
Contribution of ^{11}C -Choline Positron Emission Tomography/Computerized Tomography to Preoperative Staging of Advanced Transitional Cell Carcinoma

Ofer N. Gofrit,* Eyal Mishani, Marina Orevi, Martine Klein, Nanette Freedman, Dov Pode, Amos Shapiro, Ran Katz, Eugene Libson and Roland Chisin

From the Departments of Urology, Nuclear Medicine and Radiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Purpose: Current imaging modalities for preoperative staging of advanced transitional cell carcinoma of the bladder or upper urinary tract are not sensitive for detection of metastases. This study examines the contribution of ^{11}C -choline positron emission tomography/computerized tomography to preoperative staging of transitional cell carcinoma.

Materials and Methods: We prospectively evaluated 18 patients with 19 advanced transitional cell carcinomas (17 bladder tumors and 2 upper tract transitional cell carcinomas). All patients had computerized tomography of the chest, abdomen and pelvis negative for metastases. ^{11}C -choline positron emission tomography/computerized tomography was performed on a Discovery ST® positron emission tomography/computerized tomography system. Finally 16 patients underwent radical surgery and positron emission tomography/computerized tomography images were compared to histopathological findings. Two patients were not operated on due to the findings on ^{11}C -choline positron emission tomography/computerized tomography.

Results: ^{11}C -choline uptake was found in all primary transitional cell carcinomas, with a maximum standardized uptake value of 7.3 ± 3.2 (mean \pm SD). The series included 3 patients with refractory bladder carcinoma in situ, which was visualized in all 3, with a standardized uptake value of 6.9 ± 5.6 . In 6 patients uptake of ^{11}C -choline in lymph nodes as small as 5 mm was visualized (standardized uptake value 3.8 ± 1.4). Of these patients 4 underwent surgery and histopathology confirmed malignancy in 3 of 4. No additional patients with positive lymph nodes were found on histopathology. Metastases were visualized in bones with normal architecture on computerized tomography in 4 patients (standardized uptake value 5.2 ± 1.1) and were confirmed by followup computerized tomography.

Conclusions: In this small series ^{11}C -choline positron emission tomography/computerized tomography was highly sensitive for primary and metastatic transitional cell carcinoma. Carcinoma in situ, lymph node metastases and early bony metastases were visualized. ^{11}C -choline positron emission tomography/computerized tomography is a promising tool for preoperative staging of advanced transitional cell carcinoma.

Key Words: methyl carbon-11 choline; positron-emission tomography; tomography, x-ray computed; carcinoma, transitional cell

Preoperative staging of advanced transitional cell carcinoma of the bladder or upper urinary tract includes assessment of extent of local invasion of the bladder and adjacent organs, as well as the presence of lymph node and systemic metastases. The risk of lymph node metastases in a patient with muscle invasive bladder cancer is about 20%.¹ An accurate imaging modality identifying these patients may contribute to their management, since patients with positive lymph nodes benefit from chemotherapy more than from radical surgery.²

Computerized tomography and to a lesser extent MRI are the most frequently used diagnostic tools for staging of muscle invasive bladder cancer. Both modalities depend on en-

largement of the lymph node (more than 1 cm in most studies) as a criterion for cancerous involvement. However, a smaller node may harbor a metastasis and reactive non-metastatic nodes are sometimes enlarged beyond 1 cm. Paik et al reported that CT visualized involved lymph nodes in 6 of 82 patients with invasive bladder cancer. Only 4 of them were pathologically confirmed. A total of 13 other patients with lymph node metastases were not identified by CT.¹ In another CT study of 28 patients with lymph node metastases only 5 had a positive scan and another 4 had a suspicious scan.³ Thus, the accuracy of CT for lymph node metastases detection is far from satisfactory.

MRI may be more sensitive. Using MRI Kim et al identified 4 of 6 patients with lymph node metastases.⁴ However, these lymph nodes were quite enlarged since all 4 cases were also correctly identified by CT. In another MRI study 2 patients with enlarged lymph nodes were identified and on histopathology 1 of them had reactive nodes.⁵ Special techniques like the 3-dimensional, magnetization prepared rapid gradient echo technique and ferumoxtran-10 enhanced MRI may provide better sensitivity rates.^{6,7}

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Study received hospital ethics committee approval.

* Correspondence: Department of Urology, Hadassah University Hospital, P.O. Box 12000, Jerusalem 91120, Israel (telephone: +972-2-6776874; FAX: +972-2-6430929; e-mail: ong1000@netvision.net.il).

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Data on the accuracy of CT for staging upper tract TCC are sparse. Scolieri et al reported that the accuracy of CT in staging advanced upper tract TCC is about 60%.⁸ CT under staged or did not detect 40% of the tumors and did not alter the treatment of any patient. These authors concluded that CT is rarely helpful in diagnosing or staging this type of cancer.⁸

PET imaging is based on metabolic changes and, therefore, has a potential advantage in detecting metastases in small lymph nodes compared to modalities which image only morphology. The uptake of the radiotracer in a tissue is expressed by the standardized uptake value. SUV is defined as the average activity per tissue volume normalized by the average whole body activity.⁹ SUV is a semiquantitative index of tracer uptake. While high SUV can be indicative of malignancy, no strict cutoff values can be defined. The main radiotracer used in PET is 2-FDG. The spatial resolution of PET using FDG for visualizing bladder cancer and pelvic lymph nodes is significantly limited by urinary excretion of the radiotracer. This explains the relatively low detection rate of lymph node metastases by FDG-PET in patients with bladder cancer.^{10,11} Choline labeled with ¹¹C is rapidly taken up by malignant cells by active transport, is retained by phosphorylation and has a negligible urinary excretion.^{12,13} Using CHOL PET de Jong et al correctly identified 2 of 3 patients with bladder cancer with lymph node metastases.¹⁴

Combined PET/CT is a modern modality for tumor staging. CT images provide structural information and the attenuation map for PET image attenuation correction. In a mixed group of patients with various malignancies, PET/CT staging with FDG was found to be significantly more accurate than CT alone, PET alone, and side-by-side PET and CT.¹⁵ In a similar patient group PET/CT was also found to be more accurate than MRI and had a greater impact on patient management compared to MRI.¹⁶

In view of the difficulties of preoperative staging of advanced TCC of the bladder and upper urinary tract with CT, MRI and FDG-PET, we set out to confirm the previously suggested advantages of CHOL as a PET tracer for identification of lymph nodes and bone metastases in this patient population, using a PET/CT scanner to provide further precision in anatomical localization.

MATERIALS AND METHODS

Patients

A total of 18 patients with 19 TCCs of the bladder or upper tract underwent preoperative metastatic evaluation with CHOL PET/CT before radical surgery. One patient had both types of tumors. Candidates for the study had advanced bladder cancer (stage T2 or carcinoma in situ refractory to intravesical immunotherapy and chemotherapy) confirmed by transurethral resection, or extensive upper tract TCC (tumor diameter more than 3 cm) confirmed by retrograde pyelography. All patients underwent CT (Marconi M8000, Coventry) of the chest, abdomen and pelvis, referred as the diagnostic CT to distinguish it from the CT done as part of the PET/CT. Diagnostic CT was performed within 1 month before the PET/CT. Intravenous contrast medium was injected in 16 patients. Two patients were not given intravenous contrast due to renal failure (serum creatinine greater than 300 μ g/l). Diagnostic CT was interpreted by a urologist (EL).

Any pelvic node larger than 10 mm was considered suspicious for lymph node metastases, and any focal osteoblastic or osteolytic lesion was considered suspicious for bone metastases. The diagnostic CT was negative for metastases in all patients. The PET/CT findings were compared to the results of subsequent surgery. The study protocol was approved by the hospital ethics committee and all patients signed an informed consent form.

CHOL PET/CT Protocol

PET studies were performed with ¹¹C-choline produced at the hospital cyclotron by a modified automated preparation method.¹⁷ An improved method for the quality assurance of this production was used.¹⁸ ¹¹C-choline was produced with specific radioactivity of 2.7 Ci/ μ mol (99.9 GBq/ μ mol) at end of bombardment and radiochemical purity of 98%. PET/CT scans were performed using the Discovery ST® PET/CT system. Image acquisition started 5 minutes after intravenous injection of 444 to 518 MBq (12 to 14 mCi) of ¹¹C-choline according to patient weight. Imaging proceeded from the pelvis to the base of the skull, with 4 minutes scan time per bed position. Any round or elongated structure that showed uptake of choline and any focal bony uptake were considered cancerous.

Surgical Procedure

Following PET/CT the patients proceeded to surgery. Radical cystectomy included removal of the bladder, prostate and seminal vesicles in men, and the removal of the bladder, uterus, parametria, urethra and upper vaginal wall in women. Dissection of the pelvic lymphatics included removal of the obturator fossa, internal, external and common iliac nodes. The boundaries of the dissection were superiorly the bifurcation of the common iliac artery, inferiorly the inguinal ligament, laterally the genitofemoral nerve and medially the obturator nerve. These boundaries were not modified according to the PET/CT findings. The lymph node pathological staging was done by a uropathologist. Suspicious macroscopic lymph nodes were analyzed separately, with specific indication of their location. Otherwise, evaluation of the lymph nodes status was done according to the pelvic side only. The average number of lymph nodes harvested from each hemipelvis was 6.5 (range 3 to 12). In cases of upper tract involvement the patient underwent radical nephrectomy including removal of the kidney, the ureter, a bladder cuff and dissection of the ipsilateral retroperitoneal lymph nodes from the diaphragmatic crura to the pelvic brim.

RESULTS

A total of 19 tumors in 18 patients (13 men, 5 women, mean age 74 years) with advanced transitional cell carcinomas were evaluated. There were 14 patients with muscle invasive bladder TCC (T2), with average tumor size of 3.8 cm (range 2.5 to 6). Three patients had carcinoma in situ (Tis) of the bladder refractory to intravesical immunotherapy and chemotherapy, and 2 had extensive TCCs of the ureter and renal pelvis (1 patient had upper tract and bladder carcinomas).

¹¹C-choline uptake was found in all primary TCCs (100% sensitivity for primary tumor detection) with an average maximum SUV of 7.3 ± 3.2 . A total of 13 exophytic bladder

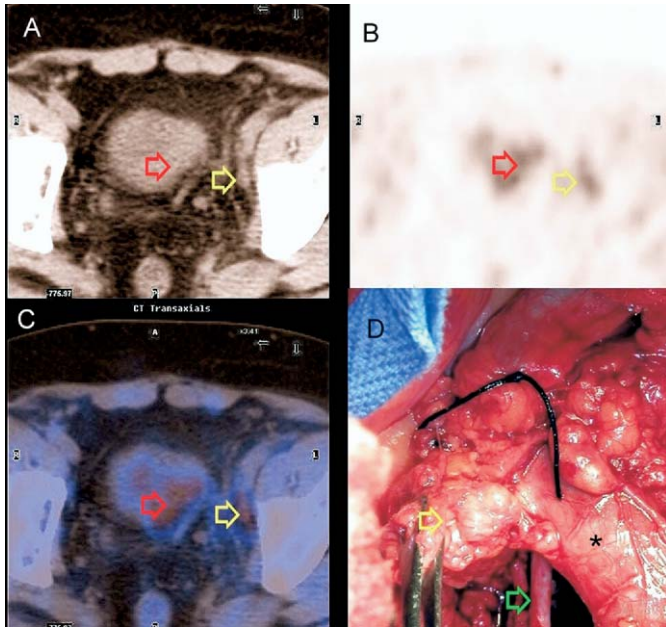


FIG. 1. Case 1. PET/CT axial images of pelvis. A to C, CT, PET and superimposed CT and PET at level of bladder base. Primary tumor (red arrow) and 8 mm lymph node (yellow arrow) are visualized on PET. D, intraoperative view. Involved lymph node is held by pin-cette (yellow arrow). External iliac vein is marked by asterisk and obturator nerve by green arrow. Ligated ureter is recognizable by stitch.

tumors were visualized with an SUV of 7.6 ± 2.8 . Finally, 12 of them were operated with a pathological finding of T2 in 9 patients and T3 in 3. Tis of bladder present in 3 patients showed ¹¹C-choline uptake with SUV of 6.9 ± 5.6 . Upper tract TCC was visualized in 2 patients, with SUV of 7.6 and 5.2.

In 6 patients suspicious lymph nodes 5 to 18 mm in diameter were demonstrated, with SUV of 3.8 ± 1.4 (range 2.6 to 6.2). These lymph nodes were located in the common and external iliac, common femoral, presacral, and para-aortic regions. The large lymph nodes in a patient not given intravenous contrast were identified in retrospective analysis of the CT (case 5). Of these patients 4 underwent surgery. Histopathology confirmed the PET/CT findings in 3. Up to 3 involved lymph nodes for each pelvic side were found in these patients. In 1 patient a positive lymph node on PET/CT was found to be a reactive node on histology (false-positive). No additional cases of positive lymph nodes were found on histopathology (100% sensitivity for lymph node metastases detection). Bone metastases were visualized in bones with normal architecture on CT in 4 patients with an SUV of 5.2 ± 1.1 . These findings were confirmed by followup CT. In 2 patients advanced disease was found on PET/CT with multiple bone and lymph node metastases. Therefore, it was considered unethical to operate on these patients and instead they were treated with chemotherapy. Disease progression despite chemotherapy was documented in both cases at followup CT 3 and 4 months after PET/CT.

CASE HISTORIES

Case 1

A 70-year-old man presented with macrohematuria. Trans-urethral resection of a T2 TCC of the left bladder wall was

done. Diagnostic CT was negative for metastases and the patient was scheduled for radical cystectomy. On PET/CT the bladder tumor was well visualized with SUV 3.9 (fig. 1). Two small lymph nodes up to 8 mm in large diameter with choline uptake (SUV of 2.6) were found in the left external and common iliac areas. Single nodes were found also in the right common iliac, presacral and para-aortic areas. Radical cystectomy was performed and a T3 bladder carcinoma was found. Histology showed metastases in the suspected lymph node in the left common iliac fossa. Micrometastases were found in a lymph node in the same side and in a lymph node in the right pelvis.

Cases 2 to 4

Three men (72, 68 and 73 years old) were scheduled for radical cystectomy as a treatment for Tis of bladder refractory to multiple intravesical chemotherapy and immunotherapy. Patchy CHOL uptake (SUV 2.4, 5.2 and 13.2) was noted in the bladder on PET/CT, consistent with the surgical findings (fig. 2).

Case 5

A 78-year-old woman presented with macrohematuria and right flank pain. A tumor was found occupying the bladder trigone and obstructing the right ureter. The diagnostic CT was performed without intravenous contrast due to renal failure (serum creatinine of $343 \mu\text{g/l}$). CHOL PET/CT demonstrated high tumor uptake (SUV 7.2), with uptake in 4 right and 3 left common and external iliac lymph nodes up to 18 mm in multiple presacral and para-aortic lymph nodes up to 10 mm (SUV 3.3 to 3.5) (fig. 3). Uptake was also found in the right pubis and femoral head (SUV 3.8 and 3.9). Retrospective reading of the diagnostic CT failed to show any bone lesions. However, lymph node enlargement was visualized in the right external iliac chain. The PET/CT findings were discussed with the patient who chose radical surgery hoping to save the right kidney. Histopathology confirmed the presence of bilateral lymph node metastases. Followup CT 1 month after surgery confirmed the bony findings.

Case 6

An 83-year-old man presented with macrohematuria and uremia (creatinine $350 \mu\text{mol/l}$). A noncontrast CT showed

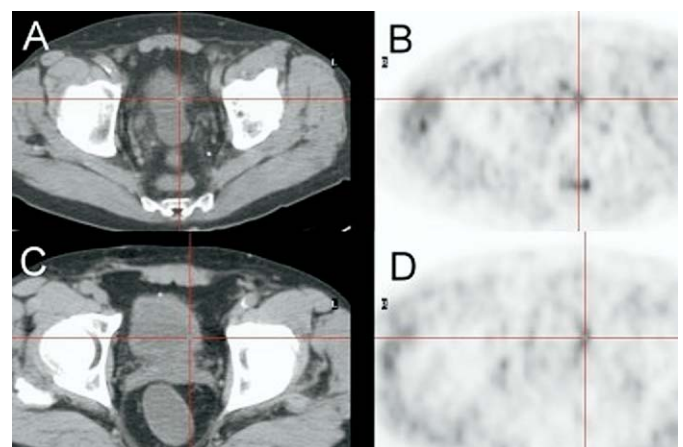


FIG. 2. Axial PET/CT. A and B, case 2. C and D, case 3. Crosshairs indicate areas of increased CHOL uptake.

the presence of bladder tumor, bilateral hydronephrosis and 70 to 100 HU dense material in the left ureter. A right nephrostomy was inserted. Creatinine decreased to 240 $\mu\text{mol/l}$. CHOL PET/CT showed uptake in the bladder tumor (SUV 8.3) in the left lower ureter (SUV 7.4) and in several foci in the upper ureter (SUV 8.1) (fig. 4). Despite this extensive disease lymph node metastases were not identified on PET/CT. Operative findings matched the CHOL PET/CT predictions for negative lymph nodes as well as tumor foci.

DISCUSSION

Accurate preoperative staging of advanced TCC of the bladder or upper urinary tract is of great clinical significance since patients with metastases may benefit from chemotherapy rather than from radical surgery. Most current imaging tools for diagnosing metastases are not accurate. CT and MRI rely on lymph node size as a criterion for metastasis detection and often miss involved nodes smaller than 1 cm.^{1,6,7} We hypothesized that PET/CT using ¹¹C-choline which has a low urinary excretion would be sensitive for detection of pelvic lymph node metastases. Preoperative CHOL PET/CT was performed in patients with advanced TCC with diagnostic CT negative for metastases. PET/CT findings were compared to histopathological staging.

We found that CHOL PET/CT was highly sensitive for lymph node metastases. All patients with lymph node metastases (including nodes as small as 5 mm, fig. 1) were identified by PET/CT (sensitivity and negative predictive value of 100%). However, there was 1 case of false-positive identification. Some choline positive nodes larger than 10 mm had not been identified as lymph nodes on prior diagnostic CT. CHOL PET/CT detected bone metastases in 4 patients (fig. 3). These must have been early metastases since no changes in bony architecture on CT were noted. On followup CT the presence of metastases was confirmed in all patients.

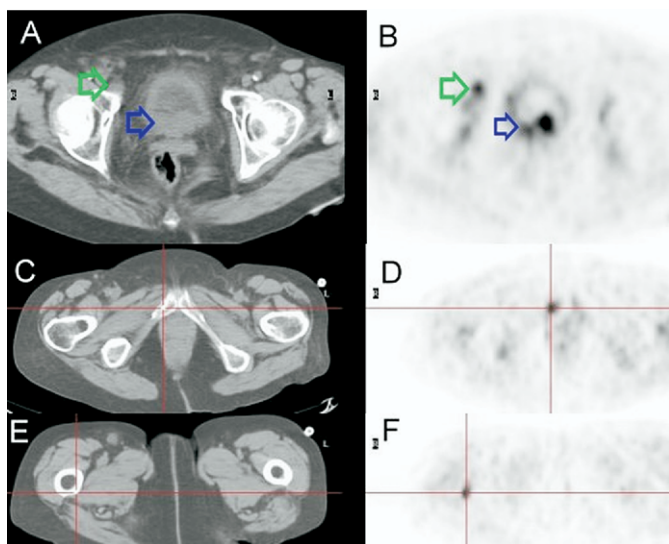


FIG. 3. Case 5. A and B, CT and PET views at level of bladder. Primary tumor (blue arrow) and suspicious lymph node (green arrow) are seen. C to F, CT and PET views at level of pubis and femurs. Bone metastases are visualized only on PET (crosshairs) while CT is normal.

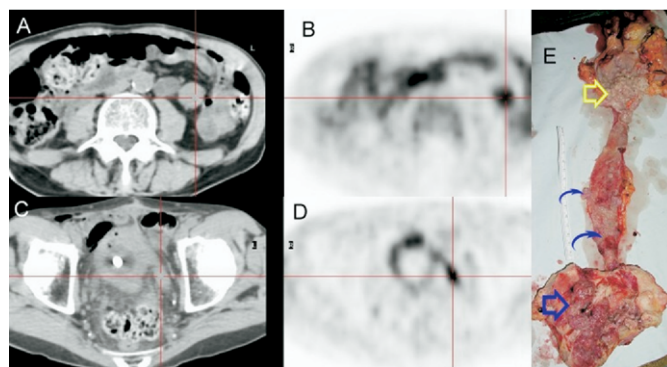


FIG. 4. Case 6. A and B, CT and PET show CHOL uptake in upper ureteral TCC (crosshairs). C and D, CT and PET of pelvis reveals circumferential bladder and lower ureter (crosshairs) CHOL uptake. E, nephroureterectomy-cystectomy specimen. Bladder tumor is marked by straight blue arrow, lower ureteral tumors by curved blue arrows and upper ureteral/renal pelvis tumor by yellow arrow.

In addition, CHOL PET/CT visualized all primary TCCs with a high SUV of 7.3 ± 3.2 . Exophytic bladder tumors showed ¹¹C-choline uptake of 7.6 ± 2.8 , higher than the values reported by de Jong et al (4.7 ± 3.6), who used ¹¹C-choline on a PET system without CT.¹⁴ The higher SUVs obtained in this study may be due in part to the differences between PET/CT compared to conventional PET.¹⁹ The improved resolution and sensitivity of the PET/CT may also have contributed to our visualization of carcinoma in situ (Tis). All these tumors were well delineated by CHOL PET/CT (fig. 2), with SUVs of 2.4 to 13.2. Tis was not visualized in the study of de Jong et al,¹⁴ and to our knowledge CHOL PET/CT is the first imaging modality capable of visualizing Tis. High ¹¹C-choline uptake (SUV of 8.1 and 5.2) was observed in the 2 cases of upper tract TCC studied. This could be particularly useful for evaluation of patients who have obscure segments of the urinary tract like a ureteral stump after nephrectomy.

The results presented in the study must be viewed as preliminary due to the small number of patients. In addition, the accuracy of the diagnostic CT was limited in 2 patients in whom contrast media was not injected intravenously because of renal failure. However, this condition is not rare among patients with advanced TCC.

CONCLUSIONS

CHOL PET/CT is a promising imaging modality that may provide an important contribution to the preoperative staging of advanced TCC of the urinary tract. Larger series are needed to verify these results.

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Abbreviations and Acronyms

CHOL	=	¹¹ C-choline
CT	=	computerized tomography
FDG	=	¹⁸ F-fluorodeoxyglucose
MRI	=	magnetic resonance imaging
PET	=	positron emission tomography
SUV	=	standardized uptake value
TCC	=	transitional cell carcinoma

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EDITORIAL COMMENT

Accurate clinical staging of localized or regionally advanced transitional cell tumors of the bladder remains a challenge. Preoperative staging of regional lymph nodes has relied on imaging to identify nodes that meet anatomical criteria for suspicion of involvement. Approximately 25% of contemporary patients with bladder cancer treated with radical cystectomy will demonstrate pathological evidence of regional lymph node involvement, most without evidence of gross disease on preoperative imaging. The authors present encouraging data on the use of modern metabolic imaging based on ¹¹C-choline PET/CT for bladder cancer. The lack of urinary excretion of this agent appears particularly useful in imaging the bladder primary and regional lymph nodes compared to ¹⁸F-fluorodeoxyglucose, which is mainly eliminated via the urinary system. Given the importance of neoadjuvant chemotherapy in patients with invasive disease, preoperative identification of high risk patients with extravesical spread will help to identify optimal candidates for combined modality treatment.

Bernard H. Bochner

Department of Urology
Memorial Sloan-Kettering Cancer Center
New York, New York