Metabolic Imaging of Cancer

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INTRODUCTION

There are still significant limitations to diagnose cancer, to select optimal therapeutic modalities, to evaluate the therapeutic response to tumors at an early stage, and to distinguish between recurrent tumor and fibrotic or inflammatory changes of therapy. While tumors can be diagnosed and classified with reasonable accuracy by biopsy, no noninvasively applicable method is available which has acceptable specificity for cancer diagnosis. Sensitivity for detection of anatomic lesions or masses is more approachable with modern imaging methods, although limitations still exist in many clinical situations in which tumors are small or differ little in physical properties from adjacent tissue. Following diagnosis, selection and application of optimal therapy is hampered by many factors. The staging process suffers from many of the same deficiencies which affect the original diagnosis. If primary, palliative or adjuvant radiotherapy or chemotherapy is contemplated to treat solid tumors, the presence of ischemic or hypoxic zones within the tumor lesion constitutes a major obstacle to the success of such therapy. There appears no noninvasively applicable method available for detecting or quantifying such zones. Once nonsurgical therapy is begun, it is often difficult to individually optimize the sequence of treatment or to evaluate the therapeutic response before gross changes in its size begin to occur. Following completion of therapy, it is sometimes obscure whether anatomic changes at the site of the tumor represent recrudescence of tumor, or a benign response to the therapy.

In addition to these pragmatic clinical problems, many aspects of tumor biology and metabolism in vivo are not completely understood. This is the case with normal tissues as well, but the problem is magnified in tumors by the wide variety of their degrees of differentiation, and by the complexity of their interaction with the host. It has been generally agreed that cancerous tissue differs from norml tissue. How to use these differences in tumor identification, both in vitro and in vivo, is less clear.

Propelled by advances in computers and electronics, diagnostic imaging has experienced impressive growth recently. The development of positron emission tomography (PET) and nuclear magnetic resonance (NMR) imaging (MRI) guided spectroscopy (MRS) has moved us into the era of metabolic imaging. A metabolic image is a picture in which each pixel has an anatomical correspondence to the body, and also represents the numerical value of a measured biochemical or physiological parameter. In the past, the only true functional images were produced in the nuclear imaging laboratories,

but these generally lacked the ability to present the physiological parameters in absolute units. PET and MRS allow us to obtain absolute values of many parameters, particularly those concerned with metabolism. Because metabolism provides the basis for understanding function and physiology in living systems, any method that can provide localized metabolic information noninvasively is of extreme importance in medicine.

PRINCIPLES AND METHODS

1. Positron Emission Tomography (PET)

PET is a form of computer tomography that produces images reflective of biochemical and physiological processes[1]. To carry out a PET scan, a positron-emitting radionuclide tagged to a suitable substrate must be administered either intravenously or via inhalation. The tracer then becomes distributed in and around the target organ and decays with the emission of a positively charged ion, called a positron. This positron travels approximately 2 to 3 mm before colliding with a negatively charged electron, resulting in the annihilation of both particles. The annihilation energy is emitted as two 511-KeV energy gamma photons at 180 degrees to each other. The simultaneous detection of these photons by paired detectors, often referred to as annihilation coincidence detection (ACD), forms the basis of PET. ACD provides uniform and high spatial resolution, high detection efficiency, and simultaneous collection of linear and angular data[2]. A PET imaging system collects data, sorts it, processes it through a reconstruction algorithm and displays the true spatial distribution of radioactivity in the transaxial plane. These data are then processed further to provide images of regional radionuclide distribution. The most important advantage of PET is its ability to correct for tissue attenuation. The most accurate corrections are measured using an external ring of a positron emitter such as gallium-68 to carry out a transmission scan. Commercial scanners are now being constructed with a full-width half-maximum (FWHM) resolution of 6 mm and the ability to collect data

Table 1. Common Positron-Emitting Radionuclides with Their Half-Lives, Tracer Forms, and Applications

Radionuclide	Physical Half-Life (min)	Labeled Tracer	Application
Fluorine - 18	110.0	^{18}F-2-deoxy-D-glucose	Glucose metabolism
Oxygen - 15	2.1	$C^{15}O_2$	Blood flow
		$H_2{}^{15}O$	Blood flow
		$^{15}O_2$	Oxygen metabolism
Carbon - 11	20.4	^{11}CO and $C^{15}O$	Blood volume
		^{11}C-L-methionine	Amino acid uptake / protein synthesis
		$^{11}CO_2$	Cerebral pH
Nitrogen - 13	10.0	$^{13}NH_3$	Blood flow
		^{13}N-glutamate	Amino acid uptake / protein synthesis
Rubidium - 82	1.2	^{82}Rb-Cl	Blood-brain barrier integrity
Gallium - 68	68.3	^{68}Ga-EDTA	Blood-brain barrier integrity / cerebral blood volume

from axial tomographic slices simultaneously. A phototype scanner is under construction with a FWHM resolution of 2 mm[3]. The most useful positron emitters for PET are fluorine-18, oxygen-15, carbon-11 and nitrogen-13 (Table 1). All these isotopes must be produced by an on-site cyclotron, as their short half-lives essentially preclude transporting them any significant distance. On the other hand, the radiation-absorbed doses incurred during the administration of these tracers are minimized by their short physical half-lives. Two other positron emitters, Ga-68 and rubidium-82, are produced in generators, which contain a longer-lived parent isotope that decays into the positron-emitting product. Although such generators are convenient sources of some isotopes, the compounds with the most biologic and medical interest are those labeled with isotopes of carbon, nitrogen, oxygen, and fluorine, which are not available from generators. About 300 substrates and drugs have been labeled with positron emitting isotopes[4].

2. Magnetic Resonance Spectroscopy (MRS)

Both MRI and MRS are based on the fact that certain nuclei exhibit a magnetic moment. When a body is placed in a strong magnetic field, the nuclei tend to align with the magnetic field. To obtain the NMR signals, the applied magnetic field is impressed on the body and then an oscillating magnetic field is applied as a pulse at the Larmor frequency. This constitutes a condition of resonance. At resonance, the nuclei absorb energy and are thus perturbed from their state of equilibrium. After the pulse, the nuclei release this absorbed energy and tend to realign with the magnetic field. This produces a signal by inducing a current in a coil placed near or on the body[5].

MRS has been available for many years longer than MRI. It was originally applied to small quantities of homogeneous compounds that could be conveniently studied in the laboratory. In recent years the magnetic gradient based techniques that have made MRI possible have been applied to spectroscopic problems, and it is now possible to obtain localized NMR spectra originating from various tissues or organs. The spectroscopy involves separating the signal from a given element into its different chemical forms. This is possible because the magnetic field experienced by an atomic nucleus by neighboring atoms on the same molecule. This produces a chemical shift or small variation in the resonance frequency; a display of the NMR signal as a function of frequency is a spectrum, with different chemical forms of an element forming peaks at characteristic positions.

When the lesion has been characterized by MRI, dicisions regarding the MRS portion of the study are in order. These involve principally the nucleus to be monitored, the choice of radiofrequency coil, and the method of spatial localization to be employed. The nuclei that appears to have most promise for metabolic studies are phosphorus-31, hydrogen-1, sodium-23, carbon-13, and fluorine-19. The relative sensitivities of the various nuclei routinely monitored by MRS are listed in Table 2. These data are used in reference to physiologic concentrations of various metabolites to estimate the volume of tissue that will give rise to localized spectra with reasonable signal-to-noise (S/N) ratios. Phosphorus-31 MRS provides simple spectra with fairly well-separated resonances of important metabolites and has been most extensively

Table 2. NMR Properties of Select Nuclei of Biomedical Interest

Nucleus	Spin	Natural Abundance	Frequency at 1.5 T	Physiologic Concentration, mol	Relative Sensitivity*	Receptivity at 1.5T†
^{1}H	1/2	100.000	63.89	110.00	1.00	1.0
^{2}H	1	0.015	9.80	110.00	2.40×10^{-6}	2.4×10^{-6}
^{1}H	(metabolites)		63.89	0.01–0.10	1.00	$10^{-5} - 10^{X6}$
^{13}C	1/2	1.180	16.06	0.10	2.50×10^{-4}	2.5×10^{-8}
^{19}F	1/2	100.000	60.08	0.10≠	0.85	8.5×10^{-5}
^{23}Na	3/2	100.000	16.89	0.80	0.13	9.5×10^{-5}
^{31}P	1/2	100.000	25.85	0.10	8.30×10^{-2}	8.3×10^{-6}
^{39}K	3/2	93.100	2.99	0.45	1.00×10^{-3}	4.1×10^{-4}

* Relative sensitivity at 1.5T, computed by multiplying the intrinsic sensitivity at constant field by the natural abundance of the nucleus.

† Relative sensitivity multiplied by the physiologic concentration present. For reference, an entry for proton-containing metabolites such as lactate is included.

≠ Introduced exogenously as a fluorinated drug such as 5-fluorouracil.

studied in biological systems. The key metabolites can be classified generally into 2 subgroups: bioenergetics and membrane metabolites. These metabolites may be involved in biochemical pathways that are coupled to each other. The rate of synthesis and utilization of adenosine triphosphate (ATP) and phosphocreatine (PCr) can reflect the viability of cells and the rate and extent of cell proliferation. Cells deficient in nutrients and/or oxygen have relatively lower levels of high-energy phosphates (ATP and PCr) and a generally higher inorganic phosphate (Pi) level, and the cells tend to have acidic pH. The intracellular pH can be measured by the chemical shift separation of Pi from PCr or ATP. Using the concentrations reported for N-acetylaspartate (NAA) and phosphocreatine (PCr) as measured by conventional wet chemical analysis, we can estimate the minimum voxel volumes achievable at 1.5T by comparing the minimum volumes detectable by MRI at 1.5T. Generally, field strengths of about 1.5T or greater are required for MRS. At a given field strength, the phosphorus resonance frequency will be less than half that of hydrogen, so either separate or broadly tunable radiofrequency electronics are needed. Crude localization is achieved through proximity to the coil, and DRESS (depth-resolved surface coil spectroscopy), CSI (chemical shift imaging) and ISIS (image-selected in vivo spectroscopy) are common techniques[6].

CLINICAL APPLICATIONS

1. PET

The attractiveness of PET lies in its versatility. No other technique has the ablility to provide quantitative data on the relationship between blood flow and a range of metabolic processes.

1) Blood Flow, Volume and Oxygen Utilization

Employing the sequential inhalation of $C^{15}O_2$, $^{15}O_2$, and ^{11}CO permits measurement of regional cerebral blood flow (rCBF), the fraction of oxygen extracted from the arterial blood (rOER), the oxygen metabolic rate ($rCMRO_2$) and the

blood volume (rCBV).

In a patient with a brain tumor, rCBF is lower than that of the contralateral grey matter. Tumor rCBF has been found to be variable due to the heterogeneity of tumors with areas of necrosis, hemorrhage, or cyst formation. The $rCMRO_2$ is also low, and this low demand for oxygen is reflected in the low rOER. After radiotherapy, tumors show a progressive fall in oxygen utilization and blood flow. The effects of dexamethasone on patients with brain tumors have shown a fall in cortical rCBF and rCBV[7].

2) Glucose Metabolism

Glucose normally supplies about 95% of the brain's energy, which is primarily used for neuronal activity. The glucose analog ^{18}F-2-fluoro-2-deoxyglucose (FDG) is metabolized to FDG-6-phosphate after it is transported into the brain from the blood. Under oxidative conditions, the glucose-derived radiolabel enters the Krebs cycle and is temporarily trapped in intermediate metabolite pools. With glycolysis, however, the glucose-derived radiolabel is diverted to form lactate (Fig. 1 & 2). Di Chiro et al[8] showed that FDG uptake by tumors correlated with the clinical grade of the glioma. Uptake of FDG by tumors has been used as an indicator of prognosis and also as a differential diagnosis between therapeutic tissue necrosis with a low glucose uptake and recurrent tumor where the glucose uptake was increased (Fig. 3). Studies of ^{18}FDG PET in patients with breast cancer have also demonstrated the usefulness of this technique[9]. The metabolic rate was lower in tumor tissue, which suggests an increase in nonoxidative metabolism of glucose. Yonekura et al[10], who also used ^{18}FDG to study patients with hepatic metastases from colonic tumors, demonstrated that the radioactivity in the metastatic tumor increased continuously after injection, whereas it decreased in normal liver tissue.

3) Amino Acid Metabolism and Protein Synthesis

Amino acid uptake may be greater in cancer

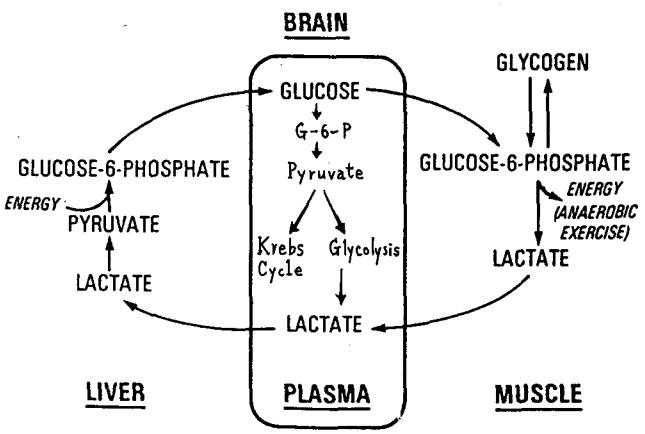

Fig. 1. Cori cycle, by which lactate produced in muscle is converted to glucose by the liver and then returned to muscle. Glucose supplies about 95% of the brain's energy. In normal resting conditions, glucose metabolism in the brain is primarily oxidative: however, in stimulated condition, glycolysis increases out of proportion to oxidative metabolism.

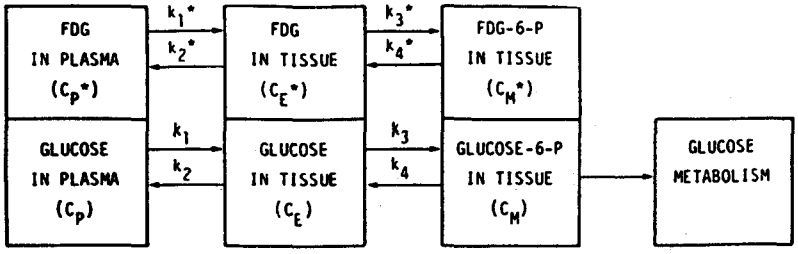

Fig. 2. Tracer kinetic model for glucose metabolism with three compartments: Fluorodeoxyglucose (FDG) reflects total glucose metabolism because FDG-derived radiolabel accumulates as FDG-6-phosphate. The rate constants k_1 and k_2 describe the forward and reverse transport of FDG or glucose, while k_3 and k_4 refer to phosphorylation and dephosphorylation of FDG and FDG-6-PO_4 respectively.

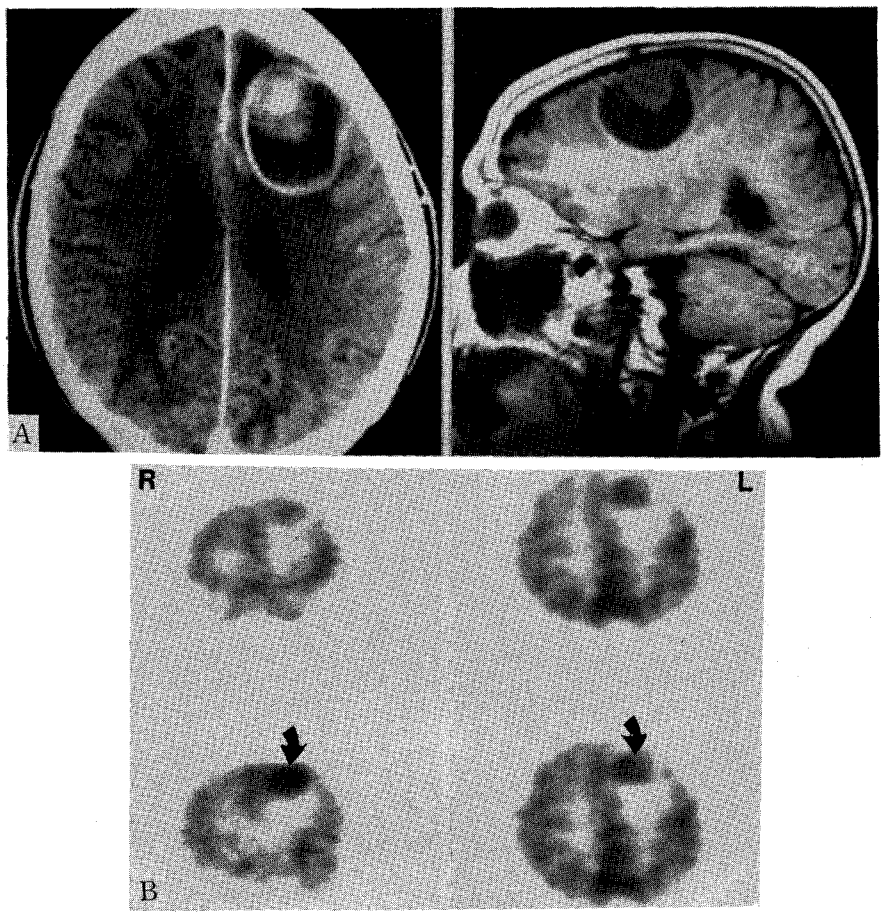

Fig. 3, A. T1-weighted sagittal MR (upper) and transaxial CT (lower) images of the head show a lesions in the left fronto-parietal lobe with cystic and solid components.

B. Selected coronal (left) and transaxial (right) images of the brain show an intense uptake of ^{18}F-FDG (arrows) in the solid component of metastatic ovarian tumor.

cells as a consequence of cell membrane changes that permit increased amino acid transport. A comparison of tumor imaging with PET using ^{68}Ga-EDTA, ^{11}C-glucose, and ^{11}C-methionine has been made. The first two tracers showed similar tumor extensions to the enhanced CT scan; however, ^{11}C-methionine demonstrated further tumor extension in tissue judged normal by the other methods[11]. ^{11}C-methionine has been used to delineate lung cancer and involved lymph nodes[12].

4) Tumor pH

^{11}C-dimethyl-oxazolidinedione (DMO) and ^{11}C-H_2CO_3 are weak acids with apparent pka's of 6.1 in serum. When administered, the neutral acid forms, but not the anion, cross the blood brain barrier (BBB). As a consequence, the relative arterial plasma-to-regional cerebral ^{11}C distributions reflect the pH differences between the plasma and brain compartment. Tyler et al[13] reported that intracellular tumor pH differed significantly from the pH in contralateral brain; alkalotic pH values were consistently seen.

5) Drug Distribution and Effect

Several drugs commonly used in oncology have been labeled with positron-emitting radionuclides to examine their distribution qualitatively. It has been shown that initial uptake of ^{11}C-and ^{13}N-labeled BCNU was dependent on tumor blood flow and that increased BBB disruption, achieved by administering 20% mannitol intravenously, led to an increased BCNU uptake in the glioma[11]. Considerable research is being directed toward the in vivo detection of breast tumors by using ^{18}F- or ^{77}Br-estradiol[14]. There is increasing interest clinically in the ability of hyperthermia alone or in combination with radiotherapy to cause tumor regression. The PET study has shown regional blood flow five times higher in the heated area than in the untreated thigh[9].

6) Others

Patients with prolactin-secreting pituitary adenomas have already been examined with PET using ^{11}C-methionine to monitor the effect of dopamine agonist treatment on the amino acid metabolism in these tumors. Type I dopamine receptors may be labeled with ^{11}C-methyl-bromocriptine or ^{11}C-methyl-spiperone, a dopamine agonist and antagonist, respectively[15]. Monoclonal antibodies, when tagges with ^{55}Co or ^{68}Ga, can be used for glioma localization[9]. As tumor vasculature is not subject to autoregulation, vasoactive drugs such as Ca^{II} antagonists and angiotensin could increase tumor blood flow relative to that of normal brain tissue. The delivery of cytotoxic drugs to tumors could be improved if PET studies suggested sufficient differential effects of Ca^{II} antagonists on organ and tumor blood flow[9].

2. MRS

It is obvious that NMR studies can have great potential in the elucidation of the basic biology of tumors. There appears a potential for MRS to provide increased specificity in separating malignant tumors from normal tissue. It is possible that perturbations of the subject's physiology (such as induced hyperglycemia) may be required, or that isotopic enrichment (such as ^{13}C or ^{19}F-glucose or glucose analogues, or ^{13}N-amino acids) will prove useful. Differences inmetabolism between malignant and benign tumors or abnormal but nonneoplastic tissues have been little studied so far[16].

Hypoxic tumor cells, in addition to their lack of proliferation, may be resistant to various antitumor agents for reasons including achiev-

able concentrations of drug in ischemic tissue, dependence upon aerobic metabolic activation, or participation of molecular oxygen in the drug' s action. There is reason to believe that there must exist metabolic indicators of tumor response to therapy at an early stage. If unequivocal detection and characterization of such changes could be accomplished, it would permit minimizing the toxicity of radiotherapy or chemotherapy to normal tissues while perhaps also improving therapeutic response. Analysis of tumor differentiation or de-differentiation resulting from therapy could also be of great value. The potential of NMR directly to monitor toxic effects of therapy on normal tissues is also important as is the ability to use certain nuclei such as ^{18}F to minor metabolism of chemotherapeutic agents.

A substantial effort has been directed to MRS of tumors. Increases in the relative concentrations of phosphomonoesters (PME), and alterations in some cases of the phosphodiesters (PDE) peak, are seen in tumors (Fig. 4) compared with most non-neoplastic tissues[17]. pH has been found to be elevated in many tumors, and variation in relative PCr, Pi, and ATP levels have been described[18]. However, there is a great deal of overlap in all observed parameters. Much of the excitement inherent in phosphorus spectroscopy of tumors to assess therapeutic response. An increase in PCr in patients with breast cancer in response to therapy has been reported[19]. Some studies show a reduction in high energy phosphate levels consistent with necrosis. A

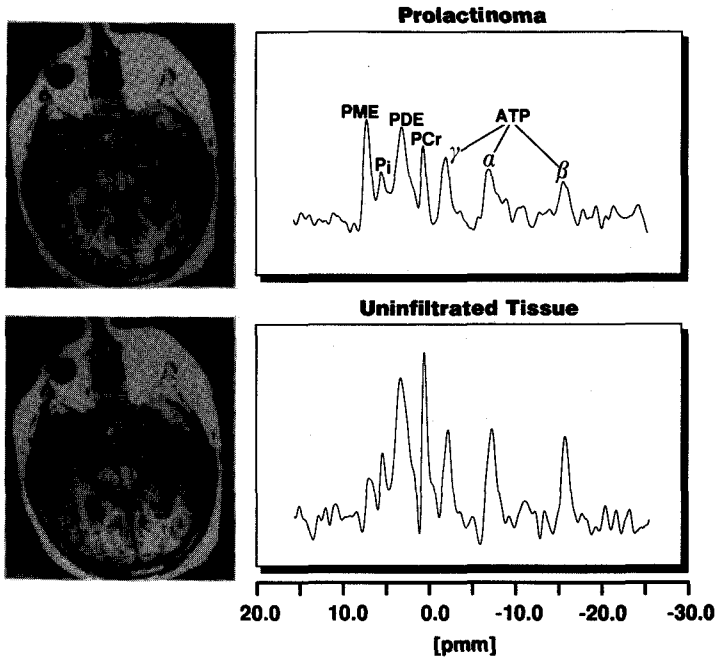

Fig. 4. Proton MRI and ^{31}P MRS in a patient with a large invasive prolactinoma. T1-weighted axial images of the brain at the level of skull base show one volume of interest (VOI) (left upper) centered on the tumor and another VOI (left lower) centered on uninfiltrated tissue. The tumor spectrum (right upper) shows an increase of PME and a decrease of PCr, while the uninfiltrated tissue spectrum (right lower) resembles a normal spectrum (Permission from Radiology).

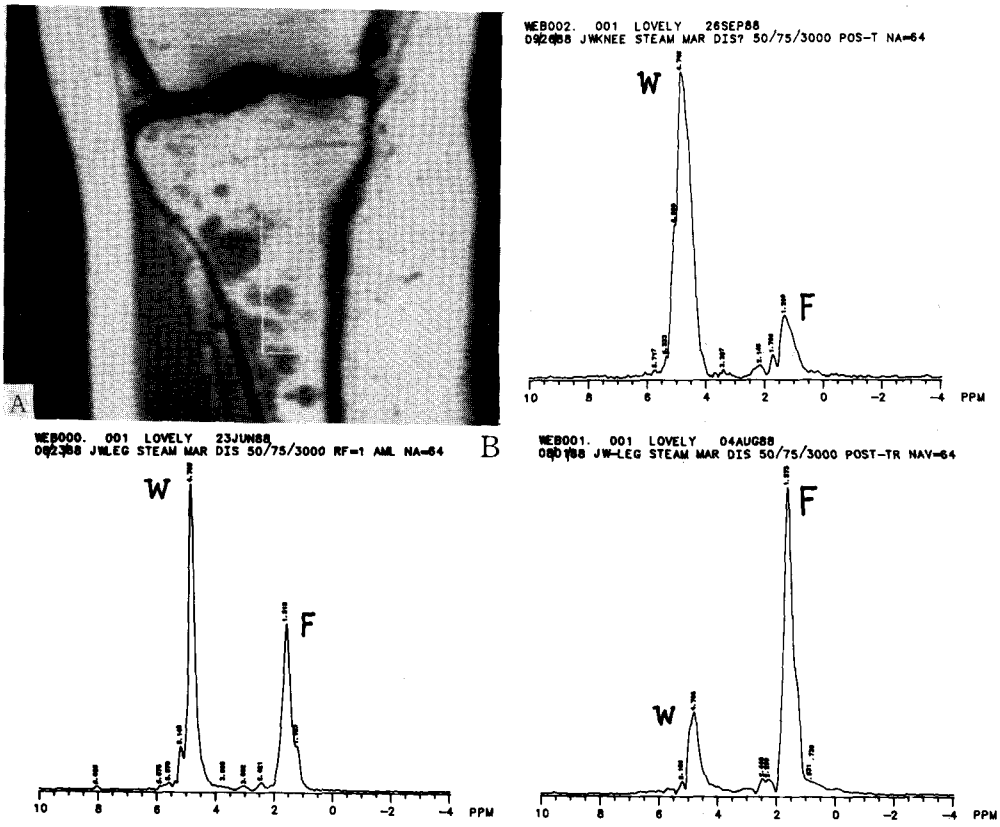

Fig. 5, A. T1-weighted coronal image shows multiple focal areas of low signal intensity in the bone marrow due to leukemic infiltration and rectangular area of interest for proton spectroscopy.

B. Serial ^{1}H-spectra before (left upper) and after (right upper) treatments show markedly decreased water (W) peak relative to fat (F) peak, compatible with clinical improvement. Spectrum (bottom) after recurrence of leukemia again shows a high water peak.

consistent pattern has not yet emerged for the special changes in treated tumors, both in the membrane-related PDE/PME peaks, and in the energy-related PCr, Pi, and ATP resonances. This may reflect the heterogeneous nature of the tumor models studied and the degree and kinds of therapies administered. Work has also been carried out using proton spectroscopy (Fig. 5) to investigate tumors, involving both changes in the shape of the large, presumable multicomponent lipid peak, and the identification of peaks which correspond to specific, as yet unidentified, compounds for cancers[16].

CONCLUSION

PET provides a relatively noninvasive means of studying regional organ physiology and metabolism in cancer patients and of evaluating the effects of therapy on tumor and normal organ function. Distinction between therapeutic necrosis and tumor recurrence, which cannot be made by either CT or MRI, may be possible with PET. The ultimate value and efficacy of PET in clinical practice must be proven by experience in medical practice.

MRS is a powerful tool for examining a limited number of metabolic compounds in the body. There are relatively few NMR studies of tumor metabolism. NMR studies confirm that the relative levels of ubiquitous metabolites, such as Pi and ATP, are regularly different in tumors from those in a variety of normal cells. Reported results make it clear that NMR experiments can monitor changes in the composition and metabolic status of tumors in real time, as they can in nontumor tissues. Obvious alterations in spectral of tumor tissue have been observed consequent upon hypoxia, ischemia, growth, differentiation, nutritional status and antitumor therapy. It is reasonable to expect that MRS will likely play a major role in the clinical arena.

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