Tc-99m-PSMA imaging allows successful radioguided surgery in recurrent prostate cancer

Christian Kratzik[2] MD,
Susanne Dorudi[3] MD,
Martina Schatzl[2] MD,
Helmut Sinzinger[1,2] MD

1. Isotopix, Institute for Nuclear Medicine,
2. Faculty of Medicine, Sigmund Freud Private University, Vienna, Austria,
3. DSD Pharma, Purkersdorf, Austria

Keywords: Prostate cancer
- ^{99m}Tc-PSMA
- Radioguided surgery

Corresponding author:
Helmut Sinzinger MD, Prof.
Nadlergasse 1
1090 Vienna, Austria
Tel.: +43-1-4082633
helmut.sinzinger@chello.at

Received:
27 September 2018
Accepted revised:
10 October 2018

Abstract

Objective: The introduction of the prostate specific membrane antigen (PSMA) offers the possibility to discover prostate cancer recurrences being frequently so small that they cannot be detected by conventional imaging modalities, such as magnetic resonance or computed tomography. **Subject and Methods:** A 78 years old patient after radical prostatectomy and lymphadenectomy suffered from recurrence of the disease and galium-68-PSMA (^{68}Ga-PSMA) showed a single hot spot. Therefore, the first time in this indication in Austria radioguided surgery was performed after application of technetium-99m (^{99m}Tc)-PSMA, which confirmed the single lesion already shown by ^{68}Ga-PSMA. **Results:** The lymph node was located dorsal to the urinary bladder dome in the presacral area, where normally no lymphadenectomy is performed, he was identified by the probe and removed. Postoperatively PSA-monitoring showed a decline from 13,1ng/mL (preoperatively) to <0,1ng/mL within 1 month. **Conclusion:** The use of radiolabeled PSMA (primary diagnosis with ^{68}Ga, radioguided surgery with ^{99m}Tc and finally treatment with ^{177}Lu) seems to be a major breakthrough in diagnosis and treatment of prostate cancer.

Hell J Nucl Med 2018; 21(3): 202-204 *Epub ahead of print: 10 November 2018* *Published online: 5 December 2018*

Introduction

The available imaging modalities in primary prostate cancer as well as in recurrent disease so far are of low value. The introduction diagnosis of radiolabeled prostate specific membrane antigen (PSMA) gallium-68 (^{68}Ga) [1] and to treatment of lutetium-177 (^{177}Lu) [2, 3] opened a new era in the management of prostate cancer, which is probably the largest breakthrough in nuclear medicine during the past two decades. It offers a new hope for prolonging progression-free survival in patients suffering from the second most deadly cancer in males in Europe. Techentium-99m-(^{99m}Tc-PSMA) provides the possibility to identify the majority of metastatic soft tissue and bone lesions even below 1cm in diameter [4, 5]. Meanwhile, also other tumor entities have been visualized by ^{99m}Tc-PSMA [6]. Maurer et al. (2015, 2016) [7, 8] was the first to show that all preoperatively visualized lesions by ^{68}Ga-PSMA were also detected during radioguided surgery with ^{99m}Tc-PSMA. We therefore attempted to use ^{99m}Tc-PSMA for radioguided surgery, to the best of our knowledge for the first time in Austria.

Patient

The patient, now 78 years of age was under permanent urological control since 2011. He had no urological complaints apart from nykturia (1-2x/night) and was sexually active. His PSA-levels were between 3 and 4ng/mL in this period and testosterone levels were around 4ng/mL. In February 2017 his PSA was 4.38ng/mL but he presented in July 2017 because the general practitioner found a PSA of 9,3ng/mL. He had no complaints, urinary test was normal, and all other sonographic and physical examinations showed no pathological features. A control in September revealed again no abnormalities but PSA had risen to 12,2ng/mg. In October 2017 a prostate biopsy was performed and in 5 biopsies out of 12 a prostate carcinoma (Gleason score 8) was found, all on the left side. Since the patient was in excellent health a radical prostatectomy and lymphadenectomy was performed. The histologic examination of the operation specimen revealed a prostate carcinoma (Gleason 9, pT2c, resection margins negative).

Postoperatively the patient was continent but PSA never reached negative values. In April 2018 the patient experienced urinary retention and bladder neck resection was necessary-histological examination revealed no carcinoma only scar tissue. After this procedure the urinary flow was perfect and the patient was continent.

Due to the elevated PSA-values, all therapeutic options were discussed with the patient and he voted for a positron emission tomography (PET) scan. This was done in May and revealed a single 10/15mm positive lymph node cranial of the bladder on the left side. This finding was discussed with the patient and he opted to be operated.

Procedure

Technetium-99m-PSMA I + S, a highly specific PSMA tracer provided by DSD Pharma (Purkersdorf, Austria), was used. 800MBq ^{99m}Tc-pertechnetate in isotonic saline were added and gently mixed. Thereafter, the mixture was exposed for 10 minutes to 100°C in a pre-heated water-bath and cooled thereafter for about 10 minutes at room temperature. Finally the volume was brought to 10mL with isotonic saline before intravenous injection.

Due to the half-life of ^{99m}Tc and the optimal imaging time the timing window for a surgical intervention is crucial. A surgical interval of 16 to 18 hours, thus considered by us being optimal.

On July 5th and 6th, 2018, we performed the first radioguided surgery with 99mTc-PSMA in Austria. On July 5th the patient received 800MBq ^{99m}Tc-PSMA intravenously. Four and 6 hours thereafter whole body, local and SPET images of the pelvic region were performed. Eighteen hours after injection on the next day, the patient underwent surgery. Intraoperative detection was performed with C Trak® Galaxy Gamma Probe System.

Results

Imaging

Gamma-camera imaging revealed a single lymph node on the left hand side which was easily visible at 4 and 6 hours after injection of the radioactive material as well (Figure 1), the target to background ratio being somewhat higher in the 6 hours images. The lesion identified by ^{68}Ga-PSMA was identical to the one discovered by means of ^{99m}Tc-PSMA. The single photon emission tomography (SPET) images (Figure 2) clearly outlined the lesion.

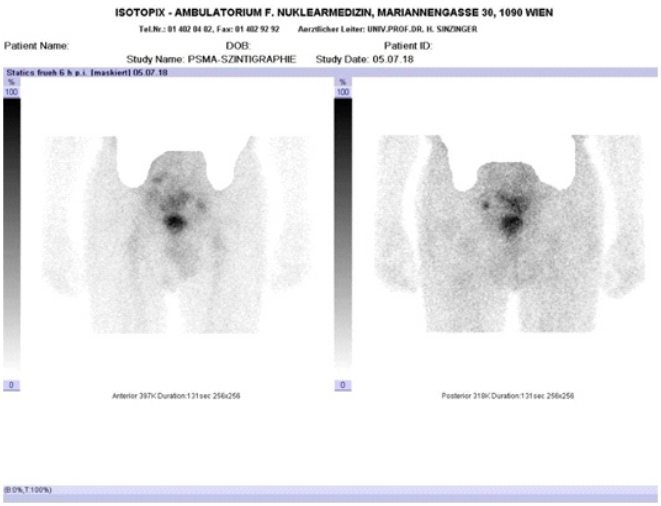

Figure 1. Static image 6 hours after injection of ^{99m}Tc-PSMA in anterior and posterior view (arrow indicates solitary lesion).

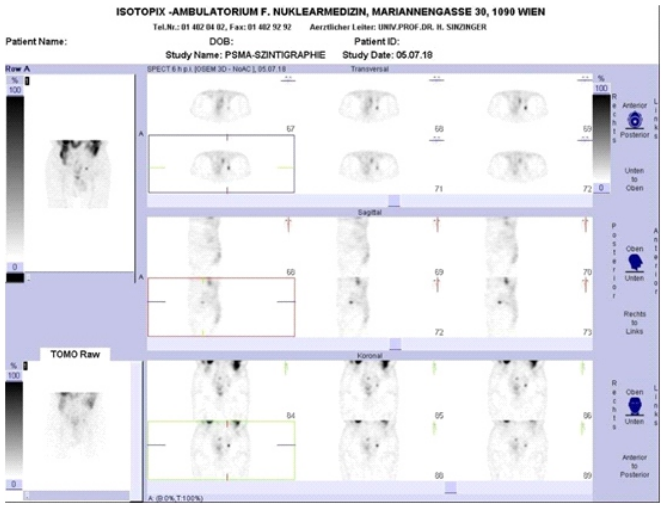

Figure 2. Single photon emission tomography image of the identification of the single lesion in the presacral region (arrow indicates lesion visible in 3 to 5 layers).

Surgery description

On July 6th the radioguided surgery was performed. A left sided hockey-stick incision was used and an extensive lymphadenectomy of the left side was done. Frozen section revealed only negative lymph nodes. Then the C Trak® Galaxy Gamma Probe System was used to search for the lymph-node having been imaged before by ^{68}Ga and ^{99m}Tc-PSMA. The node was situated dorsal of the bladder dome in the presacral region where normally no lymphadenectomy is performed. Therefore, without the probe we would never have found the lymph node at this site. This lymph node was taken out and histological examination revealed a solid carcinoma. There were no postoperative complications.

Prostate specific antigen was measured postoperatively on the 16th of July (0.7ng/mL) and on 6th of August showing a value of <0.1ng/mL (vs. the preoperative value of 13.1ng/mL).

Discussion

Technetium-99m labeled PSMA does not detect all lesions that can be identified by means of ^{68}Ga-PSMA, however, due to the excellent results in the pelvic region [9, 10] it opens a new promising approach for radioguided surgery in patients with biochemical relapse after radical surgery. This potentially allows even small and atypically localized secondary lesions of prostate cancer to be discovered intraoperatively by a gamma probe.

In an ex-situ analysis of lymph nodes Mix et al. (2018) [9] showed that indium-111 (^{111}In)-PSMA-617 was excellent to discriminate between affected and non-affected lymph nodes, a prerequisite for successful real-time measurement during surgery. Indium-111-PSMA has been shown to be of high value for intraoperative detection of even small recurrences in patients with prostate cancer scheduled for salvage lymphadenectomy. Similarly, Robu and coworkers (2017) [10] found a high ^{99m}Tc-PSMA-uptake in all suspect lesions having been identified before by ^{68}Ga-HBED-CCPSMA PET/computed tomography (CT). Maurer et al. (2018) [11] were able to show in 31 consecutive patients that ^{99m}Tc-PSMA-RGS visualized all lesions which were visible using ^{68}Ga-PSMA-11 PET. Even more, in 2 patients recurrences with a size of 3mm only could in addition be successfully detected by ^{99m}Tc-PSMA-RGS only. Furthermore, they showed that 41.9% of the patients remained free of recurrences for a mean follow-up period of 13.8 months. In a non-systematic review [12] the authors conclude that ^{99m}Tc-PSMA-RGS is of high value in patients with localized prostate cancer recurrence for the exact localization and successful resection. These promising reports stimulated us to start this procedure routinely with this first patient. Our findings and particularly the drop of PSA to <0.1ng/mL confirm the great clinical potential.

In conclusion, due to the physical characteristics, an available easy kit preparation and the high cost-effectiveness, ^{99m}Tc-PSMA may have a great future for radioguided surgery to discover local recurrences secondary to prostate cancer.

Acknowledgement

The detection device was kindly provided by Dr. Susanne Dorudi, DSD-Pharma, Austria. The technical assistance by Susanna Frank and Susanne Presl is kindly acknowledged.

Bibliography

1. Afshar-Oromieh A, Malcher A, Eder M et al. PET imaging with a [^{68}Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. *Eur J Nucl Med Mol Imaging* 2013; 40(4): 486-95.
2. Weineisen M, Schottelius M, Simecek J et al. ^{68}Ga-and ^{177}Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies. *J Nucl Med* 2015; 56(8): 1169-76.
3. Kratochwil C, Giesel FL, Eder M et al. [^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging* 2015; 42(6): 987-8.
4. Vallabhajosula S, Nikolopoulou A, Babich JW et al. ^{99m}Tc-labeled small-molecule inhibitors of prostate-specific membrane antigen: pharmacokinetics and biodistribution studies in healthy subjects and patients with metastatic prostate cancer. *J Nucl Med* 2014; 55 (11): 1791-8.
5. Hillier SM, Maresca KP, Lu G, Merkin RD et al. ^{99m}Tc-labeled small-molecule inhibitors of prostate-specific membrane antigen for molecular imaging of prostate cancer. *J Nucl Med* 2013; 54(8): 1369-76.
6. Singh D, Horneman R, Nagra NK. More than the prostate: Intrapancreatic accessory spleen and papillary thyroid cancer detected with ^{18}F-PSMA PET/CT. *Hell J Nucl Med* 2018; 21(2): 145-7.
7. Maurer T, Weirich G, Schottelius M et al. Prostate-specific membrane antigen-radioguided surgery for metastatic lymph nodes in prostate cancer. *Eur Urol* 2015; 68(3): 530-4.
8. Maurer T, Eiber M, Wirtz M et al. PSMA-radioguided surgery for recurrent prostate cancer - mid-term follow-up and novel developments. *Eur Urol Suppl* 2016; 15(3): e438.
9. Mix M, Reichel K, Stoykow C et al. Performance of ^{111}In-labelled PSMA ligand in patients with nodal metastatic prostate cancer: correlation between tracer uptake and histopathology from lymphadenectomy. *Eur J Nucl Med Mol Imaging* 2018. doi: 10.1007/s00259-018-4094-0. [Epub ahead of print]
10. Robu S, Schottelius M, Eiber M et al. Preclinical Evaluation and First Patient Application of ^{99m}Tc-PSMA-I&S for SPECT Imaging and Radioguided Surgery in Prostate Cancer. *J Nucl Med* 2017; 58(2): 235-42.
11. Maurer T, Robu S, Schottelius M et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen-radioguided Surgery in Recurrent Prostate Cancer. *Eur Urol* 2018. pii: S0302-2838(18)30189-1.
12. Rauscher I, Düwel C, Wirtz M et al. Value of ^{111}In-prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up. *BJU Int* 2017; 120(1): 40-7.