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[18F]FDG-PET/CT and MRI for initial pelvic lymph node staging in patients with cervical carcinoma: The potential usefulness of [18F]FDG-PET/MRI

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Abstract. The current study aimed to determine the optimum diagnostic imaging technique out of magnetic resonance imaging (MRI), 18F-fludeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT, otherwise known as PET/CT) and [18F]FDG-PET/MRI (otherwise known as PET/MRI) for the pelvic lymph node staging (N-staging) of untreated cervical carcinoma (CC). A total of 27 patients were included in the present study. All patients had undergone pre-treatment with PET/CT and MRI ≤45 days prior to undergoing a lymphadenectomy. The results from PET (separated from PET/CT), MRI and the statistically combined results of (virtual) PET/MRI were compared to those from histological analyses (the gold standard). A per-patient-based analysis of the detection of pelvic lymph node metastases indicated that PET/MRI had a sensitivity of 64%. The specificity of PET/CT and MRI were 69 and 62%, respectively. The positive predictive value (PPV) was 69 and 64% for PET/CT and MRI, respectively. The negative predictive value (NPV) was 64 and 62% for PET/CT and MRI, respectively. The sensitivity of the PET-guided PET/MRI and the MRI-guided PET/MRI was 64% for both. The specificity of the PET-guided PET/MRI and the MRI-guided PET/MRI was 77 and 62%, respectively. The PPV was 75% for PET-guided PET/MRI and 64% for MRI-guided PET/MRI, and the NPV was 67 and 62%, respectively. PET/CT and the virtual PET/MRI exhibited the same low sensitivity (64%). PET/MRI exhibited slightly better results than PET/CT regarding specificity (77 vs. 69%, respectively), PPV (75 vs. 69%, respectively) and NPV (67 vs. 64%, respectively). The results of the present study suggested that PET/CT and MRI are not optimal diagnostic modalities, and that PET/MRI does not necessarily lead to better results than PET/CT, in the pelvic N-staging of CC.

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Introduction

Cervical carcinoma (CC) is the only major gynecological malignancy that is clinically staged (1,2). Pelvic lymph node staging (N-staging) is an important prognostic factor in early-stage CC, as patients with lymph node metastasis (LNM) have significantly lower survival rates than those without detectable nodal metastases (3-7).

In recent years, diagnostic modalities, including 18F-fludeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT) and magnetic resonance imaging (MRI), have been used in the initial assessment of nodal involvement (8). However, neither method has been formally included as part of the International Federation of Gynecology and Obstetrics staging of CC (9). MRI and CT exhibit low sensitivity and specificity and thus cannot be used to detect nodal involvement (8). Functional imaging modalities such as [18F]FDG-PET and [18F]FDG-PET/CT have shown a better performance than MRI and CT and, therefore, the National Comprehensive Cancer Network clinical guidelines recommend the use of [18F]FDG-PET/CT as a routine procedure in the assessment of patients with CC (10).

Conclusions regarding the sensitivities and specificities of these diagnostic modalities have been based on studies with heterogeneous study designs that have only included a small number of patients (8,11,12) which demonstrates the difficulty of evaluating the pelvic N-staging of CC patients by [18F]FDG-PET/CT and MRI. Identifying a secure and objective method for the detection of LNM in CC patients would improve the management of therapy and enable a

realistic evaluation of the prognosis of patients. Integrated [^{18}F]FDG-PET/MRI devices are currently commercially available and thus may benefit patients in this context.

The aim of the present retrospective study was to assess the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of [^{18}F]FDG-PET/CT (PET/CT), MRI and [^{18}F]FDG-PET/MRI (PET/MRI), in order to determine the optimum method for performing pelvic N-staging of patients with untreated CC.

Patients and methods

Patients. Between January 2008 and July 2011, 152 women were referred to the PET/CT center of the Vienna General Hospital (Vienna, Austria) for initial staging of verified CC. From these 152 patients, 192 PET/CT images were acquired. Of the 152 patients, 27 patients with different stages [International Federation of Gynecology and Obstetrics staging system (8); 12 with ≥IB2, 12 with <IB2 and 3 with unknown stages], and with an average age of 46 years (age range, 22-68 years), fulfilled the inclusion criteria for the present study. The inclusion criteria were as follows: The patient had undergone PET/CT and MRI scans prior to treatment; diagnostic imaging results had been obtained <45 days prior to adenectomies to exclude further tumor progression; and there had been a period of <45 days between the two diagnostic imaging sessions. The gold standard for the current retrospective study was the histological analysis of specimens obtained via lymphadenectomies. PET/CT and MRI images were analyzed by two experts (one expert in MRI/CT and one expert in PET). Increased uptake of FDG on the PET images and lesions detected from CT and MRI were used to conduct pelvic N-staging. Subsequently, the experts' findings were compared with the histopathological results from the corresponding lymphadenectomies. The present study was approved by the ethics committee of the Medical University of Vienna, Austria and, as the current study was a retrospective study, informed consent from the patients was not required.

Pelvic N-staging. Pelvic N-staging was performed by looking at nine anatomical localizations using CT and/or MRI for the presence of LNMs, including the arteria iliaca communis dexter (A), the arteria iliaca communis sinister (B), the arteria iliaca externa dexter (C), the arteria iliaca externa sinister (D), the arteria iliaca interna dexter (E), the arteria iliaca interna sinister (F), the musculus obturatorius dexter (G), the musculus obturatorius sinister (H) and the sacrum (I). Pelvic N-staging was confirmed by standard histological analyses, including immunohistochemistry or hematoxylin and eosin staining. PET/CT, MRI and PET/MRI were the diagnostic modalities assessed in the current study.

Histological analysis. Serial paraffin sections (2-μm thickness) of formalin-fixed lymph nodes were cut, deparaffinized using xylol, rehydrated and stained with hematoxylin/eosin. Pretreatment of deparaffinized and rehydrated sections and immunostaining was performed using the BenchMark Ultra fully automated slide staining system (Ventana Medical Systems, Inc., Tucson, AZ, USA). After pretreatment for 60 min with Cell Conditioner 1 (pH 8, Ventana Medical Systems, Inc.), the sections were stained for 32 min at 36˚C with pancytokeratin antibody (clone AE1/AE3; cat. no. M351501; Dako Österreich GmbH, Vienna, Austria) at a dilution of 1:100. Chromogenic visualization was performed with the ultraView Universal DAB Detection kit (Ventana Medical Systems, Inc.), after which counterstaining with hematoxylin and bluing with Bluing Reagent (Ventana Medical Systems, Inc.) was performed with the appropriate Ventana Ancillary Reagents, according to the manufacturer's protocol.

PET/CT. PET/CT was performed using a 64-row, multi-detector PET/CT system (Biograph™ TruePoint™ 64; Siemens AG, Munich, Germany). Prior to imaging, patients fasted for 5 h; the glucose cut-off level was 150 mg/dl. PET was performed 50-60 min after the intravenous administration of 300 MBq of ^{18}F-FDG, with a three-minute acquisition period per bed position. PET images were reconstructed using the Siemens TrueX algorithm, with four iterations per 21 subsets, a 5 mm slice thickness and a 168x168 matrix. Venous-phase contrast enhanced CT was performed by the intravenous injection of 100 ml Iomeron 300 (Bracco, Milan Italy), which is a tri-iodinated, non-ionic contrast medium, at a rate of 2 ml/sec, followed by a 50 ml saline flush and CT with the following parameters: A tube voltage of 120 mA, a tube current of 230 kV, collimation of 64x0.6 mm, a slice thickness of 3 mm with 2 mm increments and a 512x512 matrix. On CT, lymph nodes with a short-axis diameter ≥10 mm, in combination with a lack of a fatty hilum or inhomogeneous density, were regarded as pathological. On PET, an increased ^{18}F-FDG uptake, as assessed visually, with a maximal standardised uptake value (SUV) higher than the mediastinal blood pool was regarded as pathological.

MRI. MRI was performed using a 3 Tesla MRI scanner, the Magnetom Trio (Siemens AG), with a standard body array coil. Sagittal, axial and coronal T2 Turbo Spin-Echo (TSE) sequences were obtained, with a repetition time (TR) of 4,630 msec, an echo time of 89 msec and a layer thickness of 3 mm. The axial sequence included T1 TSE with a TR of 652 msec, an echo time (TE) of 12 msec and a layer thickness of 4.5 mm. Additionally, there was an axial and sagittal T1 TSE with fat saturation following the intravenous application of 10 ml Dotarem, with a TR of 650 msec, a TE of 12 msec and a layer thickness of 4 mm. Lymph nodes with a short-axis diameter ≥10 mm, in combination with a lack of a fatty hilum or inhomogeneous signal on unenhanced or contrast-enhanced sequences, were regarded as pathological.

(Virtual) PET/MRI. The PET data, which was extracted from the hybrid PET/CT study, and MRI were combined to provide a virtual PET/MRI study and were compared with the histology results. Virtual PET/MRI results were calculated in two different ways. One group of results was PET-guided, meaning that if LNM was considered positive on PET but negative on MRI, the combined result was positive. The other group of results was MRI-guided, meaning that if LNM was considered positive on MRI but negative on PET, the combined result was positive.

Statistical analysis. The current study was an open, single-site, retrospective data analysis. The results obtained by the two

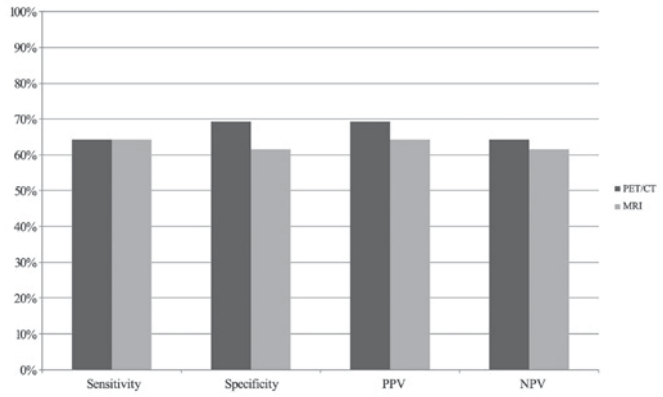

Figure 1. Per-patient-based analysis exhibited a low sensitivity and moderate specificity, PPV and NPV for PET/CT and MRI. PPV, positive predictive value; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging.

experts were compared with the histopathological results. Specificity, sensitivity, likelihood ratios, PPV and NPV were calculated for PET/CT, PET (extracted from PET/CT), MRI and (virtual) PET/MRI on a per-patient basis. The (virtual) PET/MRI results were obtained by combining the results from the extracted PET and MRI surveys. If the results were concordant, the combined PET/MRI result was considered either positive or negative. In case of a discrepancy between the MRI and PET results, consent was obtained from the experts (radiologists and nuclear physicians) in terms of considering the diagnosis of PET and the diagnosis of MRI together as the final outcome. The final evaluation was performed in two different ways; as either MRI- or PET-guided. Statistical analysis was performed using SPSS Statistics ver. 22.0 (IBM SPSS, Armonk, NY, USA).

Results

PET/CT. In total, 14 patients (52%) had no positive LNM detected by PET/CT (no pathological FDG uptake, no suspicious lymph nodes. A further 12 patients had positive FDG-uptake in different pelvic lymph node regions and different numbers of positive LNM. In one patient, positive FDG-uptake was not identified by FDG-PET; however, a pathological lymph node was detected by CT. Therefore, 13 patients (48%) had positive LNM detected by PET/CT. In total, 27 pelvic lymph node regions with LNM were detected in eight different locations. The average SUVmax was 7.7 (range, 3.7-12.7). The most common areas LNM was observed in were B (12/17, 44%), A (6/27, 22%) and D (3/27, 11%). The average LNM detected per lymph node region was 2.1 metastases (range, 1-6 metastases). The sensitivity and specificity of PET/CT in detecting pelvic LNM were 64 and 69%, respectively. The PPV and NPV for PET/CT was 69 and 54%, respectively (Fig. 1). The positive likelihood ratio was 2.06 and the negative likelihood ratio was 0.52. In one patient, a singular osseous metastasis was detected. However, the other patients had no distant metastases.

MRI. Of the 27 patients, 13 had no positive LNM detected by MRI and 14 had positive LNM detected by MRI. In total, 27 pelvic lymph node regions with LNM were detected in nine different locations. The most common areas were B (9/27, 33%), A (8/17, 30%) and G (3/27, 11%). The average number of detected LNM was 2.1 (range, 1-4 metastases).

The sensitivity of MRI was 64%, the specificity was 62%, the NPV was 64% and the PPV was 64% (Fig. 1). The positive likelihood ratio was 1.68 and the negative likelihood ratio was 0.58.

Virtual PET/MRI. Of the 27 patients, 15 (56%) were considered negative on the PET-guided PET/MRI. The remaining 12 patients (44%) were considered positive. In the MRI-guided PET/MRI, 13 of the 27 patients (48%) were classified as negative and the remaining 14 (52%) were considered positive. The sensitivity of both the PET-guided PET/MRI and the MRI-guided PET/MRI was 64% and the specificity was 77 and 62%, respectively. The PPV was 75% for PET-guided PET/MRI and 64% for MRI-guided PET/MRI, and the NPV was 67 and 62%, respectively (Fig. 2). The positive likelihood ratio was 2.29 for the PET-guided PET/MRI and 1.68 for the MRI-guided PET/MRI. The negative likelihood ratios were 0.5 and 1.68 for the PET-guided PET/MRI and the MRI-guided PET/MRI, respectively. The results of all diagnostic modalities (PET/CT, MRI and the virtually combined PET/MRI), according to our criteria for pathological/non-pathological status, were compared to the results from the histological analysis (affected/non-affected) in terms of the sensitivity, specificity, PPV, NPV and likelihood ratio.

PET/CT vs. virtual PET/MRI. PET/CT and the virtual PET/MRI exhibited the same low sensitivity (64%). PET/MRI exhibited slightly better results than PET/CT regarding specificity (77 vs. 69%, respectively), PPV (75 vs. 69%, respectively) and NPV (67 vs. 64%, respectively) (Fig. 2).

Histology. Of the 27 patients included in the present study, >329 pelvic lymph nodes were removed (average, 12 lymph nodes/patient). Histological reports indicated that there were 13 patients (48%) with no pelvic LNM. In the remaining 14 patients (52%), positive LNM was detected and verified by histology. In total, 28 pelvic LNM were detected in seven different locations. The most common areas were B (7/28, 25%), A and D, (both 6/28, 21%) and H (3/28, 11%). The average number of detected LNM was 2 per patient (range, 1-5 metastases).

There were 10 patients with squamous cell carcinoma and 5 patients with adenocarcinoma; 13 histological reports did not describe the type of CC. Of the 12 patients with CC <IB2, 4 exhibited histologically verified LNM, while, of the 12 patients with ≥IB2, LNM was detected in 8 patients.

Discussion

N-staging is one of the most important factors in predicting the prognosis and survival of CC patients (13). CC first spreads to the pelvic area along the external and internal iliac vascular system, as well as to the presacral space (14). The incidence of pelvic LNM in the early stages of CC ranges from 10.9-44.7% (15,16). In the current study, a third of patients with CC <IB2 had histologically verified LNM, whereas 66% of patients with higher-stage CC had LNM. For patients with

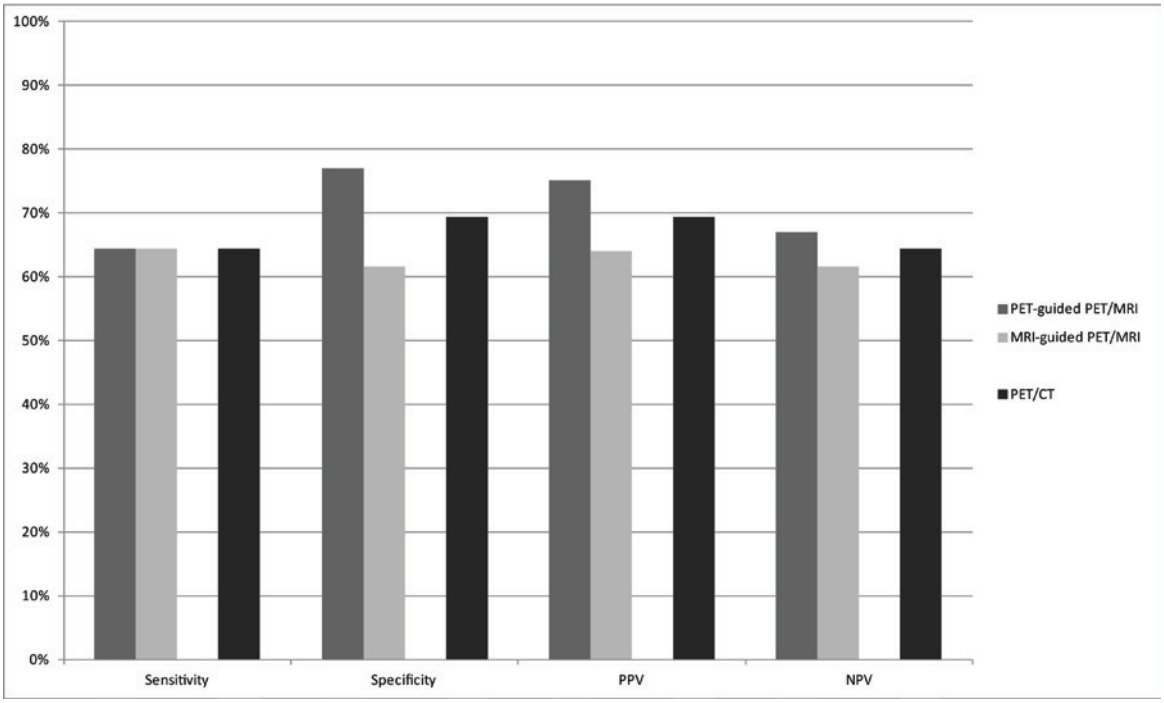

Figure 2. PET/MRI (PET- and MRI-guided) exhibited the same low sensitivity as PET/CT. The specificity, PPV and NPV were superior for PET-guided PET/MRI compared with MRI-guided PET/MRI. PET/MRI did not demonstrate clearly superior results to PET/CT. PPV, positive predictive value; NPV, negative predictive value; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

higher-stage CC, treatment is usually a combination of radiation therapy and chemotherapy (8). Information regarding pelvic lymph node status may not be important, since such patients usually receive pelvic external beam radiation therapy, which improves survival rates (15,16). The region within the pelvic area where LNM is most commonly detected obturatural [57.5-76.4% (15,16)]. Of the 27 patients included in the present study, 14 (52%) had histologically verified pelvic LNM. Data analysis verified that the area where LNM was detected most frequently was region B, with 44% detected by PET/CT, 33% by MRI and 25% by histological analysis. Lymph nodes showing an increased uptake of ^{18}F-FDG, or enlarged lymph nodes (short-axis diameter ≥10 mm) with no fatty hilum and an inhomogeneous density (on CT) or signal (on MRI), were considered to be pathological. In all other cases, the lymph nodes were considered to be normal.

Wright *et al* (17) and Sironi *et al* (18) analyzed the preoperative lymph nodes of early-stage CC patients by PET/CT, and compared the results to histological outcomes. The results suggested a specificity of 90-97%, a sensitivity of 53-73% and a PPV of 71% for the detection of LNM in patients with CC. Williams *et al* (19) evaluated the accuracy of CT, MRI and FDG-PET in detecting pelvic LNM and verified the outcomes with histopathological results. The authors evaluated 8 cases and determined that CT was the most specific method, with a 97% accuracy rate, followed by MRI and PET, with 90 and 77% accuracy rates, respectively (19). However, the sensitivity of all diagnostic modalities assessed was low: 48% for CT, 54% for MRI and 25% for PET (19). With regard to the results of the Second International Conference on Cervical Cancer, PET seems to be the best diagnostic modality, as well as the best non-invasive method, for the N-staging of CC (9).

Each diagnostic modality has its own individual strengths and weaknesses. In existing guidelines for the N-staging of CC, different studies have made various suggestions regarding the use of PET, PET/CT and MRI (20,21). The Information Centre for Standards in Oncology of the German Cancer Society recommended neither PET/CT nor MRI for N-staging in CC patients, although they recommend the use of PET or ultrasound scanning for N-staging in specific cases (20). The European Society of Urogenital Radiology suggested that lymph node detection should be performed with axial T1-weighted sequences (MRI) to assess suspicious pelvic and abdominal lymph nodes, as well as the intravenous administration of gadolinium-chelate for lesions <2 cm (21). The variety of different guidelines reflects the discussions and controversies regarding the optimum method for the N-staging of CC.

The current study aimed to critically assess the usefulness of PET/CT and MRI in the N-staging of diagnosed but untreated CC patients. Relatively low sensitivity and moderate specificity, PPV and NPV was observed for PET/CT and MRI in the pelvic N-staging of CC. However, it is well known that physiologically enhanced FDG activity in the gut may lead to false-positive or false-negative results (22). Furthermore, in the present study, MRI and PET/CT scans were performed at different time-points; therefore, the anatomic conditions of the urinary bladder and gut may have been different. Compared with the published data on this topic, the current study demonstrated that these diagnostic modalities did not achieve satisfactory results in the N-staging of CC.

Further medical progress and future technical developments are necessary to enable the generation of accurate guidelines for the pelvic N-staging of CC. MRI is already a valuable diagnostic modality in staging CC and its use has been suggested in staging guidelines for CC (23). PET/CT

is currently effective at detecting early recurrences in CC patients (24).

In 2006, combined PET/MR imaging was proposed for imaging patients and the first prototype designs became available (25,26). Since then, huge progress has been made regarding methodological approaches and technical versatility (27-29). At present, three major companies specializing in imaging hardware offer PET/MRI with various system designs (30). General expectations for PET/MRI are high. A recent study assessed the efficacy of integrated PET/MRI for the whole body staging of patients with primary CC (31). In their preliminary results, the authors concluded that integrated PET/MRI had a high potential to accurately assess primary tumors and detect LNM in patients with CC.

In the present study, the potential usefulness of PET/MRI in the N-staging of CC was evaluated in a virtual setting. This virtual setting comprised the superior and inferior results of the combined modalities. PET/MRI exhibited a low sensitivity and moderate specificity, PPV and NPV and, therefore, was not clearly superior to PET/CT or MRI in the pelvic N-staging of CC. Improved and optimized protocols for PET/MRI (including contrast-enhanced MRI, combining FDG uptake with diffusion weighted imaging and simultaneous data acquisition) may improve the interpretation of images. However, with regards to N-staging for CC patients, PET/CT will remain the preferred diagnostic modality for the foreseeable future, due to its high availability and shorter image acquisition time.

The current study was limited in a number of ways. The most significant limitations were the small population, the retrospective study design and the potential discrepancy between the results of the diagnostic modalities and histological analysis (lymph node mapping). With regards to histology, all calculations were based on a per-patient analysis. PET/MRI was evaluated virtually; the results were not obtained on an actual PET/MRI device.

In conclusion, pelvic N-staging in CC remains an unresolved problem in the clinical setting. Based on the data analysis performed in the current study, PET/CT and MRI are suboptimal diagnostic modalities for the pelvic N-staging of CC. However, they are recommended because of the lack of superior non-invasive imaging modalities. PET/MRI does not necessarily lead to better results than PET/CT, and expectations regarding the use of PET/MRI in this context may be too optimistic.

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