 female patients with histologically proven LACC according to the FIGO classification underwent whole-body \(^{18}\)F-FDG PET/CT and 1.5 T pelvic MRI before, 2 weeks after and at the end of nCRT. Patient characteristics were as follows: (a) patients with untreated histologically confirmed LACC (FIGO stage IB2 bulky - IVA), candidates for nCRT; (b) age \# 75 years; (c) Eastern Cooperative Oncology Group performance (ECOG) status < 2; (d) no distant metastasis or other concurrent oncologic diseases at basal staging; (e) no general contraindications to MRI examination (pacemaker, metal fragments, vascular stents) or claustrophobia; (f) no medical or surgical conditions that contraindicate chemoradiation therapy or radical hysterectomy and lymphadenectomy; (g) exclusion of condition of pregnancy or breast-feeding.

Only patients showing an increased uptake on pre-treatment PET-CT in pelvic lymph nodes with MR short-axis \# 5 mm were included in this study.

Institutional ethics committee approved this study and written informed consent was obtained from all patients.

MRI and DWI techniques

All patients underwent MRI examination with DWI using 1.5 T scanner prior to (pre-treatment MRI), after 2 weeks (early MRI) and at the end of nCRT (final MRI). To reduce bowel peristalsis, 1 mg of butylscopolamine was administered intramuscularly to all patients 10 minutes before beginning the examination. Patients were recommended to fast for 4-6 hours prior to imaging.

A pelvic phased-array coil was used in all patients. Our imaging protocol included sequences illustrated in Table 1.
Table 1: MRI protocol for cervical cancer.

References: Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT

Imaging Analysis

In patients included in this study (PET-CT positive nodes and MR short-axis # 5 mm), ADCs and short-axis diameters of pelvic lymph nodes were measured at each MR assessment (pre-treatment, early and pre-surgery MR imaging). Maximal short-axis diameters were measured using the transverse plane on T2-weighted images.

For imaging analysis, data were transferred to an independent workstation and analyzed using a specific software. ADCs were calculated at each assessment on a pixel-by-pixel basis to generate ADC maps. Regions of interest (ROI) were manually drawn on the DW images. ROI dimensions were around 20 mm². The corresponding T2-weighted images were observed to assist the identification of pelvic lymph nodes. When very small lymph nodes had to be considered, ROIs were drawn as small as possible. Care was taken to avoid areas of necrosis within the nodes in order to avoid biased results. MR images were analyzed by two radiologists with 10 and 5 years of experience in MRI examination for gynecological pathologies. Interpretation discrepancies were resolved by consensus.
PET-CT technique

All studies were performed using an integrated PET-CT device combining a dedicated full-ring PET scanner with gadolinium-oxyortho-silicate (GSO) crystals and a multislice spiral CT scanner.

All patients had fasted for at least 6 h prior to $^{18}$F-FDG injection and had blood glucose levels of < 200 mg/dl at the time of the tracer injection. Before PET-CT acquisition the patients were hydrated with NaCl 0.9% solution. Images were acquired after intravenous injection of 111-555 MBq of $^{18}$F-FDG. The CT scan was performed from the base of the skull to the proximal femora with a voltage of 110-120 kV and a tube current of 20-40 mAs. This scan was used for the anatomical localization, the attenuation correction of PET emission data and fusion with attenuation-corrected PET images. PET emission scans were acquired in three-dimensional mode, from the proximal femora to the base of the skull with a FOV of 15 cm. PET images were reviewed in transverse, sagittal and coronal planes. To view the images, the PET and CT data sets were transferred to an independent computer workstation using Digital Imaging and Communications in Medicine (DICOM) transfer.

Treatment

After clinical staging, neoadjuvant 3D-conformal radiotherapy was administered through a schedule of 3960 cGy in 22 fractions plus a concomitant boost on tumor and parametria (total dose 1080 cGy in 12 fractions). During the first and the last 4 days of treatment, a combination of cisplatin and 5-fluorouracil (5FU) was administered.

Radiotherapy was delivered with a 4 field box technique to the pelvic region, using a linear accelerator in 5 days/wk with photon energies of 10 MV (22 fractions). All patients were treated in the prone position on an up-down table. The clinical target volume 2 (CTV2) including the tumor, the internal iliac, obturators, external iliac nodes, and the upper two-thirds of vagina received a dose of 39.6 Gy. In patients with stage IIIA disease, inguinal lymph nodes were included in the irradiation field. Concomitant boost was delivered to the primary tumor mass and parametria (CTV1), determined by simulation CT scan compared with the staging MRI through 4 coplanar, 2 by 2 opposite, oblique fields, during whole pelvis irradiation.

Surgery
4 weeks after post-treatment MRI, all patients underwent bilateral pelvic lymphadenectomy (± para-aortic lymphadenectomy) during radical hysterectomy. Pelvic bilateral lymphadenectomy was performed systematically with dissection of all pelvic lymph node groups.

**Histopathological evaluation**

Surgical specimens were provided for histologic correlation. All pelvic lymph node sites were dissected by the surgeon and submitted separately. Thin sections were stained with hematoxylin and eosin and examined microscopically by a single experienced pathologist. At histopathologic examination, the presence of malignant cells, intranodal necrosis and inflammatory tissue were assessed. Post-surgical histopathological results from dissected lymph nodes were used as reference standards and divided into 2 groups: 1) metastatic lymph nodes (N⁺); 2) non-metastatic lymph nodes (N⁻).

**Statistical analyses**

Statistical analyses were performed by using statistical software. Independent samples Student t-test was used to compare the mean Apparent Diffusion Coefficient (mADC) and mean short-axis diameter (msa) in metastatic and non-metastatic lymph nodes for all the three MRI assessments. T-test was also performed in order to identify mADC and msa intragroup differences. Two-sided P values <0.05 were considered statistically significant.

**Images for this section:**
<table>
<thead>
<tr>
<th>Sequence</th>
<th>Axial T1w</th>
<th>Sagittal T2w</th>
<th>Axial T2w</th>
<th>Axial DWI</th>
<th>Axial Oblique T2w</th>
<th>Coronal Oblique T2w</th>
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<td>FC, TRF, Fast, ZIP512, FR</td>
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<td>0:36</td>
<td>3:05</td>
<td>3:05</td>
<td>0:33</td>
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</tbody>
</table>

**Table 1:** MRI protocol for cervical cancer.
**Results**

A total of 57 pelvic lymph nodes in 34 patients (median age: 51.97 ± 12.68 years; age range: 23-75 years) were indicated as metastatic by pre-treatment PET-CT and were chosen for measuring ADC in pre-treatment, early and pre-surgery MRI examinations.

At histopathology, 5 nodes (5/57, 8.8%) in 4/34 patients (11.8%) were found positive for neoplastic cells (N⁺) (*Case 1: fig. 1-3*), one of which being positive for micrometastasis (*Case 2: fig. 4-6*), while 52 nodes (52/57, 91.2%) in 30/34 patients (88.2%) were indicated as negative for metastatic involvement, showing in some cases signs of reactive lymphadenitis (N⁻) (*Case 3: fig. 7-9*).

The location of metastatic lymphadenopathy included obturator station (4 N⁺) and external iliac station (1 N⁺).

ADC values and short-axis maximum diameters in metastatic and non-metastatic lymph nodes are resumed for the three MRI assessments in *Table 2* and *Table 3* respectively.

**Case 1 (macroscopic metastasis)**

(Fig. 1-3)
**Fig. 1:** Basal MRI in a patient with a positive right obturator lymph node (macroscopic metastasis at histopathology). (a) Axial T2-weighted image. (b) Lymph node short-axis diameter (17 mm) on axial T2-weighted image. ROI (21 mm2) on (c) axial DW image and (d) ADC map (ADC value = 1.49).

**References:** Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT
Fig. 2: Early MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (15.2 mm) on axial T2-weighted image. ROI (16 mm²) on (c) axial DW image and (d) ADC map (ADC value = 1.21).

References: Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT
Fig. 3: Final MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (8.2 mm) on axial T2-weighted image. ROI (25 mm2) on (c) axial DW image and (d) ADC map (ADC value = 1.03).

References: Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT

Case 2 (micrometastasis)

(Fig. 4-6)
Fig. 4: Basal MRI in a patient with a positive left obturator node (microscopic metastasis at histopathology). (a) Axial T2-weighted image. (b) Lymph node short-axis diameter (8.8 mm) on axial T2-weighted image. ROI (25 mm2) on (c) axial DW image and (d) ADC map (ADC value = 1.81).

References: Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT
Fig. 5: Early MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (6.4 mm) on axial T2-weighted image. ROI (16 mm2) on (c) axial DW image and (d) ADC map (ADC value = 0.87).

References: Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT
**Fig. 6:** Final MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (3.3 mm) on axial T2-weighted image. ROI (12 mm$^2$) on (c) axial DW image and (d) ADC map (ADC value = 0.4).

**References:** Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT

**Case 3 (reactive lymphadenitis)**

(Fig. 7-9)
**Fig. 7:** Basal MRI in a patient with a negative right obturator node (reactive lymphadenitis at histopathology). (a) Axial T2-weighted image. (b) Lymph node short-axis diameter (10.5 mm) on axial T2-weighted image. ROI (22 mm²) on (c) axial DW image and (d) ADC map (ADC value = 0.61).

**References:** Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT
Fig. 8: Early MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (7.1 mm) on axial T2-weighted image. ROI (24 mm²) on (c) axial DW image and (d) ADC map (ADC value = 1.18).

References: Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT
Fig. 9: Final MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (3.8 mm) on axial T2-weighted image. ROI (14 mm2) on (c) axial DW image and (d) ADC map (ADC value = 1.06).

References: Department of Radiological Sciences, "A. Gemelli" Hospital, Catholic University of Sacred Heart - Rome/IT

<table>
<thead>
<tr>
<th>Metastatic nodes (n = 5)</th>
<th>Pre-tm MR</th>
<th>Early MR</th>
<th>Final MR</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Average (min-max; ±SD)</td>
<td>Average (min-max; ±SD)</td>
<td>Average (min-max; ±SD)</td>
</tr>
<tr>
<td>ADC ($10^{-3}$mm$^2$/s)</td>
<td>0.96 (0.8-1.1; ±0.11)</td>
<td>1.02 (0.8-1.2; ±0.18)</td>
<td>1.02 (0.9-1.1; ±0.08)</td>
</tr>
<tr>
<td>Short-axis diameter (mm)</td>
<td>13 (9-20; ±4.53)</td>
<td>10.2 (3.14;±4.66)</td>
<td>7.8 (2-15; ±4.71)</td>
</tr>
</tbody>
</table>

Table 2: ADC values and short-axis diameters in metastatic nodes in pre-treatment (pre-tm), early and final MRI.
Table 3: ADC values and short-axis diameters in non-metastatic nodes in pre-treatment (pre-tm), early and final MRI.

Pre-treatment mean ADC value (mADC) did not statistically differ (P=0.46) between N⁺ (0.96 ± 0.11 x 10⁻³ mm²/s) and N⁻ (1.00 ± 0.18 x 10⁻³ mm²/s) and mean short-axis maximum diameter (msa) was not significantly greater in N⁺ than in N⁻ (13 ± 4.53 and 9.97 ± 4.04 mm respectively; P=0.21).

At early MRI performed during nCRT, a statistically significant increase of mADC was observed in N⁻ as compared with pre-treatment MRI (1.29 ± 0.25 vs. 1.0 ± 0.18 x 10⁻³ mm²; P<0.01), while early and pre-treatment mADC in N⁺ did not show a statistically significant increase (1.02 ± 0.18 vs. 0.96 ± 0.11 x 10⁻³ mm²/s; P=0.55). Regarding msa, comparing early and pre-treatment MRI, a statistically significant decrease of msa was observed only in N⁻ (7.3 ± 4.22 vs. 9.97 ± 4.04 mm; P=0.001), while in N⁺ no statistically significant difference was found (10.2 ± 4.66 vs. 13 ± 4.53 mm; P=0.36).

At final MRI mADC was significantly higher in N⁻ than in N⁺ (1.27 ± 0.22 vs. 1.02 ± 0.08 x 10⁻³ mm²/s; P=0.02); msa was respectively 4.51 ± 3.17 and 7.80 ± 4.81 mm and did not show statistically significant intergroup difference (P=0.2).

Images for this section:
Fig. 1: Basal MRI in a patient with a positive right obturator lymph node (macroscopic metastasis at histopathology). (a) Axial T2-weighted image. (b) Lymph node short-axis diameter (17 mm) on axial T2-weighted image. ROI (21 mm2) on (c) axial DW image and (d) ADC map (ADC value = 1.49).
Fig. 2: Early MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (15.2 mm) on axial T2-weighted image. ROI (16 mm²) on (c) axial DW image and (d) ADC map (ADC value = 1.21).
Fig. 3: Final MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (8.2 mm) on axial T2-weighted image. ROI (25 mm²) on (c) axial DW image and (d) ADC map (ADC value = 1.03).
**Fig. 4:** Basal MRI in a patient with a positive left obturator node (microscopic metastasis at histopathology). (a) Axial T2-weighted image. (b) Lymph node short-axis diameter (8.8 mm) on axial T2-weighted image. ROI (25 mm²) on (c) axial DW image and (d) ADC map (ADC value = 1.81).
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**Fig. 7:** Basal MRI in a patient with a negative right obturator node (reactive lymphadenitis at histopathology). (a) Axial T2-weighted image. (b) Lymph node short-axis diameter (10.5 mm) on axial T2-weighted image. ROI (22 mm²) on (c) axial DW image and (d) ADC map (ADC value = 0.61).
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**Fig. 9:** Final MRI assessment. (a) Axial T2-weighted image. (b) Short-axis diameter (3.8 mm) on axial T2-weighted image. ROI (14 mm²) on (c) axial DW image and (d) ADC map (ADC value = 1.06).

**Table 2:** ADC values and short-axis diameters in metastatic nodes in pre-treatment (pre-tm), early and final MRI.
Table 3: ADC values and short-axis diameters in non-metastatic nodes in pre-treatment (pre-tm), early and final MRI.

<table>
<thead>
<tr>
<th>Negative nodes (n = 52)</th>
<th>Pre-tm MR Average (min-max; ±SD)</th>
<th>Early MR Average (min-max;± SD)</th>
<th>Final MR Average (min-max;±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC (x 10⁻³mm²/s)</td>
<td>1.00 (0.6-1.6; ±0.18)</td>
<td>1.29 (0.9-1.9; ± 0.25)</td>
<td>1.27 (0.8-1.9; ±0.22)</td>
</tr>
<tr>
<td>Short-axis diameter (mm)</td>
<td>9.97 (5-30;±4.04)</td>
<td>7.32 (2-20;±4.22)</td>
<td>4.51 (1.5-16;±3.17)</td>
</tr>
</tbody>
</table>
Conclusion

Our preliminary results show that a statistically significant increase in mADC can be found at early MRI in histologically proven non-metastatic lymph nodes as well as significant msa decrease. However in neoplastic nodes the increase of mADC and the decrease of msa were not significant. These results confirm the potential role of ADC as an adding value to the short-axis measure in early identifying lymph nodes responding to chemoradiation therapy. DWI is a non-invasive imaging biomarker that may have huge potentials in predicting and monitoring the therapeutic response to nCRT in patients with metastatic pelvic nodes from cervical cancer.

Limitation

There were several limitations in the current study. The population of patient with histologically proven metastatic lymph nodes after treatment was significantly smaller than that with negative nodes (4 pts vs. 30 pts respectively; 5 N+ vs. 52 N-). There was a possibility of error in ADC calculation in smallest nodes after therapy. Further studies are required in order to confirm this preliminary results and standardization of the procedure will also be required to ensure its clinical applicability.

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References


