Journal of Nuclear Medicine, published on June 8, 2017 as doi:10.2967/jnumed.117.190215

Detection of Synchronous Primary Malignancies with ^{68}Ga-PSMA PET/CT in Patients with Prostate Cancer: Frequency in 764 Patients

Medhat M. Osman[1], Amir Iravani[2], Rodney J. Hicks[2,3], Michael S. Hofman[2,3]

1. Division of Nuclear Medicine, Department of Radiology, St. Louis University Hospital, St. Louis, Missouri, USA.

2. Centre for Molecular Imaging, Department of Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia.

3. Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia.

Corresponding Author:

Medhat M. Osman, MD

Division of Nuclear Medicine & PET/CT

3635 Vista Avenue

Saint Louis, Missouri 63110

314-577-8047

mosman@slu.edu

Key Words: Synchronous primary malignancy, prostate cancer, ^{68}Ga-PSMA, PET/CT

Short Running Title: Synchronous Malignancy with ^{68}Ga-PSMAPET/CT

ABSTRACT

We evaluated the incidence of synchronous primary malignancies in patients being evaluated by ^{68}Ga-PSMA PET/CT for prostate cancer (PC).

Methods: Reports for 764 PC patients were reviewed. Incidental lesions atypical for PC metastases and suggestive of a synchronous primary malignancy were identified. Follow-up was obtained to confirm etiology.

Results: Lesions atypical for PC metastases were found in 49 of 764 (6.4%) patients with a confirmed synchronous primary in 5 (0.7%) patients (2 lung, 1 lymphoma, thyroid, and base of tongue). In 8 (1.0%) patients, lesions were proven to be atypical metastases from PC. In 24 (3.1%) patients, lesions were due to a benign etiology. Follow-up was not available in 12 (1.6%) patients.

Conclusion: Synchronous PSMA–avid malignancies were rare (0.7%) in PC patients with atypical lesions being more commonly unusual PC metastases (1%) or benign (3.1%).

INTRODUCTION

In the United States, prostate cancer (PC) is the most common cancer and second most frequent cause of cancer-related death in men *(1)*. Early diagnosis, accurate staging and tumor characterization are critical for appropriate selection of patient-tailored therapy. CT, MRI, and bone scanning, although widely utilized in the diagnosis, staging and restaging of patients with PC, have suboptimal accuracy. These limitations have recently been addressed by the introduction of ^{68}Ga–Prostate Specific Membrane Antigen (PSMA) PET/CT. Several studies revealed higher diagnostic accuracy of ^{68}Ga-PSMA PET/CT compared to conventional imaging, including PET with other tracers *(2-4)*. However, clinical experience with reading ^{68}Ga-PSMA PET/CT is limited pending FDA approval and CMS payment. Despite its promise, it has been reported that ^{68}Ga-PSMA uptake and avidity is not completely specific to PC with recent case reports of uptake in benign as well as non-PC malignancies *(5-13)*. The objective of our study was to determine the incidence of synchronous PSMA-avid malignancies in a large group of patients being evaluated for known PC.

MATERIALS AND METHODS

Patient Population

A total of 764 patients (mean age 68 y, range 48-85) who have undergone PSMA-PET/CT from 2013 to 2016 for known PC (73 staging and 691 restaging) were included. This single center retrospective study was approved by the Institutional Human Research Ethics Committee with waiver of informed consent of patients, who had been scanned for clinical indications.

^{68}Ga-PSMA PET/CT Image Acquisition and Protocol

^{68}Ga was eluted from a ^{68}Ga/^{68}Ge generator (Isotope Technology Group, Garching, Germany) and compounded with HBED-PSMA11 (Advanced Biochemical Compounds, Radeberg, Germany). PET images were acquired approximately 60 minutes (range 40-85) following injection of 2 MBq/kg of ^{68}Ga-HBED-PSMA11 (166MBq, range 91-246). Acquisition was performed on a GE Discovery PET/CT 690 or 710 (GE Healthcare, Milwaukee, WI), or Siemens Biograph 64 PET/CT (Siemens Healthcare, Erlangen, Germany). The CT was performed with either a low-dose non-contrast technique (old protocol) or 10 minutes (range 8-15) following intravenous injection of 50 mls of Omnipaque 300g/ml contrast medium (GE Healthcare, Princeton, NJ) for optimal ureteric enhancement (new protocol as of mid-2015).

Data Analysis

All reports from clinical PSMA-PET/CT were reviewed. Lesions with or without PSMA uptake that had not been previously detected by other modalities, and were considered atypical in location for PC metastases on the PET/CT and interpreted by the reporting PET specialist as being suggestive of a synchronous primary were selected for further evaluation. Histopathologic, imaging and clinical follow-up was obtained to confirm the etiology of these findings.

RESULTS

Possible synchronous malignant tumors were reported in 49 (6.4%) of 764 PC patients (Table 1). In 42 (85.7%) of these 49 patients, the lesions were PSMA-avid, whilst the remaining 7 (14,3%) were detected only on the contemporaneous CT component of the study.

In 8 (1.0%) of 764 patients, these PSMA-avid lesions were histologically proven to be metastases from PC (Fig. 1); lung (4 cases) and lymph nodes (4 cases). However, in 5 (0.7%) these PSMA-avid lesions were pathologically proven to be a synchronous primary (Figs. 2 and 3). Proven sites were lung (2 cases), thyroid (1 case), base of the tongue (1 case) and lymphoma (1 case).

In 22 patients (5 lung, 4 thyroid, 3 liver, 3 lymph node, 2 spleen, 1 brain, 1 pancreas, 1 bone, 1 soft tissue, 1 skin), there was no progression on follow-up imaging (Figs. 4A, B and C) or clinical examination suggesting benign diagnoses. One patient had normal endoscopic evaluation for a suspected laryngeal lesion which likely represented physiologic salivary pooling. One thyroid lesion was biopsy-proven benign hyperplastic nodule (Figs. 4D and E). All biopsy proven cases are listed in Table 2. In 12 (1.6%) of 764 patients, the follow-up record was not yet available or the final diagnosis of the detected lesion has not yet been clarified.

For the 7 patients with PSMA-negative lesions identified on contemporaneous CT, 5 were in lung and 2 in thyroid. PC metastases or additional non-PC malignancy were not confirmed for any of these lesions.

DISCUSSION

PSMA is a transmembrane glycoprotein expressed in normal prostate epithelium but over-expressed in virtually all-prostate cancers *(14)*. PSMA-PET/CT produces images with high tumor-to-background contrast resulting in high sensitivity and specificity for the detection of PC *(4)*. The accuracy of PSMA-PET/CT in the detection of PC was recently evaluated in a

systematic review and meta-analysis of sixteen articles involving 1309 patients *(15)*. On per-patient analysis, the summary sensitivity and specificity were both 86%.

PSMA is also expressed on the neo-vasculature of many solid tumors *(16)*. Owing to the relatively limited clinical experience with PSMA-PET/CT, examples of incidental detection of synchronous PSMA-avid malignancies are limited to recent case reports *(7-13)*. In our study, atypical PSMA-avid lesions were confirmed to be a second primary in only 5/764 (0.7%) patients. In our experience, it was more uncommon to encounter PSMA-avid lymph nodes at unexpected locations, either as atypical PC metastases (Fig. 1) or due to additional primary (Fig. 2). In most cases, the intensity of metabolic activity in nodal or distant metastases parallels that in primary site of malignancy *(17)*. Therefore, encountering a discordant low-grade PSMA-activity in multiple enlarged lymph nodes should raise the level of suspicion for a second primary such as lymphoma (patient #8 in Table 2). In our experience, a PSMA-avid thyroid lesion could be an exception to the rule in PSMA where a benign nodule may present with higher PSMA avidity than that of the primary PC (Fig. 4, patient #9 in Table 2).

In our study, lesions atypical for PC metastases (with or without PSMA avidity) were found in 49/764 (6.4%) patients. In 8/764 (1.0%) patients, atypical PSMA-avid lesions were proven to be metastases from PC. Due to the high sensitivity and specificity of PSMA-PET/CT for PC evaluation, the differentiation between typical and atypical metastases is evolving as the modality is redefining patterns of PC spread. Given the age population of patients with PC, encountering lung lesions with or without PSMA avidity is not uncommon and the degree of uptake may not be reliable in differentiating PC metastases from lung cancer (Figs. 1D vs 3). In fact, quantitative analysis of PSMA-PET/CT does not reliably discriminate between pulmonary

metastases and primary lung cancer in PC patients *(9)*. Therefore, isolated atypical PSMA-avid lung lesions may need pathological confirmation. Also, non-PSMA-avid lung lesions may need further CT surveillance, FDG PET/CT or biopsy. In 24/764 (3.1%) patients, atypical lesions (with or without PSMA avidity) were due to a benign etiology based on additional follow-up imaging or investigations. To confirm benign causes, stability over time should be confirmed. Also, in the absence of nodal disease, an isolated PSMA-avid lesion at an atypical location is unlikely to be PC-related distant metastases. For example, liver metastases from PC are typically multiple so an isolated PSMA-avid liver lesion as the only metastatic site is less likely. In such cases, multiphase CT or MRI should be performed for further characterization (Fig. 4).

Correct and careful interpretation of the CT scan as part of the PSMA-PET/CT examination is of special importance, not only in differentiating physiologic uptake in ganglia or ureter versus in lymph nodes, but also in the detection of non-PSMA-avid lesions. Seven (14.3%) of those 49 patients with lesions atypical for PC metastases had non-PSMA-avid lesions detected only by the contemporaneous CT of the PET examination (5 lung and 2 thyroid). However, none of these were a second primary or metastases from PC, suggesting indeterminate CT findings are frequently benign. Of importance, intravenous contrast was not routinely used for the contemporaneous CT for all patients; therefore, non-PSMA avid but morphologically suspicious lesions could be underestimated in our analysis.

Our study is limited by retrospective analysis. Reporting styles vary between readers and our results may not be generalizable to other centers. We aim to report with high specificity, acknowledging the consequent trade-off in sensitivity in order to minimise the likelihood of adverse patient outcomes from false positive results *(17)*. In addition, the advanced stage of PC

patients undergoing PSMA-PET/CT coupled with the relative short follow-up period and high percentage of cases from remote facilities lead to relatively high number of patients without follow-up record or final diagnosis of the detected lesion.

CONCLUSION

Synchronous PSMA–avid malignancies were rare (0.7%) in PC patients with atypical lesions being more commonly unusual PC metastases (1%) or benign (3.1%). These findings support the high specificity of PSMA-PET/CT in PC with further investigations for atypical PSMA-avid lesions or CT findings required in a minority of cases.

DISCLOSURE

None.

References:

1) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
2) Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic efficacy of gallium-PSMA positron emission tomography compared to conventional imaging in lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. *J Urol*. 2016;195:1436-1443.
3) Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2015;56:668–674.
4) Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:197–200.
5) Kanthan GL, Drummond J, Schembri GP, et al. Follicular thyroid adenoma showing avid uptake on 68Ga PSMA-HBED-CC PET/CT. *Clin Nucl Med*. 2016;41:331-332.
6) Krohn T, Verburg FA, Pufe T, et al. [(68)Ga]PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. *Eur J Nucl Med Mol Imaging*. 2015;42:210–214.
7) Schwenck J, Tabatabai G, Skardelly M, et al. In vivo visualization of prostate specific membrane antigen in glioblastoma. *Eur J Nucl Med Mol Imaging*. 2015;42:170–171.
8) Rowe SP, Groin MA, Hammers HJ, et al. Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted 18F-DCFPyL PET/CT. *Ann Nucl Med*. 2015;29:877–882.

9) Pyka T, Weirich G, Einspieler I, et al. 68GaPSMA-HBED PET for differential diagnosis of suspicious lung lesions in patients with prostate cancer. *J Nucl Med*. 2016;57:367-371.

10) Verburg FA, Krohn T, Heinzel A, Mottaghy FM, Behrendt FF. First evidence of PSMA expression in differentiated thyroid cancer using [68Ga]PSMA-HBED-CC PET/CT. *Eur J Nucl Med Mol Imaging*. 2015;42:1622–1623.

11) Sathekge M, Modiselle M, Vorster M, et al. 68Ga-PSMA imaging of metastatic breast cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:1482–1483.

12) Huang YT, Fong W, Thomas P. Rectal carcinoma on 68Ga-PSMA PET/CT. *Clin Nucl Med*. 2016;41:167–168.

13) Sasikumar A, Joy A, Nanabala R, et al. (68)Ga-PSMA PET/CT imaging in primary hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging*. 2016;43: 795-796.

14) Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. *Journal of cellular biochemistry.* 2004; 91: 528-539.

15) Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: A systematic review and meta-analysis. *Eur Urol.* 2016;70:926-937.

16) Chang SS, O'Keefe DS, Bacich DJ, Reuter VE, Heston WD, Gaudin PB. Prostate-specific membrane antigen is produced in tumor-associated neovasculature. *Clin Cancer Res* 1999; 5: 2674-2681.

17) Hofman MS, Hicks RJ. How we read oncologic FDG PET/CT. *Cancer Imaging*. 2016;16:35-49.

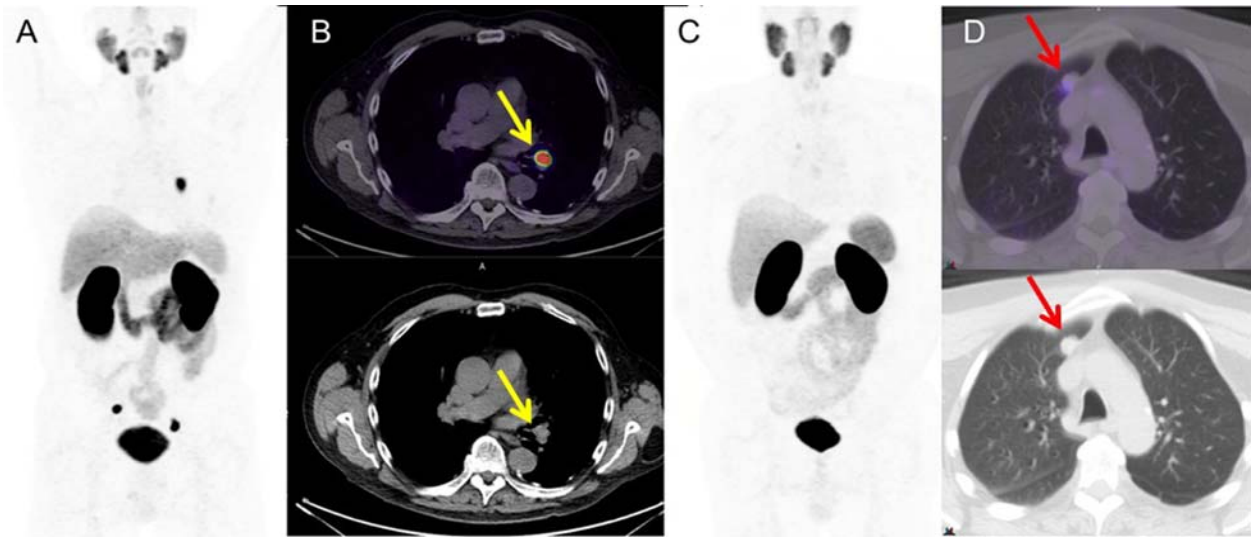

Figure 1. Biopsy confirmed PC examples: (A) and (B), left hilar node (SUVmax 30), (C) and (D), right upper lobe nodule (SUVmax 3).

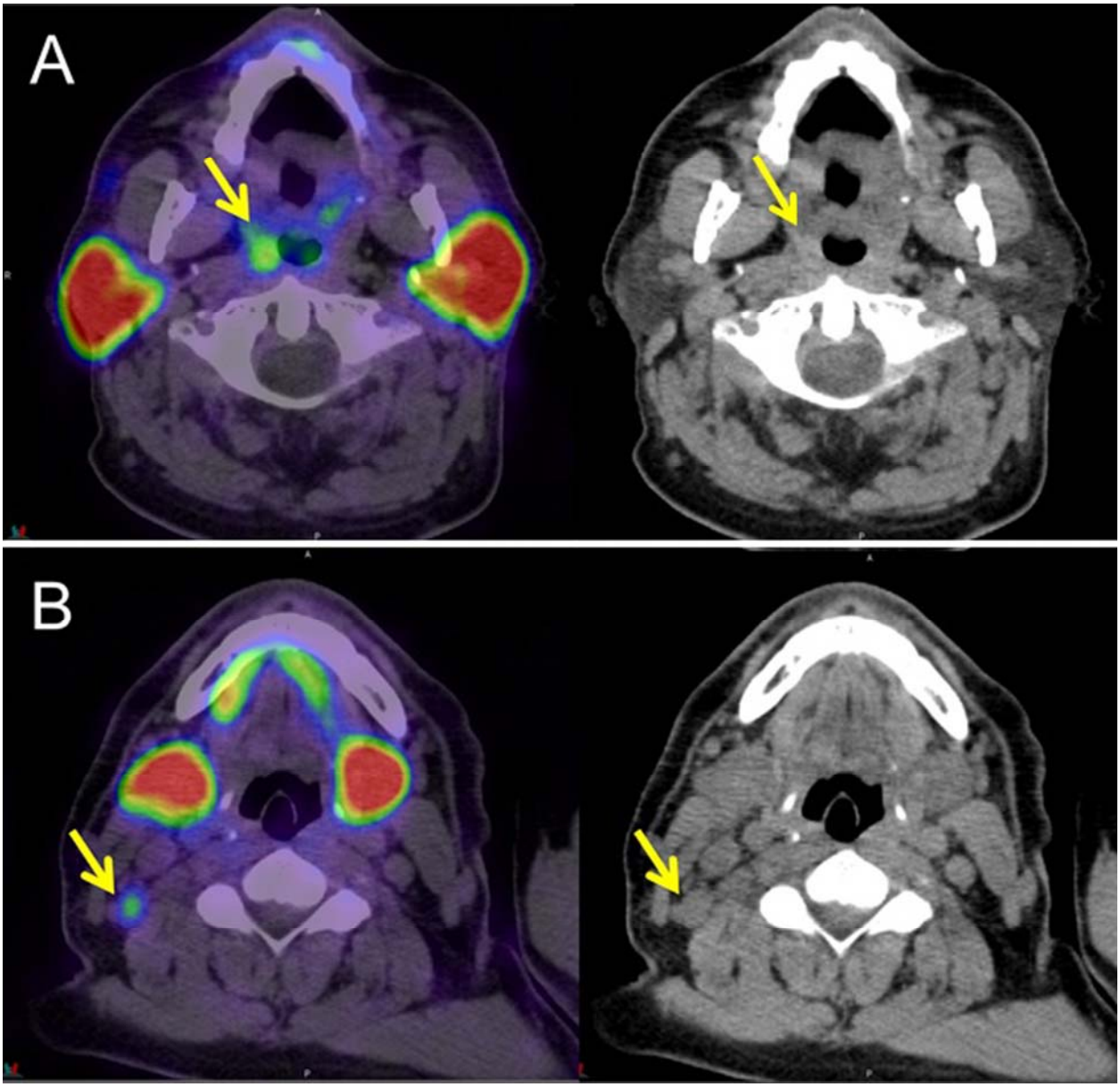

Figure 2. Incidental finding on PSMA PET/CT of focal uptake (SUVmax 5.3) in the right oropharynx (A) and ipsilateral mildly enlarged level II lymph nodes (SUVmax 3.6) (B). Biopsy demonstrated squamous cell carcinoma.

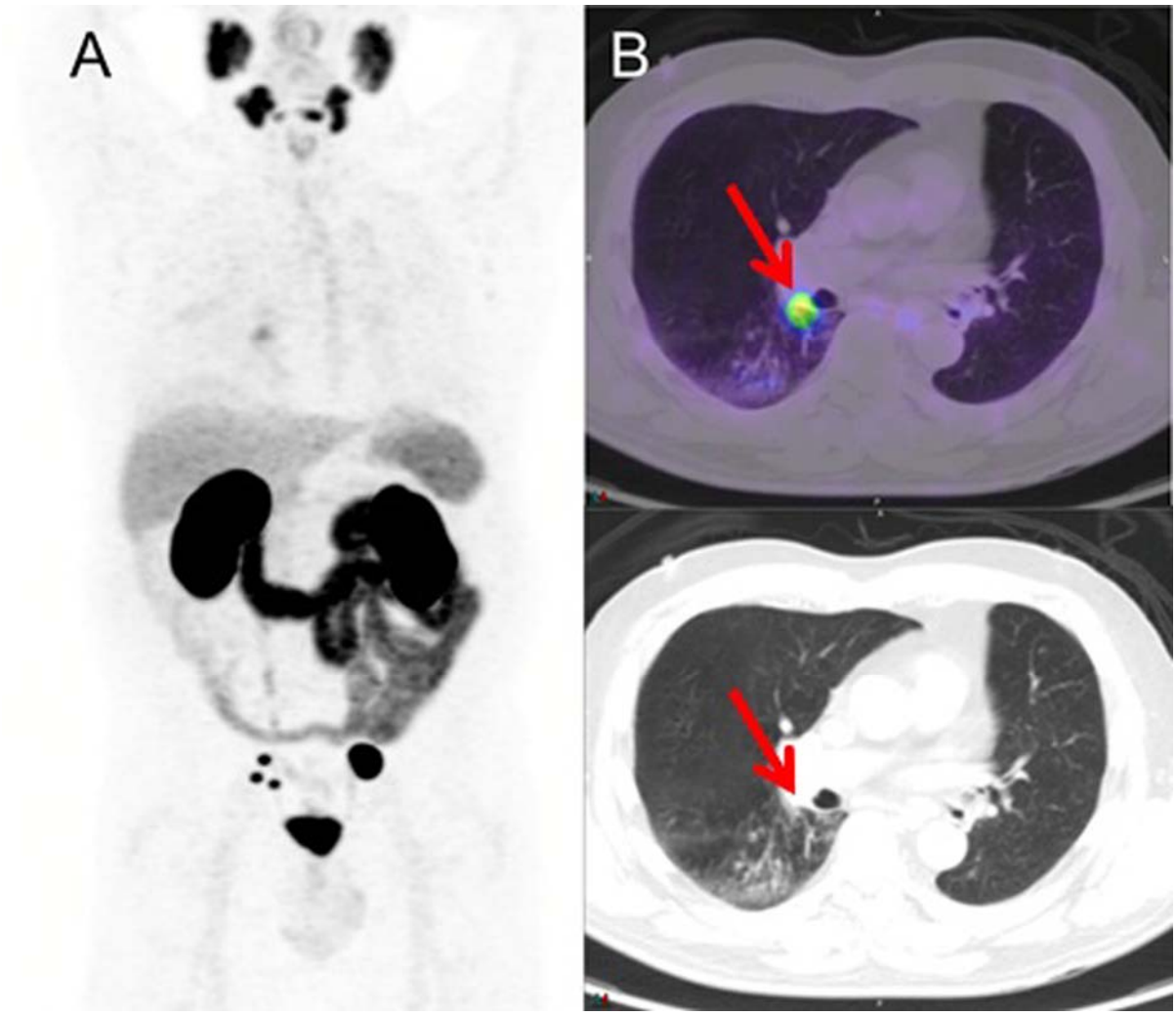

Figure 3. (A): MIP, (B): fused axial PET/CT and CT. Focal uptake (SUVmax 7) in a small right hilar mass on the background of more intense uptake in several pelvic nodes (SUVmax 79). Biopsy demonstrated lung adenocarcinoma.

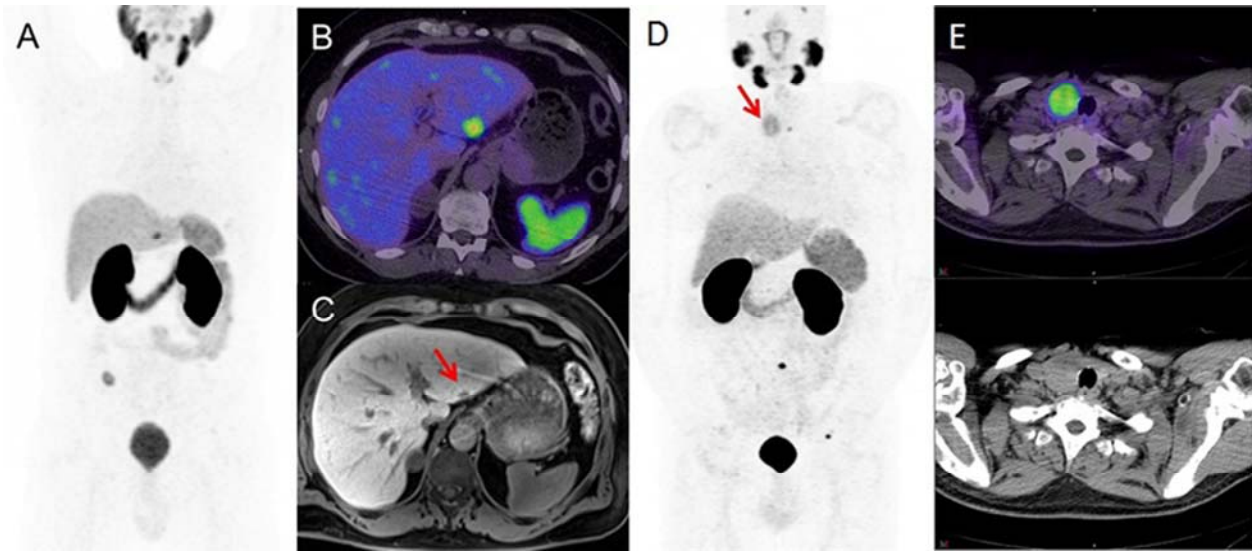

Figure 4. (A): MIP, (B): PET/CT, C: delayed contrast MRI. Small liver lesion (SUVmax 15) with no abnormality seen on low dose CT. MRI demonstrated arterial phase enhancement matching blood pool consistent with a hemangioma. (D): MIP, (E): fused axial PET/CT and CT. A 40mm thyroid nodule (SUVmax 6.3). Ultrasound demonstrated predominantly solid, mainly hyperechoic lesion with low echoic rim and increased vascularity. Biopsy demonstrated benign hyperplastic nodule (Bethesda category 2).

TABLE 1. Summary of Results

Parameter	Patients	Follow up
	N (%)	
Total	764 (100)	
Suspected 2nd primary	49 (6.4)	
PC atypical metastases	8 (1.0)	
Metastases proven by biopsy		
Lung	2	Lung metastases
Lymph node	2	Atypical nodal metastases
Metastases by imaging or clinically		
Lung	2	Lung metastases
Lymph node	2	Nodal metastases
Path. proven 2nd primaries	5 (0.7)	
Thyroid	1	Papillary thyroid carcinoma
Lung	2	1 Adenocarcinoma and 1 SCC
Tongue	1	SCC
Lymphoma	1	DLBCL
Proven benign	24 (3.1)	
Path. proven benign		
Thyroid	1	Hurthle cell adenoma
Benign by endoscopy		
Larynx	1	Normal larynx
Benign by imaging or clinically		
Lung	5	3 stable and 2 resolved
Thyroid	4	Stable
Liver	3	2 Haemangioma, 1 resolved
Lymph node	3	Stable
Spleen	2	Stable
Brain	1	Atypical meningioma
Pancreas	1	Stable
Bone	1	Resolved
Soft tissue	1	Stable
Skin	1	Stable
Not yet confirmed	12 (1.6)	

SCC: Squamous Cell Carcinoma

DLBCL: Diffuse Large B Cell Lymphoma

TABLE 2. Pathology-Proven Cases

Patient no. Age (Y)	PSMA SUVmax of Prostate, Nodal metastases, Distant metastases (Size)	Location of suspected lesion (size)	PSMA SUVmax	Biopsy result
1 (77)	Prostate (-) R. external iliac LN (1.3 x 1.4 cm) SUV max: 3.7	Lung (0.9 x 1.1cm)	1.6	Lung metastases (PC)
2 (69)	Prostate (-) Nodal (-)	R. upper lung (1x1.2 cm) R. lower lung (1.7 x 2.0 cm)	3.4 2.3	Lung metastases (PC)
3 (75)	Prostate (-) R. external iliac LN SUVmax: 53.4 (0.7 x 1.2cm) L. external iliac LN SUVmax:40.4 (1.1 x 1.6cm)	Hilar LN (1.3 x 1.5 cm)	30.3	Nodal metastases (PC)
4 (59)	Prostate (-) L. external iliac LN SUVmax:12.2 (1.0 x 3.4cm) Bone metastases SUVmax:29.2	Thyroid nodule (0.7cm)	1.9	Papillary thyroid carcinoma
5 (67)	Prostate SUVmax:14.4 (4.5 x3.7cm) Nodal (-)	Lung (1.8cm x 1.6 cm)	3.7	Lung adenocarcinoma
6 (69)	Prostate (-) R. external iliac LN SUVmax:23 (0.6 x 0.9 cm) L. external iliac LN SUVmax:79 (2.8 x 2.1 cm)	Lung (1.6x2.4cm)	7	Lung adenocarcinoma
7 (55)	Prostate (-)	R. cervical LN (2.0 x 2.4cm) Tongue base	3.6 5.3	Tongue base SCC
8 (78)	Prostate SUVmax 26.1 (2.3 x 1.4cm)	L. paraaortic LN (1.7 x 1.7cm)	2.6	Lymphoma (DLBCL)
9 (70)	Prostate (-) L. pelvic LN SUVmax 3.6 (0.6 x 1.0cm) Osseous metastases SUVmax 20.6	R. thyroid Nodule (3.0 x 3.2 cm)	6.3	Benign hyperplastic nodule