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WORD COUNT 3759
TIME SUBMITTED 01-DEC-2023 03:59PM
PAPER ID 104811782

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 88393
Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Evaluation of Response to Gemcitabine plus Cisplatin-Based Chemotherapy Using 18FDG-PET/CT for Metastatic Bladder Cancer

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Abstract

BACKGROUND

The purpose of the present study was to examine retrospectively the contribution of ^{18}FDG-PET/CT to the evaluation of response to first-line gemcitabine plus cisplatin-based chemotherapy in patients with metastatic bladder cancer.

AIM

To evaluate the response to Gemcitabine plus Cisplatin (GC)-based chemotherapy using ^{18}FDG-PET/CT imaging in patients with metastatic bladder cancer.

METHODS

Between July 2007 and April 2019, 79 patients underwent ^{18}FDG-PET/CT imaging with the diagnosis of Metastatic Bladder Carcinoma (M-BCa). A total of 42 patients (38 male, 4 female) were included in the study, and all had been administered Gemcitabine plus Cisplatin-based chemotherapy. After completion of the therapy, the patients underwent a repeat ^{18}FDG-PET/CT scan and the results were compared with the PET/CT findings before chemotherapy according to EORTC criteria. Mean age was 66.1 years and standard deviation was 10.7 years (range: 41 – 84 years).

RESULTS

Of the patients, seven (16.6%) were in complete remission, 17 (40.5%) were in partial remission, six (14.3%) had a stable disease, and 12 (28.6%) had a progressive disease. The overall response rate (ORR) was 57.1 percent.

CONCLUSION

^{18}FDG-PET/CT can be considered as a successful imaging tool in evaluating response to first-line chemotherapy for metastatic bladder cancer. Anatomical and functional data obtained from PET/CT scans may be useful in the planning of secondline and thirdline chemotherapy.

INTRODUCTION

Bladder cancer is the ninth most common cancer all over the world with 380.000 new cases annually. Ration of male:female patients is 3.8:1[1]. According to database of Surveillance, Epidemiology and End Results (SEER), no significant change has occurred over the last 30 years in the number of patients dying of bladder cancer[2]. 10 to 15% of the patients with bladder cancer are metastatic at the time of diagnosis. The local recurrence rate after a radical cystectomy is 30% in muscle-invasive bladder carcinoma, and the rate of metastatic disease is even higher, at 60%[3,4]. Metastases are the main cause of death in this disease, and despite all therapies, 50% of patients with local disease develop metastasis within two years[5]. Metastatic bladder carcinoma is associated with extremely poor prognosis. Systematic chemotherapy is the standard therapy for metastatic disease.

Bladder transitional cell carcinoma (TCC) are usually chemosensitive tumors but response to a single agent is limited. Cisplatin, cyclophosphamide and vinblastine (CMV), cisplatin, doxorubicin and cyclophosphamide (CISCA) and methotrexate, vinblastine, adriamycin and cisplatin (M-VAC) induced 12 to 78% overall response rate (ORR)[6]. The combination of gemcitabine with cisplatin (GC) has become the first-line

chemotherapy and has further improved results with higher ORR (57%) and complete remission (CR) (15 to 21%)[7].

Diagnosing occult metastases in bladder cancer is still a challenge, and there is much more need for a diagnostic test for monitoring response to therapy and predicting residual disease in patients after chemotherapy. ^{18}FDG-PET/CT is the most important imaging modality in this regard. The re-staging of bladder cancer still constitutes a challenge using conventional techniques such as US, CT, MRI and bone scintigraphy, with success rates approximately 70 percent in literature[8]. It has been proposed that ^{18}FDG-PET/CT can provide additional diagnostic knowledge in the clinical management of bladder cancer[9]. We used the GC-based chemotherapy protocol described by European Association of Urology (EAU) in our patients, and the ^{18}FDG-PET/CT findings from before and after treatment were recorded[10].

The purpose of the present study was to examine retrospectively the contribution of ^{18}FDG-PET/CT to the evaluation of response to first-line gemcitabine plus cisplatin-based chemotherapy in patients with metastatic bladder cancer. An accurate primary staging of the disease is particularly important for the planning of second-line chemotherapy protocols and the determination of complete and incomplete response at this stage of the disease. The histological findings or the clinical and radiological workup (US, CT, MRI and bone scintigraphy) were used as a standard reference. There are a few number of studies in literature evaluating ^{18}FDG-PET/CT in the detection of residual disease and the evaluation of response to therapy after GC-based chemotherapy in patients with metastatic bladder carcinoma.

MATERIALS AND METHODS

A total 10,553 ^{18}FDG-PET/CT scans were performed in the Nuclear Medicine Department of Sifa University and Tinaztepe University, Izmir, Turkey between July 2007 and April 2019. In this group of patients, 79 patients underwent ^{18}FDG-PET/CT because of metastatic bladder cancer. The PET/CT findings of 42 patients before and after first-line chemotherapy were recorded.

Thirty-eight (90.4%) of these patients were male and 4 (9.6%) were female. Mean age was 66.1 years and standard deviation was 10.7 years (range: 41–84 years). Written informed consents was obtained from all patients.

All (100%) patients had data on histological sub-types of muscle-invasive bladder cancer (high-grade TCC) based on pathological investigations. In the patients, the primary tumor was confined within the bladder in 38 (90.4%) of the patients, whereas four patients (9.6%) had bladder tumors and concomitant upper tract urothelial carcinoma (UTUC). Baseline characteristics of the patients are summarized in Table 1.

Imaging and interpretation of data

370 MBq of 18F FDG injected intravenously after at least six hours of fasting and when blood glucose level was lower than 200 mg/dL. One hour after 18F FDG injection, a total body CT scan without IV contrast agent and whole-body 3D PET acquisition with 8 bed positions of 3 min of emission scan time, covering the area from the vertex to the proximal thigh, each using a dedicated PET/CT scanner (HI-REZ Biograph 16, SIEMENS) which provides an in-plane spatial resolution of 4.8 mm, an axial field view of 16.2 cm. The PET data were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (3 iterations, 8 subsets), re-oriented in transverse, coronal and sagittal planes.

PET scans were analyzed visually and semi-quantitatively using SUV_{max} measurement. One experienced nuclear medicine expert reviewed blindly and independently the FDG PET/CT scans regardless of as positive or negative for a primary tumour site. It was thought that ingestion of any radioactive substance that deviated from the physiological distribution was in favor of the spread of the disease.

RESULTS

A total of 144 metastatic foci in 42 patients with metastatic bladder carcinoma were evaluated using ^{18}FDG-PET/CT before chemotherapy, which 65 (53.2%) foci of lymph node's metastasis (mean SUV_{max}: 7.4), 30 (24.6%) foci of bone's metastasis (mean

SUV_{max}: 8.8), 26 (21.3%) foci of lung's metastasis (mean SUV_{max}: 6.6), 10 (8.1%) foci of liver's metastasis (mean SUV_{max}: 7.8), 10 (8.1%) foci of soft tissue's metastasis (mean SUV_{max}: 9.6), two (1.6%) foci of adrenal's metastasis (mean SUV_{max}: 9.3) and one (0.8%) foci of penile's metastasis (SUV_{max}: 14.4) were detected. Additionally, four (3.2%) foci of contomitant upper urothelial carcinoma (UTUC) were also detected (mean SUV_{max}: 13.3). The distribution of metastatic foci and mean SUV_{max} are summarized in Table 2. The patients underwent second ^{18}FDG-PET/CT scan after gemcitabine plus cisplatin-based chemotherapy to allow an evaluation of response to chemotherapy. The mean time interval between the two ^{18}FDG-PET/CT scans was 6 months (range: 3–14 months), and the same chemotherapy protocol was used in all patients during this period. Responses to chemotherapy were evaluated using the criteria of the European Organisation for the Research and Treatment of Cancer (EORTC), which it was found that seven patients (16.6%) were in complete remission, 17 (40.5%) were in partial remission, 6 (14.3%) had a stable disease and 12 (28.6%) had a progressive disease (Table 3). The overall response rate (ORR) was 57.1%.

DISCUSSION

Recurrent and metastatic bladder TCC has a poor prognosis. An accurate re-staging is crucial for the justification of additional toxic and expensive therapy. There is still only limited data on the benefits of ^{18}FDG-PET/CT in the identification of recurrences and new metastases after first-line chemotherapy for metastatic bladder cancer, and evaluating responses to therapy in cancer patients is still just as challenging as before. The reason for this is that; with current imaging techniques it is not possible to detect with absolute accuracy after chemotherapy to what extent of metastatic focus has been affected by the chemotherapeutics. In 1976, Moertel and Hanley reported that a decrease of 50 percent or more in tumor size must be regarded as a complete response to chemotherapy, which was accepted by WHO in 1979[11]. Evaluation of response to chemotherapy based solely on anatomic criteria was added to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria in 2000, in which a decrease < 30 percent or

an increase of < 20 percent was defined as a response to chemotherapy, although the RECIST criteria have undergone two modifications since then, one in 2009 and the other in 2010[12]. False negative results caused by the use of anatomic criteria in evaluating response to chemotherapy have resulted in the incorporation of functional/metabolic criteria into the assessment. The EORTC criteria were published in 2009, followed by the PET Response Criteria in Solid Tumors (PERCIST) criteria in 2009[12]. The present study has been conducted based on the EORTC criteria, which are summarized in Table 4.

High uptake of FDG in cancerous lesions of the transitional carcinoma was first demonstrated by Harney et al. in rats[13]. Drieskens et al. found that metabolism-based anatomical information gathered by the addition of FDG-PET to CT provided high diagnostic accuracy in pre-operative staging of invasive transitional cancers particularly invasive bladder carcinoma[14]. Nowadays, FDG-positron emission tomography combined with computed tomography (FDG-PET/CT) is an established standard for pre-operative staging and detecting metastatic lesions of bladder cancer[15-17].

The accumulation of FDG in metastatic cells is closely related to such transport proteins as GLUT-1 and hexokinase enzyme activities. However, P-glycoprotein (MDR-1) expression, metallothionein over-expression, altered p53 expression MRP (multi-drug resistance-associated protein) mRNA induction and epidermal growth factor receptor over-expression in metastatic bladder cancer are all considered to be potential predictors of response to chemotherapy[18]. Accordingly, FDG accumulation and response to chemotherapy cannot be evaluated only with GLUT-1 and hexokinase enzyme activities in tumor cells without elucidating the molecular biologic basis of the disease, and so it is obvious that this area requires further research (Figure 1).

Why is therapy planning in cases of metastatic bladder cancer using ^{18}FDG-PET/CT imaging so important? What contribution does ^{18}FDG-PET/CT make in decisions to continue with second-line chemotherapy after initial chemotherapy treatment? Figure 2 shows the metabolic activity of cancer before an anatomic visualization of the tumor as a general rule, applicable for all cancers, and this stage is extremely important in

diagnosis, staging, targeted therapy and the planning of radiotherapy. In order to spare the patient from additional toxic therapies, the detection of occult metastases and the evaluation of response to chemotherapy are only possible if there is a thorough understanding of the molecular/functional findings. This figure outlines the importance of molecular imaging, and the represented data is particularly important in the planning of treatments.

Recent Studies suggest that solid organ metastasis from bladder cancer, particularly metastasis to the liver, is an independent risk factor resulting from poor prognosis. There is a correlation between the Karnowsky score and disease specific survival, and so the detection of solid organ and occult metastases with high accuracy and the detection of residual active disease after therapy using ^{18}FDG-PET/CT contribute significantly to survival figures.

Bladder TCC are chemosensitive tumors. In metastatic disease, chemotherapy is the only therapeutic option. Imaging studies of metastatic urogenital malignancies are the main part of initial staging, response assessment and follow-up after systemic therapy. In particular, the clinically important question of the most accurate method to monitor therapeutic response during cytotoxic therapy or treatment with molecular approaches has been much neglected[19]. The mean overall response rate (ORR) for metastatic bladder cancer after GC-based chemotherapy ranges between 40 and 70 percent in literature, and similar rates were reported by Bellmunt et al. in a study of 637 patients in 2007 and by Bamias et al. in a study of 175 patients in 2011[20,21]. The mean ORR was 57.1 percent in the present study, which falls within the range of values in literature. Second or third-line chemotherapy is used in cases where the disease proves to be resistant to cisplatin-based chemotherapy; although there is no consensus on this issue[22]. In a recent published case study, the authors obtained a CR with FOLFOX4 chemotherapy in a metastatic urothelial cancer patient, after failure of GC combination[23]. As shown in Table 5, a precise re-staging is pivotal in the planning of second and third-line chemotherapy.

Metastasis may also appear in normal-sized lymph nodes. In bladder cancer, primary lymphatic drainage is to the internal iliac, common iliac and retroperitoneal lymph nodes. Therefore, metastasis occurs in these areas. Conventional CT is wrong 30% of the time. Conventional CT is wrong 30% of the time[24]. The functional and metabolic datas of PET/CT provide both accurate staging and evaluating of response to therapy higher sensitivity. In a population-based study in 2023, Patients with MIBC who underwent pre-treatment staging with FDG-PET/CT were more often staged as lymph node positive, regardless of cT stage[25]. In a recent study by Voskuilen et al., FDG-PET/CT provides important incremental staging information, which potentially influences clinical management in 18% of MIBC patients, but leads to false positive results as well[26]. In a study by Lodde et al., ^{18}FDG-PET/CT provided 100 percent PVV and specificity, compared to CT (33% vs 57%) in the detection of lymph node metastases, indicating the superiority of ^{18}FDG-PET/CT over standard CT in detecting lymph node metastasis[27]. In a study by Taguchi et al., found that liver metastases represented the highest risk to survival when compared to other metastates. In their study, all liver metastases died within 9.3 months of diagnosis after being unresponsive to chemotherapy[28]. This and other studies in literature suggest that the precise recognition of metastases is vitally important in predicting survival, evaluating response to chemotherapy and determining the most appropriate therapy.

Precise evaluations of metastases after chemotherapy are also particularly important. In a study by Lehmann et al. of 44 patients, a 28 percent five-year survival rate was reported in patients with metastatic bladder carcinoma[29]. Furthermore, in a recent study conducted in 2014, Mertens et al. evaluated the relationship between ^{18}FDG-PET/CT results and mortality in patients with MIBC (n = 211), in which the median follow-up period was 18 mo. Disease-specific survival was 50 months in the PET-negative patients, and this rate decreased to 16 months in the PET-positive patients. The presence of extravesical disease was found to be an independent prognostic factor in mortality in PET-positive patients[30].

Kibel et al. studied 43 patients with T2-3N0M0 stage urothelial cancer and reported a sensitivity of 70 percent, specificity of 94 percent, a positive predictive value of 78 percent and negative predictive value of 91 percent for ^{18}FDG PET/CT. They found occult metastatic disease in 7 of 42 patients, and concluded that pre-operative ^{18}FDG-PET/CT may affect decisions related to treatment prior to a radical cystectomy. The same study also evaluated the relationship between PET findings and survival, finding a rate of 24-mo recurrence-free survival of 24 percent in patients with positive PET findings and 55 percent in patients with negative PET findings[17]. Drieskens et al. provided valuable data on the prognosis of patients showing a longer median survival rate after negative results from a PET examination compared to patients with positive results for bladder cancer[14].

Additionally, based on an observation of 276 patients who had undergone cisplatin-based chemotherapy, Herr et al. concluded that those recording a complete or partial response to chemotherapy and those with limited nodal or a solitary visceral metastasis would be most likely to benefit from metastasectomy. The study also concluded that surgery should be avoided in the event of multiple liver metastases, metastases involving more than one visceral site or abdominal organ, or in cases of bone metastases, especially involving the pelvis or axial skeleton[31,32].

Drieskens et al. reported 60, 88 and 78 percent sensitivity, specificity and accuracy respectively for ^{18}FDG-PET/CT in the detection of metastatic disease in 55 patients with MIBC[14]. Apolo et al. evaluated 135 metastatic lesions in 47 patients with metastatic disease, recording 88 percent sensitivity and 87 percent specificity in an organ-based analysis. In this study, ^{18}FDG-PET/CT detected malignant disease in 40 percent more patients when compared to such conventional techniques as CT and MRI; furthermore, the results of ^{18}FDG-PET/CT imaging brought about a change in the treatment plan of 68 percent of the patients. The authors found that ^{18}FDG-PET/CT provides data of sensitivity and specificity for the detection of metastatic Bladder Cancer, and provides the diagnostician with more detailed diagnostic information than that supplied by

CT/MRI alone[16]. In the present study, 132 metastatic foci in 42 patients were evaluated.

In a series of 46 patients studied by Liu et al., ^{18}FDG-PET/CT registered a sensitivity of 77 percent and a specificity of 97 percent in the detection of metastatic disease in patients who had not undergone chemotherapy[33]. In a recent study by van Ginkel et al., The percent of sensitivity, specificity and accuracy of FDG-PET/CT was 36, 93 and 77 in turn, versus 12, 97 and 74 of CT only in MIBC[34]. In a study by Moussa et al., On a patient-based analysis, PET-CT, and CT showed a sensitivity of 40.3% and 13.4 %, respectively, a specificity of 79.5% and 86.7 %, respectively, positive predictive value (PPV) of 61.4% and 45%, respectively, and negative predictive value (NPV) of 62.3% and 55.4%, respectively in MIBC[35].

In a systemic review and meta-analysis by Lu et al., a sensitivity of 89 percent and a specificity of 82 percent were reported in the detection of metastatic lesions in cases of bladder cancer[15]. In the meta-analysis, ^{18}FDG-PET/CT scans provided sufficient diagnostic accuracy for the staging and re-staging of patients with MIBC and metastatic cancer; however, the ^{18}FDG-PET/CT scans achieved a less than sufficient diagnostic performance in the detection of primary bladder cancer on the bladder wall. In this regard, the study found that the method may lack sufficient data for the "T" stage of the bladder and for the identification of detrusor lesions due to the urinary excretion of FDG, although the method may be used for staging purposes and for the detection of metastatic disease.

The existing studies in literature measuring the diagnostic performance of ^{18}FDG-PET/CT in cases of metastatic bladder cancer are summarized in Table 6.

Jadvar et al. evaluated the diagnostic performance of ^{18}FDG-PET/CT in patients with muscle-invasive bladder carcinoma (MIBC) retrospectively and reported that the method led to a change in the clinical management of 17 percent of the patients[36]. The aim of the present retrospective study has been to evaluate response to therapy in patients with metastatic bladder carcinoma after primary chemotherapy using ^{18}FDG-PET/CT, allowing informed decisions to be made related to follow-up treatment

programs and a precise re-staging prior to the planning of additional toxic therapy. In this regard, the method more accurately determines the response to chemotherapy when compared to conventional methods. Although this falls outside the scope of the study, it is suggested that there may be a theoretical benefit in deciding in favor of a salvage cystectomy.

Metastatic transitional cells show a high affinity to FDG due to high glucose utilization, and progressive and hypermetabolic behavior. In the present study, the mean SUV_{max} for lymph nodes was 7.4, the mean SUV_{max} for visceral metastases was 6.6–7.8 and the mean SUV_{max} for bone metastases was 8.8.

In a metastatic lesion, the FDG uptake is dependent upon several factors. A strong relationship exists between FDG uptake and the number of cancer cells – a decreased FDG uptake points to a decrease in the number of viable tumor cells, while an increase in FDG uptake points to an increase in the number of viable tumor cells and tumor growth. Diagnoses of metastatic cancer are often established after the lesion reaches 10–100 grams in weight or a 10^{10}–10^{11} cell population, however the resolution of current PET/CT systems in cancer imaging ranges between 0.4 and 1.0 cm in diameter, corresponding to a tumor weight of 0.1–0.5 and 1.0 gr, and a cell number of 10^{8}–10^{9}. By using PET/CT, a diagnosis of metastatic bladder cancer can be established before the 100-fold increase occurs in the number of malignant cells (2 logarithms), meaning that a response to cancer therapy can be determined before a 100-fold decrease has occurred in the number of malignant cells (2 logarithms). After therapy, negative findings from ^{18}FDG-PET/CT imply a lack of cancer cells or a lack of lesions harboring more than 10^{7} cells. FDG-PET/CT cannot differentiate between a minimal tumor load and the lack of a tumor; however, a completely negative PET/CT scan after post-therapy indicates a good prognosis, while positive findings in PET/CT indicate the presence of a residual tumor (in the absence of inflammation). Figure 3 shows the relationship between FDG and tumor cells.

Limitations

Disease-specific limitations: The lack of information on why known active TCC cells fail to uptake FDG as to become visible on the detector, negative predictive which has not yet reached 100%, and the lack of data on a sufficient number of patients in literature can be regarded as disease-specific limitations.

Technical limitations: Diagnostic failures in ^{18}FDG-PET/CT are associated mostly with the lungs and liver, as PET technologies may fail to identify small lung metastases measuring less than 5 mm, even when used in conjunction with CT in the correction of anatomical location and attenuation. It is unclear if this observation of a decline in sensitivity is caused by pulmonary motion artifacts or by the low metabolic activity of the lung metastases. Respiratory gate and time-of-flight technologies might help detect motion artifacts and improve diagnostic correctness by reducing the smearing effect, and may provide a good spatial resolution, offering higher accuracy and more precise calculation of SUV[37].

Study limitations: The retrospective design of the study, the relatively small number of patients and the lack of histological correlation can be regarded as the limitations of the study.

CONCLUSION

^{18}FDG-PET/CT seems to be a considerably successful and applicable diagnostic tool in the evaluation of response to therapy after first-line chemotherapy for metastatic bladder cancer. The addition of metabolic/functional data to the anatomical findings may allow greater accuracy in the diagnosis. The re-staging of the disease is of particular importance in the planning of second- and third-line chemotherapy protocols, as all possible additional chemotherapy protocols will increase morbidity and mortality in a patient with impaired performance status after having undergone first-line chemotherapy. It is suggested that the presented method will allow a better explanation of the requirement for additional chemotherapy protocols to both the patient and their relatives, although further studies are required in order to standardize additional therapy protocols.

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