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

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 gallium-68-PSMA (\(^{68}\text{Ga-PSMA}\)) showed a single hot spot. Therefore, the first time in this indication in Austria radioguided surgery was performed after application of technetium-99m (\(^{99m}\text{Tc-PSMA}\)), which confirmed the single lesion already shown by \(^{68}\text{Ga-PSMA}\). 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 \(^{68}\text{Ga}\), radioguided surgery with \(^{99m}\text{Tc}\) and finally treatment with \(^{177}\text{Lu}\)) seems to be a major breakthrough in diagnosis and treatment of prostate cancer.

Introduction

The available imaging modalities in primary prostate cancer as well as in recurrent disease are of low value. The introduction diagnosis of radiolabeled prostate specific membrane antigen (PSMA) gallium-68 (\(^{68}\text{Ga}\)) [1] and to treatment of lutetium-177 (\(^{177}\text{Lu}\)) [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. Technetium-99m-(\(^{99m}\text{Tc-PSMA}\)) 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 \(^{99m}\text{Tc-PSMA}\) [6]. Maurer et al. (2015, 2016) [7, 8] was the first to show that all preoperatively visualized lesions by \(^{68}\text{Ga-PSMA}\) were also detected during radioguided surgery with \(^{99m}\text{Tc}\). We therefore attempted to use \(^{99m}\text{Tc-PSMA}\) 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 nycturia (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, urinaty 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.

Keywords: Prostate cancer
- \(^{99m}\text{Tc-PSMA}\)
- Radioguided surgery
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 $^{99mTc}$-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 $^{99mTc}$ 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 radio-guided surgery with $^{99mTc}$-PSMA in Austria. On July 5th the patient received 800MBq $^{99mTc}$-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 $^{68Ga}$-PSMA was identical to the one discovered by means of $^{99mTc}$-PSMA. The single photon emission tomography (SPET) images (Figure 2) clearly outlined the lesion.

**Figure 1.** Static image 6 hours after injection of $^{99mTc}$-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 radio-guided 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 ⁶⁷Ga and ⁹⁹mTc-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 (0.7 ng/mL) and on 6th of August showing a value of <0.1 ng/mL (vs. the preoperative value of 13.1 ng/mL).

**Discussion**

Technetium-⁹⁹m labeled PSMA does not detect all lesions that can be identified by means of ⁶⁷Ga-PSMA, however, due to the excellent results in the pelvic region [9, 10] it opens a new promising approach for radio-guided 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 (¹¹¹In)-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 ⁹⁹mTc-PSMA-uptake in all suspect lesions having been identified before by ⁶⁷Ga-HBED-CCPSMA PET/computed tomography (CT). Maurer et al. (2018) [11] were able to show in 31 consecutive patients that ⁹⁹mTc-PSMA-RGS visualized all lesions which were visible using ⁶⁷Ga-PSMA-11 PET. Even more, in 2 patients recurrences with a size of 3mm only could in addition be successfully detected by ⁹⁹mTc-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 ⁹⁹mTc-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 <0.1 ng/mL confirm the great clinical potential.

In conclusion, due to the physical characteristics, an available easy kit preparation and the high cost-effectiveness, ⁹⁹mTc-PSMA may have a great future for radio-guided surgery to discover local recurrences secondary to prostate cancer.

**Acknowledgement**

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

**Bibliography**

6. Singh D, Horneman R, Nagra NK. More than the prostate: Intrapancreatic accessory spleen and papillary thyroid cancer detected with this first patient. Our findings and particularly the drop of PSA to <0.1 ng/mL confirm the great clinical potential.

In conclusion, due to the physical characteristics, an available easy kit preparation and the high cost-effectiveness, ⁹⁹mTc-PSMA may have a great future for radio-guided surgery to discover local recurrences secondary to prostate cancer.

**Bibliography**

6. Singh D, Horneman R, Nagra NK. More than the prostate: Intrapancreatic accessory spleen and papillary thyroid cancer detected with this first patient. Our findings and particularly the drop of PSA to <0.1 ng/mL confirm the great clinical potential.

In conclusion, due to the physical characteristics, an available easy kit preparation and the high cost-effectiveness, ⁹⁹mTc-PSMA may have a great future for radio-guided surgery to discover local recurrences secondary to prostate cancer.

**Acknowledgement**

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

**Bibliography**

6. Singh D, Horneman R, Nagra NK. More than the prostate: Intrapancreatic accessory spleen and papillary thyroid cancer detected with this first patient. Our findings and particularly the drop of PSA to <0.1 ng/mL confirm the great clinical potential.

In conclusion, due to the physical characteristics, an available easy kit preparation and the high cost-effectiveness, ⁹⁹mTc-PSMA may have a great future for radio-guided surgery to discover local recurrences secondary to prostate cancer.