INVITED COMMENTARY

^{18}F-Fluorocholine: A New Oncologic PET Tracer

Although considerable progress has been made using ^{18}F-FDG in PET oncologic imaging, there are some well-known limitations to its use. These include the inability of FDG to visualize very small tumors, to visualize brain tumors and intrapelvic tumors, and to differentiate between malignancy and chronic inflammation.

Many efforts have been made to develop a new ^{18}F-labeled PET tracer that complements these weak points. Our group developed ^{11}C-choline as a new PET tracer for cancer detection and succeeded in visualizing brain tumors (*1*), lung cancer (*2*), esophageal cancer (*3*), colon cancer (*4*), bladder cancer (*4*), prostate cancer (*5*), and many other cancers (*4*). Motivated by this success, we also synthesized an ^{18}F-labeled choline analog, ^{18}F-fluoroethylcholine, as a PET tracer with the belief that ^{18}F would be superior to ^{11}C because of the longer half-life and the shorter positron range (*6*). An animal experiment indicated the possible usefulness of this compound (*6*), but the clinical application was postponed because of the difficulty in completely eliminating a toxic substance, Kryptofix 2.2.2. (Merck, Schuchardt, Germany) (which was used as a catalyst for the synthesis), from the product.

DeGrado et al. (*7*) conceived that ^{18}F-fluorocholine (fluoromethylcholine) would be a better biologic analog of choline than ^{18}F-fluoroethylcholine and succeeded in synthesizing it in an injectable form (they used preparative gas chromatography for elimination of Kryptofix 2.2.2.). They confirmed selective uptake of this compound in tumor cells in vitro and then showed its high uptake in brain tumors and in prostate cancer.

Their achievement appears to be the second advent of ^{18}F-labeled PET tracer in the history of PET oncology. The article by DeGrado et al. (*8*) in this issue of *The Journal of Nuclear Medicine* indicates that the behavior of ^{18}F-fluorocholine in the body may be similar to that of natural choline.

The behavior of natural choline is shown by ^{11}C-choline PET, which our group has used in >1,500 patients with various kinds of cancers. We have compared these results with those using FDG PET in the same patients. This experience may help one to anticipate the possible uses of ^{18}F-fluorocholine (as developed by DeGrado et al. (*8*)). A summary of our experience with ^{11}C-choline PET and FDG PET of various cancers follows.

BRAIN TUMORS

Low-grade and high-grade tumors were characterized by low uptake and high uptake of ^{11}C-choline, respectively. In addition, after the tumor was treated by surgery or radiotherapy, accurate information on the residual tumor, tissue necrosis, recurrence of tumor, and complete cure of the tumor was given only by ^{11}C-choline PET. FDG PET was almost useless.

HEAD AND NECK CANCER

^{11}C-Choline PET and FDG PET showed positive tumor uptake. Healthy organs of positive uptake (e.g., salivary glands in ^{11}C-choline PET) provided good landmarks for the localization of tumors. When the head and neck cancer was treated by radiotherapy, the therapeutic response measured by ^{11}C-choline PET was rapid, but the response shown by FDG PET was very slow.

BREAST CANCER

^{11}C-Choline PET and FDG PET exhibited high tumor uptake in breast cancer and local metastasis.

LUNG CANCER

In the patients studied, ^{11}C-choline PET gave a positive image of lung cancer when the mass was >5 mm in diameter. In contrast, FDG PET gave a positive image of lung cancer only when the mass was >1 cm. Mediastinal lymph node metastases were always visualized with ^{11}C-choline PET, but this was not the rule with FDG PET because the metastatic lymph nodes were not always >5 mm. In addition, the combination of ^{11}C-choline PET and FDG PET was effective in differentiating lung cancer and chronic inflammation. The standard uptake value of ^{11}C-choline in lung cancer was almost the same as that of FDG; however, in chronic inflammation, it was much smaller with ^{11}C-choline than with FDG.

The high uptake of FDG in chronic inflammation is well known (*9*), and this high uptake can be explained by the pathology of chronic inflammation: predominant cellular infiltration of macrophages in the tissue (granulomatous reaction), scanty or completely absent blood vessels in the granulomatous tissue, and markedly enhanced glycolysis in the macrophages that are still viable in the anaerobic environment (*10*).

ESOPHAGEAL CANCER

Esophageal cancer and lymph node metastases were always visualized with ^{11}C-choline PET when the size was >5 mm. They were visualized by FDG PET if the size was >1 cm. Occasionally, uptake in healthy myocardium interfered with FDG images of esophageal cancer. If the cancer was

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localized under the diaphragm, ^{11}C-choline PET was useless because of the normal uptake of ^{11}C-choline in the liver. However, it was visualized by FDG PET.

LIVER CANCER

Primary and metastatic liver tumors were always visualized with FDG PET. ^{11}C-Choline PET was useless because of the normal uptake of ^{11}C-choline in the liver.

KIDNEY CANCER

Kidney cancer was visualized by FDG PET, but this finding had no practical meaning because there was a great deal of radioactivity in the renal pelvis. ^{11}C-Choline PET was useless because of the normal uptake in the renal tissue.

COLORECTAL CANCER

Colon cancer was visualized with FDG over the whole range of the colon. Colon cancer was visualized with ^{11}C-choline if it was localized in the rectum.

PROSTATE CANCER

Prostate cancer was always visualized with ^{11}C-choline, and the distribution of radioactivity was heterogeneous over the 2 lobes of the prostate. (In benign hyperplasia of the prostate, the radioactivity was lower and the distribution was homogeneous.) Metastases of prostate cancer to the pelvic lymph nodes and the pelvic bones were visualized with ^{11}C-choline. Hormonal therapy for the prostate cancer was clearly shown by ^{11}C-choline PET. The recurrence of prostate cancer after surgical treatment, indicated by an increase in the level of prostate-specific antigen, was visualized by ^{11}C-choline PET. FDG PET was useless in the imaging of prostate cancer and metastases because of the very high radioactivity in the urinary bladder.

UTERINE AND OVARIAN CANCERS

Uterine and ovarian cancers were visualized by ^{11}C-choline PET and FDG PET. The peritoneal dissemination of ovarian cancer was visualized only by ^{11}C-choline PET.

MALIGNANT LYMPHOMA

^{11}C-Choline PET and FDG PET were effective in detecting malignant lymphoma as long as the organs of normal uptake did not interfere with the image.

PROSPECT

All cells in the body absolutely require choline. Choline is needed for the synthesis of phospholipids in cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid-cholesterol transport and metabolism (*11*). There is a pathway for the de novo synthesis of choline using methionine and folate to meet, in part, the body's demand for choline (*11*). However, in certain situations, choline should be supplemented directly as such. Humans may develop a fatty liver and liver damage if they are given total parenteral nutrition devoid of choline but adequate for methionine and folate. This condition resolves if choline is supplemented directly (*11*).

Another example involves brain development. If pregnant rats are fed a choline-deficient diet, they may give birth to newborns with memory deficit, but choline supplementation during fetal development prevents this. The memory deficit and its prevention have been shown to correlate with biochemical and morphologic changes in the hippocampus (*12,13*). In humans, whose development of the hippocampus continues for years after birth, there have been no corresponding studies. In general, our knowledge of choline metabolism and nutrition is too limited to answer a variety of questions. However, in 1998, the Food and Nutrition Board of the Institute of Medicine in the United States promoted choline to vitamin status and set the adequate intake at 550 mg for males and 425 mg for females (*14*).

The uptake mechanism of choline and fluorocholine in tumor cells is of great interest. The backbones of cell membranes are made of phospholipid bilayers, of which the major component is phosphatidylcholine. The cell membranes are duplicated at the same rate as the rate of cell duplication. Tumor cells appear to be destined to incorporate choline rapidly to meet the need of rapid synthesis of the cell membranes. The levels of choline and phosphorylcholine are increased in a variety of tumor cells, probably representing the activation of choline uptake and phosphorylation in tumor cells (*15–18*).

Choline metabolism in tumor cells is directed primarily toward membrane synthesis, and the de novo synthesis of choline is negligible in tumor cells. On the basis of this evidence, if it is proven that the uptake of radiolabeled choline and fluorocholine represents exactly the duplication rate of tumor cells, these radiolabeled compounds may be extremely useful as cancer detection probes.

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