Preoperative Staging of Pelvic Lymph Nodes in Prostate Cancer by ^{11}C-Choline PET

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Prostate cancer is known for its difficulties in preoperative staging of pelvic lymph nodes by conventional imaging techniques. Thus, a histopathologic examination of the pelvic lymphadenectomy specimen is mandatory for patients at risk for metastatic disease. The aim of this study was to evaluate the strength and accuracy of ^{11}C-choline PET in preoperative noninvasive staging of pelvic lymph nodes in prostate cancer. **Methods:** In a prospective study we examined 67 consecutive patients with histologically proven prostate cancer with ^{11}C-choline PET. The results of PET were compared with the results of histology of the pelvic lymph nodes and with the follow-up data. Conventional axial imaging was routinely performed using MRI or CT. The sensitivity, specificity, and accuracy of ^{11}C-choline PET were calculated. **Results:** Fifteen patients had histologically proven lymph node metastases. ^{11}C-Choline PET was true-positive in 12 of 15 patients and false-negative in 3 patients. Fifty-two patients had no lymph node metastases. ^{11}C-Choline PET was true-negative in 50 of 52 patients and false-positive in 2 patients. We calculated a sensitivity of ^{11}C-choline PET for staging metastatic lymph node disease of 80%, a specificity of 96%, and an accuracy of 93%. Next, ^{11}C-choline PET detected solitary extraregional lymph node metastases in 5 of 12 patients with nodal metastases. **Conclusion:** This study showed that ^{11}C-choline PET is sensitive and accurate in preoperative staging of pelvic lymph nodes in prostate cancer.

Key Words: PET; ^{11}C-choline; prostate cancer; lymph node staging

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Lymph node metastases are found in up to 25% of the patients with prostate cancer depending on the tumor stage and grade (1,2). Lymph node involvement is correlated with progressive disease in most of the patients, and the 5-y disease-free survival rate subsequently decreases from 85% (nonmetastatic) to approximately 50% for pN1 disease (1). Determination of tumor involvement of regional lymph nodes is of key importance for the proper planning of treatment. Pelvic lymphadenectomy is the gold standard for lymph node staging in prostate cancer, but this invasive procedure is associated with morbidity (3).

Conventional imaging techniques such as CT and MRI have been shown to have a low sensitivity in determination of tumor involvement of pelvic lymph nodes, because nodal involvement is not always correlated with enlargement (4–6). Therefore, imaging techniques that are not dependent on anatomic distortions could be of use for lymph node staging. In this respect, PET has been studied widely using ^{18}F-FDG as the radiopharmaceutical. Preliminary data were encouraging (7); nevertheless, ^{18}F-FDG PET has not gained broad use in lymph node staging in prostate cancer so far (8). Also, the urinary radioactivity seen with ^{18}F-FDG has practical implications such as bladder irrigation for the proper use of this technique.

[11]C-Choline has recently been reported as a new radiopharmaceutical for PET imaging of prostate and bladder cancer, which lacks the urinary radioactivity seen with ^{18}F-FDG (9,10). Choline is one of the components of phosphatidylcholine, an essential element of phospholipids in the cell membrane (11). Malignant tumors show a high proliferation and increased metabolism of cell membrane components that will lead to an increased uptake of choline (12).

This study was designed to evaluate ^{11}C-choline PET in staging of pelvic lymph nodes in patients with prostate cancer and to determine its sensitivity, specificity, and accuracy.

MATERIALS AND METHODS

Patients

Patients with newly diagnosed and histologically proven adenocarcinoma of the prostate were eligible. Patients with a clinically T4 tumor or known distant metastases were excluded from this study. Patients were recruited prospectively and were informed about the purpose and hazards of the study, both orally and in writing, and gave their written informed consent. Approval from the Hospital Medical Ethics Committee was obtained. A total of 67 patients participated in this study.

Pretreatment Evaluation

The primary tumor was staged clinically according to palpable findings and transrectal ultrasound. The histopathologic diagnosis of prostate cancer was obtained by transrectal sextant biopsies. An MRI or CT scan of the pelvis was obtained to image lymph node

metastases preoperatively. Bone scintigraphy was performed to exclude bone metastases.

Radiopharmaceuticals

[11]C-Choline was produced using a robotic system by the method of Hara et al. (13). ^{11}C-Choline was produced with specific activities of >3,700 GBq/mmol and dissolved in 4 mL of saline. The solution was isotonic, colorless, and sterile with a radiochemical purity of >95%.

Imaging Protocol

To minimize postbiopsy effects, all imaging studies were performed at least 2 wk after transrectal biopsy. Before the PET study the subjects fasted overnight with the exception of water and their usual medication. The PET studies were performed using an ECAT 951/31 or an ECAT Exact HR+ PET camera (Siemens/CTI, Knoxville, TN). A transmission scan was obtained over 3 bed positions (10 min per position), covering the pelvis and the lower part of the abdomen, and immediately followed by intravenous injection of 400 MBq ^{11}C-choline. Data acquisition was started at 5 min after injection over the same area for 7 min per bed position.

Image Reconstruction and Data Analysis

Attenuation-corrected images were made using an iterative reconstruction algorithm (ordered-subset expectation maximization). PET images were analyzed by 2 independent experienced PET physicians, who were unaware of the clinical data. The location of each lesion was marked on case record forms and qualitatively scored as − (no uptake), + (low uptake, just above background), ++ (intermediate uptake, clearly above background), or +++ (high uptake).

Pelvic Lymphadenectomy and Histologic Examination

Histology was studied on the surgical specimens after pelvic lymphadenectomy. The specimens were processed according to standard methods. The primary histologic diagnosis was made on sections stained with hematoxylin and eosin and, if necessary, additional immunohistochemical staining to optimize the histologic diagnosis.

Pelvic lymphadenectomy was not routinely performed on those patients with grade 1 carcinoma (Gleason sum maximum, 6) and a serum prostate-specific antigen (PSA) of <15 ng/mL. According to clinical standards, these patients were classified as N0. The clinical follow-up of PSA at 1 y was used to identify any occult metastatic disease at the time of the study in all patients.

Statistical Analysis

The sensitivity, specificity, and accuracy were calculated according to the number of patients detected with or without lymph node metastases by ^{11}C-choline PET.

RESULTS

The characteristics of the patients, serum PSA, and clinical tumor stage and grade are summarized in Table 1. In 14 patients with grade 1 carcinoma and a serum PSA of <15 ng/mL, lymphadenectomy was not required and these patients were staged N0 according to international clinical standards. Ten patients were preoperatively staged by CT or MRI only because of their high age (age range, 74–83 y) in 8 cases, 1 patient (PSA, 28; Gleason sum, 6) refused surgery, and in 1 patient bone metastases as well as gross

TABLE 1
Preoperative Clinical and Pathologic Data for All Patients

Parameter	Value
Patients (n)	67
Age (y)	67.2 ± 6.9
Clinical stage	
T1c	17 (25.4)
T2	23 (34.3)
T3	27 (40.3)
PSA (ng/mL)	34 (3–500)
PSA range (ng/mL)	
<4	1 (1.5)
4.1–10	7 (10.4)
10.1–20	19 (28.4)
>20	40 (59.7)
Gleason sum score biopsy	
2–5	1 (1.5)
6	31 (46.2)
7	25 (37.3)
8–10	10 (15.0)

Data are presented as number of patients, with percentages in parentheses, except for age, for which data are mean ± SD, and for PSA, for which data are median and range.

lymph node metastases were detected preoperatively and lymphadenectomy was cancelled. Pelvic lymphadenectomy was performed on 43 patients. Fifteen patients had histologically proven lymph node metastases. ^{11}C-Choline PET was true-positive in 12 patients with uptake of ^{11}C-choline in pelvic lymph nodes with metastases with a mean standardized uptake value of 3.9 (range, 1.3–9.1) (Table 2). ^{11}C-Choline PET was false-negative in 3 patients: in 1 patient a micrometastasis was not visualized, in 1 patient bowel activity was interfering with evaluation of the pelvic area, and in the third patient the uptake of ^{11}C-choline was not increased in an obturator nodal metastasis of 2 cm. A total of 27 metastatic lymph nodes were identified after pelvic lymphadenectomy. ^{11}C-Choline PET identified 19 of 27 (70%) of these metastatic nodes. A solitary lymph node metastasis was found in the common iliac region with negative regional (obturator) lymph nodes in 5 of the 15 N+ patients. ^{11}C-Choline PET correctly identified all of these 5 extraregional lymph node metastases. Conventional imaging with either MRI or CT identified nodal metastases in 7 of the 15 patients but failed to detect any of the extraregional regional lymph node metastases.

In 52 patients without lymph node metastases, ^{11}C-choline PET was true-negative in 50 patients. The follow-up of serum PSA at 1 y did not show any false-negative case. In 2 patients without lymph node metastases, ^{11}C-choline PET was false-positive. First, in a patient with a cT3G2 pN0 M0 prostate carcinoma, PSA = 100 ng/mL, in which the pelvic lymphadenectomy specimen showed a lymph node with only inflammatory changes. The second false-positive ^{11}C-choline PET scan was seen in a patient with a cT1c pN0 M0 carcinoma, PSA = 15.8 ng/mL, in which case a recurrent

TABLE 2
Patient Details, Pelvic Lymph Node Dissection, and Uptake of ^{11}C-Choline in Lymph Node–Positive Patients

Patient no.	Age (y)	PSA (ng/mL)	Gleason sum score	Lymph node metastases	^{11}C-Choline Visual uptake	^{11}C-Choline SUV nodes	Treatment	Follow-up at 12 mo
1	67	37	6	Obturator right	+	3.2	HORM	PSA < 0.1
2	59	12.8	7	Obturator right (micrometastasis)	−	−	XBRT + HORM	PSA = 0.3
3	61	500	6	Bilateral obturator and iliac	+++	9.1	WW	PSA = 500
4	69	22	7	Bilateral obturator	+	2.9	XBRT + HORM	PSA < 0.1
5	69	148	8	Iliac left	+	2.0	HORM	PSA = 52, relapse
6	75	58	7	Iliac left	++	4.3	HORM	PSA = 0.1
7	66	47	7	Iliac left, obturator right	+++	4.7	HORM	PSA = 5.2
8	64	35	6	Iliac/obturator left	+	1.3	HORM	PSA = 0.1
9	59	47	9	Iliac/paraaortal	++	1.9	HORM	HRPC at 10 mo
10	78	39	7	Iliac left	++	1.3	HORM	PSA = 0.76
11	70	83	7	Iliac right	+++	4.3	HORM	PSA = 15.3
12	66	108	9	Left obturator	−	−	HORM	PSA = 0.49
13	65	283	8	Bilateral iliac/aorta	++	4.6	HORM	PSA = 161, relapse
14	56	376	6	Iliac left	+++	6.7	HORM	NA
15	63	63	9	Obturator right	−	−	HORM	NA

SUV = standardized uptake value; HORM = androgen-deprivation therapy; XBRT = external-beam radiation therapy; WW = watchful waiting; HRPC = hormone-refractory prostate cancer; NA = not available.

inguinal hernia with adherent small bowel was found at pelvic lymphadenectomy. Focal bowel activity mimicked nodal metastases in this patient. MRI was true-negative in this patient. The calculated sensitivity, specificity, and accuracy of ^{11}C-choline PET and of conventional imaging techniques are shown in Table 3.

DISCUSSION

Detection of pelvic lymph node metastases in prostate cancer by conventional imaging methods is rather restricted. Axial imaging using CT lacks sensitivity to detect nodal metastases; a sensitivity of 25%–70% is reported in the literature (4,5,14). Neither MRI nor lymphangiography has demonstrated higher sensitivity than CT scanning for the detection of nodal metastases (15,16). Recent improvements with contrast-enhanced MRI and rapid imaging sequences

(6), as well as with CT using lower cutoff values for pathologic lymph nodes combined with fine-needle aspiration (17,18), have led to an increased sensitivity of 75%–78%. Still, for accurate nodal staging, a histopathologic examination of pelvic lymph nodes dissected by pelvic lymphadenectomy is needed. This invasive procedure, performed by either laparoscopy or by open surgery, has a morbidity of 5%–7% (3,19). Therefore, an accurate noninvasive method for pelvic lymph node staging in prostate cancer would be welcomed.

In this study we investigated the accuracy of ^{11}C-choline PET as a noninvasive method for staging of pelvic lymph nodes in prostate cancer. Choline, after phosphorylation to phosphatidylcholine, is an essential component of the cell membrane (11). Cancer is associated with cell proliferation and upregulation of the enzyme choline kinase (which catalyzes the phosphorylation of choline), providing the rationale for the use of choline as a radiopharmaceutical in oncologic PET (12). High contents of phosphorylcholine have already been demonstrated in, for instance, breast cancer and in cerebral gliomas using ^{31}P magnetic resonance spectroscopy imaging (20,21). In prostate cancer, alterations in choline/citrate ratios were also seen using magnetic resonance spectroscopy (22). The intracellular mechanisms by which choline acts are not completely clear yet, but a function in the cell's signal transduction and in apoptosis has been shown (23). So far, ^{11}C-choline PET has been shown to visualize prostate cancer, both primary tumor and metastatic sites, with good contrast (9,10) but no data are available on the sensitivity, specificity, and accuracy in preoperative staging of pelvic lymph nodes.

TABLE 3
Sensitivity, Specificity, and Accuracy of ^{11}C-Choline PET and Conventional Imaging for Lymph Node Staging

	PET* Positive	PET* Negative	PET* Total	MRI or CT† Positive	MRI or CT† Negative	MRI or CT† Total
N0	2	50	52	1	47	48
N+	12	3	15	7	8	15
Total	14	53		8	55	

*Sensitivity = 80%, specificity = 96%, and accuracy = 93%.
†Sensitivity = 47%, specificity = 98%, and accuracy = 86%.
Data are presented as number of patients.

In our series of 67 consecutive patients with prostate cancer, 15 patients had histologically proven lymph node metastases. ^{11}C-Choline PET detected nodal metastases in 12 patients and false-negative ^{11}C-choline PET scans were found in 3 patients. In 1 patient a micrometastasis of 3 mm was not visualized. The failure to detect a micrometastasis could be due to the limitations of the resolution of the present generation of PET cameras, which is around 5 mm. Future generations of PET cameras will have intrinsic resolutions of approximately 2 mm. However, next to the intrinsic resolution of the system, the signal-to-noise ratio (contrast) is also of importance in PET imaging. A low contrast will decrease the visualization, whereas high contrast can lead to an increase of visualization, which may extend beyond the intrinsic resolution. It is still expected that the imaging of microscopic disease with PET, as with any in vivo imaging device, will remain cumbersome. In the second patient, the uptake of ^{11}C-choline in an obturator nodal metastasis of 2 cm was not above the background activity of the pelvic region. In the third patient with a false-negative ^{11}C-choline PET scan, the activity in the small bowel interfered with evaluation of the pelvic area and masked a 2-cm lymph node metastasis with extranodal extension located on the right external iliac vein. Activity in the small bowel was first reported by Hara et al. (9) and was explained by excretion of pancreatic juice in the nonfasting state, not seen in patients studied in a complete fasting state. Bowel activity was also reported by Kotzerke et al. (10) in patients with prostate cancer. In our experience with ^{11}C-choline PET in the prostate, bladder, lung, and cervical and esophageal cancer, varying bowel activity is a general phenomenon. The uptake of ^{11}C-choline in the bowel is probably due to the high proliferation rate of the intestinal mucosa.

In 52 patients without lymph node metastases 2 false-positive ^{11}C-choline PET scans were seen. In 1 patient the uptake of ^{11}C-choline was increased in a lymph node with inflammatory changes. In the absence of proliferation, uptake of choline in reactive tissue could be explained by simple diffusion, one of the transport mechanisms, next to an energy-dependent choline-specific transport channel, known so far in all mammalian cells (23,24). Because we did not find any inflammatory changes in lymph nodes in other lymphadenectomy specimens, it is not clear whether uptake of ^{11}C-choline is increased in reactive tissue as well as in cancer. In the second patient with a false-positive ^{11}C-choline PET scan, focal bowel activity in a recurrent inguinal hernia mimicked a nodal metastasis. Although the visual analysis in 3 planes on a computer display will discriminate bowel activity from tumor activity in general, it can be difficult in individual cases to identify lymph nodes from adjacent bowel.

In this study on lymph node staging in prostate cancer, ^{11}C-choline PET showed a sensitivity of 80%, a specificity of 96%, and an accuracy of 93%. So far, there are only limited data available on staging of prostate cancer with PET. Heicappell et al. (25) reported on preoperative staging of prostate and bladder cancer using ^{18}F-FDG PET. They presented 6 patients with lymph node metastases, of which ^{18}F-FDG PET detected 4. To our knowledge, there have been no other reports on the value of ^{18}F-FDG PET in primary nodal staging of prostate cancer. In general, ^{18}F-FDG has not met the expectations in its use in both metastatic and newly progressive prostate cancer (8,26,27). We believe that additional studies on nodal staging of prostate cancer with ^{18}F-FDG PET will not change these results.

In a recent study by Oyama et al. (28), ^{11}C-acetate was proposed as a new radiopharmaceutical for the imaging of prostate cancer with PET. In their first series of 22 patients, 5 patients had lymph node metastases that were identified by ^{11}C-acetate PET in all 5 patients. More data will be needed to confirm the accuracy of ^{11}C-acetate PET in primary lymph node staging.

This study was not designed to compare ^{11}C-choline PET with conventional imaging, but the sensitivity of 47% and the specificity of 98% of conventional axial imaging in this series corroborate the data from the literature (4,5). Oyen et al. (17) improved lymph node staging by CT using fine-needle aspiration biopsy of lymph nodes of >6 mm on 1-mm sliced tomograms. They reported a sensitivity of 78%, a specificity of 100%, and an accuracy of 96%, a result quite equivalent to our data. Our results are similar when compared with 3-dimensional T1-weighted magnetization-prepared rapid gradient-echo sequence MRI, with a sensitivity of 75%, a specificity of 98%, and an accuracy of 90% as reported by Jager et al. (6).

In another attempt to overcome the limitations of the conventional imaging techniques, radioimmunoscintigraphy has also been studied. is a monoclonal antibody directed against prostate-specific membrane antigen, a glycoprotein that is expressed by the prostate epithelium and is upregulated in (metastatic) prostate cancer. ^{111}In-Capromab pendetide was used for noninvasive lymph node staging in a prospective study in 198 patients with a high risk for metastases on the basis of serum PSA, Gleason sum score, and clinical stage. A sensitivity of 61% and a specificity of 67% were reported by Polascik et al. (29). In a recent review on ^{111}In-capromab pendetide in >640 patients, a sensitivity and specificity of 62% and 72%, respectively, were reported by Rosenthal et al. (30).

Our data on ^{11}C-choline PET showed the existence of solitary lymph node metastases outside the field of the modified lymphadenectomy. ^{111}In-Capromab pendetide scintigraphy showed the same phenomenon in a large series of patients, and recently the results on radioimmunoguided lymphadenectomy revealed solitary nodal metastases outside the obturator region (31). This precludes that pelvic lymphadenectomy is not completely reliable unless it has been extended to the parailiac and paraaortal lymph nodes as has been proposed by some authors (32).

Finally, the use of nomograms to predict the risk for lymph node metastases is generally accepted in clinical

practice (*33–35*). This has already resulted in a reduction of pelvic lymphadenectomies in low-risk patients. On the basis of these nomograms, the patients at risk for metastases can be depicted. In general, these patients have high PSA values, a high Gleason pattern, or clinically advanced tumors and are not candidates for local therapy. This means that for these patients a pelvic lymphadenectomy will be an independent procedure. For this group of patients, an accurate noninvasive imaging technique would be welcome. This could not only reduce morbidity and lead to faster planning of treatment but could also be very cost-effective. ^{11}C-Choline PET is a good candidate for noninvasive lymph node staging and could be a substitute for pelvic lymphadenectomy in the near future in this group of patients.

CONCLUSION

This study showed that ^{11}C-choline PET is sensitive and accurate in preoperative staging of pelvic lymph nodes in prostate cancer.

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