Physical and Biological Targeting of Radiotherapy

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Acta Oncologica Suppl. 13, pp. 75–83, 1999

Targeting of radiotherapy can be based on improving physical dose distribution of radiation delivered or on utilization of specific biological processes for targeting. Tools for physical targeting include brachytherapy, hadron therapy, conformal radiotherapy, stereotactic radiotherapy, stereotactically guided conformal fractionated radiotherapy, and intensity-modulated radiotherapy. Biological targeting can be based on specific metabolic pathways such as uptake of iodine-131 by thyroid cancer cells, difference in substrate uptake between cancer cells and normal cells (e.g. boronophenylalanine in boron neutron capture therapy), targeting of radioactive isotopes by specific carrier molecules (radioimmunotherapy, labeled hormone derivatives or bone-seeking phosphonates), or on the distribution of elements in the body (therapy of bone metastases with a calcium analog strontium-89 or phosphorus-32).

Targeting of radiotherapy to cancer cells and avoiding irradiation of normal tissues plays a central role in improving the efficacy of radiotherapy. Approaches that aim at improving targeting of radiotherapy may be divided into physical and biological targeting methods (Table 1). Physical targeting typically requires precise imaging of the target and use of a fixation device during therapy, and it often results in a small target volume. Biological targeting, in turn, requires a systemically given radioactive agent or a non-radioactive compound that interacts with radiation, and the degree of targeting is critically dependent on the specificity of the metabolic process utilized rather than accurate localization of the target (Table 2).

Table 1

Examples of physical and biological methods for targeting radiotherapy

Physical Targeting
Brachytherapy
Conformal radiotherapy
Stereotactic radiotherapy
Stereotactically guided conformal radiotherapy
Intensity modulated radiotherapy
Hadron therapy
Biological Targeting
Radioactive iodine therapy of thyroid cancer
Boron neutron capture therapy (BNCT)
Bone-seeking isotope therapy of bone metastases
Radioimmunotherapy (RIT)
Radiolabeled hormone derivatives

PHYSICAL TARGETING METHODS

Brachytherapy

In brachytherapy physical targeting is achieved by placing the radioactive source directly into the tissue being treated (interstitial brachytherapy, e.g. with iridium-192 wires) or into a body cavity (intraluminal brachytherapy), or it is achieved by placing the source in direct contact with the tumor (e.g. contact therapy of uveal melanoma). These techniques have been used successfully in the treatment of many types of human cancer for decades.

Three-dimensional conformal radiation therapy

Three-dimensional conformal radiation therapy (3D-CRT) refers to a technique where the prescribed dose is given to a strictly defined target volume through portals that have been individually shaped to closely match the shape of the target volume in three dimensions. This results in exclusion of a maximum amount of normal tissue from the clinical target volume, which may allow dose escalation without an increase in acute or late toxicity. 3D-CRT requires an immobilization device, volumetric 3-dimensional planning computed tomography or another imaging method, and a 3-dimensional radiation treatment planning computer workstation. Shaping of the portals is usually done with a multileaf collimator. 3D-CRT has allowed dose escalation for example in the treatment of prostate cancer (G.E. Hanks, in this issue).

Table 2

Comparison of physical and biological targeting

Characteristic	Physical targeting	Biological targeting
Precise target volume imaging required	Yes	No
Target volume size	Often small and ingle	May be largeo
Fixation device	Often needed	Not needed
Systemically given agent needed	No	Yes
Specific metabolic process required	No	Yes

Stereotactic radiotherapy

Stereotactic radiotherapy can be given either as single fraction therapy ('radiosurgery') or as fractionated stereotactic radiotherapy. Single fraction therapy can be given either with the gamma knife or with a linac-based stereotactic apparatus, whereas fractionated stereotactic radiotherapy can be given with the linac-based stereotactic systems only. Stereotactic radiotherapy is now commonly given to intracranial targets that are no larger than a maximum of about 3 to 4 cm in diameter, but the linac-based stereotactic system can be successfully used also for small extracranial targets (1). In the gamma knife targeting is based on 201 ^{60}Co rods that are arranged hemispherically around the cranium in a helmet and carefully focused to the isocenter, whereas the linac-based system is based on multiple rotations of the gantry around the isocenter. Both methods require a firm head fixation device and allow the use of a planning target volume that is only 1–2 mm larger than the clinical target volume. More than one isocenter can be used in the treatment of non-spherical lesions.

Table 3

Treatment results of linac-based stereotactic radiotherapy

Arteriovenous malformation	Angiographic cure rate ~70%
Meningeoma	Local control rate 80%–90%
Acoustic schwannoma	Local control rate ~90%
Pituitary adenoma	Local control rate ~90%
Brain metastases	Local control rate 80%–90%
Malignant glioma	Experimental use only

The treatment results achieved with the linac-based radiotherapy systems do not appear to be inferior to those obtained with the gamma knife (Table 3). Only limited data are available on the long-term results of stereotactic radiotherapy of intracranial targets. In one recent study where acoustic neuromas of the eighth cranial nerve were treated with the gamma knife up to the median margin dose of 16 Gy, 62% of the neuromas shrank in size during a follow-up period of 10 years, 33% of the neuromas remained similar in size, and only 6% increased in size (2). Toxicity was acceptable. The function of the facial nerve did not deteriorate in 85% of the patients who had normal facial nerve function before radiosurgery, and 51% of the patients had no change in hearing. Moreover, the patients found the therapy to be highly acceptable; 95% of the patients would have recommended the same type of therapy to their family members for a similar disease, and only 2% would not. Even patients with an ominous prognosis, such as patients with melanoma brain metastases, can benefit from stereotactic radiotherapy. In one series consisting of 60 patients with brain metastases from malignant melanoma and treated with radiosurgery with the gamma

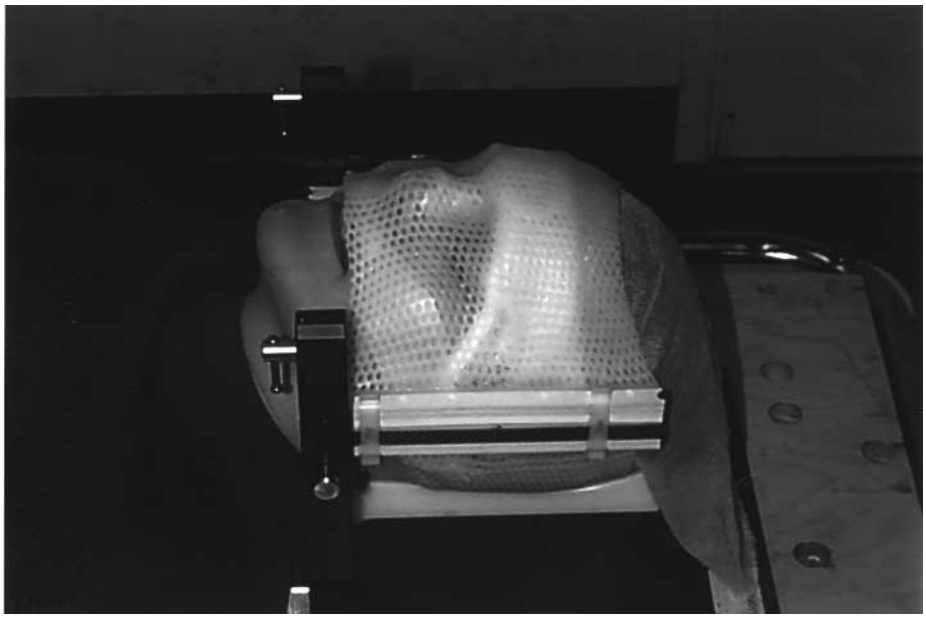

Fig. 1. A removable head mask used as suitable for fractionated stereotactic radiotherapy or stereotactically guided fractionated conformal radiotherapy (Department of Oncology, Helsinki University Central Hospital).

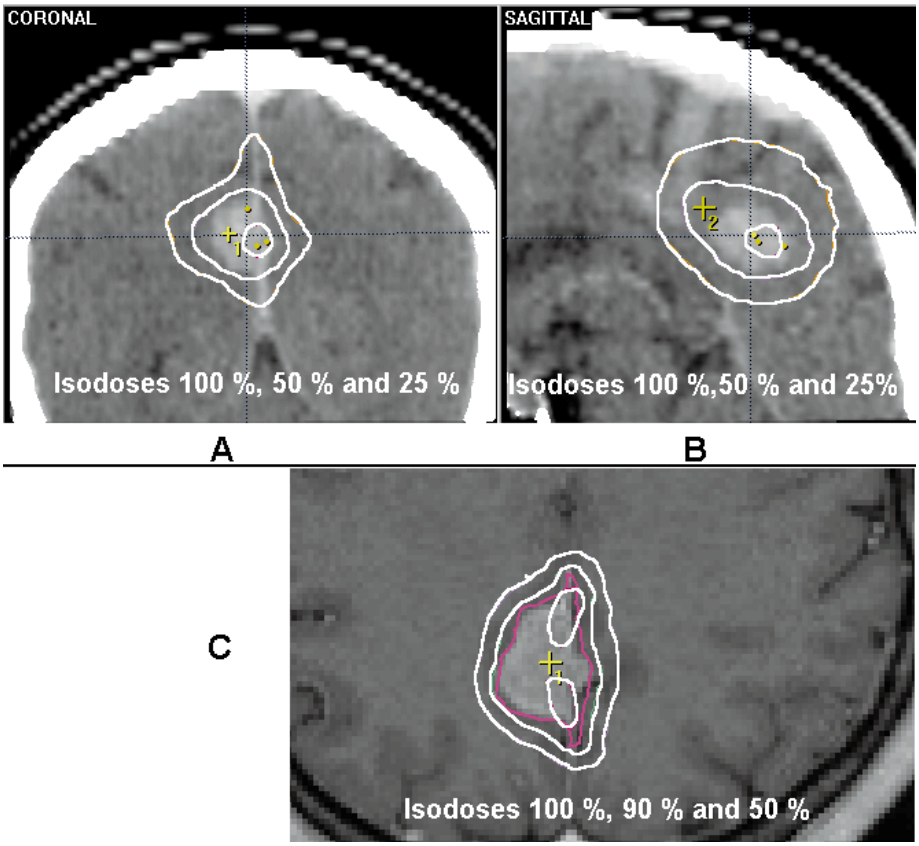

Fig. 2. A: A falx meningeoma treated with linac-based single fraction stereotactic radiotherapy (radiosurgery). The tumor was treated to the marginal dose of 15 Gy represented by the 50% isodose using 4 isocenters. B: A sagittal view. C: A falx meningeoma treated with stereotactically guided fractionated conformal radiotherapy. The 90% isodose representing the 2 Gy dose conforms to the shape of the tumor. Note the rapid dose fall-off outside the target lesion (Department of Oncology, Helsinki University Central Hospital).

knife and whole-brain irradiation, only 7% of patients died from of radiosurgically managed tumor, and a few patients without any active systemic disease survived for several years after therapy (3).

Stereotactically guided conformal fractionated radiotherapy

The linac-based stereotactic fixation and computer planning system can be used also for fractionated stereotactically guided conformal radiotherapy (SG-CRT). Unlike stereotactic radiotherapy, where the arched fields obtained by rotating the gantry are focused to one or more isocenters, SG-CRT uses fixed fields that are usually focused on one isocenter. Each of the fixed fields is individually shaped to conform to the shape of the target volume as in conventional conformal radiotherapy. If a relocatable fixation device is used, such as a head mask (Fig. 1) or the Gill-Thomas-Cosman teeth fixation device, conventionally fractionated therapy (2 Gy/day, 5 fractions a week) can be given to intracranial targets for several weeks. Because conformally shaped portals, small treatment volumes and fractionation are used, the technique allows maximal sparing of the surrounding brain tissue, and it is likely to be associated with a low frequency of acute and late complications.

The target volume may be larger in SG-CRT than in stereotactic radiotherapy without markedly increasing the risk of complications, because fractionation is used. Hence, the technique can be used to treat benign intracranial lesions and small gliomas. The portals may be shaped

Table 4

Comparison of linac-based stereotactic radiotherapy and stereotactically guided conformal radiotherapy (SG-CRT)

Feature	Stereotactic radiotherapy	SG-CRT
3D-stereotactic dose planning	Yes	Yes
Gantry rotation during irradiation	Yes	No
Incoming beam shape	Circular	Conformally shaped
No. of isocenters used	Usually 1 to 4	Usually one
No. of fractions	Usually 1 or 2	Usually 20–30
Overall treatment time	Often one fraction	A few weeks
Maximum lesion diameter	3–4 cm	6–8 cm

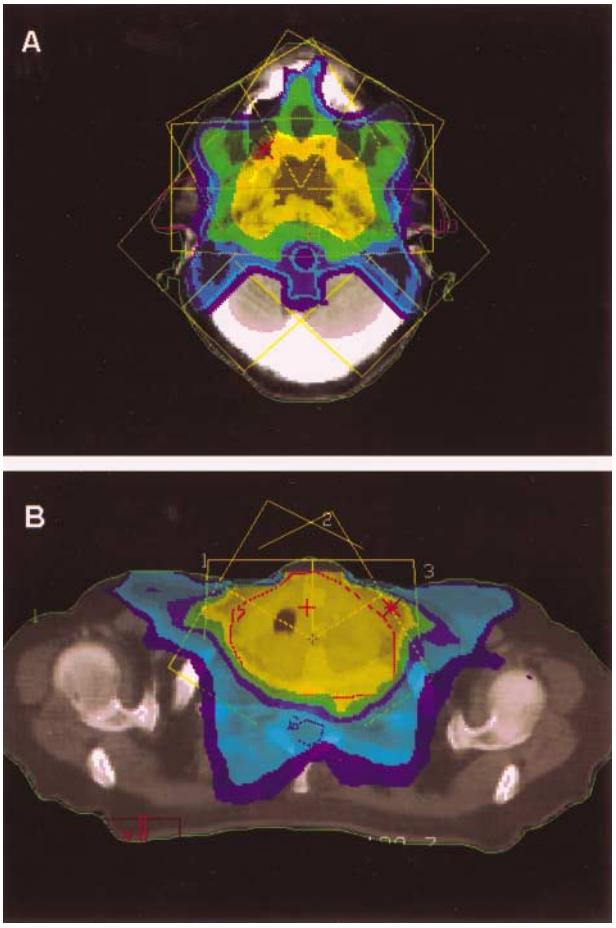

Fig. 3. A: Dose distribution obtained by 6-field intensity-modulated radiotherapy in treatment of nasopharyngeal cancer. Note the concave dose distribution sparing the medulla. B: Three-field intensity modulated radiotherapy in the treatment of thyroid cancer. Yellow, > 90%; green, > 70%; blue, < 50% of the isocenter dose (Department of Oncology, Helsinki University Central Hospital).

with low melting alloy blocks or with a microleaf collimator. Examples of a falx meningeoma treated by stereotactic radiosurgery or by SG-CRT are shown in Fig. 2. Stereotactic radiotherapy and SG-CRT are compared in Table 4.

Intensity-modulated radiotherapy

Intensity-modulated radiotherapy is a novel type of radiotherapy, in which the intensity of the beam is modified in a planned manner during radiotherapy. It involves optimum assignment of non-uniform intensities or weights to tiny subdivisions of beams. In practice, this can be achieved, for example, by using a multileaf collimator run in the dynamic mode, which means that the leaves of the multileaf collimator are moved individually in a planned manner while irradiation is ongoing. This provides an opportunity to produce complex dose distributions at the target volume.

Intensity-modulated radiotherapy requires a powerful computer program for dose planning. It may use so-called inverse dose planning, where, in the first phase, the designed dose constraints in the target and in the critical organs are defined. Mathematical optimization is used in solving such parameters for the incoming beam subdivisions that will reproduce the required dose distribution. This procedure is the opposite of conventional dose planning, where parameters are first set for the beams followed by computing their effect on the dose distribution at the target. Typically, 3 to 5 portals are used in intensity-modulated radiation therapy. As conformal radiation therapy, the technique can allow for improved sparing of the normal tissues and dose escalation. One of the practical advantages of intensity-modulated radiation therapy as compared with conformal radiotherapy is that concave dose distributions can be produced by intensity modulation of the beams. For example, concave dose distributions can be of benefit when avoiding irradiation of the rectum in the treatment of prostate cancer, or in decreasing the dose to the parotid glands in head and neck cancer therapy (Fig. 3).

Hadron therapy

Hadrons used in radiotherapy include protons, neutrons, pi-mesons and heavy ions such as helium, carbon and oxygen ions. Targeting with hadrons is based on their different dose distribution in tissue as compared with photons and electrons. Protons have a well-defined range in tissue, and their depth dose-distribution curve is superior to that of photons. They show maximum dose deposition at the end of their track (the Bragg peak) and a steep dose fall-off thereafter. The location of the Bragg peak in tissue depends on the energy of the proton beam and on the composition of the tissue, and therefore its depth from the skin can be varied by either varying the energy of the beam or by modulating the beam by using absorbers. By these means many Bragg peaks can be superimposed, which allows high-dose irradiation of the target tissue without exceeding the tolerance of the surrounding tissues.

Impressive local control rates of 96% have been described when uveal melanomas have been treated with proton therapy, and local control rates of about 80% and 50% have been reported for skull base chondrosarcomas and chordomas, respectively (4). Neutron therapy may be superior to photon therapy in achieving local control in the treatment of salivary gland cancers, inoperable sarcomas and locally advanced prostate cancer (5). However, so far the high start-up costs involved in building hadron therapy centers have limited the clinical availability of hadron therapy, and targeting of radiotherapy by means of hadrons is currently an option that is open to only a few cancer patients.

BIOLOGICAL TARGETING METHODS

An example of biological targeting of radiation therapy is the treatment of thyroid cancer with radioactive iodine. The thyroid gland, as well as papillary and follicular thyroid cancers, accumulate iodine since it is needed for the synthesis of thyroxine. Because accumulation of iodine to the thyroid remnant after thyroidectomy or to well-differentiated thyroid cancer after thyroid ablation is fairly specific, no physical targeting is required for successful therapy, and ^{131}I can be given systemically relying entirely on biological targeting. Unfortunately, similar simple and effective biological targeting is not yet available for other human cancers.

Boron neutron capture therapy

Boron neutron capture therapy (BNCT) is another example of biological targeting of radiation therapy in the treatment of cancer. The therapy is based on the nuclear reaction between boron-10 (^{10}B) and low-energy (< 0.4 eV) thermal neutrons, or epithermal neutrons (0.4 eV–10 keV), which become thermalized in tissues. The reaction produces densely ionizing lithium and helium ions, and gamma radiation:

$$n + 10B \rightarrow 7Li + 4He + \gamma \quad [1]$$

The resulting Li nucleus and α particle have a short range in tissue (5 and 9 μm, respectively, (6)), and when they are produced close to or within the cancer cell nucleus they are likely to cause as high LET particles intense ionization within the nucleus. The success of BNC therapy depends on cancer cell selective uptake of boron carrier molecules, which are needed in targeting ^{10}B to cancer cells and to produce a therapeutic window.

L-boronophenylalanine (BPA) and sulfhydryl borane (BSH) are the most commonly used boron carrier molecules in BNCT. BPA is transported across the blood–brain barrier into the normal brain, and tumor uptake of BPA is related to an elevated rate of amino acid transport at the tumor cell membrane, whereas BSH does not cross an intact blood–brain barrier in the normal brain. Passive diffusion from blood through an incomplete blood–brain barrier appears to be the primary mode of accumulation of BSH (6). The concentration of BPA in glioma is 2 to 4 times higher than in the normal brain or in the blood. It is very soluble as a fructose complex, and its toxicity is low when given 200–400 mg/kg as an i.v. infusion over about 2 h. Typically, irradiation starts about one hour after the BPA infusion has ended and after the blood BPA concentration is first determined.

Only a part of the total dose delivered to the target tissue in BNCT is derived from the reaction between thermic neutrons and ^{10}B (referred to as the boron neutron capture absorbed dose, D_B). Gamma ray absorbed dose (D_g) is generated by the γ radiation present in the primary beam, and γ radiation also results from the neutron capture reaction in tissue

$$n + 1H \rightarrow 2H + \gamma \quad [2]$$

Nitrogen neutron capture absorbed dose (D_N) is delivered by the secondary protons resulting from nitrogen capture

$$n + 14N \rightarrow 14C + p \quad [3]$$

and neutron absorbed dose (D_n) is produced by the thermal, epithermal and fast neutrons and their secondary generated particles. The total dose in the target tissue is obtained by adding up all four components

$$DT = D_B + D_\gamma + D_N + D_n \quad [4]$$

When calculating the biological dose one has to take into account that the biological effects of the different dose components are not equal, and the physical radiation doses need to be corrected using appropriate weighting factors in order to arrive at the biological dose. The biological dose is often expressed as weighted units, Gy (W), to differentiate the biological dose from the physical dose (expressed in Gy). For example, in the Finnish BNCT beam located at Otaniemi, Espoo, about 50% of the weighted dose is derived from the boron reaction, 30% from gamma irradiation, 15% from the nitrogen capture reaction, and 5% from fast neutrons (T. Seppälä, personal communication).

Mostly malignant gliomas and melanomas have been treated with BNCT so far. At present, it is not known whether BNC therapy is superior to conventional radiation therapy, but high single fraction tumor doses of 20 to 50 Gy (W) can be delivered to gliomas using the technique while keeping the average whole brain dose lower than 10 Gy (W). However, malignant gliomas are often heterogeneous and may contain cells that may not accumulate boron, and the presence of ^{10}B in the blood or in the interstitial fluid next to the endothelial cells might lead to endothelial cell damage. The clinical value of BNC therapy is currently being evaluated in early clinical trials.

Bone-seeking isotope therapy of bone metastases

Bone-seeking radioactive isotopes or radiopharmaceuticals can be used to target radiotherapy to bone metastases or to primary bone neoplasms (7). Targeting may be based on accumulation of the isotope in bone, or it can be achieved by combining the radioactive isotope onto a phosphonate or another carrier molecule. Strontium-89 (^{89}Sr) is chemically similar to calcium, and it is quickly taken up into the bone mineral matrix. Once incorporated into the metastatic lesion, ^{89}Sr is not removed metabolically and remains deposited for as long as 100 days (8), whereas normal bone takes up only a fraction of the injected dose and retains it for a much shorter time. ^{89}Sr is usually given in doses of 100 to 370 MBq (3 to 10 mCi), but there may

be little benefit in using doses larger than 1.5 to 2 MBq/kg. The total absorbed dose to bone lesions has been estimated to range from 1.3 to 64 Gy (0.9–43 cGy/MBq) with a mean value of 18 Gy (12 cGy/MBq), whereas the dose in normal bone and bone marrow has been estimated to be only about one-tenth of this dose (1 cGy/MBq) (9). Similarly, the bones contain the largest pool of phosphate in the body as hydroxyapatite, and phosphorus-32 (^{32}P) orthophosphate enters readily in metabolic processes that require phosphorus, such as the bone reparative processes in bone metastases (10). Samarium-153 (^{153}Sm), in turn, is effectively targeted to bone lesions when complexed to ethelenediamine tetramethylene phosphonate (EDTMP) and rhenium-186 (^{189}Re) when complexed to hydroxyethylidene diphosphonic acid (HEDP) (9). ^{153}Sm and ^{186}Re produce a gamma component on decay allowing imaging with a gamma camera, but they also produce greater radiation hazards compared with pure β-emitters such as ^{89}Sr and ^{32}P. The dose of ^{153}Sm is usually 18–74 MBq/kg (0.5–2.0 mCi/kg) and that of ^{186}Re about 18 MBq/kg (0.5 mCi/kg). About 70% to 80% of patients treated with each of these four radiopharmaceuticals experience pain relief, and the main toxicity is bone marrow depression (Table 5).

^{89}Sr has been compared with placebo in a trial that accrued 126 patients with endocrine therapy refractory prostate cancer from eight Canadian cancer centers to evaluate the effectiveness of ^{89}Sr as an adjunct to local field radiotherapy. After local radiotherapy the patients were randomly assigned either to 400 MBq (10.8 mCi) ^{89}Sr as a single injection or to placebo. Patients who received ^{89}Sr took fewer analgesics, had fewer sites of new pain and reduced tumor markers, less need for further radiotherapy and improved quality of life, but had increased hematological toxicity and a tendency to shorter survival (Table 6) (11).

^{89}Sr given as a single 200 MBq (5.4 mCi) intravenous injection has been compared with either local radiotherapy

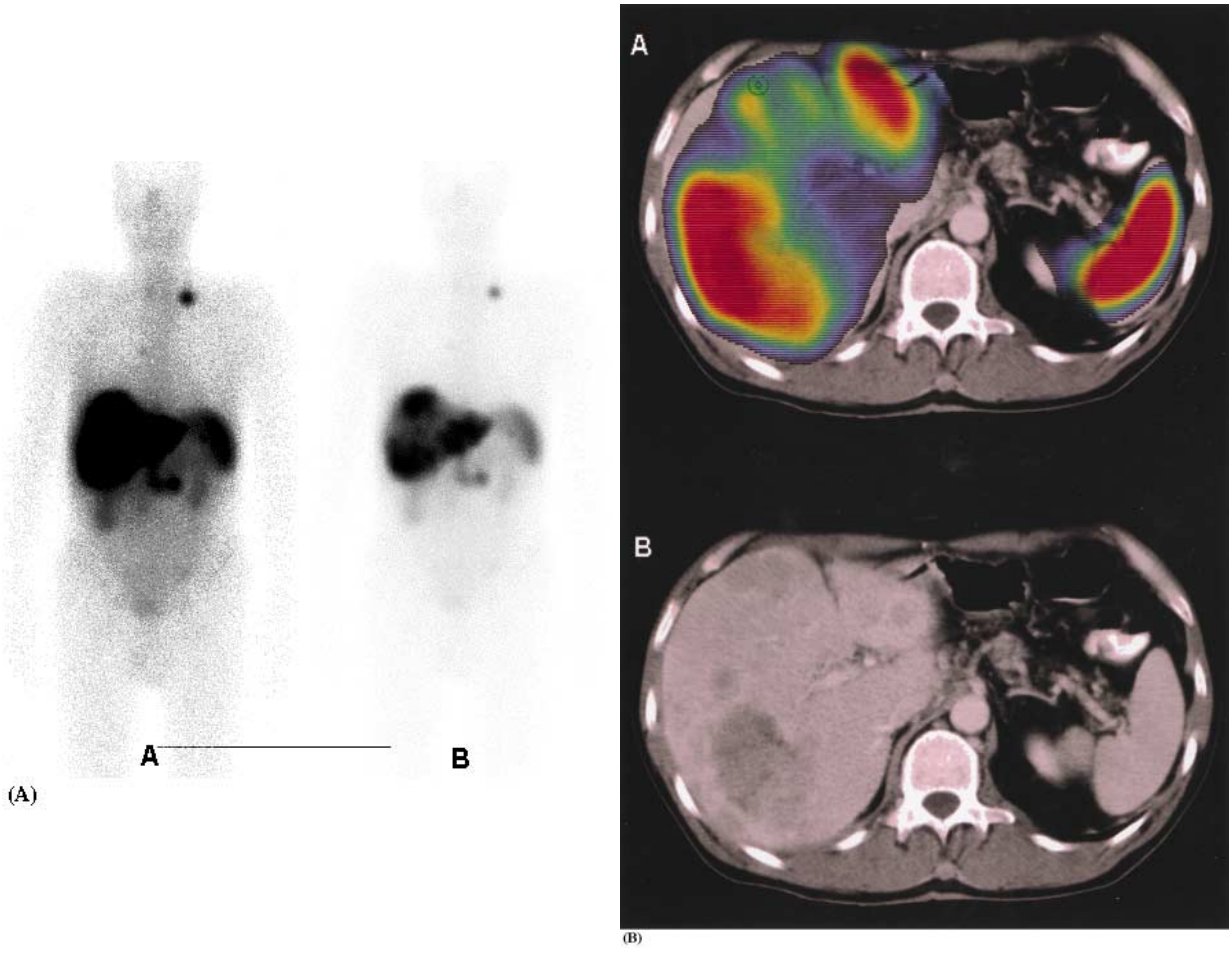

Fig. 4. ^{111}In-DTPA-Phe-octreotide scans of a patient with metastatic mid-gut carcinoid tumor causing diarrhea and flushing. A: A whole-body scan showing multiple liver metastases and a left upper mediastinal metastasis. B: A fusion image of a CT scan (B) and a superimposed SPECT scan (A). The liver metastases and the spleen accumulate labeled octreotide. The patient received 3.7 GBq (100 mCi) as a single i.v. bolus, after which the bowel function normalized but flushing continued (Department of Oncology, Helsinki University Central Hospital).

Table 5

Comparison of four radiopharmaceuticals used in isotope therapy of bone metastases

Agent	Decay	Physical half-life	Pain relief (%)	Average onset	Main toxicity
^{89}Sr	β	50.6 d	50–90	10–30d	Thrombocytopenia
^{32}P	β	14.3 d	60–80	<14d	Pancytopenia
^{153}Sm EDTMP	$\beta+\gamma$	1.9 d	60–75	<14d	Thrombocytopenia
^{186}Re HEDP	$\beta+\gamma$	3.8 d	70–80	<14d	Thrombocytopenia

or hemibody radiotherapy in a randomized trial involving 305 patients with prostatic cancer who had painful bone metastases and who progressed after endocrine therapy (12). All treatments provided effective pain relief, but fewer patients reported new pain sites after receiving ^{89}Sr than after local or hemibody radiotherapy. Platelets and leukocytes fell by an average of 30%–40% after giving ^{89}Sr, but other adverse sequelae were uncommon, and there was less gastrointestinal toxicity in the ^{89}Sr arm than in the hemibody arm. No difference in survival was noted in association with the type of treatment (Table 7). These data indicate that ^{89}Sr is an effective therapy for patients with bone metastases, although the bone marrow toxicity may be a disadvantage in metastatic cancers that are commonly treated with other myelotoxic cytostatic therapy, such as breast cancer with bone metastases.

Radioimmunotherapy

In radioimmunotherapy, targeting is achieved by specific monoclonal antibodies labeled with radioactive isotopes, usually with ^{131}I or yttrium-90 (^{90}Y). Many monoclonal antibodies are currently being tested in cancer therapy and in several types of human cancers (Table 8). The greatest experience comes from lymphomas, where B-cell lymphomas have been effectively treated with ^{131}I-labeled anti-CD20 monoclonal antibodies (13) or antibodies that preferentially target malignant lymphocytes (14). Durable remissions lasting for longer than 4 years can be induced with radiolabeled monoclonal antibodies even in heavily pretreated lymphoma patients (13). Fifty to 65% of all treated patients have responded to radioimmunotherapy; 70–80% of those who complete the therapy respond, and about 50% of the responses are complete (Table 9). Toxicity has been acceptable, the main toxicity being thrombocytopenia and other bone marrow toxicities. A few patients develop human anti-mouse antibodies (HAMA) that may preclude further therapy, but protein engineering techniques to humanize murine antibodies have diminished the immune response which develops against murine monoclonal antibodies, allowing for multiple doses. However, a few patients may develop human anti-human antibodies (HAHA) even against humanized monoclonal antibodies or human antichimeric antibodies (HACA) against chimeric antibodies, but these may appear only at low levels (15, 16).

Monoclonal antibodies can also be coupled to drugs and toxic agents, producing immunotoxins, in addition to radionuclides. Immunotoxins have shown powerful antitumor activity in vitro and in mice, and preclinical trials have shown activity in a proportion of patients, but tumor responses have generally been partial and transient (17). Radioimmunotherapy overcomes some of the problems associated with immunotoxins, because not all tumor cells need to be antigen positive. In heterogeneous tumors the antigen-negative cells will be irradiated if located in the vicinity of antigen-positive tumor cells. Unlike radioimmunotherapy, in immunotoxin therapy host immune response may become directed against both the toxin and the immunoglobulin moieties.

In solid tumors marked responses to radioimmunotherapy can only be expected when absorbed doses greater than 50 Gy are delivered to the tumor, unless the tumor is very radiosensitive (16). For bone marrow, about 2 Gy is considered to be the maximum-tolerated radiation dose in

Table 6

^{89}Sr vs. placebo as an adjunct to radiotherapy in the management of endocrine resistant metastatic prostate cancer (11)

Parameter	^{89}Sr (400 MBq)	Placebo	p
No new pain sites	59%	34%	<0.002
Stopped analgesic intake	17%	2%	<0.05
Median time to radiotherapy	35 wk	20 wk	0.006
Response rate	80%	60%	Not significant
Median survival	27 wk	34 wk	0.06
PSA decrease	Greater with ^{89}Sr		<0.01
Quality of life	Better with ^{89}Sr		0.006
Grade III–IV leukopenia	12%	0%	Not given
Grade III–IV thrombocytopenia	33%	3%	Not given

Table 7

^{89}Sr vs. local or hemibody radiotherapy (12)

Parameter	^{89}Sr	Radiotherapy	p
^{89}Sr vs. local radiotherapy (n = 148)			
Response rate	65%	67%	Not significant
Decreased analgesic intake	40%	33%	Not significant
No new pain sites	64%	42%	< 0.05
^{89}Sr vs. hemibody(n = 157)			
Response rate	70%	67%	Not significant
Decreased analgesic intake	28%	35%	Not significant
No new pain sites	73%	51%	<0.05
^{89}Sr vs. local or hemibody (n = 305)			
Median survival	33 wk	28 wk	Not significant
Leukopenia	More with ^{89}Sr		
Thrombocytopenia	More with ^{89}Sr		
Infections	More with ^{89}Sr		
Gastrointestinal toxicity	Less with ^{89}Sr		

radioimmunotherapy. This limitation can be overcome by bone marrow or peripheral blood stem cell transplantation, but another approach is to use radioimmunotherapy only for treatment of minimum residual disease following another cytoreductive therapy. When radioimmunotherapy is used in combination with external beam radiotherapy or with brachytherapy, it is advantageous if the dose distributions obtained by radioimmunotherapy can be computed and taken into account with those produced by other types of radiotherapy. This can now be done and the tissue dose distributions produced by radioimmunotherapy can be calculated, if the activity distribution of the radioimmunoconjugate and its physical and biological half-lives are known. The activity distribution can be measured with a gamma camera and the biological half-life from serial SPECT scans, after which the dose distribution can be calculated with a modified dose-planning computer system used for conventional radiotherapy planning (18).

Radiolabeled hormone derivatives

Hormones and cytotoxic agents can also be complexed with radioactive isotopes. At present, few such conjugates are in clinical use. ^{111}In-labeled octreotide is an example of a hormone derivative that can be labeled with a radioactive isotope and targeted to somatostatin receptor expressing tissues (19). Octreotide is an analog of the peptide hormone somatostatin, and it binds to the somatostatin receptors located on the plasma membrane and expressed by a variety of neoplasms, especially those arising from the neuroectoderm. After ligand-receptor binding, the complex is internalized to the cytoplasm where it dissociates. Labeled octreotide is then transported into the nucleus, allowing for targeted radiotherapy with the short-range Auger electrons as ^{111}In decays.

^{111}In-labeled octreotide-based targeted radiotherapy has been used in therapy of neuroendocrine tumors, notably of carcinoid tumors. Uptake of ^{111}In-labeled octreotide (^{111}In-DTPA-Phe-octreotide) can be visualized by imaging

Table 8

Some radioimmunoglobulins used for cancer therapy

Disease	Labeled antibody
Lymphoma	^{131}I-labeled anti-CD20 mAb
	^{131}I-labeled mAb Lym-1
Renal cell cancer	^{131}I-labeled mAb G250
Colorectal cancer	^{131}I-labeled anti-CEA mAb
	^{131}I-labeled anti-TAG-72 mAb
Prostate cancer	^{131}I-labeled anti-TAG-72 mAb
	^{131}I-labeled mAb CC49

Table 9

Radioimmunoglobulin therapy of non-Hodgkin's lymphoma (NHL)

Parameter	Wahl et al. (1998)	DeNardo et al. (1998)
Study population	NHL, B-cell	NHL, advanced
No. of prior therapies for NHL	4	4
Antibody used	^{131}I-B1	^{131}I-Lym-1
Dose	Whole body dose of 25–85 cGy	1.5–3.7 GBq/m^2 (40–100 mCi/m^2)
No. of patients treated	34	20
Completed therapy	28	14
Response rate	22/28 (79%)	10/14 (71%)
Complete response rate (CR)	14/28 (50%)	7/14 (50%)
Median duration of CR	15 mo	14 mo
Main toxicity	Myelotoxicity	Myelotoxicity
Maximum tolerated dose	75 cGy	3.7 GBq/m^2 (100 mCi/m^2)
Human anti-mouse abs (HAMA)	4/34 (12%)	
Median survival	4.2 yrs	

with a gamma camera after giving the patient a 111 MBq to 222 MBq (3 to 6 mCi) test dose, after which the larger therapeutic dose of 3.7 to 6 GBq (100 to 160 mCi) is given only for patients who show a positive scan (Fig. 4). The therapeutic dose of ^{111}In-labeled octreotide may be repeatedly given several times up to a total dose of 45–60 GBq at about 4-week intervals (20). Toxicity is generally low and consists mainly of thrombocytopenia. In addition to neuroendocrine tumors, patients with lymphoma, breast cancer and thyroid cancer have also been treated with ^{111}In-labeled octreotide.

CONCLUSIONS

The possibilities of targeting radiation therapy physically have improved considerably during the past decades in parallel with improving imaging methods, fixation devices, dose-planning systems and treatment units. With increasing knowledge of cancer biology and improved biotechnology, novel biological targeting methods have been discovered, and they are likely to play an increasingly important role in the radiation therapist's armament in the next millennium. However, techniques for physical and biological targeting of radiation therapy are not mutually exclusive, and many of them are likely to be used in combination in both the curative and palliative therapy of cancer.

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