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Feasibility of ^{99m}Tc-MIP-1404 for SPECT/CT imaging and subsequent PSMA-radioguided surgery in early biochemical recurrent prostate cancer: a case series of 9 patients

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Short running title: ^{99m}Tc-MIP-1404 in RGS of recurrent PCa

ABSTRACT

This case series evaluated the feasibility of prostate-specific membrane antigen (PSMA) radioguided surgery (RGS) with ^{99m}Tc-MIP-1404 in recurrent prostate cancer. **Methods:** 9 patients with PSMA-positive lesions on PET/CT received ^{99m}Tc-MIP-1404 (median 747 MBq, interquartile range (IQR) 710 – 764) 17.2 hours (IQR 16.9 – 17.5) before SPECT/CT and 22.3 hours (IQR 20.8 – 24.0) before RGS. **Results:** 17 PSMA-positive lesions were detected on PET/CT (median short axis diameter 4 mm, IQR 3 – 6; median SUVmax 8.9, IQR 5.2 – 12.6). 9/17 (52.9%) were visible on SPECT/CT (median SUVmax 13.8, IQR 8.0 – 17.9). Except for 2 foci, all PET/CT-positive findings demonstrated intraoperative count rates above the background (median counts 31, IQR 17 – 89) and were lymph node metastases. Moreover, PSMA-RGS identified 2 additional metastases compared to PET/CT. Prostate-specific antigen values decreased after RGS in 6/9 (67%) patients. **Conclusion:** PSMA-RGS with ^{99m}Tc-MIP-1404 identified lymph node metastases in all patients including two additional lesions compared to PET/CT.

Key words: Prostate cancer, biochemical recurrence, PSMA, salvage therapy

INTRODUCTION

Prostate specific membrane antigen (PSMA) targeted PET/CT has demonstrated to be a highly sensitive and accurate diagnostic tool for the localization of recurrent prostate cancer (PCa) with a significant impact on clinical decision making *(1–3)*. In the case of locally confined recurrent disease, there are various options for salvage therapy *(4)*. PSMA-radioguided surgery (RGS) is a novel technique in which γ-emitting radiotracers are utilized to identify metastatic soft-tissue lesions intraoperatively with a gamma probe *(5,6)*. ^{99m}Tc-MIP-1404, a small molecule PSMA inhibitor, was introduced for SPECT/CT imaging *(7,8)*. Studies evaluating its utilization in RGS are lacking. The presented case series examines the feasibility of PSMA-RGS with ^{99m}Tc-MIP-1404 in patients with positive nodal disease on PSMA PET/CT in early recurrent PCa.

MATERIALS AND METHODS

Between June and September 2021, 9 patients (median age 62 years, interquartile range (IQR) 61 – 67) received ^{99m}Tc-MIP-1404 prior to RGS in recurrent PCa with PSMA PET/CT-positive lymph nodes exclusively within the pelvis (median prostate-specific antigen (PSA) 0.74 ng/ml, IQR 0.41 – 1.54; Supplemental Table 1). Biochemical recurrence (BCR) was defined as a PSA of ≥0.2 ng/ml in two or more separate measurements ≥6 weeks after prostatectomy or ≥2 ng/ml above the PSA nadir after radiotherapy. Except for patient 7 (PSA nadir 0.3 ng/ml after radiotherapy), all individuals had undergone prostatectomy (interval primary treatment to RGS: median 36 months, IQR 15 – 42; interval PSMA PET/CT to RGS: median 36 days, IQR 26 – 54). The local institutional review board approved this retrospective analysis (2019-PS-09). All patients were informed about the experimental nature of PSMA-RGS and the associated administration of ^{99m}Tc-MIP-1404. All patients provided written informed consent for the procedure.

PSMA PET/CT Imaging and Analysis

PET/CT scans were performed at different institutions (Supplemental Table 2). Short and long axis diameters were measured for each lesion on axial plane. The SUVmean of the background was calculated from a 10 ml spherical region of interest in the gluteus muscle. The SUVmax and SUVmean of each lesion were determined with isocontours set at 40% of the maximum. All lesions were analyzed visually using a 4-point scale according to the PROMISE criteria *(9)*.

PSMA SPECT/CT Imaging and Analysis

^{99m}Tc-MIP-1404 (ROTOP Pharmaka GmbH, Dresden, Germany) was produced under the conditions of §13 (2b) of the Arzneimittelgesetz (German Medicinal Products Act; median radioactivity concentration 212 MBq/ml, IQR 199 – 228; median purity 95 %, IQR 95.0 – 95.5). Patients received a median dose of 747 MBq (IQR 710 – 764) 17.2 hours (IQR 16.9 – 17.5) before SPECT/CT. Scans were obtained with a Mediso AnyScan® Trio (Mediso Medical Imaging Systems, Budapest, Hungary: patients 1 – 4 and 6 – 9) or a Siemens Symbia Intevo Bold™ (Siemens Healthineers, Erlangen, Germany: patient 5) (Supplemental Table 3). All lesions encountered on PET/CT were evaluated semiquantitatively on SPECT/CT corresponding to the description for PET/CT. Moreover, a visual 4-point scale according to uptake was applied (no: 0, minimal: 1, moderate: 2, strong: 3).

PSMA-Radioguided Surgery and Specimen Preparation

22.3 hours (IQR 20.8 – 24.0) after the injection of ^{99m}Tc-MIP-1404, RGS was conducted using a gamma probe (Crystal Probe CXS-SG603; sensitivity maximum: 13500 cps/MBq, resolution: 14 mm, energy range: 50 – 511 keV; Crystal Photonics, Berlin, Germany) and count rates were considered positive if they were at least double the rate of the background as reported previously *(6)*. The template of dissection was based on the pre-operative PSMA PET/CT resulting

in either a uni- or a bilateral lymph node dissection. The pathological work-up of specimens was performed separately according to their region of origin. Also, adjacent tissue without elevated counts was dissected resulting in a complete template-based surgical resection. PSA-values were determined 1 month after PSMA-RGS (median 31 days, IQR 30 – 35). A complete biochemical response was defined as a PSA decrease below the threshold for BCR (see above).

Statistical Analysis

Continuous variables are described with median and IQR. Statistical analyses were conducted with STATA® version 17.0 (STATA Corp, College Station, Texas, USA).

RESULTS

Patient Based Results

Figure 1 shows representative images of positive lesions on pre-operative PSMA PET/CT and PSMA SPECT/CT. ^{99m}Tc-MIP-1404 SPECT/CT demonstrated correlates for PET/CT-positive lesions in 6 patients (67%). Lymph node metastases with count rates above background were found in all cases. PSA decreased in 6/9 patients (67%) meeting the definition of complete biochemical response in 5/9 (56%).

Lesion Based Imaging Results

Lesion based information is provided in Table 1. The median short axis diameter of all lesions was 4 mm (IQR 3 – 6) and the median SUVmax was 8.9 (IQR 5.2 – 12.6). Of 17 findings identified on PET/CT, 9 (52.9%) were visible on SPECT/CT (median SUVmax 13.8, IQR 8 – 17.9). These SPECT/CT-positive lesions showed a higher median SUVmax to background ratio on PET/CT compared to SPECT/CT-negative lesions (30.8, IQR 19.6 – 42.2 and 13.7, IQR 9.4 – 17.2, respectively).

RGS Results and Histological Correlation

Except for 2 foci (patient 2, CIL prox. and IIL int.), all PET/CT-positive lesions demonstrated count rates above the background regardless of their visualization on SPECT/CT (88.2% positive; median counts 31, IQR 17 – 89; median counts to background ratio 17, IQR 10 – 30). The 2 RGS-negative lesions could also not be identified in the histological workup of the resected tissue. The remaining 15 lesions were PCa related lymph node metastases including 3 lymph node conglomerates (Table 1: patient 1, IIR dist., 3 lymph nodes; patient 4, IIL, 2 lymph nodes; patient 8, IIL dist., 2 lymph nodes). In addition to the PET/CT-positive lesions, 2 additional lymph node metastases were identified during RGS (patient 3: left external iliac, counts 8, counts to background ratio 3, long axis diameter 6 mm; patient 6, left external iliac artery, counts 11, counts to background ratio 4, long axis diameter 2 mm). 3 lymph node metastases were neither positive on PSMA-imaging nor during RGS and could only be identified on histology (patient 1, external iliac right, 2 lymph nodes, long axis diameter 3 mm; patient 6, common iliac left, 1 lymph node, long axis diameter 2 mm). No tissue specimen with negative histology showed elevated counts (specificity: 100%).

In conclusion, 24 of 154 resected lymph nodes were PCa metastases. 19 were correctly identified on PET/CT (79.2%) and 12 on SPECT/CT (50%). 21 lymph node metastases were localized during RGS (sensitivity: 87.5%).

DISCUSSION

PSMA-radioguided surgery with ^{99m}Tc-MIP-1404 was able to identify lymph node metastases in all patients regardless of their visualization on SPECT/CT including lesions with a long axis diameter of only 2 mm.

Comparable to the results in the presented group, detection rates of ^{99m}Tc-MIP-1404 SPECT/CT in recurrent prostate cancer were reported to be 50 – 60% per patient in cases with

low PSA values of <1 ng/ml *(7,10)*. Data regarding the direct comparison of PSMA PET/CT and PSMA SPECT/CT are lacking for ^{99m}Tc-MIP-1404. Detection rates are expected to be lower for SPECT compared to PET due to the inferior spatial resolution. Lawal et al. reported that ^{99m}Tc-HYNIC PSMA SPECT/CT was able to identify 62.5% of nodal lesions that were seen on PSMA PET/CT in patients admitted for primary staging or BCR (median PSA of 45.2 ng/ml) *(11)*. In the presented case series, ^{99m}Tc-MIP-1404 SPECT/CT detected 52.9% of all PET/CT-positive lesions. The low median PSA of 0.74 ng/ml in the investigated group and the overall small lesion size may be assumed as the major causes for this. However, RGS about 22 hours after the injection of ^{99m}Tc-MIP-1404 identified lymph node metastases in all cases and was able to detect two additional lesions compared to pre-operative PSMA PET/CT. These results are similar to data on radioguided surgery with ^{111}In-PSMA-I&T *(5)* and ^{99m}Tc-PSMA-I&S *(6)* indicating that PSMA-RGS with ^{99m}Tc-MIP-1404 is feasible using a comparable uptake time. The additional lymph node metastases found during RGS demonstrated lower count rates than most other lesions. A positive correlation of the PSMA-expression and tumor volume with the tracer uptake of a lesion has been described *(12)* and a similar relationship may be assumed regarding the intraoperative count rates. This implies a lower PSMA-expression/tumor volume in these lymph nodes which may have led to their missing visualization on imaging.

Two PET/CT-positive foci with slight tracer uptake in patient 2 could not be found during RGS and were not identified in the histopathology. The elevated PSA-value after RGS may indicate that the lesions were missed. Alternatively, false positive results on PET/CT and occult metastases at a different location are possible. Likewise, the PSA-values did not decrease in patients 4 and 9 although the PET/CT-positive lymph node metastases were resected successfully. Thus, tumor deposits at other sites that were not detected by preoperative imaging are likely. Follow up examinations were not available limiting the interpretation of these cases. Other limitations are the retrospective design, small cohort, and inconsistent PET/CT imaging protocols. Moreover, PSMA-RGS is still an experimental method in which thresholds of

intraoperative count rates to differentiate benign from malignant tissues are unclear. Like in other metastasis directed therapies, its clinical utility still has to be determined. Especially, the task of reliably identifying tumor burden in patients with BCR to reduce the chance of PSA failure after surgery should be addressed in future studies. However, the large number of correctly identified lymph node metastases by ^{99m}Tc-MIP-1404 RGS is encouraging and should be explored further.

CONCLUSION

PSMA-RGS utilizing ^{99m}Tc-MIP-1404 identified lymph node metastases in all patients with early recurrent PCa regardless of their visualization on prior SPECT/CT imaging. Thus, ^{99m}Tc-MIP-1404 represents a promising radiotracer for radioguided surgery.

DISCLOSURE

There was no external financial support for this study. The authors declare that they have no conflict of interest.

KEY POINTS

Question: Is RGS with ^{99m}Tc-MIP-1404 feasible in patients with early recurrent prostate cancer?

Pertinent Findings: RGS with ^{99m}Tc-MIP-1404 discovered prostate cancer related lymph node metastases in all patients including two additional lesions compared to PET/CT.

Implications for patient care: RGS with ^{99m}Tc-MIP-1404 is feasible and may represent an alternative to PSMA-RGS with other radiotracers.

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Figures

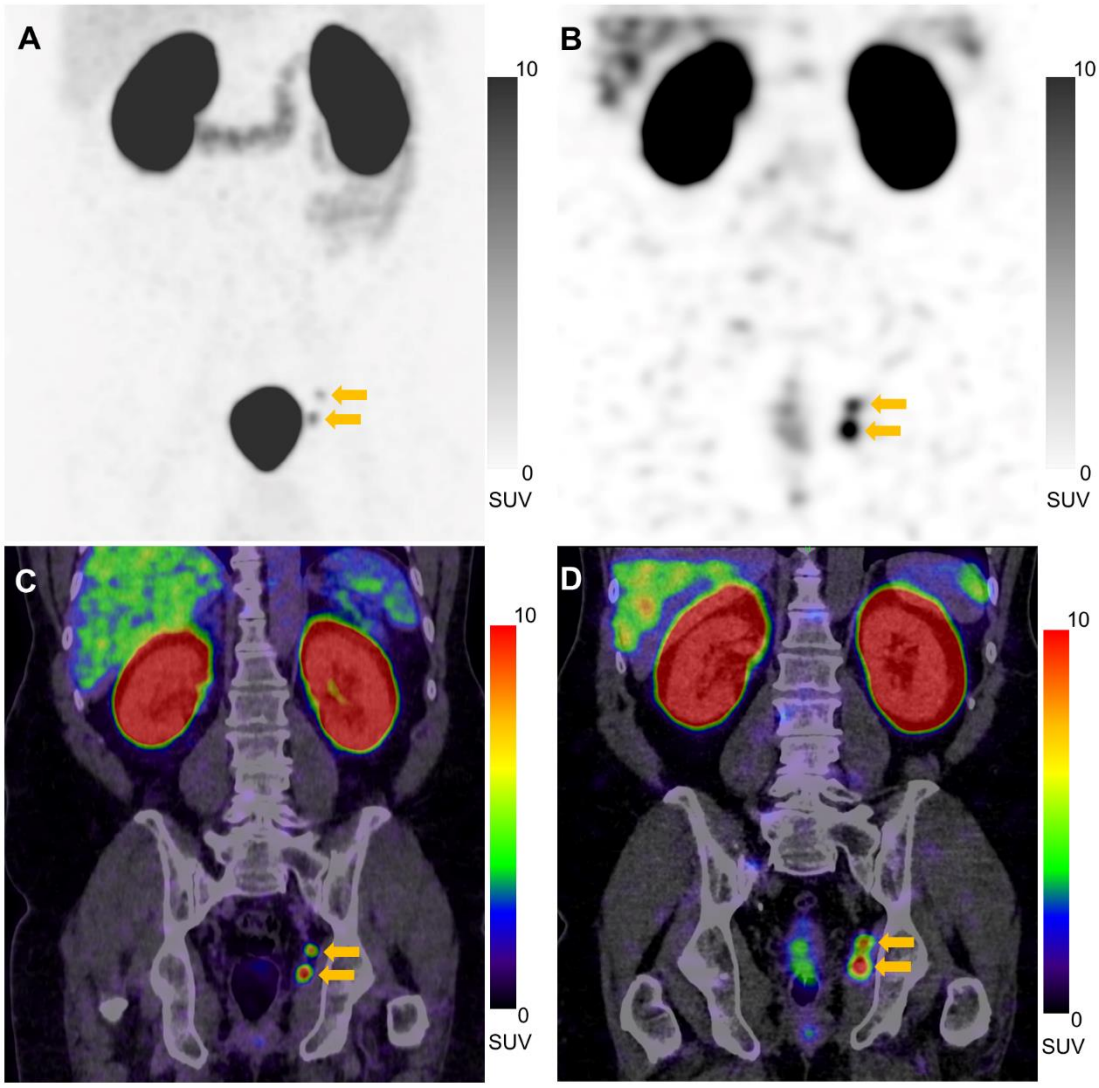


FIGURE 1. ^{68}Ga-PSMA I&T PET/CT (A and C) and ^{99m}Tc-MIP-1404 SPECT/CT (B and D) of patient 8 (A, B: maximum intensity projections; C, D: coronal fusion images, slice thickness 3 mm) with PSMA-positive lymph node metastases adjacent to the left internal iliac artery (arrows).

Tables

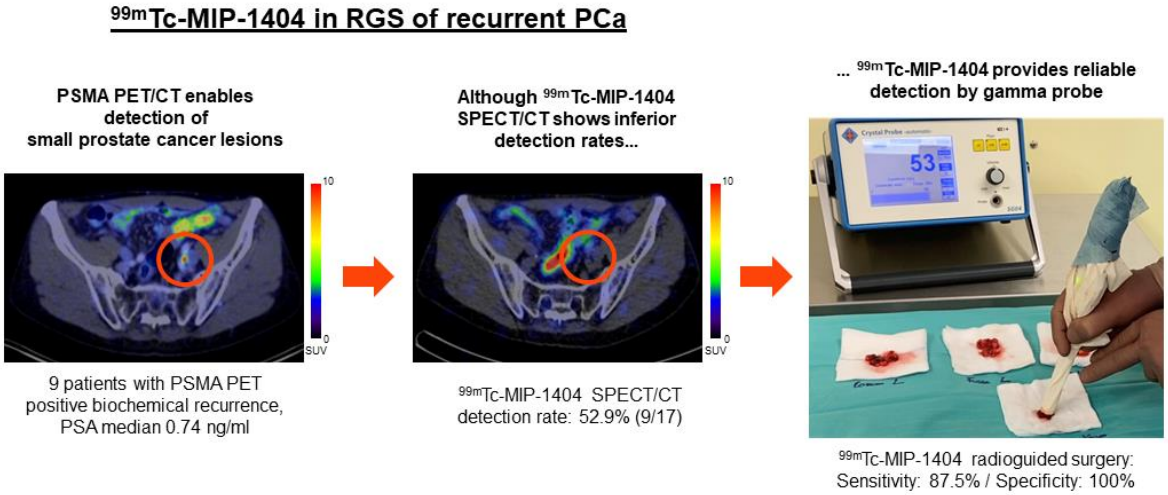
TABLE 1

Lesion based case characteristics

Pat.	Lesion loc.	PET/CT					SPECT/CT			Radioguided surgery		Histology
		SAD	LAD	SUVmax	SUV max to BG	Visual Score	SUV max	SUV max to BG	Visual Score	Counts ex vivo (max)	Counts ex vivo (max to BG)	Prostate cancer
1	IIR prox.	3	5	8.2	17	2	1.2	3.7	0	54	18	yes
	IIR dist.	4	5	15.3	31.7	3	9.4	28.8	2	54	18	yes
2	CIL prox.	2	2	3.6	6	1	1.2	3.5	0	1	1	no
	CIL dist.	4	7	10.5	17.4	3	0.9	2.8	0	8	8	yes
	IIL prox.	4	5	6.9	11.3	2	1.1	3.1	0	8	8	yes
	IIL int.	3	4	5.2	8.6	2	1.2	3.5	0	1	1	no
	IIL dist.	4	6	12.6	20.7	3	3.2	9.4	1	17	17	yes
3	CIL prox.	13	20	5.7	19.6	3	17.9	100.5	3	30	10	yes
	CIL int.	19	24	9	30.8	3	28.5	160.2	3	31	10	yes
	CIL dist.	11	28	4.7	16	2	13.8	77.8	3	30	10	yes
4	IIL	3	5	3.4	10.2	2	0.8	3.8	0	30	10	yes
5	pararectal	6	13	3.4	9.3	2	6.7	26.8	2	35	18	yes
6	IIL	3	5	17.2	35.8	3	1.1	4.6	0	89	30	yes
7	EIL	11	15	51	114.6	3	112.9	407.6	3	354	118	yes
8	IIL prox.	2	5	11.4	42.2	3	8	46.3	3	104	35	yes
	IIL dist.	5	5	15.2	56.3	3	14.8	86.1	3	129	43	yes
9	presacral	2	2	8.9	16.1	2	0.8	4.5	0	11	6	yes

Pat.= patient, loc. = localization, SAD = lesion short axis in mm, LAD = lesion long axis in mm, SUV = standard uptake value, max = maximum, BG = background, IIR = internal iliac right, prox. = proximal, dist. = distal, CIL = common iliac left, IIL = internal iliac left, int. = intermediate, EIL = external iliac left.

Graphical Abstract



Supplemental Tables

Supplemental Table 1

Patient based clinical characteristics

Pat.	iPSA	Primary therapy	T stage	N stage	Surgical margin	Gleason grade group	Adjuvant RT	PSA at RGS	Positive LN at RGS	PSA after RGS
1	7.62	RP	pT3a	pN0 (0/30)	R1	III	Yes	0.21	6/25	0.04
2	17.25	RP	pT3a	pN0 (0/11)	R0	III	Yes	0.87	3/4	1.02
3	1.72	RP	pT3b	pN0 (0/25)	R0	V	No	10.74	4/23	0.12
4	9.09	RP	pT3a	N/A	R0	III	No	0.41	2/23	0.40
5	3.84	RP	pT2c	pN0 (0/7)	R0	III	No	0.41	1/16	0.28
6	42	RP	pT3b	pN0 (0/17)	R1	II	Yes	1.54	3/20	0.17
7	11.5	RT	cT2	N/A	N/A	N/A	No	3.01	1/10	0.59
8	11.98	RP	pT3b	pN0 (0/25)	R0	V	No	0.74	3/19	0.02
9	24.55	RP	pT3b	pN0 (0/15)	RX	III	Yes	0.22	1/14	0.22

Pat. = patient, iPSA = initial prostate-specific antigen before primary therapy, RT = radiotherapy, PSA = prostate-specific antigen, RGS = radioguided surgery, LN = lymph nodes, RP = radical prostatectomy, N/A =not applicable. PSA values are given in ng/ml.

Supplemental Table 2

Patient based imaging characteristics

Pat.	Tracer PET/CT	Injected dose PET/CT (MBq)	i.v. contrast PET/CT	No. of lesions PET/CT	Time from PET/CT to SPECT/CT in days	Injected dose SPECT/CT (MBq)	Injection to SPECT/CT in hours	Injection to RGS in hours	No. of lesions SPECT/CT
1	^{68}Ga-PSMA I&T	125	yes	2	61	764	17.1	20.8	1
2	^{18}F-rhPSMA-7	225	yes	5	49	747	16.7	20.3	1
3	^{68}Ga-HBED	227	yes	3	21	701	17.5	24.3	3
4	^{68}Ga-PSMA I&T	151	yes	1	35	778	18.3	24	0
5	^{68}Ga-PSMA I&T	126	yes	1	68	750	17.5	24.6	1
6	^{18}F-PSMA-1007	265	yes	1	36	710	16.5	20	0
7	^{18}F-PSMA-1007	246	no	1	23	787	16.9	23.3	1
8	^{68}Ga-PSMA I&T	142	yes	2	26	745	17.2	20.9	2
9	^{18}F-rhPSMA-7	249	yes	1	54	669	17.5	22.3	0

Pat. = patient, RGS = radioguided surgery

Supplemental Table 3

Imaging parameters SPECT/CT

		Mediso AnyScan® Trio	Siemens Symbia Intevo Bold™
Planar scintigraphy	Scan speed	120 mm/min	120 mm/min
SPECT parameters	Number of projections	96	128
	Time per projection	40	20
	Collimator	LEHRHS	LEHR
	Reconstruction algorithm	Tera-Tomo Q 3D	Flash 3D
	Reconstruction parameters	105 iterations, 5 subsets CT-based attenuation correction Monte Carlo based scatter correction	12 (sub)-iterations, 2 subsets CT-based attenuation correction Energy window based scatter correction
	Matrix	128 x 128	128 x 128
	Voxel size [mm]	4.26	4.80
Low dose CT parameters	Tube voltage	100 - 130 kV	100 - 130 kV
	Tube current	Automatic tube current modulation	Automatic tube current modulation
	Slice thickness	0.6 mm	0.6 mm
	Slice thickness reconstructed images	3 mm	3 mm