FAKULTNÍ NEMOCNICE OSTRAVA

EVALUATION OF PREOPERATIVE POSITRON EMISSION TOMOGRAPHY WITH COMPUTED TOMOGRAPHY FOR DETECTING LYMPH NODE METASTASIS IN BULKY TUMORS OF CERVICAL CANCER

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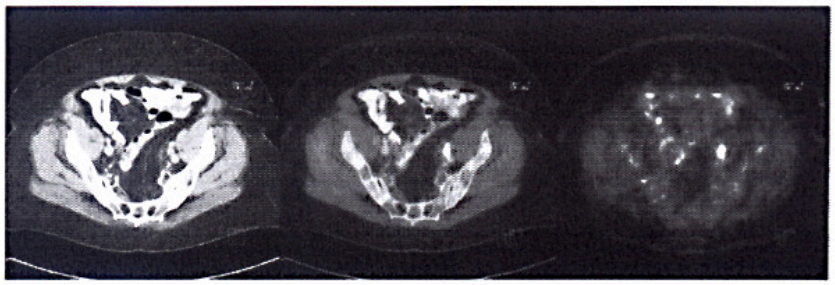
Introduction: Cervical cancer (CC) is the third most common neoplasm in women. Recent data reports the incidence rate is about 530,000 new cases per year in the World [1]. Regional lymph node (LN) status is the most important prognostic factor although this factor is not included in the most widely accepted FIGO staging guidelines based on clinical examination [2-4]. Major errors in staging are related to undiagnosed LN metastases, which lead to suboptimal treatment modality [5-7]. Survival rates of LN positive patients are significantly lower than in patients without node metastases. Patients with locally advanced tumors with negative LN, pelvic LN metastases or para-aortic LN metastases have 5 years survival rate 57%, 34%, and 12% respectively [8]. The identification of LN metastases is crucial point in order to plan the treatment strategy and to improve prognosis [9]. Notwithstanding this fact, a standardized protocol for staging including LN status has not been established yet [10]. Moreover, the LN status may beyond the prognosis influence the treatment since early stages of CC are treated predominantly surgically, whereas advanced stages are managed with chemo-radiotherapy. Integrated positron emission tomography and computed tomography (PET/CT), combining benefits of functional and anatomic imaging, localize areas of increased 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) uptake in metastases with better anatomic specificity.

Objective: The aim of the study was to analyze the usefulness and accuracy of preoperative positron emission tomography combined with computed tomography (PET/CT) in detection of regional lymph node metastases in patients with bulky tumors of cervical cancer (CC) with histological status of sentinel lymph nodes (SLN) evaluated by ultramicrostaging after lymphatic mapping as the reference standard.



Patients and methods: In the time period from November 2008 to October 2012 seventeen patients with CC stage IB2-IIA2 of the Oncogynaecologicalcentre of University Hospital Ostrava (mean age 46 years, range 27-74), who had supposed to undergo surgery were enrolled in the study after signing the informed consent. Preoperative blood sampling, ECG, chest X – ray examination, tumor volumometry by transvaginal or transrectal ultrasound and PET/CT scanswere performed in all patients. All patients underwent a dose-dense neoadjuvant chemotherapy(3 courses of 75 mg/m2 cis-platine + 2g/m2ifosfamide in 10 day interval), preoperative and intraoperative SLN identification followed by radical surgery with lymphatic mapping, frozen section of SLN and complete regional lymphadenectomy level 2 and in cases of pelvic SLN positivity level 3 by Querleu-Morrow. Cervical conisation was performed prior to radical surgery in none of the patients.The detection of lymph node (LN) metastases by PET/CT was compared with the results of histological evaluation. The size of metastatic foci in each LN were recorded.

Clinical and histopathological characteristics of the study population are summarized in tables 1 and 2.

PET- CT imaging protocol

All the PET/CT scans were performed within 10 days before surgery or neoadjuvant chemotherapy. Prior to PET/CT examination, the patients had to fast for at least 6 hours and their blood glucose levels were measured. If the glucose concentration did not exceed 8 mmol/l, fluoro-deoxy-glucose (FDG, Lacomet, Czech republic) was administered parenterallyin a dose corresponding to 400 MBq per 70 kg of body weight. Sixty minutes after the administration of FDG and oral administration of a contrast agent (Micropaque, Guerbet, France), the PET/CT examination with the Biograph 16 HI-REZ scanner (Siemens, Germany) was initiated, typically from the skull base to the upper third of the thighs with arms upwards. Spiral CT scans were carried out after intravenous administration of a nonionic contrast agent (Ultravist, Bayer Healthcare Pharmaceuticals, Germany). This was followed by caudocranial PET scanning with iterative reconstruction of the images. Transmission correction to attenuate gamma radiation was carried out by CT.

The images were prospectively evaluated by a review team whose members were aware of the results of only the initial diagnostic assessment, which included histopathologic confirmation of cervical cancer and the clinical stage of the disease, as determined on the basis of the FIGO scheme for preoperative staging. The review team interpreted the PET/CT imaging findings in consensus and consisted of both experienced nuclear medicine physician and a radiologic physician.

The PET/CT images were interpreted in standard clinical fashion, both separately and in fused mode. A lymh node has considered PET – positive if its FDG uptake was greater than blood pool activity or surrounding background tissues (with the exclusion of physiologic bowel and urinary activity), depending on the size of the node size [11]. When abnormal uptake was present, its exact anatomic location was indicated on the basis of CT findings.

Preoperative SLN detection

Fifty MBq of SENTISCINT (Medi-Radiopharma Ltd. Hungary) or NANOCOL (GE Healthcare S r l., Italy) were injected one hour before scintigraphy and two hours before surgery under direct visual control peritumorally. Static images were obtained using a SPECT/CT (Symbia T2, Siemens, Germany). The first appearing persistent focal accumulation was considered to be a SLN.

Intraoperative lymphatic mapping and SLN detection

Blue dye (Blue Patenté V, Guebert, Aulnay-Sous-Bios, France) was injected after exploration of the abdominal cavity in general anesthesia at the same locations as the tracer. Retroperitoneal spaces were opened and SLN was indentified visually or by radionavigation, removed separately, recorded by its relative position to the major pelvic vessels and all SLN were submitted for frozen sections examination. Subsequently a radical surgery with regional lymphadenectomy was performed.

Pathological evaluation

SLN weresubmittedforperioperativeexamination as separatespecimens. Fordefinitiveultramicrostagingexamination, SLN werefixed in 10 % buffered formaline, cutperpendicularly to the long axis into 2 mm thicksectionsthatweresubmittedfor parafin embedding. Serial step sections 100 um apart and 5 um thickwerestainedwith hematoxylin – eosin and withimmunohistochemistry to lookforthe presence ofmicrometastases. Immunohistochemistrywascarriedoutusing a monoclonal antipody directedagainstcytokeratins AE1 – AE3 (DAKO, Carpinteria, CA Denmark). Whole SLN werecevaluatedatmultiplelevels.

A false - negative case wasdefined as one in which SLN identifiedwashistologically negative but neoplasticspreadwaspresent in other non – SLN fromthedrainage area. Thefalse – negative ratewasobtained by dividingthenumberoffalse – negative cases by thenumberofprocedureswith a positive lymphnodes. Other non sentinel lymph nodes were examined according to the size in 1-4 sections.

Statistical analysis

Calculation of sensitivity, specificity, positive predictive value, negative predictive value and accuracy for metastases detection with PET/CT was performed in relation to definitive results of histological ultramicrostaging evaluation. For the purposes of statistical analysis, a true positive lesion was a lesion seen on PET/CT scans and found to be positive at histological ultramicrostaging evaluation. A false positive lesion was a lesion seen on PET/CT scans and found to be negative at histological evaluation. A true negative lesion was documented when no lesion was seen on PET/CT scans and histological evaluation was negative for tumor cells. A false negative lesion was a lesion that was missed at PET/CT scans, but histological evaluation was positive for tumor cells. The accuracy is the proportion of true results, both true positives and true negatives.

Results Six patients (35,3%) had LN metastases confirmed by histological evaluation. The overall patient-specific sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT were 83,3 %, 81,8 %, 71,4 %, 90,0 % and 82,4 % respectively.

SLN were detected bilateral in 70,6%, unilateral in 5,9%. Mean number of acquired LN in regional lymphadenectomy was 32. Among these patients 2 had bilateral and 4 unilateral metastases. Among all LN 2 patients (11,8%) had macrometastases, 4 patients (23,5%) had micrometastases. PET/CT detected correctly metastases in 5 patients (83,3%). PET/CT examination were false negative in 1 patient with histological proven metastases with median of maximal diameter 1,5 millimeters. PET/CT examinations were false positive in 2 patients with maximal diameter of LN metastases 13 and 16 millimeters.

Discussion: Preoperative staging of patients with early stage CC is different from histopathological staging in about 40%. Surgical LN assessment during lymphadenectomy is the standard for information of LN status but is connected with increased risk of immediate and delayed complications and high morbidity. Therefore a non-invasive technique that would be able to identify LN metastases is beneficial. Assessment of LN metastases in CT or MRI evaluation is based on morphologic parameter with measurements of LN, with accuracy of these cross-sectional imaging methods between 70-88%.[12-22]. Integrated PET/CT in contrast to CT and MRI is able to depict malignant primary or secondary tumors without morphologic changes and localize areas of increased FDG uptake and detect macrometastases of regional LN with better anatomic specificity and diagnostic accuracy. In a recent meta-analysis authors confirmed that PET/CT present better accuracy than CT and MRI [23]. Previous study has shown that use of PET/CT evaluation before recommendation of treatment modality is associated with more frequent upstaging and changing of therapeutic plan [24]. Sensitivity and specificity of PET/CT evaluation of LN metastases vary in literature from 25% to 91 % and from 57% to 100%, respectively, and depends on tumor stage and tumor size [25-34]. Our study describes high sensitivityandspecificity. Sensitivity depends on tumourvolume,whichinflueces probability of lymphatic spreadingand and lymph node metastases. The main reason of the low sensitivity rate in other studies is the enrollment of patients with low stages of the disease. In other our study of 80 patients with CC FIOGO stage IA2- IIA2 only 3 from 40 (7,5%) patients with tumor less than 2 cm in largest diameter had LN metastases. The size threshold for detection of LN metastases during PET/CT evaluation is diameter about 5-8 mm at present. We can expect that this threshold will be lower in the future, but it will hardly reach the size of macrometastases. The results of most studies have shown that false negativity is caused by small diameter of the metastatic foci. False negativity rate in our study was 5,9 % and diameter of non-diagnosed metastasis was 4,0 mm. The limit of PET/CT is represented by significant number of false negative LN due to limited spatial resolution of the CT.

A randomized study by Landoni showed that a combination of surgery and radiotherapy has a higher morbidity than surgery or radiotherapy alone. This fact increases the necessity of correct staging in order to offer the optimal treatment modality with lower morbidity [36]. PET/CT is safe, non-invasive imaging procedure giving us useful information about real status of the disease and can play an important role in the management of these patients.

The use of PET/CT for assessment LN status should be taken into account for patients with high probability of LN metastases, which is dependent on size of tumor. All patients in our study underwent neoadjuvant chemotherapy, which may reduces the number of histologically verified LN metastasis and thus may increase the number of false positive patients and so decrease specificity and positive predictive value. A few patient may escape which were in fact false negative, but according to our findings, these patients would have only small LN metastases and they will profit from radical surgery.

FDG is not a specific cancer tracer and false positive foci can occur due to uptake in some benign or inflammatory tumors or due to misinterpretation of physiological uptake or excretion of FDG in ovaries, intestines and urinary tract. Notwithstanding false positive results by PET/CT were very low in this study, histological confirmation of positive foci is mandatory in some cases before change of treatment and the PET/CT scan can be used for biopsy guidance.

Conclusions: Bulky tumors of CC are prognostic unfavorable disease with high risk of recurrence in which combination of therapeutic appreach increase morbidity. The results of our study revealed that 29.4% patients would be underdiagnosed without PET/CT evaluation.

Preoperative PET/CT evaluation may be useful tool for identifying patients with macrometastases which could profit rather from primary chemo – radiotherapy, or extended-field radiation therapy in case of positive para-aortic LN, rather than radical surgery. Such correction in treatment modality will decrease the morbidity and increase quality of life.