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REVIEW ARTICLE

The role of positron emission tomography using carbon-11 and fluorine-18 choline in tumors other than prostate cancer: a systematic review

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Abstract To systematically review published data on the role of positron emission tomography (PET) or PET/computed tomography (PET/CT) using either Carbon-11 (^{11}C) or Fluorine-18 (^{18}F) choline tracer in tumors other than prostatic cancer. A comprehensive literature search of studies published in PubMed/MEDLINE and Embase databases through January 2012 and regarding ^{11}C-choline or ^{18}F-choline PET or PET/CT in patients with tumors other than prostatic cancer was carried out. Fifty-two studies comprising 1800 patients were included and discussed. Brain tumors were evaluated in 15 articles, head and neck tumors in 6, thoracic tumors (including lung and mediastinal neoplasms) in 14, liver tumors (including hepatocellular carcinoma) in 5, gynecologic malignancies (including breast tumors) in 5, bladder and upper urinary tract tumors in 5, and musculoskeletal tumors in 7. Radiolabeled choline PET or PET/CT is useful to differentiate high-grade from low-grade gliomas and malignant from benign brain lesions, to early detect brain tumor recurrences and to guide the stereotactic biopsy sampling. The diagnostic accuracy of radiolabeled choline PET is superior compared to Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET in this setting. Radiolabeled choline PET or PET/CT seems to be accurate in differential diagnosis between malignant and benign thoracic lesions and in staging lung tumors; nevertheless, a superiority of radiolabeled choline compared to ^{18}F-FDG has not been demonstrated in this setting, except for the detection of brain metastases. Few but significant studies on radiolabeled choline PET and PET/CT in patients with hepatocellular carcinoma (HCC) and musculoskeletal tumors are reported in the literature. The combination of radiolabeled choline and ^{18}F-FDG PET increases the detection rate of HCC. The diagnostic accuracy of radiolabeled choline PET or PET/CT seems to be superior compared to ^{18}F-FDG PET or PET/CT and conventional imaging methods in patients with bone and soft tissue tumors. Limited experience exists about the role of radiolabeled choline PET and PET/CT in patients with head and neck tumors, bladder cancer and gynecologic malignancies including breast cancer.

Keywords Positron emission tomography · PET/CT · Choline · Fluorine-18 · Carbon-11 · Oncology

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Introduction

Positron emission tomography (PET) and PET/computed tomography (PET/CT) using Carbon-11 (^{11}C) or Fluorine-18 (^{18}F) radiolabeled choline are diagnostic tools that are increasingly used in clinical oncology [1–6]. Abnormal choline metabolism is emerging as a metabolic hallmark that is associated with oncogenesis and tumor progression. Following transformation, the modulation of enzymes that control anabolic and catabolic pathways causes increased levels of choline-containing precursors and breakdown products of membrane phospholipids [7]. As tumor cells present a high metabolic rate, choline uptake increases in

tumor tissue to keep up with the demands of the synthesis of phospholipids in cellular membranes [8]. The increased levels of choline-containing compounds are associated with proliferation, and recent studies emphasize the complex reciprocal interactions between oncogenic signalling and choline metabolism [9].

Choline can be radiolabeled using ^{11}C or ^{18}F for PET imaging. ^{11}C-choline is biochemically indistinguishable from natural choline, thus, it can be considered as a true tracer of cancer cell metabolism. However, the ^{11}C relatively short half-life (20 min) requires an on-site cyclotron and image acquisition has to be performed early after injection. Practical issues led to the development of fluorinated compounds as ^{18}F-fluoroethyl-choline (FEC) or ^{18}F-fluoromethyl-choline (FCH). FEC and FCH have shown some differences in their biokinetics. In fact, FCH revealed phosphorylation by choline-kinase similarly to choline while the rates of FEC phosphorylation were 30 % lower. The phosphorylation step is thought to be crucial for PET imaging because of metabolic retention of the tracer within the tumor. Both compounds participate further in the synthesis of membrane phospholipids, although the rate of their incorporation into phospholipids may be slower than that of choline. The cancer cells uptake of FEC was one-fifth of that of FCH [10]. However, despite these differences in molecular behavior, no significant differences were observed in the clinical setting. Thus, the PET results can be considered as equal for both ^{18}F-choline tracers.

^{11}C- and ^{18}F-labelled choline is rapidly cleared up after injection; both tracers' uptake is most pronounced in kidneys and liver. However, only 2 % of injected dose of ^{11}C-choline is excreted in the urine during 1.5 h after injection, compared to the high urinary bladder activity of ^{18}F-choline. Thus, ^{11}C-choline seems to be more advantageous in pelvis evaluation compared to ^{18}F-choline.

Nevertheless, at the moment it is not established which choline derivative is most advantageous in the clinical setting because of the lack of direct comparative studies on individual compounds.

The role of radiolabeled choline PET or PET/CT is mainly recognized in the evaluation of prostate cancer patients, particularly when a biochemical relapse occurs [2, 3, 5, 6]. However, PET and PET/CT with radiolabeled choline have been largely tested also for the non-invasive assessment of a variety of malignancies other than prostate cancer [3, 4].

To date, a systematic review article about the usefulness of radiolabeled choline PET and PET/CT in prostatic cancer already exists [6]. Conversely, a systematic review article about the usefulness of radiolabeled choline PET or PET/CT in tumors other than prostatic cancer is still lacking in the literature. The aim of this study is to update and to analyze the current evidence for the use of radiolabeled choline PET and PET/CT in the management of patients with malignancies other than prostate cancer.

Methods

A comprehensive computer literature search of the PubMed/MEDLINE and Embase databases was carried out to find relevant peer reviewed articles on the use of ^{11}C- or ^{18}F-choline PET or PET/CT in patients with either histologically proven or suspected tumors other than prostatic cancer.

A search algorithm based on a combination of the terms: (a) ''PET'' or "positron emission tomography" and (b) "choline" was used. No beginning date limit was used and the search was updated until January 20th, 2012. To expand our search, references of the retrieved articles were also screened for additional studies. No language restriction was used.

All studies or subsets in studies investigating the role of ^{11}C- or ^{18}F-choline PET or PET/CT in patients with suspected tumors other than prostatic cancer were eligible for inclusion.

The exclusion criteria were: (a) articles not within the field of interest of this review; (b) review articles, editorials or letters, comments, conference proceedings; and (c) case reports or small case series (less than five patients included).

Two researchers (GT and EG) independently reviewed the titles and the abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. The same two researchers then independently reviewed the full-text version of the articles to confirm their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

For each included study, information was collected concerning basic study (author names, journal, year of publication, country of origin), patient characteristics (number of patients and type of tumors evaluated), and PET tracers used.

Results

The comprehensive computer literature search from the PubMed/MEDLINE and Embase databases revealed 576 articles. Reviewing titles and abstracts, 524 articles were excluded applying the criteria mentioned above. Fifty-two articles, including 1800 patients referred to PET or PET/CT with radiolabeled choline, were selected and retrieved in full-text version (Fig. 1). No additional study was found screening the references of these articles [11–62]. The

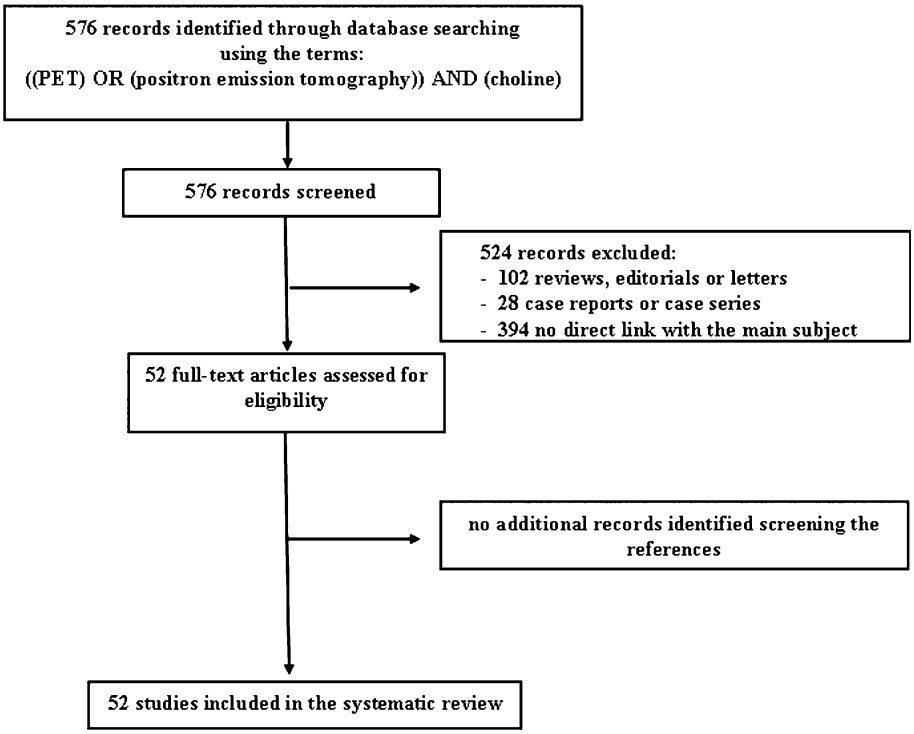

Fig. 1 Flow chart of the search for eligible studies on the role of radiolabeled choline PET or PET/CT tumors other than prostate cancer

characteristics of the included studies are presented in Table 1.

Brain tumors were evaluated in 15 articles, head and neck tumors in 6, thoracic tumors (including lung and mediastinal neoplasms) in 14, liver neoplasms (including hepatocellular carcinoma) in 5, gynecologic malignancies (including breast tumors) in 5, bladder and upper urinary tract tumors in 5, and musculoskeletal tumors in 7.

Radiolabeled choline PET in brain tumors

The first report on the use of PET and radiolabelled choline was in 1997, by Hara et al. [11]. They evaluated the feasibility of brain tumor imaging using ^{11}C-choline PET in patients with suspected gliomas, demonstrating that this functional imaging method could provide clear images of brain tumors. The uptake in normal brain tissue is, in fact, very low. Conversely, the uptake in venous sinuses, lateral ventricles and pituitary is high. A high uptake of ^{11}C-choline PET was reported in malignant brain tumor in all cases ($n = 24$) and in pituitary adenoma in two cases; particularly relevant was the very low uptake of surrounded background. ^{11}C-choline uptake was independent of the blood flow rate in the tumor, as assessed using ^{15}O-water PET [11].

Ohtani et al. [12] compared ^{11}C-choline PET, contrast-enhanced magnetic resonance (MR) imaging and Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET findings in 22 patients with suspected brain tumors. ^{11}C-choline PET could differentiate between low-grade gliomas and high-grade gliomas, characterized by a higher choline uptake than low-grade gliomas, but could not differentiate between low-grade gliomas and non-neoplastic lesions. The authors suggested that a combination of ^{11}C-choline PET and MR imaging may be useful to identify high-grade gliomas [12].

Conversely, Utriainen et al. [13] found that ^{11}C-choline uptake did not differ between low- and high-grade gliomas. These authors, comparing MR spectroscopy and ^{11}C-choline PET in 12 patients with suspected brain tumors, demonstrated that both the imaging methods could be helpful in differential diagnosis between lymphomas, non-neoplastic lesions and gliomas, being histopathologic methods superior in the estimation of tumor grade [13].

In 2003, Hara et al. [14] tested both ^{18}F- and ^{11}C-choline PET to visualize gliomas prior to stereotactic biopsy procedures. Stereotactic biopsy sampling was performed in 12 patients, in those areas presenting an increased radiolabeled choline uptake on PET images. The radiolabeled choline uptake in high-grade gliomas resulted higher than that of low-grade tumors. Only in one case of oligodendroglioma, the tumor showed no uptake of ^{18}F- and ^{11}C-choline. With this exception, radiolabeled choline PET could be useful to guide the stereotactic biopsy sampling [14].

In two studies, Tian et al. [15, 16] compared the usefulness of ^{11}C-choline and ^{18}F-FDG PET for the differentiating between benign and malignant brain lesions. ^{11}C-choline uptake in malignant lesions was significantly higher than that in benign lesions and it was correlated with ^{18}F-FDG uptake. Accuracy in differentiating between

Table 1 Basic study characteristics

Authors	Year	Country	Tumors evaluated (histology)	Patients performing radiolabeled choline PET or PET/CT	Radiolabeled choline used	Other PET tracers used
Hara et al. [11]	1997	Japan	Brain (various)	31	^{18}C-choline	^{15}O-water
Ohtani et al. [12]	2001	Japan	Brain (glioma)	22	^{18}C-choline	^{18}F-FDG
Utriainen et al. [13]	2003	Finland	Brain (glioma)	12	^{18}C-choline	–
Hara et al. [14]	2003	Japan	Brain (glioma)	12	^{18}F- and ^{11}C-choline	–
Tian et al. [15]	2004	Japan	Brain (various)	25	^{18}C-choline	^{18}F-FDG
Tian et al. [16]	2004	Japan	Brain (various)	7	^{18}C-choline	^{18}F-FDG
Kwee et al. [17]	2007	USA	Brain (various)	30	^{18}F-choline	–
Huang et al. [18]	2008	China	Brain (various)	94	^{11}C-choline	^{18}F-FDG
Kato et al. [19]	2008	Japan	Brain (glioma)	95	^{11}C-choline	^{18}F-FDG, ^{11}C-MET
Giovacchini et al. [20]	2009	Italy	Brain (meningioma)	7	^{11}C-choline	^{18}F-FDG
Takenaka et al. [21]	2011	Japan	Brain (glioma)	46	^{11}C-choline	^{18}F-FDG, ^{11}C-MET
Rottenburger et al. [22]	2011	Germany	Brain (metastases)	8	^{11}C-choline	^{11}C-MET
Tan et al. [23]	2011	China	Brain (various)	55	^{11}C-choline	^{18}F-FDG
Roelcke et al. [24]	2012	Switzerland	Brain (glioma)	6	^{18}F-choline	^{18}F-FET
Li et al. [25]	2012	China	Brain (glioma)	16	^{11}C-choline	^{18}F-FDG
Tian et al. [15]	2004	Japan	Head/Neck (various)	51	^{18}C-choline	^{18}F-FDG
Ninomiya et al. [26]	2004	Japan	Head (squamous cell carcinoma)	22	^{18}C-choline	^{18}F-FDG
Khan et al. [27]	2004	Japan	Head/Neck (various)	45	^{18}C-choline	^{18}F-FDG
Ito et al. [28]	2010	Japan	Head/Neck (squamous cell carcinoma)	53	^{11}C-choline	^{18}F-FDG
Ito et al. [29]	2010	Japan	Head/Neck (non-squamous cell tumors)	14	^{11}C-choline	^{18}F-FDG
Wu et al. [30]	2011	China	Head/Neck (nasopharingeal carcinoma)	15	^{11}C-choline	^{18}F-FDG
Kobori et al. [31]	1999	Japan	Esophagus	33	^{18}C-choline	^{18}F-FDG
Jager et al. [32]	2001	Netherlands	Esophagus	18	^{18}C-choline	^{18}F-FDG
Liu et al. [33]	2006	China	Mediastinum (various)	32	^{11}C-choline	–
Peng et al. [34]	2008	China	Mediastinum (various)	35	^{11}C-choline	–
Hara et al. [35]	2000	Japan	Lung (non-small cell cancer)	29	^{18}C-choline	^{18}F-FDG
Pieterman et al. [36]	2002	Netherlands	Lung (various)	17	^{18}C-choline	^{18}F-FDG
Khan et al. [37]	2003	Japan	Lung (various)	17	^{18}C-choline	^{18}F-FDG
Hara et al. [38]	2003	Japan	Lung (various)	116	^{18}C-choline	^{18}F-FDG
Tian et al. [15]	2004	Japan	Lung (various)	16	^{18}C-choline	^{18}F-FDG
Tian et al. [16]	2004	Japan	Lung (various)	6	^{18}C-choline	^{18}F-FDG
Wang et al. [39]	2006	China	Lung (various)	39	^{11}C-choline	–
Wang et al. [40]	2010	China	Lung (various)	58	^{11}C-choline	^{18}F-FLT, ^{11}C-MET, ^{11}C-AC
Balogova et al. [41]	2010	France	Lung (adenocarcinoma)	15	^{18}F-choline	^{18}F-FDG
Peng et al. [42]	2012	China	Lung (various)	108	^{11}C-choline	–
Talbot et al. [43]	2006	France	Liver (hepatocellullar carcinoma)	12	^{18}F-choline	^{18}F-FDG
Yamamoto et al. [44]	2008	Japan	Liver (hepatocellullar carcinoma)	12	^{11}C-choline	^{18}F-FDG
Talbot et al. [45]	2010	France	Liver (hepatocellullar carcinoma)	81	^{18}F-choline	^{18}F-FDG
Esschert et al. [46]	2011	Netherlands	Liver (hepatocellullar adenoma)	21	^{18}F-choline	–
Wu et al. [47]	2011	China	Liver (hepatocellullar carcinoma)	28	^{11}C-choline	^{18}F-FDG

Table 1 continued

Authors	Year	Country	Tumors evaluated (histology)	Patients performing radiolabeled choline PET or PET/CT	Radiolabeled choline used	Other PET tracers used
Jong et al. [48]	2002	Netherlands	Bladder (urothelial carcinoma)	18	^{18}C-choline	–
Picchio et al. [49]	2006	Italy/Germany	Bladder (urothelial carcinoma)	27	^{11}C-choline	–
Gofrit et al. [50]	2006	Israel	Bladder and urinary tract (urothelial carcinoma)	18	^{11}C-choline	–
Maurer et al. [51]	2011	Germany	Bladder (urothelial carcinoma)	44	^{11}C-choline	–
Golan et al. [52]	2011	Israel	Bladder (urothelial carcinoma)	20	^{11}C-choline	^{18}F-FDG
Torizuka et al. [53]	2003	Japan	Gynecologic (various)	21	^{18}C-choline	^{18}F-FDG
Sofue et al. [54]	2009	Japan	Uterus (uterine carcinoma)	22	^{11}C-choline	–
Contractor et al. [55]	2009	UK	Breast (various)	32	^{11}C-choline	–
Kenny et al. [56]	2010	UK	Breast (various)	21	^{11}C-choline	–
Contractor et al. [57]	2011	UK	Breast (various)	21	^{11}C-choline	^{18}F-FLT
Zhang et al. [58]	2003	Japan	Musculoskeletal (various)	43	^{18}C-choline	^{18}F-FDG
Tian et al. [15]	2004	Japan	Musculoskeletal (various)	38	^{18}C-choline	^{18}F-FDG
Tian et al. [16]	2004	Japan	Musculoskeletal (various)	21	^{18}C-choline	^{18}F-FDG
Tian et al. [59]	2011	China	Musculoskeletal (various)	36	^{11}C-choline	^{18}F-FDG, ^{18}F-FAMT
Yanagawa et al. [60]	2003	Japan	Musculoskeletal (various)	33	^{18}C-choline	^{18}F-FDG
Tateishi et al. [61]	2006	Japan	Musculoskeletal (sarcoma)	16	^{11}C-choline	–
Nanni et al. [62]	2007	Italy	Bone (myeloma)	10	^{11}C-choline	^{18}F-FDG

FET fluoroethyltyrosine, *FDG* fluorodeoxyglucose, *FLT* fluorothymidine, *FAMT* fluoro-a-methyltyrosine, *MET* methionine, *AC* acetate, *O* oxygen

benign and malignant brain lesions was 79 % for ^{11}C-choline PET and 58 % for ^{18}F-FDG PET. The authors suggested that ^{11}C-choline PET is a useful method for differentiating between malignant and benign brain lesions. However, a high uptake of ^{11}C-choline was also reported in some benign tumors and tumor-like lesions [15, 16].

Evaluating with ^{18}F-choline PET 30 solitary brain lesions enhancing at MR, Kwee et al. [17] demonstrated that high-grade gliomas, metastases, and benign lesions can be distinguished on the basis of ^{18}F-choline uptake. The tracer uptake was, in fact, significantly higher in metastases compared to gliomas and benign lesions, and in gliomas compared to benign lesions. In particular, increased peritumoral ^{18}F-choline uptake is a distinguishing characteristic of high-grade gliomas [17].

In 2008, Huang et al. [18], evaluating 94 patients with suspected brain tumors by comparatively using ^{11}C-choline PET and ^{18}F-FDG PET, reported an accuracy in the diagnosis of brain tumors of 84 and 71 % for ^{11}C-choline PET and ^{18}F-FDG PET, respectively. These authors also reported five false positive cases (one abscess, one tuberculosis, one benign gliocyte proliferation, one inflammatory granuloma and one demyelination) and four false negative cases (two metastases from lung cancer, one lymphoma, one grade II glioma) using ^{11}C-choline PET. The authors underlined that ^{11}C-choline PET seems to be superior compared to ^{18}F-FDG PET for the detection of brain tumors. Nevertheless, false positive and false negative results should be kept in mind when interpreting ^{11}C-choline PET findings [18].

In the same year, Kato et al. [19] compared ^{11}C-choline, ^{11}C-methionine (a tracer which evaluate amino acid metabolism) and ^{18}F-FDG PET in 95 patients with gliomas and correlated PET findings with histopathological features. Significant differences were evident between the different grade of gliomas and PET tracers uptake. Tumor type influenced only ^{11}C-methionine uptake. In all cases, significant correlations among ^{11}C-choline, ^{11}C-methionine and ^{18}F-FDG uptake were shown. The authors reported that, in terms of visual evaluation of tumor localization, ^{11}C-methionine PET is superior to ^{11}C-choline and ^{18}F-FDG PET in gliomas, due to its straightforward detection of "hot lesions" [19].

Increased ^{11}C-choline uptake was also reported in benign brain tumors, as reported by Giovacchini et al. [20] in a study comparing ^{11}C-choline and ^{18}F-FDG PET uptake in 7 patients with meningiomas. All cases of meningiomas showed an increased ^{11}C-choline uptake (the uptake was higher in patients with grade II than in grade I meningiomas), whereas ^{18}F-FDG uptake was increased only in one

of the 7 meningiomas evaluated. The authors concluded that ^{11}C-choline PET may detect meningiomas better than ^{18}F-FDG PET [20].

Recently Tatenaka et al. [21], comparing ^{11}C-choline, ^{11}C-methionine and ^{18}F-FDG PET in differential diagnosis between gliomas and monofocal acute inflammatory demyelination (MAID), found that ^{11}C-methionine was superior compared to ^{11}C-choline and ^{18}F-FDG in discriminating between MAID and gliomas [21].

Conversely, in the direct comparison to ^{11}C-methionine PET, ^{11}C-choline seems to be promising for the imaging of brain metastases (in particular in patients previously treated with radiation therapy), as demonstrated in a preliminary study of Rottenburger et al. [22], presenting a higher lesion to normal brain uptake ratio in tumor tissue compared with ^{11}C-methionine, without evidence for a lower specificity of ^{11}C-choline PET than that of ^{11}C-methionine PET [22].

Recently Tan et al. [23] compared MR imaging, ^{18}F-FDG and ^{11}C-choline PET/CT in differentiating brain tumor recurrence from necrosis after radiotherapy in 55 patients. The authors reported sensitivity in tumor recurrence diagnosis for MR imaging, ^{18}F-FDG and ^{11}C-choline PET/CT of 87, 77, and 92 %, respectively. The specificity of MR imaging, ^{18}F-FDG and ^{11}C-choline PET/CT was 81, 62.5, and 87.5 %, respectively. These results suggest that ^{11}C-choline PET/CT is superior in distinguishing recurrent brain tumor from radionecrosis compared with both ^{18}F-FDG PET/CT and MR imaging [23].

In a preliminary report, Roelcke et al. [24] showed that ^{18}F-fluoroethyltyrosine (^{18}F-FET, a tracer which evaluate amino acid metabolism) and ^{18}F-choline uptake is similar in low-grade gliomas. These authors stated that, for clinical purposes, ^{18}F-choline PET is not superior to PET using radiolabeled amino acid, such as ^{18}F-FET [24].

Lastly, Li et al. [25] explored the usefulness of ^{11}C-choline PET in optimization of target volume delineation and treatment regimens in postoperative radiotherapy for brain gliomas [25]. These authors found that the tumor target volume was well contrasted using ^{11}C-choline PET (^{11}C-choline uptake correlated with the grade of gliomas), and the boundaries between lesions and surrounding normal brain tissues could be better defined compared with MR imaging and ^{18}F-FDG PET. Furthermore, as differences between ^{11}C-choline PET and MR imaging could be found in the definition of residual tumor in patients with brain gliomas, the authors underlined that for an accurate definition of tumor target volume ^{11}C-choline PET is to be used in combination with MR imaging [25].

Radiolabeled choline PET in head and neck tumors

In 2004, Tian et al. [15] demonstrated that ^{11}C-choline PET is feasible for differentiating between malignant and benign lesions in the head and neck. Furthermore, head and neck lesions showed higher contrast with ^{11}C-choline PET than with ^{18}F-FDG PET [15].

Ninomiya et al. [26] also evaluated the usefulness of ^{11}C-choline PET in the diagnosis of head and neck tumors. These authors studied 22 patients with suspected malignant tumors in the nasal cavity and paranasal sinuses, using both ^{11}C-choline and ^{18}F-FDG PET. These functional imaging methods could depict squamous cell carcinoma showing an increased tracer uptake, significantly higher than that of normal tissue and benign lesions. ^{11}C-choline uptake in squamous cell carcinoma was lower than ^{18}F-FDG uptake but more homogeneous [26].

Khan et al. [27] confirmed the clinical value of ^{11}C-choline PET in differentiating between malignant and benign head and neck lesions. These authors, evaluating 45 patients with suspected head and neck lesions, reported an accuracy of ^{11}C-choline and ^{18}F-FDG PET in this setting of 84 and 80 %, respectively. Malignant tumors presented a significantly higher tracer uptake than that of benign lesions both with ^{11}C-choline and with ^{18}F-FDG PET. ^{11}C-choline PET seemed to detect malignant head and neck tumors as effectively as ^{18}F-FDG PET, with the advantages of a shorter examination period and a low uptake in the muscles. However, both methods have some limitations in the evaluation of salivary gland lesions [27].

Ito et al. [28] assessed the usefulness of ^{11}C-choline and ^{18}F-FDG PET/CT for detecting recurrences of advanced head and neck squamous cell carcinoma after combined chemotherapy and radiotherapy in 53 patients. ^{11}C-choline PET/CT was not superior to ^{18}F-FDG PET/CT for the detection of recurrent head and neck cancer (sensitivity and specificity were 83 and 80 % for ^{11}C-choline PET/CT and 89 and 91 % for ^{18}F-FDG PET/CT, respectively) [28].

The same authors reported that the abilities of ^{11}C-choline and ^{18}F-FDG PET/CT for detecting recurrences of non-squamous cell head and neck malignancies after chemotherapy and radiotherapy were comparable [29].

^{11}C-choline PET/CT has a superior potential for imaging skull base and intracranial lesions compared to ^{18}F-FDG PET/CT because the normal brain is not choline avid [30]. For this reason, ^{11}C-choline PET/CT improves tumor staging in patients with nasopharyngeal carcinoma, as recently demonstrated by Wu et al. [30].

Radiolabeled choline PET in thoracic neoplasms

Esophageal carcinoma

In 1999, Kobori et al. [31] demonstrated that the combination of ^{11}C-choline and ^{18}F-FDG PET was very effective in preoperatively lymph nodal staging in patients with esophageal carcinoma. ^{11}C-choline PET was more effective

than ^{18}F-FDG PET and CT in detecting very small metastases localized in the mediastinum. It was ineffective, however, in detecting metastases localized in the upper abdomen, because of the physiological uptake of ^{11}C-choline in the liver [31].

Also Jager et al. [32] compared ^{11}C-choline and ^{18}F-FDG PET for staging esophageal cancer in 18 patients. These authors demonstrated that ^{11}C-choline PET is able to visualize esophageal carcinoma and its metastases, but appears to be more limited with respect to ^{18}F-FDG PET in terms of diagnostic accuracy. Presumably, this is due to a lower tumoral uptake of ^{11}C-choline compared to ^{18}F-FDG and to a considerable non-specific uptake of ^{11}C-choline in liver, stomach wall, pancreas and small intestine [32].

Mediastinal lesions

In 2006, Liu et al. [33] assessed the role of ^{11}C-choline PET/CT in the evaluation of mediastinal masses in 32 patients. ^{11}C-choline PET/CT proved to be a valuable diagnostic tool for differential diagnosis of benign versus malignant lesions with an accuracy of 75 %. ^{11}C-choline uptake in malignant lesions appeared to be higher than that of benign lesions. Nevertheless, ^{11}C-choline PET/CT may provide misdiagnosis in a substantial proportion of patients with mediastinal masses compared to videomediastinoscopy [33].

The same group reported that dual time point ^{11}C-choline PET/CT may improve the accuracy. In particular, they used an imaging protocol including a first PET scanning 5–10 min after the radiopharmaceutical injection and a second PET scanning after 25–30 min. However, videomediastinoscopy remains the gold standard in differentiation of malignant and benign mediastinal lesions [34].

Lung cancer

In 2000, Hara et al. [35] compared the diagnostic accuracy of ^{11}C-choline and ^{18}F-FDG PET in detecting mediastinal lymph node metastases originating from non-small cell lung cancer (NSCLC). The authors found that ^{11}C-choline PET was very effective in detecting lymph node metastases in the mediastinum originating from NSCLC, with a detection rate of 100 % [35].

Pieterman et al. [36] reported that ^{11}C-choline PET can be used for staging thoracic cancers. In the 17 patients evaluated, primary tumors were visualized both with ^{11}C-choline and ^{18}F-FDG PET, although the accuracy in the detection of lymph node metastases with ^{11}C-choline PET was inferior compared to that of ^{18}F-FDG PET. Nevertheless, ^{11}C-choline PET provided a better accuracy in the detection of brain metastases compared to that of ^{18}F-FDG PET [36].

Khan et al. [37] also compared the diagnostic value of ^{11}C-choline and ^{18}F-FDG PET in the detection of primary lung cancer and mediastinal lymph node metastases. The authors demonstrated that both techniques present a clinical value for the non-invasive detection of primary lung cancer equal or larger than 2 cm in size. However, ^{18}F-FDG PET is superior to ^{11}C-choline PET in the detection of lung cancer smaller than 2 cm in diameter and of mediastinal lymph node metastases [37].

In 2003, Hara et al. [38] evaluated the combined role of ^{11}C-choline and ^{18}F-FDG PET to differentiate between lung cancer and mycobacteriosis. In lung cancer patients, the uptake of both ^{18}F-FDG and ^{11}C-choline was high. In patients with tuberculosis, the uptake of ^{18}F-FDG was high, but the uptake of ^{11}C-choline was low. In patients with atypical mycobacterial infection, the uptake of both ^{18}F-FDG and ^{11}C-choline was low [38].

In 2004, Tian et al. [15, 16] showed that ^{11}C-choline PET is similar to ^{18}F-FDG PET in differentiation between malignant and benign pulmonary lesions. In fact, both ^{11}C-choline and ^{18}F-FDG uptake in malignant tumors was significantly higher than that of benign lesions [15, 16].

In 2006, Wang et al. [39] performed ^{11}C-choline PET in 39 patients with suspected lung cancer and reported that sensitivity, specificity and diagnostic accuracy of ^{11}C-choline PET in the diagnosis of malignant lung nodules was 89, 60 and 77 %, respectively. Moreover, the authors found that ^{11}C-choline PET can effectively evaluate lymph nodal staging and accurately depict brain metastases in patients with lung cancer [39].

In 2010, the same authors [40] demonstrated that ^{11}C-choline PET is a valuable tool in the diagnosis of lung cancer but also lead to false positive and false negative results. The authors found that the sensitivity, specificity and accuracy of ^{11}C-choline PET were 84, 58 and 75 %, respectively [40].

Recently, Balogova et al. [41] compared ^{18}F-choline and ^{18}F-FDG PET/CT in the diagnosis of well-differentiated lung adenocarcinoma and in the evaluation of patients with ground-glass opacities, demonstrating that both imaging methods had similar diagnostic performance [41].

Lastly, Peng et al. [42] compared the diagnostic abilities of ^{11}C-choline PET/CT and contrast-enhanced CT in 108 patients with pulmonary lesions or loco-regional lymph nodal metastases from lung cancer. The accuracy, sensitivity, and specificity of ^{11}C-choline PET/CT for diagnosing lung cancer were 82, 85, and 73 %, respectively, compared with 73, 77, and 61.5 %, respectively, of CT. The accuracy, sensitivity and specificity of ^{11}C-choline PET/CT for lymph nodal metastatic disease were 84, 82 and 84 %, respectively, compared with 69, 64, and 71 %, respectively, of CT. Differences between ^{11}C-choline PET/CT and CT were statistically different for lymph nodal detection but not for pulmonary lesions characterization [42].

Radiolabeled choline PET in liver neoplasms

In 2006, Talbot el al. [43] compared ^{18}F-choline with ^{18}F-FDG PET/CT in patients with hepatocellular carcinoma (HCC). ^{18}F-choline provided a high detection rate for HCC (12/12 patients evaluated were correctly detected using ^{18}F-choline PET/CT), making it potentially useful in the initial evaluation of HCC or in the detection of recurrent disease compared to ^{18}F-FDG PET/CT (of the 9 patients who underwent both methods, all 9 were positive with ^{18}F-choline whereas only 5 were positive with ^{18}F-FDG) [43].

Yamamoto et al. [44] demonstrated that ^{11}C-choline is a promising PET tracer to complement ^{18}F-FDG in detection of HCC lesions. These authors found that ^{11}C-choline PET showed a slightly higher detection rate than that of ^{18}F-FDG PET for the detection of HCC (63 vs. 50 %, respectively). ^{11}C-choline PET presented a better detection rate than that of ^{18}F-FDG PET for moderately differentiated HCC lesions, but not for poorly differentiated HCC lesions (75 vs. 25 %, respectively). ^{18}F-FDG PET produced the opposite results (42 vs. 75 %, respectively) [44].

In 2010, Talbot et al. [45] suggested that performing PET/CT using both ^{18}F-choline and ^{18}F-FDG represents the best option for detection and surveillance of HCC. Per patient- and per lesion-based sensitivity of ^{18}F-choline PET/CT (88 and 84 %, respectively) was superior to that of ^{18}F-FDG PET/CT (68 and 67 %, respectively), and ^{18}F-choline PET/CT is superior compared to ^{18}F-FDG PET/CT in patients with well-differentiated HCC. In contrast, ^{18}F-FDG PET/CT appeared more sensitive in detecting other liver malignancies and more specific than ^{18}F-choline PET/CT (for example ^{18}F-FDG PET/CT was negative in patients with focal nodular hyperplasia in contrast to ^{18}F-choline PET/CT) [45].

In this regard, a recent pilot study of Esschert et al. [46] showed that ^{18}F-choline PET/CT can differentiate hepatocellular adenoma (HCA) from focal nodular hyperplasia (FNH) because the radiopharmaceutical uptake was superior in HCA compared to FNH [46].

Wu et al. [47] recently reported that the combination of ^{18}F-FDG in conjunction with ^{11}C-choline PET/CT could increase the detection rate of HCC, from 63 % using ^{18}F-FDG PET/CT alone to 89 % using both PET tracers. Furthermore, compared with ^{18}F-FDG PET/CT, ^{11}C-choline PET/CT showed an improved detection of well-differentiated HCC (66.7 vs. 35.7 %). For the detection of moderately differentiated HCC, the sensitivity of ^{11}C-choline and ^{18}F-FDG PET/CT was similar [47].

Radiolabeled choline PET in tumors of the urinary tract

In 2002, Jong et al. [48] demonstrated that ^{11}C-choline uptake in bladder cancer was avid, yielding the tumor visualization in the virtual absence of urinary radioactivity. Nevertheless, no increased uptake of ^{11}C-choline could be detected either in pre-malignant lesions or in small non-invasive tumors [48].

Four years later, Picchio et al. [49] compared the diagnostic accuracy of contrast-enhanced CT and ^{11}C-choline PET for the staging of bladder cancer in 27 patients. The resulted data suggested that ^{11}C-choline PET is comparable to CT for detecting residual bladder cancer after transurethral resection, but appears to be superior to CT for the evaluation of potential additional lymph nodal metastases [49].

Gofrit et al. [50] evaluated the contribution of ^{11}C-choline PET/CT in the staging of 18 patients with advanced transitional cell carcinoma. ^{11}C-choline PET/CT was highly sensitive for primary and metastatic transitional cell carcinoma. Moreover, carcinoma in situ, lymph node metastases and early bone metastases could be detected [50].

Recently Maurer et al. [51] also assessed the diagnostic accuracy of ^{11}C-choline PET/CT compared with CT in lymph nodal staging of patients with bladder cancer. On patient-based analysis, sensitivity, specificity, and accuracy for ^{11}C-choline PET/CT were 58, 66, and 64 %, respectively; for CT, the results were 75, 56, and 61 %, respectively. The authors concluded that preoperative lymph node staging with ^{11}C-choline PET/CT was not able to improve diagnostic efficacy compared with conventional CT alone [51].

Lastly, Golan et al. [52] compared ^{11}C-choline with ^{18}F-FDG PET/CT for staging bladder cancer in 20 patients. ^{11}C-choline PET/CT did not show any significant diagnostic advantage compared to ^{18}F-FDG PET/CT in the detection of metastatic bladder cancer [52].

Radiolabeled choline PET in gynecologic malignancies including breast cancer

In 2003, Torizuka et al. [53] demonstrated the feasibility of ^{11}C-choline PET for imaging of gynecologic tumors in 21 patients. The main advantage of this tracer compared to ^{18}F-FDG was the lower urinary radioactivity. However, intestinal background activity may interfere with the interpretation of ^{11}C-choline PET [53].

In 2009, Sofue et al. [54] evaluated the role of ^{11}C-choline PET/CT in the staging of uterine carcinoma in 22 patients. Based on PET/CT findings, the reviewers correctly classified T stage in 8 patients (47 %), N stage in 21 patients (96 %), M stage in 20 patients (91 %). The authors found that the combination of ^{11}C-choline PET/CT and MR imaging could increase the accuracy of staging in patients with uterine carcinoma [54].

In 2009, Contractor et al. [55] examined the ability of ^{11}C-choline PET to detect clinically aggressive phenotype in patients with estrogen receptor (ER)-positive breast

cancer. Breast tumors were well visualized in 30 of 32 patients and ^{11}C-choline uptake correlated with tumor grade [55].

The same authors demonstrated that ^{11}C-choline uptake can be reproducibly assessed in patients with breast cancer [56] and that choline metabolism and proliferation (assessed by ^{18}F-fluorothymidine PET) were correlated in ER-positive breast cancer [57].

Radiolabeled choline PET in musculoskeletal tumors

In 2003, Zhang et al. [58] compared ^{11}C-choline PET with ^{18}F-FDG PET for the differentiation between benign and malignant bone and soft tissue tumors in 43 patients. The study showed that ^{11}C-choline PET was superior to ^{18}F-FDG PET in differentiation between malignant and benign lesion in bone and soft tissue tumors. In fact, ^{11}C-choline uptake in malignant lesions was significantly higher than that in benign lesions and correlated with ^{18}F-FDG uptake. The sensitivity, specificity and accuracy of ^{11}C-choline PET were 100, 64 and 76 %, respectively. The sensitivity, specificity and accuracy of ^{18}F-FDG PET were 86, 42 and 56 %, respectively [58]. These findings were further confirmed by other papers of the same group [15, 16, 59].

Yanagawa et al. [60] also compared ^{11}C-choline PET with ^{18}F-FDG PET in the evaluation of musculoskeletal tumors in 33 patients. The authors found a significant correlation between ^{11}C-choline and ^{18}F-FDG uptake for all lesions. ^{11}C-choline and ^{18}F-FDG uptake in malignant lesions was significantly higher than that of benign lesions. The sensitivity, specificity and accuracy of ^{11}C-choline PET were 92, 90 and 91 %, respectively. The sensitivity, specificity and accuracy of ^{18}F-FDG PET were 85, 80 and 82 %, respectively. The authors demonstrated that ^{11}C-choline PET is not inferior to ^{18}F-FDG PET for differentiating malignant from benign musculoskeletal tumors. The advantages of ^{11}C-choline PET were the shorter examination time and the negligible retention in the bladder. Therefore, this modality may thus be useful for preoperative planning for musculoskeletal tumors, especially for lesions in the region of hip joints [60].

In 2006, Tateishi et al. [61] compared the diagnostic accuracy of ^{11}C-choline PET/CT and conventional imaging for the staging of bone and soft tissue sarcomas in 16 patients. The overall TNM staging and N staging accuracy of ^{11}C-choline PET/CT was significantly higher than that of conventional imaging. The authors concluded that ^{11}C-choline PET/CT is more accurate than conventional imaging regarding clinical staging of patients with bone and soft tissue sarcomas [61].

As multiple myeloma (MM) bone lesions may present low ^{18}F-FDG uptake, Nanni et al. [62] assessed the possible added value of ^{11}C-choline PET/CT in 10 patients with MM. Overall, ^{11}C-choline PET/CT scans detected 37 bone lesions and ^{18}F-FDG PET/CT scans detected 22 bone lesions but the difference was not significant. ^{11}C-choline PET/CT appeared to be more sensitive than ^{18}F-FDG PET/CT for the detection of MM bone lesions [62].

Conclusion and general remarks

Radiolabeled choline PET or PET/CT has been widely used to evaluate brain tumors, in particular gliomas. These techniques seem to be useful to differentiate high-grade from low-grade gliomas, and malignant from benign brain lesions, to early detect brain tumor recurrences and to guide the stereotactic biopsy sampling. The diagnostic accuracy of radiolabeled choline PET is superior compared to ^{18}F-FDG PET. However, false positive and false negative results should be kept in mind when interpreting radiolabeled choline PET findings. Further studies comparing radiolabeled choline to amino acid, PET tracers in brain tumors are needed.

Limited experience exists about the role of radiolabeled choline PET and PET/CT in patients with head and neck tumors. These techniques seem to differentiate between malignant and benign tumors but a superiority in terms of diagnostic accuracy compared to ^{18}F-FDG PET has not been clearly demonstrated. Promising results of radiolabeled choline PET in the detection of skull base and intracranial lesions have been reported.

As for thoracic tumors, the diagnostic accuracy of radiolabeled choline PET is not proven to be superior to that of ^{18}F-FDG PET in staging esophageal cancer. Radiolabeled choline PET is able to differentiate between malignant and benign mediastinal lesions but its diagnostic accuracy is inferior compared to that of videomediastinoscopy. Several studies evaluated patients with lung cancer using radiolabeled choline PET or PET/CT. These methods seem to be accurate in differential diagnosis between malignant and benign lung lesions and in staging lung tumors; nevertheless, a superiority of radiolabeled choline compared to ^{18}F-FDG has not been demonstrated in this setting, except for the detection of brain metastases.

Few but significant studies on radiolabeled choline PET and PET/CT in patients with HCC are reported in the literature. The combination of radiolabeled choline and ^{18}F-FDG PET increases the detection rate of HCC. Radiolabeled choline PET is more sensitive for well-differentiated HCC compared to ^{18}F-FDG PET. Conversely, ^{18}F-FDG PET is more sensitive in poorly differentiated HCC compared to radiolabeled choline PET.

Limited studies evaluated the usefulness of radiolabeled choline PET or PET/CT in bladder cancer staging; the diagnostic accuracy of these methods does not seem to be

superior compared to ^{18}F-FDG PET/CT; furthermore, the superiority of radiolabeled choline PET compared to CT is not yet clearly evident in the literature.

Some authors evaluated the feasibility of radiolabeled choline PET in gynecologic tumors and breast cancer, but further studies are needed.

Few but significant studies reported a high accuracy of radiolabeled choline PET or PET/CT in the detection of bone and soft tissue tumors. These methods seem to be superior compared to ^{18}F-FDG PET or PET/CT and conventional imaging method, but further studies are warranted. The encouraging preliminary data obtained with radiolabeled choline PET in patients with MM should be confirmed in a larger series of patients.

Conflict of interest None.

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