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Case Series of the Month

Prostate-specific Membrane Antigen–radioguided Surgery for Metastatic Lymph Nodes in Prostate Cancer

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Abstract

With the advent of ^{68}Ga-labeled prostate-specific membrane antigen-*N*,*N*′-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N*,*N*′-diacetic acid (^{68}Ga-PSMA-HBED-CC) positron emission tomography (PET) hybrid imaging in prostate cancer (PCa), even small metastatic lymph nodes (LNs) can be visualized. However, intraoperative detection of such LNs may not be easy owing to their inconspicuous morphology and/or atypical localization. The aim of our feasibility study was to evaluate PSMA-radioguided surgery for detection of metastatic LNs. One patient with primary PCa and evidence of LN metastases and four PCa patients with evidence of recurrent disease to regional LNs on ^{68}Ga-PSMA-HBED-CC PET hybrid imaging received an intravenous injection of an ^{111}In-PSMA investigation and therapy agent 24 h before surgery. Metastatic LNs were tracked intraoperatively using a gamma probe with acoustic and visual feedback. All radioactive-positive LN specimens detected in vivo were confirmed by ex vivo measurements and corresponded to PSMA-avid metastatic disease according to histopathology analysis. Intraoperative use of the gamma probe detected all PSMA-positive lesions identified on preoperative ^{68}Ga-PSMA-HBED-CC PET. Detection of small subcentimeter metastatic LNs was facilitated, and PSMA-radioguided surgery in two patients revealed additional lesions close to known tumor deposits that were not detected by preoperative ^{68}Ga-PSMA-HBED-CC PET. However, greater patient numbers and long-term follow-up data are needed to determine the future role of PSMA-radioguided surgery.

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1. Case series

This feasibility study included one patient with primary prostate cancer (PCa) and evidence of lymph node (LN) metastases, and four patients with biochemical-recurrent PCa and evidence of metastatic disease solely to regional LNs on ^{68}Ga-labeled prostate-specific membrane antigen-*N*,*N*′-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N*,

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Table 1 – Patient characteristics and results of PSMA-ligand–radioguided surgery

Patient	1		2		3		4		5	
Age (yr)	64		75		69		75		75	
Primary treatment	–		RP (Jan 2010)		RP (Sept 2013)		RP (Feb 2006)		HIFU + TURP (2007)	
Initial histological classification	–		pT2c pN0 cM0 R0 GS7		pT3a pN0 cM0 R0 GS7b		pT3b pN0 cM0 R0 GS8		cT2 cN0 cM0 GS6	
Further treatment	–		Salvage PLND (Nov 2010) RTX (May–Aug 2012_		–		RTX (Aug 2006)		RTX (2009)	
PSA at examination (ng/ml)	244		0.46		0.42		4.36		2.45	
Suspicious lesions on PSMA-ligand PET imaging	5		1		1		4		2	
Resected tissue specimens [a]	Histology		Histology		Histology		Histology		Histology	
	+	–	+	–	+	–	+	–	+	–
PSMA-ligand RGS positive	6	0	1	0	1	0	5 [b]	0	2	0
PSMA-ligand RGS negative	0	4	0	1	0	6	0	2	0	0
Histological classification	pT4 pN1 (6/25) cM0 GS10		pN1 (1/2)		pN1 (1/1)		pN1 (10/20)*		pN1 (2/2)	
Location of positive LN fields (size of largest positive LN within field)	Right side: obturator fossa (6 mm) external iliac (12 mm) internal iliac (4 mm) common iliac (2 mm) Left side: obturator fossa (8 mm) external iliac (5 mm)		Paravesical left (10 mm)		Paravesical right (6 mm)		Left side: obturator fossa (8 mm) external iliac (3 mm) internal iliac (9 mm) common iliac (5 mm) pararectal (11 mm)		Pararectal right (10 mm) presacral (7 mm)	

RP = radical prostatectomy; HIFU = high-intensity focused ultrasound; TURP = transurethral resection of the prostate; GS = Gleason score; PLND = pelvic lymph node dissection; RTX = radiotherapy of the prostate bed; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.
[a] LNs found in tissue specimens varied in number (0–5).
[b] Five different resected tissue specimens rated positive contained a total of ten histology-proven LN metastases.

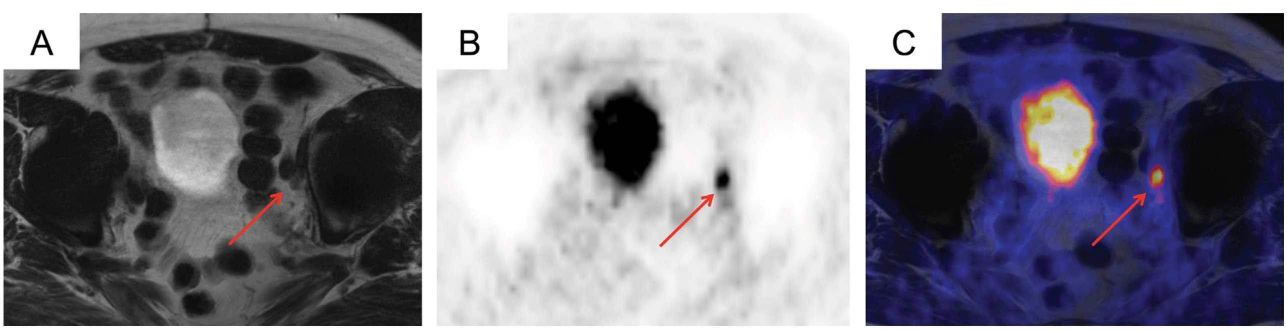

Fig. 1 – Example results for a patient with recurrent prostate cancer to pelvic lymph nodes (patient 4). (A) Axial T2-weighted magnetic resonance imaging (MRI) shows a small (6 mm) lymph node in left the obturator fossa (arrow). (B) Axial ^{68}Ga-labeled prostate-specific membrane antigen (PSMA)-ligand positron emission tomography (PET) and (C) axial ^{68}Ga-PSMA-*N,N′*-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N,N′*-diacetic acid (HBED-CC) PET/MRI fusion images show a distinct signal for this lymph node that is highly suspicious for metastasis, subsequently confirmed by histology after radioguided surgery using an ^{111}In-PSMA investigation and therapy agent. Note the susceptibility artifacts in the region of the hip joints caused by bilateral hip prostheses, as well as the activity of excreted ^{68}Ga-PSMA-HBED-CC in the bladder.

N′-diacetic acid (^{68}Ga-PSMA-HBED-CC) positron emission tomography (PET) hybrid imaging (Table 1; Fig. 1). All patients were treated only after providing consent once they had been informed of the experimental nature of PSMA-radioguided surgery as an individual treatment concept.

For PSMA-radioguided surgery, a gamma-emitting ^{111}In-labeled PSMA ligand was used as a radiotracer because of its favorable half-life of 2.8 d. However, owing to the instability of ^{111}In-PSMA-HBED-CC, a 1,4,7,10-tetraazacyclododecane,1-(glutaric acid)-4,7,10-triacetic acid (DOTAGA)-conjugated peptide-based ligand targeting PSMA (PSMA-I&T; investigation and therapy) was used for ^{111}In labeling and PSMA-radioguided surgery [1]. At 24 h before surgery, patients received an intravenous injection of 146 MBq (mean; range 110–169 MBq) ^{111}In-PSMA-I&T. Intraoperatively, metastatic LNs were detected using a gamma probe (Crystal Probe CXS-SG603; Crystal Photonics, Berlin, Germany) with live acoustic and visual feedback of the count rate; a higher rate indicates the presence of a radioactive hotspot (Fig. 2). In this technique the surgeon cognitively maps the count information onto the surgical field, without the possibility of image guidance. This approach was improved by the use of a freehand single-photon emission computed tomography system (declipseSPECT; SurgicEye, Munich, Germany) that allows visualization of radioactivity within a reconstructed three-dimensional (3D) image. The