

# <sup>18</sup>F-FDG PET in Evaluating Patients Treated for Metastatic Colorectal Cancer: Can We Predict Prognosis?

**C**olorectal cancer is the third most common solid malignant neoplasm in the western world. Patient prognosis is directly related to stage of disease. Metastatic disease is treated surgically if the disease is limited. In patients with advanced colorectal cancer, chemotherapy is effective in prolonging time to disease progression and survival (1). Response to therapy is dependent on a multitude of factors such as tumor burden, tumor cell heterogeneity, and drug resistance. It is therefore crucial to identify nonresponders early in the course of therapy, in order to implement alternative therapy regimens and to preclude unnecessary drug toxicity.

Traditionally, response to therapy is determined primarily by change in tumor size on morphologic imaging modalities. However, anatomic imaging modalities are suboptimal for early assessment of tumor response, as the decrease in tumor size lags behind the biologic response to therapy. Furthermore, residual nontumoral masses may remain after successful tumor therapy. PET is an emerging imaging modality in oncology and has been shown to be more specific and sensitive than morphologic imaging in identifying disease sites during primary staging of many tumor types, including colorectal cancer (2). In addition, PET has been

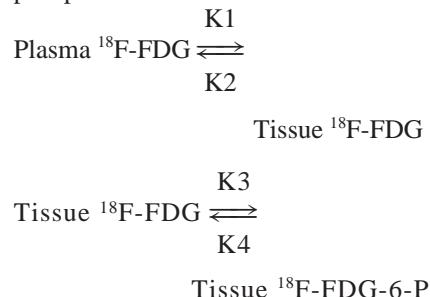
shown to be accurate in detecting tumor recurrence and assessing response to therapy (3,4).

Two principal approaches for monitoring response to therapy have been used: visual and semiquantitative PET assessment and the kinetic approach measuring <sup>18</sup>F-FDG uptake over time. In routine clinical practice, response to therapy is monitored primarily by visual interpretation, lesion-to-background ratios, or standardized uptake values (SUVs). With visual analysis alone, subtle changes in tumor uptake of radiotracers may be difficult to determine. Various investigators have suggested that the change in lesion-to-background ratios during therapy is beneficial for response assessment. Findlay et al. reported that with the use of lesion-to-background ratios, <sup>18</sup>F-FDG PET was able to predict the antitumor effect of chemotherapy with an overall sensitivity of 100% and specificity of 90% on a per-lesion basis in 18 patients with liver metastases from colorectal cancer 4–5 wk after institution of therapy (5).

SUVs normalize radiotracer concentration for injected activity and body weight. Other than anticancer therapy, various factors affect SUV measurement of sequential studies. Specifically, changes in blood glucose levels, changes in body weight between scans (due to reduced uptake of <sup>18</sup>F-FDG in fat), differences in time between injection and acquisition, partial-volume effects, and inaccuracies in measured injected activity (for example, due to partial extravasation at the injection site) may all potentially influence serial SUV measurements and possibly lead to false conclusions. Although

helpful in a clinical context, SUV has its limitations.

Compartmental modeling enables detailed quantitative assessment of tracer kinetics. Since first introduced by Sokoloff et al., tracer kinetic modeling has been used for in vivo analysis of various PET tracers, including <sup>18</sup>F-FDG (6). In compartmental models, each compartment represents a tracer in a different space or in a different chemical form. The compartments interact with each other by tracer movement bound by conservation of mass. A schematic representation of <sup>18</sup>F-FDG compartmental modeling is given below, with K<sub>1–4</sub> representing the rate constants between the different compartments: K<sub>1</sub> and K<sub>2</sub> represent respective rate constants for transport of <sup>18</sup>F-FDG into and out of cells by glucose transporter proteins, K<sub>3</sub> represents the rate constant for phosphorylation of <sup>18</sup>F-FDG by hexokinase, and K<sub>4</sub> represents dephosphorylation by glucose-6-phosphatase.



Studies on various tumor types have shown that clinically useful information can be obtained by kinetic models using dynamic PET acquisition. Malignant lung lesions continue to accumulate <sup>18</sup>F-FDG beyond the 60-min uptake time traditionally used for PET, whereas inflammatory lesions (which may potentially cause

Received May 8, 2004; revision accepted May 20, 2004.

For correspondence or reprints contact: Ur Metser, MD, Department of Nuclear Medicine, Tel-Aviv Sourasky Medical Center, 6 Weizman St., Tel-Aviv, 64239 Israel.

E-mail: umetser@tasmc.health.gov.il

false-positive PET interpretation) show a relatively rapid washout of  $^{18}\text{F}$ -FDG. Therefore, higher influx rate constants ( $K_1$ ) are measured for malignant lesions, resulting in better discrimination between benign and malignant lung lesions, mainly those with borderline SUVs (7). Dimitrakopoulou-Strauss et al. have shown that use of dynamic data allows better grading of soft-tissue sarcomas and better differentiation between benign and malignant lesions than does use of visual inspection or semi-quantitative methods (8). In a study on germ cell tumors, Sugawara et al. found kinetic modeling useful in differentiating mature teratoma from necrosis or scarring (9).

A few studies have used kinetic models to assess tumor response to therapy. On pages 1480–1487 of this issue of *The Journal of Nuclear Medicine*, Dimitrakopoulou-Strauss et al. (10) examine the ability of serial semiquantitative and quantitative dynamic  $^{18}\text{F}$ -FDG PET examinations to predict response to therapy as reflected by individual survival times of patients with colorectal cancer. Patients selected for the study failed to respond to first-line chemotherapy and were candidates for second-line chemotherapy (5-fluorouracil, folinic acid, and oxaliplatin, or FOLFOX). For the purpose of the study, 41 metastatic lesions in 25 patients underwent baseline scanning before initiation of therapy (and at least 1 mo after previous chemotherapy). Two additional scans were acquired, after the first and third cycles of FOLFOX. Patients were classified as short- or long-term survivors (defined as survival for less than 1 y or more than 1 y, respectively), and the ability of the data from each metastatic deposit to predict short- or long-term survival was assessed. In addition, a multiple linear regression model was used to determine the relationship between actual survival time and the data collected on each lesion, as well as combinations of parameters. The

investigators tested semiquantitative analysis (SUV), as well as dynamic datasets obtained using both a 2-tissue-compartment model and a non-compartmental model based on the fractal dimension, that being a parameter of the deterministic distribution of tracer over time (11). Dimitrakopoulou-Strauss et al. previously demonstrated that malignant tumors have a higher fractal dimension than benign lesions, presumably indicating heterogeneity in tumor  $^{18}\text{F}$ -FDG uptake (12).

As expected, metastases with baseline SUVs greater than 6 or fractal dimensions greater than 1.35 were associated with poor survival. Although higher SUVs correlated with poorer prognosis, SUVs alone were inadequate for accurately classifying patients as responders, nonresponders, or partial responders or for classifying patients according to survival time. SUV alone from any of the series predicted long- or short-term survival in 59.5%–62.8% of lesions—only slightly better than the toss of a coin. Combinations of SUVs from 2 studies yielded somewhat better results, with a correct prediction of survival in 58.3%–66.7% (best correlation was for combination of the baseline and third scans). Dimitrakopoulou-Strauss et al. encountered similar results in a previous study when comparing the same set of patients with clinical response after 3 mo of therapy. SUVs alone predicted progressive disease but failed to reliably predict partial responders or those with stable disease (13).

In the study of Dimitrakopoulou-Strauss et al. reported in this issue (10), combination of kinetic data and SUV from the baseline study and from the third scan (approximately 3 mo later) yielded the best results, with 77.8% correct classification into short- and long-term survival groups. The best correlation for individual survival was for kinetic parameters ( $K_3$ ,  $K_4$ ) of the second and third studies ( $K_{1-4}$ , VB, SUV).

One shortcoming of the study is the comparison of multiple metastases in a single patient to survival of that patient. Metastatic disease in a single patient may not respond uniformly to systemic therapy, and presumably, overall prognosis is related to tumor deposits least responsive to therapy. This point was not addressed in the study. In addition, although the baseline scan was obtained at least 1 mo after completion of previous chemotherapy, some of the metastases evaluated could have been partially treated lesions, and these results may not apply to patients treated with first-line chemotherapy.

Nonetheless, failure of first-line treatment in metastatic colon cancer patients is a frequent clinical scenario. As indicated by the findings of Dimitrakopoulou-Strauss et al. (10), prediction of response to chemotherapy in metastatic colon cancer and use of  $^{18}\text{F}$ -FDG PET to predict survival of these patients are complex tasks and require consideration of multiple kinetic parameters on sequential studies. Further research on larger groups of patients may be needed to verify these results and to establish optimal timing for follow-up studies.

Ur Metser, MD  
Tel-Aviv University  
Tel-Aviv, Israel

## REFERENCES

1. Jonker DJ, Maroun JA, Kocha W. Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. *Br J Cancer*. 2000;82:1789–1794.
2. Kantorov I, Lipsk L, Bohlvek O, Visokai V, Trubac M, Schneiderov M. Routine  $^{18}\text{F}$ -FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. *J Nucl Med*. 2003;44:1784–1788.
3. Guillem JG, Puig-La Calle J Jr, Akhurst T, et al. Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. *Dis Colon Rectum*. 2000;43:18–24.
4. Kalff V, Hicks RJ, Ware RE, et al. The clinical impact of  $^{18}\text{F}$ -FDG PET in patients with sus-

- pected or confirmed recurrence of colorectal cancer: a prospective study. *J Nucl Med.* 2002;43:492–499.
5. Findlay M, Young H, Cunningham D, et al. Non-invasive monitoring of tumor metabolism using fluorodeoxyglucose and positron emission tomography in colorectal cancer liver metastases: correlation with tumor response to fluorouracil. *J Clin Oncol.* 1996;14:700–708.
6. Sokoloff L, Reivich M, Kennedy C, et al. The [<sup>14</sup>C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem.* 1977;28:897–916.
7. Gupta N, Harmindar G, Graeber G, Bishop H, Hurst J, Stephens T. Dynamic positron emission tomography with F-18 fluorodeoxyglucose imaging in differentiation of benign from malignant lung/mediastinal lesions. *Chest.* 1998;114:1105–1111.
8. Dimitrakopoulou-Strauss A, Strauss LG, Schwarzbach M, et al. Dynamic PET <sup>18</sup>F-FDG studies in patients with primary and recurrent soft-tissue sarcomas: impact on diagnosis and correlation with grading. *J Nucl Med.* 2001;42:713–720.
9. Sugawara Y, Zasadny KR, Grossman HB, Francis IR, Clarke MF, Wahl RL. Germ cell tumor: differentiation of viable tumor, mature teratoma, and necrotic tissue with FDG PET and kinetic modeling. *Radiology.* 1999;211:249–256.
10. Dimitrakopoulou-Strauss A, Strauss LG, Burger C, et al. Prognostic aspects of <sup>18</sup>F-FDG PET kinetics in patients with metastatic colorectal carcinoma receiving FOLFOX chemotherapy. *J Nucl Med.* 2004;45:1480–1487.
11. Dimitrakopoulou-Strauss A, Strauss LG, Mikolajczyk K, et al. On the fractal nature of positron emission tomography (PET) studies. *World J Nucl Med.* 2003;4:306–313.
12. Dimitrakopoulou-Strauss A, Strauss LG, Schlag P, et al. Intravenous and intra-arterial oxygen-15-labeled water and fluorine-18-labeled fluorouracil in patients with liver metastases from colorectal carcinoma. *J Nucl Med.* 1998;39:465–473.
13. Dimitrakopoulou-Strauss A, Strauss LG, Rudi J. PET-FDG as predictor of therapy response in patients with colorectal carcinoma. *Q J Nucl Med.* 2003;47:8–13.

