Radiolabelled PSMA PET/CT or PET/MRI in hepatocellular carcinoma (HCC): a systematic review

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Abstract

Introduction Radiolabelled prostate-specific membrane antigen PSMA-based PET/CT or PET/MRI is a whole-body imaging technique usually performed for the detection of prostate cancer lesions. PSMA has been also demonstrated to be expressed by the neovasculature of many other solid tumors. The aim of this review is to evaluate the possible diagnostic role of radiolabelled PSMA PET/CT or PET/MRI in patients with hepatocellular carcinoma, by summarizing the available literature data.

Methods A wide literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was made to find relevant published articles about the diagnostic performance of radiolabelled PSMA binding agents in PET/CT or PET/MRI imaging of patients with hepatocellular carcinoma.

Results Ten case reports and three studies showed that hepatocellular carcinoma is PSMA-avid.

Conclusion Radiolabelled PSMA imaging seems to be useful in analyzing hepatocellular carcinoma. Further studies enrolling a wider population are needed to clarify the real clinical and diagnostic role of radiolabelled PSMA in this setting.

Keywords PSMA · HCC · Positron emission tomography · PET/CT · PET/MRI

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy and it is one of the most common cancer in the world with high mortality rate. Although there are epidemiological differences according to the geographical area considered, risk factors for the development of HCC include chronic hepatitis B and C, hepatic steatosis, alcohol consumption, genetic factors and liver inflammation or injury [1]. Patients with early HCC, who receive

potentially curative therapy (liver transplantation or resection) reach 5-year survival rates near 70%; on the other hand patients with advanced HCC have a median survival of less than 1 year. An early diagnosis is therefore fundamental to improve survival. Imaging is pivotal in the management of HCC allowing screening populations at risk, confirming the diagnosis, guiding therapy, following up and aims to characterize the tumor and to define the remote extent. Many cases of HCC are diagnosed via imaging as (computed tomography) CT or (magnetic resonance) MRI, with several grading or scoring systems available including LI-RADS and OPTN-UNOS [2–4]. For example, LI-RADS systems offers the opportunity to report imaging in terms of arterial enhancement, washout appearance, capsule appearance, diameters and threshold growth to categorize liver lesions in terms of malignancy probability; when applied to MRI imaging, LI-RADS demonstrated a strong interobserver agreement [3, 4].

Surgical resection and liver transplantation are the mainstay of treatment, offering the best chance of cure and early diagnosis usually results in a better outcome. Trans-arterial chemoembolization (TACE) and radiofrequency ablation

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(RFA) are also important therapeutic techniques used for treatment management of HCC [1].

In this context, positron emission tomography (PET) with several positron emitters radiopharmaceuticals has been used to investigate patients with HCC [5]. Radiolabelled Gallium-68 (^{68}Ga) or Fluorine-18 (^{18}F) prostate-specific membrane antigen (PSMA)-based positron emission tomography/computed tomography or magnetic resonance imaging (PET/CT or PET/MRI) are imaging techniques normally used for the evaluation and the diagnosis of prostate cancer (PCa) lesions. PSMA-based imaging is usually performed for the initial staging of intermediate to high risk PCa; restaging after biochemical disease relapse (rising prostate-specific antigen levels) in patients with prior radical prostatectomy or radical external beam radiation are also important field of application [6–8].

PSMA has recently been suggested as a target for radionuclide imaging and treatment of PCa [9, 10]. Human PSMA is a metalloenzyme containing zinc composed of 750 amino acids, with a 3-part structure consisting of a large extracellular domain, a transmembrane portion and an intracellular component. PSMA is normally internalized in PCa cells with a ligand-binding process by clathrin-coated pits and subsequent endocytosis, making it a useful target for diagnostic and therapeutic applications in nuclear medicine. Moreover, it has been demonstrated that PSMA can be expressed by the neovasculature of many solid tumors (for example gastrointestinal neoplasms) and also in some non-neoplastic conditions [11–21].

The aim of this review is to evaluate the possible diagnostic role of radiolabelled PSMA PET/CT or PET/MRI in patients with HCC by summarizing the available literature data.

Methods

Search strategy

A wide literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was made to find significant published articles about the role of radiolabelled PSMA PET/CT or PET/MRI in patients affected by HCC. We used a search algorithm that was based on a combination of the terms: (a) “PSMA” OR “prostate-specific membrane antigen” AND (b) “hepatocellular carcinoma” OR “HCC”. No beginning date limit was applied; the search was updated until September 3rd 2020. Only articles in the English language were considered; pre-clinical or non in-vivo studies, conference proceedings, reviews and editorial were excluded. To expand our search, references of the retrieved articles were also screened for additional papers.

All literature studies collected were managed using EndNote Web 3.3.

Study selection

All articles reporting patients with HCC evaluated by radiolabelled PSMA PET/CT or PET/MRI in 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/MRI), number of patients evaluated, number of patients who underwent further investigations and malignancies detected. The main findings of the articles included in this review are reported in the Results.

Results

Literature search

A total of 55 articles were extrapolated with the computer literature search and by reviewing the titles and abstracts 43 of them 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 [22–33]; one additional study was found screening the references of these articles [34]. A total of 13 articles were then included in the systematic review [22–34] (Fig. 1).

Qualitative analysis (systematic review)

Findings of several studies have shown that radiolabelled PSMA PET imaging may identify HCC. The characteristics of the studies and results are briefly presented in Tables 1 and 2.

Discussion

Several PET tracers have been explored for potential use in detection of HCC, including ^{18}F -fluorodeoxyglucose (^{18}F FDG), ^{18}F - and ^{11}C -choline and ^{11}C -acetate. The detection rate of HCC by ^{18}F FDG PET/CT is generally low with the exception of poorly differentiated histotype; the reason for this suboptimal rate is thought to be a combination

Fig. 1 Flow chart of the search of eligible studies on the diagnostic performance of [^{68}Ga] Ga-PSMA PET/CT for the detection of HCC

of variable expression of glucose transporters and glycolytic enzymes in HCC. High background liver uptake is also a known reason. Normally, [^{18}F]FDG uptake by cells is mediated by facilitative glucose transporters (GLUT), mainly 1 and 3; when inside the cell [^{18}F]FDG is phosphorylated by the hexokinase enzyme into [^{18}F]FDG-6-phosphate. As known, cancer cells are characterized by increased levels of GLUT1 and GLUT3 expression, as well as high levels of hexokinase and phosphorylation activity, resulting in high levels of [^{18}F]FDG uptake. Once inside cells, [^{18}F]FDG-6-phosphate cannot be metabolized in the oxidative or glycolytic pathways, unlike glucose-6-phosphate. Many cancer cells have a low expression of glucose-6-phosphatase and therefore glucose-6-phosphate or [^{18}F]FDG-6-phosphate are dephosphorylated only in small quantity, remaining trapped within the cell. As a result, [^{18}F]FDG-6-phosphate can be detected by PET [35].

In normal liver cells, glucose-6-phosphate or [^{18}F]FDG-6-phosphate can undergo dephosphorylation and can

therefore exit the cells. Glucose-6-phosphatase concentration is normally high in liver cells and this fact is responsible for its mild FDG uptake [35]. Regarding enzymatic expression, well-differentiated HCC is similar to normal liver and this could be the reason for its mild appearance when using [^{18}F]FDG; this is the reason for the impairment of lesion detectability and the low sensitivity of [^{18}F]FDG PET or PET/CT. Instead, the higher levels [^{18}F]FDG uptake by moderately to poorly differentiated HCC are the result of low levels of glucose-6-phosphatase and high levels of hexokinase [36–39]. In this context, it is clear that a negative [^{18}F]FDG PET/CT scan is not able to exclude HCC and, moreover, it has been considered as a negative prognostic marker in patients affected by this disease [40–42].

In this scenario, new tracers for the evaluation of well-differentiated HCC have been proposed and are currently desirable, to improve the low sensitivity of [^{18}F]FDG. Radiolabelled choline is a tracer used to evaluate lipid metabolism and its application in HCC is based on the presence of high

Table 1 Characteristics of studies about radiolabelled PSMA

First author	References	Year	N.Pts	Gender	Type of study	Country	Device	Isotope
Erhamamcý	[22]	2020	1	M	CR	Turkey	PET/CT	[68Ga]Ga-PSMA ^b
Das	[23]	2019	1	M	CR	India	PET/CT	[68Ga]Ga-PSMA ^b
Kesler	[24]	2019	7	5M/2F	P	Israel	PET/CT	[68Ga]Ga-PSMA ^b
Kuyumcu	[25]	2019	19	16M/3F	P	Turkey	PET/CT	[68Ga]Ga-PSMA ^b
Kunikowska	[26]	2020	15	13M/2F	P	Poland	PET/CT	[68Ga]Ga-PSMA-11
Perez	[27]	2019	1	M	CR	USA	PET/CT	[68Ga]Ga-PSMA-11
Tolkach	[28]	2019	1	NA	CR ^a	the Netherlands	PET/CT	[68Ga]Ga-PSMA-11
Huang	[29]	2018	1	M	CR	Singapore	PET/CT	[68Ga]Ga- HBED-CC (68Ga-PSMA)
Alipour	[30]	2017	1	M	CR	Australia	PET/CT	[68Ga]Ga-PSMA ^b
Patel	[31]	2017	1	M	CR	Australia	PET/CT	[68Ga]Ga-PSMA ^b
Sasikumar	[32]	2016	1	M	CR	India	PET/CT	[68Ga]Ga-PSMA ^b
Taneja	[33]	2016	1	M	CR	India	PET/MRI	[68Ga]Ga- HBED-CC (68Ga-PSMA)
Soydal	[34]	2016	1	M	CR	Turkey	PET/CT	[68Ga]Ga-PSMA ^b

Ref. reference, *N.Pts* cases examined, *P* prospective, *CR* case report, *M* male, *F* female, *NA* not available, *PET/CT* positron emission tomography/computed tomography, *PET/MRI* positron emission tomography/magnetic resonance, *PSMA* prostate-specific membrane antigen;

^aCase report in a immunohistochemistry study

^bNot better specified

Table 2 PSMA results and final diagnosis

First author	References	PET/CT positive	SUVmax	Final diagnosis	Gold standard final diagnosis	Notes
Erhamamcý	[22]	1	20.3	HCC	Histology (biopsy)	
Das	[23]	1	8.66	HCC	Histology (biopsy)	
Kesler	[24]	36 out of 37 lesions	Range 3.7–41.2	HCC	CT and MRI criteria	Diagnosis proven before PET/CT
Kuyumcu	[25]	16	17.4 ± 9 (range 3.8–36.9) ^a	HCC	NAp	Diagnosis proven before PET/CT
Kunikowska	[26]	15	13.5 ± 7.1 (range 2.2–29.3) ^a	HCC	Histology (biopsy)	Diagnosis proven before PET/CT
Perez	[27]	1	NA	HCC	Histology (biopsy)	
Tolkach	[28]	1	NA	HCC	NAp	Diagnosis proven before PET/CT
Huang	[29]	1	NA	HCC	Histology (surgery)	
Alipour	[30]	1	9.9	HCC	Histology (biopsy)	Combined with colan-giocarcinoma
Patel	[31]	1	11.2	HCC	Histology (biopsy)	
Sasikumar	[32]	1	NA	HCC	Histology (biopsy)	
Taneja	[33]	1	15.7	HCC	Histology (biopsy)	
Soydal	[34]	1	NA	HCC	Histology (biopsy)	

Ref. reference, *NA* not available, *NAp* not applicable, *HCC* hepatocellular carcinoma, *PET/CT* positron emission tomography/computed tomography, *SUVmax* maximum standardized uptake value body weight max, *CT* computed tomography, *MRI* magnetic resonance

^aMean SUVmax ± SD

expression of choline, as demonstrated by proton MR spectroscopy [43]. Malignant tumor are characterized by high proliferation ratio and increased metabolism of membrane cell compounds, resulting in high uptake of labeled choline. Despite the small amount of available data, good results have

been reported by [¹¹C]C- or [¹⁸F]F-choline for HCC assessment and pooled estimated detection rate reported in literature is 84%. Radiolabelled choline has shown better performance than [¹⁸F]FDG in the detection of HCC, especially in well to moderately differentiated lesions; conversely [¹⁸F]

FDG seems to be more useful in the evaluation of poorly differentiated and higher-stage HCC [44].

Recently PET/CT with PSMA has been considered for the detection and the evaluation of HCC. A wide amount of large and well-designed studies addressing the role of radiolabelled PSMA PET/CT imaging targeting have been produced, but the expression of this protein on tumors other than PCa are lacking. In this context, the direction of the literature is to give an expansion to the potential of this radiopharmaceutical in this setting.

PSMA is a type II transmembrane protein normally expressed by prostate tissue and has significant overexpression by most PCa cells. However, not only prostate tissue can express PSMA [11–19]; pathophysiological processes other than PCa, such as the neovasculature of multiple malignant lesions, are able to overexpress this protein.

Many normal tissue types (liver, kidney, breast, salivary glands, lacrimal glands and prostate tissue) and tumor histotypes other than PCa express PSMA, mostly on endothelial cells of tumor vessels; in this context, this radiotracer is being considered as a potential diagnostic tool in many tumor types.

The majority of HCC shows high levels of PSMA expression on tumor vessels and on canalicular membrane of cells [26, 28] and therefore important implications for PSMA-targeted imaging and therapy arise. PSMA-targeted imaging of HCC in clinical practice has been evaluated only by a few studies and most of these studies are case reports [22, 23, 27–34], probably because of the small number of centers that currently use radiolabelled PSMA PET/CT or PET/MRI, resulting in a reduction of the population of patients overall studied.

Notably, beyond the available case reports, three prospective studies confirmed the radiolabelled PSMA avidity by HCC. Kesler et al. [24] prospectively analyzed 7 patients with a new diagnosis of HCC with 41 liver lesions: 37 suspected malignant lesions and 4 regenerative nodules. Patients underwent both [^{18}F]FDG and [^{68}Ga]Ga-PSMA PET/CT. Thirty-six of the 37 tumor lesions and none of the regenerative nodules showed elevated [^{68}Ga]Ga-PSMA uptake. Moreover, in 2 of the 7 patients [^{68}Ga]Ga-PSMA PET/CT identified unexpected extrahepatic metastases. [^{68}Ga]Ga-PSMA PET/CT was demonstrated to be superior to [^{18}F]FDG PET/CT for imaging patients with HCC and a potential novel modality for imaging. Interestingly, the authors also compared [^{68}Ga]Ga-PSMA uptake with contrast-enhanced CT (ceCT) results reporting that tracer uptake was significantly higher in enhancing tumor areas than in nonenhancing. Moreover, they reported a correlation between PSMA uptake and histological grade of vascularization.

Less enthusiastic results have been reported by Kuyumcu et al. [25]: 19 patients with a previous diagnosis of HCC who underwent [^{18}F]FDG PET as part of restaging

procedure also underwent [^{68}Ga]Ga-PSMA PET imaging. [^{18}F]FDG PET was positive in 15 patients while 16 patients demonstrated PSMA expression. The only extrahepatic finding was one metastatic lymph node identified by both tracers. On a visual and semi-quantitative comparative evaluation, the radiopharmaceutical uptake was higher with PSMA in 9 patients, higher with [^{18}F]FDG in 4 cases and similar among the two tracers in 3 patients. One of the [^{18}F]FDG positive patients was PSMA negative whereas two patients were PSMA positive but [^{18}F]FDG negative. Heterogeneous uptake pattern was observed in three patients. The authors concluded that advanced HCC can be evaluated by [^{68}Ga]Ga-PSMA PET but this imaging method is not clearly superior to [^{18}F]FDG PET; however it has been reported as potentially useful for identifying HCC patients with restricted therapeutic options. Moreover, maximum standardized uptake value body weight max (SUVmax) of [^{68}Ga]Ga-PSMA PET/CT scan showed medium strength of correlation with overall survival of patients.

Recently, Kunikowska et al. [26] enrolled 15 patients in their prospective study, 10 with newly diagnosed HCC and 5 with recurrence, to evaluate the feasibility of using PET/CT with [^{68}Ga]Ga-PSMA-11 in HCC. They reported uptake in 44 total lesions (38 located in the liver and 6 metastatic ones) and moreover they reported tumor-to-liver ratio (TLR) as 3.6 ± 2.1 while SUVmax of the lesions was 13.5 ± 7.1 ; no significant differences in terms of SUVs or TLR was demonstrated between newly and previously diagnosed patient. A comparison with contrast-enhanced CT or MRI was also performed by the authors, reporting that PSMA uptake was present in contrast-enhancing part of the tumor while in necrotic parts it was not present, such as previously demonstrated [24]; moreover [^{68}Ga]Ga-PSMA-11 PET/CT demonstrated more lesions in the liver than CT or MR leading to a change in previously planned treatment. The authors also reported that PET/CT with PSMA did not show false positive findings, compared to histopathology.

To the best of our knowledge this is the first systematic review to evaluate the diagnostic performance of radiolabelled PSMA PET/CT or PET/MRI in HCC. As a consequence, considering the very low number of reports and patients analyzed, no high quality evidence could be drawn about the role of radiolabelled PSMA in HCC. Further studies and prospective large trials are needed to clarify the real clinical and diagnostic role of radiolabelled PSMA in this field and its possible position in the diagnostic flow-chart. Overall, available literature data demonstrate that HCC are radiolabelled PSMA-avid tumors. These insights, if confirmed, could open up the way to a possible future use of radiolabelled PSMA PET/CT or PET/MRI in this particular type of tumors.

Conclusion

Despite the limitation of our review due to the few studies currently available and to the very low number of patients analyzed, it can be concluded that radiolabelled PSMA is not specific for PCa, as several benign and malignant lesions have been reported to show a relevant expression, especially in tumor-associated endothelial cells. Radiolabelled PSMA imaging could be a valuable tool in detecting HCC and it could be better than [^{18}F]FDG PET/CT, especially in well to moderately differentiated lesions. Dual tracer PET imaging should be considered to increase the diagnostic accuracy. Large clinical trials and cost-effectiveness analyses on the use of radiolabelled PSMA or dual tracer PET imaging in this setting are desirable to strengthen the usefulness of these functional imaging methods; this analysis could clarify the real clinical and diagnostic role of radiolabelled PSMA PET and its possible position in the imaging flow-chart.

Author contributions FD: literature search, data analysis and writing. DA: data analysis and editing. EC: data analysis. MG: data analysis and literature review. RG: editing. GT: literature search and editing. FB: content planning, literature search, data analysis, writing, literature review, editing and idea for the article.

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Compliance with ethical standards

Conflict of interest All 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. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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