Original
Nuclear Medicine Review 2015, 18, 2: 56–60
DOI: 10.5603/NMR.2015.0015

ISSN 1506–9680

VIA MEDICA

The nonspecific lymph node uptake of ^{18}F-choline in patients with prostate cancer — a prospective observational study

Anja Tea Golubić[1], Andrea Mutvar[1], Marijan Žuvić[1], Dražen Huić[1, 2]
[1]Department of Nuclear Medicine and Radiation Protection, University Hospital Center Zagreb, Zagreb, Croatia
[2]School of Medicine, Zagreb, Croatia

[Received 26 I 2015; Accepted 7 V 2015]

Abstract

BACKGROUND: The aim of this study was to observe and characterize the nonspecific ^{18}F-choline lymph node uptake in patients with prostate cancer.
MATERIAL AND METHODS: In this single center, prospective observational study which was done in University Hospital Center Zagreb between December 2012 and October 2014, 69 patients (median age 71 years; range 50–92) with prostate cancer were included. Patients underwent ^{18}F-choline PET/CT for staging or restaging of prostate cancer. The mean follow-up period was 11.5 months. Kruskal-Wallis test was used to find out if the differences between SUV values of specific and nonspecific accumulation of the tracer are statistically significant.
RESULTS: Nonspecific accumulation of ^{18}F-choline in lymph nodes was found in 36 patients (52.7%). Most of these findings (n = 24) were nonspecific accumulation of the tracer in mediastinal lymph nodes. Other sites of nonspecific tracer uptake were pulmonary hila (n = 20), inguinal lymph nodes (n = 15), and axillary lymph nodes (n = 10). Mean SUV values for mediastinal lymph nodes, pulmonary hila, axillary and inguinal lymph nodes were 4.8, 4.3, 3.1 and 4.1, respectively. Mean SUV value of nonspecific sites of tracer accumulation was lower (not significantly; (p = 0.2) than tracer uptake values measured in metastases sites (bone metastases mean SUVmax value — 13.2, metastatic lymph nodes mean SUVmax value — 9.2).
CONCLUSIONS: ^{18}F-choline PET/CT is a valuable and an established functional diagnostic imaging method for staging and restaging prostate cancer. However, nonspecific uptake of the tracer can often be seen in lymph nodes not related to primary disease. Patient history, clinical examination, laboratory tests and correlation with other imaging methods, must be taken into consideration when interpreting ^{18}F-choline PET/CT findings.

KEY words: ^{18}F-choline, prostate cancer, false positive uptake, pitfalls

Nuclear Med Rev 2015; 18, 2: 56–60

Background

Prostate cancer is the most common malignancy in men in Europe and the US [1, 2]. Diagnostic procedure from clinical suspicion to diagnosis includes determination of PSA serum value, transrectal ultrasound (TRUS) with or without biopsy, magnetic resonance imaging (MRI), computerized tomography (CT) and bone scintigraphy in patients with highly elevated PSA values [3–5].

Correspondence to: Anja Tea Golubić, MD
Department of Nuclear Medicine and Radiation Protection
University Hospital Center Zagreb
Kišpatićeva 12, 10000 Zagreb, Croatia
Tel: +385 1 2388 587
Fax +385 1 2376 040
E-mail: anja.tea.golubic@gmail.com

Defining the Gleason score, evaluating local disease extent, locoregional lymph node involvement and presence of distant metastases is crucial in patient management and deciding on correct follow-up modality. Increasing demands for correct disease characterization and extent, as well as variable biological behavior of prostate cancer, have led to the extensive use of functional imaging, positron emission tomography coupled with computed tomography (PET/CT). PET/CT imaging is most often used as a restaging modality, especially after completed primary radiotherapy or radical prostatectomy followed by an increase of PSA levels [6, 7]. Because of prostate cancer low avidity for the currently most used radiopharmaceutical, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), as well as its urinary tract elimination and accumulation in the urinary bladder, other radiopharmaceuticals have been developed. In use today are ^{18}F and ^{11}C-labeled choline and ^{11}C-acetate. In growing tumor

tissue, increased lipid synthesis is found, as well as the increased activity of choline kinase enzyme activity which increases choline uptake. On the cell level imported choline becomes part of the cell membrane, as phosphatidylcholine [8]. Physiological tracer uptake is found in the liver and pancreas, spleen, salivary and lachrymal glands. Variable uptake can be present in the bone marrow, the small and large intestines kidneys, urinary bladder and ureters [9]. ^{18}F-choline has been recognized as a valuable imaging method for prostate cancer evaluation, notably after primary treatment has been done [10–12]. As with each diagnostic tool, apart from all the benefits and relevant data it provides, some drawbacks have been noticed. Nonspecific uptake of ^{18}F-choline is seen in lymph nodes, whether a low-grade lymphoma or, more often, inflammatory altered inguinal, axillary or mediastinal lymph nodes, as has been reported by some scientific groups [9, 13].

The purpose of this study was to observe and characterize nonspecific lymph node uptake of ^{18}F-choline in order to expand the awareness of broader physiological ^{18}F-choline uptake.

Material and methods

Design and setting

This prospective observational study was done in University Hospital Center Zagreb from December 2012 till October 2014.

Participants

Sixty nine patients underwent ^{18}F-choline PET/CT for staging or restaging of their disease. The patients have been referred from their oncologists mostly because of increased PSA values observed after primary therapy.

Their median age was 71 years, range 50–92 years. The median PSA value was 5.3 ng/ml (doubling time less than 6 months in 9 patients). PSA values exceeding 0.2 ng/ml for patients with radical prostatectomy and 2 ng/ml higher than the lowest known PSA value for patients with only radiotherapy treatment were considered as biochemical relapse. PSA values that doubled in less than 6 months previous to PET/CT scan and the increase of 1 ng/ml of prostate specific antigen over the past year were also considered as clinically relevant. In 38 patients radical prostatectomy was performed, 18 of which had received hormonal therapy. Twenty three patients underwent radiotherapy, and in 12 it had followed radical prostatectomy. Thirty four patients have received hormonal therapy, while 13 patients received no therapy before ^{18}F-choline PET/CT examination (Table 1).

^{18}F-choline PET/CT examination

All patients fasted 6 hours before the examination. Mean administered activity was 183 MBq (4.9 mCi) of ^{18}F-choline (2 MBq/kg, IASOcholine was purchased from IASON GmbH A-8054 Graz-Seiersberg, Austria). The whole-body PET/CT was acquired 20 minutes after the intravenous F-choline administration (Siemens Biograph mCT, Siemens Medical Solutions USA, Inc., USA PET/CT; 3 minutes per bed position).

The follow-up was at least 6 months, median 11, range 6–22 months.

Table 1. Prostate cancer patient population therapy modalities before ^{18}F-choline PET/CT exam

Procedures performed	Patients (n = 69)
Radical prostatectomy (RP)	38 (55.1%)
Radiotherapy (RT) with or without RP	23 (33.3%)
Hormonotherapy with or without RP and RT	34 (49.3%)
Orchidectomy	10 (14.5%)

Interpretation of ^{18}F-FDG PET/CT scans

All PET/CT scans were interpreted by two board-certified nuclear medicine physicians (DH, AM). An increased uptake was defined as focal activity higher than that of surrounding background tissue not located in areas of physiological ^{18}F-choline uptake, without similar activity seen on the contralateral side. SUV value was calculated for each lesion. A normal uptake was defined as no abnormal ^{18}F-choline uptake.

As true positive were considered patients with clearly visible increased uptake in the lymph nodes or bone structures in the regions where prostatic cancer metastases can be often found (pelvis, central skeleton). Those patients received further treatment (most often radiotherapy or hormonal therapy) suggested by their referring physicians.

Reference standard

In patients with increased tracer uptake in easily reachable lymph nodes a fine needle aspiration cytology (FNAC) or biopsy was performed. A true negative finding was noted if the FNAC or biopsy analysis reported a benign lesion or the follow-up period was at least 6 months without any disease progression observed.

Ethics

Signed informed consent was obtained from all patients for imaging and using patient data for further research.

Statistical analyses

Kruskal-Wallis test was used to determine differences between SUV values of specific and nonspecific accumulation of the tracer.

Results

Specific accumulation of the tracer

True positive focal uptake in prostate bed (local recurrence) was found in 6 (9%) patients, with a mean SUVmax value of 10.2. Bone metastases were found in 15 patients (21.7%; SUVmax mean value 13.2, range 4.7–21.3). True positive findings in the abdominal, retroperitoneal (Figure 1) and iliac lymph nodes were noted in 27 patients (39.1%, SUVmax mean value 9.2, range 3.9–16.1) (Table 2). Pulmonary metastases have been observed in two patients with the SUVmax values of 6.8 and 2.3. All of our patients with positive findings and tracer uptake in abdominal lymph nodes, bone and lung metastases were scheduled for subsequent treatment, mostly radiotherapy.

Nonspecific accumulation of the tracer

Nonspecific tracer uptake to the lymph nodes was observed in 36 patients (52.7%). Most of the false-positive lymph nodes were identified in the mediastinum (24 patients; mean SUVmax value of 4.8) (Figure 2), and pulmonary hila (20 patients, mean SUVmax

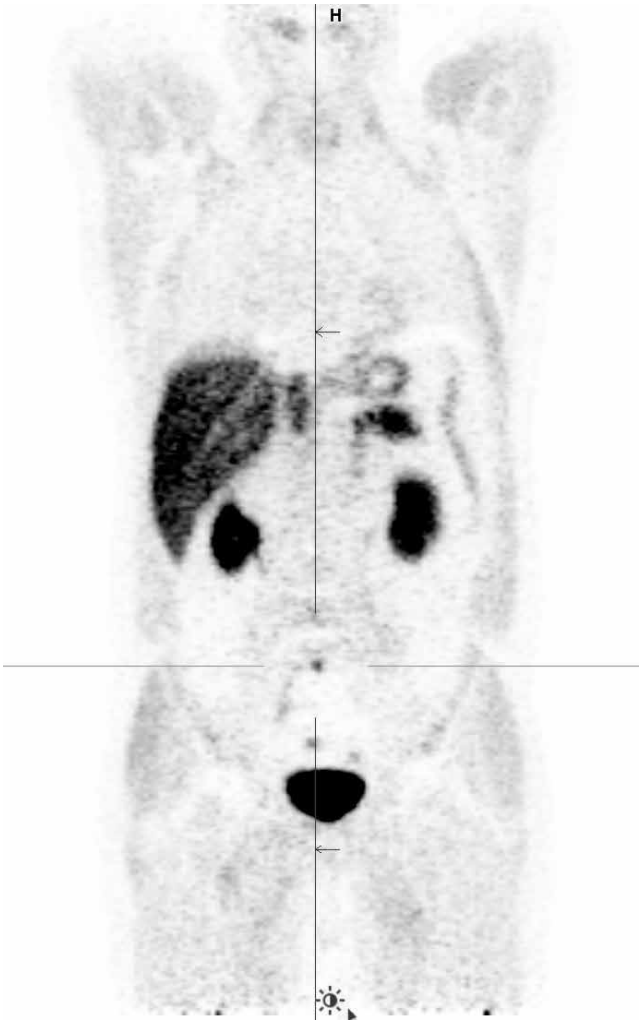

Figure 1. Retroperitoneal lymph node metastasis in the pelvis in patients with prostate cancer. SUVmax value 10.2, PSA value 0.5 ng/ml, radical prostatectomy performed in December 2013, imaged in April 2014. Radiotherapy and hormonal therapy followed PET/CT examination; SUV — standardized uptake value, PSA — prostate-specific antigen

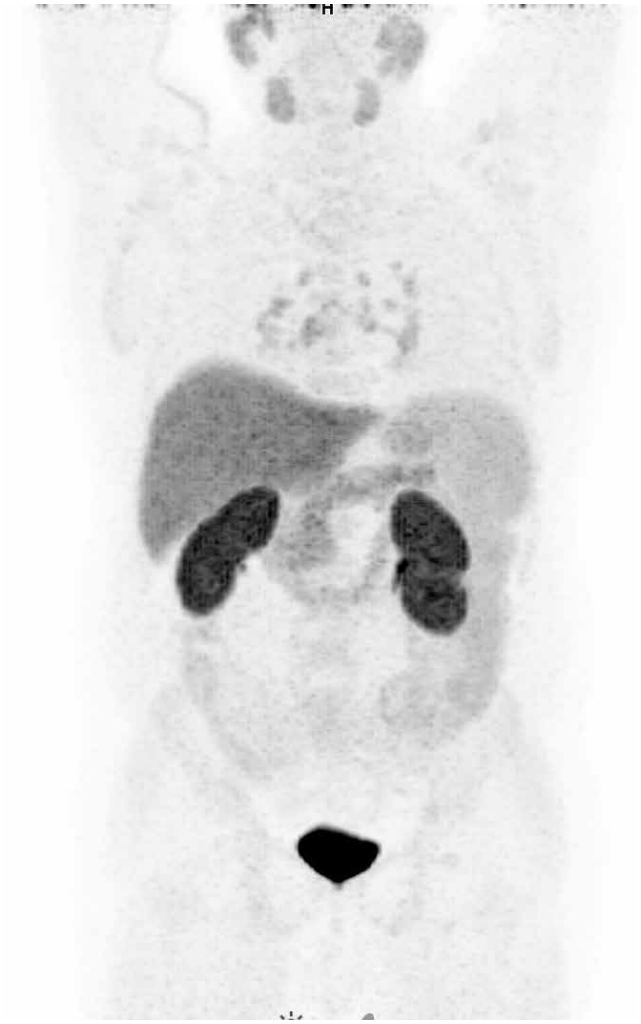

Figure 2. Nonspecific ^{18}F-choline uptake in mediastinal lymph nodes in patients with prostate cancer, SUVmax 8.8, PSA value 2.3 ng/ml. Patient had radical prostatectomy in November 2010, and was imaged in our facility in February 2014; SUV — standardized uptake value, PSA — prostate-specific antigen

Table 2. ^{18}F-choline true positive focal lesions

Location	Patients (n = 35)	Mean SUVmax value
Prostate bed (local recurrence)	6 (8.7%)	10.2
Bone metastases	15 (21.8)	13.2
Abdominal lymph node metastases	27 (39.1%)	9.2

SUV — standardized uptake value

values of 4.3). The uptake in axillary lymph nodes was found in 10 patients with a mean SUVmax value of 3 and in inguinal lymph nodes in 15 patients (Figure 3), with mean SUVmax value of 4.1 (Table 3).

Median PSA value in patients with nonspecific tracer uptake was 5.8, while it was found to be 8.8 in patients with ^{18}F-choline true positive lesion (not statistically significant, p = 0.2).

Additional ultrasound examination with fine needle aspiration cytology of available lymph nodes was performed in 5 patients; 4 were found to have nonspecific inguinal lymph nodes enlargement where cytological analysis showed only fatty tissue or cystic contents, while in one a relapse of CLL lymphoma was observed.

Mean SUV value of the sites of nonspecific accumulation of the tracer (mean 4.1) was not statistically significantly lower (p = 0.2) than tracer uptake values measured in metastases sites (mean 11.2).

Discussion

Results of this study showed that in over half of our patient population, nonspecific sites of tracer uptake have been observed in lymph nodes out of the pelvis, not suggestive for prostate cancer metastases. The obtained SUV values in those uptake sites were lower than in metastatic sites, but not enough to be statistically significant. In most cases, we have observed accumulation of ^{18}F-choline in the mediastinal lymph nodes (35% of patients). The main limitation of our study is that pathohistological confirmation has not been performed, but during patient follow-up there have been no evidence of disease progression, rise in PSA levels or patient deaths due to prostate cancer. Additional ultrasound exami-

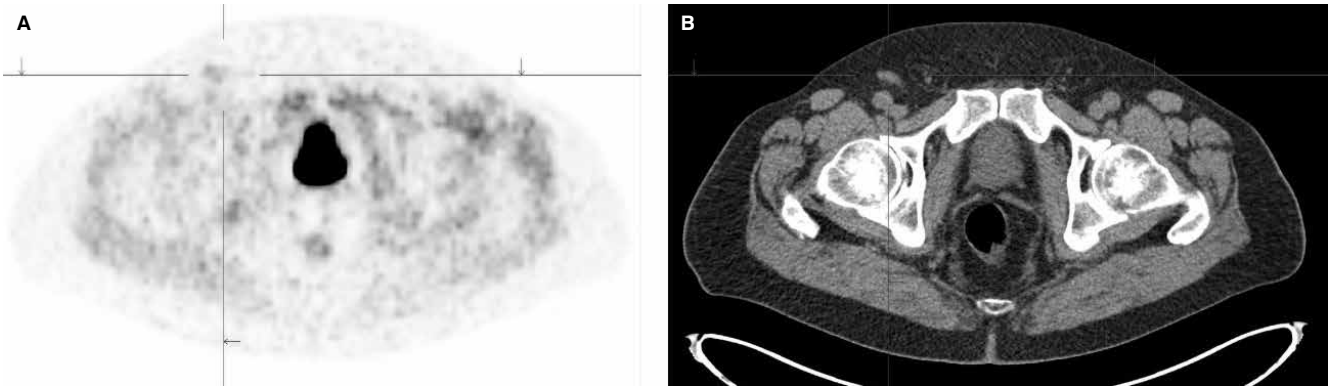

Figure 3. Nonspecific tracer uptake in enlarged right inguinal lymph node in patients with prostate cancer, SUVmax 2.1, PSA 0.5 ng/ml. Radical prostatectomy was performed in June 2008 and patient was imaged in January 2013

Table 3. Nonspecific ^{18}F-choline uptake

Location	Patients (n = 36)	Mean SUVmax value
Mediastinal lymph node uptake	24 (34.7%)	4.8
Hilar lymph node uptake	20 (28.9%)	4.5
Axillary lymph node uptake	10 (14.5%)	3
Inguinal lymph node uptake	15 (21.7%)	4.1

SUV — standardized uptake value

nation with fine needle aspiration cytology of axillary and inguinal lymph nodes with low tracer uptake has shown fatty infiltration in four patients and a relapse of low grade lymphoma in one patient. No similar false positive, nonspecific radiotracer uptake was found in abdominal or pelvic lymph nodes, making the interpretation easier. In the minimal 6 month follow-up (median of 11.5 months), no clinically apparent sign of disease progression was found, pertaining to patients with nonspecific lymph node uptake. Other limitations of this study were relatively small sample size and clustering patients with variable disease stages and treatment options. Also, in patients with very suggestive findings for prostate cancer metastases (local recurrence in pelvis, central skeleton) we didn't obtained final pathology confirmation since referring physicians ordered a further therapy without any delay.

Variability in physiological distribution, pitfalls and image artifacts of F-18-FDG has been the topic of numerous articles [14, 15], and the same considerations should be made when imaging with ^{18}F-choline.

Up to date only one study (Rietbergen et al [13]) reported similar percentage of patients with nonspecific choline uptake, not pertaining to prostate cancer disease extent. Liu et al [16] have shown increased choline uptake in various thoracic diseases, such as sarcoidosis, noncaseating granuloma, tuberculosis and lymphomas.

^{18}F-choline accumulation is found to be specific in true positive lesions with a prevailing morphological and statistical correlate. Nonspecific tracer uptake will follow an increased cell membrane production not connected to prostate cancer, but rather due to acute or chronic inflammatory process or low grade immunoproliferative diseases.

^{18}F-choline PET/CT is considered a particularly useful diagnostic tool in several stages of patient care, with the added information gained from revealing multiple pathophysiological processes. It has found its role especially in restaging prostate cancer patients, with the recommended use in patients with PSA levels > 1 ng/ml following radical disease treatment [6]. Increasing demands of imaging modalities have been observed in recent years because of aging population, screening methods and growing incidence of prostate cancer.

The need for unequivocal disease extent estimation has introduced functional imaging methods, such as ^{18}F-choline PET/CT, in regular clinical practice [17], and the future of prostate cancer imaging will lie in the more specific radiotracers, such as the PSMA tracer [18–20].

Conclusions

Although ^{18}F-choline PET/CT has demonstrated valuable information in staging and restaging of prostate cancer, moderate tracer accumulation in lymph nodes out of the pelvis should be carefully evaluated since in many cases it is false positive. Variability in physiological uptake, as well as benign causes of accumulation, such as inflammation, should be kept in mind when interpreting unusual sites of increased uptake, with no association with the primary disease. Recognizing the importance of patient follow-up is crucial.

References

1. ESMO Guidelines Task Force: ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of prostate cancer. Ann Oncol 2005; 16 (suppl. 1): i34–i36.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374–1403. doi: 10.1016/j.ejca.2012.12.027.
3. Clements R. Ultrasound of prostate cancer. Eur Radiol 2001; 11: 2119–2125.
4. Tamsel S, Killi R, Altay B, Soyden S, Demirpolat G. Transrectal ultrasound in selecting prostate cancer compared with serum total prostate specific antigen levels. J Med Imag Rad Oncol 2008; 52: 24–28.
5. Akin O, Sala E, Moskowitz CS et al. Transition zone prostate cancers: features,detection, localization, and staging at endorectal MR imaging. Radiology 2006; 239: 784–792.
6. Picchio M, Briganti A, Fanti S et al. The role of choline positron emission tomography/computed tomography in management of patients with

prostate-specific antigen progression after radical treatment of prostate cancer. Eur Urol 2011; 59: 51–60.
7. Castellucci P, Picchio M. 11-C Choline PET/CT and PSA kinetics. Eur J Nucl Med Mol Imaging 2013; 40 (suppl. 1): S36–S40.
8. Yoshimoto M, Waki A, Obata A et al. Radiolabeled choline as a proliferation marker: comparison with radiolabeled acetate. Nucl Med Biol 2004; 31: 859–865.
9. Schillaci O, Calabria F, Tavolozza M et al. 18F-choline PET/CT physiological distribution and pitfalls in image interpretation: experience in 80 patients with prostate cancer. Nucl Med Commun 2010; 31: 39–45.
10. Di Muzio N, Fodor A, Berardi G et al. Lymph nodal metastases: diagnosis and treatment. Q J Nucl Med Mol Imaging 2012; 56: 421–429.
11. Picchio M, Crivellaro C, Giovacchini G, Gianolli L, Messa C. PET-CT for treatment planning in prostate cancer. Q J Nucl Med Mol Imaging 2009; 53: 245–268.
12. Langsteger W, Heinisch M, Fogelman I. The role of fluorodeoxyglucose, 18F-dihydroxyphenylalanine, 18F-choline, and 18F-fluoride in bone imaging with emphasis on prostate and breast. Semin Nucl Med 2006; 36: 73–92.
13. Rietbergen DD, van der Hiel B, Vogel W, Stokkel MP. Mediastinal lymph node uptake in patients with prostate carcinoma on F18-choline PET/CT. Nucl Med Commun 2011; 32: 1143–1147.
14. Kostakoglu L, Hardoff R, Mirtcheva R, Goldsmith SJ. PET-CT fusion imaging in differentiating physiologic from pathologic FDG uptake. Radiographics 2004; 24: 1411–1431.
15. Sureshbabu W, Mawlawi O. PET/CT imaging artefacts. J Nucl Med Technol 2005; 33: 156–161.
16. Liu Q, Peng ZM, Liu QW et al. The role of 11C-choline positron emission tomography-computed tomography and videomediastinoscopy in the evaluation of diseases of middle mediastinum. Chin Med J 2006; 119: 634–639.
17. Fuccio C, Rubello D, Castellucci P, Marzola MC, Fanti S. Choline PET/CT for prostate cancer: Main clinical applications. Eur J Radiol 2011; 80: e50–e56. doi: 10.1016/j.ejrad.2010.07.023.
18. Osborne JR, Akhtar NH, Vallabhajosula S et al. Prostate-specific membrane antigen-based imaging. Urol Oncol 2013; 31: 144–154. doi: 10.1016/j.urolonc.2012.04.016.
19. Mease RC, Foss CA, Pomper MG. PET imaging in prostate cancer: focus on prostate-specific membrane antigen. Curr Top Med Chem 2013; 13: 951–962.
20. Yu CY, Desai B, Ji L, Groshen S, Jadvar H. Comparative performance of PET tracers in biochemical recurrence of prostate cancer: a critical analysis of literature. Am J Nucl Med Mol Imaging 2014; 4: 580–601.