Nuclear Medicine in Monitoring Response to Cancer Treatment

There is an emerging role for nuclear medicine techniques in monitoring and predicting response in cancer patients undergoing radio- and chemotherapy. Progress in medical science is characterized by the development of new understanding which suggests ways to diagnose, predict, and monitor diseases before the ultimate result of the effect of treatment becomes clear (*1*). The outcome of a disease may be difficult to predict during the course of treatment; it is especially difficult in cancer where the criterion for effectiveness is subsequent survival. This is an unsuitable criterion for monitoring treatment in the individual patient. Furthermore, control of cancer by systemic therapy depends on the ability to monitor serially the effect of treatment and replace protocols which do not induce response by more effective ones. Cancer cells often develop resistance and this should be recognized early, and noncross resistant therapy should be applied. Heterogeneity is a hallmark of cancer (*2*) and it is expressed by marked variability in patient response to treatment even in patients with cancer of the same histology. It is therefore essential to monitor each patient individually.

The potential of nuclear medicine techniques for monitoring response may be best utilized in diseases in which chemotherapy and radiotherapy induce a significant rate of remissions and cures and it appears that nuclear medicine will be superior to other techniques. Diagnostic imaging methods such as x-rays, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), which enable a better demonstration of mass lesions, do not provide information about the nature of the mass lesions they detect so effectively. This does not constitute, in general, a major problem in the initial evaluation and staging of a disease. As a rule, histologic diagnosis is sought by operation or biopsy. It is much more difficult to evaluate the effect of treatment on the primary or secondary tumor. Nuclear medicine techniques which are beginning to fulfil this need are still underutilized. It is the purpose of this review to draw attention to some problems in the assessment of cancer treatment and to solutions that nuclear medicine techniques may provide.

Monitoring Response to Treatment of Lymphoma

It is of great importance to determine if a mass lesion which remains after treatment consists of a viable tumor or just of necrotic and fibrotic tissue. This is a major problem in treatable tumors such as Hodgkin's disease and other lymphomas where patients often achieve remission and even cure (*3*). While the role of gallium-67 in the diagnostic staging of lymphoma as compared with other imaging modalities is still being defined (*4*) there is growing evidence about its value in monitoring response to treatment (*5–8*). It appears that gallium will have a unique role which, at present, cannot be achieved by other imaging modalities. There is definitive evidence that some tumor mass may remain after successful treatment of lymphomas, which does not contain active tumor (*7, 9–13*). This is a common finding in patients who present with bulky disease. When analyzed, such a mass is found to contain only necrotic and fibrotic tissue. It is not associated with a significantly higher relapse rate. Thomas et al. found positive CT in 47% of patients with lymphomas who were clinically asymptomatic after treatment (*12*). Israel et al. (*7*) found that the specificity of CT in patients who achieved remission was 57%. During follow-up period and without any additional treatment some patients became CT negative. Radford et al. (*13*) recently found that after treatment 59% of residual radiographic abnormalities underwent change after a year of follow up; 45% becoming negative, indicating a complete remission. They found no relation between relapse and the mediastinum being normal or abnormal after treatment. In a series of Jochelson et al. (*11*) there was no correlation between the extent of the abnormal findings on radiography after treatment and the subsequent relapse of the disease. These studies indicate that evaluation of tumors after treatment by "anatomic imaging" modalities is frequently misleading. They incorrectly show that patients have achieved only partial remission while they may be in a complete remission (*3*).

These findings stand in sharp contrast with the ability of ^{67}Ga to monitor response to treatment. Ga-scintigraphy became negative in 20 of the 21 patients of Israel et al. (*7*) who achieved remission, for a specificity of 95%. Of these, six subsequently relapsed. In the experience of the Dana Farber Cancer Institute of 21 gallium negative patients after treatment four subsequently relapsed (*14*). In the study of Israel et al. (*7*) four patients with six involved sites did not achieve a remission and Ga scintigraphy remained positive in all six. Kaplan et al. (*8*) found that 11 of 32 patients with diffuse large cell lymphoma had positive Ga scintigraphy after chemotherapy despite chest x-rays and CT which showed partial or complete response. Ten of these 11 patients subsequently proved to have a progressive disease. These findings show that persistent ^{67}Ga uptake after treatment predicted a poor outcome of the disease. Ga scintigraphy appears to be superior to CT and radiography for monitoring response in lymphoma patients.

The ability of both ^{67}Ga and also of deoxyglucose to monitor response to treatment received tissue validation in animal studies reported by Iosilevsky et al. in the Journal some time ago (*15*). It was found that when using both ^{67}Ga and hydrogen-3 (^{3}H) deoxyglucose in a mouse tumor model there was a good correlation between the amount of viable tumor remaining after treatment and the uptake of ^{67}Ga and [^{3}H]deoxyglucose. There was no correlation between the weight of the tumor and the number of viable cells in the tumor. Minn and his collegues have recently suggested, in the Journal, a technique for using fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) to evaluate the response to radiotherapy of head and neck cancer (*16*). They found that there was a significant decrease in tumor uptake of FDG after irradiation of 30 Gy in patients who responded to radiotherapy, while there was no such decrease in nonresponders. FDG, then, can be used during treatment in head and neck cancer in a similar way ^{67}Ga is used in lymphoma to identify patients who respond favorably and prevent unnecessary radiation of patients who will not respond.

Monitoring Response to Treatment of Bone Metastases

Bone scintigraphy has contributed significantly to the staging of diseases where hematogenous bone metastases occur. It has become the gold standard for the diagnosis of bone involvement in neoplastic diseases. The value of bone scintigraphy after treatment is less clear. The effect of treatment on the survival of patients with bone metastases depends on a number of variables (*17*). It depends on the extent of bone involvement expressed on scintigraphy as the number of lesions. It also depends, however, on the extent of involvement in other organ systems such as liver or lungs, the rate of tumor growth, and evidence of complications such as hypercalcemia or bone marrow infiltration causing anemia (*18–20*). In addition, there is a large difference in the median survival of patients with bone metastases from the thyroid carcinoma, prostatic and breast carcinoma and lung cancer. Longest survival is in thyroid carcinoma and the shortest in lung cancer (*18–20*). Even if accurate scintigraphic criteria for response in patients with bone metastases will be established, the relation between scintigraphy and survival will be difficult to assess.

Bone scintigraphy may be helpful in predicting the outcome of treatment by excluding metastases in patients with breast cancer. Patients with no evidence of bone involvement have a longer survival after adjuvant chemotherapy if tumors do not recur rapidly (*18–21*). The appearance of metastases indicates the need to replace therapy. In general patients with slow growing bone metastases have a better survival than those with rapidly growing tumors which show on scintigraphy early bone metastases.

The findings on bone scintigraphy in response to treatment in patients with known bone metastases have been the subject of numerous studies (*18–36*). However, firm criteria of scintigraphic findings for separating complete response from partial response or no response have still to be established. It has been suggested that response to treatment of bone metastases has been underestimated (*19,20*). This is probably the result of lack of accuracy of the imaging methods in establishing criteria of response.

Radiologic criteria for response (*19,34*) demand sclerosis of lytic lesions and no evidence for new lesions. Sclerosis as an indication of response may not appear until 4 to 6 mo after treatment. Sclerosis, however, appears in prostate cancer and sometimes without any treatment in breast cancer. There is a lower radiologic response rate for the bone than the general

patient response rate (*19*, *20*, *37*). It is not clear if this is due to the fact that bone metastases are less available for treatment or it is the result of a lower sensitivity of x-rays. CT which has an important value in staging by confirming or ruling out the presence of metastases in patients with a single abnormal uptake on bone scintigraphy has no definite role in monitoring response to treatment (*34*). There is also no evidence for any significant contribution by MRI.

There are a number of factors which confound the interpretation of bone scintigraphy after treatment (*18–36*). It is often unclear how increased uptake, decreased uptake and the appearance of new lesions early after treatment should be interpreted on serial scintigraphy. At times after treatment lesions with increased and decreased uptake appear in the same patient. When bone metastases occur osteoclasts activated by factors secreted by neoplastic cells in the bone marrow cause bone lysis (*28*, *38*, *39*). This results in an osteoblastic reaction which accounts for abnormal uptake on bone scintigraphy. Only late in the process, when systemic therapy is effective osteoclast activity decreases and healing of bone occurs through osteoblastic activity which gradually returns to normal if healing continues. At this stage favorable response on scintigraphy is seen as decreasing uptake with, rarely, the total disappearance of abnormal findings. Also, decreased uptake should be carefully assessed since it can occur in a rapidly growing aggressive bone metastasis showing predominantly lytic lesions (*19*).

Increased uptake may be the expression of a favorable osteoblastic response to treatment. Bone scintigraphy performed early after effective treatment may show a "flare" phenomenon. Increased uptake is seen in existing lesions and new lesions appear which were undetected on scintigraphy before treatment and become evident on serial scans as an expression of healing (*21*, *32*, *36*). A rational approach to monitoring the response to treatment has been suggested recently by Fogelman and Coleman (*36*). They have shown that with healing of lytic lesions on x-rays, within 3 mo after treatment flare phenomenon on scintigraphy was the rule rather than the exception. Early after treatment a flare could not be differentiated from progressive disease. However, after 6 mo if treatment was successful there was decreased uptake in existing lesions and no new lesions appeared. They suggested that using scintigraphy at 3 and 6 mo after treatment with serial biochemical assessment of osteocalcin and alkalyne phosphatase bone izoenzyme allows a correct interpretation of scintigraphic findings. It was possible using this technique to separate response from disease progression. The value of their method in the clinical management of patients has still to be confirmed and a number of questions remain unanswered. It is not clear that scintigraphic follow up of 6 mo is better than radiography or that it correlates with the patient's response to treatment.

It was recently suggested that it would be useful to have quantitative scintigraphic values to assess response and that units similar to Hounsfield units in CT would be helpful for diagnosis and reevaluation (*40*). While theoretically this possibility makes sense, in practice it is extremely complicated. The need for quantitation is obvious since it is difficult to evaluate the exact degree of increased uptake on scans done at different times even when the use of the same parameters for acquisition and display is attempted. A number of quantitative methods have been suggested to evaluate response on bone scintigraphy. Citrin et al. have suggested measuring the tumor-to-bone ratio by using the activity profile (*22*). Castronovo and his group have suggested a method based on the percent of change of the lesion (*31*). Such methods are semiquantitative at best. Even true quantitative methods using angle photon emission computed tomography (SPECT) (*41*) do not solve the need for objective criteria for response. Bone metastases in an individual patient do not respond in a uniform fashion, in some metastases uptake increases after treatment while in others it remains unchanged or is lowered (unpublished data). This is a predictable result when the heterogeneity of cancer is considered.

Monitoring Response to Treatment of Brain Tumors

Treatment of brain tumors is difficult (*42*,*43*). Monitoring of therapy is limited by the fact that surgery, chemotherapy, external radiation therapy and brachytherapy are associated with edema and necrosis which may be mistaken for tumor progression. Efforts at determining effective dosimetry without causing major complications and attempts of assessment of the

temporal development of necrosis on one hand and recurrence of the tumor on the other have not been satisfactory (*44*). It is therefore, of critical importance for the development of better treatment of brain tumors and for monitoring the individual patient who may benefit from the treatment to determine if clinical symptoms are due to tumor progression or complications of treatment.

CT and MRI which accurately diagnose brain tumors are of no use in assessing their response to treatment (*45–48*). These modalities are not able to distinguish between necrosis, residual tumor and tumor recurrence. Even histologic examination sometimes does not provide an answer. The results depend on the region from which the biopsy has been obtained. Furthermore, it has been shown recently that the finding of what appears to be viable tumor cells in addition to regions of necrosis in specimens obtained from a mass lesion had no effect on the clinical outcome (*48*). It indicates that these cells are not biologically active and are not important in predicting patient response.

The group of DiChiro has pioneered the use of PET and [^{18}F]deoxyglucose (FDG) to differentiate necrosis from viable tumor tissue and to predict the outcome of patients with brain tumors (*49–52*). The use of FDG is based on increased trapping of 2-deoxyglucose 6 phosphate by tumors with a higher malignancy grade. A correlation has been found between the grade of the glioma and the glycolytic metabolism shown on FDG studies. This is of value since the biologic behavior varies among patients even with the same histology. There was a correlation between the metabolism of tumors and survival; a higher metabolic ratio indicated poor prognosis. It was suggested that no false-positive or false-negative have been found even when lesions were extensive. If tumor existed it was always recognized by PET. The usefulness of FDG has been further confirmed by Valk et al. (*48*) who also used rubidium-82 as a blood-brain barrier agent and were able to diagnose active tumor recurrence. The correlation between tumor FDG utilization and tumor grade has not been universally accepted (*53,54*) and the heterogeneity of tumors complicates the assessment of individual tumors.

Kaplan et al. have introduced thallium-201 (^{201}Tl) for the evaluation of tumor response (*55*). They have shown that ^{201}Tl is taken up by viable tumor but not by edema and necrosis and is therefore practical in patients undergoing treatment. Their findings were confirmed by Mountz et al. (*56*) who suggested a method of semiquantitation by tumor/cardiac ratio estimation of residual mass. The use of the less expensive ^{201}Tl scintigraphy could be more widely accepted than that of FDG-PET. The accuracy of the method and clinical use has still to be tested in a large population of patients. In general it must be remembered that, the evaluation of tumors after treatment by FDG PET or by thallium will be of true clinical significance only when treatment of brain tumors will be, as in the case of lymphoma, associated with a significant degree of remission.

Future Trends

The possibility to monitor and predict response by radionuclide techniques should be further explored by using tissue specific agents and exact criteria which will indicate long term response. Radioiodine uptake by thyroid carcinoma has been classically used to predict tissue response to iodine treatment and for monitoring response. There is a special attraction to tissue specific radiopharamceuticals such as radioiodine MIBG in which uptake could be used not only for diagnosis but to predict response to therapy with [^{131}I]MIBG. Quantitation of the uptake of labeled chemotherapeutic drugs by sensitive tumors can potentially predict the availability of an individual tumor for chemotherapy (*57,58*). Since response is dose dependent, uptake will ultimately determine patients response. Nuclear medicine techniques may provide clinically significant information beyond that of mere diagnosis. The functional capabilities of these techniques are now being applied to the assessment of treatment. Judicious use in the future should be aimed at establishing criteria for a more effective cancer therapy.

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REFERENCES

1. Stoll BA: Serial monitoring in systemic therapy of cancer. In: Stoll BA, ed. *Screening and monitoring of cancer.* London: John Wiley and Sons, 1985: 407–428.
2. Schnipper LE. Clinical implications of tumor cell heterogeneity. *N Engl J Med* 1986; 314: 1423–1431.
3. Canellos GP. Editorial. Residual mass in lymphoma may not be residual disease. *J Clin Oncol* 1988; 6:931–933.
4. Beckerman C, Hofer PB, Bitran JD, et al. The role of gallium-67 in the clinical evaluation of cancer. *Semin Nucl Med* 1985; 15:72–103.
5. Glass RB, Fernbach SK, Conway JJ, et al. Gallium scintigraphy in american Burkitt lymphoma: accurate assessment of tumor load and prognosis. *Am J Roentgenol* 1985; 145:671–676.
6. Anderson KC, Leonard RC, Canellos GP, et al. High-dose gallium imaging in lymphoma. *Am J Med* 1983; 75:327–331.
7. Israel O, Front D, Lam M, et al. Gallium 67 imaging in monitoring lymphoma response to treatment. *Cancer* 1988; 61:2439–2443.
8. Kaplan W, Jochelson M, Herman T, et al. Ga-67 imaging: a predictor of residual tumor viability in patients with diffuse large cell lymphoma (DLCL). *Proc Am Soc Clin Oncol* 1988; 7:230.
9. Lewis E, Bernardino ME, Salvador PG, et al. Posttherapy CT detected mass in lymphoma patients: is it viable tissue? *J Comp Assist Tomogr* 1981; 6:792–795.
10. Stewart FM, Williamson MR, Innes DJ, et al. Residual tumor masses following treatment for advanced hystiocytic lympyhoma: diagnostic and therapeutic implications. *Cancer* 1985; 55:620–623.
11. Jochelson M, Mauch P, Balikian J, et al. The significance of the residual mediastinal mass in treated Hodgkin's disease. *J Clin Oncol* 1985; 3:637–640.
12. Thomas F, Cosset JM, Cherel P, et al. Thoracic CT-scanning follow up of residual masses after treatment of Hodgkin's disease. *Radiotherapy and Oncology* 1988; 11:119–122.
13. Radford JA, Cowan RA, Flanagan M, et al. The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkin's disease. *J Clin Oncol* 1988; 6:940–946.
14. Canellos GP. Residual mass and gallium scanning. Reply to letter to the Editor. *J Clin Oncol* 1989; 7:144–145.
15. Iosilevsky G, Front D, Bettman L, et al. Uptake of gallium 67 citrate and 2-H-3 deoxyglucose in the tumor model following chemotherapy and radiotherapy. *J Nucl Med* 1985; 26:278–282.
16. 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.
17. Stoll BA. Natural history, prognosis and staging of bone metastases. In: Stoll BA, Parbhoo S, eds. *Bone metastases: monitoring and treatment.* New York: Raven Press, 1983: 1–20.
18. Bhardwaj S, Holland JF. Chemotherapy of metastatic cancer in bone. *Clin Orthop Rel Res* 1982; 169:28–37.
19. Coleman RE, Rubens RD. Bone metastases and breast cancer. *Cancer Treat Rev* 1985; 12:251–270.
20. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987; 55:61–66.
21. McNeil BJ. Value of bone scanning in neoplastic disease. *Semin Nucl Med* 1984; 14:277–286.
22. Citrin DL, Tuohy JB, Bessent RG, et al. Quantitative bone scanning: a method for assessing response of bone metastases to treatment. *Lancet* 1974; 1:1132–1133.
23. Hayward JL, Meakin JW, Stewart HJ, et al. Assessment of response and recurrence in breast cancer. *Semin Oncol* 1978; 5:445–449.
24. Langhammer H, Sintermann G, Hor G, et al. Serial bone scintigraphy for assessing the effectiveness of treatment of osseous metastases from prostatic cancer. *Nuklearmed* 1978; 17:87–91.
25. McNeil BJ, Pace PD, Gray EB, et al. Preoperative and follow up bone scans in patients with primary carcinoma of the breast. *Surg Gynec & Obstet* 1978; 147:745–748.
26. Bishop HM, Blamey RW, Morris AH, et al. Bone scanning: its lack of value in the follow up of patients with breast cancer. *Br J Surg* 1979; 66:752–754.
27. Furnival CM, Blumgart LH, Citrin DL, et al. Serial scintiscanning in breast cancer: the indications and prognostic value. *Clin Oncol* 1980; 6:25–32.
28. Citrin DL. The role of the bone scan in the investigation and treatment of breast cancer. In: *CRC critical reviews in diagnostic imaging.* Boca Raton, Florida: CRC Press, 1980: 39–55.

29. Bitran JD, Bekerman C, Desser RK. The predictive value of serial bone scans in assessing response to chemotherapy in advanced breast cancer. *Cancer* 1980; 45:1562–1568.
30. McNeil BJ, Hanley J. Analysis of serial radionuclide bone images in osteosarcoma and breast carcinoma. *Radiology* 1980; 135:171–176.
31. DeLuca SA, Castronovo FP, Rhea JT. The effects of chemotherapy on bony metastases as measured by quantitative skeletal imaging. *Clin Nucl Med* 1983; 8:11–13.
32. Hortobagyi GN, Libshitz HI, Seabold JE. Oseous metastases of breast cancer; clinical, biochemical, radiographic and scintigraphic evaluation of response to therapy. *Cancer* 1984; 53:577–582.
33. Kim EE, Haynie TP. Role of nuclear medicine in chemotherapy of malignant lesions. *Semin Nucl Med* 1985; 15:12–20.
34. Kagan RA, Steckel RJ, Bassett LW, et al. Radiologic contributions to cancer management:bone metastases. *Am J Roentgenol* 1986; 147:305–312.
35. McKillop JH. Bone scanning in metastatic disease. In Fogelman I, ed: Bone scanning in clinical practice. London, Berlin, Heidelberg: Springer Verlag, 1987: 46–48.
36. Coleman RE, Mashiter G, Whitaker KVB, et al. Bone scan flare predicts successful systemic therapy for bone metastases. *J Nucl Med* 1988; 29:1354–1359.
37. Stewart J, King R, Hayward J, et al. Estrogen and progesterone receptors: correlation of response rates, site and timing of receptor analysis. *Breast Can Res Treat* 1982; 2:243–246.
38. Parbhoo SP. Serial scintiscans in monitoring patients with bone metastases. In: Stoll BA, Parbhoo SP, eds. *Bone metastasis—monitoring and treatment.* New York: Raven Press, 1983: 201–239.
39. Mundy GR. The hypercalcemia of malignancy. *Kidney Int* 1987; 31:142–153.
40. Brodeur GM, Seeger RC, Barrett A, et al. International criteria for diagnosis, staging and response to treatment in patients with neuroblastoma. *J Clin Oncol* 1988; 6:1874–1881.
41. Front D, Israel O, Jerushalmi J, et al. Quantitative bone scintigraphy (QBS) using SPECT. *J Nucl Med* 1989; 29:240–245.
42. Wilson CB, Levin VA, Hoshino T. In: Youmans JR, ed. *Neurological surgery, Vol. 5: chemotherapy of brain tumors.* Philadelphia: W.B. Saunders, 1982: 3065–3095.
43. Shapiro WR. Therapy of adult malignant brain tumors: what have the clinical trials taught us? *Semin Oncol* 1986; 13:38–45.
44. Lampert PW, Davis RL. Delayed effects of radiation on the human central nervous system. "Early" and "late" delayed reactions. *Neurology* 1964; 14:912–917.
45. Brismar J, Roberson GH, Davis KR. Radiation necrosis of the brain. Neuroradiological considerations with computed tomography. *Neuroradiology* 1976; 12:109–113.
46. Deck DMF. Imaging techniques in the diagnosis of radiation damage to the central nervous system. In: Gilbert HA, Kagan AR, eds. *Radiation damage to the central nervous system.* New York: Raven Press, 1980: 107–127.
47. Kingsley DPEm Kendall BE. CT of the adverse effects of therapeutic radiation of the central nervous system. *AJNR* 1981; 2:453–460.
48. Valk PE, Budinger TF, Levin VA, et al: PET of malignant cerebral tumors after interstitial brachytherapy. Demonstration of metabolic activity and correlation with clinical outcome. *J Neurosurg* 1988; 69:830–838.
49. DiChiro G, DeLaPaz L, Brooks RA, et al. Glucose utilization of cerebral gliomas measured by F-18 fluorodeoxyglucose and positron emission tomography. *Neurology* 1982; 32:1323–1329.
50. DiChiro G. Positron emission tomography using F-18 Fluorodeoxyglucose in brain tumors. A powerful diagnostic and prognostic tool. *Invest Radiol* 1987; 22:360–371.
51. DiChiro G, Hatazawa J, Katz DA, et al. Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study. *Radiology* 1987; 164:521–526.
52. DiChiro G, Oldfield E, Wright DC, et al. Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies. *Am J Roentgenol* 1988; 150:189–197.
53. Tyler JL, Villemure JG, Evans AC, et al. Metabolic and hemodynamic evaluation of gliomas using positron emission tomography. *J Nucl Med* 1987; 28:1123–1133.
54. DiChiro G, Brooks RA. PET-FDG of untreated and treated gliomas. Letter to the editor. *J Nucl Med* 1988; 29:421–422.
55. Kaplan WD, Takvorian T, Morris JH, et al. Thallium-201 brain tumor imaging: a comparative study with pathologic correlation. *J Nucl Med* 1987; 28:47–52.
56. Mountz JM, Stafford Schuck K, McKeever PE, et al. Thallium-201 tumor/cardiac ratio estimation of residual astrocytoma. *J Neurosurg* 1988; 68:705–709.
57. Front D, Israel O, Iosilevsky G, et al. Human lung tumors: SPECT quantitation of differences of Co-57 bleomycin uptake. *Radiology* 1987; 165:129–133.
58. Iosilevsky G, Israel O, Frenkel A, et al. A practical SPECT technique for quantitation of drug delivery to human tumors and organ absorbed radiation dose. *Semin Nucl Med* 1989; 19:33–46.