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Review Article

The clinical use of PET with ^{11}C-acetate

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Abstract: The aim of this review is to evaluate clinical applications of ^{11}C-acetate positron emission tomography (PET). Acetate is quickly metabolized into acetyl-CoA in human cells. In this form it can either enter into the tricarboxylic acid cycle, thus producing energy, as happens in the myocardium, or participate in cell membrane lipid synthesis, as happens in tumor cells. ^{11}C-acetate PET was originally employed in cardiology, to study myocardial oxygen metabolism. More recently it has also been used to evaluate myocardial perfusion, as well as in oncology. The first studies of ^{11}C-acetate focused on its use in prostate cancer. Subsequently, ^{11}C-acetate was studied in other urological malignancies, as well as renal cell carcinoma and bladder cancer. Well differentiated hepatocellular carcinoma represents an ^{18}F-fluoro-deoxyglucose (^{18}F-FDG) PET pitfall, so many authors have proposed to use ^{11}C-acetate in addition to ^{18}F-FDG in studying this tumor. ^{11}C-acetate PET has also been used in other malignancies, such as brain tumors and lung carcinoma. Some authors reported a few cases in which ^{11}C-acetate PET incidentally found multiple myeloma or rare tumors, such as thymoma, multicentric angiomyolipoma of the kidney and cerebellopontine angle schwannoma. Lastly, ^{11}C-acetate PET was also employed in a differential diagnosis case between glioma and encephalitis. The numerous studies on ^{11}C-acetate have demonstrated that it can be used in cardiology and oncology with no contraindications apart from pregnancy and the necessity of a rapid scan. Despite its limited availability, this tracer can surely be considered to be a promising one, because of its versatility and capacity to even detect non ^{18}F-FDG-avid neoplasm, such as differentiated lung cancer or hepatocellular carcinoma.

Keywords: Positron emission tomography (PET), ^{11}C-acetate, cancer, cardiology, prostate cancer, liver cancer, brain tumor

Introduction

Positron emission tomography (PET) is rapidly increasing its role in nuclear medicine imaging, thanks to the development of new tracers and more accurate techniques in images acquisition, which allows the patients to be scanned in a relative short time and in whole body modality. ^{18}F-fluoro-deoxyglucose (^{18}F-FDG) is still the most widespread among PET tracers, since it is useful in oncologic and not oncologic field (infection, inflammation, brain blood perfusion, epilepsy, etc.), but also because of its long half life (about 120 minutes) [1], which permits PET centers not to be obliged to produce the tracer on site.

^{18}F-FDG PET has though proven ineffective in a number of neoplasms, such as differentiated hepatocellular carcinoma (HCC) [2], or well differentiated lung adenocarcinoma [3], where it resulted in false negatives. Moreover, ^{18}F-FDG can turn positive in inflammation, thus being a false positive if the scan is performed to evaluate tumor localization. It has also been proven that physiological ^{18}F-FDG uptake in the urinary tract makes the tracer not helpful to investigate urinary tract malignancy [4-7], especially in primary evaluation of bladder cancer, while it is considered a good tool in detecting lymph node (LN) involvements and distance recurrence both in bladder and in renal malignancy. Regarding renal cancer, some authors noticed a correlation between ^{18}F-FDG-avidity and tumor grade, GLUT-1 receptors and degree of tumor necrosis [6].

For these reasons, new metabolic tracers have been developed. ^{11}C-choline or ^{18}F-choline, for instance, are widely used to investigate not only prostate cancer [5-6] but also HCC or urological and brain tumor [7-9], while ^{11}C-methionine is

used to investigate brain tumor [8-9]. Among the less diffuse tracers, ^{11}C-acetate seems to have a promising role in PET investigations.

As we will discuss more extensively further, ^{11}C-acetate is rapidly picked-up by cells and metabolized into acetyl-CoA. It is doubly involved in cell metabolism, in fact in heart cells acetyl-CoA is rapidly converted into carbon dioxide (CO_2) and water (H_2O), while in cancer cells acetyl-CoA is employed to build membrane fatty acid. For its versatile uptake mechanism, it can be considered useful in many diagnostic fields and particularly in cardiologic and oncologic studies. The aim of this work is to evaluate the current role of ^{11}C-acetate PET in nuclear medicine investigations and to predict future employment of the tracer.

General features of the tracer

Cell metabolism of acetate

Acetate, or acetic acid, is a molecule quickly picked-up by cells and converted into acetyl-CoA by acetyl-CoA synthetase (EC 6.2.1.1 according to Enzyme Commission Number). In this form, it can be involved in two different and opposite methabolic pathways, the first being anabolic and the second being cathabolic. In particular, it can be used to synthesize cholesterol and fatty acids, thus forming cell membrane (anabolic pathway), or it can be oxidized (cathabolic way) in mitochondria by the tricarboxylic acid cycle (TCA) to CO_2 and H_2O, thus producing energy. Only in a few cases, acetate may be converted into amino acids.

The predominant pathway is strictly linked with the type of cell: in myocardial tissue, acetate is mainly metabolized to CO_2 via the TCA, as Randle and his colleague put in evidence in 1970 in preclinical studies [10], while tumor cells over-express the enzyme fatty acid synthetase, [FAS(EC 2.3.1.85 according to Enzyme Commission Number)] [11], thus converting most of the acetate into fatty acids and incorporating them into intracellular phosphatidylcholine membrane microdomains, that are important for tumor growth and metastasis [12]. In 2001 Yoshimoto and his colleagues studied the uptake of acetate, labelled with ^{14}C, by four tumor cell lines in vitro [13]. They noticed that acetate uptake was higher than ^{18}F-FDG and that tumor cells incorporated ^{14}C into the lipid-soluble fraction (phosphatidylcholine and neutral lipids).

Vavere and his co-workers demonstrated both in vitro and in vivo that inhibition of FAS reduces ^{11}C-acetate uptake [14], thus confirming the hypothesis that ^{11}C-acetate uptake in tumors is related to FAS expression. Some authors, such as Schiepers [15], are not in agreement with this theory, as will be discussed further (see ^{11}C-acetate PET in prostate cancer), since the cathabolic pathway is more rapid than the anabolic one and, if the scan starts into 20 minutes, also in tumor cells the TCA cycle way will be predominant. In cancer cells, above all in prostatic ones, another enzyme has proven to be over-expressed and involved in the increase of fatty acid synthesis: acetyl-CoA carboxylase (6.4.1.2 according to Enzyme Commission Number) [16].

Radiopharmaceutical synthesis of ^{11}C-acetate

For nuclear medicine purposes, acetate is labelled with ^{11}C and the derived compound is called ^{11}C-acetate. ^{11}C-acetate is produced by proton bombardment of natural nitrogen through the ^{14}N(p,a)^{11}C nuclear reaction. A gas mixture of 2% oxygen in nitrogen will produce radioactive CO_2 ($^{11}CO_2$), while 5% hydrogen in nitrogen will produce methane ($^{11}CH_4$).

Many methods have been developed to product automatically ^{11}C-acetate, starting from Grignard reagent, that is to say methyl magnesium chloride or bromide (CH_3MgBr or CH_3MgCl), and based on reaction of methyl magnesium bromide or chloride and $^{11}CO_2$. In 1995, Kruijer and his co-workers suggested a practical method to product ^{11}C-acetate [17]: this method gives ^{11}C-acetate ready for injection within only 15 minutes. In 2002, Moerlein suggested another method [18], based on five steps (trapping, heating, extraction, filtration, and assay), which guarantees 223-300 mCi of acetate within 23 min. Finally Roeda suggested an improvement of ^{11}C-acetate synthesis by using less Grignard reagent and commercial cartridges [19].

Dosimetry of ^{11}C-acetate

Regarding dosimetry, it was estimated in healthy volunteers by intravenous injection of 14.2 mCi of ^{11}C-Acetate [20]. The organs receiving the highest adsorbed doses were pancreas

(62.9 mrad/mCi), bowel (mrad/mCi), kidneys (34.0 mrad/mCi), and spleen (34.0 mrad/mCi). The tracer has not urinary excretion. According to this biodistribution and considering the short half-life of ^{11}C, extimated to be of about 20.38 minutes [21], images are often obtained soon. For example, a patient with prostate cancer is usually scanned 10-20 min after intravenous injection [22], while, in case of heart studies, the scan starts immediately after injection, even when dobutamine infusion is performed [23-24]. Lastly, in patients with suspected or certain hepatocellular carcinoma the scan usually starts 10 minutes after injection [25]. Most authors suggest to keep the patients on fasting.

Main applications of ^{11}C-acetate PET

^{11}C-acetate PET has been used to to measure myocardial oxygen consumption, to study prostate cancer, HCC, renal cell carcinoma (RCC), bladder carcinoma and brain tumors. Some authors referred about rare conditions incidentally found with ^{11}C-acetate PET, as well as thymoma, cerebellopontine angle schwannoma, angiomyolipoma of the kidney, or encephalitis, and finally multiple myeloma was tried to be studied with this tracer.

^{11}C-acetate PET in cardiologic studies

Historically, the first application of ^{11}C-acetate PET was in heart studies. In 1987 Brown and co-workers published a paper regarding the use of ^{14}C and ^{11}C-acetate PET in studying myocardial oxygen utilization (oxidative metabolic rate) in male New Zealand rabbits [26]. The authors noticed that the average steady state extraction fraction of ^{11}C-acetate was significantly higher in ischemic hearts than in normal hearts and that ^{14}C-acetate oxidation is strictly connected with oxygen consumption rate. ^{11}C-acetate clearance was demonstrated to be closely correlated with ^{14}C-acetate one.

In 1989 the same author and his colleagues demonstrated in dogs that the myocardial turnover rate constant (k) can be measured non-invasively with ^{11}C-acetate PET and that myocardial oxidative metabolism (MVO2) is independent from myocardial substrate utilization [27]. In 1991 Lear tried to clarify myocardial ^{11}C-acetate kinetics and above all to explain the relationship between ^{11}C-acetate clearance and myocardium oxygen metabolism, suggesting that acetate (and after acetyl-CoA) radiolabeled carbon atom can be lost as CO_2 (for the most part) but it can also be incorporated into amino-acids through transaminases [28].

A study investigated the role of ^{11}C-acetate PET in evaluating myocardial blood flow (MBF) in normal subjects and in subjects with hypertrofic cardiomyopathy [29]. Four different models for calculating MBF with ^{11}C-acetate were compared and finally ^{11}C-acetate PET results were compared with ^{15}O-H_2O PET. The authors established that ^{11}C-acetate PET is a good tracer to study MBF and that the best model was the one based on a single tissue compartment with standardized correction for recirculating metabolites and for partial volume and spill over.

In 2010, Sörensen and his colleagues evaluated feasibility of ^{11}C-acetate PET in "myocardial perfusion, oxidative metabolism, cardiac efficiency and pump function at rest and during supine bicycle exercise" [30]. They performed ^{11}C-acetate PET to five athletes during rest and supine bicycle stress, and they were able to obtain some parameters related to cardiac function (MBF, oxidative metabolic rate, cardiac output, cardiac efficiency) in a non-invasive way.

Finally, Arakawa and his co-workers evaluated abnormal energy production and response to L-arginine administration in mitochondrial cardiomyopathy by using ^{11}C-acetate PET [31]. According to the authors, ^{11}C-acetate PET is a useful non-invasive method to investigate the change in oxidative methabolism typical of mitochondrial cardiomyopathy, that is to say the shift from aerobiosis into anaerobiosis; this is evident as an increased acetate uptake in myocardial cells. To have a synoptic vision of all the clinical applications of ^{11}C-acetate PET in cardiologic studies (**Table 1**).

^{11}C-acetate PET in oncology: prostate cancer

Prostate cancer is the most spread cancer (excluding skin cancer) among occidental men and the second leading cause of cancer-related death in men [32]. Epidemiology of this tumor is still discussed, risk factors have been identified in age, race, genetic susceptibility, but other ones are still discussed, as like as hormones, vasectomy, smoking, obesity and sedentariness [33].

A recent work by Heijmink and his colleagues examines all the diagnostic investigation tech-

Table 1. Role of ^{11}C-acetate PET in myocardic studies

Aim of the study	Results	References
Investigating MBF in normal subjects and in subjects with hypertrofic cardiomyopathy, in comparison with ^{15}O-water PET	^{11}C-acetate PET is a good tracer to study MBF.	[29]
Obtaining information about MBF, oxidative metabolic rate, cardiac output, cardiac efficiency	^{11}C-acetate PET is good for evaluating MBF, oxidative metabolic rate, cardiac output and cardiac efficiency both in rest and in stress conditions.	[30]
Studying mithocondrial cardiomyopathy and its response to L-arginine administration	^{11}C-acetate PET is a useful non-invasive method to investigate the change in oxidative methabolism typical of mitochondrial cardiomyopathy, that is to say the shift from aerobiosis into anaerobiosis.	[31]

nique in detecting prostate cancer [34]: transrectal ultrasound (TRUS), specifically with intravenous contrast agents, is an excellent tool for population screening and it can be used also to direct biopsy while magnetic resonance imaging (MRI) allows for highly accurate detection and localization of prostate carcinoma, above all in patients with prior negative ultrasound guided biopsies. Bonekamp and his colleague put in evidence that MRI can also be a guide for targeted prostate biopsy, which is an alternative to the current standard of transrectal ultrasonography-guided biopsy [35]. Lastly, both spectroscopy and magnetic resonance spectroscopic imaging (MRSI) are considered as a valid imaging method [36].

As regards PET, gold standard in prostate cancer detection is considered to be choline, labelled with ^{11}C or ^{18}F, as we previously discussed in the introduction. ^{11}C-acetate PET has been extensively used to evaluate prostate cancer. Schiepers and his co-workers studied a kinetic model of ^{11}C-acetate in prostate cancer and they concluded that acetate is used as substrate for many intracellular processes (inside mitochondria for energy metabolism, in the cytosol for lipid synthesis), but if the acquisition scan starts into 20 minutes, the only possible pathway is oxidation in the TCA cycle to CO_2 and H_2O [15]. Other Authors, as Vāvere [14], are not in agreement with this hypothesis, as discussed in the introduction.

On the other hand, also the most widespread tracer used in studying prostatic cancer, ^{11}C or ^{18}F-choline, is also considered as a marker of membrane cell proliferation. One of the first papers regarding this tracer [37] put in evidence that prostatic cells, and above all neoplastic ones, are choline-avid because they incorporate it in phosphatidylcholine and so in membrane, whose synthesis is increased in prostatic tumor cells.

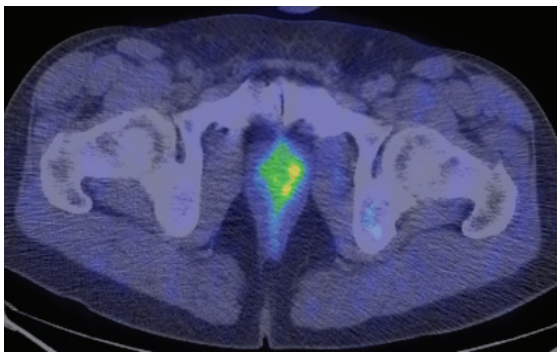

Figure 1. ^{11}C-acetate PET scan (fused image) of a patient with prostate cancer. The figure shows increased ^{11}C-acetate uptake in the prostate of this patient.

The use of ^{11}C-acetate PET has been tested in detecting primary tumor (**Figure 1**), in staging, and in particular in evaluating lymph-node involvement and distant metastasis, as well as detecting relapse, even when prostate-specific antigen (PSA) is low (**Table 2**). As regards detecting primary tumor, in 2002 Oyama and his coworkers enrolled 22 patients with histologically proved prostate adenocarcinoma and subjected them to ^{11}C-acetate PET [22]. Eighteen of these patients also underwent ^{18}F-FDG PET. The results of this study were surprising: ^{11}C-acetate PET showed primary prostate cancer lesions in all of patients (sensitivity of 100%), while primary lesions were seen in 15 of 18 patients scanned with ^{18}F-FDG (sensitivity of 83%).

Table 2. Role of ^{11}C-acetate PET in prostate cancer.

Aim of the study	Results	References
Lymph node involvement	5/5 involved lymph nodes detected	[22]
Bone metastasis	6/7 bone metastasis detected	[22]
	83% of sensitivity	[39]
	No sensitivity difference between ^{11}C-acetate and choline	[38]
Relapse detection if PSA is low	Good sensitivity even PSA is low	[42]
	Good sensitivity in detecting recurrence even when PSA is low	[43]

As regards lymph node metastases, 5 patients in Oyama's work had lymph node metastases, and ^{11}C-acetate PET showed all of these sites, while ^{18}F-FDG PET saw intrapelvic accumulation in only 2/5 patients. As regards bone metastasis, in Oyama'study 7 of the patients had proved bone metastases: high ^{11}C-acetate accumulation was observed in 6/7 patients, while ^{18}F-FDG showed bone accumulation in 4/7 cases. Kotzerke found no difference between ^{11}C-acetate and ^{11}C-choline in detecting bone metastasis [38]. In a report by Fricke, sensitivity of ^{11}C acetate PET in bone metastasis detection was found to be 83% [39].

As regards relapse, many authors investigated the role of ^{11}C-acetate PET in prostate cancer in detecting relapse [40-41], finding the tracer able to detect local recurrence. If ^{11}C-acetate PET/CT (Computed Tomography) is performed, early evaluation of relapse is also possible. Some authors suggested performing ^{11}C-acetate PET to detect residual or progressive subclinical disease when PSA level is very low (<1 ng/mL) after radical prostatectomy [42]: their studies concluded that ^{11}C-acetate PET/CT is able to detect residual or recurrent disease in about half the patients with PSA levels of <1 ng/mL, but it can't be considered the only diagnostic tool this case. Sondblom evaluated 22 patients who had undergone radical prostatectomy and had an increasing PSA [43] and he suggested to use ^{11}C-acetate in detecting recurrence after radical prostatectomy even when PSA is 0.5ng/mL, but he found three false positive.

Some authors proposed to use ^{11}C-acetate PET (and contrast-enhanced MRI) to evaluate cancer aggressiveness [44]. For this purpose, 21 patients with untreated localized prostate cancer were enrolled. Sensitivity, specificity, and accuracy in detecting primary tumor were found to be 80%, 29%, and 71%, respectively for ^{11}C-acetate PET/CT, and 89%, 29%, and 79%, respectively, for contrast-enhanced MRI, but they both failed in giving information about cancer aggressiveness. Other authors put in evidence that, using ^{11}C-acetate, Standardized Uptake Value (SUV) and early-to-late-activity ratio (E/L ratio) for the normal prostate and for benignant prostatic hyperplasia (BPH) overlap significantly with those for prostate cancer and stressed the importance of careful interpretation of images [45].

^{11}C-acetate PET in oncology: HCC

HCC is the third leading cause of cancer mortality worldwide and its incidence in the United States continues to increase [46]. Risk factors have been identified as previous infection by Hepatitis B (HBV) or Hepatitis C (HCV) Virus, alcohol, aflatoxin B1, drugs (steroids), hemochromatosis and other conditions which led to cirrhosis (Wilson's disease or primary sclerosing cholangitis). New diagnostic techniques are needed, to estabilish a more capillary screening and treatment of localized-stage tumors.

Traditionally, diagnostic tools in evaluating HCC are considered: ultrasound (US) and contrast-enhanced ultrasound (CEUS), which can discriminate between HCC and other liver lesions [47], MRI [48] and CT, even if it has lower sensitivity than MRI [49]; all the described techniques can also guide liver biopsy.

One of the first study about using ^{11}C-acetate PET in detecting HCC and other liver masses was published by Ho and his co-workers in 2003 and it evaluated a total of 45 patients (39

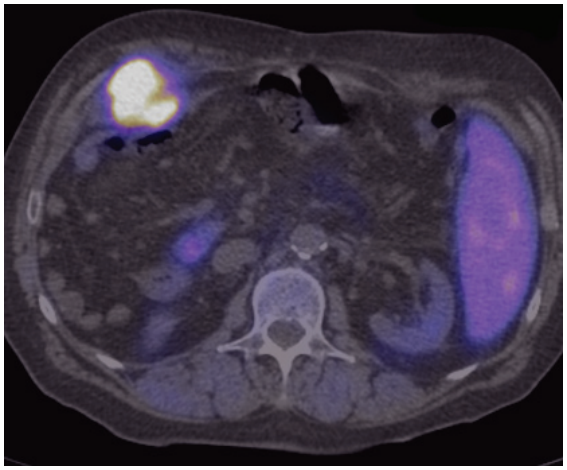

Figure 2. ^{11}C-acetate PET scan (fused image) of a patient with HCC who had undergone partial liver resection. We can notice abnormal uptake in right hypochondrium of this patient, just below the liver.

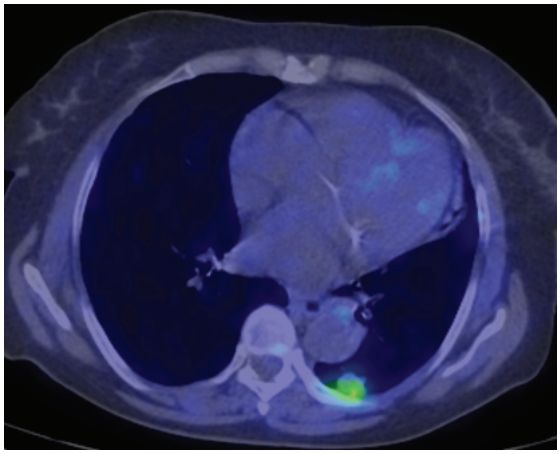

Figure 3. ^{11}C-acetate PET scan (fused image) of a patient with metastatic HCC. We can notice left lung metastasis (sub-pleurical region) derived from HCC.

of them with HCC, 3 with cholangiocarcinomas; 10 with hepatic metastases) [2]. The study was based on the comparison between ^{11}C-acetate and ^{18}F-FDG PET. According to this study, in those patients with a small number of lesions (<3), sensitivity of ^{11}C-acetate PET was 87.3%, while sensitivity of ^{18}F-FDG PET was only 47.3%. The use of both tracers could detect 34% of the lesions. This work provides several important conclusions: first, the two tracers have to be considered complementary; second, there is a correlation between histological type of HCC and its imaging, since well-differentiated HCC tumors are detected by ^{11}C-acetate while the poorly differentiated ones are detected by ^{18}F–FDG; third, non-HCC liver malignancy is not characterized by a significant increase of ^{11}C-acetate uptake; lastly, both cholangiocarcinomas and metastatic liver masses showed no abnormal acetate uptake. **Figure 2** shows the ability of ^{11}C-acetate PET/CT in detecting HCC recurrence.

In 2009, Park investigated the use of ^{11}C-acetate PET/CT in detection of primary and metastatic HCC (**Figure 3**) in 112 patients and compared this tracer sensitivity to ^{18}F-FDG sensitivity [50]. The results were comparable to a previous study [2]: sensitivities of ^{18}F-FDG, ^{11}C-acetate, and dual-tracer PET/CT in patients with primary HCC were 60.9%, 75.4%, and 82.7%, respectively, while in patients with metastatic lesions sensitivities of ^{18}F-FDG, ^{11}C-acetate, and dual-tracer PET/CT were 85.7%, 77.0%, and 85.7%, respectively. The authors concluded that ^{11}C-acetate PET is more sensitive in detection of primary HCC, while ^{18}F-FDG PET is more sensitive in detection of metastasis; besides those HCC which were more aggressive and poorly differentiated (i.e. which are associated with elevated serum alpha-fetoprotein levels, portal vein tumor thrombosis or are multiple) were significantly linked with positive ^{18}F-FDG PET/CT results and have a poor prognosis.

^{11}C-acetate was proved to be unable to distinguish HCC from focal nodular hyperplasia (FNH, **Figure 4**). FNH is a nodule composed of normal hepatocytes occurring in a normal liver, it is often an incidental finding even if it is the second most common benign liver tumor after hemangioma and has a prevalence of 1% [51]. Magini and his colleagues put in evidence [52] that ^{11}C-acetate PET/CT does not enhance usefulness of ^{18}F-FDG PET/CT in differentiating between FNH and other hepatic lesions (non HCC lesions), in particular hepatocellular adenoma (usually occurring during the use of oral contraceptive) and malignant lesions. In this work 31 patients with 43 lesions were enrolled (36 with FNH, 5 with hepatocellular adenoma, 1 with hepatoma, and 1 with metastasis). They underwent Doppler and CEUS, contrast-enhanced CT, and/or MRI. In some cases fine needle biopsy was performed. All patients underwent ^{18}F-FDG and ^{11}C-acetate PET: on ^{18}F-FDG PET, 6/7 of non HCC lesions were positive (sensitivity of 85.7%), and

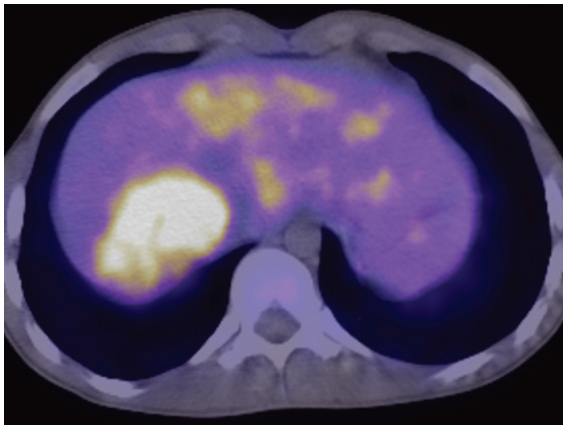

Figure 4. ^{11}C-acetate PET scan (fused image) of a patient with proved FNH. We can notice abnormal uptake of acetate in the liver (VII segment); this finding could not be distinguished from a focal HCC.

33/36 FNH finds were true-negative (specificity of 91.7%), while using ^{11}C-acetate PET, only 2/7 of non-HCC disease lesions were positive (sensitivity of 28.6%), and 34/36 FNH finds were true negative (specificity of 94.4%).

A study published by Huo suggests to perform a dual time point ^{11}C-acetate PET in order to distinguish FNH from HCC [53]. According to this study, both FNH and HCC are ^{11}C-acetate-avid, but in the first case the uptake decreased, being so lower in late acquisition than in the early one, while in the second case the uptake increased, being so lower in the early acquisition than in the late one. In **Table 3** main applications of ^{11}C-acetate are summarized.

^{11}C-acetate PET in oncology: RCC

RCC, also-called renal adenocarcinoma, arises from the cells of the renal tubule and it is relatively rare if compared with other cancers, but an increase in its incidence was observed in the past five decades in the US [54]. If the patients have localized RCC, the prognosis is good, but those with advanced disease do not respond to the majority of traditional treatment options.

In the past, RCC was found in patients presenting with pain in the flank, but now the first diagnostic step is considered US, while CT and MRI provide information about staging system. Some authors tried to investigate RCC with ^{18}F-FDG PET, for instance, Schöder and his colleague put in evidence that ^{18}F-FDG PET is not useful in diagnosis, staging and recurrence detection of renal cell carcinoma, even if it is characterized by a high specificity and positive predictive value [55].

Low sensitivity of ^{18}F-FDG is well explained by Kochhar and his colleague [56]: they underline that the tracer is excreted via the urinary tract, but also that, in RCC, expression of GLUT-1 is variable and finally they justified the lack of uptake in some RCC because big tumors are characterized by central necrosis.

In 1995 Shreve and his co-workers were the first to be interested in using ^{11}C-acetate to detect renal tumor [57]. They enrolled 18 patients, who underwent 30-minutes dynamic PET, and noticed that ^{11}C-acetate uptake was quick and that the tracer had not urinary clearance. They also concluded that RCC had ^{11}C-acetate up-

Table 3. Role of ^{11}C-acetate PET in HCC

Aim of the study	Results	References
Comparison between ^{11}C-acetate and ^{18}F-FDG in detection of liver masses	Sensitivity of ^{11}C-acetate: 87.3%, sensitivity of ^{18}F-FDG 47.3%,34% of lesions are avid of both tracers; the two tracers are complementary (specificity of 100%); ^{11}C -acetate is more useful in well differentiated neoplasm while in cholangiocarcinomas and in metastatic liver masses no abnormal uptake has been detected	[2]
Detecting primary HCC	^{11}C-acetate is more sensitive (75.4%) in detecting primary HCC than ^{18}F-FDG (60.9%)	[50]
Detecting HCC metastasis	^{11}C-acetate is less sensitive in detecting metastasis (77%) than ^{18}F-FDG (85.7%); the two tracers are complementary	[50]
Distinguishing HCC from FNH	^{11}C-acetate is not useful in distinguish HCC from FNH	[52]
	Dual point ^{11}C-acetate PET can distinguish HCC from FNH	[53]

Table 4. Role of ^{11}C-acetate PET in RCC and bladder carcinoma

Aim of the study	Results	References
Detecting primary RCC with ^{11}C-acetate dynamic PET	RCC had ^{11}C-acetate is similar in normal tissue and in RCC, but the rate of clearance is lower in cancer cells, so the acquisition is suggested to be stated beyond 10 min of tracer administration	[57]
	Sensitivity of ^{11}C-acetate PET in detecting RCC is 70%; no abnormal uptake is seen in benign cysts	[58]
Evaluating sunitinib response in RCC	^{11}C-acetate PET is an early predictor of this therapy response (case report)	[60]
Staging bladder cancer before radical cystectomy and after neoadjuvant chemotherapy	Good sensitivity in detecting bladder cancer and LN metastases; false positive uptake can be due to inflammation, infection and previous intravescical BCG therapy	[^{6}6]

take image similar to the normal tissue, but the rate of clearance was significantly lower in cancer cells. Therefore, if the acquisition starts beyond 10 min of tracer administration, a differentiation between neoplastic and normal cells was possible (see **Table 4**).

In 2008, Oyama and his co-workers found a sensitivity of ^{11}C-acetate PET in detecting RCC of 70% (14/20 lesions histologically proven); in particular, papillar carcinoma (1/20) showed a greater uptake than clear-cell carcinoma, while benign cyst turned to be negative. They finally suggest to start acquisition at least 15 minutes after injection, to give the tracer the opportunity to be entrapped in neoplastic cells [58] (**Table 4**).

Figure 5 shows the ability of ^{11}C-acetate PET in detecting bone metastasis deriving from RCC. In 2006 a case report was published about the ability of ^{11}C-acetate PET in detecting a renal oncocytoma, which was incidentally found because prostate cancer was suspected [59]. Renal oncocytomas are uncommon and often benign tumors of the renal collecting duct, they can be hardly distinguished from RCC using non-invasive methods.

More recently, ^{11}C-acetate PET is becoming a tool to evaluate sunitinib response [60]. Sunitinib is a multitargeted tyrosine kinase inhibitor which turns out to have a promising role in RCC therapy. Madeddu and her colleague published a case report regarding the use of ^{11}C-acetate PET as an early predictor of this therapy response (**Table 4**). Other authors tried to evaluate therapy response with ^{18}F-FDG PET and they noticed a correlation between decreasing of this tracer uptake and positive response to therapy, concluding that ^{18}F-FDG uptake is still high in more aggressive tumor [61].

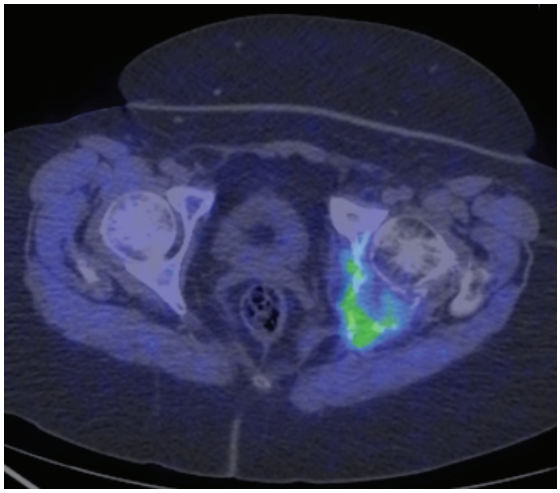

Figure 5. ^{11}C-acetate PET scan (fused image) of a patient with metastatic RCC. The figure shows bone metastasis and in particular we can notice abnormal uptake of the tracer in the left ischium.

^{11}C-acetate PET in oncology: bladder carcinoma

Bladder cancer is the fourth most common malignancy among western men, following prostate, lung, and colon cancers (for 5% to 10% in Europe and the United States). Epidemiological risk factors are considered male sex, smoking, exposure to β-naphthylamine, 4-aminobiphenyl (ABP), benzidine, polychlorinated biphenyls, formaldehyde, asbestos, solvents (benzene, dioxane, and methylene chloride), aluminium, iron, previous urinary tract infections, radiother-

apy and assumption of ciclofosfamide [62].

As regards conventional imaging, the accuracy of CT for the staging of bladder cancer has been estimated ranging form 78 to 89.7% [63], while the one of MRI is considered approximately ranging from 60 to 85% [64]. With regard to ^{18}F-FDG PET, many authors give limited value to this tracer in investigating bladder cancer because of its physiological uptake. Some efforts have been made to reduce the amount of excreted ^{18}F-FDG in the bladder (forced diuresis, bladder catheter with continuous irrigation), but the results were not encouraging. Some authors put in evidence that ^{18}F-FDG PET may be useful in distinguishing local recurrent disease from postsurgical or postirradiation fibrosis or in detecting distant metastases [65].

An interesting paper is going to be published; the aim of the authors is to study sensitivity of ^{11}C-acetate PET in staging bladder cancer before radical cystectomy (17 patients) and after neoadjuvant chemotherapy (10 patients) [66]. According to the authors, ^{11}C-acetate PET has good sensitivity for bladder cancer and LN metastases, even if they noticed a false positive uptake due to inflammation or granulomatous infection; this artefacts limit the staging utility of ^{11}C-acetate in those patients who received intravescical BCG therapy (**Table 4**).

^{11}C-acetate PET in oncology: brain tumors

Gliomas represents about 70% of all brain tumors; there are four different histological types of gliomas: pilocytic astrocytomas [World Health Organization (WHO) grade I] has the best prognosis, while glioblastoma is the most frequent and the most malignant histological type (WHO grade IV) with a poor prognosis. Some risk factors of gliomas have been evaluated: they can be components of several inherited tumor syndromes, or linked with occupation, environmental carcinogens and diet; the only factor certainly associated with glioma is therapeutic X -irradiation, above all if received during childhood [67].

Yamamoto and his colleagues investigated the usefulness of ^{11}C-acetate PET in evaluating brain glioma in fifteen patients with initial diagnosis (5/15 with grade II, 3/15 with grade III and 7/15 with glioblastoma) and they compared it with ^{11}C-methionine and ^{18}F-FDG PET [68]. They found sensitivities of ^{11}C-acetate, ^{11}C-methionine and ^{18}F-FDG PET respectively 90%, 100%, and 40%, but acetate provided also information regarding grade, since mean ^{11}C-acetate SUV in high grade gliomas (IV) was significantly higher than in low grade ones (II). Besides the contrast between tumor and normal tissue uptake (T/N ratio) was higher using ^{11}C-acetate and ^{11}C-methionine than using ^{18}F-FDG. In fact, using ^{11}C-acetate and ^{11}C-methionine, the mean T/N ratios were significantly higher than using ^{18}F-FDG.

In 2008, Tsuchida and his co-workers also published a work regarding the comparison between ^{11}C-acetate and ^{18}F-FDG PET in detecting glioma (ten patients) [69]. They found a significant difference between the uptake of high grade glioma and the one of low grade glioma with ^{11}C-acetate, while ^{18}F-FDG missed the difference, so they concluded that ^{11}C-acetate can be considered as a promising tracer in studying the grading of glioma.

With regard to astrocytoma, a study in 2006 aimed to test ^{11}C-acetate (in comparison with ^{18}F-FDG) in detecting these tumors and above all in characterizing them. 26 patients were studied and both SUV and tumor to cortex ratio (T/C ratio) were considered; all the astrocytoma showed an increased uptake of ^{11}C-acetate, while ^{18}F-FDG was not positive in all of them. Using a cut-off value of 0.75 for ^{18}F-FDG T/C ratio, the sensitivity and specificity of the ^{18}F-FDG in discriminating high-grade from low-grade astrocytoma were 79% and 100%, respectively, while using a cut-off value of 2.33 for ^{11}C-acetate T/C ratio, the sensitivity and specificity were 42% and 86%, respectively, so they conclude that ^{18}F-FDG was better than ^{11}C-acetate in discriminating high-grade from low-grade astrocytoma [70].

In 2010, Liu and his co-workers published a work to compare sensitivity of ^{18}F-FDG and ^{11}C-acetate PET in detecting meningioma (an often benign tumor of the brain) and monitoring radiosurgery response [71]. In this work, twenty-two patients with the neuroradiologic diagnosis of meningioma were examined, high uptake of ^{11}C-acetate was observed in all 20 meningiomas, but ^{18}F-FDG could differentiate grade I from grade II-III meningiomas, while acetate could not. Both ^{18}F-FDG and ^{11}C-acetate PET were positive in a case of tuberculosis granu-

Table 5. Role of ^{11}C-acetate PET brain tumors

Aim of the study	Results	References
Evaluating usefulness of ^{11}C-acetate PET in detecting brain glioma, in comparison with ^{11}C-methionine and ^{18}F-FDG	Sensitivity of ^{11}C-acetate is 90%, lower than ^{11}C-methionine (100%) but higher than ^{18}F-FDG one (40%).	[68]
Evaluating usefulness of ^{11}C-acetate PET in grading brain glioma, in comparison with ^{11}C-methionine and ^{18}F-FDG	^{11}C-acetate can provide information about tumor grading, since mean SUV in high grade gliomas is significantly higher than in low grade ones	[68]
	^{11}C-acetate showed a significant difference between the uptake of high grade glioma and the one of low grade glioma while ^{18}F-FDG does not.	[69]
Evaluating usefulness of ^{11}C-acetate PET in grading brain astrocytoma, in comparison with ^{18}F-FDG	Sensitivity and specificity of the ^{18}F-FDG in discriminating high-grade from low-grade astrocytoma were 79% and 100%, respectively, while for ^{11}C-acetate sensitivity and specificity were 42% and 86%;^{18}F-FDG is more accurate in grading brain astrocytoma	[70]
Evaluating usefulness of ^{11}C-acetate PET in detecting meningioma	Good sensitivity of ^{11}C-acetate	[71]
Evaluating usefulness of ^{11}C-acetate PET in grading meningioma	^{18}F-FDG could differentiate grade I from grade II-III meningiomas, while ^{11}C acetate could not.	[71]
Evaluating usefulness of ^{11}C-acetate PET in monitoring radiosurgery response in meningioma	^{11}C-acetate performed better than ^{18}F-FDG in monitoring radiosurgery response	[71]

loma; ^{11}C-acetate performed better in monitoring five patients who had received gamma-knife surgery. This work also provides an explanation to the uptake mechanism of ^{11}C-acetate in these tumors: probably it is metabolized by astrocytes and it is quickly incorporated into glutamate and glutamine within the first 15 minutes from injection, while after 30 minute it is used for FFA synthesis. To have a synoptical vision of ^{11}C-acetate PET usefulness in investigating brain tumors, see **Table 5**.

Other ^{11}C-acetate PET clinical applications

Multiple myeloma is a rare neoplasm (accounting for about 0.8% of all new cancer cases) originating from plasma cells; it is usually investigated with routine laboratory exams, bone marrow examination, conventional radiography of the bone region suspected to be involved, MRI and CT, but also ^{18}F-FDG PET [72]. A recent case report relates about a multiple myeloma incidentally found by ^{11}C-acetate PET, in a man who was affected by HCC [73].

Lung cancer is the leading cause of cancer-related mortality not only in the United States but also around the world; risk factors can be considered cigarette smoking (active and passive), pollution, professional exposure to silica or asbesto, genetic factors, lack of physical activity, a diet poor in vitamins [74]. It is usually classified in non small cell lung cancer (NSLC, 85% of all lung cancers in the US) and small cell lung cancer; among NSLC, bronchioloalveolar carcinoma accounts for less than 3% of all lung cancer and it is more frequent in male [75], while lung adenocarcinoma is the most frequent histological type in females (smokers or non-smokers) and in non-smoking males and its incidence trend seems to be increasing even if there are many geographical differences [76].

A paper published by Shibata and co-workers evaluated the usefulness of ^{11}C-acetate PET for lung adenocarcinoma imaging and in particular to evaluate its aggressiveness [3]. They compared these results with ^{18}F-FDG PET (**Table 6**). According to the authors, ^{11}C-acetate PET has a good sensitivity (better than ^{18}F-FDG) in detecting bronchioloalveolar carcinoma and well-differentiated adenocarcinoma (stage IA) and there is also a significant correlation between ki67 staining scores and tracer uptake, while ^{18}F-FDG uptake is superior in tumors with pathological advanced stages (lymphatic, vascular

Table 6. Role of ^{11}C-acetate PET in lung cancer

Aim of the study	Results	References
Evaluating usefulness of ^{11}C-acetate PET in detecting bronchioloalveolar and well differentiated adenocarcinoma	^{11}C-acetate PET has a good sensitivity (better than ^{18}F-FDG one) in detecting bronchioloalveolar carcinoma and well-differentiated adenocarcinoma (stage IA)	[3]
	^{11}C-acetate is more sensitive than ^{18}F-FDG for detecting differentiated adenocarcinoma.	[77]
Evaluating usefulness of ^{11}C-acetate PET in detecting aggressiveness of lung adenocarcinoma	^{18}F-FDG uptake is superior in tumors with pathological advanced stages (lymphatic, vascular and/or pleural involvements).	[3]

and/or pleural involvements).

A multicentric study involving seven Japanese institutes suggested that ^{11}C-acetate can substitute ^{18}F-FDG in the imaging of differentiated adenocarcinoma, since ^{18}F-FDG sensitivity is lower in these cases [77]. The authors tried to give an explanation to this result: well differentiated adenocarcinoma have a slow glucose metabolism, while membrane lipid synthesis is rapid.

In 2006 Ohtsuka and colleagues reported three cases of thymoma (a rare and often benign tumor originating from thymus cells and usually detected by CT), investigated with ^{11}C-acetate PET [78]. All of three patients with thymoma had a positive scan with ^{11}C-acetate, while ^{18}F-FDG PET scan missed one case. The uptake mechanism of acetate is not clear in thymoma, even if the authors supposed it is similar to the other tumors uptake and different from the myocardial one.

A case report dealing with a patient who had amnesia and syncope episodes and whose MRI was inconclusive (encephalitis or glioma?) was published in 2009 [79]. ^{18}F-FDG PET was performed, and it was still inconclusive. Finally a ^{11}C-acetate PET was performed and it did not demonstrate any abnormal uptake, thus suggesting the inflammatory (and not neoplastic) nature of the illness. In the same year Lee and his co-workers published another case report describing the usefulness of ^{11}C-acetate in detecting cerebellopontine angle Schwannoma, a very rare tumor, occurring in a ten years old child; the tracer was found to be able to detect the recurrence of the tumor [80].

In 2011 Ho and his colleagues published a case report regarding a multicentric angiomyolipoma of the kidney [81]; the diagnosis was not possible with CT and ^{18}F-FDG PET, while using ^{11}C-acetate PET/CT identified an exophytic lesion in the left kidney and left para-aortic nodes. In **Table 7** incidental findings with ^{11}C-acetate PET are summarized.

Table 7. Incidental findings with ^{11}C-acetate PET

Type of malignancy	References
Multiple myeloma	[73]
Thymoma	[78]
Cerebellopontine angle schwannoma	[80]
Angiomyolipoma of the kidney	[81]

Conclusion

The large number of published works demonstrates a clear interest in development of acetate PET. ^{11}C is a short half life isotope and needed to be produced on site, so ^{11}C-acetate is not readily available; nonetheless many centres started to use ^{11}C-acetate. It is probably due to its versatility, since into the cells it is can go through a double way, the catabolic one (via TCA cycle), which made it useful for cardiologic studies, and an anabolic one (via FAS), which made it useful for oncological purpose.

Many neoplasm with a relatively low grade of proliferation, as like as well differentiated HCC or lung carcinomas, are not ^{18}F-FDG-avid, so in these cases a ^{11}C-acetate PET has been suggested; on the contrary, acetate uptake is less dependent from inflammatory states than ^{18}F FDG, thus permitting an easier differential diagnosis between neoplasm and inflammation. In our opinion, ^{11}C-acetate PET should be consid-

ered as a promising tracer, alone or combining with other tracers.

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