FDG-Positron Emission Tomography/Computerized Tomography for Monitoring the Response of Pelvic Lymph Node Metastasis to Neoadjuvant Chemotherapy for Bladder Cancer

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Purpose: We evaluated FDG-positron emission tomography/computerized tomography for monitoring the response of pelvic lymph node metastasis to neoadjuvant chemotherapy for bladder cancer. We compared this to contrast enhanced computerized tomography.

Materials and Methods: Included in study were 19 consecutive patients with lymph node positive bladder cancer who underwent FDG-positron emission tomography/computerized tomography and contrast enhanced computerized tomography before and after a median of 4 cycles (range 2 to 4) of neoadjuvant chemotherapy between September 2011 and April 2012. Metabolic response was assessed according to EORTC (European Organisation for Research and Treatment of Cancer) recommendations based on the change in FDG uptake on FDG-positron emission tomography/computerized tomography. Radiological response was assessed on contrast enhanced computerized tomography according to RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. All patients underwent pelvic lymph node dissection. Histopathological evaluation served as the gold standard for the nodal response.

Results: Before neoadjuvant chemotherapy, hypermetabolic FDG uptake was seen in all 19 patients, which matched the lymph node metastasis. Evaluating the nodal response with positron emission tomography/computerized tomography was feasible in all patients. On histopathology 16 patients were responders, including 14 with a complete pathological response of the lymph nodes. Positron emission tomography/computerized tomography and contrast enhanced computerized tomography correctly distinguished responders from nonresponders (18 of 19 patients or 94.7% and 15 of 19 or 78.9%) and complete responders from patients with residual disease (13 of 19 or 68.4% and 12 of 19 or 63.2%, respectively).

Conclusions: Although no definitive conclusions can be drawn from these preliminary data, positron emission tomography/computerized tomography appears feasible for evaluating the nodal response to neoadjuvant chemotherapy and distinguishing responders from nonresponders.

Key Words: urinary bladder, urothelium, carcinoma, positron-emission tomography and computed tomography, fluorodeoxyglucose F18

Abbreviations and Acronyms

CBCC = cisplatin based combination chemotherapy
CECT = contrast enhanced CT
CT = computerized tomography
FDG = ^{18}F-fluorodeoxyglucose
GEM = gemcitabine
LN = lymph node
NAC = neoadjuvant chemotherapy
NPV = negative predictive value
PET = positron emission tomography
PLND = pelvic lymph node dissection
PPV = positive predictive value
SUV_{max} = maximum standardized uptake value
UC = urothelial carcinoma

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NEOADJUVANT chemotherapy is an established standard that improves the overall survival of patients with bladder UC.[1] The pathological response to NAC appears to be an intermediate surrogate for survival.[1] However, the

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nonresponse rate is high. Approximately 50% of patients do not respond to NAC.[2–4] Patients with no or a weak nodal response to NAC may not benefit from surgery.[5] Therefore, monitoring the nodal response to NAC is crucial since it enables patient selection for surgery.

Evaluation of the nodal response with conventional imaging modalities is usually difficult and inaccurate. A discrepancy between clinical and pathological staging is noted in approximately 30% of cases.[6] This is mainly due to difficulty with identifying viable tumor in residual (necrotic) masses and small tumor deposits in LNs of normal size.[7] An imaging modality that allows for better patient selection would be of great value.

PET/CT has been investigated for detecting LN metastasis of UC.[8–11] For other malignancies PET/CT has accurately predicted nodal status after NAC.[12,13] However, to our knowledge no study has indicated the potential value of PET/CT for assessing the response of pelvic LN metastasis to NAC for UC compared to the conventional clinical response evaluation. We evaluated FDG-PET/CT for monitoring the response of pelvic LN metastasis to NAC for UC.

METHODS

Patients

We studied the records of all consecutive patients with LN positive UC of the bladder who underwent FDG-PET/CT before and after 4 cycles of NAC between September 2011 and April 2012. Patients eligible for analysis study had 1) muscle invasive UC of the bladder, as proven by transurethral resection, 2) 1 or more LN metastases, 3) a minimum of 2 cycles of NAC, 4) subsequent surgery consisting of at least PLND and 5) conventional CECT of the chest and abdomen before and after NAC. A total of 19 patients were eligible for analysis. This study was done in accordance with institutional ethical guidelines, based on good clinical practice.

Pretreatment Staging

At the bladder cancer outpatient clinic all patients are routinely staged by physical examination, cystoscopy, laboratory studies, CECT of the abdomen and chest, and whole body FDG-PET/CT. Pretreatment TNM stage is determined according to the UICC (Union for International Cancer Control).[14] Radiological evidence of LN metastasis is considered in cases of pathologically enlarged LNs greater than 1 cm in diameter or strong suspicion on PET/CT.

LN involvement was confirmed preoperatively by biopsy results in 13 of 19 patients. If there were multiple suspicious LNs, only 1 was biopsied. Since biopsy was unavailable in 6 patients, we used postoperative chemotherapy induced histological changes indicating the eradication of metastatic foci as a proxy for LN tumor positivity. These histological changes included fibrosis, chronic inflammatory cell infiltrate and stromal edema.

Neoadjuvant Chemotherapy

At our hospital NAC is considered in patients with UC who have pelvic LN metastasis without evidence of distant (visceral) metastasis. The decision to administer NAC is made after a multidisciplinary tumor board meeting. The treatment of choice is CBCC. CBCC consisted of an accelerated regimen of MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) or GEM/cisplatin. Carboplatin based combination chemotherapy was offered to patients considered unfit for CBCC. Selection criteria corresponded to those described by Galsky et al, including impaired renal function, comorbidity and low performance status.[15] We previously described the chemotherapy regimens in detail.[16]

Response Evaluation

Response was assessed at least 2 weeks after the last NAC course. The median number of NAC cycles was 4. Two patients who did not complete 4 courses due to toxicity underwent response evaluation after 2 and 3 courses, respectively. Restaging CECT of the abdomen and chest, and whole body FDG-PET/CT were performed. CECT and PET/CT images were obtained within a 2-week interval but preferably the same day.

CECT Protocol

CECT of the chest and abdomen was done using certain acquisition parameters, including slice thickness 5×5 mm, table speed 1.2×24 mm per rotation, pitch 1.2 to 0.844, and reconstruction intervals 1 and 5 mm. As intravenous contrast injection parameters, we used Omnipaque™ 300 as the agent, dose weight plus 40 ml (maximum 130 and minimum 90), concentration 300 mg iodide per ml and injection time 3 cc per second. The patient was positioned supine with the arms above the head.

Clinical Response Evaluation

CECT images were reviewed by an experienced radiologist blinded to all patient data, including PET/CT and histopathology results. The treatment effect of NAC on pelvic LN metastases was determined according to RECIST 1.1.

FDG-PET/CT Protocol

The patients were requested to fast for at least 6 hours before PET/CT and received oral prehydration. Blood glucose was measured to ensure blood glucose less than 10 mmol/L. FDG (190 to 240 MBq) was then administered intravenously. PET/CT commenced 1 hour after FDG injection. Whole body PET images were acquired with the patient supine with the arms above the head. All PET acquisitions were constructed with low dose CT with dose modulation adapted to attenuation using Dose-Right™ for anatomical correlation and attenuation correction.

Metabolic Response Evaluation

FDG-PET/CT images were reviewed by an experienced nuclear medicine physician blinded to all patient data, including CECT and histopathology results. Images were evaluated semiquantitatively. Tumor FDG uptake was quantified using SUV_{max}. Before chemotherapy SUV_{max} in the lesions corresponded to the SUV_{max} per pixel in the lesion volume, measured using circular regions of interest. For prechemotherapy and postchemotherapy FDG-PET/