



$^{13}\text{N-NH}_3$ PET/CT in oncological disease

Domenico Albano¹ · Raffaele Giubbini¹ · Francesco Bertagna¹

Received: 28 August 2019 / Accepted: 30 September 2019 / Published online: 10 October 2019
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Abstract

^{13}N -Ammonia ($^{13}\text{N-NH}_3$) is widely used positron emission tomography/computed tomography (PET/CT) radiotracer for the measurement of myocardial blood perfusion; the possible role of $^{13}\text{N-NH}_3$ PET or PET/CT in oncological disease is not yet clear. Aim of this review is to evaluate the diagnostic performances of $^{13}\text{N-NH}_3$ PET in this field. A comprehensive computer literature search of the PubMed/MEDLINE, Scopus, and Embase databases was conducted including articles up to June 2019. Eighteen articles were finally included in the review. From the analyses of the selected studies, the following main findings could be drawn: (1) $^{13}\text{N-NH}_3$ PET is useful in discriminating between gliomas and non-neoplastic brain lesions, and among gliomas between high-grade and low-grade gliomas; (2) $^{13}\text{N-NH}_3$ PET have better diagnostic performance than $^{18}\text{F-FDG}$ in studying gliomas; (3) a combination of $^{13}\text{N-NH}_3$ PET and $^{18}\text{F-FDG}$ PET may be useful to differentiate between several cerebral lesions (gliomas, cerebral lymphoma, meningioma); (4) only preliminary results about the positive impact in liver and prostate cancer.

Keywords $^{13}\text{N-NH}_3$ · PET/CT · Oncological disease · Review · Glioma

Introduction

^{13}N -Ammonia ($^{13}\text{N-NH}_3$) is a radiotracer currently used for the study of patients affected by coronary artery disease and useful for the measurement of myocardial blood perfusion [1, 2]; this radiotracer was approved by US Food and Drug Administration for myocardial perfusion imaging positron emission tomography (PET) scan in patients with suspected or existing coronary artery disease [3, 4]. Ammonia is labelled with the isotope ^{13}N which is a positron emitter with a very short physical half life ($t_{1/2}$) of 9.965 min compared to other PET tracers. NH_3 is fundamental in many metabolic pathways of several organs and leads to the production of some amino acids, like urea and purine [5]. It is produced from the deamination of amino acids and the deamination of amides. In normal physiologic conditions, ammonia is present in the blood mainly as free base (NH_3) and ionized species (NH_4^+), and they are in equilibrium as the reaction $\text{NH}_4^+ \leftrightarrow \text{NH}_3 + \text{H}^+$. NH_3 is lipophilic compound with small molecular weight, this low mass allows to diffuse

itself across membranes easily [6]. Instead in extra-hepatic tissues, $^{13}\text{N-NH}_3$ is trapped mainly in the form of ^{13}N -glutamine with a reaction catalyzed by the enzyme glutamine synthetase (GS) [7, 8]. GS activity is the main reason for the metabolic trapping of ^{13}N -ammonia in extra-hepatic tissues and its up-regulation might be a potential target for $^{13}\text{N-NH}_3$ PET imaging. The short $t_{1/2}$ of ^{13}N needs necessarily an on-site cyclotron for the production of radiotracer, a short synthesis time and a good organization. After intravenous injection, $^{13}\text{N-NH}_3$ rapidly clears from the circulation and it is taken up mainly by the myocardium, brain, liver, kidneys, and skeletal muscle.

So far, the possible role of $^{13}\text{N-NH}_3$ PET or PET/CT in oncological disease is not completely clear despite several promising results [9, 10]. The aim of our review is to evaluate the diagnostic performance of $^{13}\text{N-NH}_3$ PET or PET/CT in this particular setting analyzing the literature.

Materials and methods

Search strategy

A comprehensive literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted to

✉ Domenico Albano
doalba87@libero.it

¹ Nuclear Medicine, University of Brescia and Spedali Civili Brescia, P.le Spedali Civili 1; 25123, Brescia, Italy

find relevant published articles about the role of $^{13}\text{N-NH}_3$ PET or PET/CT in patients with neoplastic disease. We used a search algorithm based on a combination of the terms: (a) “ammonia” OR “ $^{13}\text{N-NH}_3$ ” AND (b) “cancer” OR “oncological” or “neoplastic” or “neoplasm “. No beginning date limit was used; the search was updated until June 30, 2019. Only articles in the English language were selected and conference proceedings 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

Studies or subsets in studies investigating the role of $^{13}\text{N-NH}_3$ PET or PET/CT in patients with neoplastic disease were eligible for inclusion. Exclusion criteria were: (a) articles not in the field of interest of this review; (b) review articles, editorials, letters, conference proceedings; (c) small case series (< 5 patients) or case reports. Two researchers (DA and FB) independently reviewed the titles and abstracts of the retrieved articles, applying the above-mentioned inclusion and exclusion criteria. Articles were rejected in case of clear ineligibility. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved by a third opinion (RG). Moreover, in case of studies that included the same population, the report with the highest number of enrolled patients was considered for the analysis.

Data abstraction

For each included study, information were collected concerning the basic study (author names, year of publication, study design), the main clinical features (age, sex) and technical characteristics (PET device used, administered $^{13}\text{N-NH}_3$ activity), number of patients evaluated, and lesions detected. The main findings of the articles included in this review are reported in the “[Results](#)” section.

Results

This review was performed according to the ‘preferred reporting items for systematic reviews and meta-analyses’ statement, which describes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses [11].

Literature search

The comprehensive computer literature search from the PubMed/MEDLINE, Embase and Scopus databases revealed 114 articles collected and managed by EndNote®Basic (ThompsonReuters). Reviewing titles and abstracts, 77 articles were excluded because reported data were not within the field of interest of this review; 17 articles were excluded as case reports, small case series, editorials, comments, reviews or conference proceedings. Lastly, 18 articles were selected and screened in the full-text version [12–29]. No additional studies were found screening the references of these papers (Fig. 1). Thirteen articles evaluated the possible role of $^{13}\text{N-NH}_3$ PET or PET/CT in glioma [12–24], one paper evaluated the role in meningioma [25], 2 articles were focused on prostate cancer [26, 27] and 2 article were focused on hepatic tumours [28, 29].

$^{13}\text{N-NH}_3$ PET/CT in glioma

Glioma is one of the most common cerebral tumor and arises from the glial cells of the brain or the spine. Gliomas are typically subdivided into astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas. Computed tomography (CT) and magnetic resonance imaging (MRI) with contrast are excellent tools for tumor localization, but are often unable to characterize the underlying histopathology, to define tumor grade and to differentiate tumor

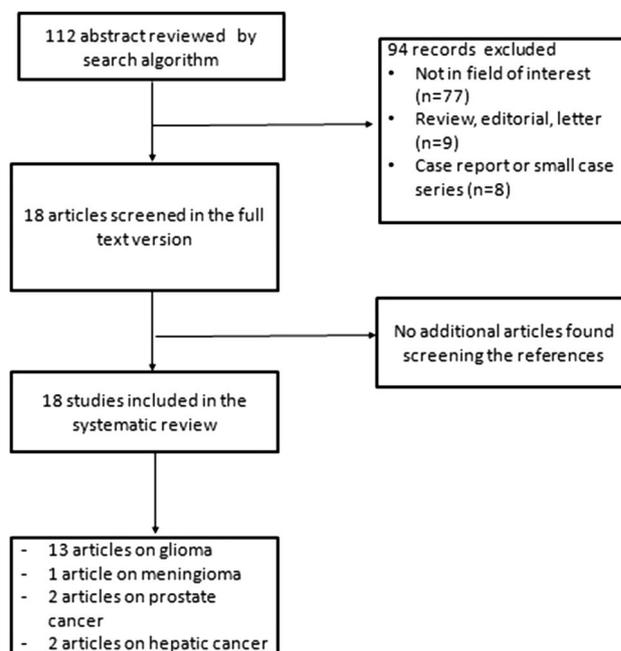


Fig. 1 Literature search flow-chart

recurrence from necrosis or scar. In this field dynamic PET with $^{13}\text{N-NH}_3$ have demonstrated significant impact in several papers (Tables 1, 2, 3) [12–29].

Xiangsong et al. [12] demonstrated that astrocytomas are generally $^{13}\text{N-NH}_3$ -avid and $^{13}\text{N-NH}_3$ uptake is related to histological tumor grade, underlying the possible usefulness of $^{13}\text{N-NH}_3$ PET in differentiating astrocytomas and non-neoplastic lesions. They analyzed 25 patients with suspected cerebral gliomas or recurrent cerebral astrocytomas: all high-grade tumours (11/11) were $^{13}\text{N-NH}_3$ -avid, while only 6 of 9 low-grade gliomas were $^{13}\text{N-NH}_3$ -avid. There was a significant different tumour-to-white matter ratio (T/W) and perfusion index (PI) between high-grade

and low-grade gliomas ($p < 0.001$) and between low-grade gliomas and non-neoplastic disease ($p < 0.001$).

Also in differential diagnosis between recurrent astrocytoma and radiation necrosis after radiation therapy, $^{13}\text{N-NH}_3$ PET showed high accuracy [13]; in all patients with recurrent astrocytoma, PET resulted positive showing significant uptake corresponding to the cerebral recurrence; moreover $^{13}\text{N-NH}_3$ uptake was documented in lesions with absent or low radiation necrosis. These results were partially discordant to $^{18}\text{F-FDG}$ PET/CT scans that showed one case of false positive (a patient with radiation necrosis $^{18}\text{F-FDG}$ -avid) and one case of false negative (a patient with astrocytoma and low $^{18}\text{F-FDG}$ -uptake), suggesting a better diagnostic performance of $^{13}\text{N-NH}_3$ in this field.

Table 1 Characteristics and main findings of the studies included on the possible role of $^{13}\text{N-NH}_3$ PET or PET/CT on gliomas

First author	Year	Study design	No. pts	Mean age (range)	Sex ratio (M:F)	Type of lesions
Xiangsong [12]	2006	Retrospective	25	39 (18–64)	19:6	9 LG G 11 HG G 5 Non-neoplastic lesions
Xiangsong [13]	2007	Prospective	7	37 (22–54)	5:2	5 G 3 Radiation necrosis
Yi [14]	2019	Retrospective	111	44	63:48	27 LG-G 46 HG-G 34 Inflammation lesions
Xiangsong [15]	2011	Prospective	18	42.4 (20–68)	13:5	6 LG G 4 HG G 2 Extra-axial tumors 6 Non-neoplastic lesions
Shi [16]	2013	Retrospective	45	47.46 (na)	29:16	16 LG gliomas 29 HG gliomas
He [17]	2019	Prospective	90	40 (3–78)	54:36	30 LG-G 27 HG-G 10 Non glioma tumors 23 Non-neoplastic lesions
Khangembam [18]	2014	Prospective	56	38.8 (7–63)	35:21	38 LG-G 18 HG-G
Mattakarottu [19]	2011	Retrospective	9	na	7:2	6 LG G 2 HG G 1 Extra-axial tumors
Jora [20]	2011	Retrospective	23	43.25 (na)	14:8	8 LG G 12 HG G 1 Extra-axial tumors 2 Non-neoplastic lesions
Xiangsong [21]	2008	Prospective	42	39.5 (11–68)	30:12	10 LG gliomas 15 HG glioma 4 Extra-axial tumors 13 Non-neoplastic lesions
Khangembam [22]	2013	Prospective	52	39.8 (na)	33:19	38 LG-G 14 HG-G
Shi [23]	2013	Retrospective	25	51.7 (14–74)	15:10	15 G 10 PCNSL
Shi [24]	2015	Retrospective	24	56.4 (22–75)	16:8	13 HG-G 11 Abscess

Pts patients, *M* male, *F* female, *LG G* low-grade gliomas, *HG G* high grade gliomas; *na* not available, *PCNSL* primary central nervous system lymphoma

Table 2 Main PET/CT features of studies included on the possible role of $^{13}\text{N-NH}_3$ PET or PET/CT on gliomas

First author	Sensitivity PET or PET/CT	Specificity PET or PET/CT	PPV PET or PET/CT	NPV PET or PET/CT	Accuracy PET or PET/CT	Semiquantitative analysis (mean value)
Xiangsong [12]	All gliomas 85% HG-G 100% LG-G 66.7%	All gliomas 100% HG-G 100% LG-G 100%	All gliomas 100% HG-G 100% LG-G 100%	All gliomas 62.5% HG-G 100% LG-G 62.5%	All gliomas 88% HG-G 100% LG-G 78.6%	HG-G → T/W: 5.92 PI: 5.22 LG-G → T/W: 1.66 PI: 1.6 NNL → T/W: 0.97 PI: 0.99
Xiangsong [13]	100%	100%	100%	100%	100%	Gliomas → T/W: 3.56 PI: 3.3 NNL → T/W: 0.9 PI: 0.96
Yi [14]	75.3%	55.8%	75.3%	55.8%	67.8%	HG-G → T/G: 1.43 LG-G → T/G: 1.04 NNL → T/G: 0.88
Xiangsong [15]	58.3%	100%	100%	54.6%	72.2%	Gliomas → T/C: 1.24 NNL → T/C: 0.70
Shi [16]	HG-G 94% LG-G na	HG-G 94% LG-G 88%	na	na	na	HG-G → T/G: 1.57 LG-G → T/G: 0.7
He [17]	62.7%	95.7%	97.8%	46.8%	71.1%	Gliomas → T/W: 2.25 NNL → T/W: 1.5
Khangembam [18]	All gliomas 82.6% HG-G 83.3% LG-G 83.3%	All gliomas 86.2% HG-G 75% LG-G 90.5%	All gliomas 82.6% HG-G 71.4% LG-G 87.5%	All gliomas 86.2% HG-G 85.7% LG-G 86.3%	All gliomas 84.6% HG-G 78.6% LG-G 86.8%	na
Mattakarottu [19]	33.33%	na	100%	na	33.33%	na
Jora [20]	25%	na	100%	na	25%	Gliomas → T/C: -1.71
Xiangsong [21]	82.8%	100%	100%	72.2%	88.1%	Gliomas → T/C: 1.64 NNL → T/C: 0.71
Khangembam [22]	77.8%	86.2%	84%	80.7%	82.1%	Gliomas → T/W: 1.8* T/G: 0.7*
Shi [23]	na	na	na	na	96.9%	Gliomas → T/G: 2.11 PCNSL → T/G: 1.38
Shi [24]	84.6%**	90.9%**	91.7%**	83.3%**	87.5%**	Gliomas → T/G: 1.38 NNL → T/G: 0.84

PPV positive predictive value, NPV negative predictive value; na not available, PI perfusion index, T/W tumour-to-white matter, T/C tumor-to-contralateral brain tissue, T/G tumour-to-gray matter, HG-G high grade gliomas, LG-G low-grade gliomas, PCNSL primary central nervous system lymphoma, NNL non-neoplastic lesions

*Median values

**Using a cutoff value of T/G of 1

The ability to differentiate neoplastic lesions and brain inflammatory lesions was confirmed in a recent article [14] describing a detection rate of 91.3% for high-grade gliomas, 51.6% for low-grade gliomas and 29.4% for inflammation diseases with a significant difference among high-grade and low-grade gliomas considering tumor-to-grey matter (T/G) ratio. Instead there was no statistical difference between low-grade gliomas and inflammatory disease

and among inflammatory lesions between infective and demyelinating lesions. The authors suggested a cutoff of 1.21 with area under the curve (AUC) of 0.78 of T/G ratio for distinguishing gliomas from inflammations and a cutoff of 1.06 (AUC 0.78) for distinguishing high-grade and low-grade gliomas.

Also in $^{18}\text{F-FDG}$ -hypometabolic brain lesions $^{13}\text{N-NH}_3$ may have an impact [15]: $^{13}\text{N-NH}_3$ uptake was significantly

Table 3 Technical features about PET studies in glioma

First author	Device	Type of scanner	Activity injected MBq	Uptake time min	Time of acquisition min
Xiangsong [12]	PET	ECAT HR+ (Siemens/CTI)	444–592	5 min	19 min
Xiangsong [13]	PET	ECAT HR+ (Siemens/CTI)	555–740	5 min	19 min
Yi [14]	PET/CT	GEMINI GXL-16 (Philips)	370–740	5–10 min	10 min
Xiangsong [15]	PET/CT	ECAT HR+ (Siemens/CTI) or GEMINI GXL-16 (Philips)	555–740	5 min	15 min
Shi [16]	PET/CT	GEMINI GXL-16 (Philips)	370–740	5 min	10 min
He [17]	PET/CT	GEMINI GXL-16 (Philips)	7.4/Kg	5 min	10 min
Khangembam [18]	PET/CT	Biograph 2 (Siemens)	444–592	3–5 min	5 min
Mattakarottu [19]	PET/CT	Biograph 2 (Siemens)	555–740	5 min	15 min
Jora [20]	PET/CT	Biograph 2 (Siemens)	555–740	5 min	10 min
Xiangsong [21]	PET	ECAT HR+ (Siemens/CTI)	500	5 min	15 min
Khangembam [22]	PET/CT	Biograph 2 (Siemens)	444–592	3–5 min	5 min
Shi [23]	PET/CT	GEMINI GXL-16 (Philips)	370–740	5 min	10 min
Shi [24]	PET/CT	GEMINI GXL-16 (Philips)	370–740	5 min	15 min

higher in neoplastic lesions than in non-neoplastic ones ($p < 0.05$) and was correlated with histologic grade.

The superiority of $^{13}\text{N-NH}_3$ compared to $^{18}\text{F-FDG}$ was confirmed also in a paper that studied 45 patients with 48 untreated gliomas [16]; $^{13}\text{N-NH}_3$ PET/CT identified 29 of 32 (91%) high-grade gliomas showing higher uptake than normal gray matter with a detection rate superior than $^{18}\text{F-FDG}$ PET/CT that demonstrated only 21 (66%) lesions. The optimal T/G cutoff value for $^{13}\text{N-NH}_3$ was 0.86 (AUC 0.943) while T/G cutoff value for $^{18}\text{F-FDG}$ was 0.64 (0.910). The sensitivity and specificity of predicting high-grade gliomas were 94% and 94% for $^{13}\text{N-NH}_3$ and 83% and 93% for $^{18}\text{F-FDG}$, respectively.

A recent prospective study [17] confirmed a better sensitivity and specificity of $^{13}\text{N-NH}_3$ compared to $^{18}\text{F-FDG}$ PET/CT in differentiating gliomas from non-neoplastic lesions and a higher specificity but lower sensitivity compared to $^{11}\text{C-methionine}$. ROC analysis for differentiation between brain tumors and non-neoplastic lesions yielded an optimal T/W ratio of 1.92 for NH_3 (AUC 0.819). Considering semi-quantitative analysis, lesion-to-normal white matter uptake (L/W) ratios were significantly higher in brain tumors than non-neoplastic lesions and in high-grade gliomas than in low-grade gliomas.

On the other hand, Khangembam et al. [18] found similar performances of $^{13}\text{N-NH}_3$ and $^{18}\text{F-FDG}$ PET/CT in studying treated glioma presenting with clinical suspicion of recurrence and theorizing a “perfusion-metabolism coupling” phenomenon in this type of cancer. $^{13}\text{N-NH}_3$ and $^{18}\text{F-FDG}$ PET/CT scans were concordant in 55/56 cases (k agreement 0.964), with an overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 77.8%, 86.2%, 84%, 80.7%, and 82.1% for $^{13}\text{N-NH}_3$ and 77.8%, 89.7%, 87.5%, 81.2%, and

83.9% for $^{18}\text{F-FDG}$ and no differences considering histologic grade.

In contrast, other papers [19, 20] found very low detection rate of $^{13}\text{N-NH}_3$ PET/CT in studying gliomas and other brain lesions, not related to histologic grade. They compared diagnostic accuracy of $^{13}\text{N-NH}_3$ PET/CT with other PET tracers ($^{18}\text{F-FDG}$ and $^{18}\text{F-DOPA}$) and MRI studies. A lower accuracy of $^{13}\text{N-NH}_3$ than $^{18}\text{F-DOPA}$ PET/CT was present with many cases of false positive or negative results both in preoperative and postoperative field.

Comparing $^{13}\text{N-NH}_3$ PET/CT with conventional imaging studies, especially MRI, a positive correlation was demonstrated between $^{13}\text{N-NH}_3$ uptake and contrast-enhancing cerebral lesions on MRI [21]; all except one contrast-enhancing brain tumors exhibited increased $^{13}\text{N-NH}_3$ uptake, five of 9 non-enhancing tumors exhibited increased uptake of $^{13}\text{N-NH}_3$. Instead none of non-neoplastic lesions showed $^{13}\text{N-NH}_3$ uptake, despite nine of 13 non-neoplastic lesions had MRI contrast enhancement. In another study $^{13}\text{N-NH}_3$ PET/CT and contrast-enhanced MRI were compared [22]; PET/CT showed higher accuracy with sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 82.6, 86.2, 82.6, 86.2 and 84.6%, compared to 96.7, 48.3, 59.5, 93.3 and 69.2% of MRI, respectively. This was true especially for low-grade gliomas with a significant difference in accuracy (86.8 versus 68.4% $p = 0.003$). Receiver operating characteristic curve analysis revealed a significant cutoff value of 2.16, 1.00 and 0.56 for T/W, T/G and tumor to pituitary (T/P), respectively, for the diagnosis of recurrent tumour, with the largest AUC (0.825) for T/P ratio.

Another topic studied was the usefulness of the combination of $^{13}\text{N-NH}_3$ and $^{18}\text{F-FDG}$ PET/CT in discriminating gliomas and primary central nervous system lymphomas (PCNSL) [23]. It is well known the metabolic behavior of

PCNSL at ^{18}F -FDG PET/CT: they are ^{18}F -FDG-avid in most cases and their ^{18}F -FDG-avidity is correlated with tumor size and morphological appearance [29, 30]. Generally, PCNSLs were characterized by higher uptake of ^{18}F -FDG and relatively lower uptake of ^{13}N -ammonia, whereas solid gliomas displayed contrary imaging features. The T/G ratios of ^{13}N - NH_3 in solid gliomas were higher than in PCNSL lesions ($p < 0.001$), while T/G ratios of ^{18}F -FDG in PCNSL lesions were higher than in solid gliomas ($p < 0.001$).

Moreover, the combination of ^{13}N - NH_3 and ^{18}F -FDG PET/CT may also be useful in discriminating high-grade gliomas from brain abscess with an accuracy of 95% as reported by Shi et al. [24]; only one case of necrotic glioma without significant ^{13}N - NH_3 uptake was considered as an abscess. The uptake of ^{13}N -ammonia was higher in high-grade gliomas than in abscess lesions ($p < 0.001$). They determined the optimal T/G cutoff value with ^{13}N - NH_3 of 1 with AUC of 0.94 and an overall accuracy of 87.5%.

^{13}N - NH_3 PET/CT in non-glioma brain tumours

As described above, meningiomas are brain tumours with high ^{13}N - NH_3 uptake [24]. Only one retrospective study [25] focused on the role of ^{13}N - NH_3 PET/CT in intracranial meningiomas with the aim to discriminate them from healthy tissue, and compare ^{13}N - NH_3 PET/CT results with ^{18}F -FDG PET/CT ones. ^{13}N - NH_3 uptake was increased in all 11 meningiomas with a good contrast to the surrounding normal brain tissues, higher than ^{18}F -FDG one (T/W ratio of 7.03 vs. 1.44; $p < 0.005$). On the other hand, ^{13}N - NH_3 uptake was not useful to discriminate between benign (grade I) and atypical (grade II) meningiomas. These preliminary reports suggest that ^{13}N - NH_3 has relatively greater uptake in meningiomas in comparison with ^{18}F -FDG and open a possible clinical application of ^{13}N - NH_3 for studying and follow-up of meningiomas. These preliminary results need to be assessed in further studies with large population.

^{13}N - NH_3 PET/CT in prostate cancer

Only two studies were focused on the role of ^{13}N - NH_3 PET/CT in prostate cancer. Shi et al. [26] evaluated the role of ^{13}N - NH_3 PET/CT in 34 patients (27 with prostate cancer and 7 with benign prostatic hyperplasia, BPH) and the expression of glutamine synthetase (GS) in PC3 and DU145 prostate cancer cells. They analyzed PET/CT images both qualitatively and semiquantitatively by measuring SUV_{max}. The uptake of ^{13}N - NH_3 in PC3 and DU145 cells increased with the reduction of GS expression; also the activity of GS messenger ribonucleic acid elevated when glutamine was lack. Moreover in biopsy samples, the GS expression scores were significantly higher in neoplastic tissue than in benign lesions ($p < 0.001$) and a good correlation between

the GS expression scores and Gleason scores was demonstrated (Spearman $r = 0.52$). ^{13}N - NH_3 PET/CT resulted positive in 25 patients (22 with prostate cancer and 3 with BPH) with a sensitivity and positive predictive value of 81.5% and 88%, respectively. Also on a sextant basis, ^{13}N - NH_3 uptake in prostate cancer segments (average SUV_{max} 2.08 ± 1.14) was significantly higher than in BPH (average SUV_{max} 1.56 ± 0.58 , $p = 0.006$) and focal prostatitis (average SUV_{max} 1.14 ± 0.22 , $p = 0.01$), while there was a weak correlation between SUV_{max} and GS expression scores (Spearman $r = 0.47$) in all segments.

Also Yi et al. [27] found a good detection rate of ^{13}N - NH_3 PET/CT compared to ^{18}F -FDG in advanced prostate cancer (Gleason score 8–10 or PSA > 20 ng/ml or clinical tumor extension $\geq \text{T2c}$). ^{13}N - NH_3 and ^{18}F -FDG PET/CT were performed on the same day (^{18}F -FDG followed ammonia, with an interval of at least 2 h) in 26 patients. On a patient-based analysis, in the detection of primary tumor the sensitivity of ^{13}N - NH_3 PET/CT was 100% and of ^{18}F -FDG PET/CT 96.2%; for nodal metastases sensitivity and specificity were 83.3 and 92.9% for ammonia and 83.3 and 64.3% for ^{18}F -FDG; for bone metastases 100% and 100% with ammonia and 100% and 83.3% with ^{18}F -FDG. On a lesion-based analysis, sensitivity and specificity for primary tumor were 60.2% and 100% with ^{13}N - NH_3 and 54.5% and 83.3% with ^{18}F -FDG; for lymph node metastases 77.5% and 96.3% with ^{13}N - NH_3 and 75% and 44.4% with ^{18}F -FDG. In bone osteogenic lesions ^{13}N - NH_3 had higher detection rate than ^{18}F -FDG (97.4% vs 91.3%), while in osteolytic lesions detection rate was 100% for both. They concluded that both ^{18}F -FDG and ^{13}N - NH_3 PET/CT were accurate and complementary modalities to study advanced prostate cancer.

^{13}N - NH_3 PET/CT in liver cancer

In 1988 Shibata et al. [28] performed dynamic ^{13}N - NH_3 PET in 16 patients with primary hepatocellular carcinoma (HCC) showing a relationship between tumor vascularization and tracer uptake: in 12 cases with hypervascular HCC, high radiotracer uptake was registered since the first scan, while ammonia distribution was moderate in the remaining non-neoplastic parenchyma and tumor to liver ratio (T/L) decreased in later scans. Instead 4 patients with hypovascular HCC had low ^{13}N - NH_3 uptake and low T/L ratio. Similar evidences resulted considering 7 patients with metastatic liver tumours (three from colon, two from breast, one from lung and one from parotid gland cancer): these metastases had poor blood supply from the hepatic artery and resulted as cold area at PET/CT. Thus ^{13}N - NH_3 PET/CT seemed to be accurate in cases of hypervascular HCC, showing high uptake in the tumor since early scan and with optimal contrast compared to physiological parenchyma.

Considering $^{13}\text{N-NH}_3$ metabolic behavior of liver tumors, some authors [29] tried to study dynamic $^{13}\text{N-NH}_3$ PET during $^{18}\text{F-FDG}$ PET/CT-guided liver tumor ablation. They included prospectively 8 patients with 11 $^{18}\text{F-FDG}$ -avid liver metastases who underwent microwave ablation and dynamic $^{13}\text{N-NH}_3$ PET scan 5–15 min after $^{18}\text{F-FDG}$ PET/CT. Eleven of 11 (100%) ablation margins were fully assessable by using intraprocedural $^{13}\text{N-NH}_3$ PET; six of eleven (55%) margins were fully assessable at postprocedural 24-hour magnetic resonance imaging. In conclusion, they suggested that $^{13}\text{N-NH}_3$ perfusion PET during $^{18}\text{F-FDG}$ PET/CT-guided liver tumor ablations can potentially be used to assess the entire ablation margin.

Discussion

Despite the use of multimodal imaging studies, glioma is one of the most difficult brain tumor to identify; the correct definition of regions involved and margins remains a diagnostic challenge. This definition is crucial especially because maximal surgical resection is considered to be the most effective therapy for this type of tumor. MRI has been performed as gold standard study to define the anatomical spread of the tumor and the size of the surgical margin required to achieve a correct resection, but sometimes MRI doesn't identify right infiltration beyond the enhanced region. Consequently, current radiological techniques are not sufficient for the correct evaluation of the spread glioma and other modalities are needed. 18-fluorine fludeoxyglucose PET/CT has been investigated in this setting with suboptimal results related to the physiological accumulation of FDG in the brain and high uptake in inflammatory conditions. Glioma cells have an increased supply for amino acids, and consequently the transport system activity and metabolism of amino acids are increased [31]; this phenomena explain the usefulness of methionine raditoracers in this kind of patients [32]. But also $^{13}\text{N-NH}_3$ seems to have an increased uptake in glioma. The uptake of ^{13}N -ammonia is supposed to be linked with regional blood perfusion and glutamine synthesis and in some aggressive cancer probably these phenomena are more evident than benign conditions. NH_3 passes the cerebral tissue mostly from new vessels that have high cell permeability and combines with glutamate for the production of glutamine. High-grade gliomas, aggressive for definition, are characterized by active neovasculature activity, high regional cerebral blood flow, elevated permeability of blood brain barrier and amplified capillary surface. In addition, neoplastic disease often presented increased active metabolism such as GS, which is crucial for ammonia pathway [33, 34]. Based on the available literature, there is strong consensus among the authors about the uselessness of $^{13}\text{N-NH}_3$ PET or PET/CT in discriminating between malignant and non-neoplastic

lesions as abscess, radation necrosis and inflammation. In particular, it is well demonstrated that gliomas are more $^{13}\text{N-NH}_3$ avid than non neoplastic lesions. Also histological grade of lesions is correlated with detection rate of this tracer; patients with high-grade gliomas (stage III an IV) have significantly higher detection rate ratio and uptake than low-grade gliomas (stage I and II) [12, 13, 15, 17].

These evidences are true both for visual and semi-quantitative evaluation, also using different parameters like T/G ratio, T/C ratio, T/W ratio or PI. These results can be explained by a possible connection between radiotracer uptake and tumor grade and/or histological aggressiveness of disease, which was already showed for other type of radiotracers (like $^{18}\text{F-FDG}$) and cancers [35, 36]. For this reason, $^{13}\text{N-NH}_3$ PET may be helpful in distinguishing high-grade gliomas from low-grade ones and/or inflammations, while it has more difficult and low accuracy in distinguishing low-grade gliomas from inflammatory diseases. Despite this considering patients who need a differential diagnosis among glioma and inflammation, a positive $^{13}\text{N-NH}_3$ PET could accurately exclude non neoplastic conditions, affecting significantly the clinical decision making. Although low-grade gliomas express GS, inactive neovasculature that provides a limited amount of radiotracer for trapping [37, 38] and reduced tumor cell density and tumor metabolism, might be another reason for the lower uptake of ammonia in low-grade lesions.

In comparison to $^{18}\text{F-FDG}$ PET/CT, $^{13}\text{N-NH}_3$ PET seems to be better [13, 16, 17] in studying gliomas and to differentiate between intracranial cancers [23, 24]. The combination of dual tracers ($^{13}\text{N-NH}_3$ and $^{18}\text{F-FDG}$) allows to discriminate with good accuracy between gliomas and not-gliomas (PCNSL and meningioma) [23] or between gliomas and abscess [24]. Malignant meningioma and high-grade gliomas show high $^{13}\text{N-NH}_3$ and $^{18}\text{F-FDG}$ uptake; benign meningioma show high $^{13}\text{N-NH}_3$ uptake but low $^{18}\text{F-FDG}$, PCNSL show high $^{18}\text{F-FDG}$ uptake but low $^{13}\text{N-NH}_3$ and low-grade gliomas show low uptake of both tracers.

Despite this, $^{18}\text{F-DOPA}$ have demonstrated higher diagnostic accuracy than $^{13}\text{N-NH}_3$ [19, 20] because this amino acid tracer is able to detect low-grade gliomas with high sensitivity.

Compared to other raditoracers, as $^{18}\text{F-FDG}$ and $^{18}\text{F-DOPA}$, $^{13}\text{N-NH}_3$ has the limitations to have very short half-life (about 10 min) which leads the need to have an on-site cyclotron for the production. Thus, only in selected centers that have the availability of a cyclotron this kind of radiotracer production is possible. On the contrary, a short half-like has the advantage to reduce the radiation exposure of the patient.

Considering semiquantitative evaluation, a comparison between papers is difficult because of the non homogeneous studies present in literature non homogeneous population,

low samples and different semiquantitative parameters analyzed. It is not possible to suggest an ideal cutoff to discriminate between different cerebral lesions.

Considering other cancers beyond glioma, only few articles are present in literature: one about meningioma, two about prostate carcinoma and 3 about liver cancer. Also in these lesions, ammonia uptake seem to be determined by cellular properties (vascularization, GS expression, cell proliferation). Despite promising preliminary results, the effective role of this radiotracer need to be clarify in larger populations. However, nowadays an introduction in clinical practice of this modality seems to be premature.

Limitation of the studies and open questions

Many limitations potentially affect the quality of these analyses about the role of $^{13}\text{N-NH}_3$ PET or PET/CT in oncological diseases such as the low number of studies available, also due to the rare diffusion of radiotracer, the absence of multicentric and prospective studies, and globally the low number of patients included. Besides, most of studies are retrospective and no randomized trials are available. Another potential limitation is that in many papers $^{13}\text{N-NH}_3$ PET or PET/CT is compared with $^{18}\text{F-FDG}$ imaging, a well-known radiotracer. The absence of systematic histological confirmation of the imaging reports, which is ethically impossible but clinically justified, is methodologically questionable. Finally, another limitation is the possible overlap of patients included in the same period between studies from the same center.

Conclusion

Despite several limitations affecting this analysis, $^{13}\text{N-NH}_3$ PET or PET/CT seems to be useful in studying gliomas and seems to have potential benefit also in other cancers. However, more extensive studies are desirable to suggest its possible introduction in the diagnostic flow chart.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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