# PET for Prostate Cancer Imaging: Still a Quandary or the Ultimate Solution?

Carcinoma of the prostate (PCA) is one of the most common tumors with increasing incidence in elderly men (*1*). By the time of diagnosis only 50% of the tumors are clinically localized, and half of these are found to be extracapsular at pathologic staging (*2*). Metastases of PCA occur in regional lymph nodes and bone and, in late stages, in lung and liver. Tumor therapy includes surgery (radical prostatectomy), radiation, and androgen ablation with regard to tumor spread. Although androgen ablation induces apoptosis of normal prostate epithelial cells and regression of early-stage PCA with a response rate of approximately 80%, this treatment is not curative for PCA because of resurgent growth of androgen-independent cells. Even many androgen-sensitive prostate tumors appear to be resistant to induction of apoptosis; androgen withdrawal affects those tumors by decreasing proliferation (*3*). Thus, much effort is being directed toward finding ways to increase apoptosis in PCA to reduce the growth rate of the tumor. Because of the low proliferation rate of PCA, chemotherapy is indicated only as a second-line therapy in failure of hormonal therapy.

The exact estimation of the initial tumor stage is difficult with conventional imaging modalities such as sonography and CT (*1*). Early lymph node involvement is especially hard to detect by conventional imaging methods; therefore, pelvic lymph node dissection, by either open or laparoscopic techniques, is the gold standard. CT and MRI are considered to be of limited use because of their low sensitivity. However, in patients with a high risk of node metastases, clinical recognition of involved lymph nodes may be important, thus avoiding an operative procedure. Detection of skeletal metastasis is best assessed by a bone scan. This may not be indicated in asymptomatic patients if the serum level of prostate-specific antigen (PSA) is <10 ng/mL in the presence of well-differentiated or moderately differentiated tumors (*4*) because the likelihood of bone metastasis is low in this group of patients. However, after radical prostatectomy, clinical failure may be preceded (by several months) by biochemical failure with increasing PSA levels. Evidence suggests that it is rare to see a positive bone scan in patients not receiving adjuvant hormonal therapy before the serum PSA level is >40 ng/mL (*5*). No reliable data are available on the specificity or sensitivity of CT scanning after treatment with a curative intent. CT may be helpful only in detecting the presence of node metastases in patients with a negative bone scan and a PSA level of >4 ng/mL (*6*). Transrectal sonography is another diagnostic tool to establish the presence of local recurrent disease. However, the search for local recurrence must be balanced against the fact that salvage radiation therapy might be most effective if applied early, before the PSA level reaches 1 ng/mL (*7*). Therefore, salvage radiation for local recurrence is often established only on the basis of a slow PSA doubling time, which is more likely correlated with local recurrence than with distant metastasis. This unfortunate clinical situation highlights the need for new diagnostic tools with appropriate sensitivity and specificity for early detection of disseminated or recurrent PCA.

^{18}F-FDG PET has shown its effectiveness in detecting primary tumors and metastases in various tumor entities but has failed to differentiate benign hyperplasia and PCA (*8*) or even to detect the organ-confined carcinoma (*9*). However, to locate relapse in biochemical progression, ^{18}F-FDG PET might be comparable to CT (*6,10*) although it is below planar bone scintigraphy in the detection of bone metastases (*11,12*).

Unlike glucose, choline is incorporated in cells through phosphorylcholine synthesis and is integrated in membrane phospholipids. It has been suggested that malignant transformation of cells is associated with the induction of choline kinase activity, with increased demand on phospholipids attributed to proliferation, and that choline itself modulates the signaling process of cell proliferation and differentiation (*13,14*). Numerous studies using ^{31}P magnetic resonance spectroscopy have revealed the high content of phosphorylcholine in most cancers, whereas in corresponding normal tissues this choline metabolite is present at low or even undetectable levels (*15,16*).

This background provided the rationale for Hara et al. (*17*) to introduce ^{11}C-choline PET for imaging the primary PCA, and his work has been confirmed by others (*18*). Further experience is available from brain tumors (*19*), esophageal carcinoma (*20*), and mediastinal lymph node metastasis of lung cancer (*21*). After delivery by the bloodstream, choline is taken up by cells (transporter density) and is retained because of phosphorylation by the choline kinase (enzyme activity). Further pathways are oxidation to be-

taine and acetylation to acetylcholine but to a much lower extent (22). ^{11}C-Choline blood clearance is very rapid (approximately 7 min), and metabolites, betaine and betaine aldehyde, appear very quickly (22). The simple kinetic of the main amount of the tracer (e.g., fast trapping without redistribution) allows the use of simple indices (e.g., tumor-to-background ratio) instead of metabolic rates gained by several assumptions and corrections.

The preliminary reports on ^{11}C-choline as a tumor-seeking agent are very encouraging. Moreover, the synthesis of ^{11}C-choline is relatively easy to perform with regard to automation, reproducibility, and yield (23). However, its widespread application is limited by the short half-life of [11]C ($t_{1/2}$ = 20 min). The practical advantages of working with the longer-lived radioisotope [18]F ($t_{1/2}$ = 110 min) resulting in a higher specific activity led Hara et al. (24,25) to introduce ^{18}F-fluoroethylcholine (FECh) and DeGrado et al. (26) to synthesize ^{18}F-fluoromethyl-dimethyl-2-hydrochyethyl-ammonium (FCH). Dimethylethanolamine was alkylated with ^{18}F-fluorobromomethane (FBM) for FCh and with ^{18}F-fluoroethyltosylate (FET) for FECh. Both syntheses are sophisticated because demanding purification steps are involved. For FBM a gas chromatographic purification is mandatory before methylation (27). Because preparative gas chromatographic separation is not routinely a standard operation, application of FCh will be restricted. Another precursor for ^{18}F-fluoromethylation with higher reactivity is ^{18}F-fluoromethyliodide (28), which has not been investigated for FCh synthesis up to now. With regard to automation, fluoroethylation will be a more convenient way to introduce a choline analog into routine PET imaging, although FECh differs structurally more from choline than does FCh. However, Clary et al. (29) showed that substrate specificity of choline kinase is maintained when 1 of the 3 methyl groups of choline is modified by a longer alkyl chain. The ^{18}F-fluoroethylation method described by Hara et al. (25) is fully automated and yields 35%–45% of FECh. To increase the yield and purity this 1-pot reaction can be modified by isolation of FET before reaction with dimethylethanolamine, although this production route will entail more additional expenditure in the automation technique. On the other hand, preparative purification using an ion-pair reagent that is difficult to be removed completely is avoided.

The behavior of the new radiotracer FECh is similar to that of ^{11}C-choline in vitro, in animal experiments, and in humans (in terms of the biodistribution) (25). However, the most striking difference between ^{18}F-labeled choline and ^{11}C-choline is a much higher urinary elimination, an important disadvantage for investigation of the prostate region. Obtaining a delayed scan (possible because of the longer physical half-life) might reduce urinary bladder activity, thus avoiding the need for continuous bladder irrigation. Another technical advantage of the longer half-life of ^{18}F-labeled choline is the possibility of performing simultaneous transmission–emission scanning instead of separate measurements. Differences of ^{11}C-choline and ^{18}F-FECh on the image cannot be explained by the different physical properties of the isotopes, resulting in a different range until annihilation when a PET device with a spatial resolution of 6 mm is used (30), but must be addressed with regard to the chemical properties. Furthermore, the reproducibility of radiocholine uptake and the physiologic variation (e.g., age dependency of prostate uptake) need to be investigated. More important, the influence of the dietary state (e.g., glucose and insulin levels) or medication (e.g., testosterone deprivation) should be defined systematically.

Moreover, ^{11}C-acetate has been proposed for imaging PCA (31,32). The uptake mechanism was not described; however, it is reasonable to suggest that ^{11}C-acetate is incorporated in the lipid pool in cancer tissue with low oxidative metabolism and high lipid synthesis. In the near future, the specific differences of these PET tracers should be clarified with regard to the uptake in PCA, the amount of urinary elimination and accumulation in other organs (e.g., nonspecific small bowel activity, pancreatic uptake, accumulation in inguinal lymph nodes), and changes during therapy. These imaging modalities will improve the clinical situation for evaluating PCA. However, the administration of ^{18}F-labeled choline will influence PET imaging not only in PCA but also in brain tumors and will rearm us for a systematic comparison of FDG and choline with regard to staging and therapy monitoring in all other malignancies.

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## REFERENCES

1. Garnick MB, Fair WR. Combating prostate cancer. *Sci Am.* 1998;279:74–83.
2. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol.* 1991;145:907–923.
3. Westin P, Stattin P, Damber JE, Bergh A. Castration therapy rapidly induces apoptosis in a minority and decreases cell proliferation in a majority of human prostatic tumors. *Am J Pathol.* 1995;146:1368–1375.
4. Oesterling JE, Martin SK, Bergstralh EJ, Lowe FC. The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. *JAMA.* 1993;269:57–60.
5. Cher ML, Bianco FJ, Lam JS, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol.* 1998;160:1387–1391.
6. Seltzer MA, Barbaric Z, Belldegrun A, et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. *J Urol.* 1999;162:1322–1328.
7. vander Kooy MJ, Pisansky TM, Cha SS, Blute ML. Irradiation for locally recurrent carcinoma of the prostate following radical prostatectomy. *Urology.* 1997;49:65–70.
8. Effert PJ, Bares R, Handt S, Wolff JM, Bull U, Jakse G. Metabolic imaging of untreated prostate cancer by positron emission tomography with 18fluorine-labeled deoxyglucose. *J Urol.* 1996;155:994–998.
9. Liu IJ, Zafar MB, Lai YH, Segall GM, Terris MK. Fluorodeoxyglucose positron emission tomography studies in diagnosis and staging of clinically organ-confined prostate cancer. *Urology.* 2001;57:108–111.
10. Sanz G, Robles JE, Gimenez M, et al. Positron emission tomography with 18fluorine-labelled deoxyglucose: utility in localized and advanced prostate cancer. *Br J Urol Int.* 1999;84:1028–1031.
11. Shreve PD, Grossman HB, Gross MD, Wahl RL.

Metastatic prostate cancer: initial findings of PET with 2-deoxy-2-[F-18]fluoro-D-glucose. *Radiology.* 1996;199:751–756.

12. Yeh SD, Imbriaco M, Larson SM, et al. Detection of bony metastases of androgen-independent prostate cancer by PET-FDG. *Nucl Med Biol.* 1996;23:693–697.

13. Cuadrado A, Carnero A, Dolfi F, Jimenez B, Lacal JC. Phosphorylcholine: a novel second messenger essential for mitogenic activity of growth factors. *Oncogene.* 1993;8:2959–2968.

14. Zeisel SH. Choline phospholipids: signal transduction and carcinogenesis. *FASEB J.* 1993;7:551–557.

15. Kurhanewicz J, Vigneron DB, Hricak H, et al. Prostate cancer: metabolic response to cryosurgery as detected with 3D H-1 MR spectroscopic imaging. *Radiology.* 1996;200:489–496.

16. Miller BL, Chang L, Booth R, et al. In vivo ^{1}H MRS choline: correlation with in vitro chemistry/histology. *Life Sci.* 1996;58:1929–1935.

17. Hara T, Kosaka N, Kishi H. PET imaging of prostate cancer using carbon-11-choline. *J Nucl Med.* 1998;39:990–995.

18. Kotzerke J, Prang J, Neumaier B, et al. Experience with carbon-11 choline positron emission tomography in prostate carcinoma. *Eur J Nucl Med.* 2000;27:1415–1419.

19. Hara T, Kosaka N, Shinoura N, Kondo T. PET imaging of brain tumor with [methyl-^{11}C]choline. *J Nucl Med.* 1997;38:842–847.

20. Kobori O, Kirihara Y, Kosaka N, Hara T. Positron emission tomography of esophageal carcinoma using (11)C-choline and (18)F-fluorodeoxyglucose: a novel method of preoperative lymph node staging. *Cancer.* 1999;86:1638–1648.

21. Hara T, Inagaki K, Kosaka N, Morita T. Sensitive detection of mediastinal lymph node metastasis of lung cancer with ^{11}C-choline PET. *J Nucl Med.* 2000;41:1507–1513.

22. Roivainen A, Forsback S, Gronroos T, et al. Blood metabolism of [methyl-^{11}C]choline: implications for in vivo imaging with positron emission tomography. *Eur J Nucl Med.* 2000;27:25–32.

23. Hara T, Yuasa M. Automated synthesis of [^{11}C]choline: a positron-emitting tracer for tumor imaging. *Appl Radiat Isot.* 1999;50:531–533.

24. Hara T, Yuasa M. Automated synthesis of fluorine-18 labeled choline analogue: 2-fluoroethyl-dimethyl-2-oxyethylammonium [abstract]. *J Nucl Med.* 1997;38(suppl):44P.

25. Hara T, Kosaka N, Kishi H. Development of ^{18}F-fluoroethylcholine for cancer imaging with PET: synthesis, biochemistry, and prostate cancer imaging. *J Nucl Med.* 2002;43:187–199.

26. DeGrado TR, Coleman RE, Wang S, et al. Synthesis and evaluation of ^{18}F-labeled choline as an oncologic tracer for positron emission tomography: initial findings in prostate cancer. *Cancer Res.* 2001;61:110–117.

27. Bergman J, Eskola O, Lehikoinen P, Solin O. Automated synthesis and purification of [^{18}F]bromofluoromethane at high specific radioactivity. *Appl Radiat Isot.* 2001;54:927–933.

28. Zheng L, Berridge MS. Synthesis of [^{18}F]fluoromethyl iodide: a synthetic precursor for fluoromethylation of radiopharmaceuticals. *Appl Radiat Isot.* 2000;52:55–61.

29. Clary GL, Tsai CF, Guynn RW. Substrate specificity of choline kinase. *Arch Biochem Biophys.* 1987;254:214–221.

30. Nuclear medicine tomography: systems and devices. In: Sorenson JA, Phelps ME, eds. *Physics in Nuclear Medicine.* 2nd ed. Philadelphia, PA: W.B. Saunders; 1989:424–451.

31. Yoshimoto M, Waki A, Yonekura Y, Sadato N, Yokoyama A, Fujibayashi Y. Non-oxidative metabolism of C-11-acetate: new insight for lipid synthesis imaging in tumors [abstract]. *J Nucl Med.* 1999;40(suppl):232P–233P.

32. Kotzerke J, Prang J, Neumaier B, et al. ^{11}C-Acetate positron emission tomography (PET) of prostate cancer: first clinical experience [abstract]. *J Nucl Med.* 2001;42(suppl):451P.