Evaluating Cavernous Hepatic Hemangiomas

TO THE EDITOR: In their article, Rubin and Lichtenstein (*1*) presented some interesting aspects for the evaluation of cavernous hepatic hemangiomas (HCH). While we agree with the authors that ^{99m}Tc-labeled red blood cell (RBC) scintigraphy can be considered the method of choice for the diagnosis of liver hemangiomas, we were a little surprised that "planar studies may not demonstrate small (<3 cm) hemangiomas."

Many studies (*2–4*) have already shown that smaller hemangiomas also may be detected by planar scintigraphy (PS); the smallest hemangioma located in good position and detected by PS was 1.0 cm (*4*). Nevertheless, the major pitfalls of PS, as well as of SPECT, are the detection of deep-seated subphrenic lesions and the localization in the vicinity of the inferior vena cava or falciform ligament.

When mentioning that in the diagnosis of hemangiomas sensitivity of PS was improved with SPECT techniques, we are missing reports on the evaluation of dynamic displayed RBC studies. These methods, being superior to conventional static SPECT images, are able to improve sensitivity from 18% to 82% in the detection of hemangiomas <1.0 cm, even in unfavorable topographical sites (*4*).

Transmission computed tomography (TCT) is, of course, also a well established diagnostic tool in detecting hepatic hemangiomas, but it should be mentioned that the disadvantage of this method is the impossibility of contrast agent application in patients with contrast agent intolerance or hyperthyroid conditions. The latter aspect deserves particular attention in endemic goiter areas (*7,8*).

Finally, we do agree with the authors that ultrasound is not the diagnostic imaging modality of choice for HCH, but nevertheless, especially in the follow-up of very small lesions, ultrasound in combination with modified SPECT techniques certainly achieves the highest accuracy.

REFERENCES

1. Rubin RA, Lichtenstein GR. Scintigraphic evaluation of liver masses: cavernous hepatic hemangioma. *J Nucl Med* 1993;34:849–852.
2. Tumeh SS, Benson C, Nagel JS, English RJ, Holman BL. Cavernous hemangioma of the liver: detection with single-photon emission computed tomography. *Radiology* 1987;164:353–356.
3. Langsteger W, Lind P, Eber B, Költringer P, Beham A, Eber O. Diagnosis of hepatic hemangioma with ^{99m}Tc-labeled red cells: single photon emission computed tomography (SPECT) versus planar imaging. *Liver* 1989;9:288–293.
4. Krause T, Hauenstein K, Studier-Fischer B, Schuemichen C, Moser E. Improved evaluation of technetium-99m-red blood cell SPECT in hemangioma of the liver. *J Nucl Med* 1993;34:375–380.
5. Kudo M, Ikekubo K, Yamamoto K, et al. Distinction between hemangioma of the liver and hepatocellular carcinoma: value of labeled RBC-SPECT scanning. *Am J Roentgenol* 1989;152:977–983.
6. Langsteger W, Lind P, Költringer P, Eber O, Thaler H. An unusual case of hepatic hemangiomatosis: sonographic, CT and ^{99m}Tc RBC findings. *Am J Roentgenol* 1990;154:423.
7. Peter HJ, Gerber H, Studer H, Smedes S. Pathogenesis of heterogeneity in human multinodular goiter. *J Clin Invest* 1985;76:1992–2002.
8. Eber O, Langsteger W, Brence I, Wawschinek O. X-ray contrast media and induction of hyperthyrosis. *Akt Endokr Stoffw* 1992;13:98–101.

Werner Langsteger
Peter Költringer
Eiko Meister
Otto Eber
Barmherzige Brüder Graz-Eggenberg, Austria

In Vitro Assessment of FDG, Methionine and Thymidine Uptake

TO THE EDITOR: I am writing to comment on a recent article by Higashi et al. (*1*) regarding the in vitro assessment of FDG, methionine and thymidine uptake of an adenocarcinoma cell line following irradiation. This study showed that FDG, methionine and thymidine uptake actually increased after irradiation, commensurate with an increase in volume and DNA synthesis in surviving giant cells.

Giant-cell formation following irradiation is a property of cell populations that normally undergo mitotic division (*2*), such as the human adenocarcinoma cell line utilized by Higashi et al. In this cell line, increased tracer uptake following irradiation is not surprising considering the increase in volume and DNA synthesis (*3*). However, Dr. Higashi's findings are at variance with in vitro systems examined by Kubota (*4,5*) and Abe (*6*) utilizing rodent hepatoma and breast cancer cells, respectively. Unlike ovarian carcinoma cell lines, these tumor types may have cell populations with a lower mitotic index which would exhibit less marked giant-cell formation as seen in the cell line utilized by Higashi et al. Dr. Higashi said that his adenocarcinoma cell line may perhaps be more radioresistant than these other tumors.

Giant-cell formation is a manifestation of radiation damage (*2*) and, since these cells are unable to divide, they would be expected to die and be removed by host mechanisms. His findings were also at variance with those of Minn et al. (*7*) who studied patients with squamous-cell carcinomas of the head and neck following 30-Gy irradiation in daily fractions of 2 Gy each. These neoplasms may have a high mitotic index (*8*), but if giant-cell formation occurred, these cells would probably no longer be present by the time of Minn's evaluation which occurred during the 3-wk period. According to Tolmach (*9*), most giant HeLa cells have a half-time of persistence of 1–3 days and the remaining cells enter a period of rapid decay after 16 days. Radiation-induced vascular damage was mentioned as a possible cause of decreased tracer accumulation following radiotherapy. High doses of irradiation in a single exposure as used in the cited animal model causes marked normal and neoplastic cell damage. These results, however, are not applicable to Minn et al.'s clinical radiotherapy study which used conventional doses of 2 Gy.

It appears that Dr. Higashi's results are not due to radioresistance of his adenocarcinoma cell line, but are due to a characteristic response to irradiation of a cell line which has frequent mitoses and increased cell renewal, thus responding to irradiation with giant-cell formation. In vivo tumors may continue to proliferate following external irradiation, but this period is finite and the cells would eventually die because they have lost their reproductive capability (*10*). This would be expected to be the case with Higashi's cell line since he assessed uptake responses during the 12-day period. In addition to transient tumor growth following irradiation, a tumor's cellular proliferation increases with a shortening of tumor doubling time (*11*). This would be expected to increase FDG uptake. Macrophage infiltration into irradiated tumors results in increased FDG uptake is demonstrated by Kubota (*12*). These findings have clinical implications in patient studies which monitor response to treatment following irradiation. These studies by Higashi and Kubota indicate that there may be a required waiting period following a course of external irradiation to allow the processes of tumor regression and inflammatory reactions to subside before a tumor response can be accurately eval-

uated. The rate of regression of a tumor following a course of irradiation is not dependent upon the type of treatment but depends upon the individual tumor biology and the host's effectiveness in bringing about removal of nonviable tissue (*13*). Because of this, the waiting period may be variable for different tumors. We have empirically used a time of approximately 3–4 mo following treatment to obtain a PET scan and, as indicated by Knopp et al., rectal tumors may require a longer period of time. Thus, more studies may be needed to define the optimum timing of follow-up PET scans in order to accurately obtain information about tumor response.

REFERENCES

1. Higashi K, Clavo AC, Wahl RL. In vitro assessment of 2-fluoro-2-deoxy-D-glucose, L-methionine and thymidine as agents to monitor the early responses of a human adenocarcinoma cell line to radiotherapy. *J Nucl Med* 1993;34:773–779.
2. Montgomery POB, Karney D, Reynolds RC. Cellular and subcellular effects of ionizing radiations. *Am J Pathol* 1963;44:727–737.
3. Nias AHW, Paul J. DNA-content of giant cells produced by irradiation. *Int J Rad Biol* 1961;3:431–483.
4. Kubota K, Ishiwata K, Kubota R, et al. Tracer feasibility for monitoring tumor radiotherapy: a quadruple tracer study with fluorodeoxyuridine, L-[methyl-^{14}C]methionine, [6-^{3}H]thymidine, and gallium-67. *J Nucl Med* 1991;32:2118–2123.
5. Kubota K, Matsuzawa T, Takahashi T, et al. Rapid and sensitive response of carbon-11-L-methionine tumor uptake to irradiation. *J Nucl Med* 1989; 30:2012–2016.
6. Abe Y, Matsuzawa T, Fujiwara T, et al. Assessment of radiotherapeutic effects on experimental tumors using ^{18}F-2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 1986;12:325–328.
7. Minn H, Paul R, Ahonen A, et al. Evaluation of treatment response to radiotherapy in head and neck cancer with fluorine-18-fluorodeoxyglucose. *J Nucl Med* 1988;29:1521–1525.
8. Bertalanffy FD, Lau CL. Cell Renewal. *Int Rev Cytol* 1990;13:359–366.
9. Tolmach LJ, Marcus PI. Development of x-ray induced giant HeLa cells. *Exp Cell Res* 1961;20:350–360.
10. Trott KR. Relation between cell survival and gross endpoints of tumour response and tissue failure. In: Steet GG, Adams GE, Horwich H, eds. *The biological basis of radiotherapy, 2nd edition*. 1989:65–76.
11. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumour clonogen repopulation during radiotherapy. *Acta Oncol* 1988;27:131–146.
12. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of ^{18}F-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med* 1992;33:1972–1980.
13. Denekamp J. Tumour regression as a guide to prognosis: a study with experimental animals. *Br J Radiol* 1977;50:271–279.

Albert Frank
Naresh Gupta
Creighton University Medical Center
Omaha, Nebraska

REPLY: We appreciate the interest of Frank and Gupta in our work (*1*). We agree that giant-cell formation following a single dose of 30 Gy of ^{60}C radiation is an important mechanism for the increased FDG and methionine uptake seen in our study. This increase was seen both per tumor cell and per tissue culture well following irradiation of the HTB77 IP3 adenocarcinoma cell line. These cells were indeed proliferating rapidly at the time of irradiation, one day following subculture, with a proliferative index by flow cytometry of 70.4% and a 23.4% G2/M phase fraction. The cells were also at least reasonably radiosensitive, as cell number declined considerably following irradiation. Since our paper was published, we have performed additional experiments (which will be presented in detail elsewhere) which demonstrate that when a single dose of 5 Gy of ^{60}C irradiation is given to HTB77IP3 cells one day after subculture, there is not a significant increase in FDG and methionine uptake/cell versus control nonirradiated cells, nor is there giant-cell formation. Thus, the dose of irradiation used is important to the effect we observed on tracer uptake. In this follow-up study, a lack of giant-cell formation was associated with a lack of increase in tracer uptake/cell, further supporting the importance of radiation-induced giant-cell formation to the effect we observed.

It is, however, important to realize that our findings do not "contradict" those reported by other investigators, as Frank and Gupta suggest. The studies performed by Abe, Kubota and Minn were in in vivo systems representing several types of tumors, while our studies were performed in vitro (*2–4*). In addition, varying doses of radiation and fractionation were used among the studies. Thus, direct comparisons are not easily made between our in vitro study and these other reports from in vivo systems.

The reasons for the apparent difference between the in vivo and the in vitro situation warrant additional study. In general, giant-cell formation following irradiation in vivo is infrequent. In addition, there are host mechanisms for elimination of dying tumor cells, so that additional cell loss in vivo may contribute to the reduction in FDG signal (i.e., if fewer viable cancer cells are present) (*5,6*). In addition, giant-cell formation in vivo potentially may result in impairment of FDG delivery to the tumor due to edema. Other factors possibly affecting tracer uptake in vivo versus in vitro include the presence of "inflammatory cells" in vivo, although these might be expected to increase FDG uptake (*7,8*). Suffice it to say, that substantial differences exist between the in vivo and the in vitro situation which warrant additional study.

While data are limited, we share Frank and Gupta's caution, as well as that by Haberkorn et al., that declines in FDG uptake following radiotherapy should not be assessed too soon following the initiation of radiotherapy (*8*). Indeed, several months may be necessary to observe the maximal treatment-induced response. Certainly, avoidance of very early imaging during or after radiotherapy would preclude the possibility of imaging in vivo any increase in tracer uptake caused by the effect we describe in our in vitro system. Clearly, more study of the subject of tumor radiation response and PET tracer uptake is warranted, particularly in vivo using PET, to determine the optimal imaging time following radiotherapy and to better understand the nature of the PET signal from a variety of tracers.

REFERENCES

1. Higashi K, Clavo AC, Wahl RL. In vitro assessment of 2-fluoro-2-deoxy-D-glucose, L-methionine and thymidine as agents to monitor the early response of a human adenocarcinoma cell line to radiotherapy. *J Nucl Med* 1993;34:773–779.
2. Abe Y, Matsuzawa T, Fujiwara T, et al. Assessment of radiotherapeutic effects on experimental tumors using ^{18}F-2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 1986;12:325–328.
3. Kubota K, Ishiwata K, Kubota R, et al. Tracer feasibility for monitoring tumor radiotherapy: a quadruple tracer study with fluorine-18-fluorodeoxyglucose or fluorine-18-fluorodeoxyuridine, L-[methyl-^{14}C]methionine, [6-^{3}H]thymidine, and gallium-67. *J Nucl Med* 1991;32:2118–2123.
4. Minn H, Paul R, Ahonen A. Evaluation of treatment response to radiotherapy in head and neck cancer with fluorine-18-fluorodeoxyglucose. *J Nucl Med* 1988;29:1521–1525.
5. Brown RS, Fisher SJ, Wahl RL. Autoradiographic evaluation of the intratumoral distribution of 2-deoxy-D-glucose and monoclonal antibodies in xenografts of human ovarian adenocarcinoma. *J Nucl Med* 1993;34:75–82.
6. Higashi K, Clavo AC, Wahl RL. Does FDG uptake measure proliferative