

Radiolabelled PSMA PET/CT in breast cancer. A systematic review

Francesco Bertagna¹ (0), Domenico Albano¹ (0), Elisabetta Cerudelli¹ (0), Maria Gazzilli¹ (0), Davide Tomasini² (0),

Marco Bonù² 跑 Raffaele Giubbini¹ 跑 Giorgio Treglia^{3,4,5} 🔟

Nuclear Medicine, University of Brescia and Spedali Civili di Brescia, Brescia, Italy

²Department of Radiation Oncology, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy

³Department of Nuclear Medicine and PET/CT Center, Imaging Institute of Southern Switzerland, Bellinzona and Lugano, Switzerland ⁴Department of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

⁵Health Technology Assessment Unit, General Directorate, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

[Received 18 XII 2019; Accepted 8 I 2020]

Abstract

BACKGROUND: Radiolabelled prostate-specific membrane antigen (PSMA)-based PET/CT is a whole-body imaging technique currently performed for the detection of prostate cancer lesions. PSMA has been also demonstrated to be expressed by the neovasculature of many other solid tumours. The aim of this review is to evaluate the possible diagnostic role of radiolabelled PSMA PET/CT in breast cancer.

MATERIAL AND METHODS: A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane Library databases was conducted to find relevant published articles about the diagnostic performance of radiolabelled PSMA PET/CT in breast cancer.

RESULTS: The comprehensive computer literature search revealed 652 articles. On reviewing the titles and abstracts, 640 articles were excluded because the reported data were not within the field of interest of this review. Twelve articles were selected and retrieved in full-text version; no additional study was found when screening the references of these articles. In total, 12 articles were included in the systematic review.

CONCLUSIONS: Further studies enrolling a wider population are needed to clarify the real clinical and diagnostic role of radiolabelled PSMA in this setting and its possible position in the diagnostic flow-chart.

KEY words: PSMA; prostate specific membrane antibodies; breast cancer; PET; positron emission tomography.

Nucl Med Rev 2020; 23, 1: 32-35

Introduction

Radiolabelled Gallium-68 (⁶⁸Ga) of Fluorine-18 (¹⁸F) prostate-specific membrane antigen (PSMA)-based positron emission tomography/computed tomography (PET/CT) are whole-body imaging techniques currently performed to detect prostate cancer (PCa) lesions. The main diagnostic field of PSMA-based imaging is the whole body primary staging of intermediate and high-risk PCa or PCa restaging after biochemical disease relapse (rising prostate-specific antigen levels) in patients with prior radical prostatectomy or external beam radiation [1–3].

Human PSMA is a zinc containing metalloenzyme (750 amino acids) with a unique 3-part structure composed of a large

Correspondence to: Francesco Bertagna, M.D. Nuclear Medicine, University of Brescia and Spedali Civili di Brescia Ple Spedali Civili, 1, 25123 Brescia, Italy e-mail: francesco.bertagna@unibs.it Tel.: +39-30-3995468, Fax: +39-30-3995420 extracellular domain, a transmembrane portion, and an intracellular component. PSMA has recently emerged as a target for radionuclide imaging and treatment of PCa as this protein is significantly overexpressed by most PCa cells [4–14]. High expression of PSMA in PCa and upon ligand-binding internalization of PSMA by clathrin-coated pits and subsequent endocytosis makes it a useful target for diagnostic and therapeutic applications in nuclear medicine. However, PSMA has been demonstrated to be expressed by the neovasculature of many solid tumours (for example colon, gastric, lung, gliomas/glioblastomas, adrenal, bladder, renal cell carcinoma), in some non-neoplastic conditions and also as incidental findings in other organs like thyroid [6–14]. High expression of PSMA and upon ligand-binding internalization of PSMA by clathrin-coated pits and subsequent endocytosis makes it a useful target for diagnostic and therapeutic applications in nuclear medicine.

The aim of this literature systematic review is to evaluate the possible diagnostic role of radiolabelled PSMA PET/CT in patients with breast cancer and to expand the knowledge about PSMA uptake in cancers in addiction to prostate one focusing in particular on breast cancer.

Material and methods

Search Strategy

A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane Library databases was conducted to find published articles about the role of radiolabelled PSMA PET/CT in breast cancer. We used a search algorithm that was based on a combination of the terms: a) "PSMA" OR "prostate-specific membrane antigen" AND b) "breast". No beginning date limit was used; the search was updated until July 30th 2019. Only articles in the English language were selected, pre-clinical or not in vivo studies, conference proceedings, editorials and reviews were excluded. To expand our search, references of the retrieved articles were also screened for additional studies. All literature studies collected were managed using EndNote Web 3.3.

Study selection

All articles reporting patients with breast cancer evaluated by radiolabelled PSMA PET/CT in the clinical setting were eligible for inclusion. Two researchers independently reviewed the titles and abstracts of the retrieved articles. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion.

Data abstraction

For each included study, information was collected concerning the basic study (author names, year of publication, country of origin, type of study) and PET device used (PET/CT or PET), number of patients evaluated and final diagnosis. The main findings of the articles included in this review are reported in the Results.

Results

Literature search

The comprehensive computer literature search revealed 652 articles (Fig. 1). On reviewing the titles and abstracts, 640 articles were excluded because the reported data were not within the field of interest of this review. Twelve articles were selected and retrieved in full-text version [15–26]; no additional study was found when screening the references of these articles. In total, 12 articles were included in the systematic review [15–26].

Qualitative analysis (systematic review)

Findings of several studies have documented that radiolabelled PSMA PET/CT imaging may identify breast cancer and its metastases. The characteristics of the studies and results are briefly presented in Table 1 and Table 2.

Discussion

Imaging of breast cancer has always been challenging for the nuclear medicine physicians and the radiologists. The PSMA is a type II transmembrane protein physiologically, mapped to chromosome 11q14, expressed by prostate tissue and significantly over-expressed by most PCa cells. However, PSMA is not solely expressed by prostate tissue [6–14]. Importantly, PSMA



Figure 1. Flow-chart of the search strategy

over-expression also occurs in pathophysiologic processes other than PCa, especially in the neovasculature of multiple malignancies. Among the most common non-PCa to demonstrate PSMA expression are breast, lung, colorectal, and renal cell carcinoma; in particular, it has long been hypothesized and documented the PSMA expression in breast carcinomas [27–29]. These findings suggest that PSMA may have broader potential as a tumour-associated neo-vascular target in addition to one that is tumour-specific (prostate) and consequently the insight that radiolabelled PSMA PET/CT could be suitable and useful in evaluating breast cancer. In the study by Wernicke et al. [29] is demonstrated that PSMA expression in the neovasculature of primary breast cancers (74%), as well as, distant metastatic disease (100%) is largely restricted to endothelial cells within the pathologically defined tumour area.

So far, the clinical (in vivo) use of radiolabelled PSMA PET/CT is only preliminary explored; in fact, from the results of our review only 12 articles have been found, 11 of which were case reports [15–23, 25, 26].

Considering the 11 cases reports, in all 11 patients radiolabelled PSMA PET/CT was positive identifying primary or metastatic lesions, despite in two cases of male patients the radiolabelled PSMA uptake was determined by gynecomastia [16, 23] and in one case by pseudoangiomatous stromal hyperplasia [25]. Interestingly, the number of male patients who underwent radiolabelled PSMA PET/CT and in which a breast uptake was identified was not negligible (2 out of 5); breast cancer was incidentally diagnosed in 2/5 male patients [15, 17] and benign lesions in 3/5 [16, 23, 25].

Only the study by Sathekge et al. [24] was a prospective evaluation enrolling 19 female patients; ⁶⁸Ga-PSMA PET/CT imaging was performed in 9 "de novo" diagnosed breast carcinoma patients, in 5 patients presenting with a loco-regional recurrence of breast carcinoma, and in a pre-treatment metastasized setting in another 5 patients. They documented a robust expression of PSMA by breast cancer lesions as evidenced using ⁶⁸Ga-PSMA PET/CT imaging and

Table 1. Characteristics of studies about radiolabelled PSMA

First author	Ref.	Year	N.Pts	Gender	Type of study	Country	Device	Isotope
Polverari	15	2019	1	М	CR	Italy	PET/CT	68Ga
Daglioz Gorur	16	2018	1	М	CR	Turkey	PET/CT	68Ga
Kumar	17	2018	1	М	CR	India	PET/CT	68Ga
Malik	18	2018	1	F	CR in CS	India	PET/CT	68Ga
Medina-Ornelas	19	2018	1	F	CR	Mexico	PET/CT	68Ga
Parihar	20	2018	1	F	CR	India	PET/CT	68Ga
Passah	21	2018	1	F	CR	India	PET/CT	68Ga
Tolkach	22	2018	1	F	CR in study	Germany	PET/CT	68Ga
Sasikumar	23	2017	1	М	CR	India	PET/CT	68Ga
Sathekge	24	2017	19	F	Р	South Africa	PET/CT	68Ga
Malik	25	2016	1	М	CR	India	PET/CT	68Ga
Sathekge	26	2015	1	F	CR	South Africa	PET/CT	68Ga

Ref. - reference; N.Pts - cases examined; P - prospective; CR - case report; CS - case series; M - male; F - female

Table 2. PSMA results and final diagnosis

First author	Ref.	N.Pts	PET/CT positive	Final diagnosis	Gold standard final diagnosis
Polverari	15	1	1	Invasive ductal breast cancer, nonspecial type	Histology
Daglioz Gorur	16	1	1	Gynecomastia	US
Kumar	17	1	1	Infiltrating ductal carcinoma	Fine-needle aspiration cytology/histology
Malik	18	1	1	Breast cancer MM	NA
Medina-Ornelas	19	1	1	Brain MM from breast cancer	Histology
Parihar	20	1	1	Triple-negative signet ring cell adenocarcinoma (primary lesion and MM	Histology
Passah	21	1	1	MM from triple-negative breast carcinoma	Histology
Tolkach	22	1	1	MM from triple-negative breast cancer and local persistence of disease	Histology
Sasikumar	23	1	1	Gynecomastia	US and Mx
Sathekge	24	19	19	Breast cancer (primary site, local relapse or MM)*	Histology ^ ^/ clinical
Malik	25	1	1	Pseudoangiomatous stromal hyperplasia	Histology
Sathekge	26	1	1	MM from breast cancer	Clinical/18FDG-PET/CT

Ref. — reference; N.Pts — cases examined; NA — not available; US — ultrasonography; MM — metastases; Mx — mammography; * — 13 ductal, 2 lobular, 1 neuroendocrine, 3 NA; ^ ^ — for patients with "de novo" diagnosed breast carcinoma

the absence of PSMA expression on normal vascular endothelium as well as its limited expression on the luminal side of the intestinal epithelium (which is not accessible via the vasculature); these facts have suggested that PSMA could be an interesting potential target for antiangiogenic therapy of breast carcinoma.

Considering the very low number of reports and patients analyzed in literature, no high-quality evidence could be drawn about the role of radiolabelled PSMA PET/CT in breast cancer but this evaluation can be helpful in better understanding the diagnostic potential of the tracer and the underlying metabolic mechanisms; further studies and prospective large studies are desirable to clarify the real diagnostic role of radiolabelled PSMA in this field and its possible position in the diagnostic flow-chart. However, the available literature data demonstrate that breast cancers are radiolabelled PSMA-avid tumours. These insights, if confirmed, could open up the way to possible future use of radiolabelled PSMA PET/CT in this tumours.

Conclusions

Despite few studies are currently available, radiolabelled PSMA is not specific for the prostate, as several benign and malignant entities have been reported by imaging and histologic studies to show a relevant expression, especially in tumour-associated endothelial cells. Radiolabelled PSMA imaging seems to be useful in analysing breast cancer despite further studies enrolling larger population are desirable to clarify the real clinical and diagnostic role of radiolabelled PSMA PET/CT and its possible position in the diagnostic flow-chart.

Funding: The authors declare that there is no funding.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

References

- Treglia G, Annunziata S, Pizzuto DA, et al. Detection Rate of F-Labeled PSMA PET/CT in Biochemical Recurrent Prostate Cancer: A Systematic Review and a Meta-Analysis. Cancers (Basel). 2019; 11(5), doi: 10.3390/cancers11050710, indexed in Pubmed: 31126071.
- Wu H, Xu T, Wang X, et al. Diagnostic Performance of Gallium Labelled Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography and Magnetic Resonance Imaging for Staging the Prostate Cancer with Intermediate or High Risk Prior to Radical Prostatectomy: A Systematic Review and Meta-analysis. World J Mens Health. 2019 [Epub ahead of print], doi: 10.5534/wjmh.180124, indexed in Pubmed: 31081294.
- Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2019 [Epub ahead of print], doi: 10.1016/j. eururo.2019.01.049, indexed in Pubmed: 30773328.
- Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015; 42(2): 197–209, doi: 10.1007/s00259-014-2949-6, indexed in Pubmed: 25411132.
- Kratochwil C, Giesel FL, Eder M, et al. [¹ Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015; 42(6): 987–988, doi: 10.1007/s00259-014-2978-1, indexed in Pubmed: 25573634.
- Chang SS, Reuter VE, Heston WD, et al. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res. 1999; 59(13): 3192–3198, indexed in Pubmed: 10397265.
- Haffner MC, Kronberger IE, Ross JS, et al. Prostate-specific membrane antigen expression in the neovasculature of gastric and colorectal cancers. Hum Pathol. 2009; 40(12): 1754–1761, doi: 10.1016/j.humpath.2009.06.003, indexed in Pubmed: 19716160.
- Kinoshita Y, Kuratsukuri K, Landas S, et al. Expression of prostate-specific membrane antigen in normal and malignant human tissues. World J Surg. 2006; 30(4): 628–636, doi: 10.1007/s00268-005-0544-5, indexed in Pubmed: 16555021.
- Hofman MS, Hicks RJ, Maurer T, et al. Prostate-specific Membrane Antigen PET: Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls. Radiographics. 2018; 38(1): 200–217, doi: 10.1148/rg.2018170108, indexed in Pubmed: 29320333.
- Verburg FA, Krohn T, Heinzel A, et al. First evidence of PSMA expression in differentiated thyroid cancer using [Ga]PSMA-HBED-CC PET/CT. Eur J Nucl Med Mol Imaging. 2015; 42(10): 1622–1623, doi: 10.1007/s00259-015-3065-y, indexed in Pubmed: 25916744.
- Taywade SK, Damle NA, Bal C. PSMA Expression in Papillary Thyroid Carcinoma: Opening a New Horizon in Management of Thyroid Cancer? Clin Nucl Med. 2016; 41(5): e263–e265, doi: 10.1097/RLU.000000000001148, indexed in Pubmed: 26914556.
- Noss KR, Wolfe SA, Grimes SR. Upregulation of prostate specific membrane antigen/folate hydrolase transcription by an enhancer. Gene. 2002; 285(1-2): 247–256, doi: 10.1016/s0378-1119(02)00397-9, indexed in Pubmed: 12039052.
- Bourgeois S, Gykiere P, Goethals L, et al. Aspecific Uptake of 68GA-PSMA in Paget Disease of the Bone. Clin Nucl Med. 2016; 41(11): 877–878, doi: 10.1097/RLU.00000000001335, indexed in Pubmed: 27556795.
- Bertagna F, Albano D, Giovanella L, et al. Ga-PSMA PET thyroid incidentalomas. Hormones (Athens). 2019; 18(2): 145–149, doi: 10.1007/s42000-019-00106-8, indexed in Pubmed: 30989578.

- Polverari G, Ceci F, Calderoni L, et al. Male Breast Cancer Detected by Ga-PSMA-11 PET/CT in a Patient With Prostate Cancer With Pelvic Lymph Node Metastasis. Clin Genitourin Cancer. 2019; 17(2): 154–156, doi: 10.1016/j.clgc.2018.11.020, indexed in Pubmed: 30587404.
- Daglioz Gorur G, Hekimsoy T, Isgoren S. Re: False Positive Uptake in Bilateral Gynecomastia on 68Ga-PSMA PET/CT Scan. Clin Nucl Med. 2018; 43(10): 785, doi: 10.1097/RLU.00000000002086, indexed in Pubmed: 29688944.
- Kumar R, Mittal BR, Bhattacharya A, et al. Synchronous Detection of Male Breast Cancer and Prostatic Cancer in a Patient With Suspected Prostatic Carcinoma on 68Ga-PSMA PET/CT Imaging. Clin Nucl Med. 2018; 43(6): 431–432, doi: 10.1097/RLU.00000000002063, indexed in Pubmed: 29538032.
- Malik D, Kumar R, Mittal BR, et al. 68Ga-Labeled PSMA Uptake in Nonprostatic Malignancies: Has the Time Come to Remove "PS" From PSMA? Clin Nucl Med. 2018; 43(7): 529–532, doi: 10.1097/RLU.00000000002103, indexed in Pubmed: 29688950.
- Medina-Ornelas SS, García-Pérez FO, Medel-Gamez C, et al. A single brain metastasis seen on Ga-PSMA PET/CT in recurrent breast cancer. Rev Esp Med Nucl Imagen Mol. 2018; 37(1): 61–62, doi: 10.1016/j.remn.2017.04.004, indexed in Pubmed: 28645683.
- Parihar AS, Mittal BR, Sood A, et al. 68Ga-Prostate-Specific Membrane Antigen PET/CT and 18F-FDG PET/CT of Primary Signet Ring Cell Breast Adenocarcinoma. Clin Nucl Med. 2018; 43(11): e414–e416, doi: 10.1097/RLU.00000000002265, indexed in Pubmed: 30247208.
- Passah A, Arora S, Damle NA, et al. 68Ga-Prostate-Specific Membrane Antigen PET/CT in Triple-Negative Breast Cancer. Clin Nucl Med. 2018; 43(6): 460–461, doi: 10.1097/RLU.000000000002071, indexed in Pubmed: 29578872.
- Tolkach Y, Gevensleben H, Bundschuh R, et al. Prostate-specific membrane antigen in breast cancer: a comprehensive evaluation of expression and a case report of radionuclide therapy. Breast Cancer Res Treat. 2018; 169(3): 447–455, doi: 10.1007/s10549-018-4717-y, indexed in Pubmed: 29455299.
- Sasikumar A, Joy A, Nair BP, et al. False Positive Uptake in Bilateral Gynecomastia on 68Ga-PSMA PET/CT Scan. Clin Nucl Med. 2017; 42(9): e412–e414, doi: 10.1097/RLU.000000000001742, indexed in Pubmed: 28682848.
- Sathekge M, Lengana T, Modiselle M, et al. Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients. Eur J Nucl Med Mol Imaging. 2017; 44(4): 689–694, doi: 10.1007/s00259-016-3563-6, indexed in Pubmed: 27822700.
- Malik D, Basher RK, Mittal BR, et al. 68Ga-PSMA Expression in Pseudoangiomatous Stromal Hyperplasia of the Breast. Clin Nucl Med. 2017; 42(1): 58–60, doi: 10.1097/RLU.00000000001445, indexed in Pubmed: 27819857.
- Sathekge M, Modiselle M, Vorster M, et al. Ga-PSMA imaging of metastatic breast cancer. Eur J Nucl Med Mol Imaging. 2015; 42(9): 1482–1483, doi: 10.1007/s00259-015-3066-x, indexed in Pubmed: 25931036.
- Uría JA, Velasco G, Santamaría I, et al. Prostate-specific membrane antigen in breast carcinoma. Lancet. 1997; 349(9065): 1601, doi: 10.1016/S0140-6736(05)61629-7, indexed in Pubmed: 9174566.
- Salas Fragomeni RA, Amir T, Sheikhbahaei S, et al. Imaging of Nonprostate Cancers Using PSMA-Targeted Radiotracers: Rationale, Current State of the Field, and a Call to Arms. J Nucl Med. 2018; 59(6): 871–877, doi: 10.2967/jnumed.117.203570, indexed in Pubmed: 29545375.
- Wernicke AG, Varma S, Greenwood EA, et al. Prostate-specific membrane antigen expression in tumor-associated vasculature of breast cancers. APMIS. 2014; 122(6): 482–489, doi: 10.1111/apm.12195, indexed in Pubmed: 24304465.