Urology Research, 2024, Volume 2, Issue 1
https://ojs.bbwpublisher.com/index.php/UR

The Usefulness of Positron Emission Tomography/Computed Tomography in the Diagnosis of Metastasis in Patients with Urothelial Carcinoma — A Secondary Publication

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Abstract: *Purpose:* This study examined the usefulness of positron emission tomography (PET)/computed tomography (CT) in the diagnosis of metastasis in patients with urothelial carcinoma. *Materials and methods:* The subjects were patients who were newly diagnosed with urothelial carcinoma in our department on whom we performed CT and PET/CT to search for metastasis. *Results:* The median age of the 92 subjects was 71 years, and bladder and upper tract urothelial cancer were underlying diseases in 41 (46%) and 51 (54%) patients, respectively. In 66 (72%) of the 92 cases, no metastasis was observed by CT, while PET/CT revealed metastasis in 9 (14%). The 57 (86%) patients in whom both CT and PET/CT showed no metastasis underwent radical surgery, while 2 patients (4%) exhibited pathological lymph node metastasis. Of the 26 patients in whom CT revealed metastasis, PET/CT showed no metastasis in 3 (12%), and the absence of pathological metastasis was confirmed in all patients. Of the 23 patients found to have metastasis in both CT and PET/CT, metastasis that could not be identified by CT was discovered by performing PET/CT in 10 (43%) patients. PET/CT showed significantly higher diagnostic accuracy than CT alone ($P < 0.01$), with sensitivities of 94.1% and 67.6%, specificities of 100% and 94.8%, and accuracy rates of 97.8% and 84.7%, respectively. *Conclusions:* PET/CT of patients with urothelial cancer revealed that metastases that cannot be diagnosed by CT alone are found at a significant frequency. Since these metastases can affect treatment choices in patients with urothelial cancer, PET/CT is considered to be useful in diagnosing metastases in patients with urothelial cancer.

Keywords: Urothelial cancer; PET/CT; Diagnosis

Online publication: March 29, 2024

1. Introduction

For patients with localized urothelial carcinoma, radical cystectomy and radical nephroureterectomy are well-established treatments [1,2]. However, complications occur with a certain frequency during surgery, and postoperative quality of life (QOL) is decreased after surgery [3]. In order to avoid ineffective radical surgery in

patients who cannot be cured and unnecessary anticancer drug treatment in patients who have not undergone metastasis, accurate staging is considered important when planning treatment [4-6].

Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) is a diagnostic imaging method that observes the accumulation of ^{18}F-FDG (fluorodeoxyglucose), an analog of glucose, in tissues. Since glucose uptake is increased in many malignant tumors, it is used as an imaging evaluation method for various types of cancer [7]. ^{18}F-FDG is unsuitable for the diagnosis of primary urothelial carcinoma because it is excreted in the urine. However, its usefulness in the diagnosis of regional lymph node metastasis and distant metastasis has been reported [6,8]. On the other hand, compared to CT and MRI (magnetic resonance imaging), some reports suggest that PET/CT is not highly useful [4,5], and the significance of PET/CT in the diagnosis of urothelial carcinoma metastasis is controversial. In this study, we investigated the usefulness of PET/CT in the diagnosis of metastasis in patients with urothelial carcinoma.

2. Research subjects and methods

Patients diagnosed with urothelial carcinoma who underwent CT and PET-CT between January 2012 and December 2017 in our department were included in the study. The patients were pathologically diagnosed as having newly diagnosed invasive bladder carcinoma or carcinoma of the renal pelvis or ureter. In order to verify the accuracy of the CT and PET/CT diagnoses, we performed surgery on patients with pathologically proven metastatic disease. The diagnosis of metastasis should be verified in patients who have undergone surgery and have pathologically proven the presence of metastasis, or in patients who have undergone regular examinations for at least 6 months after the examination. The patients with metastases were included in the study. In addition, because of the anticancer treatment, it was not possible to determine the accuracy of the image evaluation, these cases were excluded. In this study, the clinical stage was determined only by CT and PET/CT results.

CT was performed with simple CT of the chest and contrast-enhanced CT of the abdomen. The PET/CT machine was a GE Healthcare Discovery ST Elite. The fasting time was 5 hours, and imaging was performed 1 hour after the administration of ^{18}F-FDG 3.0 MBq/kg. The imaging time was 21 minutes, and reconstruction was performed by the 3D OSEM method. FDG accumulation in comparison with other sites or background tissue metastasis was assessed by PET/CT. The standardized uptake value (SUV), which is a semi-quantitative measure of FDG accumulation, was not used as a reference value for determining metastasis.

In this study, we evaluated the reading results of radiologists who performed CT and PET/CT at the time of the study. The results were evaluated retrospectively. The sensitivity and specificity of the positive diagnosis of metastasis were evaluated on a case-by-case basis.

Statistical analysis was performed using EZR, and $P < 0.05$ was considered a significant difference. The difference in diagnostic accuracy by test method was analyzed using the McNemar test [9]. In conducting this study, approval was obtained from the ethics committee of Hakodate Goryoukaku Hospital (Approval number: 2020-015).

3. Results

A total of 134 patients were examined, of which 108 patients had newly diagnosed invasive bladder cancer and ureteral carcinoma of the renal pelvis. 8 patients could not be evaluated by diagnostic imaging because they were treated with anticancer drugs and 8 patients could not be evaluated by diagnostic imaging because they did not undergo periodic examinations for a sufficient period of time, after excluding them, the study included 92 patients. The 92 patients had a median age of 71 years, 73 (79%) were male, and 41 (46%) had bladder cancer

as the primary disease (**Table 1**).

Table 1. Information of 92 patients

Patient information		Cases
Age (years)		71 (46–89)
Gender	Male	73 cases (79%)
	Female	19 cases (21%)
Primary illness	Bladder cancer	41 cases (46%)
	Cancer of the renal pelvis and ureter	51 cases (54%)
Local clinical stage	cT1	11 cases (12%)
	cT2	33 cases (36%)
	cT3	37 cases (40%)
	cT4	11 cases (12%)
Example of primary site excision		69 cases (75%)

The clinical diagnoses when CT and PET/CT were performed are shown in **Table 2**. The number of cases with no metastasis, lymph node metastasis only, and distant metastasis on CT were 66 (72%), 15 (16%), and 11 (12%) cases, respectively; while the results of PET/CT were 60 (65%), 19 (21%), and 13 (14%), respectively.

Table 2. Clinical stage and metastases-positive site when performing CT and PET/CT

Method of examination	CT	PET/CT
cTanyN0M0	66 (72%)	60 (65%)
cT1N0M0	11 (12%)	10 (11%)
cT2N0M0	26 (29%)	27 (31%)
cT3N0M0	25 (27%)	21 (23%)
cT4N0M0	4 (4%)	2 (2%)
cTanyN + M0	15 (16%)	19 (21%)
cTanyNanyM+	11 (12%)	13 (14%)
Site of metastasis		
Lymph node metastasis	24 (26%)	29 (32%)
(Extra-regional lymph node metastasis)	15 (16%)	16 (18%)
Liver metastasis	3 (3%)	4 (4%)
Lung metastasis	3 (3%)	2 (2%)
Bone metastasis	1 (1%)	6 (7%)
Peritoneal dissemination		2 (2%)
Pleural metastasis		2 (2%)
Accidental cancer case		Colorectal cancer 2 (2%)

PET/CT showed metastasis in 9 (14%) of the 66 patients who did not show metastasis on CT (**Figure 1**), there were lymph node metastases in 6 cases (67%), and extra-regional lymph node metastases in 2 cases (**Figure**

2). In addition, two patients (22%) had bone metastasis and one (11%) had peritoneal dissemination. On the other hand, 57 patients (86%) who had no metastasis on PET/CT underwent radical surgery. Two patients (4%) had pathological lymph node metastases.

Of the 26 patients with metastases on CT, 23 (88%) had metastases on PET/CT, while 3 (12%) had no metastases on PET/CT. In all three cases, CT revealed lymph node involvement. However, PET/CT showed no FDG accumulation in the lymph nodes, indicating the absence of metastasis. In all three cases, lymph node dissection was performed at the time of radical surgery and pathologically confirmed that there were no metastases. On the other hand, of the 23 patients who had metastases on PET/CT, new metastasis was discovered in 10 (43%) by performing PET/CT. Of these patients, 5 (19%) had bone metastases, 2 (9%) pleural metastases, and 1 (4%) each had liver metastases, peritoneal dissemination, and abdominal wall metastases. Two patients (9%) had more extensive lymph node metastases compared to CT, and two patients (9%) were found to have colorectal cancer.

The diagnostic accuracy of using CT only and CT and PET/CT for the diagnosis of metastasis respectively, were sensitivity of 67.6% and 94.1%, specificity of 94.8% and 100%, and accuracy rate of 84.7% and 97.8%. The McNemar test was performed for diagnostic accuracy. The results of the McNemar test showed that CT and PET/CT were significantly more accurate than CT alone ($P < 0.01$).

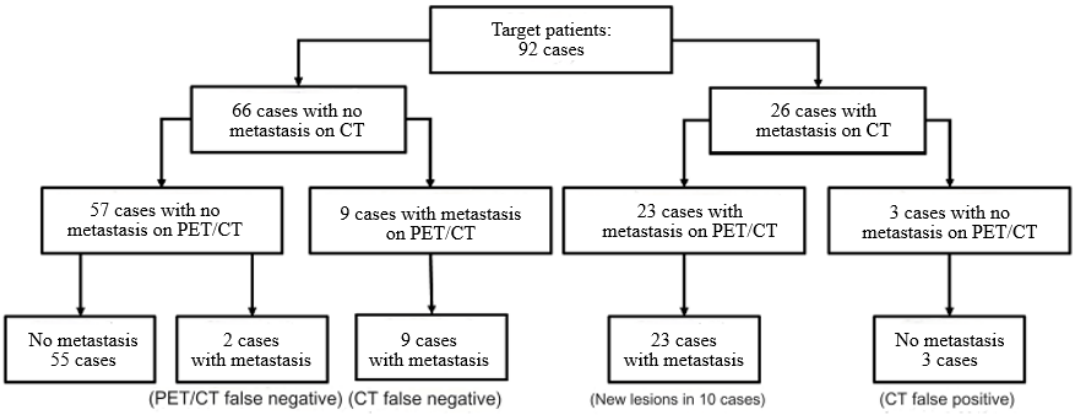

Figure 1. Diagnosis results of 92 cases of urothelial carcinoma performed by CT and PET/CT

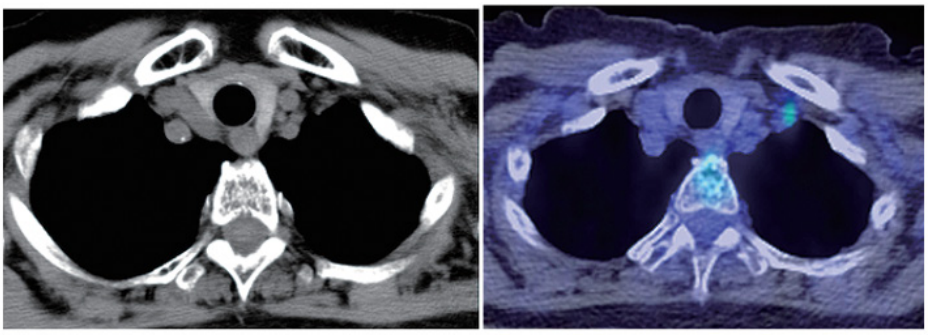

Figure 2. A case in which no metastasis was found on CT, but metastasis was found in the left supraclavicular lymph node by PET/CT. This case underwent lymph node biopsy and was pathologically diagnosed as metastasis of urothelial carcinoma.

4. Discussion

CT and MRI are often used to diagnose lymph node metastases and distant metastases, but the sensitivity of these tests alone is low. Therefore, it may influence the optimal treatment decision [5,10]. FDG-PET/CT has been reported to be useful in the diagnosis of bladder cancer metastasis. In this study, we investigated the usefulness of FDG-PET/CT in the diagnosis of metastasis of urothelial carcinoma.

The present study included patients with newly diagnosed invasive bladder cancer and renal pelvis ureteral cancer who underwent both CT and PET/CT for metastasis detection. PET/CT has been used to detect metastases that were not seen on CT in 9 (12%) patients. The results of this study were as follows. The results suggest that PET/CT was useful in the diagnosis of metastasis, and that in these cases, ineffective curative treatment could be avoided. On the other hand, PET/CT could not identify lymph node metastasis in two patients (4%), which is a limitation of PET/CT in the diagnosis of metastasis. Tanaka *et al.* performed PET/CT on patients with urothelial carcinoma and showed that 20% of patients with urothelial carcinoma had new metastases, which necessitated a change in treatment [11]. PET/CT may change the treatment strategy for a certain number of patients with urothelial carcinoma and may be useful in the diagnosis of metastasis of urothelial carcinoma.

Vind-Kezunovic *et al.* reported that performing PET/CT in patients with urothelial carcinoma allows more accurate diagnosis of lymph node metastasis. They concluded that PET/CT is useful for treatment selection [6]. Mertens *et al.* also reported that PET/CT can be used to identify the metastatic sites of urothelial carcinoma and that PET/CT is useful for predicting the prognosis of patients with urothelial carcinoma [8]. On the other hand, Goodfellow *et al.* found that PET/CT increased sensitivity by 22% compared to CT alone, and new metastases could be diagnosed in 5.6% of cases. However, the study concluded that PET/CT is not meaningful as a routine procedure because of its low diagnostic accuracy and high medical cost [4].

In the present study, the presence of FDG accumulation was considered positive for metastasis. There is no established opinion on how to judge metastasis positivity. Vind-Kezunovic *et al.* defined metastasis positivity as an SUVmax of 2 or greater [6]; Girard *et al.* judged positive for metastasis by combining SUVmax and the size of the lesion [12]; while Mertens *et al.*, on the other hand, did not define SUVmax as they did, but considered the presence of FDG accumulation to be positive for metastasis [4,5,8]. When defining SUVmax for metastasis diagnosis, a higher reference value is considered to decrease sensitivity and increase specificity. The specificity of the diagnosis is increased by increasing the standard value. At present, there are no fixed criteria for judging metastasis positivity and it is assumed that it should be evaluated comprehensively based on the degree of FDG accumulation, comparison with other sites, size of the lesion, and other factors.

The present study was a retrospective study and there was a patient selection bias in the included patients. In other words, some patients who could not be evaluated by CT or PET/CT were excluded from the study. Specifically, in cases where the success or failure of the image test was not pathologically diagnosed, only those cases for which follow-up could be performed for six months or more were included, so eight cases for which sufficient follow-up could not be performed were not excluded from the study. In addition, among the cases in which preoperative anticancer drug treatment was performed, eight cases in which a discrepancy was observed between the imaging test and the pathological test were excluded because it was not possible to evaluate whether the anticancer drug treatment was successful or whether the image diagnosis was incorrect. Furthermore, routine bone scintigraphy was not performed because there were no bone-related symptoms. Bone metastases were identified in 6 patients (7%) by PET/CT, suggesting that PET/CT may be able to identify asymptomatic bone metastases.

5. Conclusion

Performing PET/CT in patients with urothelial carcinoma reveals a certain number of metastases that cannot be diagnosed by CT alone. Since these metastases can influence the choice of treatment for patients with urothelial carcinoma, PET/CT was considered useful for the diagnosis of patients with urothelial carcinoma.

Disclosure statement

The authors declare no conflict of interest.

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