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Review paper

Anti-cancer radiopharmaceuticals

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Therapeutic nuclear medicine is rapidly developing as an additional treatment modality in oncology. A great variety of specific tumor-seeking radiopharmaceuticals is applied both for diagnostic scintigraphy and treatment, using multiple routes and mechanisms to target radionuclides at tumors. After a brief introduction of some basic principles of radionuclide tumor targeting, the available anti-cancer radiopharmaceuticals, arranged according to the site of accumulation in relation to the cell nucleus, and the results of their current clinical use for therapy are reviewed. The observed response to a number of these applications, the non-invasiveness of the procedure and the relative lack of toxicity and late effects in comparison with chemotherapy and external beam radiotherapy, make radionuclide therapy an attractive and realistic alternative approach to cancer treatment.

Key words: Therapeutic nuclear medicine, tumor targeting, oncology

Introduction

Almost half a century after the initial use of iodine-131, phosphorus-32 and strontium-89 for treatment, targeted radiotherapy using radiopharmaceuticals has now become increasingly popular in the field of oncology. This is partially due to the expanding availability of suitable radiopharmaceuticals and the recognition of new indications, partially due to the fact that 'old' therapies, e.g. ^{89}Sr for metastatic bone pain, are being 'rediscovered'.

In nuclear oncology the trend is to use more or less specific tumor-seeking radiopharmaceuticals, which depict the tumor as a 'hot spot'. Specific metabolic characteristics and biological properties of tumors are being exploited not only for the diagnosis, staging and follow-up, but also to target radionuclides at tumors for therapy. Radionuclide therapy is a unique cancer treatment modality, which offers a realistic alternative for or adjunct to radiotherapy and chemotherapy, as it can deliver radiation doses selectively in target tissue, is systemic and non-invasive and causes few immediate and long-term side effects. Beierwaltes[1] emphasized that long-term (20–40 years) follow-up studies of patients treated with ^{131}I or ^{32}P show that radionuclide therapy has in fact a much lower risk of leukemia and second cancers than chemotherapy and external beam radiotherapy. As the uptake and retention can be established by tracer studies, and because of knowledge of the efficacy and possible side effects of the radionuclide used, this form of treatment should not be regarded as experimental, but as common nuclear medicine practice.

The effect of radiation therapy on a tumor depends on the total absorbed radiation dose to which the tumor is exposed and on the sensitivity of the lesion to radiation. A high and selective uptake and a long retention of the radiopharmaceutical by the tumor is the basis for successful therapy. The simplified formulation to calculate the absorbed radiation dose delivered by a β-emitting radionuclide which is uniformly distributed and decays within water-equivalent tissue (e.g. a tumor) is: $D_\beta(\mathrm{Gy}) = 19.9 \times C \times E \times T_{\mathrm{eff}}$, in which C is the concentration in MBq per gram tissue, E is the average β-energy in MeV and T_{eff} is the effective half-life in days, which accounts for the fixed physical decay of the radionuclide and an approximation of the biological turnover of the compound, which is variable and may be different for diagnostic and therapeutic doses as a result of cell damage.

The specific activity in the target tissue/tumor can be estimated by adding volumetric information obtained by palpation, X-rays, ultrasonography, computerized tomography (CT) or magnetic resonance imaging (MRI) to the uptake measurements. As the volumetry does not always reflect the actual volume of viable tumor to be treated and as the inhomogeneity of distribution of the radiopharmaceutical is not accounted for, the formulation can not be but an approximation of the dose.

Table 1. Radiopharmaceuticals for radionuclide therapy

Site/mechanism	Radiopharmaceutical	Application
Intracellular		
DNA incorporation	[^{125}I]IUdR	Chorioncarcinoma
Metabolic	[^{131}I]iodide	Diff. thyroid cancer
	[^{131}I]/[^{125}I]MIBG	Neural crest tumors
	[^{32}P]phosphate	Polycythemia vera
	[^{131}I]Rose Bengal	Hepatoblastoma
	[^{131}I]iodide	Oncocytoma
Steroid receptor	[^{80m}Br]estrogens	Breast carcinoma
	[^{125}I]tamoxifen	Breast carcinoma
Non-specific	[^{186}Re(V)]DMSA	Medullary thyroid cancer
Cell surface		
Hormone receptor	[^{131}I]SMS analog	Neuroendocrine tumors
Immunologic	[^{131}I]anti CEA	Colon/med. Thyroid cancer
	[^{131}I]B72.3	Colon/ovarian cancer
	[^{131}I]HMFG 1 + 2	Ovarian carcinoma
	[^{131}I]/[^{90}Y]OC 125	Ovarian carcinoma
	[^{131}I]Lym-1	Leukemia/lymphoma
	[^{131}I]anti pan B	Lymphoma
	[^{131}I]/[^{90}Y]antiferritin	HCC/Hodgkin's disease
	[^{131}I]anti p97	Melanoma
	[^{131}I]3F8/UJ31A	Neuroblastoma
Extracellular		
Adsorption	[^{32}P]phosphate	Bone metastases
	[^{89}Sr]/[^{85}Sr]chloride	Bone mets/osteosarcoma
	[^{186}Re(Sn)]HEDP	Bone metastases
	[^{153}Sm]EDTMP	Bone mets/osteosarcoma
	[^{131}I]BDP3	Bone metastases
	[^{90}Y]citrate/EDTMP	Bone metastases
Cells	[^{114m}In]A31 cells	Lymphoma
Intracapillary	[^{131}I]lipiodol	Liver tumors
	[^{32}P]resin microspheres	Liver tumors
	[^{90}Y]glass microspheres	Liver tumors/sarcoma
	[^{90}Y]resin particles	Liver tumors/sarcoma
Intracavitary	[^{32}P]/[^{90}Y]/[^{186}Re]colloids	Astrocytoma/cystic craniopharyngioma
	[^{32}P]colloids	Malignant effusions
	[^{198}Au]/[^{32}P]colloid	ALL intrathecal th.
	[^{131}I]/[^{90}Y]antibodies	Malignant effusions
	[^{198}Au]colloid	Synoviorthesis
	[^{90}Y]citrate/silicate	Synoviorthesis
	[^{165}Dy]FHMA	Synoviorthesis
	[^{186}Re]colloid	Synoviorthesis
	[^{169}Er]citrate	Synoviorthesis

Table 1 shows a list of available tumor-seeking radiopharmaceuticals, indicating the principal tumor-targeting mechanism and the present or potential therapeutic uses. It is arranged according to the site of accumulation in relation to the nucleus as this determines the choice of the radionuclide. It is possible to incorporate radionuclides into the DNA of the cell nucleus or into the cellular cytoplasm by specific metabolic pathways, to attach radioisotopes to the cell membrane surface via receptor binding of hormones and antibodies or to bring radioactivity into close vicinity of the cell, e.g. by targeting at extracellular osteoid or by local or regional administration into arteries or cavities.[2]

To achieve meaningful radiation doses it is essential that the tumor cells have sufficient and accessible binding sites and that the radiopharmaceutical is 'carrier-free', i.e. not containing non-labeled molecules, which also bind to the target thereby reducing the number of binding sites available for the radioactive compound. When the radiolabeled material has reached the target the radiation effect can only be maximally exploited if it remains in that tissue for total decay. In practice this is almost never

the case because of biological turnover. However the effective half-life may be influenced by mechanisms interfering with biological turnover, such as prolongation of the residence time by drugs which inhibit efflux (e.g. lithium), re-utilization as is believed to take place in [^{131}I]MIBG therapy of neural crest tumors, slowing of the cell turnover rate, e.g. by metabolic starvation or anti-neoplastic drugs, and synchronization of cells.[2]

The choice of radionuclide by its physical characteristics also plays an important role in the delivery of an adequate radiation dose. Table 2 shows the physical characteristics of the major radionuclides available for therapeutic application. Most often low-energy β-emitters are used to attain intense irradiation of the target while sparing the surrounding tissues. The range of the β-rays must be in accordance with the distance between the site of the radiolabeled molecule and the structure in which the radiation effect is intended to take place (the nucleus or the cell membrane). In this respect the concept of linear energy transfer (LET) is essential to understand radiobiological effects. Most of the radionuclides presently available and used for therapy deliver so-called 'low-LET' radiation. Specific pharmaceuticals labeled with 'high-LET' β- or α-particle emitters, which produce intense ionization over an ultrashort pathlength, may deliver higher radiation doses, provided that the uptake of the radionuclide is highly selective. In this respect also the tumor size is important: Wheldon *et al.*[3] showed that for isotopes with different physical characteristics the optimal tumor size varies. Auger electron-emitting radionuclides also have a high relative biological effectiveness (RBE), but, due to the range being much less than a cell's diameter, would require a carrier which brings the source into or close to the DNA in the nucleus.[4]

This article will review the clinical uses of therapeutic nuclear medicine in oncology in 1991.

^{131}I Therapy for thyroid carcinoma

The more than 40 years experience of ^{131}I therapy of differentiated thyroid carcinoma, a malignancy with a relatively good prognosis allowing long-term follow-up, showing great efficacy and safety, is discussed here, as it forms the background for other forms of targeted radionuclide therapy.

About one million patients worldwide have safely and effectively been treated with ^{131}I doses, usually in the range 110–370 MBq (3–10 mCi) for hyperthyroidism.[8,9] The thyrotoxicosis follow-up study in 1970[10] established that the ^{131}I therapy results were comparable to those of surgery (partial thyroidectomy), but that in long-term follow-up, hypothyroidism, which is radiation dose-dependent, occurs in almost 35% of cases. After total or near-total thyroidectomy for thyroid carcinoma higher doses of ^{131}I in the range 1.1–5.5 GBq (29.9–150 mCi) are used to ablate residual normal thyroid tissue in order to enable scintigraphic detection and eventually radionuclide treatment of local or distant metastases, which may not sufficiently concentrate ^{131}I in the presence of thyroid remnants. The choice of the dose for this purpose remains controversial: some authors[11–14] advocate that, although total ablation may not always be achieved by a single treatment, the use of a relatively low

Table 2. Radionuclides for therapy: physical characteristics

Nuclide	Half-life	Emission	$E_{\alpha,max}$ (MeV)	$E_{\beta,max/av}$ (MeV)	Max. range	E_γ-peak (KeV)
^{80m}Br	4.42 h	Auger	—	—	<10 nm	—
^{125}I	60.0 d	Auger	—	—	10 nm	—
^{211}At	7.2 h	α	6.8	—	65 μm	—
^{212}Bi	1.0 h	α	7.8	—	70 μm	—
^{169}Er	9.5 d	β	—	0.34	1.0 mm	—
^{67}Cu	2.58 d	β, γ	—	0.58	2.2 mm	185
^{131}I	8.04 d	β, γ	—	0.61/0.20	2.4 mm	364
^{153}Sm	1.95 d	β, γ	—	0.81/0.225	3.0 mm	103
^{198}Au	2.7 d	β, γ	—	0.96/0.31	4.4 mm	411
^{186}Re	3.77 d	β, γ	—	1.08/0.35	5.0 mm	137
^{165}Dy	2.33 h	β, γ	—	1.29/0.44	6.4 mm	95
^{89}Sr	50.5 d	β	—	1.49/0.58	8.0 mm	—
^{32}P	14.3 d	β	—	1.71/0.695	8.7 mm	—
^{90}Y	2.67 d	β	—	2.28/0.935	12.0 mm	—

Sources: Adelstein,[5] Troutner,[6] Volket *et al.*[7]

dose (1.1 GBq) is justified by the lower radiation burden, lower expense, and the fact that, dependent upon the local legislation, such a treatment may be given on an out-patient basis. Others[15–17] argue that because in a considerable number of patients a 1.1 GBq dose is inadequate and therefore subsequent ^{131}I therapy is necessary to ablate the thyroid tissue, a higher dose (1.85–5.5 GBq) should be given, as it is essential to try to achieve ablation in one dose and as there is no evidence that this confers a greater risk to the patient.

Doses up to 7.4 GBq (200 mCi) are usually applied for ^{131}I treatment of metastatic differentiated thyroid carcinoma (Figure 1). Although some authors[18–20] administer even higher doses [up to 24 GBq (650 mCi)] based upon dosimetric considerations from pre-therapy tracer studies, using the rationale to achieve the maximal tumor dose by targeting for the limiting dose of 2 Gy (200 rads) to the blood, these studies have not proven greater efficacy than those with the empirically derived dose of 7.4 GBq.[21] Other reasons not to follow this procedure are: (1) for proper dosimetry prolonged tracer studies are required; (2) treatment doses often exhibit different kinetics than tracer doses; (3) the management of the radioactive patient is more of a problem (longer hospitalization, more volatile radio-iodine in the therapy unit, storage of waste) and (4) these doses carry an increased risk of complications.[18,22] Finally, because of these considerations, in most countries the ^{131}I therapy license is limited to 7.4 GBq.

Efficacy

Several series have been published showing the efficacy of ^{131}I therapy of metastatic thyroid carcinoma in terms of survival: Benua *et al.*[18] reported sustained remission in 16 of 48 patients with lung and bone metastases, Varma *et al.*[23] showed that 262 patients treated with surgery and ^{131}I had a significantly longer survival than a comparable group treated with surgery alone, and Beierwaltes *et al.*[24]

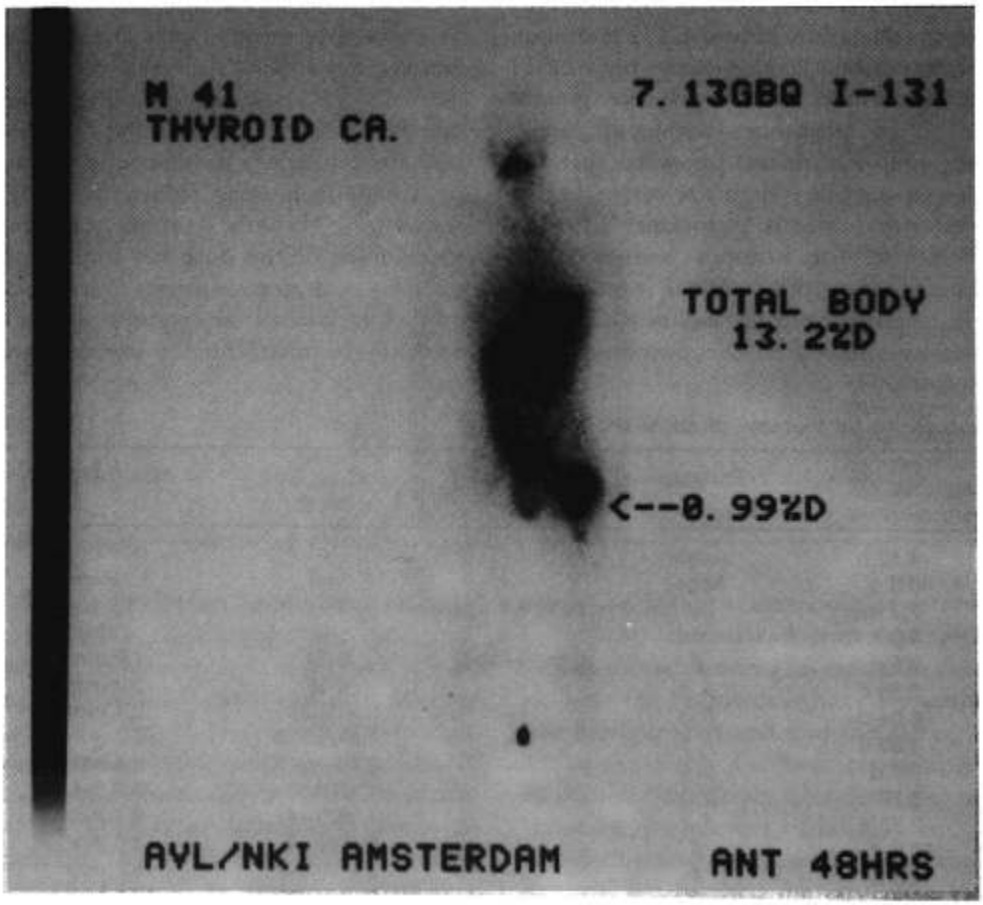

Figure 1. Post-therapeutic total body scintigram 48 h after 7.13 GBq [^{131}I]iodide for differentiated thyroid carcinoma metastatic to the proximal left femur.

emphasized that patients whose metastases were eliminated by ^{131}I have a three-fold increase in survival time. Pulmonary metastases appear to be more amenable to effective ^{131}I therapy than skeletal metastases.[18,25,26] Hundeshagen[27] reported the following results in 150 patients with thyroid carcinoma metastases: 51.3% complete remissions, 16% partial remissions, 17.3% no change and progression in 15.3%. Creutzig *et al.*[28] analysing the clinical follow-up of 1018 patients treated for thyroid cancer since 1961, showed that the 5 and 10 years survival of patients with ^{131}I concentrating metastases (73 ± 11 and 45 ± 9% respectively) compared favorably with that of patients with non-^{131}I concentrating lesions (5 years survival <20%). A survey of 5-, 10- and 15-year survival rates of patients with local recurrences, lung metastases and bone metastases treated at Villejuif[25] similarly demonstrates a much better prognosis for patients with ^{131}I avid disease. Both in thyroid remnant ablation and in ^{131}I therapy of metastatic thyroid carcinoma the effect is clearly related to the absorbed radiation dose, as far as this can be assessed accurately.[29]

Radioiodine concentration in medullary thyroid carcinoma is a rare finding, but few cases which were treated with ^{131}I have been described.[30] Saad *et al.*[31] investigated the role of post-operative ^{131}I ablation therapy in medullary thyroid carcinoma and concluded that it has no value as an adjunct to surgery.

Side effects

Major series, in which patients treated with ^{131}I have been followed up for decades, show that side effects and long-term complications of this treatment do not constitute a real problem. Halnan[32] demonstrated that, if a tumor concentrates 0.1% dose per gram with a biological half-life of 3 days, it would receive 62 Gy (6200 rads) from a 7.4 GBq dose, while at the same time the whole body dose can be kept below 1% of this, both for an ablation and a therapy dose.

Possible acute side effects are nausea and vomiting, sialadenitis, radiation sickness (hardly ever seen at dosages below 7.4 GBq and presenting with symptoms of fatigue, headache, nausea and vomiting as early as 12 hours after administration of ^{131}I), temporary painful swelling of metastases, thyroid storm and bone marrow suppression.[21,33a]

Possible long-term effects of ^{131}I therapy are hematologic effects, pneumonitis and lung fibrosis, fertility disorders, induction of leukemia and other second neoplasms.[33b]

The hematologic effects appear to be moderate and related to the whole body dose.[34–36] Lung fibrosis has not been shown to occur with less than 3.7 GBq uptake of ^{131}I in the lungs, a figure hardly ever reached.[37] Although ovarian failure and azospermia have been reported,[38] Sarkar *et al.*[39] found no incidence of decreased fertility or birth abnormalities during follow-up of 40 children treated with ^{131}I for thyroid cancer. Induction of leukemia by ^{131}I treatment is extremely rare: 13 of such cases had been reported in the literature by 1983,[20] the majority of these patients being older than 50 years and having received the highest doses [mean cumulative dose 33.3 GBq (900 mCi)]. Edmonds and Smith[33b] reported a small excess of deaths from leukemia (three cases) during long-term follow-up of 258 patients treated with high dose ^{131}I. Other major follow-up studies of thyroid carcinoma treatment with ^{131}I[24,27,32] report no incidence of leukemia, even after cumulative doses exceeding 37 GBq (1 Ci). With respect to induction of second cancers, Spencer *et al.*[40] reviewed the 25 cases in the world literature of thyroid carcinoma after ^{131}I therapy for hyperthyroidism: as in eight patients the latency period was less than 5 years, in 15 patients thyroid nodules were initially present, three patients had thyroiditis and one received external radiotherapy to the neck, he could not find substantiating evidence that any of these thyroid carcinomas had actually been caused by ^{131}I therapy. Wiseman *et al.*[41] reported two cases of non-Hodgkin lymphoma developing in the salivary glands 10 and 3 years respectively after ^{131}I therapy for thyroid carcinoma and Edmonds and Smith[33b] reported three cases of carcinoma of the bladder, which were assumed to be related to ^{131}I therapy. Lastly, the question of potential ^{131}I-induced anaplastic transformation of a previously well-differentiated thyroid carcinoma has been raised; however, this phenomenon is regarded to relate more to the natural history of the disease than to the ^{131}I therapy.[42,43]

[^{131}I]MIBG therapy

One decade after the clinical introduction of radioiodinated meta-iodobenzylguanidine (MIBG) at the University of Michigan,[44] this radiopharmaceutical has established its place in the diagnosis and treatment of tumors which are derived from the neural crest. These tumors may present characteristic features, which are responsible for the uptake and

retention of this compound, i.e. an active uptake-1 mechanism at the cell membrane and storage granules in the cytoplasm.

Table 3 shows the cumulative sensitivities of [^{131}I]MIBG scintigraphy for the major indications, as calculated by adding up published results in more than 2400 patients: MIBG imaging is a reliable test for both pheochromocytoma and neuroblastoma (sensitivity around 90%), but in carcinoid and medullary thyroid carcinoma the sensitivities tend to be lower, 70 and 35% respectively. Fewer patients with the latter conditions will thus be amenable to therapy. Figure 2 shows an example of the good concentration and long retention of [^{131}I]MIBG in neuroblastoma.

Worldwide, more than 300 patients have been reported to have received [^{131}I]MIBG therapy for pheochromocytoma, neuroblastoma, paraganglioma, carcinoid and medullary thyroid carcinoma. At The Netherlands Cancer Institute 86 patients have together received 256 therapeutic doses of [^{131}I]MIBG by February 1991: 59 for neuroblastoma (56 children), four for malignant pheochromocytoma, 19 for metastatic carcinoid and four for medullary thyroid carcinoma. A fixed dose of 3.7–7.4 GBq (100–200 mCi) of [^{131}I]MIBG with a high specific activity (1.48 GBq/mg) was infused over a 4-h period, and patients were isolated for 4–6 days using oral KI to protect the thyroid from free ^{131}I. In the case of isolation of a child the parents or grandparents participated in the patient care. An alternative approach is to administer a varying, calculated dose, as assessed by a prior tracer study, aiming for the maximal acceptable 2 Gy bone marrow dose.[45] The treatment results for the major indications are reviewed.

Table 3. MIBG scintigraphy in neural crest tumors: cumulative sensitivity per indication

Diagnosis	Patients	Cum. sensitivity (%)
Pheochromocytoma	>1000	88.2
Neuroblastoma	841	91.0
Carcinoid	237	69.8
Medullary thyroid carcinoma	178	34.5
Other neural crest tumors	144	57/144
Total reported cases	>2400	

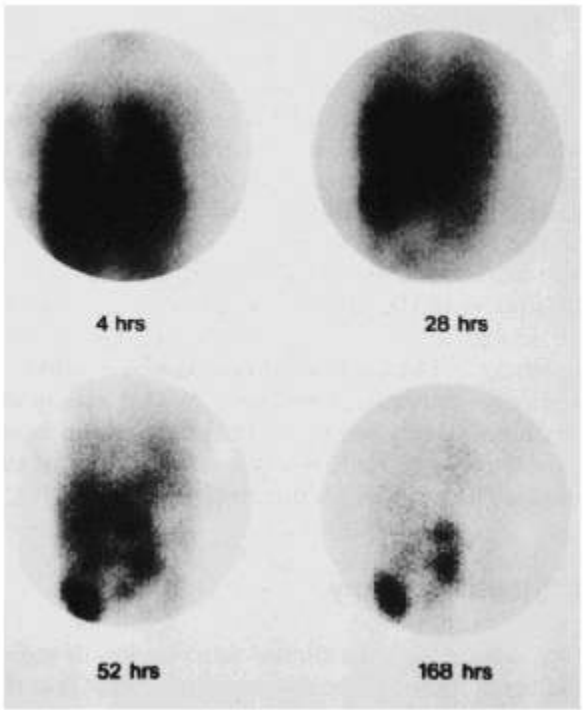

Figure 2. [^{131}I]MIBG therapy in a 4-year-old girl with neuroblastoma: repeated scintigraphy at different intervals demonstrates the concentration and retention of [^{131}I]MIBG by the tumor and the rapid clearance from the normal tissues.

Neuroblastoma

In a phase II study in 50 patients with progressive, recurrent neuroblastoma the following response was observed: seven complete remissions and 23 partial remissions, by which is meant more than 50% decrease of the tumor volume in 12 patients or significant scintigraphic improvement of non-measurable lesions in 11 patients; no change, which in practice means stabilization of previously progressive disease, in 11 patients and progressive disease despite therapy in eight patients. One patient was lost to follow-up.[46] The duration of the remissions varied from 2 to 38 months and the best results were attained in patients with voluminous soft tissue disease. In general both the MIBG treatment and the isolation were well tolerated by children and the following side effects were observed: hematological effects occurred most frequently, predominantly as an isolated thrombocytopenia in 30 patients; 12 patients had severe bone marrow depression related to bone marrow involvement, and in three the renal function, which had already been compromised by intensive pretreatment with cisplatin and Iphosphamide, deteriorated.

In 1987 data from 80 neuroblastoma patients treated with [^{131}I]MIBG by major groups were published together, including the initial 18 from Amsterdam:[47–54] of 64 evaluable patients four attained complete and 27 partial remission and in 21 patients the disease was arrested, encouraging results, taking into account that most of these patients had stage IV, progressive and intensely pre-treated disease. In addition, MIBG therapy provided valuable palliation and improved quality of life to many patients and its non-invasiveness is in striking contrast to other treatment modalities. In the more recent UKCCSG study, using calculated doses of [^{131}I]MIBG aiming for escalating dose limits for the bone marrow, the following results in 24 patients were reported: seven partial responses, stable disease in nine and progression in six patients.[55]

The observed response in advanced neuroblastoma, the non-invasiveness of the procedure and the high metabolic activity of untreated tumors have permitted us to use [^{131}I]MIBG in newly diagnosed patients pre-operatively instead of combination chemotherapy. The advantages of this approach are that the child's general condition is unaffected or even improved prior to surgery and that chemotherapy is reserved to treat minimal residual disease. So far six patients with inoperable stage III or IV neuroblastoma have received a minimum of two therapeutic doses of [^{131}I]MIBG before being submitted to surgery. Decrease of the volume of the primary tumor (Figure 3) was observed in five patients and the urinary excretion of catecholamines decreased in all patients. Five children have now been successfully operated with total or >95% excision of the tumor.[56] Four additional patients are on treatment.

An alternative approach to the management of neuroblastoma may be the use of [^{125}I]MIBG for therapy. This may have a role in the treatment of micrometastases and bone marrow infiltration, particularly as the results of [^{131}I]MIBG therapy under these circumstances are poor. Although the range of the ^{125}I Auger electrons in the storage vesicles would seem to be inadequate to deliver a meaningful radiation dose to the nucleus, the finding that in neuroblastoma extragranular storage contributes considerably to the total MIBG retention[57] may provide a basis for this treatment. Preliminary experience in five patients with neuroblastoma has been reported by Hoefnagel *et al.*[58,59] and Sisson *et al.*[60] Arrest and slight regression of disease (Figure 4) has been observed by both authors, but these initial results require confirmation in a greater number of patients. As the whole body dose per mCi of [^{125}I]MIBG is about four times lower than that of [^{131}I]MIBG, higher doses may be administered without causing toxicity, although the problem of radioactive waste would require extra attention.

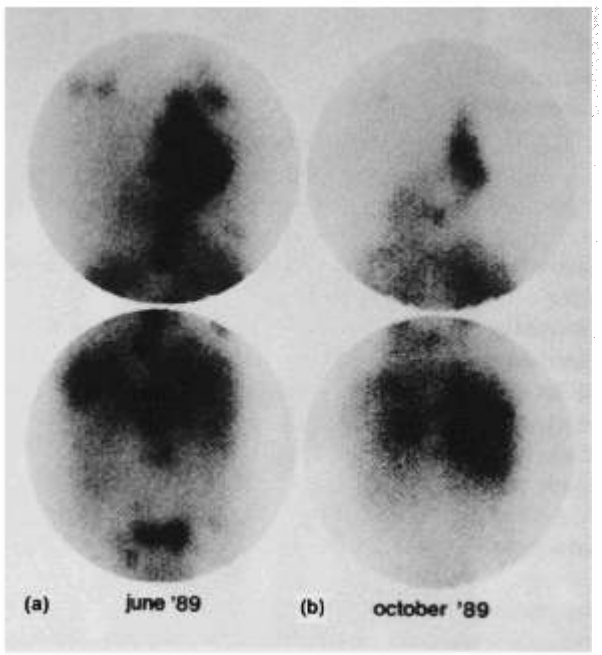

Figure 3. Pre-operative [^{131}I]MIBG therapy in a 13-year-old girl with a large inoperable thoracic neuroblastoma, metastatic to the lymph nodes and bone (a); after four cycles of [^{131}I]MIBG there is no further evidence of metastases and the volume of the primary tumor has been reduced to 30% of the original size, enabling successful surgical resection.

Pheochromocytoma

Table 4 shows the observed response to [^{131}I]MIBG therapy in 63 patients worldwide with malignant pheochromocytoma, as reported in the literature.[61–71] A clinical response in this condition can be defined as a decrease of symptoms and blood pressure, a >50% decrease in catecholamine excretion, a >50% reduction in tumor volume or significant scintigraphic improvement if lesions can not be measured.

It may be disappointing to see that only one complete and 13 partial remissions (>50% decrease in tumor volume) and seven scintigraphic improvements of non-measurable lesions have been recorded to date. However, in more than 60% of the patients subjective improvement of symptoms, lowering of blood pressure, as well as pain relief

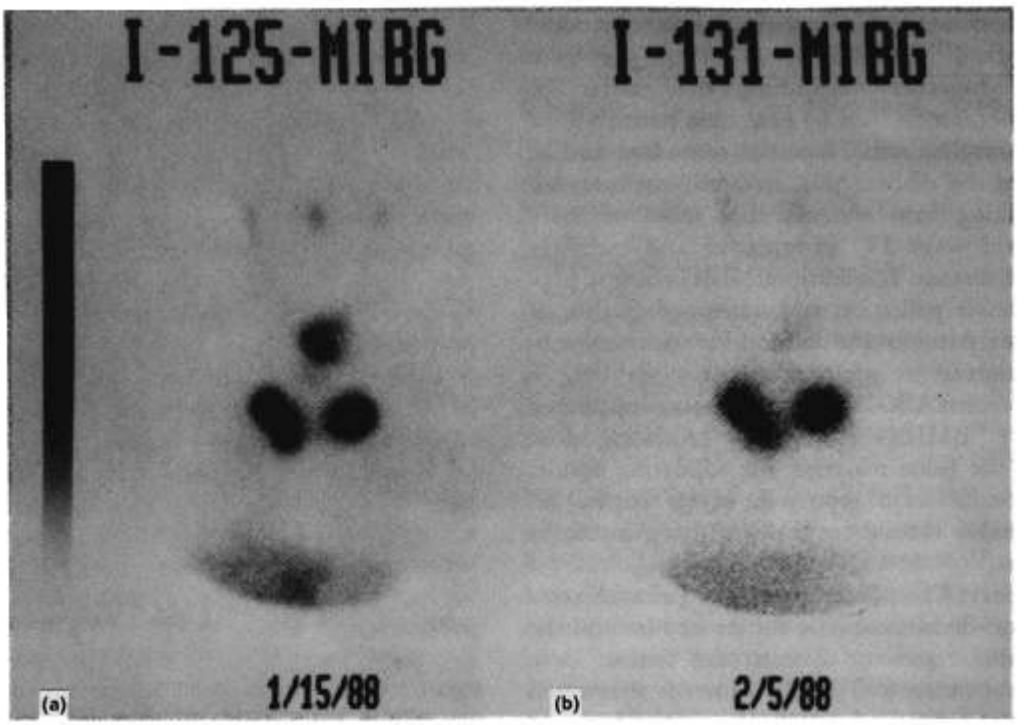

Figure 4. Therapy of neuroblastoma in the neck and mediastinum, using [^{125}I]MIBG and [^{131}I]MIBG, respectively. Three weeks after 7.4 GBq [^{125}I]MIBG (a), the [^{131}I]MIBG scintigram (b) shows a mixed response: although an objective regression of the lesion in the neck was attained, there was slight progression of disease in the mediastinum.

were achieved. Against a background of a widespread metastatic disease, which is little or non-responsive to external beam radiotherapy and chemotherapy, the palliative value of [^{131}I]MIBG therapy should not be underestimated. For patients who respond, the tumor regression, reduction of hormonal activity and the relief of pain are certainly meaningful and may be long lasting, whereas the therapy itself is relatively non-invasive and the patients generally feel well during the entire interval between treatments. In all reported series the side effects were minimal. Like in neuroblastoma, in most published series it was recognized that soft tissue disease responded better than skeletal metastases.

Especially in pheochromocytoma one must be aware of the medication the patient is using, as there is a long list of drugs which may interfere

Table 4. Response to [^{131}I]MIBG therapy in 63 patients with malignant pheochromocytoma

Center	Patients	Objective response				Subjective Symptoms
		CR	PR	Scintigram	Catecholamines	
Southampton	15	—	3	—	7	10
Ann Arbor	13	—	2	2	4	4
France	12	—	3	1	6	7
Münster	6	—	1	1	?	6
Rome	4	1	1	—	1	4
Amsterdam	4	—	1	—	2	4
Warsaw	3	—	—	1	1	1
Heidelberg	3	—	1	—	?	1
London	2	—	—	2	2	2
Copenhagen	1	—	1	—	1	1
Total	63	1	13	7	24	40

CR, complete remission; PR, partial remission.

with the uptake and retention of [^{131}I]MIBG.[72] Patients should be taken off these drugs for at least 2 weeks prior to diagnostic scintigraphy or therapy using MIBG, and, if necessary, may be put on propanolol and dibenilene to control hypertension. Further studies on dose scheduling and dose distribution as well as on pharmacologic modulation of tracer uptake and retention are required to allow a more optimal therapeutic use of [^{131}I]MIBG. In the latter respect the observations of increased uptake and retention of [^{131}I]MIBG by the use of nifedipine, a calcium channel blocker, by Blake *et al.*,[73] are encouraging.

Paraganglioma

There are two reports in the literature of [^{131}I]MIBG therapy of paraganglioma. Khafagi *et al.*[74] treated a patient with widespread bone metastases from paraganglioma, non-responsive to radiotherapy and chemotherapy, with 3.85 GBq [^{131}I]MIBG: no objective regression of the tumor size was observed, but the patient was relieved of bone pain. Baulieu *et al.*[75] described successful [^{131}I]MIBG therapy in a patient with malignant, non-functioning paraganglioma, metastatic to the bone: an objective partial remission with a 3-year follow-up, together with pain relief and a dramatic improvement in the quality of life were attained.

Carcinoid

At The Netherlands Cancer Institute 19 patients with symptomatic, metastatic carcinoid have received 7.4 GBq doses of [^{131}I]MIBG for palliation.[58,76,77] Most patients had multiple large metastases in the liver showing no response to other therapies. No objective remission (i.e. $>50\%$ reduction of the tumor volume) was ever observed. However, 12 patients were relieved of symptoms, such as flushes, diarrhea, anorexia and pain. Palliation in some of these patients was meaningful and long lasting. Other groups[78–80] have reported one partial response and palliation in six of 14 carcinoid patients who were treated with [^{131}I]MIBG. The palliative effect associated with a lack of objective response may be explained by observations in [^{131}I]MIBG SPECT and post-mortem studies, that carcinoid liver metastases may present both as hot and cold lesions;[81] the [^{131}I]MIBG concentrates exclusively in the metabolically active metastases, which are responsible for the patient's symptoms. On the other hand, a pharmacological effect of MIBG can not entirely be ruled out, a reason why therapeutic studies using unlabeled MIBG in these conditions are underway.

Medullary thyroid carcinoma

Reviewing the 14 cases of medullary thyroid carcinoma in the literature treated with [^{131}I]MIBG,[82] the following results were gathered; two complete remissions, three partial remissions, more than 50% decrease of calcitonin levels in at least three patients and palliation in eight patients (Figure 5). Taking into account that the two complete and one of the partial remissions were attained in an integrated treatment protocol involving surgery, ^{131}I ablation, radiotherapy and [^{131}I]MIBG therapy,[67] the objective response appears to be limited; however, it is emphasized that the palliation provided to these patients, for whom there is little other therapy, may be very meaningful.[83]

In summary, [^{131}I]MIBG therapy is an effective treatment for several neural crest tumors, which can be safely applied, even in children, provided that the bone marrow is free of tumor cells; in patients with invaded bone marrow [^{131}I]MIBG therapy should only be considered when bone marrow salvage methods are available. Dosimetry in clinical practice remains difficult, with calculated absorbed radiation doses to the tumor not always matching the observed response. Animal models, such as the xenografted MIBG-concentrating neuroblastoma in the nude mouse,[84] enable the study of the pharmacokinetics, dose-scheduling, dose–response relations and pharmacological intervention.

^{32}P in polycythemia vera

Since the introduction of radiophosphorus in 1936, this radionuclide has been used as orthophosphate (PO_4^{3-}) in the treatment of myeloproliferative disease, particularly in polycythemia vera. Incorporation of ^{32}P orthophosphate into the nucleic acids of rapidly proliferating cells was considered to be the targeting mechanism. Polycythemia vera is a relatively rare disease, which is characterized by an autonomous proliferation of marrow cells and can be treated by repeated phlebotomies, radioactive phosphorus and chemotherapy. If untreated, the prognosis is poor (median survival 1.5 years). Both chemotherapy (chlorambucil or busulphan)

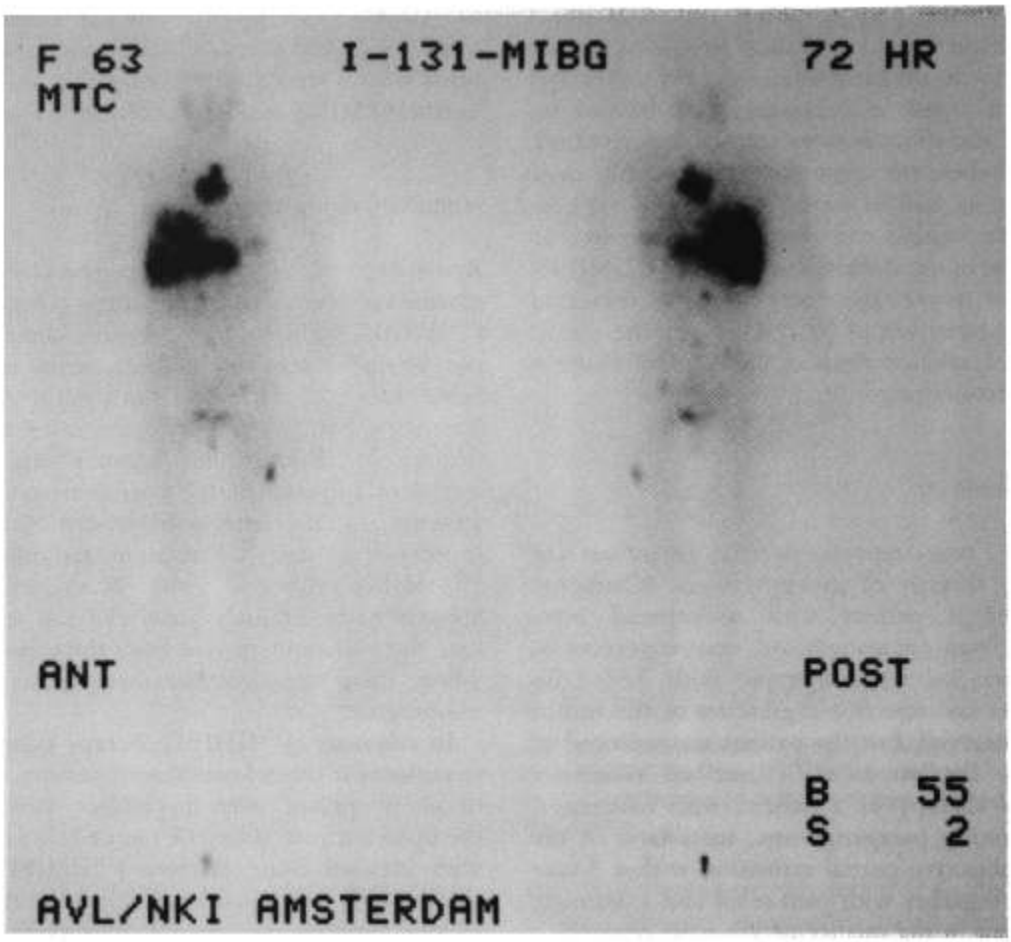

Figure 5. Post-therapeutic total body scintigrams of a 63-year-old female with medullary thyroid carcinoma, metastatic to the mediastinum, liver, abdomen and left femur, 72 h after administration of 7.4 GBq [^{131}I]MIBG.

and ^{32}P treatment yield better results than phlebotomy alone. Early studies[85–88] demonstrated objective remissions and prolonged survival after ^{32}P therapy (median survival 11–15 years).

An initial dose of 74–111 MBq (2–3 mCi) per m^2 body surface but not exceeding 185 MBq (5 mCi) is administered intravenously. Alternatively a fixed dose of 111 MBq (3 mCi) can be given. If no response is observed by 12 weeks, the treatment may be repeated, increasing the dose by 25% up to a maximum of 260 MBq (7 mCi).[89] Spiers *et al.*[90] calculated the bone marrow dose to be 0.65 cGy/MBq (24 cGy/mCi). Therefore the induction of acute leukemia is a concern. In a long-term follow-up study in 431 patients by the Polycythemia Vera Study Group, this was found to occur more frequently after chlorambucil chemotherapy than after ^{32}P treatment (11 vs 6%). In contrast, a European multicenter randomized phase II study of busulphan vs ^{32}P in 293 polycythemia vera patients between 1967 and 1978 showed that the duration of the first remission as well as the overall survival was significantly longer in the busulphan group. The occurrence of malignant complications was identical, but there were significantly more vascular complications (bleeding and thromboembolism) in patients treated with ^{32}P.[91]

^{32}P therapy, as well as chemotherapy, may also be used in the management of essential thrombocythemia.[92] Other uses of radiophosphorus will be discussed under bone and intracavitary therapy, respectively.

Other intracellular agents

[^{131}I]Rose Bengal

The observations of uptake of hepatobiliary radiopharmaceuticals by hepatoma,[93] hepatocellular

carcinoma[94,95] and hepatoblastoma[96] led De Kraker *et al.*[97] to administer a therapeutic dose of 1.85 GBq (50 mCi) [^{131}I]Rose Bengal to a 7-month-old child with hepatoblastoma, which was progressive after radiotherapy and chemotherapy and which demonstrated considerable uptake and retention of [^{131}I]Rose Bengal (tumor uptake 28.7% of the dose at 24 h). Like combination chemotherapy and radiotherapy had done, [^{131}I]Rose Bengal therapy induced central necrosis of the tumor and a striking decrease of the tumor-marker (AFP) level, but was later followed by a relapse. The hypothesis for the targeting mechanism is metabolic uptake of [^{131}I]Rose Bengal by the hepatoblastoma cells followed by a prolonged retention due to the abnormal or non-communicating bile ducts in the tumor.

^{131}I for oncocytoma

A similar trapping mechanism is considered to be the explanation for retention of ^{131}I by oncocytoma, a usually benign tumor of the salivary glands. Kosuda *et al.*[98] describe successful ^{131}I therapy in a single case of recurrent, inoperable parotid oncocytoma.

[^{186}Re(V)]DMSA

^{99m}Tc-labeled pentavalent DMSA is successfully applied in the scintigraphic detection of medullary thyroid carcinoma.[99,100] It is the pentavalent form of the renal agent [^{99m}Tc(III)]DMSA, which, because of its TcO_4^{3-} core, exhibits tumor-seeking properties, similar to the PO_4^{3-} ion. It is therefore not specific for MTC but is mostly used for this indication. After the substitution of ^{99m}Tc by ^{186}Re Clarke *et al.*[101] found the whole body distribution and tumor uptake in MTC to be identical. Dosimetry revealed that, if used for therapy, the radiation dose to the kidney would be relatively high, probably due to trivalent [^{186}Re]DMSA in the solution. If this can be eliminated by pharmacological modification, and after assessment of the tumor-seeking property of individual pentavalent DMSA isomers, [^{186}Re(V)]DMSA promises to be an alternative to [^{131}I]MIBG and radiolabeled antibodies in the treatment of MTC.

Hormone receptor binding radiopharmaceuticals

Several malignant tumors have been shown to be hormone-dependent in their development and growth and may be treated either by hormones or anti-hormone therapy. Many tumors contain hormone receptors in the cytoplasm or at the cell membrane, to which radiolabeled hormones, analogues or anti-hormone drugs may be targeted. Examples are the use of estrogens, labeled with ^{75}Br or ^{18}F for PET and ^{77}Br or ^{123}I for scintigraphy/SPECT,[102] the use of the somatostatin analogue [^{123}I]Tyr^3-octreotide[103] and the radioiodinated anti-estrogen drug tamoxifen.[104]

If indeed these agents would sufficiently and selectively be accumulated and retained in tumors, they may eventually be used for treatment, labeled with ^{131}I, ^{125}I, ^{80m}Br or ^{211}At. To date there are no reports of such use in humans. For the Auger electron emitters it would be essential that, upon passing the cell membrane and binding to the receptor, translocation of the complex into the nucleus takes place, as is the case for steroid receptors. By *in vivo* studies in the immature female rat, using various routes of administration, DeSombre *et al.*[105,106] showed specific localization of ^{80m}Br-labeled triphenylethylene, and steroidal estrogen in estrogen target tissues, which could be inhibited by diethylstilbestrol (DES), suggesting a good potential for the treatment of estrogen receptor-positive tumors. Bloomer *et al.*[104,107] demonstrated the differential radiotoxicity of [^{125}I]tamoxifen by *in vitro* studies in human breast cancer cells.

Radioimmunotherapy

After the first use of radiolabeled antibodies in the rat kidney by Pressman and Keighly in 1948,[108] and the isolation of the tumor-specific carcinoembryonic antigen (CEA), the greatest milestone for the clinical use of antibodies was the development of the hybridoma technique by Köhler and Milstein in 1975,[109] allowing the production of numerous monoclonal antibodies raised against a variety of tumors and subsequent separation into $F(ab')_2$ and Fab fragments. It is not intended here to go into details of the technologies involved nor into the many published reports of the use of a great variety of radiolabeled monoclonal antibodies for diagnostic scintigraphy. Suffice to say, that the experience varies considerably and that reported sensitivities and specificities in every study relate to the use of an individual antibody or fragment with a particular label in the particular tumor type and can not be generalized for radioimmunoscintigraphy as a technique.

As, in many cases, the accumulation of radiolabeled monoclonal antibodies (in percentage dose) is not very high, the retention not very long, and the volumes of tumors which can be imaged relatively large, their therapeutic application has till now been limited. Major problems include the heterogenic intratumoral distribution of monoclonal antibodies, the dilution factor in humans, the shedding of antigen into the circulation, the induction of human antimouse antibodies, the tumor penetration and the dosimetry/microdosimetry of radiolabeled monoclonal antibodies.[110–112] For some indications the regional or intracavitary application of radioimmunotherapy may decrease several of these problems.

Limiting factors for radioimmunotherapy are: (1) acute toxicity, which can present with symptoms like fever, chills, flushing, urticaria, rash, headache, nausea, vomiting, dyspnea, hypotension, tachycardia, anaphylaxis, serum sickness, bronchospasm; (2) the human antimouse antibody (HAMA) response limiting repeated application; and (3) the bone marrow toxicity due to binding to the reticulo-endothelial system. The latter problem may be alleviated by bone marrow transplantation, the use of hematopoietic growth factors, interleukin-1 protection and removal of non-targeted activity.[113]

Table 5 summarizes a number of clinical results of radioimmunotherapy in patients with malignant disease published in the literature, which are briefly discussed.

DeNardo *et al.*[114,124] reported objective response, including two complete and 17 partial remissions, to repeated injections of [^{131}I]Lym-1, a B-cell lymphoma antibody, in 28 patients with non-Hodgkin's lymphoma or chronic lymphocytic leukemia. Eary *et al.*[125a] used ^{131}I-labeled anti-pan B-cell antibodies in escalating doses up to 24.35 GBq (658 mCi) in the treatment of B-cell lymphoma. The administered dose was based on the estimated highest dose to the normal tissue excluding bone marrow (EHDNT). In the first three patients a dose aimed at an EHDNT of 10 Gy induced three complete remissions as well as thrombocytopenia, which was overcome by platelet transfusions. In the next three patients with an EHDNT of 15 Gy severe aplasia, requiring autologous bone marrow transplantation, occurred. Two complete and one partial remission were attained. A seventh patient receiving an even higher dose had not been evaluated at the time of this report.[115]

By far the greatest number of patients receiving radioimmunotherapy were treated for hepatoma and Hodgkin's disease by the group at The Johns Hopkins Oncology Center in Baltimore, who use ^{131}I- and ^{90}Y-labeled polyclonal antibodies, raised against the tumor-associated antigen ferritin in multiple animal species, in integrated phase I and II protocols of external beam irradiation, chemotherapy and antiferritin. A total of 105 patients with inoperable hepatocellular carcinoma received [^{131}I]antiferritin (most of them repeated cycles of 1.11 GBq or 30 mCi) after induction therapy consisting of 21 Gy external beam radiotherapy and doxorubicin and 5-FU chemotherapy or in combination with the same chemotherapy. Of 66 patients with measurable liver tumors CT objectivated four complete and 26 partial remissions. The overall objective response rate of the entire

Table 5. Radioimmunotherapy: published clinical results

Diagnosis	Antibody/route	Patients	Obj. response	Reference
Leukemia/lymphoma	[^{131}I]Lym-1	28	2 CR, 17 PR	114
Lymphoma	[^{131}I]anti pan B	7	5 CR, 1 PR	115
Hepatoma	[^{131}I]antiferritin (+radio/chemotherapy)	105	4 CR, 26 PR	116
M. Hodgkin	[^{131}I]antiferritin	37	1 CR, 14 PR	117
Melanoma	[^{131}I]anti p97 Fab	16	1 PR	118
Neuroblastoma	[^{131}I]3F8	10	2 PR	119
Colon cancer	^{131}I various i.p.	16	2 CR, 4 PR	120
Ovarian cancer	^{131}I various i.p.	24	3 CR, 6 PR	121
	^{131}I various i.p.	13	2 PR	120
	[^{131}I]OC 125 i.p.	17	3 PR	122
	[^{90}Y]OC 125 i.p.	6	None	123
All indications		279	17 CR, 76 PR (33%)	

CR, complete remission; PR, partial remission.

treatment regimen was 50% and the median survival of the responders was 11 months with 15% survivors beyond 2 years. The major toxicity was thrombocytopenia, especially after the antiferritin/chemotherapy combination.[116] In subsequent studies dosimetry of [^{111}In]antiferritin prior to and after external beam irradiation revealed 1.1- to 5.8-fold increases in tumor uptake, and [^{90}Y]antiferritin, the distribution of which was identical to that of [^{131}I]antiferritin, was used for therapy of hepatoma.[125b]

The same polyclonal [^{131}I]antiferritin is also used without other treatment modalities in patients with advanced Hodgkin's disease relapsing after or not responding to combination chemotherapy. In the first 37 patients, receiving repeated cycles of 1.11 GBq (30 mCi) on day 0 and 740 MBq (20 mCi) on day 5 at 8-week intervals, one complete and 14 partial remissions were attained, with no change in 16 patients and progression in six.[117]

In patients with metastatic melanoma, a condition which shows little response to any treatment modality, only minimal objective response has been reported: in 16 patients treated with ^{131}I-labeled anti-p97 Fab fragments a partial response was observed in only one patient and stabilization of disease in two further patients.[118,126]

Several monoclonal antibodies against neuroblastoma have been developed, two of which, 3F8 and UJ31A, have been used in humans for therapy.[127] Cheung *et al.*[119] reported a phase I toxicity study in 10 children with metastatic neuroblastoma, using [^{131}I]3F8, a murine IgG_3 antibody specific for disialoganglioside G_{D2} in escalating doses of 222–444 MBq/kg (6–12 mCi/kg). The following results were attained: two partial remissions, one minimal objective response and stabilization of disease in six patients. All 10 patients required analgesics to control the pain during infusions and became pancytopenic; eight of them required autologous bone marrow transplantation.

There are several examples of the intracavitary application of radioimmunotherapy. Riva *et al.*[120] treated 16 patients with gastrointestinal carcinoma (15 colorectal and one gastric) by intraperitoneal (i.p.) and/or intravenous administration of a variety of radioiodinated monoclonal antibodies directed against tumor-associated antigens (AUA1, B72.3, BW494/32, FO23C5). Two complete and four partial remissions were reported, as well as stabilization and palliation in several other patients. Because of the relatively low radiation burden to the bone marrow, the toxicity was mild. HAMA production was demonstrated in all patients following therapy. The same group also reported two partial remissions in 13 patients with ovarian carcinoma treated by i.p. [^{131}I]MoAbs.[120] Previously Epenetos *et al.*[121] had published their results in 24 patients with ovarian carcinoma, who were treated with i.p. administration of ^{131}I-labeled monoclonal antibodies HMFG1, HMFG2, AUA1 and/or H17E2. There were nine objective responses and it was concluded that small-volume disease responded better and that high doses [>5.18 GBq (140 mCi)] were more effective than lower doses. Further examples are the i.p. use of OC 125 antibodies labeled with ^{131}I[122] or ^{90}Y,[123,128] yielding limited objective response. Lashford *et al.*[129] treated five patients with leptomeningeal metastases from diverse primary tumors by intrathecal administration of 0.4–1.48 GBq (11–40 mCi) ^{131}I-labeled antibodies. A variety of monoclonal antibodies corresponding to the tumor type was used. Four patients attained an objective response, which was sustained for 7 months to 2 years. More recently the dosimetric aspects of intrathecal radioimmunotherapy were described.[130]

Future developments of radioimmunotherapy include the use of other labels, such as ^{67}Cu, ^{186}Re and ^{211}At, neutron capture therapy using ^{10}B, the combination of modalities (e.g. antibodies + radiotherapy/chemotherapy), the conjugation of antibodies with drugs and toxins, and the use of biological response modifiers.

Bone therapy

After the use of radioactive strontium for the treatment of bone metastases had been described as early as in 1942,[131] a revival of radionuclide bone therapy is seen in recent years, partly due to increased efforts by the industry to promote and make available suitable agents, partly due to the greater appreciation of therapeutic nuclear medicine in general.

Bone therapy may be the treatment of primary bone tumors, such as osteosarcoma,[132] which produces osteoid and in which bone-seeking radiopharmaceuticals are in fact tumor-seeking, also targeting at lung and soft tissue metastases (Figure 6).[133,134] Bone therapy may also be the treatment of painful skeletal metastases, which may be palliated due to the absorbed radiation dose in the zone of reactive bone surrounding the tumor. Of course bone metastases of some tumors may also be treated

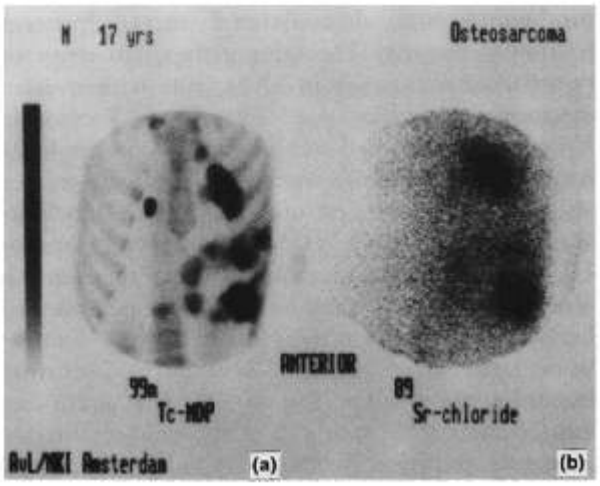

Figure 6. Bone scintigraphy using [^{99m}Tc]MDP (a) in a 17-year-old male with intense accumulation in pulmonary metastases from osteosarcoma; image (b) shows the scintigram using the Bremsstrahlung 24 h after therapy with 370 MBq [^{89}Sr]chloride.

by specific tumor-seeking radiopharmaceuticals, as described elsewhere in this review.

Pain from bone metastases is a frequent cause of physical and psychological stress in patients with advanced malignancies. When these symptoms do not respond to chemotherapy, hormone therapy or mild analgesics, and the disease becomes too widespread for local radiotherapy, there is a need for a palliative treatment which should be easily tolerated, systemic and have a long-lasting effect. Radiotherapists give 8 Gy by external beam to the hemi or total body with success: around 80% of patients respond. However, all other tissues in the body receive a similar radiation dose, which may cause considerable side effects, particularly gastrointestinal and hematopoietic. Radionuclide therapy is less invasive, better tolerated and produces a similar response, limiting the radiation dose to the site of the metastases and sparing the normal tissues.

Table 6 summarizes the major physical and clinical characteristics of four available β-emitters for bone therapy: ^{32}P, ^{89}Sr, ^{186}Re and ^{153}Sm. In addition [^{85}Sr]chloride,[135] radioiodinated diphosphonates[136] and [^{90}Y]citrate[137] have been used. ^{32}P and ^{89}Sr have a relatively long half-life (14.3 and 50.5 days, respectively), ^{186}Re and ^{153}Sm have a shorter half-life and the advantage of emitting suitable gamma-rays allowing gamma-camera imaging and dosimetry. However, it is possible to obtain an image of the Bremssrahlung of ^{89}Sr and ^{32}P (Figure 6) to demonstrate that the therapy is actually reaching the target.

Reported results so far indicate response rates similar to radiotherapy and minimal side effects, except for ^{32}P which, due to the incorporation into the metabolic pathways of bone marrow cells, may cause significant bone marrow depression, which limits its applicability for the purpose of palliation. The principal clinical experience with individual bone-seeking agents is reviewed here.

Radioactive phosphorus

Although ^{32}P has been available in several chemical forms for palliation of bone pain since 1937, it has not been widely employed for this indication. To stimulate ^{32}P uptake in bone metastases, pretreatment (priming) with testosterone and parathormone has been advocated. Cheung and Driedger[138] observed substantial palliation of brief duration in 17 of 33 (51.5%) patients with metastatic breast carcinoma and in 14 of 15 (93%) patients with bone metastases from prostate cancer, using 7–10 daily doses of 55.5–111 MBq (1.5–3 mCi) of ^{32}P up

Table 6. Radionuclide bone therapy: physical properties and clinical considerations of four major radiopharmaceuticals

	^{32}P	^{89}Sr	^{186}Re	^{153}Sm
Physical half-life (days)	14.3	50.5	3.77	1.95
$E_{\beta,max}$ in MeV	1.71	1.49	1.08	0.81
Maximal range (mm)	8.7	8	5	3
E_γ in keV	—	—	137	103
Imaging	Bremsstrahlung	Bremsstrahlung	Yes	Yes
Isolation	—	—	Yes	Yes
Administered dose	0.33–0.66 GBq	1.5–2.0 MBq/kg	0.9–1.3 GBq	10–37 MBq/kg
Chemical form	Phosphate	Chloride	HEDP	EDTMP
Response rate (%)	65–74	79	79	65–80
Side effects	Significant	Minimal	Minimal	Minimal
Advantage	—	Out-patient	Imaging + dosimetry	Imaging + dosimetry
Disadvantage	Bone marrow dose	Cost	Cost, availability	Availability

to a total of 333–666 MBq (9–18 mCi). Comparing different priming regimens of androgen and parathormone (non-randomized), they observed no significant difference in the overall response, but expressed a preference for parathormone over androgen, because of the initial exacerbation of bone pain by androgens and the potential danger of hormonal stimulation of the malignancy. Myelosuppression occurred in 16 patients (33.3%) and symptomatic hypercalcemia in four. Roberts,[139] using seven daily doses of 55.5 MBq (1.5 mCi) [^{32}P]sodium phosphate together with testosteron priming and adjuvant chemotherapy, observed good results in 34 of 46 (73.9%) patients with metastatic breast or prostate carcinoma. The onset of response was only after 2–4 weeks. Ten patients required transfusions because of myelosuppression.

[^{89}Sr]Chloride

Greater numbers of patients have been treated with [^{89}Sr]chloride for painful bone metastases. Like ^{32}P, ^{89}Sr is a pure β-emitter, which may have the advantage of out-patient use, dependent on local legislation. Despite the lack of gammas it is possible to get a qualitative dosimetric assessment by the combination of quantitative [^{99m}Tc]MDP bone scintigraphy with ^{89}Sr Bremsstrahlung images, to study the early pharmacokinetics with the gamma-emitter ^{87m}Sr (physical half-life of 2.5 h), and to perform dosimetry by adding ^{85}Sr to the therapy for external counting and imaging. Using the latter technique in 10 patients treated with ^{89}Sr for disseminated prostatic carcinoma, Blake *et al.*[140] found the mean absorbed radiation to vertebral metastases to be 23 cGy/MBq (850 rads/mCi) with a range from 6 to 61 cGy/MBq (220 to 2260 rads/mCi). Essentially the same ^{85}Sr concentration at tumor sites for about 100 days was observed, whereas the concentration in normal bone gradually decreased, according to the ICRP-10 model.[141]

Firusian and Schmidt[142] reported palliation of bone pain in 34 of 43 (79%) patients with skeletal metastases from various primary tumors occurring 1–13 days after single injection of 37–74 MBq (1–2 mCi), with a duration ranging from 4 to 32 weeks. Only two cases of thrombocytopenia after therapy were observed.

Kloiber *et al.*[143] and Silberstein and Williams[144] showed a lower response rate, with 27 of 48 patients not responding to ^{89}Sr therapy and advocated double-blind studies to establish the role of a placebo effect. There are two conflicting examples of such studies. Correns *et al.*,[145] comparing [^{89}Sr]chloride with physiologic saline as placebo in 24 patients, found more pain relief in the placebo group together with a longer survival in the ^{89}Sr group. The fact that thrombocytopenia also occurred in the placebo group demonstrates that hematological complications in these patients are not necessarily due to ^{89}Sr radiotoxicity. In contrast, a UK multicenter randomized double-blind trial of [^{89}Sr]chloride vs 'cold' strontium-chloride as the placebo in 33 patients with prostatic carcinoma demonstrated a clear advantage of ^{89}Sr over placebo in the relief of pain.[146]

Robinson *et al.*[147,148] have treated around 400 patients with ^{89}Sr to palliate bone pain with an overall response of 79%; the best results were in patients with carcinoma of the prostate and breast (response rates 80 and 89%, respectively). A decrease in pain level was generally observed after 2–3 weeks, and the toxicity was mild: 80% of the patients had a mean 15–20% decrease in platelet and leukocyte counts.

A UK multicenter study of ^{89}Sr therapy in 117 patients with painful metastases from prostatic carcinoma similarly showed a 79% response rate, broken down into dramatic improvement (24%), substantial improvement (32%) and some improvement (23%). After a transient exacerbation of pain in the first 48 h in some patients, the onset of pain relief generally occurred 10–20 days after administration of ^{89}Sr. The mean duration of response was 6 months and an average of 30% reduction of platelet counts, maximally at 6 weeks, was observed: 1.5–2.0 MBq/kg (in practice 111–148 MBq or 3–4 mCi) was considered to be the optimal dose.[149]

[^{186}Re(Sn)]HEDP

Both ^{186}Re and ^{153}Sm have much shorter physical half-lifes (3.8 and 1.95 days, respectively) and are reactor produced by neutron irradiation of enriched ^{185}Re and ^{152}Sm at relatively low cost.[150] As the chemistry of rhenium and technetium are similar, because of their position in the periodic table, it has been possible to label hydroxyethilidenediphosphonate (HEDP) to ^{186}Re after reduction to perrhenate by stannous ions.

In a biodistribution study in five patients with skeletal metastases, Maxon *et al.*,[151] using subtherapeutic doses up to 185 MBq (5 mCi) of [^{186}Re(Sn)]HEDP, found an excellent correlation

between [^{186}Re(Sn)]HEDP and [^{99m}Tc]MDP images (89% of 173 lesions shown by both techniques). Extrapolating the dosimetric measurements of their diagnostic studies, they calculated that for the palliation of skeletal metastases 0.9–1.3 GBq (25–35 mCi) would deliver 10–140 Gy (1000–14 000 rads) doses to the metastases, while the dose to the bone marrow would be kept down to 0.75 Gy (75 rads). At the 1990 meeting of the European Association of Nuclear Medicine, Schroder and Maxon presented the clinical results in the initial 36 patients (26 with prostatic carcinoma) treated with [^{186}Re(Sn)]HEDP, measuring the effectiveness by quality of life parameters such as the pain index and the analgesics index. Seventy-nine per cent of the patients experienced a significant reduction in pain and 17% were completely relieved. The onset of the response was sooner than with the previous two radionuclides, i.e. within 1 week in 80% of the responders. This can be explained by the higher dose rate in the first days, due to the short half-life. No major side effects were observed: five patients had a transient pain flare reaction and there was a minimal reduction in the platelet and leukocyte counts after 3 weeks.

[^{153}Sm]EDTMP

Ethylenediaminetetramethylenephosphonate (EDTMP) is a chelate, which can be labeled with ^{153}Sm with great *in vitro* stability, preferentially localizes in bone metastases and is rapidly cleared from the blood by the kidneys. In a pharmacokinetic study of [^{153}Sm]EDTMP in five patients with skeletal metastases, Singh *et al.*[152] found an excellent correlation of the lesion-to-normal bone and lesion-to-soft-tissue ratios for [^{153}Sm]EDTMP and [^{99m}Tc]HDP.

In a phase I study of [^{153}Sm]EDTMP therapy in 35 patients with painful bone metastases Turner *et al.*,[153] using a dose schedule which aimed for escalating doses to the bone marrow ranging from 100 to 280 cGy as calculated by [^{153}Sm]EDTMP tracer studies, administered doses of 10–31 MBq/kg (0.28–0.84 mCi/kg). Within 2 weeks pain relief was obtained in 22 of 34 evaluable patients (65%), five of whom were completely relieved. The duration of response varied from 4 to 35 weeks and after the recurrence of pain five of nine patients responded to retreatment. The hematological toxicity was found to increase when the absorbed bone marrow dose exceeded 200 cGy, but palliation could be achieved with lower, less toxic doses. Higher doses were used in veterinary nuclear medicine by Lattimer *et al.*,[154] who treated 40 dogs with primary and metastatic bone tumors with one or two doses of 37 MBq/kg (1 mCi/kg) and showed that therapy of bone tumors with curative intent is feasible. Seven dogs attained complete remission of disease with a mean survival of 26.9 months. Twenty-five dogs had a partial response with a mean survival of 5.2 months, whereas eight non-responders died within 2–4 weeks. Although there was significant hematological toxicity, no complications occurred.

Radiolabeled cells

In lymphoid cell malignancies the tumor cells (lymphocytes) may retain their ability to migrate and recirculate into the lymphoreticular tissues (spleen, liver, bone marrow and lymph nodes). After harvesting, labeling and re-injection, these cells may carry and deliver the radiation to the lymphoreticular system where the tumor cells reside. Cobb and Butler[155] studied the effects of ^{114m}In-labeled lymphoma A31 cells after re-injection into B-cell lymphoma (A31) bearing mice. ^{114m}In decays to ^{114}In with a physical half-life of 50 days, predominantly emitting β-particles with a maximal β-energy of 1.988 MeV. A significant prolongation of survival was observed after the administration of 370 kBq amounts of [^{114m}In]A31 cells, in contrast to the use of lower doses, [^{114m}In]oxine, total body irradiation or no treatment at all. Only splenectomy also increased survival, an indication that the beneficial effects of [^{114m}In]A31 cells were due to the cumulative radiation dose to the spleen, which was calculated to amount to 167 Gy.

In a pharmacokinetic and dosimetric study of ^{114m}In-labeled autologous lymphocytes in seven patients with active non-Hodgkin's lymphoma, Hamilton *et al.*[156] demonstrated that these cells are rapidly cleared from the blood, preferentially localizing in the spleen and, to a lesser extent, in the liver and bone marrow ($<5\%$). As the excretion of activity from these tissues is slow and the ^{114m}In half-life relatively long, it was concluded that, by delivering a significant radiation dose to the spleen and the recirculating lymphocyte population, higher doses of ^{114m}In-labeled lymphocytes have a potential therapeutic role in the management of lymphoma and clinical studies are underway.

Intra-arterial therapy

An attractive mode of targeting radiopharmaceuticals at tumors which are localized or regional is via the intra-arterial route using formulations which preferentially lodge in arterioles and capillaries of the tumor. The basis of such therapy lies in the fact that tumors are usually rich in vasculature and that liver metastases for instance are almost exclusively dependent on arterial blood supply in contrast to the normal liver which receives most of its flow from the portal vein.

The observation that oil contrast material was selectively retained in tumor vessels, as well as in the tumor cells, led to the use of [^{131}I]lipiodol or -ethiodol in liver tumors.

Although initially treatment of liver tumors with ^{32}P and ^{90}Y absorbed on ceramic or resin microspheres had achieved objective responses and prolongation of survival, serious complications were encountered: leaching of the radionuclide from the carrier led to myelosuppression, arteriovenous shunting led to pulmonary embolization and radiation fibrosis, and gastrointestinal complications occurred because of passage of microspheres into the gastroduodenal vessels.

Several improvements have been realized since. A major breakthrough, to overcome the problem of leaching of activity, was the production of glass microspheres into which stable ^{31}P or ^{89}Y has been incorporated, to be activated to ^{32}P and ^{90}Y by subsequent neutron bombardment.[157] Modern arteriographic techniques, using balloon catheters and embolic coils enable a more precise delivery of particles in the target tissue, and 3-dimensional imaging techniques, such as CT and MRI, allow a more accurate dosimetric assessment. Hepatic artery scintigraphy using [^{90m}Tc]MAA (Figure 7) has become an essential aid to verify the correct positioning of the arterial catheter, to quantify the arteriovenous shunting to the lungs and to assess tumor-to-normal-liver ratios just prior to radioactive particle therapy.[158] The selectivity of intra-arterial radioactivity to the tumor may even be increased by the use of vasoactive drugs, such as epinephrine and norepinephrine, which cause vasoconstriction of the normal liver arterioles, but to which tumor vessels, lacking smooth muscle, are insensitive.[159] Some of the more recent experience with intra-arterial radionuclide therapy is reviewed here.

[^{131}I]Lipiodol

Park *et al.*[160] treated 47 patients with hepatocellular carcinoma with [^{131}I]lipiodol with or without embolization by polyvinyl sponge (Ivalon). Dependent on the tumor size, 2–20 ml of lipiodol

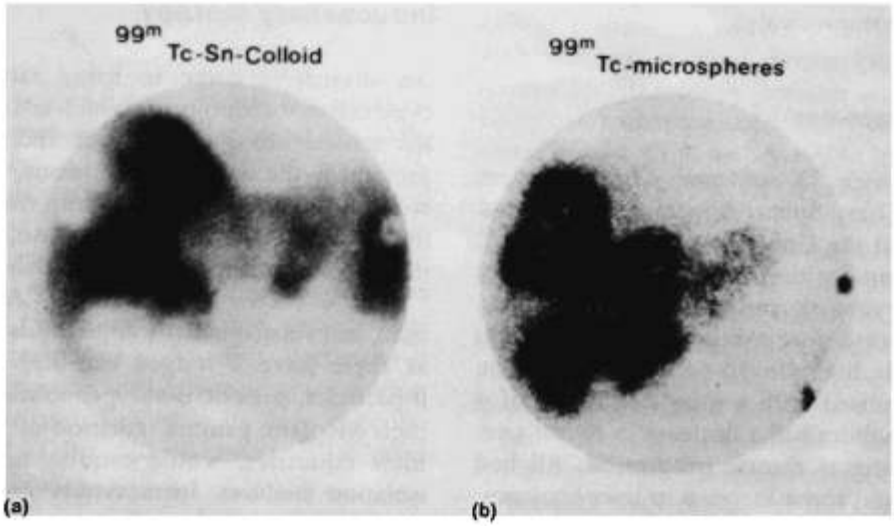

Figure 7. Liver metastases demonstrated as defects on the liver scintigram after intravenous administration of [^{99m}Tc]colloid (a) and as hot spots after the administration of [^{99m}Tc]microspheres into the hepatic artery (b). The scintigram confirms the selectivity of the targeting mechanism, the correct positioning of the catheter and the absence of shunting to the lungs.

labeled with 74 MBq–4.44 GBq (2–120 mCi) of ^{131}I was administered via the hepatic artery to deliver a 100 Gy radiation dose. The mean tumor-to-non-tumor ratio was 20:1 and the mean effective half-life 6 days. Shrinkage of solitary lesions and palliation were achieved and there were no pulmonary complications. In a more recent evaluation of the more than 100 patients treated from 1986 to 1990[161] the authors concluded that the smaller the vascular tumor the better the response was, that large tumors (>4.5 cm) were treated more effectively by a combination of [^{131}I]lipiodol and intra-arterial chemotherapy, embolization or hyperthermia. The side effects of this treatment included transient fever, nausea, vomiting, pain in the upper abdomen and elevation of liver function tests.

After a phase I study in 15 patients with liver cell carcinoma and eight with liver metastases[162] a multicenter phase II study was carried out in France.[163] Fifty patients with hepatocellular carcinoma received 1.5–2.5 GBq [^{131}I]lipiodol intra-arterially. The efficacy was assessed by the tumor size (CT), the alpha-foetoprotein (AFP) serum level and the survival. The mean absorbed radiation doses to the tumor were 62.4 ± 54 Gy, to the normal liver 5.5 ± 8.7 Gy and 2.9 ± 2.2 Gy to the lungs. No complete remissions were reported, but in 26 patients there was a reduction in tumor size (more than 50% in 16), in 16 patients the AFP serum levels decreased (more than 50% in 14), and eight of 11 patients with pain were relieved of this symptom. The survival at 6, 12 and 24 months was 60, 31 and 23%, respectively.

[^{90}Y]Glass microspheres

Several studies with ^{90}Y-activated 20–30 μm glass microspheres (Thera Spheres) have been reported from Canada and the United States. Herba *et al.*[164] treated 14 patients with hepatic metastases from gastrointestinal tumors and one with hepatoma aiming at escalating dose levels of 50, 75 and 100 Gy to the whole liver. In 10 patients the hepatic disease was stabilized with a mean follow-up of 4 months, one of whom had a decrease in tumor size. In five other patients disease progressed. All had transient fever and some increase in liver enzymes, in three patients antral and pyloric ulceration and duodenitis occurred, but there was no hematological toxicity. Shapiro *et al.*[165] reported objective tumor responses in 21 patients with liver metastases treated with the same microspheres at various dose levels starting at 50 Gy to the liver with 25 Gy increments: three patients attained a partial remission, six had a minor response, one a mixed response and stabilization of disease occurred in eight. Three patients had progression of disease. Fever occurred in five, elevation of liver enzymes in some and gastrointestinal symptoms in four patients. As in the previous study there was no pulmonary and hematological toxicity. Houle *et al.*[166] evaluated the therapeutic potential of [^{90}Y]glass microspheres in 16 patients with hepatocellular carcinoma. Six patients had to be excluded from treatment because of significant shunting to the lungs, and in the 10 patients who did receive 1.5–6.3 GBq (40–170 mCi) doses no objective response other than tumor growth arrest in two patients and no toxicity, except gastric ulceration in one patient, were observed.

[^{90}Y]Resin particles

Roesler *et al.*[167] reported preliminary results of superselective tumor embolization 80 μm [^{90}Y]resin particles in 15 patients with liver and bone tumors. After selection by [^{99m}Tc]MAA and due to meticulous catheter technique tumor shrinkage in association with doses exceeding 200 Gy was observed in several patients without serious complications.

Intracavitary therapy

An alternative route to bring radioactivity into close contact with tumors which are spread out over the serosal linings of cavities and to tumor cells present in the malignant effusions, is to inject the radiopharmaceutical directly into these cavities. For this purpose colloids, chelates and, more recently, monoclonal antibodies are used, labeled with either ^{198}Au, ^{32}P ^{90}Y or ^{131}I. Initially [^{198}Au]colloids were used, but subsequently [^{32}P]colloids were preferred, as these have a longer half-life, more energetic β-particles, greater tissue penetration and lack the high energetic gamma radiation of ^{198}Au, which, in most countries, would require hospitalization in isolation facilities. Intracavitary radionuclide therapy can be applied to the pleural, pericardial and peritoneal cavities, intrathecally into the cerebrospinal fluid, and into cystic tumors. In addition, intra-articular injection of a variety of radionuclides is practised in rheumatology. Examples of each of these applications are reviewed.

Intrapleural therapy

After administration into the pleural cavity by thoracentesis (usually in the seventh interspace in the posterior axillary line), radiocolloids have been used effectively to control malignant pleural effusion in 50–74% of the cases,[168] successful control meaning a complete or significant reduction of the production of pleural fluid. The therapy is generally considered not to have an effect on the survival of metastatic carcinomas and should be regarded as palliative. An indication for intrapleural therapy with more than palliative intent may be the primary pleural malignancy, mesothelioma.[169]

Jackson and Blosser[170] described intracavitary [^{32}P]colloid therapy in 289 patients with pleural and/or peritoneal metastases from a variety of primary tumors. Of these patients, 115 received 370 MBq (10 mCi) ^{32}P injections into the pleural cavity: in patients who survived 3 months this therapy had been successful in 75%, but as most of the patients did not survive that period the overall response rate at 3 months was only 28%. Better initial results are reported by Pectasides *et al.*,[171] using higher doses of ^{131}I-labeled tumor-associated monoclonal antibodies HMFG1, HMFG2 and AUA1. From their dosimetric assessment it was apparent that intrapleural instillation of 2.2 GBq (60 mCi) of radiolabeled antibodies could safely achieve radiation doses in the order of 100 Gy to the pleura.

Intrapericardial therapy

Few series of patients with pericardial effusions treated by intrapericardial instillation of 185 MBq (5 mCi) of [^{32}P]colloid in saline solution, following pericardiocentesis, have been reported. Martini *et al.*[172] and Firusian[173] reported a 71–91% success rate in 39 patients with a mean survival of 6 months. No early side effects were recorded, but the repeated intrapericardial ^{32}P therapy in one patient was complicated by restrictive pericarditis. Pectasides *et al.*[171] described effective antibody-guided irradiation of malignant pericardial effusion in three patients, using 0.74–1.11 GBq (20–30 mCi) ^{131}I-labeled monoclonal antibodies.

Intraperitoneal therapy

The use of intraperitoneal radioactive colloids has been described for the therapy of malignant peritoneal effusions as well as for adjuvant therapy of ovarian carcinoma either immediately following first surgery or after second-look laparotomy revealing no or minimal residual disease. Studying the distribution of intraperitoneal colloidal [^{32}P]-chromic phosphate bolus injections by sequential scintigraphy using the Bremsstrahlung in 24 patients with ovarian or endometrial cancer, Kaplan *et al.*[174] found long persisting focal accumulations of the radionuclide and advocated that alternative methods of administration be developed to achieve a more uniform distribution of the therapy. Sullivan *et al.*[175] demonstrated that large volume infusions as well as frequent changes in the patient's position contribute to accomplish this. Provided a uniform distribution over the serosal surface is obtained, Boye *et al.*[176] estimated the dose to the peritoneum at 30 Gy per 370 MBq (10 mCi) of [^{32}P]colloid.

Jackson and Blosser[170] treated 178 patients with malignant peritoneal effusions by two bolus injections of 370 MBq (10 mCi) of [^{32}P]chromic phosphate colloidal suspension and obtained improvement in 85% of the patients who were evaluable at 3 months, with an overall response rate of 41%.

Varia *et al.*[177] used intraperitoneal ^{32}P as adjuvant therapy after second-look laparotomy in patients who were in a clinical complete remission of ovarian carcinoma. 555 MBq (15 mCi) of ^{32}P divided in two doses, each mixed with 500 cc saline solution, was instilled. In 43 patients with no evidence of disease the 4-year survival was 89 vs 67% in patients not treated with ^{32}P. Of 29 patients with minimal residual disease (<2 cm) 17 were treated by ^{32}P with or without chemotherapy and 12 by chemotherapy only. The 4-year survival rates were 59 and 22%, respectively. It was concluded that intraperitoneal ^{32}P therapy contributes to controlling occult abdominal disease, which may be present in spite of a negative second-look laparotomy, and that it may improve survival without causing essential toxicity. Complications of the combination of pelvic external beam irradiation prior to intraperitoneal ^{32}P have been reported, however.[178]

More recently intraperitoneal radioimmunotherapy using ^{131}I- or ^{90}Y-labeled monoclonal antibodies in patients with peritoneal metastases[120–123,128] has induced objective remissions (see section on radioimmunotherapy). Superiority of monoclonal antibodies over colloids is expected due to the greater selectivity in the deposition of the radiation dose, but remains to be proven by comparative studies.

Intrathecal therapy

Radioactive colloids have also been used for the treatment and prophylaxis of meningeal leukemia, as they are phagocytized in the arachnoid, the principal site of this manifestation of the disease. Sackmann Muriel *et al.*[179] maintained the successful induction treatment of 32 patients with meningeal leukemia by either intrathecal chemotherapy or intrathecal [^{32}P]chromic phosphate (111 MBq or 3 mCi) and observed no significant difference in the duration of remission, but fewer and less serious side effects in the ^{32}P group. Metz *et al.*[180] successfully used [^{198}Au]colloid plus methotrexate instead of telecobalt irradiation of the neurocranium for the prophylaxis of meningeal leukemia in 73 children in remission of acute lymphocytic leukemia. Dosimetric assessment in prophylactic intrathecal [^{198}Au]colloid therapy in 77 children by Döge and Hliscs[187] showed that 400 MBq (1.1 mCi) of this radiopharmaceutical can deliver an absorbed radiation dose of 18 Gy to the cerebral meninges. The dose to the spinal meninges was found to be four times higher, with the cauda equina as the critical region. Therapy of tumors metastatic to the leptomeninges by intrathecal administration of radiolabeled monoclonal antibodies was described by Lashford *et al.*[129]

Intracystic therapy

Some intracranial tumors are partly or totally cystic and as neurosurgery of these lesions may be hazardous, intracystic instillation of colloidal β-emitting radionuclides via stereotaxis or indwelling catheter may be a safer alternative for the control of tumor and cyst recurrence. Examples of this form of treatment are the use of [^{32}P]colloid in cystic grade IV astrocytoma[182] and the use of [^{90}Y]colloid[183] and [^{186}Re]sulphur colloid[184] in craniopharyngioma. The latter group reported on the satisfactory use of this procedure in 41 patients, who, after a tracer study had confirmed the absence of leakage from the cyst, received a dose of 0.7–1.8 GBq dependent on the cyst volume and retention time.

Conclusion

The present clinical use of nearly 50 radiopharmaceuticals for tumor therapy by multiple targeting mechanisms, discussed in this review, indicates that therapeutic nuclear medicine in 1991 is very much alive and in full development.

Taking into account that for most indications radionuclide therapy still finds itself in a last position among other treatment modalities, the response reported to date can certainly be considered as promising. By moving radionuclide therapy forward in treatment protocols, as is now being explored in neuroblastoma, the efficacy of this modality in view of the overall management of oncological disease can be optimized, appreciating that the invasiveness and toxicity compare favorably with that of chemotherapy, immunotherapy and external beam radiotherapy.

Many aspects need to be studied. The mechanisms of uptake and retention, the dose scheduling as well as pharmacological intervention to enhance the radiation dose delivered to the tumor and to minimize toxicity to non-target tissues are being further investigated. Dosimetry requires more attention to allow a better assessment of the tumor dose and to account for the exposure of the normal tissues and the environment. Animal model studies, microdosimetry using intratumoral thermoluminescence measurements and autoradiography, as well as pharmacokinetic computer modeling may all be helpful in this respect. Many more pathways into the tumor cell are to be explored and more agents will be identified to selectively target radioactivity. For some of these agents high-LET labels, such as ^{125}I, ^{90}Y and ^{211}At, may increase the radiotoxicity to these cells.

Lastly, nuclear medicine therapy requires a multidisciplinary approach and must be recognized as a separate specialty, quite different from radiotherapy and medical oncology. It should, however, not be in competition with any of the other modalities in finding its optimal place in the overall management of every individual indication. Successful therapeutic nuclear medicine requires responsible action of both specialists in designing and carrying out these treatments, of hospital directors and health authorities to create the proper environment for such treatment and of legislators to see to it that safety regulations on the one hand protect the environment but on the other ensure that treatment of cancer patients remains feasible.

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