

Metabolic positron emission tomography imaging of cancer: Pairing lipid metabolism with glycolysis

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Abstract

The limitations of fluorine-18 fluorodeoxy-D-glucose (FDG)

in detecting some cancers has prompted a longstanding search for other positron emission tomography (PET) tracers to complement the imaging of glycolysis in oncology, with much attention paid to lipogenesis based on observations that the production of various lipid and lipid-containing compounds is increased in most cancers. Radiolabeled analogs of choline and acetate have now been used as oncologic PET probes for over a decade, showing convincingly improved detection sensitivity over FDG for certain cancers. However, neither choline nor acetate have been thoroughly validated as lipogenic biomarkers, and while acetyl-CoA produced from acetate is used in de-novo lipogenesis to synthesize fatty acids, acetate is also consumed by various other synthetic and metabolic pathways, with recent experimental observations challenging the assumption that lipogenesis is its predominant role in all cancers. Since tumors detected by acetate PET are also frequently detected by choline PET, imaging of choline metabolism might serve as an alternative albeit indirect marker of lipogenesis, particularly if the fatty acids produced in cancer cells are mainly destined for membrane synthesis through incorporation into phosphatidylcholines. Aerobic glycolysis may or may not coincide with changes in lipid metabolism, resulting in combinatorial metabolic phenotypes that may have different prognostic or therapeutic implications. Consequently, PET imaging using dual metabolic tracers, in addition to being diagnostically superior to imaging with individual tracers, could eventually play a greater role in supporting precision medicine, as efforts to develop small-molecule metabolic pathway inhibitors are coming to fruition. To prepare for this advent, clinical and translational studies of metabolic PET tracers must go beyond simply estimating tracer diagnostic utility, and aim to uncover potential therapeutic avenues associated with these metabolic alterations.

Key words: Glycolysis; Lipogenesis; Fatty acid metabolism; Positron emission tomography; Choline; Acetate; Cancer; Prostate cancer; Hepatocellular carcinoma

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Core tip: Positron emission tomography (PET) imaging using multiple distinct metabolic tracers could eventually play a greater role in supporting precision medicine as efforts to develop small-molecule metabolic pathway inhibitors are coming to fruition. To prepare for this advent, clinical and translational studies of metabolic PET tracers must go beyond simply estimating tracer diagnostic utility, and aim to uncover potential therapeutic avenues associated with metabolic alterations in cancer.

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INTRODUCTION

The clinical success of positron emission tomography (PET) can be attributed largely to the broad and robust diagnostic utility of the imaging radiopharmaceutical fluorine-18 fluorodeoxy-D-glucose (FDG). In oncology, FDG PET/CT has no less than revolutionized cancer diagnosis, staging, and assessment of inter-treatment response^[1]. As a fluorinated analog of glucose, FDG behaves as a terminal substrate for hexokinase (HK), the initiating enzyme of glycolysis. The observation that glycolytic metabolism is frequently activated in malignant tumors under conditions otherwise suitable for oxidative metabolism, a phenomenon known as the Warburg effect^[1], forms the primary rationale for imaging cancer with FDG. However, aerobic glycolysis is not a universal feature of all malignancies, and low FDG avidity may predominate in common malignancies such as hepatocellular carcinoma (HCC) and prostate cancer, with rates for detecting the primary tumor with FDG PET/CT falling as low as 55% and 4%, respectively^[2,3].

Because FDG has these limitations, there is demand for other PET tracers to complement the imaging of glycolysis in oncology, with a significant amount of attention paid to lipogenesis given that lipid-related pathways are also frequently upregulated in cancer^[4]. Radiolabeled acetate and choline are two prototypes for imaging lipid synthesis using small molecule PET radiopharmaceuticals. Labeled with carbon-11, both have shown clinical utility for detecting tumors elusive to detection with FDG^[5-7]. Fluorine-18 labeled analogs of choline and acetate have also been developed in an attempt to take clinical advantage of a longer-lived positron-emitting isotope label. However, while fluorine-18 labeled choline analogs have proven useful as biomarkers of choline metabolism^[8,9], ¹⁸F-fluoroacetate does not appear to behave as a functional analog of acetate for the purpose of cancer imaging^[10]. A list of published clinical studies involving 15 or more patients comparing radiolabeled choline and/or acetate to FDG for

specific cancer applications is shown in Table 1.

METABOLIC PATHWAYS COMBINE TO SUPPORT MEMBRANE SYNTHESIS

At face value, acetate metabolism may be viewed as a more direct biomarker of *de-novo* lipogenesis compared to choline metabolism. The authentic tracer ¹¹C-acetate is a substrate for acetyl CoA synthetase to produce acetyl-CoA which is then carboxylated to form malonyl-CoA as the first committed step in *de-novo* lipogenesis mediated by fatty acid synthase (FAS). Upregulated FAS expression is a frequently observed phenomenon in many tumor types^[4]. However, while the constitutive role of FAS in liver and adipose tissue is to create stored energy in the form of triglycerides, the primary role for FAS in cancer cells appears to be to supply fatty acids for phospholipid membrane synthesis^[11,12]. Glycolysis, which is also frequently upregulated in cancer^[1], can not only fuel this process by providing ATP, but also contribute substrate for *de-novo* lipogenesis by producing acetyl-CoA. This underscores a close biochemical relationship between lipogenesis, phospholipid synthesis, and glycolysis, as illustrated in Figure 1, with fatty acids produced by FAS undergoing esterification with glycerol to produce diglycerides which then react with CDP-choline to produce phosphatidylcholine (PtC) for cell membrane synthesis ostensibly in support of tumor cell proliferation.

IMAGING PHOSPHOLIPID SYNTHESIS WITH CHOLINE

PtC is composed of a glycerol backbone esterified with two fatty acids and phosphocholine. PtC structurally resembles triglycerides, which are composed of a glycerol backbone esterified to three fatty acids (Figure 2). The major synthetic route for PtC in most cells follows the Kennedy pathway, starting with the production of phosphocholine by choline kinase (CK). The activity of CK is upregulated in many types of cancer^[13], to the point that increased choline metabolism has been considered a metabolic hallmark of cancer^[14].

While there are subtle biochemical differences between carbon-11 and fluorine-18 labeled cholines, both are avid substrates for CK^[15]. On the basis of this mechanism, fluorine-18 fluorocholine PET/CT was tested in HCC, and found to be significantly more sensitive than FDG PET/CT, with a sensitivity of 84% vs 67%, respectively ($P = 0.01$)^[16]. As the most abundant membrane phospholipid, PtC is believed to be the primary metabolic destination of most fatty acids synthesized *de-novo* by cancer cells^[11,12]. Fatty acids produced by FAS may be distinguished by their relatively high saturation, and while humans lack the desaturase enzymes required to produce certain unsaturated fatty acids (*i.e.*, essential fatty acids), *de-novo* synthesized fatty acids undergo sufficient modification by elongase and desaturase enzymes to still give rise to broad structural and functional variations among phospholipids

Table 1 Results of PubMed query for clinical studies comparing ¹¹C-choline, fluorocholine, or ¹¹C-acetate over fluorodeoxy-D-glucose in 15 or more patients

Disease	Clinical role	First author	Publish year	No. of patients	Tracer(s) compared to FDG	Primary results
Prostate cancer	Diagnosis	Liu	2016	Meta-analysis 56 trials 3586 patients	¹¹ C-choline ¹⁸ F-choline, ¹¹ C-acetate	¹⁸ F-choline AUC 0.94, 95%CI: 0.92-0.96; ¹¹ C-choline AUC 0.89, 95%CI: 0.86-0.91; ¹¹ C-acetate AUC 0.78, 95%CI: 0.74-0.81; FDG AUC 0.73, 95%CI: 0.69-0.77
	Detection	Wata-nabe	2010	43	¹¹ C-choline	Sensitivity 73%, 88%, and 31% for ¹¹ C-choline, MRI, and FDG, respectively
Hepato-cellular carcinoma	Re-staging	Richter	2010	73	¹¹ C-choline	Sensitivity was 60.6% for ¹¹ C-choline and 31% for FDG
	Detection, metastatic	Ho	2007	121	¹¹ C-acetate	Patient-based sensitivity for metastasis was 64% and 79% for ¹¹ C-cetate and FDG, respectively
	Detection, primary	Ho	2003	57	¹¹ C-acetate	Sensitivity was 87% and 47% for ¹¹ C-acetate and FDG respectively
	Detection, primary/metastatic	Park	2008	112	¹¹ C-acetate	Sensitivity was 75%, 61%, and 83% for ¹¹ C-acetate, FDG, and dual-tracer PET.CT, respectively
	Detection, primary	Larsson	2012	44	¹¹ C-acetate	Detection rate was 34/44 for ¹¹ C-acetate and 13/44 for FDG (<i>P</i> < 0.001)
Malignant glioma	Detection, primary	Talbot	2010	81	¹⁸ F-choline	Sensitivity was 88% for ¹⁸ F-choline <i>vs</i> 68% for FDG
	Detection	Wu	2011	76	¹¹ C-choline	¹¹ C-choline PET was positive in 28 patients with negative FDG PET
	Diagnosis	Castilla-Lievre	2016	28	¹¹ C-choline	Sensitivity was 75%, 36%, and 93% for ¹¹ C-holine, FDG, and dual tracers, respectively
Nasopha-ryngeal cancer	Diagnosis	Yama-moto	2008	15	¹¹ C-acetate, ¹¹ C-methi-onine	Sensitivity was 90%, 100%, and 40% for ¹¹ C-acetate, ¹¹ C-methionine, and FDG, respectively
	Re-staging	Tan	2011	55	¹¹ C-choline	Sensitivity/specificity was 92%/88%, 87%/81%, and 77%/63% for ¹¹ C-choline, MRI, and FDG, respectively
Multiple myeloma	Staging	Wu	2011	15	¹¹ C-choline	Sensitivity for detecting locally advanced nasopharyngeal cancer was 100% <i>vs</i> 86% percent for ¹¹ C-choline and FDG, respectively
	Re-staging	Lin	2014	15	¹¹ C-acetate	Diffuse infiltration was detected in 100% of patients with ¹¹ C-acetate <i>vs</i> 40% with FDG
Renal cell carcinoma	Staging	Cassou-Mounat	2016	21	¹⁸ F-choline	¹⁸ F-fluorocholine detected 75% more lesions, and with higher intra-observer agreement than FDG (kappa score 0.89 <i>vs</i> 0.81)
	Diagnosis	Oyama	2014	29	¹¹ C-acetate	Detection rate was 72% for ¹¹ C-acetate <i>vs</i> 22% for FDG

AUC: Area under the curve; CI: Confidence interval; FDG: Fluorodeoxy-D-glucose; PET: Positron emission tomography.

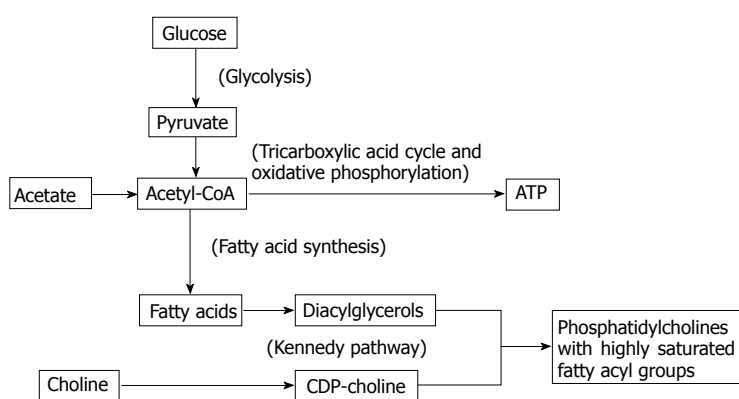


Figure 1 The interplay between glucose, acetate, and choline metabolism. By providing substrate for *de-novo* fatty acid synthesis, acetate metabolism may feed into phosphatidylcholine synthesis, explaining why tumors showing high uptake of ¹¹C-acetate may also show increased uptake of radiolabeled choline on PET. Because acetyl-CoA produced from acetate may also serve as a substrate for the citric acid cycle and other pathways, it is possible that, for some cancers, ¹¹C-acetate uptake may not always provide a consistent readout of tumor lipogenesis. The Kennedy pathway is an ATP-dependent pathway that may rely to varying degrees on glycolysis as a source of ATP. ATP: Adenosine triphosphate.

such as phosphatidylcholine (PtC)^[17].

DO WE NEED TO FURTHER VALIDATE IMAGING BIOMARKERS OF LIPOGENESIS?

Upregulated PtC synthesis may be coupled to lipogenesis

in cancer, since treatment by the FAS inhibitor Orlistat can reduce the activity of CK and lower PtC levels in breast, prostate, and ovarian cancer cells^[18]. This and other observations support speculation that imaging of choline metabolism can be used to monitor tumor lipogenesis^[12,18]. The reason why choline-based tracers may be needed to assess tumor lipogenic activity despite ¹¹C-acetate being available is that acetyl-CoA formed from acetate can also

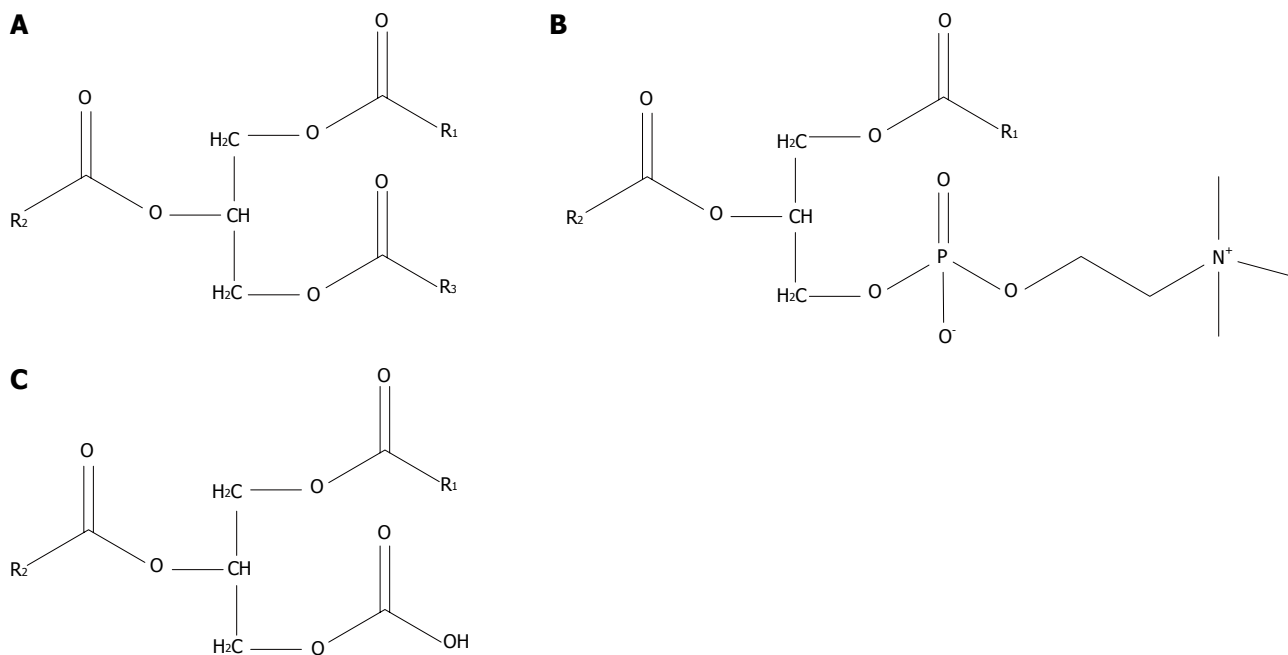


Figure 2 Lipid molecules composed of glycerol esterified to fatty acids. Triglycerides (A), phosphatidylcholines (B), and diglycerides (C) resemble each other because of their common glycerol backbone. Molecular species of these compounds, particular phosphatidylcholines, can have broad functional variations based on the length and saturation of their fatty acyl components, R₁, R₂, and R₃.

serve as a metabolic substrate for a variety of metabolic processes, including oxidative metabolism, histone modification, and cholesterol biosynthesis^[19]. Thus, uncertainty is raised about the biochemical specificity of acetate as a PET imaging biomarker of lipogenesis. Case in point, uptake of ¹¹C-acetate by xenograft human prostate cancers was found to be correlated with FAS expression, but FAS inhibition did not completely abrogate acetate uptake, raising the possibility of acetate participating in multiple metabolic pathways^[5]. Furthermore, low ¹¹C-acetate uptake has been observed in the PI3K/Met overexpressing mouse model of HCC, despite elevated expression of FAS in the tumors^[19]. Therefore, acetate and choline-based tracers do need to be further validated as PET biomarkers of lipogenesis before they are deployed to the clinic for this purpose.

EFFECT OF TUMOR DIFFERENTIATION ON METABOLIC PET IMAGING

Increases in lipid metabolism and glucose metabolism can be observed to coincide in the same tumor. Among several clinical comparisons between acetate PET and FDG PET, over 90% of poorly differentiated or metastatic HCC tumors demonstrated increased uptake of both ¹¹C-acetate and FDG, leading to the conclusion that the diagnostic advantage of acetate PET over FDG PET stems from its ability to detect more well-differentiated tumors^[20-22]. In a study involving earlier stage HCC, the overall sensitivity of ¹¹C-acetate PET for all grades of tumor was 87.3%, while the sensitivity of ¹⁸F-FDG was 47.3% in the same group of patients^[6]. A similar pattern of dual tracer uptake in well- vs

poorly-differentiated tumors was noted in a clinical trial that compared ¹⁸F-fluorocholine against FDG, with ¹⁸F-fluorocholine showing higher sensitivity for well-differentiated HCC, and both tracers showing similar sensitivity for less-differentiated HCC^[16]. The detection by ¹⁸F-fluorocholine PET/CT of a well-differentiated HCC tumor that was not found by FDG PET is illustrated in Figure 3. Along these lines, in a tissue microarray of 157 HCC tumors, we found associations with overall survival for both CK expression and HK expression, but only HK expression correlated with tumor differentiation^[23]. Thus, while choline and acetate affords PET with better overall sensitivity for HCC, only FDG PET shows promise for assessing tumor differentiation in HCC.

Biochemical insight on the relationship between choline metabolism and glycolysis can be garnered from studies involving metabolic profiling. In one pre-clinical study of ICL-CCIC-0019, a novel small molecule CK inhibitor, inhibition of choline metabolism resulted in increased glucose and acetate metabolism (without reactive oxygen species formation), ostensibly as a response to metabolic stress induced by the CK inhibitor^[9]. There is also the possibility that glycolysis increases in cancer cells to sustain the metabolic demands of lipogenesis. By producing acetyl-CoA and ATP, glycolysis produces both the substrate (*i.e.*, acetyl-CoA) and energy (*i.e.*, ATP) required for *de-novo* lipogenesis. However, it does not appear that glycolysis directly drives lipogenesis, as anoxia-induced increases in glycolysis have not been shown to increase the rate of lipogenesis in cultured human breast cancer cells^[24]. In cholangiocarcinoma, the second most common form of liver cancer, tumors may demonstrate high uptake on FDG PET/CT and low uptake on ¹⁸F-choline PET/CT, a

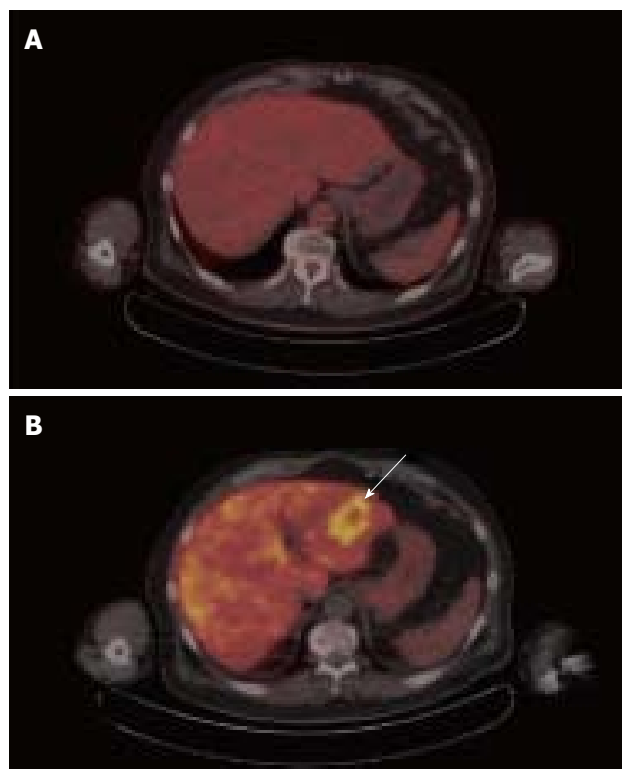


Figure 3 Corresponding ^{18}F -fluorodeoxy-D-glucose positron emission tomography/computed tomography (A) and ^{18}F -fluorocholine positron emission tomography/computed tomography (B) images of hepatocellular carcinoma obtained from the same patient on different days. The tumor is not at all evident on transaxial images of the liver from FDG PET/CT (A). Corresponding transaxial images of the liver from ^{18}F -fluorocholine PET/CT (B) shows a 5-cm diameter circumscribed area of increased uptake in the left hepatic lobe (B) This tumor contained within the left hepatic lobe was histopathologically confirmed to be a well-differentiated HCC. FDG: ^{18}F -fluorodeoxy-D-glucose; PET: Positron emission tomography; CT: Computed tomography; HCC: Hepatocellular carcinoma.

metabolic phenotype that may differ from both well- and poorly-differentiated HCC^[16,25]. We globally analyzed the gene expression from such tumors, predicting increased glucose transport and inhibited lipid metabolism based on a gene expression signature that distinguishes ICC from HCC^[25]. Consistent with these findings, cholangiocarcinomas have also been shown to uniformly demonstrate low ^{11}C -acetate uptake^[6]. The application of both FDG and choline/acetate-based PET imaging in liver tumors may therefore inform on both potential metabolic vulnerabilities as well as the tumorigenic pathways driving an individual patient's cancer.

CONCLUSION

Relationships between glycolysis, fatty acid synthesis, and choline metabolism, in terms of pathways and metabolic substrates, have been described biochemically, but this has not led to absolute clarity about what these pathways and substrates reflect as molecular imaging biomarkers in cancer. Acetate, as a precursor to acetyl-CoA, may have value as an imaging biomarker of cancer lipogenesis, however, choline biomarkers may complement or even

supplant acetate as a cancer imaging biomarker for lipogenic activity given that acetate is also a substrate for aerobic respiration and other pathways which may become abnormal in cancer. Phosphatidylcholine synthesis is reliant on *de-novo* fatty acid synthesis for its supply of diglycerides, and FAS inhibition may down-regulate CK activity and PtC production, further raising the possibility that radiolabeled cholines can indirectly serve as PET biomarkers of lipogenic activity. However, CK inhibition may cause concomitant increases in glucose and acetate metabolism, underscoring the need to further validate these metabolic PET biomarkers for specific clinical applications. With better understanding of these metabolic interactions, multi-tracer metabolic PET, in addition to affording higher sensitivity than single-tracer PET for cancer detection, is likely to provide valuable information on the metabolic vulnerabilities associated with cancer.

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