



PSMA-Targeted Positron Emission Tomography (PET) in Evaluation of Patients with Primary Prostate Cancer: The Critical Role of the Pathologists' Assistant

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Abstract

The purpose of this project is to illustrate the importance of grossing technique and the role of the Pathologists' Assistant in the research context for whole-mount prostate processing of PSMA-Targeted Positron Emission Tomography (PET) scanning in positive prostate cancer patients. Patients who were selected for robotic-assisted radical prostatectomy for positive prostate cancer were consented for this clinical trial. After undergoing a pre-operative PET scan with Gallium-68-labelled-PSMA-11, the prostatectomy was performed and sent to the pathology lab. Whole mount pathology was performed on the specimen to facilitate a dimensional histopathologic comparison to corresponding radiographic images. This process demonstrated a crucial correlation between radiologic and pathologic findings. Of the 15 patients participating in the trial, thirty cancer lesions were found on whole-mount analysis, while PSMA-PET scan detected 100% of primary lesions and 82% of secondary lesions. This correlation demonstrates how PSMA-PET scan detection is a promising method for identifying prostatic lesions in patients preoperatively. Precise whole-mount prostate grossing by a Pathologists' Assistant was invaluable for demonstrating the radiopathologic correlation in question. Both the imaging modality and the pathology process were highly specialized and worked in tandem to demonstrate that preoperative scanning is an effective diagnostic tool.

Key words: prostate cancer, PET scan, pathology, prostatectomy

Introduction

Prostate specific membrane antigen (PSMA) targeted positron emission tomography (PET) imaging has shown promising results in Germany and Australia, with the study now being conducted at Indiana University in Indianapolis, Indiana, USA. PSMA is a tumor associated antigen and type II transmembrane protein that is expressed on the membrane of all prostatic cells and overexpressed on prostate tumor cells¹. When combined with the radioisotope Gallium (Ga 68), it creates a radiologic tracer for PSMA-expressing tumors within the prostate². PET scans are radiographic imaging tests that help reveal how tissues are functioning at the cellular level by utilizing a tracer³. This combination makes for a useful diagnostic marker for highlighting lesions found radiographically and was selected as the foundation for this study.

The radiologic images obtained via the PSMA-targeted PET scan were compared against a whole-mount analysis of the prostate with precise anatomic corollaries at 6mm intervals. Whole-mount pathology is a method of serially sectioning the entirety of a specimen while preserving three-dimensional conformation to allow for a thorough examination of the full specimen⁴. The Pathologists' Assistant and staff genitourinary pathologist played a critical role in the processing of these specimens while utilizing prosection modifications and customized tools to establish the precise corollaries demanded by this research model. To do so, a specialized apparatus was developed in the lab to facilitate sectioning at precisely 6mm intervals. This recapitulates the scanning intervals by the radiologist preoperatively. Having specific knowledge of how to handle these specimens was crucial in comparing radiographic images to the microscopic slides. Without the knowledge and dexterity that the Pathologists' Assistant possess, the integrity of the whole-mount sections could be compromised and a side-by-side analysis could not occur.

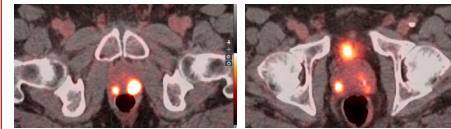
Materials & Methods

We will discuss the pathway to prostate grossing via a single patient. This patient is a 68-year-old male with a history of obstructive sleep apnea and obesity. The patient showed a prostate specific antigen (PSA) level of 9.9 ng/mL in his bloodwork in August of 2019. PSA is a protein that is normally produced by the prostate but can also be produced by malignant cells⁵. A normal range for PSA levels is debated and varies between laboratories, however a level greater than 4.0 ng/mL is considered elevated⁶. This was used as an indicator for the patient to receive additional studies. The patient then underwent the procedure to procure biopsy specimens of the suspicious gland. Twelve prostate biopsy cores were retrieved in September of 2019, with pathologic findings consistent of prostatic acinar adenocarcinoma. Specific results included Gleason scores of 4+3 and 20% of 1 core, 30% of another core, and 50% of another core. The patient had 3+4 in 4 cores and 3+3 and 2 cores. Gleason scores are a graded system for identifying prostate cancer on a scale from 1-5. Grade 1 cells resemble normal prostatic tissue, while Grade 5 are considered high-grade cancers⁷. An overall Gleason score of 6 is considered low grade, 7 is intermediate, and a score of 8 or above is high grade cancer⁸. Additionally, the patient presented with a PSA level of 11.3 ng/mL at this time. The patient denied dysuria, hematuria, or urinary frequency, and states he had good sexual ability and was interested in preserving functionality. Given the results of the biopsy and increasing PSA levels, the patient was recommended for robotic non-nerve-sparing (partial right nerve sparing) radical prostatectomy and recommended to the study. Before this procedure was done, the patient was given a PET scan. The patient was dosed with Gallium-68 PSMA-11 preoperatively, and the PET scan was then given 60 minutes post injection. Radiologic imaging was produced that showed images that highlighted areas where lesions were identified⁹. Sometime after, the patient underwent radical prostatectomy.

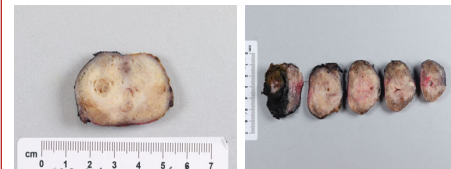
Upon completion of the radical prostatectomy, specimens were sent to the pathology lab for whole mount sectioning. Not only was whole mount sectioning of the prostate necessary, it was also imperative that sections taken maintained the scanning interval integrity of the gland. This anatomic fidelity was maintained by utilizing the aforementioned apparatus, guiding the sectioning at precisely 6mm intervals. This technique provided for the critical assessment of lesion grade, lesion heterogeneity and lesion volume, as well as producing a spatial comparison to grossly and histologically identified lesions from radiographic images. Utilization of the Pathologists' Assistant was seen as a crucial bridge between radiologic, urologic, and pathologic findings.

Specimens were fixed in 10% formalin, then weighed, measured, and inked. The apical and base margins were coned and radially sectioned. Then, the body of the gland was serially sectioned in an apex to base manner at precisely 6mm intervals parallel to the horizontal plane. This precise sectioning thickness was achieved via the aforementioned apparatus. Of note, the imaging plane was modified to accommodate the sectioning plane due to technical limitations at prosection. This was a crucial step to the whole mount pathology, as the PET scan images were taken at 6mm intervals. After processing of the prostate gland, histologic sections and images were taken that corresponded with the PET scan images. The seminal vesicles were then sectioned parallel to the junction of the prostate and submitted entirely. After the specimens were processed, each whole mount slice was digitized via a slide scanner, and each lesion was outlined digitally to calculate the overall area and ultimately volume. Eventually, percentage of Gleason scores were recorded and compared to the PET scan images.

Results



Images 1 & 2 - Result of PET radiographic imaging



Images 3 & 4 - Gross macroscopic view of 6mm interval prostatic slabs



Images 5 & 6 - Microscopic positive lesions sections post whole mount sectioning

Total patients	15	Grade group 2	5-6	Grade group 3-5	Median (IQR) <th>P-value</th> <th>TOTAL</th>	P-value	TOTAL
Age, median (IQR)	63 (58-64)						
PSA, median (IQR)	7.8 (7.4-11.4)						
Final Gleason per patient, GUS ¹							
Grade Group, N (%)							
1 (3%)	0	Whole mount analysis					
2 (14%)	8 (53%)	Number of lesions		15	25	26	26
3 (4%)	3 (20%)	Lesions per patient		1.5	2.1 (1.4-3.4)	1.8	2.1 (1.5-3.1)
4 (14%)	0	Lesion volume, total, cm ³		2.1 (1.1-3.8)	2.8 (1.2-6.0)	0.4	2.1 (1.1-3.8)
5 (14%, 54%)	4 (27%)	Lesion volume of 4% (volume * 100/4%, cm ³)		0.2 (0.09-0.61)	0.9 (0.8-9)	0.001	0.5 (0.1-2.9)
Pathologic T stage, N (%)		PSMA PET analysis					
T2	3 (20%)	Lesions detected, cm		12	11	23	23
T3a	6 (40%)	Lesions volume, cm ³		3.2 (4.9)	7.9 (5-14)	0.03	6.4 (4-11)
T3b	1 (4%)	Lesions volume of 4% (volume * 100/4%, cm ³)		0.4 (4.7)	0.6 (5-11)	0.02	5.7 (4-18)
Resect positive, N (%)	2 (13%)	Lesions stained		3	0		3
Total lesions by whole mount	30	Lesions volume, total, cm ³		1.5 (1.3-3.7)			
Lesions per patient per whole mount, median (IQR)	1 (1-3)	Lesion volume of 4% (volume * 100/4%, cm ³)		0.05 (0.05-0.08)			
PSMA PET stained lesions		PSA PET stained lesions					
Lesions detected, cm	1.5 (1.3-2.7)	Lesions detected, cm		1.5 (1.3-2.7)			
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Lesion volume of 4% (volume * 100/4%, cm ³)	0.05 (0.05-0.08)	Lesion volume of 4% (volume * 100/4%, cm ³)		0.05 (0.05-0.08)			
PSMA PET stained lesions		PSMA PET stained lesions					
Lesions detected, cm							