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PSMA FOR THE SURGICAL ONCOLOGIST: INTERPRETING EXPRESSION
BEYOND THE PROSTATE

Title Page

Invited article (PSMA Review)

PSMA FOR THE SURGICAL ONCOLOGIST: INTERPRETING EXPRESSION
BEYOND THE PROSTATE

Short title: PSMA EXPRESSION BEYOND THE PROSTATE

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ABSTRACT

The use of prostate-specific membrane antigen (PSMA) radiotracer in positron emission tomography (PET) has been successfully incorporated into the clinical management of prostate cancer. However, PSMA tracer uptake is not limited to prostate cancer tissue. We reviewed studies exploring PSMA expression beyond the prostate gland using techniques of ^{68}Ga -PSMA PET imaging and immunohistochemistry. PSMA expression has been associated with a variety of solid tumours, and the vasculature associated with neoplastic disease, suggesting that this trans-membrane glycoprotein may be involved in the neovascularisation process in malignancy. These studies demonstrate the need for more research into the potential utility for ^{68}Ga -PSMA PET imaging in patients with non-prostatic cancers.

INTRODUCTION

The use of a novel positron emission tomography (PET) radiotracer targeting prostate-specific membrane antigen (PSMA) has had a major impact on the management of patients with prostate cancer. A recent review suggested that ^{68}Ga -PSMA PET has changed management in 54% of patients (pooled average) being worked up for treatment options for prostate cancer. (1) ^{68}Ga -PSMA PET is now widely used in the staging of prostate cancer, especially in biochemical failure after primary therapy. PSMA is a trans-membrane glycoprotein comprising 750 amino acids expressed on dysplastic prostate cells at levels 100–1000 times that of normal cells in the body, and furthermore its expression is greater in proportion to higher stages and grades of prostate cancer. (2) However, PSMA has also been detected in other neoplastic organs, as well as the vasculature associated with many other solid tumours. (2, 3) Furthermore, its expression has also been found in varying concentrations on normal cells. Immunohistochemistry studies have shown PSMA to be expressed in the kidney, testis, ovary,

brain, salivary gland, small intestine, colon, liver, spleen, breast, skeletal muscle and benign fractures, as well as malignancies of these tissues. (3, 4)

Literature Search and Study Selection

A computerized search was performed using the search engine 'Discovery' which includes items from a wide variety of search engines and the University of Melbourne library catalogue. Searches were conducted until January 30, 2019. The search query was formulated based on keywords of "prostate-specific membrane antigen", "PSMA PET", "tumour expression" and "tissue expression" and their related terms. **Articles were reviewed which examined PSMA expression in tumours other than those associated with the prostate. The goal was to identify relevant published studies reporting PSMA expression in tumour cells, patient samples, or in vivo imaging. Forty-two original articles and literature reviews met the search criteria and of those twenty-eight were relevant to our review.**

PSMA Tracer Uptake in Normal Tissue and Prostate Cancer

⁶⁸Ga-PSMA PET has recently been widely adopted in identifying metastatic prostate cancer, however a complicating factor in interpreting this imaging modality has been the finding that PSMA radiotracer uptake may also occur in normal non-malignant tissue. **A study of patients with prostate cancer found that a cut-off value for the standardized maximum uptake value (SUV_{max}) of 3.2 differentiated prostate tumours from normal prostate tissue with a sensitivity of 94.3 % and a specificity of 100 %.** (5) Meanwhile, immunohistochemistry staining shows that PSMA expression occurs throughout the gastrointestinal tract, endometrial glands, salivary glands, lacrimal glands, brain, skeletal muscle, pancreatic islets and kidney tubules. (6) **However, these tissues have been shown to have non-tumour**

related uptake on ^{68}Ga -PSMA PET with a $\text{SUV}_{\text{max}} > 3$. (5) Although not always the case, expression in these tissues was found to be weak to moderate, compared to the relatively strong expression found in prostate cancer disease. (6) Uptake of PSMA tracer also occurs in primary malignancies of the breast, thyroid, lung, gastrointestinal system, kidney, bladder and brain. Furthermore studies have identified ^{68}Ga -PSMA PET uptake in healing fractures unrelated to a malignancy. (7)

Breast Cancer

Several studies have used immunohistochemistry to examine the differential expression of PSMA in normal breast tissue compared with breast cancer and breast cancer metastases. In normal breast tissue ^{68}Ga -PSMA PET expression was limited only to glandular cells, however breast malignancies and distant metastases expressed PSMA in tumour cells, the associated neovasculature, and in all known skeletal metastases. (8) Of particular clinical interest is ^{68}Ga -PSMA PET visualisation of neovasculature providing a potential therapeutic vascular target. An association between increased PSMA expression and lower overall survival in breast cancer has also been reported. (9) This study also found that greater PSMA expression correlated with larger tumours, higher cell proliferation, and higher nuclear grades. (9) PSMA expression was also more likely to be higher in tumours negative for estrogen and progesterone receptors. (9) These findings may potentially lead to new diagnostic algorithms if more research incorporates ^{68}Ga -PSMA PET into breast cancer treatment models.

Thyroid Cancer

In a study examining 91 samples of thyroid cancer, PSMA expression was expressed only in cancer neovasculature and not in the tumour cells, and was not detected in normal thyroid tissue. (10) The subtypes of thyroid cancer where neovasculature expressed the highest levels of PSMA were papillary, radioactive iodine-refractory and follicular thyroid tumours. (10) **A further study based in the Netherlands found that 92% of medullary thyroid cancers, which account for 4% of all thyroid cancers, expressed PSMA in the neovasculature.** (11) The tumor cells themselves were consistently negative for PSMA expression, however PSMA was expressed equally among neovasculature from primary tumours and that of lymph node metastatic disease. Furthermore this study found that greater PSMA-positive tumour vasculature correlated with longer survival. (11) The finding that greater than 90% of medullary thyroid cancers contained PSMA-positive vasculature is promising for further studies examining new ways to target this condition. Another study examining medullary thyroid cancers showed that PSMA PET detected 94% of lesions, whereas FDG PET/CT was positive in only 82%. (12) These findings suggest that thyroid uptake of tracer on ^{68}Ga -PSMA PET imaging even when incidental may suggest a possible malignancy, and that these patients should be considered for exclusion of thyroid cancer.

Non-Small Cell Lung Cancer (NSCLC)

A recent study used immunohistochemistry to identify PSMA expression in 275 NSCLC tissue specimens, with 49% of the NSCLC tissue specimens expressing PSMA in their neovasculature. (13) This study also found a positive correlation between higher tumour grading and the intensity of PSMA expression in the malignancy-associated neovasculature. **However PSMA expression only occurred in 6% of NSCLC tumour cells, with highest incidence in squamous cell carcinoma.** (13) Another study supported these findings, recording high PSMA expression rates (85%) in tumour neovasculature endothelial cells following the examination of 150 NSCLC specimens. (14) Of potential clinical

importance, this study showed that PSMA-positive endothelial cells were found more in early-stage disease compared to specimens of advanced NSCLC. (14) This is a favourable feature, and further studies may find clinical application for improved detection and prognostication of lung cancer patients in the endeavour to overcome the poor prognosis of cancer in these patients.

Pancreatic Cancer

Novel treatments for pancreatic cancer may depend on finding tumour biomarkers that can then be targeted. A recent study used immunohistochemistry to show that PSMA expression was found in high levels in one third of the pancreatic adenocarcinoma tissues examined. (15) This study also found that higher levels of PSMA expression correlated with higher pathological stages III and IV. (15) Another German study detected PSMA in almost two-thirds of the cases of pancreatic ductal adenocarcinoma associated neovasculature. (16) However as with many other solid tumours, PSMA was only expressed in a small proportion of actual pancreatic adenocarcinoma cells. (16) Further studies are needed to determine if these findings can be utilised in the early detection and treatment of pancreatic cancer.

Colon Cancer

Studies have demonstrated that PSMA is expressed in the colonic mucosa, specifically the chromogranin-positive cells of neuroendocrine origin in the deep aspects of the colonic crypts. (2) Immunohistochemistry techniques have found that although primary colorectal 2 tumour cells infrequently show PSMA expression, tumour neovasculature demonstrated increased PSMA expression. (17) Furthermore, expression of PSMA extended to lymph nodes containing metastatic colorectal cancer and higher grade tumours correlated with higher concentrations of PSMA expression. (17) An Egyptian study looking at 100 samples of colorectal cancer showed that PSMA was expressed

in the neovasculature of 75% of these tumours. (18) Furthermore this study also demonstrated a statistically significant positive correlation between the extent of PSMA expression and distant metastasis, as well as between PSMA expression and the presence of vascular invasion. (18) These findings highlight the need for further studies to determine the potential usefulness of PSMA as a prognostic and/or therapeutic vascular target in colorectal cancer.

Adrenal Tumours

Studies looking at PSMA expression in adrenocortical carcinoma found significantly more expression associated with adrenocortical carcinoma neovasculature than that of normal adrenal tissue or benign tumours. (19) (20) As for other solid tumours discussed, PSMA expression appeared to be isolated to the tumour neovasculature rather than the tumours themselves. Researchers in Brisbane, Australia demonstrated mild-to-moderate tracer uptake on ^{68}Ga -PSMA PET on the adrenal gland, localising to a lesion representing a lipid-rich adrenal adenoma (with an average Hounsfield unit of 7.4 on non-contrast CT). *As adrenal adenomas do not occur infrequently, this finding is clinically relevant when determining true metastatic prostate disease, as clinicians increasingly use ^{68}Ga -PSMA PET in the management of prostate cancer.*

Renal Cell Carcinoma (RCC)

Studies have also demonstrated the expression of PSMA in renal cell carcinoma (RCC) with Northern blot analysis. (21) PSMA-targeted PET imaging has been shown to have a higher sensitivity than conventional imaging techniques such as CT, MRI, and ^{18}F -fluorodeoxyglucose (FDG) PET for detecting metastatic sites of clear cell RCC. (22) This study used immunohistochemistry to

demonstrate PSMA expression within the neovasculature in the majority of clear cell RCC tumour specimens. Furthermore, a significant positive correlation was found between PSMA expression levels and disease stage, grade, and overall survival, with the association of PSMA positivity and overall survival remaining statistically significant even after controlling for the disease stage and tumour grade of clear cell RCC. (22) Another such study examining papillary RCCs found that these also expressed PSMA in neovasculature, however PSMA was not expressed on any of the chromophobe carcinomas, oncocytomas, and Wilms' tumour tissues investigated. (23) Australian study compared the diagnostic utility of FDG and PSMA radiotracers in the evaluation of metastatic RCC, finding diagnostic utility of PSMA PET imaging. (24) Furthermore, in one case the detection of additional sites of metastases through PSMA-PET had a significant impact on a patient's clinical management; overall, PSMA uptake was typically higher compared to FDG uptake. (24)

Urothelial Cancers

PSMA expression was evaluated in 167 bladder tumours of different subtypes, demonstrating that PSMA is occasionally expressed in subtypes including urothelial cell carcinoma (UCC), adenocarcinoma and small cell carcinoma of the bladder. (25) PSMA expression is only found in a small proportion of each of the various subtypes of UCC, however was present in all of the neovasculature associated with advanced bladder cancer, and has been associated with decreased patient survival. (25) The finding that PSMA may be expressed in bladder cancer tumour cells justifies caution when using PSMA uptake as the only diagnostic marker when evaluating prostatic tissue invasion into the bladder in prostate cancer.

Glioblastoma Multiforme (GBM)

In a study of 32 paraffin-embedded primary GBM specimens immunohistochemistry revealed that all exhibited staining for PSMA. Furthermore, 69% of these specimens showed PSMA staining in over half of the neovasculature contained within each sample. (26) This provides a potentially promising clinical application for targeting tumour cells, as endothelium in brain malignancy is more accessible to antibodies than the tumour substance that is protected by the blood-brain barrier. Furthermore researchers also found that PSMA expression was more concentrated in tumour vessels associated with highly vascular gliomas, such as glioblastoma multiforme, than in lower-grade gliomas. (27) These findings may potentially lead to new diagnostic algorithms if more research incorporates ^{68}Ga -PSMA PET into glioblastoma multiforme treatment models.

DISCUSSION

^{68}Ga -PSMA PET imaging is currently undergoing a period of intense clinical interest that is reflected in the literature. The articles reviewed demonstrate that PSMA is highly expressed in the endothelium of vessels in malignant solid tumours but scarcely in normal vessels. PSMA expression has been associated with a variety of solid tumours and is particularly expressed in their neovascularisation processes. PSMA might facilitate endothelial cell sprouting and invasion through its regulation of lytic proteases that have the ability to cleave the extracellular matrix (28). However further studies characterising the role of PSMA in the pathogenesis of these malignancies is required.

The studies reviewed provide strong evidence that PSMA is not solely expressed in prostatic tissue or metastatic disease related to prostate cancer. Of particular clinical interest, the expression of PSMA in malignancy-associated neovasculature, across multiple different malignancies raises the possibility of specific antibody-based therapies, and the use of ^{68}Ga -PSMA PET to target these lesions. This finding

and the potential associated therapies rely on the nature of tumour vasculature being morphologically distinct from normal vasculature. This is especially of interest for intracranial malignancies for which the endothelium is more accessible to antibodies than the tumour substance itself due to the blood brain barrier. This opens the possibility of clinical trials using a cytotoxin-conjugated antibody to PSMA, to target the vasculature of the different malignancies expressing PSMA.

Furthermore the widespread expression of PSMA on non-prostate malignancies seen in these studies is an important factor when staging prostate cancer. In some instances it may be relevant to investigate for a second primary malignancy when PSMA tracer uptake is present on ^{68}Ga -PSMA PET imaging and is not in keeping with likely disease progression for metastatic prostate cancer.

Immunohistochemical staining has compared different tumours expressing PSMA and has shown that the sensitivity and specificity of using PSMA in distinguishing prostate cancer from all other tumour types was 65.9% and 94.5%, respectively. (6)

Ultimately lesions showing PSMA tracer uptake on ^{68}Ga -PSMA PET imaging require clinical correlation in order to correctly interpret whether they reflect prostate cancer disease, normal tissue uptake or the possibility of a non-prostatic malignancy. Further studies are needed to determine the ultimate utility of ^{68}Ga -PSMA PET imaging as a diagnostic tool for neovascularity associated with non-prostatic solid organ tumours. **With the development of new tracers the use of PSMA PET imaging is an evolving modality in the treatment model for prostate cancer, the studies reviewed suggest further research is required to define the role for ^{68}Ga -PSMA PET in surgical oncology in wider surgical practice. All surgeons would be well served by an appreciation of the status of this marker and its current ability to potentially identify incidental non-prostatic cancers, and its potential utility as a broad diagnostic and therapeutic tool in the future.**

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