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The role of nuclear medicine in oncology

Hans J. BIERSACK,* Bernd BRIELE,* Andreas L. HOTZE,* Peter OEHR,*
Liu QIAN,* Mohamed A. MEKKAWY** and Wei-Jen SHIH***

*Department of Nuclear Medicine, University of Bonn
**Department of Radiotherapy and Nuclear Medicine, Assiut University Hospital, Egypt
***Nuclear Medicine Service, Department of Veterans Affairs Medical Center, Lexington KY

Nuclear Medicine offers screening methods for oncology such as bone and bone marrow scintigraphy. During the last two decades, special procedures have gained widespread application. This paper is centered around the "tumor-specific" radiopharmaceuticals. In patients with thyroid cancer, I-131 still plays a significant role. Ga-67 still has its indications in lymphoma, while in other diseases Tl-201 cloride is now the agent of choice. Especially in thyroid cancer, Tl-201 has proved to be a reliable tumor imaging radiopharmaceutical. More recently, Tc-99m MIBI was introduced for tumor imaging. Tc-99m HMPAO may also be used for tumor scintigraphy, especially in brain lesions. In addition, I-123 IMP has successfully been used for imaging malignant melanoma. Another promising field of tumor diagnosis is receptor imaging. In neuroblastoma and malignant pheochromocytoma, I-131/123 mIBG is the radiopharmaceutical of choice and may be considered as a receptor imaging agent also. First clinical results with In-111 octreotide show potentials as somatostatine-receptor radiopharmaceutical in insulinoma, islet cell carcinoma, medullary and lung cancer, while I-123 estradiol needs some improvement until it may be recommended as diagnostic tool in breast cancer. Since 1978, radiolabeled poly- or monoclonal tumor antibodies and their fragments have gained widespread application. Especially the Tc-99m 225.28S melanoma antibody, I-131 or Tc-99m CEA and In-111/I-131 labeled OC-125 antibodies have proven to be of clinical significance in melanoma, colorectal and ovarian cancer.

Key words: oncology, tumor-specific tracers, monoclonal antibodies

NUCLEAR MEDICINE OFFERS SCREENING METHODS for oncology such as bone and bone marrow scintigraphy. These procedures are most useful for the staging and follow-up of cancer patients. In patients with lung cancer, quantitative perfusion scintigraphy of the pulmonary circulation (quantitative lung scan) has proved to be useful for planning the strategy of operation. However, during the last 2 decades special imaging procedures have gained widespread application. The respective radiopharmaceuticals include non-immunological and immunological procedures.

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For reprints contact: Hans J. Biersack, M.D., Klinik für Nuklearmedizin der Universität Bonn, Sigmund-Freud-Straße 25, 5300 Bonn 1, Germany.

Each tracer is based on a specific principle of uptake (Tables 1, 2). The different procedures will now be described in detail.

Scintigraphy with I-131

Thyroglobulin (hTg) has now become a routine tumor marker in the follow-up of thyroid cancer. Despite the high significance of hTg, whole body scintigraphy with I-131—especially with therapeutic doses—still remains a useful imaging procedure in management of thyroid cancer.[1–3] Delayed "post therapy" imaging was clearly superior to "diagnostic" I-131 imaging[1]: 19/28 patients presented with positive post therapy scans, while results were significantly worse with diagnostic doses (11/29). Since positive I-131 scans are observed in approx. 5% of patients with negative hTg concentrations, whole body scintigraphy is still useful in thyroid cancer.

Table 1

"Specific Procedures"
Non-immunological
I-131, Ga-67, Tl-201, Tc-99m MIBI, I-123 IMP, Tc-99m HMPAO, Tc-99m(V)DMSA
Receptor imaging: I-123/131 mIBG, In-111 Octreotide, I-123 Estradiol
Protein Uptake: I-123 Methyltyrosine
Immunological
CEA, 225.28s, OC-125, AFP, CEA 19/9, Beta-HCG, PSA (Tc-99m, In-111, I-131)

Table 2

Principles of Uptake
I-131: iodine trap
Ga-67: increased permeability of tumor vessels and binding to intracellular proteins
Tl-201: perfusion-related uptake in tissue with increased number of mitochondria
I-123 IMP: melanine metabolism
Tc-99m MIBI: negative-charged membranes of mitochondria, increased perfusion
Tc-99m: HMPAO: perfusion ("microsphere")
Tc-99m(V)DMSA: Similarity to phosphate molecule?
I-123 IMT: enzyme inhibition (trapping)
I-123 mIBG: receptor binding+metabolism
I-123 Estradiol: receptor binding
In-111 Octreotide: receptor binding
MoABs: *in vivo* AG/AB reaction

Tl-201

Since almost 15 years, Tl-201 is used as a tumor-imaging agent, at first in lymphoma and melanoma, later in iodine-negative thyroid cancer, lung cancer and brain tumors.[4-6] Tl-201 SPECT (Fig. 1) provided good results in thyroid and lung cancer.[4,5]

Tc-99m MIBI

The Tl-201 analogue, Tc-99m MIBI, (Fig. 1) has also been successfully used for tumor imaging in iodine-negative thyroid cancer as well as in lung cancer. Despite of better imaging statistics (higher count rates), a superiority of Tc-99m MIBI was not found, especially in thyroid and lung cancer.[4,5,7]

Ga-67

Ga-67 may be considered the most widely used tumor-specific radiopharmaceutical. Since almost 25 years, this tracer has been used in a wide range of tumors. However, the development of new tracers has led to a decrease of imaging procedures. Some of the few domaines in which gallium is still useful, are staging and follow-up of lymphoma, melanoma and testicular tumors.[8-11] Especially in the evaluation of hilar lymphoma after radiation, Ga-67 plays an important role.[8,9]

I-123 Iodoamphetamine (IMP)

IMP may be used as a tumor-specific radiopharmaceutical in malignant melanoma as well as squamous cell carcinoma.[12,13] However, especially in melanoma, the significance of IMP is only limited as melanoma antibodies have taken over this position.

Tc-99m HMPAO

Since 1986, HMPAO has been used for tumor imaging,[14-17] especially in brain tumors.[14] There was no correlation between HMPAO uptake and tumor grading or type. HMPAO proved to be a useful radiopharmaceutical for the evaluation of therapeutic response in brain tumors.[14]

I-123 Alpha methyl tyrosine (IMT)

IMT had been synthesized some 15 years ago for pancreas imaging.[18] Later on, it had been used for imaging of occular melanoma.[18] Our own group published first results on IMT imaging in brain tumors in 1989.[19] IMT is a strong enzyme inhibitor. It does not represent protein metabolism, but only protein incorporation. Some of the main indications for IMT imaging are the proof or exclusion of brain tumor recurrence and the differential diagnosis abscess/glioblastoma (Fig. 2). Again, this tracer may be used to evaluate the therapeutic response in cytotoxic or radiation therapy.[18] A grading or differential diagnosis of brain tumors is not possible.[20]

Tc-99m(V) DMSA

The pentavalent Tc-99m-dimercaptosuccinate complex has been successfully used for imaging of medullary thyroid cancer and squamous cell carcinoma of the head and neck.[21,22] It is discussed that Tc-99m(V) is taken up by the tumor cells as it shows a similarity to phosphate molecules which are accumulated due to increased protein metabolism.

Receptor imaging: Tumor imaging via receptor imaging may be performed using metaiodobenzylguanidine, estradiol, and octreotide.

I-123-Estradiol[23]

The results of a German Mulicenter Trial have been published by Scheithauer et al. in 1991[24] using 16-alpha-I-123-iodoestradiol-17 beta (I-123-E2). In 42 patients (30 carcinomas (Fig. 3), 12 benign lesions), the overall sensitivity was only 66%. "False positives" were obtained in patients with fibrocystic mastopathia with positive receptor status.

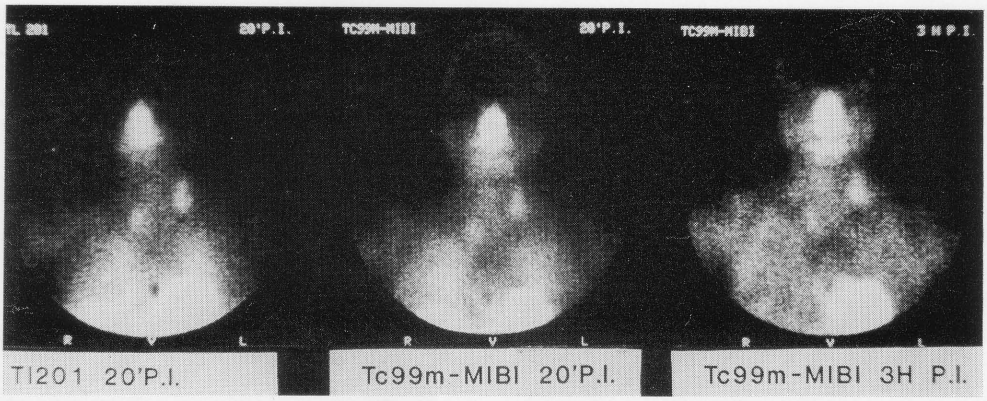

Fig. 1 Lymph node metastases of thyroid cancer: Uptake of Tl-201 (left) and Tc-99m MIBI (right).

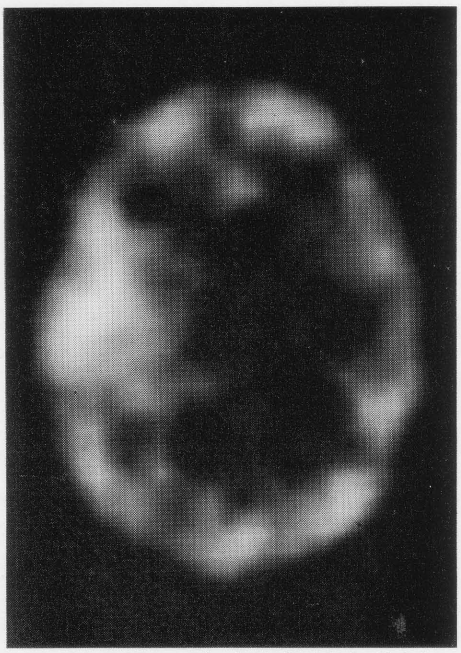

Fig. 2 I-123 IMT uptake in left-sided glioblastoma.

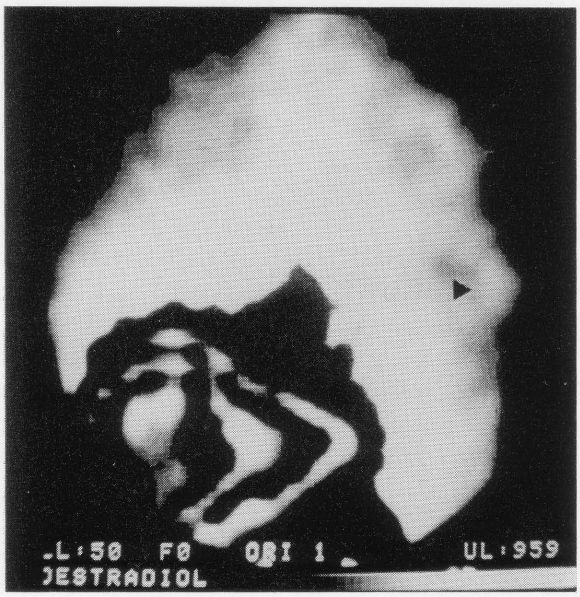

Fig. 3 I-123 Estradiol uptake in breast cancer (arrow).

I-123/131 mIBG

Since 1980, this radiopharmaceutical has been used for imaging of pheochromocytoma and neuroblastoma (Fig. 4) as well as of carcinoids and paraganglioma. Especially in pheochromocytoma and neuroblastoma, mIBG imaging is now a routine procedure in oncology.[25,26] In neuroblastoma, sensitivity was 90%, in catecholamine-positive tumors 96%, respectively. In 540 patients with pheochromocytoma, sensitivity was 87%, specificity 99% with a prevalence of 30%.[26]

In-111 Octreotide (Somatostatin receptor imaging agent)

In 1990, first results using In-111 octreotide were published in islet cell cancer, glucagenoma, insulinoma (Fig. 5) and medullary thyroid cancer.[27,28] The results of the Dutch group[27,28] are very promising. However, phase III clinical trials in Europe have to be finished to fully evaluate the clinical usefulness of octreotide imaging.

Monoclonal tumor antibodies and their fragments (MoABs): Up to now, a wide range of tumor antibodies and their fragments have been used. However, only a limited number of these tracers have been evaluated in larger patient populations. This review will only refer to radioimmunodetection (RID) in patients with melanoma, ovarian cancer and colorectal cancer.

Melanoma antibody F(ab')$_2$-Fragment 225.28s

This antibody has been evaluated for 5 years now in our institution. 181 patients with melanoma were investigated, 109 of them presenting with proven metastases. In the remaining 72 patients, metastases could be excluded by follow-up, surgery, and other imaging techniques. With respect to the number of "positive" and "negative" patients, sensitivity was 74%, specificity 88%, and accuracy 80%. A total

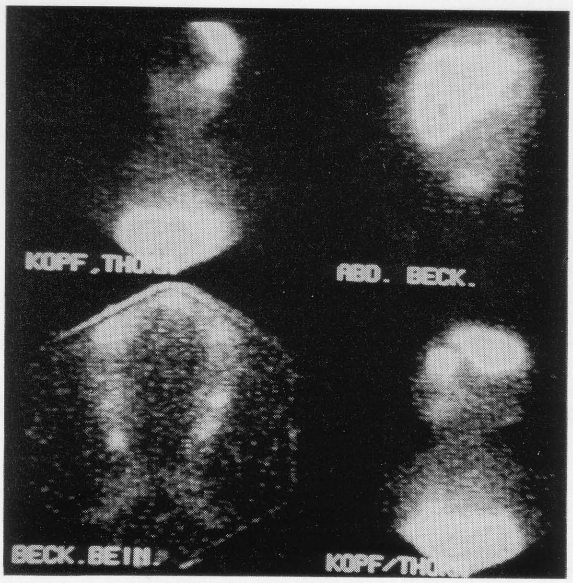

Fig. 4 I-123 mIBG uptake in bone metastasis (skull, both legs) of neuroblastoma.

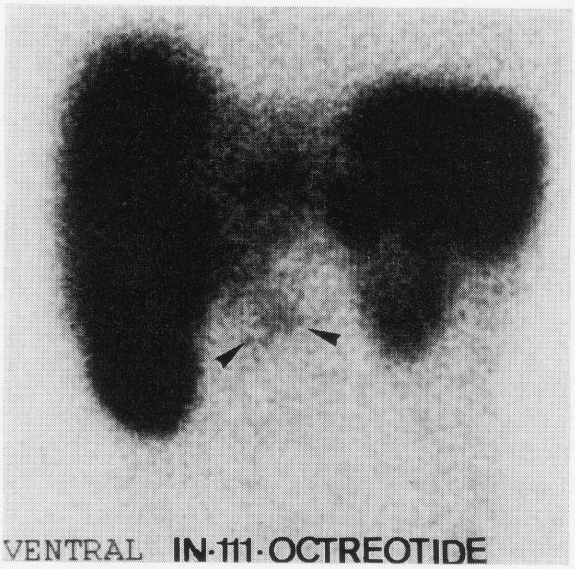

Fig. 5 In-111 Octreotide uptake in insulinona (arrows).

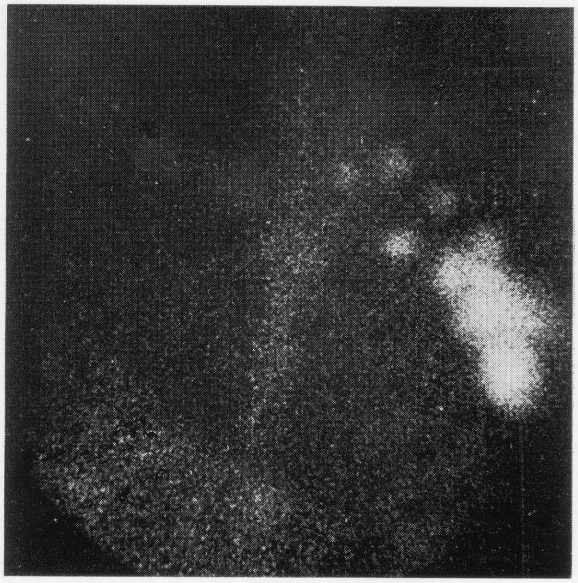

Fig. 6 Extensive axillary lymph node uptake in melanoma (melanoma antibody).

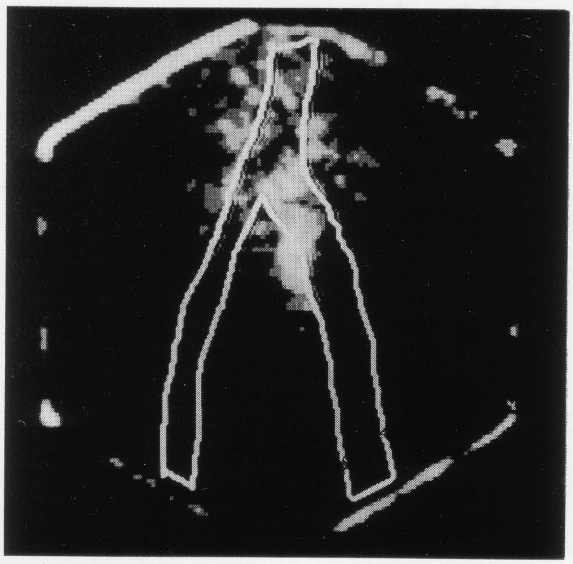

Fig. 7 Left-sided parailiacal lymph node involvement as evidenced by uptake of In-111 OC-125 antibody fragment.

of 212 tumor localization were evaluated in 181 patients. Sensitivity was 53%, specificity 88%, and accuracy 63%. However, if only lymph node metastases (94 lesions in 89 patients) were evaluated (axillary (Fig. 6) and inguinal as well as iliacal), sensitivity was 88%, specificity 83%, and accuracy 88%. These data allow the assumption that immunoscintigraphy can now be regarded as a routine procedure in the evaluation on melanoma patients with suspected lymph node metastases.[29,30] In intraocular malignant melanoma, this antibody showed also promising results.[31]

In-111/I-131 OC-125 antibody F(ab')$_2$-Fragment

In another series, 47 patients with ovarian cancer (Fig. 7) and 65 proven tumor localizations were investigated using an OC-125 antibody fragment. Sensitivity was 86%, specificity 78%, and accuracy 85%. In 21 tumor localizations who had follow-up, sensitivity was 81%, specificity 75% and accuracy 80%. Thus, immunoscintigraphy shows promising results in patients with ovarian cancer and has also become a routine tool in the follow-up of this disease.[32,33]

I-131-19-9/Anti CEA F(ab')$_2$-Fragment

This antibody is routinely available since some years now. Baum et al.[34] have published results in 92

patients with colorectal carcinoma. With respect to different localizations (abdomen, liver, peritoneum, lung, bone) the sensitivities were between 78 and 88%, the specificity between 90 and 94%. These data make evident that immunoscintigraphy has reached the stage of clinical usefulness in colorectal cancer.[35]

REFERENCES

1. Briele B, Hotze AL, Grünwald F, et al: Erhöhte Sensitivität der Ganzkörperszintigraphie mit J-131 für den Nachweis jodspeichernder Metastasen durch spätere Aufnahmezeitpunkte. *Nucl Med* 29: 264–268, 1990
2. Pacini F, Lippi F, Formica N, et al: Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with undetectable serum thyroglobulin levels. *J Nucl Med* 28: 1888–1891, 1987
3. Nemec J, Röhling S, Zamrazil V, et al: Comparison of the distribution of diagnostic and thyroablative 131-I in the evaluation of differentiated thyroid cancers. *J Nucl Med* 20: 92–97, 1979
4. Briele B, Hotze AL, Kropp J, et al: Vergleich von Tl-201 und Tc-99m-Mibi in der Nachsorge des differenzierten Schilddrüsenkarzinoms. *Nucl Med* 30: 115–124, 1991
5. Müller S, Paas M, Konietzko N, et al: Szintigraphie mit Tl-201 und Tc-99m-MIBI beim Schilddrüsen- und Bronchialkarzinom. *Zbl Radiol* 141: 206, 1990
6. Hoefnagel CA, Delprat HR, Marcuse HR, et al: Role of thallium-201 total body scintigraphy in the follow-up of thyroid carcinoma. *J Nucl Med* 27: 1854–1857, 1986
7. Hassan IM, Sahweil A, Constantinides C, et al: Uptake and kinetics of Tc-99m-hexakis 2-methoxy isobutyl isonitrile in benign and malign lesions in the lungs. *Clin Nucl Med* 14: 333–340, 1989
8. Kostakoglu L, Yeh SDJ, Portlock C, et al: Validitation of Ga-67-citrate single-photon emission computed tomography in biopsy-confirmed residual Hodgkin's disease in the mediastinum. *J Nucl Med* 33: 345–350, 1992
9. Israel O, Front D, Lam M, et al: Ga-67 imaging in monitoring lymphoma response to treatment. *Cancer* 61: 2439–2443, 1988
10. Kirkwood JM, Myers JE, Vlock DR, et al: Tomographic Gallium-67 citrate scanning: Useful new surveillance for metastatic melanoma. *Ann Intern Med* 97: 694–699, 1982
11. Botsch H: *Galliumszintigraphie*. Springer, Berlin Heidelberg, New York, Tokyo, 1985
12. Kubo K, Itoh K, Nakada K, et al: The visualization of squamous cell carcinoma of the skin with I-123 iodoamphetamine. *Clin Nucl Med* 14: 138, 1989
13. Cohen MB, Saxton RE, Lake RR, et al: Detection of malignant melanoma with iodine-123 iodoamphetamine. *J Nucl Med* 29: 1200–1206, 1988
14. Babich JW, Kieling F, Flower NA, et al: Initial experience with Tc-99m HM-PAO in the study of brain tumors. *Eur J Nucl Med* 14: 39–44, 1988
15. Suess E, Malessa S, Ungersbröck K, et al: *Tc-99m-HMPAO-Aufnahme und Glutathiongehalt zerebraler Tumoren*. In: Höfer R, Bergmann H, (Eds): Radioaktive Isotope in Klinik und Forschung; Stuttgart, New York, 1988
16. Hammersley PAG, McCready VR, Babich JW, et al: Tc-99m-HMPAO as a tumor blood flow agent. *Eur J Nucl Med* 13: 90–94, 1987
17. McCready VR, Babich J, Flower MA, et al: The use of Tc-99m-HMPAO for tumor detection and the study of tumor blood flow. *Nucl Med* 27: 116–117, 1988
18. Biersack HJ, Grünwald F, Kropp J: Single-photon-emission-computed-tomography imaging of brain tumors. *Sem Nucl Med* 21: 2–10, 1991
19. Biersack HJ, Coenen HH, Stöcklin G, et al: Imaging of brain tumors with L-3-(^{123}I)iodo-alpha-methyl-tyrosine and SPECT. *J Nucl Med* 30: 110–112, 1989
20. Langen KJ, Coenen HH, Rosen N, et al: SPECT Studies of brain tumors L-3-(^{123}I)iodo-alpha-methyl-tyrosine: Comparison with PET, 124 IMT and first clinical results. *J Nucl Med* 31: 281–286, 1990
21. Yokoyama A, Hata N, Horiuchi K, et al: The design of a pentavalent Tc-99m-dimercaptosuccinate complex as a tumor imaging agent. *Int J Nucl Med Biol* 12: 273–279, 1985
22. Watkinson JC, Lazarus CR, Mistry R, et al: Technetium-99m-(V)dimercaptosuccinic acid uptake in patients with squamous carcinoma of the head and neck—experience in imaging. *J Nucl Med* 30: 174–180, 1989
23. Zielinski JE, Yabuki H, Pahuja SL, et al: 16-(J-123) iodo-11u methoxy-17u-estradiol: a radiochemical probe for estrogen-sensitive tissues. *Endocrinology* 119: 130–139, 1986
24. Scheidhauer K, Müller S, Smolarz K, et al: Tumor-Szintigraphie mit J-123-markiertem Östradiol beim Mammakarzinom-Rezeptorszintigraphie. *Nucl Med* 30: 84–99, 1991
25. Sisson JC, Frager MS, Valk TW, et al: Scintigraphic localization of pheochromocytoma. *N Engl J Med* 305: 12–17, 1981
26. Fischer M, Vetter W, Winterberg B, et al: J-131-metaiodobenzylguanidine—a new agent for scintigraphic imaging and treatment of pheochromocytoma. *Nucl Med* 23: 77–79, 1984
27. Lamberts SWJ, Bakker WH, Reubi JC, et al: Somatostatin-receptor imaging in the localization of endocrine tumours. *N Engl J Med* 323: 1246–1249, 1990
28. Bakker WH, Krenning EP, Breeman WAP, et al: *In vivo* use of a radioiodinated somatostatin analogue: dynamics, metabolism and binding to somatostatin receptor positive tumours in man. *J Nucl Med* 32: 1184–1188, 1991
29. Buraggi SL: Radioimmunodetection of malignant melanoma with the 225.28S monoclonal antibody to HMW-MAA. *Nucl Med* 25: 220–224, 1986
30. Saxton RE, Burke MW, Torbet B, et al: Detection of malignant melanoma with monoclonal antibodies. *Dis Markers* 6: 97–108, 1988

31. Scheidhauer K, Markl A, Leinsinger G, et al: Immunoscintigraphy in intraocular malignant melanoma. *Nucl Med Comm* 9: 669–678, 1988
32. Bockisch A, Brökelmann J, Briele B, et al: Radioimmunodetection (RID) with OC-125 antibody $F(ab')_2$ fragments in the follow-up of ovarian carcinoma. *Med Nucl* 2: 281–288, 1990
33. Gitsch E, Pateisky N: Radioimmunoscintigraphy in ovarian cancer: Theoretical basis and clinical results. *Arch Gyn Obstet* 241: 365–370, 1987
34. Baum RP, Lorenz M, Hottenrott C, et al: Radioimmunoscintigraphy using monoclonal antibodies to CEA, CA 19-9 and CA 125. *Int J Biol Markers* 3: 177–184, 1988
35. Chatal JF, Saccavini JC, Fumoleau P, et al: Immunoscintigraphy of colon carcinoma. *J Nucl Med* 25: 307–314, 1984