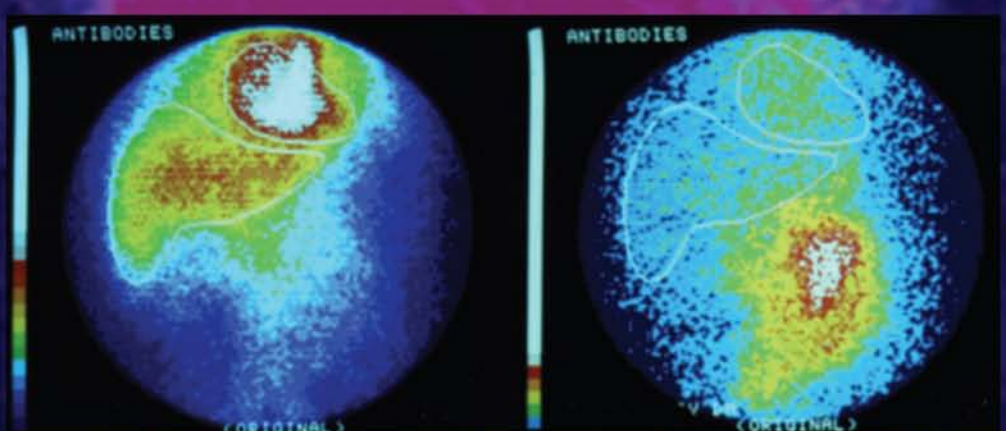
NUCLEAR MEDICINE THERAPY



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This book is respectfully dedicated to
Kenneth A. Krohn, PhD
and
Wil B. Nelp, MD

Preface

Therapy in nuclear medicine practice has a long distinguished history. To use today's phraseology, it is one of modern medicine's early "targeted therapies." By its very nature, nuclear medicine therapy is required to be highly specific and targeted, since it always involves administration of unsealed sources of radioactivity. Since the development of peaceful uses of atomic energy after the second World War, patients with specific disease processes were among the earliest who benefited by these new uses. Standard beta emitting radioisotopes, such as P-32 and I-131, as well as radioisotopes of iron were used in new therapy procedures and seminal physiology studies. Since the 1960s many of these therapies are still in use because of their effectiveness, safety, and lack of competing treatments. Most therapeutic radiopharmaceuticals are available throughout the world and different radioactive sources can be devised for regions that are farther from production facilities or have specific frequencies in disease distributions. As these needs for effective therapies continue to evolve in different world regions, radioactive therapies continue to be cost-effective and adaptable. Perhaps most exciting is the vigorous research and development in new therapeutic radiopharmaceuticals that has been ongoing over the past 20 years.

To practice nuclear medicine and include a therapy aspect of the practice is a challenge for the nuclear medicine physician. One has to be an expert in the most common aspects of nuclear medicine imaging, of course. But to successfully conduct a therapy aspect of the practice with unsealed sources of radioactivity requires a thorough knowledge of the clinical medicine aspects of the disease to be treated. This may involve elements of internal medicine, surgery, radiation oncology, and pediatrics special areas as well. The practitioner must have a complete understanding of the radiochemical and radiopharmaceutical aspects of the therapy agent with the biodistribution and pathophysiology of the disease treated. The physical aspects of imaging to quantitate and understand radiopharmaceutical behavior in a patient, both as a quality control measure and

as the basis for dosimetry estimation, is also critical. The culmination of this information synthesis for treatment with radiopharmaceuticals is dosimetry estimation and application in an individual patient. No other aspect of nuclear medicine practice demands such integration of the biological, chemical, physical, and pathological understanding of all these elements applied to patient management. This understanding for the basis of nuclear medicine therapy relies on an ongoing partnership with the patient's referring primary care physician and a careful delineation of patient care responsibilities for the nuclear medicine physician. The nuclear medicine physician must assume care of the patient during the actual treatment phase, and be involved in appropriate patient preparation and follow-up care and integration with the primary care physician–based continuing care. In nuclear medicine therapy, the nuclear medicine physician must assume the leadership role in all these aspects of patient care. This is a demanding role, but also one that provides a fulfilling and stimulating aspect to the professional career of the nuclear medicine physician.

These demands for knowledge and competence on the practicing nuclear medicine physician are the basis for the creation of this book. This book was designed to completely address the most important aspects of nuclear medicine therapy across the breadth of practice. It is first and foremost a handbook where the practitioner can easily obtain relevant practical information on how to plan, carry out, and follow-up a nuclear medicine therapy procedure. Each chapter provides background materials on a procedure for more in-depth information. But most of all, this book indicates what the practicing nuclear medicine physician needs to think about when contemplating or consulting for a nuclear medicine therapy procedure for a patient with a specific problem. The role of the nuclear medicine physician is defined. Also, enough information on requirements for therapy is provided to assist the practitioner in setting up a clinic to perform nuclear medicine–based therapies. These include patient preparation, risks, indications and contraindications for treatment, patient follow-up, and re-treatment considerations. The authors who have prepared the chapters in this book are experienced practitioners who have a complete understanding of their subject area. They have taken into consideration regional and continental variations in practices, where appropriate, and have composed solid reviews for the reader.

In a larger context, our nuclear medicine specialty has long needed such a reference. Many of us are called upon to consider performing a radioactivity-based therapy that we may only perform at long intervals or infrequently. This is a limiting factor for many nuclear physicians in their practice and often limits provision of some of the most important contributions to patient care that therapy with radioactive agents can provide.

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Principles of Therapy with Unsealed Sources

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INTRODUCTION

Since the discovery of radium by Madame Curie in the early twentieth century, it has been the dream of medical practitioners to use radioactive emissions for treatment of human disease. Indeed, Madame Curie and her coworkers found that certain superficial skin diseases underwent dramatic responses after exposure to radiation and the fields of radiobiology and radiation oncology were born (1). In the 30 years post–World War II, many new radioisotopes were discovered and purified for medical use. In fact, medical radioisotope therapy use and research has paralleled the development of all other uses of atomic energy. Colloidal gold and phosphorous (P-32) were some of the earliest radioisotopes used in therapy (2). The discovery of a myriad of new radioisotopes for medical use followed rapidly, along with new radiochemistry procedures for labeling drugs and biologic agents. The history of therapy with unsealed sources can trace its roots to the beginnings of the atomic age, the birth of radiochemistry as a discipline, radioimmunoassay, and modern nuclear medicine imaging.

PRINCIPLES OF THERAPY

Radionuclide therapy with unsealed sources has several underlying principles, which apply most to all forms of treatment. Where a treatment using a

Table 1 Important Characteristics of Therapeutic Radionuclides

Type and energy of emissions
Half-life
Chemical behavior

radionuclide is envisioned, it ideally represents a radioisotope–drug combination that is specifically suited for a disease in an individual patient. To begin with, the physical characteristics of the radioisotopes must be considered (Table 1). Critical characteristics include type and range of emissions, half-life, and chemical characteristics (Chapter 2). Most therapy agents utilize β-particle emissions for their ability to penetrate tissues. This deposition of energy in tissue by β emitters results in cellular damage. Among the β emitters there are several choices with respect to energy of the β emission. Lower energy β particles can travel a few cell diameters, or at most in the sub-millimeter range. These may be useful for microscopic targets and reducing normal tissue damage. Higher energy β particles such as those emitted by P-32, Y-90, and Ho-166 have excellent tissue penetration with a range beyond the source of several millimeters. This may be desirable when a high homogeneous dose to a large target such as a lymphoma nodule or the bone from a bone surface or marrow source is being treated. Intermediate-range β particles such as those from iodine-131 (I-131) have a

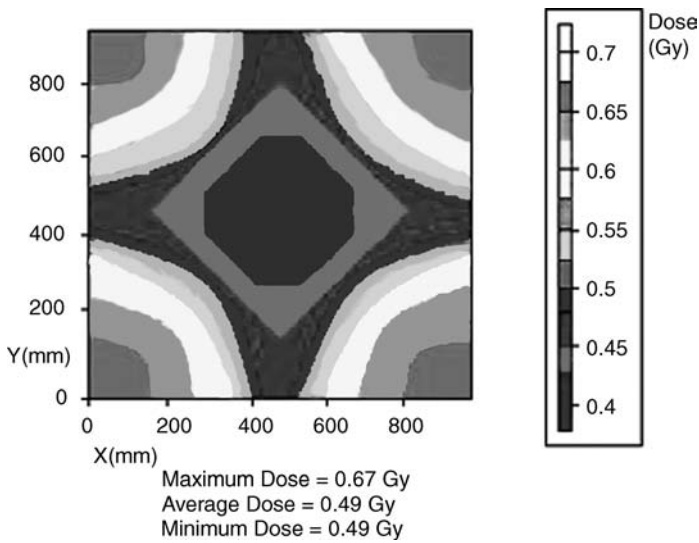

Figure 1 Calculated dose homogeneity distribution from an iodine-131-labeled anti-B cell antibody in a nodular lymphoma. Shading levels represent absorbed dose levels of the radiation, which vary considerably at the microscopic level.

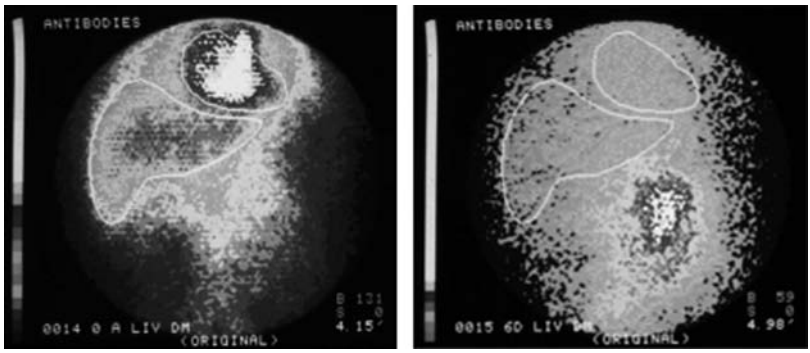

Figure 2 Iodine-131 anti-B cell antibody localization observed in a patient with a large abdominal tumor on day 6 after infusion. On day 1 (*left*) and day 6 (*right*).

shorter path length and may result in less dose homogeneity to the tissue (Fig. 1), but still retain excellent therapeutic effect. Proponents of Auger emitters for radionuclide therapy posit that these low-energy β particles can cause therapeutic effect without excess tissue toxicity because of their short energy deposition range. A somewhat similar argument has garnered favor for support of the use of α-particle emitters for therapy. At-111, Bi-213, and some of the transuranic elements have been studied with varying degrees of success. α particles are highly energetic with these emitters. Investigators hypothesize that the heavy α particle has such momentum that it results in high levels of cell killing close to the origin of the radionuclide deposition. This is thought to result in low surrounding tissue toxicity and high levels of cell killing in tumors where the radiation is deposited. Gamma emissions from therapeutic radionuclides such as the 364 KeV in I-131 are energetic enough to cause a generalized dose effect in an organ, or in the whole body and should be considered in treatment planning for the enhanced treatment effect they might provide as well as the toxicity they may cause (Fig. 2).

The physical half-life of the therapeutic radionuclide is an important consideration and underlying principle for therapy planning. Rarely, except in thyroid treatment, is the simple salt form of the radionuclide used. It is most likely attached to a drug or particle that controls its biodistribution. The ideal therapeutic radiopharmaceutical is one that remains attached to the parent drug or its metabolites, and is excreted rapidly through a known simple route. Radiopharmaceuticals that undergo complex metabolism that results in free radionuclides as well as labeled metabolites that are excreted by several routes are more difficult to use. They also create greater difficulty for realistic radiation absorbed dose estimation based on their observed biodistribution. In most cases, the most optimal combination is a radionuclide with a physical half-life that is similar to the drug or biologic agent half-life, so that the resulting effective half-life represents a length of time appropriate for maximum therapeutic effect and minimal nontarget toxicity.

Many therapeutic radionuclides are radiometals and therefore pose challenges for radiopharmaceutical design. These radiometals often have large atomic radii and can be difficult to chelate or chemically attach to drugs and biologic agents. Weak chelation associations can result in transchelation to naturally occurring metalloproteins. This can result in undesired biodistribution of radiometal away from target sites. Certainly the chemical behavior of the therapeutic radionuclide contributes a great deal to ease of preparation, stability, and biological behavior in the patient. A special case is in the use of α emitters where radionuclide daughters, being different elements may have different chemical characteristics with respect to the radiolabeling strategy compared with the parent.

BIODISTRIBUTION

An important aspect of therapy with radionuclides is biodistribution of the radiopharmaceutical. While high target tissue binding is the most important goal, nonspecific binding or blood pool residence of the compound is an important consideration. Also important is the biodistribution of metabolized components and their excretion routes. Ideally, a therapeutic radiopharmaceutical has high target binding and rapid excretion without redistribution to nontarget tissues and compartments. A major responsibility of the nuclear medicine physician is to know and understand completely the biodistribution patterns of a radionuclide therapy combination. Not only is this important for safety, but for accurate dosimetry estimation. Often, observation of biodistribution requires imaging and quantification of radionuclide tissue concentration and time-activity data (3). Additionally, knowledge of the biodistribution of the pharmaceutical that will be radiolabeled will give an indication of the correct radioisotope to be chosen for the therapy indication.

RADIOISOTOPE CHOICE

In considering the radioisotope for attachment to the pharmaceutical or biologic agent, the match between target residence time and biodistribution with physical half-life is important. As was mentioned earlier, residence times of the radiopharmaceutical and half-life should bear a relationship which results in maximum treatment efficacy. Often, the radiopharmaceutical will remain in the target tissues until decayed. This would be the case in thyroid treatment with I-131 sodium iodine and radiosynovectomy with P-32 colloid.

Another seemingly overlooked consideration for radionuclide choice for therapy is the underlying pathology of the disease. Different disease processes have variable sensitivity to the types and rates of radiation delivered. While many processes are highly radiosensitive, many other diseases are highly radioresistant. They may present as solid masses such as tumors or may be distributed in thin cell layers such as over bony trabecula in the marrow, or along the meninges. These large differences in target type point to geometrical considerations and problems for dosimetry estimation. They also pose challenges for treatment efficacy and toxicity from differences in dose homogeneity.

Radioisotope selection is extremely important in radionuclide therapy planning. Strategies that are most effective have the pathological basis of the disease process as a primary consideration.

TREATMENT ADMINISTRATION

There are several routes of administration of radionuclide therapy (Table 2). The most commonly used is I-131 sodium iodide in capsule or liquid form. The recent development of the capsule form of sodium iodide has greatly increased convenience and decreased radiation safety issues. Liquid I-131 sodium iodide is highly volatile, requiring ingestion in a fume hood and putting hospital personnel at risk of contamination and thyroid I-131 burden. The I-131 oral capsules can be carried to the patient in the radioisotope laboratory in the clinic or hospital room in a properly shielded container. The simple procedure involves swallowing one to several capsules with water, with no contamination of the surroundings.

Intravenous administration of therapy agents requires careful observation and involvement of the staff and nuclear medicine physician. An intravenous line must be of a gauge that allows free flow of the radiopharmaceutical over a period of several minutes. The clinic or hospital floor personnel have to be prepared to identify and treat adverse reactions, and monitor the patient for up to several hours as well. In our clinics, treatments can only be administered in the direct presence of a nuclear medicine physician. Usually they are administered over several minutes so that if an adverse reaction develops, the administration can be interrupted. In some therapies, such as those using radiolabeled antibodies experimentally, the treatment infusions can last up to several hours requiring the use of an infusion pump with adjustable rate. In many cases, the dose is administered through an indwelling catheter. Most radioisotopes for therapy today do not have problems with adhesion to these lines, but it should be determined ahead of time if this is a potential problem, and a peripheral vein site selected. In some cases, the treatment syringe contains sufficient radioactivity that shielding is required to prevent a high hand dose to the personnel performing the therapy administration. Automated syringe pumps are also helpful in these situations, and can have the advantage of dose delivery at a smooth, predetermined rate.

Table 2 Routes of Administration in Radionuclide Therapy

Oral
Intravenous
Intracavitary
Intra-articular
Intracystic
Intrathecal
Intraperitoneal
Subarachnoid
Intra-arterial (with catheterization)

Intracavitary treatment can be particularly interesting and rewarding in nuclear medicine practice. It varies somewhat from one practice to another depending on the patient and the referring physician mixture locally. More preparation and special procedure arrangement is often required for these therapies. Often the nuclear medicine physician performs these treatments with a practitioner of another specialty when specific skills are required. This is dependent on the level of skill and practice of the nuclear medicine physician. Examples are intra-articular and intraperitoneal treatments as well as the rare treatment of a cranial cyst. Whatever the intracavitary therapy, careful pretreatment planning and organization are very important for treatment success, patient safety, and radiation safety.

Intra-arterial treatments using radiocolloids and radiospheres are in practice in some locations. These are usually for treatment of hepatic tumors, and performed in conjunction with members of the angiography service. As angiography techniques become more widespread and sophisticated, intra-arterial therapies using particulate radiopharmaceuticals may become an important part of nuclear medicine practice.

PATIENT ASSESSMENT AND FOLLOW-UP

Each chapter in this text has a section specifically devoted to outlining the nuclear medicine physician's responsibility for patient assessment for treatment and follow-up. These specifics are also detailed in easy-to-read tables for quick reference as well. The nuclear medicine physician is responsible for final patient assessment for treatment. While this seems obvious, it sometimes seems that this responsibility is overlooked when the nuclear medicine practice is increasingly only having diagnostics as a focus. Good practice includes medical record review, including the laboratory, and diagnostic test results, consultation with the referring physician, and pretreatment consultation with the patient. This is an opportunity to educate the patient and their family of the treatment procedure, begin discussions about radiation safety, and follow-up procedures. The nuclear medicine physician is also responsible for obtaining informed consent from the patient for the procedure and making sure that radiation safety precautions are clearly understood. In the therapy process, follow-up plans are also very important. They may involve imaging, laboratory tests, and post-treatment visits with the referring physician. It is important for the nuclear medicine physician to make sure that care of the patient after radionuclide therapy is ensured, either in the nuclear medicine department, or by the referring physician.

ADVERSE EVENT REPORTING

As emphasized in the previous section, preparation for adverse events in patients treated with radionuclides is a major consideration. They can range from acute reactions during and immediately postadministration to problems that occur in the longer term. The nuclear medicine physician often must play the role of

counseling the referring physician on possible long-term adverse effects of treatment, how to monitor for them, and how to treat them. Each nuclear medicine practice should have in place an adverse events reporting plan, which involves documentation and submission to various local and state authorities.

RADIATION SAFETY

Chapter 2 details radiation safety aspects of radionuclide therapy. The nuclear medicine physician is the so-called "captain of the ship" for these procedures, with significant support from local radiation safety officers and radiation health physicists as well as the clinic nuclear medicine technologists. Essential elements begin with procedure planning and knowledge of local radiation safety regulations. This involves ongoing interactions with the hospital or clinic administration and the community, and probably state and national authorities as well. Counseling the patient and his family and the referring physician on radiation safety precautions is as important as safe treatment procedures for the patient. In today's world, patients bring all kinds of preconceived notions and distractions to the interaction with the nuclear medicine physician. These are in addition to having an illness that requires this somewhat unusual treatment (to the mind of the patient). Counseling the patient to a level of understanding about radiation safety procedures for treatment can be a rewarding experience for the nuclear medicine physician because it can fully engage the patient as an active participant in his/her own healthcare.

ROLE OF THE NUCLEAR MEDICINE PHYSICIAN

The previous brief discussions on basic aspects of radionuclide therapy really describe the role of the nuclear medicine physician. This role is summed up in Table 3. This text emphasizes our role as physicians in nuclear medicine where good medical practice is at the heart of all specialized procedures. We have designed the chapters to provide succinct backgrounds, useful reference lists, concise tables of instructions, and considerations of practice for each procedure. This text will be valuable to the new practitioner as well as the old hand who needs to brush up knowledge for an upcoming seldom-performed procedure.

Table 3 Role of the Nuclear Medicine Physician in Radionuclide Therapy

Be a physician!
Know the patient
Know the radiopharmaceutical
Know the disease
Know the referring physician
Know all the procedures and regulations

REFERENCES

1. Madame Curie. A Biography by Eve Curie. Doubleday, Doran and Co. Inc. New York, 1939.
2. Hevesy, G. Radioelements as tracers in chemistry and physics. Chem News 1913; 108:166.
3. Eary JF, Krohn KA. Will we be able to recognize a better radiopharmaceutical when we make it? Nucl Med Biol 1990; 17(3):259–260.

2

Therapeutic Radioisotopes

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INTRODUCTION

Since the discovery of radium, the medical community has been interested in the use of unsealed radioactive isotopes to target and treat cancer and benign systemic and loco-regional proliferative conditions such as arthritis. Lack of effective systemic agents, such as chemotherapy during the early period of modern oncology, coupled with the intention to use targeted therapy for treating cancer made radioisotopes an option for use in cancer. Radioactive iodine-131 (I-131), because of abundant beta and gamma emissions and normal physiological uptake of elemental iodine in the thyroid gland, was the most logical choice for treating a number of thyroid disorders. Radioactive phosphorous-32 (P-32) made its way into nuclear medicine therapy, mainly because of the ubiquitousness of phosphorous in many biological molecules. It comes as no surprise that it was the first agent utilized in treating hematological malignancies. Since that time, several new isotopes were identified and clinical uses were explored. Advances in scientific research, systematic clinical trial design, and consideration of the properties of radiopharmaceuticals have resulted in finding new effective therapy agents.

Although many radioisotopes have potential applications in nuclear medicine therapy, the ultimate choice of an agent is based on type of emission, energy, half-life, ease of production, availability, and cost. Radioisotopes for therapeutic use can be largely divided into two groups—radiometals and radiohalogens. Radiometals have long been attractive options and have gained widespread popularity for many clinical uses while radiohalogens have maintained their popularity because of their relatively simpler radiolabeling characteristics.

RADIOPHARMACEUTICALS FOR THERAPY

Radioisotopes used in therapy require certain characteristics that differ from those of diagnostic radioisotopes. Radionuclides used in therapy are predominantly beta or alpha emitters (Table 1). Pure particle emitters without any gamma component do not require special radiation safety precautions permitting out-patient treatment. Presence of gamma emission is helpful in imaging and studying the biodistribution of a particular radiopharmaceutical, not only at the time of drug development but also for estimating patient-specific radiation absorbed dose. In the absence of gamma emission, internal dosimetry for alpha or beta emitters has been attempted using surrogate isotopes, for example, indium-111 (^{111}In) for yttrium-90 (^{90}Y) (1) although arguments counter to this application have been put forth. Emitters of Auger electrons, for example, In-111 have also been introduced for treatment purposes (2).

A number of radioisotopes are used as their salts, for example, ^{131}I sodium iodide and ^{89}Sr strontium chloride, while many others have to be incorporated into compounds of biological interest to make them stable and functional in vivo. These can be chemical compounds such as diphosphonate ethylene diamine tetramethylene phosphonate (EDTMP)—samarium-153 (^{153}Sm) EDTMP or biological compounds such as antibody—^{131}I tositumomab. The resulting radiopharmaceutical

Table 1 Physical Characteristics of Commonly Used Radioisotopes in Therapy

Radionuclide	Beta E_{max} (MeV)	Mean range (mm)	Gamma energy used for imaging (keV)	Half-life (hr)
^{32}P	1.71	1.85	—	342
^{64}Cu	0.57 and 0.66	0.4	511	12.8
^{67}Cu	0.57	0.27	92 and 185	62
^{90}Y	2.27	2.76	—	64
^{131}I	0.61	0.4	364	193
^{153}Sm	0.8	0.53	103	47
^{177}Lu	0.5	0.28	113, 208	162
^{186}Re	1.07	0.92	137	89
^{188}Re	2.12	2.43	155	17
^{165}Dy	1.29	—	—	2.33?
^{225}Ac	—	—	—	240
^{211}At^{+}	5.9 (alpha)	0.06	670	7.2
	7.5 (e.c.)	0.08		
^{212}Bi	1.36 (beta)	0.09	727	1.0
	6.1 (alpha)	0.06		
^{213}Bi	5.8 (alpha)	0.06	440	0.78
	8.4 (alpha)	0.08		

Abbreviations: P, phosphorus; Cu, copper; Y, yttrium; I, iodine; Sm, samarium; Lu, lutitium; Re, rhenium; Dy, dysprosium; Ac, actinium; At, astatine; Bi, bismuth.

has the desired biodistribution and function of the drug moiety. The ultimate therapeutic function of a radioconjugate depends not only on the properties of the radioisotope but also on the biokinetic properties of the conjugate. These characteristics determine the global as well as local radiation absorbed doses for each combination.

Physical and effective half-life of the radioisotope should be paired to the drug half-life in the body. Radioisotopes with very short half-lives are often not desirable because of difficulties in availability, need for rapid labeling requirements. In spite of these drawbacks, short-lived isotopes, both alpha (^{212}Bi and ^{213}Bi) and beta emitters (^{67}Cu), have been proposed and tried in the treatment of acute leukemia (3) as well as intracavitary applications (4).

Easy availability and production are attributes affecting the cost of production. Generator-produced isotopes are attractive particularly for use in centers that are remote from production facilities, for example, rhenium-186 (^{186}Re). But cost might be a factor in their ready acceptance for routine clinical use. Simple, stable radiolabeling to biological compounds is one of the most important qualities for an ideal therapeutic isotope. Binding efficiency and stability of a radiolabeled compound results in optimal delivery of radiation in vivo. Additionally, there should not be any significant radiolysis of the compound after labeling, during storage (a potential problem when high specific activities are used in labeling), and shipment.

TISSUE TARGETING

Optimal delivery of the radioconjugate depends on several factors—pharmacokinetics of the conjugate and the biological parameters of the tissue. The physical half-life of the isotope should be longer than the time needed for targeting the tissue/tumor aiming for a maximal tissue-to-background ratio. Usually, for cancers with a large number of circulating tumor cells such as leukemia, cancer cells can be easily targeted within a short interval after administration. The size of the conjugate (e.g., antibody) is also an important factor that determines the pharmacokinetics. Similarly, the morphology of the tumor including the level of antigen expression and interstitial pressure can affect delivery of the radioconjugate. These factors result in either suboptimal delivery or poor target-to-background ratio. These are not limiting factors in treating benign or malignant pathology in cavitary lesions where the radioconjugate is either directly instilled into the resection cavity or after-loaded into an indwelling balloon catheter. However, there should be no or minimal leakage into the blood pool and the conjugate/carrier needs to be inert.

RADIOPHARMACEUTICAL QUALITY CONTROL

Before a radiopharmaceutical can be injected into patients, it needs to meet quality control standards, which include radiochemical purity, sterility,

pyrogen testing, protein binding, and immunoreactivity. Each radiopharmaceutical must be assayed for each characteristic before it can be administered to the patients (Chapter 3).

BETA PARTICLES

Radioisotopes with high proportion of beta emission have been used clinically and represent the largest group used in therapy. Beta particles have a finite and limited range in tissues and dissipate most of their energy (~95%) within an organ. While beta particles are ideal for treating larger tumors because of longer path range in tissues, much of their energy (up to 99.9%) can fall outside the small diameter microscopic tumors (5). A plastic syringe shield is used for pure beta emitters to avoid bremstrahlung that would contribute radiation dose to the hands. Several beta emitters have found appropriate role in the palliation of patients with painful bone metastases (6,7). In theory, the dose rate of particle emission has some bearing on treatment effects. Generally, radionuclides with higher dose rates are effective in treating tumors with shorter cell cycle time, that is, rapidly proliferating cells and vice versa (8,9). Radioisotopes without any gamma ray emission provide the advantage of convenient outpatient treatment, because of the lack of gamma radiation.

Copper Radioisotopes

Three radioisotopes of copper are in use in clinical nuclear medicine. Of these, two are useful in therapy: Cu-67 ($T_{1/2}$ = 2.6 days), Cu 64 ($T_{1/2}$ = 12.4 hours), with the former having properties that include a gamma emission (184 keV). Copper-64 can be produced with high specific activity (100 mCi/mg Cu) in a cyclotron (10). Cu(II) oxidation state forms thermodynamically stable complexes with several ligands including the macrocyclic compounds. Bifunctional chelates of copper are suitable for use as therapy agents, particularly radioimmunotherapy (RIT) and can be formed by side chain attachment to the carbon backbone or nitrogen atom substitution. Highly stable compounds can be produced by these methods. Chelation is rapid and complete within a few minutes.

Dysprosium-165

Dysprosium-165 (Dy-165; $T_{1/2}$ = 2.33 hours; E_{max} beta = 1.29 MeV) coupled with large inert carrier, ferric oxide macroaggregates is used in the intra-articular treatment of rheumatoid synovitis (11,12). Intra-articular injections of 250 mCi per joint are commonly used to treat chronic inflammatory joint conditions. It has extremely low leakage rates [0.12–0.3% of the injected dose (ID)] (13,14). Repeat injections in patients refractory to the first administration are feasible (15).

Erbium-169

Erbium-169 emits beta particle (E_{max} beta = 0.34 MeV) with an average soft-tissue range of 0.3 mm. It has a convenient shelf life of 9.4 days. It is used as the citrate salt in the treatment of refractory painful arthritis particularly in the smaller joints such as the metacarpophalangeal and digital interphalangeal joints. Small volumes containing 0.5–1 mCi (20–40 Mbq) with a maximum of 20 mCi (750 Mbq) per administration are used (16).

Iodine-131

Iodine-131 has a convenient half-life and energy characteristics ($T_{1/2}$ = 8.1 days; E_{max} beta = 600 keV). Normal physiological uptake of iodide (and hence its radioactive form) in functioning thyroid tissue is the primary reason for its role in treating several thyroid disorders and malignancies. This fact, coupled with the energetic beta emission, has made it a treatment standard. Sodium iodide has the convenience of easy oral administration, which further improves patient compliance. Its high-energy gamma radiation (364 keV), which requires additional radiation safety measures, can be considered advantageous for biodistribution studies and radiation-absorbed dose evaluation. Sodium iodide in liquid form is highly volatile and needs special handling in a fume hood with exhaust system to avoid inhalation of the iodide vapor during labeling. It also means that personnel handling the radiopharmaceutical should be subjected to periodic assays to exclude uptake in their thyroid glands. However, I-131 remains the most commonly used therapy radionuclide in nuclear medicine. When used for treating nonthyroid malignancies, unwanted uptake of ^{131}I in normal thyroid gland needs to be blocked by administering elemental iodide, in the form of Lugol's iodine or Strong Solution of Potassium Iodide (SSKI). Its easy labeling characteristics with the ability to covalently label proteins have made it the primary choice for labeling monoclonal antibodies while its longer half-life (eight days) is ideal in situations where there is slower penetration into a tumor.

Iodine-125

Iodine-125 ($T_{1/2}$ = 60 days; X-rays = 30 keV) is cyclotron produced. In spite of the absence of any particle emission, the low-energy characteristic X-rays make it suitable for use in brachytherapy applications in cavitary malignancies, for example, resection cavity of glio blastoma or primary breast cancer. For this purpose, it is used as an after-loading technique into an indwelling balloon catheter placed at the time of surgery. Concerns of significant leakage has been addressed by forming a stable compound and using double-layered extra strong balloon (17). The amount of radioactivity and the dwell time is based on the balloon size of the Gliasite system, which is approved by the Food and Drug Administration (FDA) for such use in patients' malignant brain tumor. I-125

has also been used in the sealed form as seeds for postsurgical treatment of brain tumors and primary treatment of prostate cancer.

Lutitium-177

Lutitium-177 (Lu-177) is a beta emitter (0.5 MeV) with a half-life of 6.73 days and gamma photopeaks of 113 (3%) keV and 210 (11%) keV, respectively. It can be produced to a high specific activity and has a half value layer (HVL) of 0.6 mm of lead. It has a range of several millimeters in tissue. Antibodies have been successfully labeled with it (e.g., CC49) for intraperitoneal treatment of ovarian cancer (18) or peptides (e.g., octreotate) for treating somatostatin-expressing tumors (19,20). It is commercially available in the United States in pharmacologic grade and is usually labeled using macrocyclic compounds such as tetraazacyclododecane-tetraacetic acid (DOTA). The higher absorbed doses and the lower tissue penetration range of ^{177}Lu has been shown to be advantageous for treating small tumors. Cumulative doses of 600–800 mCi have resulted in partial remissions of 30% in patients with neuroendocrine tumors (19).

Phosphorous-32

Phosphorous-32 is a pure beta emitter with a half-life of 14.3 days and is commonly used in the intravenous form as sodium phosphate. Because of the ubiquitousness of phosphorous in biological molecules, it was one of the first agents to be used in treating systemic cancer (particularly hematological) and effusions. However, P-32 therapy was also associated with significant hematologic toxicity. This coupled with the emergence of potent cancer chemotherapeutic agents, resulted in the waning of its use in clinical medicine. Today, it is the agent of choice for treating polycythemia vera, a malignant proliferative condition of the red blood cells. While it is rarely used in treating malignant effusions, the colloidal form (chromic ^{32}P) has found widespread use in the control of benign proliferative conditions of joint synovium (21,22) and with some success in cystic brain lesions (5,23). Other novel ways of using P-32 include coronary stents impregnated with P-32 to prevent restenosis after balloon angioplasty in treating patients with coronary artery disease (24).

Radioisotopes of Rhenium

Two radioisotopes of rhenium, ^{186}Re ($T_{1/2} = 3.72$ d; E_{max} beta $= 1.07$ Mev) and ^{188}Re ($T_{1/2} = 16.98$ h; E_{max} beta $= 2.12$ Mev) have found use in nuclear medicine therapy. On the other hand, ^{186}Re is short-lived and has rapid uptake in target and clearance from normal organs. Convenient physical half-life (89 hours) with an E_{max} of 1.07 MeV beta emission and 137 keV (9%) photon, ^{186}Re delivers more radiation than ^{188}Re in terms of rad/mCi. When chelated to hydroxyethylidene diphosphonate (HEDP), etidronate is stable and shows uptake similar to Technetium [99m] medroxy diphosphonate (^{99m}TcMDP). It

has an uptake pattern in normal skeleton and metastatic foci. Like other bone seekers, it is rapidly excreted via urine and shows optimal retention in the skeleton at 24 hours. Methods are available for the production of high purity compounds (25). ^{186}Re can be produced to very high specific activity by neutron irradiation of enriched ^{185}Re. In practical terms, production of ^{188}Re is usually achieved using a ^{188}W/^{188}Re generator system and is able to produce carrier-free ^{188}Re (26). The main advantages of rhenium are its chemical similarities to technetium and the fact that proteins can be labeled by either direct methods (to the sulfhydryl group) (26) or indirect methods (by using bifunctional chelates to biological compounds) (27).

Samarium-153

Samarium is labeled to phosphonates, for example, EDTMP, taking advantage of the bone-seeking properties of the bisphosphonates. It is produced by neutron irradiation of ^{153}Sm. ^{153}Sm is a gamma (with a principal photopeak of 103 keV) and beta emitter (E_{max} beta = 0.81 MeV for the main emission). Its convenient half-life of 1.95 days makes it useful for treating patients with widespread metastases and compromised bone marrow function (28). It has a biodistribution profile and uptake characteristics in the metastatic bone lesions [ratio of lesion to normal bone can be as high as 4:1 (29)]. As with other bone-seeking radiopharmaceuticals, the bone marrow is at risk for myelotoxicity (the calculated upper limit for marrow dose is 7 rad/mCi). Along with strontium chloride, it is one of the two radiopharmaceuticals approved by the FDA for palliation of bone pain from metastatic disease. Its shorter half-life is particularly attractive to prevent severe myelotoxicity when used in patients who have been heavily pretreated with radiation and or chemotherapy.

Strontium-89

The biodistribution of strontium was first characterized in the early 1940s. In addition to its uptake in normal bones, it was found to differentially localize in foci of active bone turnover that include tumor foci. These areas can show several fold uptake compared with normal bone. It is a fission product and pure beta emitter with an E_{max} beta of 1.46 MeV and a $T_{1/2}$ of 50.5 days. It is handled by the body in the same manner as calcium. It is excreted via the kidneys and is taken up into the bone undergoing a "self-burial" with a long effective half-life in the skeleton and slow wash-out from blastic bone lesions (30). Lack of gamma emission precludes imaging, although attempts have been made to image the bremstrahlung (resulting in a very low quality image) or by spiking with ^{85}Sr, the gamma emitting isotope of strontium (30). However, with a biodistribution identical to strontium isotopes, ^{99m}TcMDP can be used as a surrogate for studying the biodistribution of ^{89}Sr although the half-life is very different. Administration of strontium for therapy of bone metastases is based on a fixed dose scale and does not require biodistribution studies for

therapy administration. Treatment doses are nonmyelosuppressive in the prescribed dose ranges (6,7).

Yttrium-90

Yttrium-90 (Y-90) is a pure beta emitter and belongs to group III. Its high E_{max} beta (2300 keV) has made it an attractive choice for therapy applications, in spite of the lack of gamma emission. Higher energy and hence longer particle range in tissues provide the ability to treat larger tumors. Yttrium-90 is generator-produced from its parent Sr-90 and is available with high specific activity (27). Its trivalent ion is commonly used for chelation purposes. Used as the citrate salt, it shows 80% uptake in the bones. In this form it has been used for pain palliation from metastatic disease. It has the chemical properties suitable for chelation to several commonly used compounds or macrocyclic ligands such as DOTA (31,32). Several chelated forms are being evaluated for therapy and simple effective labeling methods are available (33). In spite of the need to use a surrogate radioisotope for biodistribution studies, yttrium has gained acceptance in clinical practice because its high beta particle energy and the lack of gamma radiation make out-patient treatment feasible (34,35).

Indium-111

Auger electron emitter In-111, belonging to group III is cyclotron-produced with a half-life of 2.8 days and decays by electron capture and gamma emission (184 and 296 keV). Its trivalent ion, which has thermodynamic stability, is commonly used for radiolabeling purposes. Advantages include ready availability and well-established use in diagnostic nuclear medicine applications. It is usually chelated to biological molecules using chelating complexes such as diethylene triamine pentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), or DOTA. It should be noted that because of their slow clearing properties, macrocyclic compounds are preferred for in vivo studies, for example, In-DOTA (36). ^{111}Indium can be effectively chelated using simple techniques either before or after conjugation to a biological molecule usually with the help of a buffer (32,37).

Tin–Sn-117 m

Sn-117 m ($T_{1/2} = 13.6$ days; conversion electrons) is a conversion electron emitter. Because of the low energy of these electrons, there is relative sparing of the bone marrow in treated patients and offers a large dosimetric advantage over other beta-emitting isotopes. Stannum (Tin) $(Sn)^{4+}$ DTPA localizes actively (50% of ID) in bone.

ALPHA PARTICLE EMITTERS

Alpha particles, which are helium nuclei, look attractive for therapeutic applications because of their high linear energy transfer (LET) and relative biological efficiency (RBE). Cell killing is less dependent on oxygen for radiotherapeutic

efficacy, that is, low oxygen enhancement ratio (OER) (38–40). Although their path length in tissues may exceed several cell diameters, it is not likely long enough to effectively treat larger tumors. Alpha emitters are however useful in treating micrometastases from solid tumors or in disseminated intracavitary diseases such as intraperitoneal seedling from ovarian malignancies, tumors in the meninges as well as acute leukemia. Ultra short-lived radioisotopes of bismuth, ^{212}Bi and ^{213}Bi, are under investigation for leukemia (rapid cell proliferation) treatment (3) and intracavitary malignancies (diffuse and microscopic disease) (41). Radioisotopes with longer half-life, lead-212 (^{212}Pb) and actinium-225 (^{225}Ac) may be suitable for use in systemic treatment (larger tumors). The idea of using high LET alpha emitters as targeted atomic nanogenerators is a recent proposition (42). A single atom emitting an alpha particle may kill a target cell. Investigators have targeted several cancers using novel constructs of internalizing monoclonal antibodies labeled with alpha emitters without increasing systemic toxicity (3,39). Because of the nature of their interaction with matter (short path length), no special shielding precautions are needed.

Actinium, Bismuth, and Other Alpha Emitters

^{225}Ac has the advantages of ready availability and the lack of radon isotope or high-energy gamma emitters in the decay scheme. ^{225}Ac also has a sufficiently long half-life (10 days) that results in optimal pharmacokinetics and is conveniently produced from Thorium ^{229}(Th) ($T_{1/2} = 7340$ years) generators and has the potential for continuous supply. It has been estimated that for each gram of ^{229}Th, five Ci of ^{225}Ac can be produced per year benefiting 4000 cancer patients per year (43). Current emphasis is on using chelators to label the antibody, but biodistribution problems, including clearance from the body, pose major challenges. ^{213}Bi ($T_{1/2} = 45.6$ minutes), the last alpha emitter in the decay scheme of ^{229}Th, is produced from ^{225}Ac generators (42). The eluted product can then be labeled to antibody yielding to high specific activities using established methods. Its gamma emission (440 keV) makes imaging and biodistribution studies possible.

Use of radioisotopes in treating medical conditions has always been an attractive option and takes advantage of the targeted delivery of radiation to the tissues. Beginning with P-32 and I-131, a number of useful isotopes have been added to the line up, while many have been retired. In spite of the initial negative set back on its popularity that was seen following the introduction of modern cytotoxic chemotherapy, advances in radiochemistry, and chelating techniques, coupled with a better understanding of radiation-absorbed dose estimation have made them attractive options for therapy again. A great deal of progress has been made in the synthesis, purification, and labeling of therapeutic radiopharmaceuticals. A majority of these agents are beta emitters but alpha emitters, used as nanogenerators have generated greater excitement and promise to be a powerful new tool. Recent introduction of two radiolabeled monoclonal antibody products for the treatment of non-Hodgkins lymphoma (NHL) in the United States promises to provide a strong impetus for the growth of therapeutic nuclear oncology.

REFERENCES

1. Wiseman GA, White CA, Stabin M, et al. Phase I/II 90Y-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's lymphoma. Eur J Nucl Med 2000; 27:766–777.
2. De Jong M, Valkema R, Jamar F, et al. Somatostatin receptor-targeted radionuclide therapy of tumors: preclinical and clinical findings. Semin Nucl Med 2002; 32:133–140.
3. Jurcic JG, Larson SM, Sgouros G, et al. Targeted alpha particle immunotherapy for myeloid leukemia. Blood 2002; 100:1233–1239.
4. Zalutsky MR, Bigner DD. Radioimmunotherapy with alpha-particle emitting radioimmunoconjugates. Acta Oncol 1996; 35:373–379.
5. Geerlings MW. Radionuclides for radioimmunotherapy: criteria for selection. Int J Biol Markers 1993; 8:180–186.
6. McEwan AJ. Use of radionuclides for the palliation of bone metastases. Semin Radiat Oncol 2000; 10:103–114.
7. Silberstein EB. Systemic radiopharmaceutical therapy of painful osteoblastic metastases. Semin Radiat Oncol 2000; 10:240–249.
8. Howell RW, Goddu SM, Rao DV. Application of the linear-quadratic model to radioimmunotherapy: further support for the advantage of longer-lived radionuclides. J Nucl Med 1994; 35:1861–1869.
9. Fowler JF. Radiobiological aspects of low dose rates in radioimmunotherapy. Int J Radiat Oncol Biol Phys 1990; 18:1261–1269.
10. McCarthy DW, Shefer RE, Klinkowstein RE, et al. Efficient production of high specific activity ^{64}Cu using a biomedical cyclotron. Nucl Med Biol 1997; 24:35–43.
11. Barnes CL, Shortkroff S, Wilson M, Sledge CB. Intra-articular radiation treatment of rheumatoid synovitis of the ankle with dysprosium-165 ferric hydroxide macroaggregates. Foot Ankle Int 1994; 15:306–310.
12. Chin KR, Barr SJ, Winalski C, Zurakowski D, Brick GW. Treatment of advanced primary and recurrent diffuse pigmented villonodular synovitis of the knee. J Bone Joint Surg Am 2002; 84-A:2192–2202.
13. Zalutsky MR, Venkatesan PP, English RJ, Shortkroff S, Sledge CB, Adelstein SJ. Radiation synovectomy with ^{165}Dy-FHMA: lymph node uptake and radiation dosimetry calculations. Int J Nucl Med Biol 1986; 12:457–465.
14. Sledge CB, Atcher RW, Shortkroff S, Anderson RJ, Bloomer WD, Hurson BJ. Intra-articular radiation synovectomy. Clin Orthop Relat Res 1984; 182:37–40.
15. Vella M, Zuckerman JD, Shortkroff S, Venkatesan P, Sledge CB. Repeat radiation synovectomy with dysprosium 165-ferric hydroxide macroaggregates in rheumatoid knees unresponsive to initial injection. Arthritis Rheum 1988; 31:789–792.

16. Gratz S, Gobel D, Behr TM, Herrmann A, Becker W. Correlation between radiation dose, synovial thickness, and efficacy of radiosynoviorthesis. J Rheumatol 1999; 26:1242–1249.
17. Tatter SB, Shaw EG, Rosenblum ML, et al. An inflatable balloon catheter and liquid ^{125}I radiation source (GliaSite Radiation Therapy System) for treatment of recurrent malignant glioma: multicenter safety and feasibility trial. J Neurosurg 2003; 99:297–303.
18. Alvarez RD, Partridge EE, Khazaeli MB, et al. Intraperitoneal radioimmunotherapy of ovarian cancer with ^{177}Lu-CC49: a phase I/II study. Gynecol Oncol 1997; 65:94–101.
19. Kwekkeboom DJ, Bakker WH, Kooij PP, et al. [^{177}Lu-DOTAOTyr3]octreotate: comparison with [111In-DTPAo]octreotide in patients. Eur J Nucl Med 2001; 28:1319–1325.
20. de Jong M, Breeman WA, Bernard BF, et al. [^{177}Lu-DOTA(0),Tyr3]octreotate for somatostatin receptor-targeted radionuclide therapy. Int J Cancer 2001; 92:628–633.
21. Mathew P, Talbut DC, Frogameni, A, et al. Isotopic synovectomy with P-32 in paediatric patients with haemophilia. Haemophilia 2000; 6:547–555.
22. Siegel HJ, Luck JV Jr, Siegel ME, Quines C, Anderson E. Hemarthrosis and synovitis associated with hemophilia: clinical use of P-32 chromic phosphate synoviorthesis for treatment. Radiology 1994; 190:257–261.
23. Voges J, Sturm V, Lehrke R, Treuer H, Gauss C, Berthold F. Cystic craniopharyngioma: long-term results after intracavitary irradiation with stereotactically applied colloidal beta-emitting radioactive sources. Neurosurgery 1997; 40:263–269, discussion 269–270.
24. Janicki C, Duggan DM, Coffey CW, Fischell DR, Fischell TA. Radiation dose from a phosphorous-32 impregnated wire mesh vascular stent. Med Phys 1997; 24:437–445.
25. Maxon HR, Deutsch EA, Thomas SR, et al. Re-186(Sn) HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. Radiology 1988; 166:501–507.
26. Griffiths GL, Goldenberg DM, Knapp FF Jr, Callahan AP, Chang CH, Hansen HJ. Direct radiolabeling of monoclonal antibodies with generator-produced rhenium-188 for radioimmunotherapy: labeling and animal biodistribution studies. Cancer Res 1991; 51:4594–4602.
27. Graham MC, Scher HI, Liu GB, et al. Rhenium-186-labeled hydroxyethylidene diphosphonate dosimetry and dosing guidelines for the palliation of skeletal metastases from androgen-independent prostate cancer. Clin Cancer Res 1999; 5:1307–1318.
28. Collins C, Eary JF, Donaldson G, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. J Nucl Med 1993; 34:1839–1844.

29. Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. J Nucl Med 1993; 34:1031–1036.
30. Blake GM, Zivanovic MA, McEwan AJ, Ackery DM. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. Eur J Nucl Med 1986; 12:447–454.
31. Moi MK, DeNardo SJ, Meares CF. Stable bifunctional chelates of metals used in radiotherapy. Cancer Res 1990; 50:789s–793s.
32. Deshpande SV, DeNardo SJ, Kukis DL, et al. Yttrium-90-labeled monoclonal antibody for therapy: labeling by a new macrocyclic bifunctional chelating agent. J Nucl Med 1990; 31:473–479.
33. DeNardo SJ, Kukis DL, Miers LA, et al. Yttrium-90-DOTA-peptide-chimeric L6 radioimmunoconjugate: efficacy and toxicity in mice bearing p53 mutant human breast cancer xenografts. J Nucl Med 1998; 39:842–849.
34. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002; 20:3262–3269.
35. Alcindor T, Witzig TE. Radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for patients with relapsed CD20+ B-cell non-Hodgkin's lymphoma. Curr Treat Options Oncol 2002; 3:275–282.
36. Meares CF, Moi MK, Diril H, et al. Macrocyclic chelates of radiometals for diagnosis and therapy. Br J Cancer Suppl 1990; 10:21–26.
37. Meares CF, Goodwin DA, Leung CS, et al. Covalent attachment of metal chelates to proteins: the stability in vivo and in vitro of the conjugate of albumin with a chelate of ^{111}indium. Proc Natl Acad Sci USA 1976; 73:3803–3806.
38. Imam SK. Advancements in cancer therapy with alpha-emitters: a review. Int J Radiat Oncol Biol Phys 2001; 51:271–278.
39. McDevitt MR, Sgouros G, Finn RD, et al. Radioimmunotherapy with alpha-emitting nuclides. Eur J Nucl Med 1998; 25:1341–1351.
40. Vaidyanathan G, Zalutsky MR. Targeted therapy using alpha emitters. Phys Med Biol 1996; 41:1915–1931.
41. Rotmensch J, Roeske J, Chen G, et al. Estimates of dose to intraperitoneal micrometastases from alpha and beta emitters in radioimmunotherapy. Gynecol Oncol 1990; 38:478–485.
42. McDevitt MR, Ma D, Lai LT, et al. Tumor therapy with targeted atomic nanogenerators. Science 2001; 294:1537–1540.
43. Geerlings MW, Kaspersen FM, Apostolidis C, van der Hout R. The feasibility of ^{225}Ac as a source of alpha-particles in radioimmunotherapy. Nucl Med Commun 1993; 14:121–125.

3

Radionuclide Joint Therapy

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BACKGROUND

Treatment of patients suffering from inflammatory joint disease is usually based on systemic pharmacotherapy and local treatment. In rheumatoid arthritis, for example, pain and joint swelling are often satisfactorily treated by anti-inflammatory or immunosuppressive drugs. However, it is quite common that single joints remain painful and require additional local treatment. Local therapy is also frequently indicated in degenerative osteoarthritis, where pharmacotherapy is less effective. While surgical procedures to remove the inflamed synovial membrane as well as intra-articular application of steroids are the most widely used local treatment modalities, radiation synovectomy has gained more and more acceptance during the last decade. The first animal studies using radionuclides for joint treatment were performed as early as 1923, and synovectomy by intra-articular application of β-emitting radioisotopes in patients was introduced in 1952 by Fellinger and Schmid in Vienna (1). Since that time, a large number of radionuclides have been studied and analyzed in clinical trials. Since 1968, the term radiosynoviorthesis has been used, meaning a restoration (from the Greek word "orthesis") of the synovial membrane (from the Greek word "synovia") by the use of radionuclides (2). Today, radiosynoviorthesis is an alternative or supplementary therapeutic approach in addition to pharmacotherapy for the treatment of patients suffering from painful inflammatory joint disease.

TREATMENT OF INFLAMMATORY JOINT DISEASE

One of the main reasons for joint pain and effusion is an inflammation of the synovial membrane either caused by an autoimmune response in case of rheumatoid arthritis, chronic reactive arthritis, and arthritis in other immunoarthritic "rheumatoid" disorders or caused by mechanical stress and abrasion of cartilage and/or bone in case of osteoarthritis. Treatment of inflammatory joints therefore depends on the type of the underlying disease and is based on systemic drug therapy and local joint treatment. In rheumatoid arthritis, systemic baseline treatment with anti-inflammatory and immunosuppresive drugs is considered mandatory as rheumatoid arthritis is not only a disease of the joints but also of adjacent tendon sheaths and bursae. Generalized forms of rheumatoid arthritis with vasculitis and visceral involvement are common. Pain and joint swelling are often satisfactorily treated by systemic baseline therapy but often single joints remain painful and require additional local treatment in order to avoid severe side effects which may be caused by an intensified drug regimen. Local therapy is also frequently indicated in all cases of mono- or oligoarthritis such as osteoarthritis, pigmented villonodular synovitis, chronic postarthroplasty-synovitis, or chronic reactive arthritis. Well-established local treatment options are surgical resection, intra-articular steroid application, and radiosynoviorthesis. Surgical procedures, ranging from open-joint surgery to minimally invasive arthroscopic synovectomy, are associated with risks of surgery and anesthesia, need for hospitalization, and a prolonged period of rehabilitation. Long-term success rates for surgery are about 50% to 80% with a high risk of relapse, especially in case of pigmented villonodular synovitis. Chemical synovectomy by intra-articular application of anti-inflammatory and antiproliferative substances like osmic acid, nitrogen mustards, methotrexate, and cobra venom has been almost completely abandoned because of possible joint damage caused by these highly toxic compounds. Intra-articular injection of corticosteroids was first described in 1951 (3) and is still the most frequently applied and widespread therapeutic approach in the local treatment of synovitis. However, many studies have described negative effects on articular cartilage metabolism and vitality (4–7). Furthermore, repeated intra-articular steroid applications often result in increasingly shorter time periods of effective pain relief. Therefore, only few repeated injections per joint are recommended. Owing to the limitations of local treatment modalities, radiosynoviorthesis has become an alternative and in part supplementary therapeutic approach for the treatment of painful inflammatory joint disease, chronic recurrent joint effusion, or osteoarthritis.

BASIC PHYSIOLOGY

For radiation synovectomy, β-emitting radiocolloids are used for intra-articular application. Immediately after administration, the colloids are taken up by

phagocytosis by type-A synoviocytes which partly build the surface layer in the synovial membrane as well as by phagocytosing immunocompetent cells such as macrophages. Therefore, the size of the radiocolloidal particles is an important factor determining the biokinetics of the radiopharmaceutical. The colloid has to be small enough to be taken up by the synovial cells and to achieve a homogenous distribution within the whole joint. But it also has to have a particle diameter, which is large enough to avoid leakage out of the joint cavity by venous or lymphatic drainage, which would result in an increased irradiation of the whole body and particularly of the locoregional lymph nodes, the liver, and the spleen. The most appropriate particle size was described to be between 2 and 5 μm (8). Using such radiocolloids, animal studies in rabbits demonstrated a homogenous distribution throughout the synovial tissue by autoradiography (9,10) while no uptake in the articular cartilage was observed. Most of the energy of the β particles is deposited within a range of millimeters up to 1 cm into synovial tissue depending on the chosen radionuclide. The biological effects within the irradiated tissue are caused by both direct damage and indirect interaction. Secondary oxygen radicals generated by tissue irradiation are known to destroy the cellular membranes by lipid peroxidation and result in DNA strand damage and breaks. Oxygen radicals are also potent inductors of apoptosis. All these interactions result in fibrinoid necrosis, sclerosis, and fibrosis of the synovial stroma, the inflammatory cells, and the capillaries within the synovial membrane. A reduction in volume of the synovial tissue together with a significant reduction of the inflammatory pannus tissue is seen within a few weeks (11). The occlusion of capillaries of the synovial membrane decreases the secretory activity markedly (12,13). Thus, the clinical effects of radiosynoviorthesis for the patient are reduction of pain, swelling, and effusion.

RADIOPHARMACEUTICALS

Searching for the ideal compound, a large number of different radiopharmaceuticals has been used since the beginning of radiation synovectomy (14). The energy of the β particles must be high enough to penetrate the whole depth of the inflamed synovial membrane while both the adjacent articular cartilage and subchondral bone as well as the overlying tissue should not be damaged. This prerequisite makes clear that owing to the large range of joint size there will be no single radionuclide suitable for all joints. Related to joint size, three radionuclides have gained widespread acceptance for radiosynoviorthesis in Europe (15): yttrium-90 (Y-90), rhenium-186 (Re-186), and erbium-169 (Er-169). Dysprosium-165 (Dy-165) plays an important role in radiation synovectomy of knee joints in Australia. However, the short physical half-life of 2.3 hours for Dy-165, which is favorable for the radiation dose to the patient, is a disadvantage in timing the delivery from the manufacturer to the patient, which hampers a broader use. Phosphorus-32 (P-32) is mainly used for radiation synovectomy in

Table 1 Radionuclides Used in Radiation Synovectomy and Their Physical Properties

Radionuclide	Half-life (d)	Maximum beta energy (MeV)	Gamma energy (keV)	Maximum range (mm)	Mean range (mm)	Compound
Yttrium-90	2.7	2.27	—	11	3.6	Silicate, citrate
Rhenium-186	3.7	1.07	137	3.7	1.1	Sulphide
Erbium-169	9.4	0.34	—	1.0	0.3	Citrate
Phosphorus-32	14.4	1.71	—	7.9	2.6	Chromic phosphate
Dysprosium-165	0.1	1.29	95	5.7	1.3	Ferric hydroxide

the United States. A summary of commercially available and routinely applied radionuclides for radiosynoviorthesis is given in Table 1.

Owing to its maximum tissue penetration of 11 mm, Y-90 should be used only for the treatment of knee joints. In all other joints there is a high risk of severe damage to the articular cartilage and necrosis of the overlying tissue. Re-186 is the candidate for treatment of mid-size joints while Er-169 is

Table 2 Radiopharmaceuticals and Recommended Activities for Radiosynoviorthesis

Radionuclide	Joint	Activity (MBq)
Yttrium-90	Knee	**185**–222
Rhenium-186	Shoulder	74–185 (**111**)
	Elbow	**74**–111
	Wrist	**74**
	Hip	111–**185**
	Ankle	**74**
	Subtalar	**37**–74
Erbium-169	Thumb base	30–**40**
	MCP/MTP	**25**–40
	Proximal interphalangeal	**20**
	Distal interphalangeal	10–**15**
Phosphorus-32	Knee	37–**185**
	Ankle, shoulder, elbow	18–92
	Wrist	
Dysprosium-165	Knee, hip	10,000–11,000
	Ankle	7400–9200

Activities given in bold are standard activities as used by the author.
Abbreviations: MCP, metacarpophalangeal; MTP, metatarsophalangeal.

used for all finger and toe joints, and, more recently, for the temporomandibular joint as well as the iliosacral joint. P-32 and Dy-165, their β energy ranging between the energy of Y-90 and Re-186, are usually applied in knee joints and mid-size joints such as shoulder, elbow, wrist, hip, and ankle. Recommended activities and radiopharmaceuticals for the various joints are summarized in Table 2.

INDICATIONS FOR RADIATION SYNOVECTOMY AND SUCCESS RATES

Although approved indications differ in various countries, radiation synovectomy in general is applicable for local therapy of synovitis and is therefore suitable for patients with different types of inflammatory joint disease. Indications always should be set based on a joint collaboration of the nuclear medicine specialist and the rheumatologist or orthopedic surgeon or any other clinician involved in the patient's treatment. Commonly applied indications are listed in Table 3.

As treatment success is achieved by radiogenic ablation of inflamed synovial tissue, an elevated blood-pool pattern in the joint synovia in a pretherapeutic three-phase bone scan is considered an useful tool for diagnosis of synovitis. Besides this positive "blood-pool scan" for treatment indication, the patient must suffer from pain or effusion in the respective joint. Radiation synovectomy is for symptomatic treatment only. Finally, adequate standard baseline pharmacotherapy with anti-inflammatory or antiproliferative drugs for at least six months prior to radiation synovectomy is mandatory in patients with rheumatoid arthritis, because intra-articular radiotherapy is not considered a primary treatment modality. In case of nonrheumatoid arthritis, criteria for a pharmacotherapy or local treatment prior to radiosynoviorthesis are not established. However, at least one failed or only short-lasting intra-articular injection of a long-acting steroid is usually considered mandatory prior to radiation synovectomy.

Compared with surgical procedures, the advantage of radiation synovectomy is that it is a minor ambulatory procedure which is useful even in nonoperable patients. Treatment of multiple joints with different radiopharmaceuticals

Table 3 Indications for Radiosynoviorthesis

Rheumatoid arthritis
Seronegative spondylarthritides such as psoriatic arthritis, peripheral arthritis in Bechterew's disease, and the like
Chronic reactive arthritis
Pigmented villonodular synovitis
Hemarthrosis/hemophilic arthritis in hemophilic patients
Osteoarthritis
Chronic synovitis after arthroscopic synovectomy or arthroplasty
Chronic effusion after arthroscopy or arthroplasty

can be performed in one session. The recommended limit for the total administered activity per session is 400 MBq. For practical reasons, joints of the lower extremity should be combined with joints of the contralateral upper extremity and vice versa. Another major advantage is the fact that no treatment-specific rehabilitation measures are necessary after radiosynoviorthesis. In comparison with intra-articular steroid application, symptomatic relief after radiation synovectomy usually lasts up to several years.

Owing to the slow processes of necrosis, sclerosis, and fibrosis in the inflamed synovial tissue there is a time delay in the decrease of the inflammatory activity and, thus, in the reduction of pain, swelling, and effusion. As a rule of thumb, the effects are seen faster in larger joints and occur within two to eight weeks in joints such as knee, ankle, shoulder, elbow, and wrist, while in finger and toe joints therapy effects may emerge as late as three to six months after treatment. An early improvement within hours or days is usually because of intra-articular steroid coapplication and immobilization of the joint rather than the radionuclide therapy itself. As these effects are limited to one to two weeks in most cases, a worsening of the symptoms might occur in the meantime until onset of the final effects of radiation synovectomy.

Radiosynoviorthesis is performed most often in patients with rheumatoid arthritis. The best results are achieved in patients with an early stage of the disease (16–19). Two meta-analyses published in 1993 (20) and 2002 (21) reported both an overall rate of 67% of good or very good improvement after radiation synovectomy in more than 5000 treated joints in patients with rheumatoid arthritis. Rates of clinical improvement range from 35% (22,23) to 100% (24) in knee joints treated with Y-90. A clinical study on radiosynoviorthesis with Dy-165 in 108 knee joints in 93 patients with seropositive rheumatoid arthritis revealed good results in 61% of these patients after one year (25–27) and results in the knee joint were found to be similar to the findings for Y-90 (28). In a large study on P-32 in rheumatoid arthritis, Ornetti et al. (29) reported on satisfactory clinical results in 84% of 217 treated joints including knees, ankles, hips, elbows, wrists, and finger joints. Clinical studies investigating the use of radiation synovectomy in different mid-size joints treated with Re-186 found good to excellent clinical results in 50% to 60% (30) and reached a success rate of 83% in elbow joints after one year (31). Göbel et al. (17) published a randomized, prospective trial testing radiation synovectomy with Re-186 against intra-articular corticoid injection as a monotherapy and against combined treatment. Follow-up examinations after three years in a total of 79 joints revealed a long-term success rate for the combined therapy of 82%, which was significantly higher than the success rates achieved with either one treatment modality alone. The authors were able to document a beneficial effect on the progression of osseous joint destruction for radiation synovectomy. For Er-169, clinical success rates are reported ranging from 55% (30) to 79% (18) in digital joints. One study in patients with rheumatoid arthritis reported success

rates of 58% which were significantly higher than in a control group treated with intra-articular steroids, where satisfying results were achieved in only 28% (19). Even better results were obtained by Boussina et al. (18) in 79% of the digital joints treated with Er-169 citrate.

For other immunoarthritic joint disorders such as psoriatic arthritis, ankylosing spondylarthritis, collagenosis, or chronic reactive arthritis, a rate of 80% improvement was found in 58 knee joints after treatment with Y-90 (32).

Pigmented villonodular synovitis is a rare but aggressive joint lesion that is usually treated by surgical or endoscopic synovectomy. Relapse rates of greater than 50% led to increasing interest in radiation synovectomy as a possible supplementary treatment approach. Significant clinical improvement was reported after combined surgical and radiation synovectomy in 11 patients, lasting for at least one year (33). During this time period, only two patients relapsed. Similar results were reported for a group of 10 patients with pigmented villonodular synovitis of various large joints (34).

The hemophiliac joint is becoming an increasing target for radiation synovectomy since the first description by Ahlberg in 1979 (35). Many patients are juveniles. Fernandez-Palazzi and Caviglia reported on 104 treatment procedures in 97 patients with a mean age of 10 years. Eighty percent showed excellent results without further bleeding after a follow-up of 25 years (36), which led the authors to the conclusion that radiation synovectomy is one of the best procedures to prevent hemarthrosis. A 78% success rate with improvement of motion and frequency of hemorrhage in 28 hemophiliac knee, ankle, and elbow joints treated with P-32 was reported by Siegel et al. (37). These findings were confirmed by the same group in a long-term survey in 81 hemophilia patients treated with P-32 (38,39).

Osteoarthritis is still a rare indication for radiation synovectomy. In these patients, an accompanying synovitis should be demonstrated prior to therapy. Only 7% of 13,450 intra-articular radionuclide applications in Europe between 1991 and 1993 were for osteoarthritis (15). Therefore, data on success rates of radiation synovectomy in osteoarthritic joints are less available. Spooren et al. (23) reported on some improvement after treating six osteoarthritic knee joints with 185 MBq Y-90. A retrospective study in patients treated in our own clinic revealed 34% clinical improvement in a total of 56 osteoarthritic joints ranging from 23% in digital joints to 43% in joints of the lower limb (40). More promising results with a success rate of 87% were observed in thumb base joints treated with Er-169 (41). Thus, except the common rhitzarthrosis of the thumb base, radiation synovectomy may be discussed as a last therapeutic attempt prior to surgical joint replacement or arthrodesis in severe osteoarthritis. Patients, however, should be informed that the probability of clinical success decreases with osseous destruction and concomitant damage of the juxta-articular fibromuscular system of the respective joint.

Since 1994, intra-articular application of Y-90 has been successfully used in standard dosage for treatment of recurrent knee joint effusion after

endoprosthetic joint replacement (42). A recent paper demonstrated subjective improvement in 89 of 107 patients and total deletion of joint effusion in 93 out of 107 patients with a follow-up of 10 years (43).

Although the average success rates for the various joints and the various underlying diseases are only about 60% to 75% in meta-analysis studies (20,21), it is important to keep in mind that these rates are achieved in joints that almost always had already undergone other treatment procedures with limited or no success, mostly local intra-articular steroid injection, and that patients with rheumatoid arthritis are usually under systemic baseline pharmacotherapy.

INDICATIONS FOR RERADIOSYNOVIORTHESIS

In cases of minor treatment response after the first radionuclide injection, retreatment is possible and may result in increased clinical benefit for the patient. Reradiosynoviorthesis is especially helpful in joints with initially highly thickened synovia, in joints with large and/or quickly recurrent effusion, and in finger or toe joints, in which only a portion of the radionuclide is given owing to an insufficient joint volume. Reradiosynoviorthesis is recommended not sooner than six months after the first treatment. In patients with recurrent effusion as the primary symptom, often seen in postarthroplasty synovitis of the knee, retreatment as early as three months after the first radionuclide therapy has been shown to be efficacious in our patients, as we observed no major improvement after three months in this subset of patients so far. Two failed radionuclide treatments should not be followed by another attempt of radiation synovectomy. Repeated treatment however seems justified in patients, suffering from a relapse, in whom the preceding radiation synovectomy had resulted in clinical improvement which lasted for several years. In case of reradiosynoviorthesis, the same activities and conditions apply as described for normal first-time procedures.

PATIENT PREPARATION AND TREATMENT PROCEDURE

Prior to treatment, the indication for radiation synovectomy should be carefully reviewed both by the referring physician and the nuclear medicine specialist (Table 4). This includes a detailed treatment and drug history (e.g., a previous intra-articular steroid injection may reduce or even normalize the uptake pattern on the blood-pool images as well as mask typical local findings such as swelling and effusion) and a physical examination to exclude other joint damage causes (see "Contraindications"). For the knee joint, ultrasound should be performed in addition to exclude a large or ruptured popliteal Baker's cyst. Radiographs of the joints to be treated should be reviewed in general to assess bony destruction of the joints and to exclude other reasons for pain, for example, osteochondral lesions or tumors. Further imaging such as magnetic resonance imaging (MRI) might be helpful, for example, in the knee joint to

Table 4 Patient Preparation and Treatment Procedure

Obtain history of pretreatment and drug history, review results of previous imaging, and confirm appropriateness of treatment indication
You should also check for
Allergy to contrast medium
Allergy to local anesthetics
Thyreotoxicosis (cave: contrast medium)
Diabetes (cave: steroids)
Blood clotting disorders (history of thrombosis, coagulation inhibitors, and the like)
Add missing imaging procedures such as radiographs of the joint, three-phase bone scanning, ultrasound (mandatory in knee joints), MRI if necessary
Obtain written informed consent, provide written and verbal information on radiosynoviorthesis
Pregnancy testing in women of childbearing age
Joint puncture according to the rules of asepsis in a dedicated room for articular injection procedures (the room must be also dedicated for the use of radionuclides according to national law and local regulations)
Local anesthetics if considered useful
Arthrography under fluoroscopy to prove proper needle position
Aspirate any effusion fluid
Injection of the radiopharmaceutical (use appropriate shielding devices), check for the correct radionuclide and activity
Inject steroids in the knee (e.g., 20–40 mg of triamcinolone) and mid-size joints (20 mg of triamcinolone); otherwise, flush the needle with 0.9% saline
Strict and complete immobilization of the joint with a splint or bandage for at least 48 hours
Distribution scan (except for erbium-169)

exclude damages to the menisci, joint capsule, or ligaments which might require surgical intervention. Two-phase bone scanning of the respective joint is recommended in all patients to prove synovitis.

Patients should receive written and verbal information about the procedure, and written informed consent should be obtained prior to treatment. Informed consent should include the rationale for treatment, treatment alternatives, potential side effects, and outcome. Patients should also be instructed about the need for strict joint immobilization for 48 to 72 hours.

Once the indication has been confirmed, radiation synovectomy is performed by a nuclear medicine specialist who is allowed to handle and administer radiopharmaceuticals according to national and local legislation and regulations for the use of radioactive products. For the joint puncture, the help of a physician experienced in this procedure may be necessary. Local anesthetics can be helpful but their effectiveness decreases with decreasing pH levels in an inflamed joint

capsule. According to our experiences, joint puncture can be performed without anesthetics in almost all the patients without causing more pain than, for example, in venipuncture, provided that a proper puncture technique is used. Arthrocentesis is conducted under sterile conditions in a dedicated room for intra-articular injection procedures, and followed by arthrography with a water-soluble contrast agent to ensure intra-articular needle localization. Fluoroscopic arthrography should be performed in all joints to reduce the risk of para-articular injection and subsequent tissue necrosis. Only in the knee joint, the injection can be given without imaging guidance although the radionuclide should not be injected unless correct intra-articular needle placement has been ensured by aspiration of synovial fluid. In the phalangeal joints arthrography is hampered by the small intra-articular volume. A small drop of contrast medium in the conus of the needle may be helpful to check for proper intra-articular injection in these joints although this is not mandatory. There are no reports of tissue necrosis after injection of Er-169. Synovial effusion should be aspirated whenever necessary. Then, the radionuclide in a shielded syringe is injected through the same needle by simply exchanging the syringes. This is followed by application of 10 to 40 mg of triamcinolone in the knee and mid-size joints. It is usually not possible to administer steroids in addition to the radiopharmaceutical in finger and toe joints. Steroids are given to rinse the radionuclide from the cannula and avoid tissue and skin contamination during needle extraction. Alternatively, the needle should be flushed with 0.9% saline. Intra-articular steroids prevent a transient aggravation of symptoms owing to radiogenic synovitis and reduce the risk of an early recurrence of effusion which can increase lymphatic drainage out of the joint. Finally, a passive movement of the joint is performed to achieve a homogenous intra-articular distribution of the radionuclide. Then the joint is strictly immobilized with a splint or bandage for 48 to 72 hours to prevent leakage of the radiopharmaceutical into venous or lymphatic vessels. In joints treated with Re-186 or Dy-165 (γ-radiation) and Y-90 or P-32 (bremsstrahlung), a distribution scan should be acquired with a gamma camera (a wide energy window is recommended for the bremsstrahlung in case of Y-90 and P-32) after radionuclide injection to verify successful intra-articular injection and proper distribution within the joint. In case of intra-articular injection without proper distribution of the radioactivity within the joint space shortly after injection it has been shown useful to wait for a few hours and repeat imaging. After that time, the distribution pattern usually has improved; otherwise the patient may be asked to perform some controlled joint exercise to enhance radiocolloid distribution. In case of para-articular injection, no reliable recommendations exist owing to the small number of documented cases and lack of experience. One alternative would be to wait and watch carefully until demarked necrotic tissue can be resected. Another alternative would be to perform surgery immediately to remove as much of the para-injected activity as possible by flushing the tissue and by resecting radioactive tissue around the injection site, if possible under guidance of a gamma probe such as the one used for sentinel lymph node detection (see also “Local Complications”).

Table 5 Contraindications for Radiosynoviorthesis

Absolute contraindications
Pregnancy, lactation
Septic arthritis
Local skin and tissue infections
Ruptured popliteal cyst, ruptured joint capsule
Relative contraindications
Severe joint instability or bone destruction
Children and young adults <20 years

A short guideline summarizing patient preparation and treatment procedure is published by the European Association of Nuclear Medicine (44).

CONTRAINDICATIONS

An absolute contraindication for radiation synovectomy is pregnancy. Routine pregnancy testing should be performed prior to treatment in women of childbearing age. Patients who are actively lactating or nursing also should not undergo radionuclide joint treatment. After radiation synovectomy, pregnancy should be avoided by effective contraception for four to six months (Table 5).

Radiation synovectomy is also contraindicated in septic arthritis and synovial cyst rupture. Local skin or tissue infections are also contraindications owing to the high risk of inducing a joint infection. The recommended time interval between arthroscopy or joint surgery and radiosynoviorthesis is four to eight weeks. For treatment regimens combining surgical and radiation synovectomy, radionuclide injection usually is performed six weeks to three months after surgical synovectomy (13,34,45).

Severe joint instability caused by damage to the joint capsule or ligaments as well as meniscus injuries may require surgical intervention rather than radiation synovectomy.

In children and young adults during bone growth phase, radiation synovectomy should be avoided. Activity levels may be adjusted to 50% to 100% of the recommended activity in adults for the respective joint depending on age and size of the child.

The application of iodine-containing contrast medium as well as local anesthetics may be contraindicated in patients with known allergy or adverse reactions to these drugs. Iodine-containing contrast medium is contraindicated in patients with thyreotoxicosis.

Joint puncture is contraindicated in patients with an increased risk of bleeding. In patients under anticoagulation therapy, Quick's value should be in the range of $>40\%$ to 50% for the day of treatment. In hemophilia patients, the respective factor serum levels should be a minimal of $>50\%$ of the normal level prior to joint puncture.

Another often quoted contraindication is the presence of Baker's cyst, a popliteal bulge of the posterior joint capsule. This cyst is quite common in

patients with recurrent joint effusion. A few instances of spontaneous rupture of a Baker's cyst led to the recommendation that patients with Baker's cysts should not be treated with radiation synovectomy. However, so far there are no reports in literature showing a rupture following radiosynoviorthesis while few reports in more than 150 patients demonstrated the usefulness of this treatment in the presence of a Baker's cyst with no severe side effects (46). According to our experience, a Baker's cyst can be found in about 20% to 30% of all patients scheduled for knee treatment. If there is a large cyst of greater than 15 cm in diameter, we refer the patient to surgery for consultation and possibly surgical removal. In smaller cysts with a clearly visible duct connecting the cyst to the joint space, we puncture the cyst, try to remove as much fluid as possible, and administer 20–40 mg of triamcinolone three to five days before radiation synovectomy. This usually results in a distinct shrinkage of the cyst, and radiation synovectomy can be performed without any problems. In the rare case of patients with a possible valve mechanism which could result in trapping of the radiopharmaceutical within the cyst and subsequent cyst rupture, we perform a joint cavity scintigraphy with technetium (Tc)-99 m-labeled colloids. In patients with normal distribution pattern showing the tracer within the whole joint after a period of two to three hours including activity such as knee-bending and walking, we have not encountered complications after radiosynoviorthesis.

SIDE EFFECTS AND DOSIMETRIC CONSIDERATIONS

Side effects of radiation synovectomy are related to local complications, which arise from para-articular injection and intra-articular infection (Table 6). They may also be related to radiation exposure during the normal treatment course such as a transient radiogenic synovitis, potential radiation damage to articular cartilage or subchondral bone, and irradiation of locoregional lymph nodes, liver, and spleen owing to extra-articular leakage of the radiocolloids.

Other side effects may arise from allergic reactions to the contrast medium or local anesthetics, thrombosis as a result of immobilization, or flush symptoms or hyperglycemia in diabetic patients owing to systemic resorption of the intra-articularly applied steroids. In diabetic patients, the dose of intra-articular steroids may be reduced, and the patients should be instructed to regularly check their blood glucose levels for the next two days. In patients with a history of thrombosis or other disorders with an increased risk of blood clotting, antithrombotic measures are recommended and the patients should be carefully instructed to watch for any signs of thrombosis after treatment and immobilization of joints of the lower limbs.

LOCAL COMPLICATIONS AFTER RADIATION SYNOVECTOMY

Local complications after radiation synovectomy are very rare. A transient radiogenic effusion is seen in 2% of the patients several hours after application of the

Table 6 Patient Instructions, Side Effects, and Radiation Safety Considerations

Patients should receive written and verbal information about the procedure and its side effects:
Strict immobilization of the joint is absolutely necessary for treatment efficacy and radiation safety
Patients benefit from the treatment in about 60% to 70% of the cases
Treatment response will be delayed by two to eight weeks in knee and mid-size joints and may be delayed up to three to six months in finger and toe joints
Risk of temporary worsening of the symptoms due to radiation-induced inflammation (cooling with ice packs, over-the-counter anti-inflammatory drugs)
Joint puncture is associated with the risks of local bleeding, bruising, and infection
Risks associated with application of radionuclides are local tissue necrosis as well as radiation exposure and future malignancy
Other risks associated with the procedure are allergic reactions to contrast medium and local anesthetics, hyperglycemia in diabetic patients and flush symptoms from steroids, thyreotoxicosis as a result of iodine-containing contrast medium, and thrombosis due to immobilization
Patients should be advised to report any worsening or other uncommon changes in the treated joint, and the patient should be given a contact he can reach at any time
Information about radiation safety considerations should be provided:
Radiosynoviorthesis should not be performed in pregnant or breastfeeding women
Pregnancy should be avoided after radiation synovectomy by effective contraception for four to six months
Urinary contamination should be avoided by flushing the toilet two or three times and handwashing after every toilet's use, men should urinate sitting down
No additional home precautions are required

radionuclide (47). Aggravation of local pain and swelling 6 to 48 hours after treatment has been observed in about 15% of our patients, mostly in finger and toe joints which received no steroid application. These symptoms are usually self-limited without further intervention and can be treated simply by cooling the joint with ice packs or, if necessary, with anti-inflammatory drugs such as ibuprofen.

More severe complications are local skin and needle track ulcerations which may occur if drops of the radionuclide flush back out of the needle during retraction from the joint. This can be easily avoided by flushing the needle with steroids or 0.9% saline after application of the radionuclide, as described before. Savaser et al. (48) report on a needle track ulceration after radiation synovectomy of an ankle joint with Re-186, which showed healing by scar formation after a few weeks without any further treatment. Necrosis of periarticular tissue is the worst local complication in radiation synovectomy and is caused by accidental para-articular injection of the radionuclide. A very low frequency of two cases of necrosis out of 11,000 treatment procedures was reported by Kolarz and Thumb in 1982 (49). With at least 23,000 radiation synovectomy

procedures performed in Europe in 2001, there is only one documented case of radionecrosis in a knee joint after application of Y-90 (50). Apart from these data, very few cases have been reported in literature. Interestingly, there are no reports on radionecrosis for Er-169.

Besides an insufficient technique during joint puncture, the use of an inappropriate radionuclide is another possible reason for radionecrosis. A case of severe necrosis with an open wound was reported after injection of Y-90 into an ankle joint, which should be treated with a radionuclide of lower energy and a lower tissue range such as Re-186 (51). Therapy was performed by immediate surgical excision of the necrotic soft tissue and closure was achieved with a fasciocutaneous lap. In other cases (unpublished data, personal communications), hyperbaric oxygen was successfully used for treatment of superficial radiogenic ulcers. However, owing to the small number of well-documented cases, no reliable guidelines exist for the treatment of radionecrosis after radiation synovectomy.

RADIATION EFFECTS TO ARTICULAR CARTILAGE AND BONE

Experimental data and morphological studies on radiation effects to diarthrodial tissues, especially articular cartilage and subchondral bone are rare and sometimes contradictory. Intra-articular injection of 15 MBq of Y-90 in rabbit knee joints was reported to cause both focal clustering of chondrocytes and fibrillation of the collagenous matrix of the articular cartilage (11). Similar results with focal damage of chondrocytes and surrounding extracellular matrix were observed in eight patients with rheumatoid arthritis after treatment of the knee joint with 185 MBq of Y-90 (52). Contradictory results with no microscopic signs of cartilage degeneration were found after application of 150 MBq of Y-90 into knee joints of dogs (12) and 370 MBq of gold-198 (Au-198) in adult rats (53). Ongoing studies concerning the effects of Y-90 on vitality and metabolism of bovine articular cartilage chondrocytes in a three-dimensional alginate culture system show that chondrocytes survive even the highest activity of 3 MBq of Y-90 per milliliter of the medium, which is an activity concentration similar to the in vivo situation in a patient (54). Photometric assessment of membrane integrity showed no signs of membrane destruction by lipid peroxidation. However, biochemical analysis of cell metabolism demonstrated a significant decrease in the synthesis of type II collagen (54). In light of these in vitro studies, a radiogenic decrease of collagen synthesis must be taken into account if potential side effects of radiation synovectomy are discussed. However, because similar effects can be observed in rheumatoid arthritis as well, the clinical impact of these findings is not clear.

Bone surface and red bone marrow are also regarded as potentially critical organs (55). The bone surface dose was described to be 25% of the synovial surface dose in case of Y-90, 4% in case of Re-186, and negligible for Er-169 (56). The dose to the bone surface further decreases with a thickening of the synovial membrane in inflammatory joint disease, which was demonstrated in an

arthritic joint model with tissue slabs of synovial membrane, articular cartilage, and bone in synovial fluid (57). For the bone surface, a maximum dose of 18 Gy was calculated for 185 MBq of Y-90, which is not considered to be a dose to cause significant bone damage or necrosis. The dose to the bone marrow in large or mid-size joints is considered negligible owing to the fact that the distance to the radiation source is greater than the mean tissue penetration of the β-emitting radionuclides used for radiation synovectomy.

WHOLE-BODY RADIATION EXPOSURE

Whole-body radiation dose and lymph node irradiation were the first disadvantages reported after radiation synovectomy of the knee joint with Au-198 (11,58). Today, significant whole-body radiation dose and lymph node irradiation can result from extra-articular leakage of the applied radiopharmaceutical by both lymphatic and venous drainage. Leakage rates of up to 48% have been published and a 10% leakage rate is regarded as reasonable assumption in clinical routine. For Y-90, this is mainly because of the lack of strict size control of the colloidal radionuclide. Very small particles leave the joint more easily and can lead to high leakage rates (8). Moreover, colloidal solutions of Y-90 with a pH <6 may contain free Y-90 ions which can easily be transferred from the treated joint (59). After radiation synovectomy with Re-186, the activity in lymph nodes was found to be 6% of the injected activity one week after injection, and 2.1% of the activity was seen in the hepatosplenic area (60). Leakage data on Er-169 colloid report a maximum rate of 14% of the injected activity (61). For Dy-165, leakage rates seem to be comparatively low with no detectable leakage at all in 22 of 27 (62) treated knee joints. In cases of leakage, the mean leakage rate was always lower than 1% of the injected activity resulting in doses to the lymph nodes ranging from 0.5 to 2.4 Gy (63,64) and 0.03 Gy to the liver (65). Low leakage rates are also reported for P-32. Chromic phosphate colloidal particles are about ten times the size of Y-90 colloid particles (66). In 125 joints treated with P-32, leakage rates of less than 2% of the injected activity were found by Siegel et al. in locoregional lymph nodes (38) while Mathew et al. (66) observed no leakage to locoregional lymph nodes, liver, or spleen in 11 pediatric hemophilia patients.

The degree of leakage is influenced by the particle size and radiochemical stability of the radiopharmaceutical and also by the degree of joint movement during the first days after treatment. One single active use of the respective joint was reported to result in a leakage up to 40% of the injected activity (67). Therefore, strict immobilization for at least 48 hours is regarded as mandatory to reduce extra-articular drainage to a minimum. Whole-body radiation-absorbed doses were reported ranging from 9 to 99 mSv after application of 200 MBq of Y-90 into the knee joint with a median of 37 mSv (68). In the same study, the total gonadal dose was 0.1 mSv in women and 0.2 mSv in men. Physical dosimetry using blood sample counts and scintigraphic data showed an effective whole-body dose of 26.7 ± 5.1 mSv in radiation synovectomy with 70 MBq of

Re-186 while the effective dose after application of 30 MBq of Er-169 was described to be lower than 1 mSv (60).

Apart from physical dosimetry, biological dosimetry data were obtained in patients after radiation synovectomy. An increase of chromosomal aberrations with a three-fold frequency of dicentric lymphocytes in the regional lymph nodes was described first by Daker in 1979 (69) after treatment of knee joints with Y-90. A French group found an increased rate of chromosomal damages in blood lymphocytes after radiation synovectomy with Y-90 and Re-186 in 11 out of 16 patients for three weeks of follow-up (70). Er-169 failed to induce any chromosomal aberrations, but treatment with Re-186 led to a cumulative increase of dicentric lymphocytes from 5 to 16 out of 10,000 (60). However, other patient studies failed to demonstrate a significant increase of chromosomal aberrations in lymphocytes for P-32 (71) or Dy-165 and Y-90 (72), although some single cases with a raised dicentrics frequency were observed compared with pretreatment findings. Furthermore, no adverse changes of biomarkers for cytogenic damage such as the micronucleus frequency in lymphocytes or urinary excretion of hydroxy-deoxy-guanosine were found in patients treated with Dy-165 (62). Based on these findings, some authors do not recommend radiation synovectomy in patients below the age of 40 owing to the possible risk of malignant induction (22,69). However, the long-lasting clinical practice and the lack of any well-documented cases of malignancy resulting from radiation synovectomy suggest a very low and acceptable risk compared with the benefit for the patient (60). The tumor morbidity rate as a result of whole-body irradiation was calculated as 0.4 per 1000 related to International Commission on Radiological Protection (ICRP) 60 risk data (73) and the genetic radiation risk related to United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) data was described to be several orders of magnitude below one per 1000 (74).

TREATMENT MONITORING AND PATIENT FOLLOW-UP

After radionuclide injection, a distribution scan should be acquired with a gamma camera (except for Er-169) to document successful intra-articular injection and proper distribution within the joint.

For the follow-up which is usually performed by the referring physician in close collaboration with the nuclear medicine specialist, no standard guidelines

Table 7 Treatment Monitoring and Patient Follow-Up

An early check-up for side effects or other complications is recommended at four to seven days after treatment; this might be done by phone as well
Clinical follow-up examinations to assess treatment response are recommended 3–4, 6, and 12 months after therapy
Reradiosynoviorthesis should not be scheduled sooner than six months after the first therapy; treatment of other joints can be performed anytime

exist (Table 7). It is recommended to observe for early side effects or complications at four to seven days after treatment. Furthermore, patients should be advised to report any worsening or other uncommon changes in the treated joint, and the patient should be given a contact that he can reach at any time. Owing to intense effusion it might become necessary to puncture a treated joint. Within the first two to four weeks, joint punctures should be performed in the nuclear medicine department in order to properly handle and store the contaminated fluid in accordance with national radiation safety regulations.

Clinical follow-up examinations to assess treatment response are recommended 3, 6, and 12 months after radiation synovectomy. Reradiosynoviorthesis should not be scheduled sooner than six months after the first therapy.

RADIATION SAFETY CONSIDERATIONS FOR PERSONNEL

So far, few data exist on radiation exposure to personnel. As all the commonly used radionuclides are β emitters and only Re-186 and Dy-165 have an additional γ component, significant radiation exposure is only achieved during handling and application of the radiopharmaceuticals. Performing the radionuclide application under fluoroscopy results in an additional radiation exposure to the personnel. For a standard application of 10 GBq Dy-165, the finger doses for the applying physician and the technologist were 0.7 mSv and 0.3 mSv, respectively, while whole-body doses were reported to be 0.1 mSv for the technologist and 0.04 mSv for the physician (75). Liepe et al. (76) found that the highest radiation dose during radionuclide injection is received by the left index finger in right handers. The maximum received doses were 22.1, 1.8, and 0.8 mSv/MBq for Y-90, Re-186, and Er-169, respectively. This translates into finger doses of 4 mSv per knee joint treated with 200 MBq of Y-90, about 0.1–0.2 mSv per mid-size joint treated with 70–185 MBq of Re-186, and 0.03 mSv per finger or toe joint treated with 15–40 MBq of Er-169, respectively. To minimize the high finger doses especially in cases of Y-90 and P-32, holding forceps and special shields are highly recommended which have been shown to decrease the radiation exposure by a factor of up to 50.

RADIATION SAFETY CONSIDERATIONS FOR THE PATIENT

Under current regulations of most countries, standard radiopharmaceuticals for radiation synovectomy may be administered in the outpatient setting and hospitalization is not required. As P-32, Y-90, and Er-169 are β emitters, and the bremsstrahlung they produce is not of significance for other persons, no precautions are necessary when these patients are released, except for good hygiene to avoid urine contamination. The only concern during the first two days after treatment is a possible urinary excretion of radioisotopes dissociated from the radiocolloid. Therefore, men should urinate sitting down, and the toilet should be flushed two or three times. Handwashing should be performed routinely after

urination. There is no need for the use of separate toilets. Measurements of radiation coming from patients who have received gamma-emitting Dy-165 or Re-186 indicate that no additional home precautions are required other than those noted before. For Dy-165, the maximum radiation dose to other persons at 1-m distance was found to be lower than 0.1 mSv (75). Owing to these data there is no need to avoid proximity to one's spouse, children, or pregnant women.

REFERENCES

1. Fellinger K, Schmid J. Local therapy of rheumatic diseases. Wien Z Inn Med 1952; 33:351–363.
2. Delbarre F, Cayla J, Menkes C, et al. Synoviorthesis with radioisotopes. Presse Med 1968; 76:1045–1050.
3. Hollander JL, Brown EM Jr, Jessar RA, Brown CY. Hydrocortisone and cortisone injected into arthritic joints; comparative effects of and use of hydrocortisone as a local antiarthritic agent. J Am Med Assoc 1951; 147: 1629–1635.
4. Barrueco JL, Gazquez A, Redondo E, Regodon S. Changes in the coxofemoral articular cartilage in Wistar rats after systemic administration of corticoids. Anat Anz 1993; 175:47–51.
5. Fubini SL, Todhunter RJ, Burton-Wurster N, Vernier-Singer M, MacLeod JN. Corticosteroids alter the differentiated phenotype of articular chondrocytes. J Orthop Res 2001; 19:688–695.
6. Robion FC, Doize B, Boure L, et al. Use of synovial fluid markers of cartilage synthesis and turnover to study effects of repeated intra-articular administration of methylprednisolone acetate on articular cartilage in vivo. J Orthop Res 2001; 19:250–258.
7. Podbielski A, Raiss R. Dose related effects of dexamethasone treatment on the ultrastructure of articular cartilage in rats. Agents Actions 1986; 17: 322–324.
8. Noble J, Jones AG, Davies MA, et al. Leakage of radioactive particle systems from a synovial joint studied with a gamma camera: its application to radiation synovectomy. J Bone Joint Surg Am 1983; 65:381–389.
9. Isomaki AM, Inoue H, Oka M. Uptake of 90 Y resin colloid by synovial fluid cells and synovial membrane in rheumatoid arthritis. A radioautographic and electron microscopic study. Scand J Rheumatol 1972; 1:53–60.
10. Webb FW, Lowe J, Bluestone R. Uptake of colloidal radioactive yttrium by synovial membrane. Ann Rheum Dis 1969; 28:300–302.
11. Pavelka K, Meier-Ruge W, Muller W, Fridrich R. Histological study of effects of colloidal 90 yttrium on knee joint tissues of rabbits. Ann Rheum Dis 1975; 34:64–69.
12. Myers SL, Slowman SD, Brandt KD. Radiation synovectomy stimulates glycosaminoglycan synthesis by normal articular cartilage. J Lab Clin Med 1989; 114:27–35.
13. Kerschbaumer F, Kandziora F, Herresthal J, Hertel A, Hor G. Combined arthroscopic and radiation synovectomy in rheumatoid arthritis. Orthopäde 1998; 27:188–196.
14. Harbert JC. Nuclear Medicine Therapy. New York: Thieme, 1987.

15. Clunie G, Ell PJ. A survey of radiation synovectomy in Europe, 1991–1993. Eur J Nucl Med 1995; 22:970–976.

16. Gobel D, Gratz S, von Rothkirch T, Becker W. Chronic polyarthritis and radiosynoviorthesis: a prospective, controlled study of injection therapy with erbium 169 and rhenium 186. Z Rheumatol 1997; 56:207–213.

17. Gobel D, Gratz S, von Rothkirch T, Becker W, Willert HG. Radiosynoviorthesis with rhenium-186 in rheumatoid arthritis: a prospective study of three treatment regimens. Rheumatol Int 1997; 17:105–108.

18. Boussina I, Toussaint M, Ott H, Hermans P, Fallet GH. A double-blind study of erbium169 synoviorthesis in rheumatoid digital joints. Results after one year. Scand J Rheumatol 1979; 8:71–74.

19. Menkes CJ, Go AL, Verrier P, Aignan M, Delbarre F. Double-blind study of erbium 169 injection (synoviorthesis) in rheumatoid digital joints. Ann Rheum Dis 1977; 36:254–256.

20. Deutsch E, Brodack JW, Deutsch KF. Radiation synovectomy revisited. Eur J Nucl Med 1993; 20:1113–1127.

21. Kresnik E, Mikosch P, Gallowitsch HJ, et al. Clinical outcome of radiosynoviorthesis: a meta-analysis including 2190 treated joints. Nucl Med Commun 2002; 23:683–688.

22. Boerbooms AM, Buijs WC, Danen M, van de Putte LB, Vandenbroucke JP. Radio-synovectomy in chronic synovitis of the knee joint in patients with rheumatoid arthritis. Eur J Nucl Med 1985; 10:446–449.

23. Spooren PF, Rasker JJ, Arens RP. Synovectomy of the knee with 90Y. Eur J Nucl Med 1985; 10:441–445.

24. Bowen BM, Darracott J, Garnett ES, Tomlinson RH. Yttrium-90 citrate colloid for radioisotope synovectomy. Am J Hosp Pharm 1975; 32:1027–1030.

25. Sledge CB, Zuckerman JD, Zalutsky MR, et al. Treatment of rheumatoid synovitis of the knee with intraarticular injection of dysprosium 165-ferric hydroxide macroaggregates. Arthritis Rheum 1986; 29:153–159.

26. Zalutsky MR, Venkatesan PP, English RJ, et al. Radiation synovectomy with 165Dy-FHMA: lymph node uptake and radiation dosimetry calculations. Int J Nucl Med Biol 1986; 12:457–465.

27. Sledge CB, Noble J, Hnatowich DJ, Kramer R, Shortkroff S. Experimental radiation synovectomy by 165Dy ferric hydroxide macroaggregate. Arthritis Rheum 1977; 20:1334–1342.

28. Edmonds J, Smart R, Laurent R, et al. A comparative study of the safety and efficacy of dysprosium-165 hydroxide macro-aggregate and yttrium-90 silicate colloid in radiation synovectomy—a multicentre double blind

clinical trial. Australian Dysprosium Trial Group. Br J Rheumatol 1994; 33:947–953.

29. Onetti CM, Gutierrez E, Hliba E, Aguirre CR. Synoviorthesis with 32P-colloidal chromic phosphate in rheumatoid arthritis—clinical, histopathologic and arthrographic changes. J Rheumatol 1982; 9:229–238.
30. Menkes CJ. Radioisotope synoviorthesis in rheumatoid arthritis. Rheumatol Rehabil 1979; Suppl 1:45–46.
31. Gregoir C, Menkes CJ. The rheumatoid elbow: patterns of joint involvement and the outcome of synoviorthesis. Ann Chir Main Memb Super 1991; 10:243–246.
32. Aleksieva T, Kunev K. The treatment of gonarthritis with yttrium-90. Vutr Boles 1990; 29:59–61.
33. Kat S, Kutz R, Elbracht T, Weseloh G, Kuwert T. Radiosynovectomy in pigmented villonodular synovitis. Nuklearmedizin 2000; 39:209–213.
34. Shabat S, Kollender Y, Merimsky O, et al. The use of surgery and yttrium 90 in the management of extensive and diffuse pigmented villonodular synovitis of large joints. Rheumatology (Oxford) 2002; 41:1113–1118.
35. Ahlberg A, Pettersson H. Synoviorthesis with radioactive gold in hemophiliacs. Clinical and radiological follow-up. Acta Orthop Scand 1979; 50:513–517.
36. Fernandez-Palazzi F, Caviglia H. On the safety of synoviorthesis in haemophilia. Haemophilia 2001; 7(suppl 2):50–53.
37. Siegel HJ, Luck JV Jr, Siegel ME, Quines C, Anderson E. Hemarthrosis and synovitis associated with hemophilia: clinical use of P-32 chromic phosphate synoviorthesis for treatment. Radiology 1994; 190:257–261.
38. Siegel HJ, Luck JV Jr, Siegel ME, Quinones C. Phosphate-32 colloid radiosynovectomy in hemophilia: outcome of 125 procedures. Clin Orthop Relat Res 2001:409–417.
39. Silva M, Luck JV Jr, Siegel ME. 32P chromic phosphate radiosynovectomy for chronic haemophilic synovitis. Haemophilia 2001; 7(suppl 2):40–49.
40. Kampen WU, Brenner W, Kroeger S, et al. Long-term results of radiation synovectomy: a clinical follow-up study. Nucl Med Commun 2001; 22:239–246.
41. Kampen WU, Hellweg L, Massoudi-Nickel S, et al. Clinical efficacy of radiation synovectomy in digital joint osteoarthritis. Eur J Nucl Med Mol Imaging 2005; 32:575–580.
42. Moedder G. Radiosynoviorthesis in patients with knee prosthesis (abstract). Nuklearmedizin 1994; 33:A39.

43. Moedder G, Moedder-Reese R. Radiosynoviorthesis after total knee replacement: effective therapy of "polyethylene disease" (in German). Der Nuklearmediziner 2001; 24:97–103.

44. http://www.eanm.org/scientific_info/guidelines/guidelines_intro.php?navid=54.

45. Chin KR, Barr SJ, Winalski C, Zurakowski D, Brick GW. Treatment of advanced primary and recurrent diffuse pigmented villonodular synovitis of the knee. J Bone Joint Surg Am 2002; 84-A:2192–2202.

46. Klett R, Steiner M, Puille M, Bauer R. Einfluß der Radiosynoviorthese des Kniegelenks auf bestehende Bakerzysten (abstract). Nuklearmedizin 2000; 39:A90.

47. Gratz S, Gobel D, Becker W. Radiosynoviorthesis in inflammatory joint diseases. Orthopäde 2000; 29:164–170.

48. Savaser AN, Hoffmann KT, Sorensen H, Banzer DH. Radiosynoviorthesis in the treatment plan of chronic inflammatory joint diseases. Z Rheumatol 1999; 58:71–78.

49. Kolarz G, Thumb N. Methods of Nuclear Medicine in Rheumatology. Stuttgart: Schattauer, 1982.

50. Highgenboten CL. Arthroscopic synovectomy. Orthop Clin North Am 1982; 13:399–405.

51. Peters W, Lee P. Radiation necrosis overlying the ankle joint after injection with yttrium-90. Ann Plast Surg 1994; 32:542–543.

52. Kerschbaumer F, Bauer R, Falser N, Altmann H. Effects and side effects of radiosynovectomy with Yttrium 90 on rheumatic joint cartilage. Arch Orthop Trauma Surg 1979; 93:95–102.

53. Rubin P, Casarett G, Farrer P. The effects of intra-articular 198 Au instillations on articular cartilage. Radiology 1972; 103:685–690.

54. Kampen WU, Ailland J, Kurz B, et al. Effects of gamma-radiation on chondrocyte viability and metabolism in vitro (abstract). J Nucl Med 2001; 42(suppl 5):335.

55. IRCP. IRCP-26: Recommendations of the IRCP: International Commission on Radiation Protection, 1977.

56. Johnson LS, Yanch JC, Shortkroff S, et al. Beta-particle dosimetry in radiation synovectomy. Eur J Nucl Med 1995; 22:977–988.

57. Johnson LS, Yanch JC. Absorbed dose profiles for radionuclides of frequent use in radiation synovectomy. Arthritis Rheum 1991; 34:1521–1530.

58. Virkkunen M, Krusius FE, Heiskanen T. Experiences of intra-articular administration of radioactive gold. Acta Rheumatol Scand 1967; 13:81–91.

59. Neves M, Waerenborgh F, Patricio L. Palladium-109 and holmium-166 potential radionuclides for synoviotherapy—radiation absorbed dose calculations. Int J Rad Appl Instrum [A] 1987; 38:745–749.

60. Manil L, Voisin P, Aubert B, et al. Physical and biological dosimetry in patients undergoing radiosynoviorthesis with erbium-169 and rhenium-186. Nucl Med Commun 2001; 22:405–416.

61. Ruotsi A, Hypen M, Rekonen A, Oka M. Erbium-169 versus triamcinolone hexacetonide in the treatment of rheumatoid finger joints. Ann Rheum Dis 1979; 38:45–47.

62. Pirich C, Pilger A, Schwameis E, et al. Radiation synovectomy using 165Dy ferric-hydroxide and oxidative DNA damage in patients with different types of arthritis. J Nucl Med 2000; 41:250–256.

63. Pirich C, Prufert U, Havlik E, et al. Monitoring of the biodistribution and biokinetics of dysprosium-165 ferric hydroxide with a shadow-shield whole-body counter. Eur J Nucl Med 1997; 24:398–402.

64. Pirich C, Wanivenhaus A, Graninger W, et al. Radiosynovectomy with dysprosium-165 iron hydroxide. Acta Med Austriaca 1993; 20:49–53.

65. Sledge CB, Zuckerman JD, Shortkroff S, et al. Synovectomy of the rheumatoid knee using intra-articular injection of dysprosium-165-ferric hydroxide macroaggregates. J Bone Joint Surg Am 1987; 69:970–975.

66. Mathew P, Talbut DC, Frogameni A, et al. Isotopic synovectomy with P-32 in paediatric patients with haemophilia. Haemophilia 2000; 6:547–555.

67. Gratz S, Gobel D, Behr TM, Herrmann A, Becker W. Correlation between radiation dose, synovial thickness, and efficacy of radiosynoviorthesis. J Rheumatol 1999; 26:1242–1249.

68. Klett R, Puille M, Matter HP, et al. Activity leakage and radiation exposure in radiation synovectomy of the knee: influence of different therapeutic modalities. Z Rheumatol 1999; 58:207–212.

69. Daker MG. Prospective chromosomal study of 30 patients undergoing 90Y synovectomy. Rheumatol Rehabil 1979; Suppl 1:41–44.

70. Houvenagel E, Debouvry L, Leloire O, et al. Cytogenetic anomalies after isotope synoviorthesis in rheumatoid polyarthritis. Rev Rhum Mal Osteoartic 1991; 58:31–34.

71. Rivard GE, Girard M, Belanger R, et al. Synoviorthesis with colloidal 32P chromic phosphate for the treatment of hemophilic arthropathy. J Bone Joint Surg Am 1994; 76:482–488.

72. Prosser JS, Izard BE, Brown JK, et al. Induction of micronuclei in peripheral blood lymphocytes of patients treated for rheumatoid or osteo-arthritis of the knee with dysprosium-165 hydroxide macroaggregates or yttrium-90 silicate. Cytobios 1993; 73:7–15.

73. IRCP. IRCP-60: Recommendations of the IRCP: International Commission on Radiation Protection, 1991.

74. Lueders C, Feinendegen LE. Radiosynoviorthesis. Strahlenther Onkol 1993; 169:383–386.

75. Havlik E, Pirich C, Preitfellner J, et al. Radiation exposure from patients treated with 165Dy-ferric hydroxide. Nucl Med Commun 2001; 22:79–82.

76. Liepe K, Andreeff M, Mielcarek J, et al. Beta-radiation exposure at the finger tips during the radionuclide synovectomy. Nuklearmedizin 2003; 42:104–108.

4

Treatment of Differentiated Thyroid Carcinoma

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INTRODUCTION

Thyroid cancer is one of the most common endocrine malignancies. It has an increasing population incidence (1,2). The annual incidence per 100 individuals ranges from 1.2 to 2.6 in men and from 2.0 to 3.8 in women. Most of the tumors have a relatively indolent clinical course. However, subgroups of patients may have an aggressive clinical course or a high risk of developing recurrence (3). The optimum treatment for thyroid carcinoma is still debated and a number of controversies exist with respect to the extent of surgery, use of radioactive iodine, and postoperative thyroxine suppression.

The correct assessment of prognostic factors helps to determine patients at high risk for developing recurrences and facilitates the development of a selective approach to therapy. Most important is the appropriate selection of the type and extent of treatment (4).

This chapter evaluates the current concepts for management of differentiated thyroid carcinoma.

EPIDEMIOLOGY AND CLASSIFICATION

Although thyroid nodules are extremely common (in countries without iodine deficiency, thyroid nodules are clinically detectable in about 4% to 7% of the general population while this number can rise up to 30% of the population in areas with iodine deficiency) (5), malignant lesions derived from thyroid cells are relatively rare. Less than 1% of all malignant tumors are clinically recognized thyroid carcinomas. However, it is the most common endocrine malignant lesion comprising 90% of all endocrine malignant tumors. It is responsible for more deaths than all the other endocrine cancers combined (6).

Thyroid cancer occurs at all ages but is most common among middle-aged and postmenopausal women and in older men (7). According to reproductive status, the female to male incidence ratio varies, from being almost one in childhood, increasing to three from puberty to menopause, and declining to 1.5 by 65 years of age. Overall death rate is less than 10% (7).

Carcinoma of the thyroid is usually of follicular cell origin with four distinct subtypes (Table 1) or it can arise from the parafollicular or C-cells. Other malignant nonepithelial tumors of the thyroid are extremely rare (8,9).

Table 1 Classification of Thyroid Tumors

Epithelial thyroid carcinoma	
Papillary carcinoma	80% of the thyroid carcinomas are of the follicular variant subtype
Follicular carcinoma Oxyphilic or Hürthle cell carcinoma	20% of thyroid carcinomas with higher incidence rates in iodine-deficient areas
Poorly differentiated carcinoma	With morphological and biologic attributes intermediate between differentiated and anaplastic carcinomas
Undifferentiated or anaplastic carcinoma	Highly malignant cancer with undifferentiated cell populations
C-cell-derived thyroid carcinoma or medullary carcinoma	Arises from the parafollicular cells that secrete calcitonin. Sporadic or familial
Nonepithelial thyroid carcinoma	
Malignant lymphoma	
Sarcoma	
Hemangioendothelioma	
Secondary tumors	

Source: From Ref. 20.

Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are together referred to as differentiated thyroid cancer (DTC). These cancers synthesize thyroglobulin (Tg) and are usually characterized by radioiodine uptake. They tend to be sporadic although occasionally PTC is familial.

Anaplastic and medullary carcinomas and lymphomas comprise about 10% of all thyroid cancers (10) and they differ substantially from DTC relative to initial mode of spread, subsequent pattern of recurrence, and metastatic involvement. They have different prognosis and treatment.

DIFFERENTIATED THYROID CANCER—HISTOLOGIC TYPES AND VARIANTS

Papillary Thyroid Cancer

Common Histologic Type

Diagnosis is based on the presence of follicular differentiation with papillary and/or follicular structures and typical nuclear features. Nuclei are larger than normal and overlap. They may be fissured, with hypodense chromatin, and irregularly bordered with cytoplasmatic invagination (11).

Papillary thyroid cancers appear as firm, unencapsulated, or partly encapsulated tumors. Extension beyond the capsule has been reported in 8% to 32% of the cases (9). PTCs may be partly necrotic and some undergo cystic degeneration. PTC is often multifocal when it occurs in a single thyroid lobe and occurs in bilateral lobes in 20% to 80% of the cases (12). Lymph-node metastatic involvement is found in 15% to 80% of the cases depending on the extent of lymph node dissection and examination of the surgical specimen. From the ipsilateral thyroid lymph node chains they may spread to more distant lymph node groups to the upper mediastinal nodes. Vascular invasion is rare and distant metastases (mostly to lungs) are observed in 5% to 10% of the cases, mostly as a result of lymphatic spread (11). Lymph node metastases as the first clinical finding in patients with PTC are not uncommon. The mean 10-year survival rates in PTC are 80% to 90%, with optimal treatment.

Papillary Thyroid Cancer Variants

Encapsulated variant: A tumor capsule similar to that of an adenoma is present but with focal invasion. It has a good prognosis.

Follicular variant: There is total predominance of follicles over papillae. This type is found in young patients and the clinical behavior is similar to pure PTC (13,14).

There are three follicular carcinoma subtypes:

Macrofollicular variant
Encapsulated variant
Diffuse follicular variant—this subtype is more aggressive than the others with frequent lung metastases (15,16).

Thyroid diffuse sclerosing variant: This cancer is characterized by diffuse involvement of one or both thyroid lobes, widespread lymphatic permeation, prominent fibrosis, squamous metaplasia, psammoma body formation, and lymphoid infiltration. Lymph-node metastases are almost always present and lung metastases are frequent. It occurs more frequently in children and young adults (17).

Tall cell variant: This tumor is characterized by papillae structures covered with cells that are twice as tall as they are wide. Tumors are usually large, extend beyond the capsule, show frequent vascular invasion, lymph node and distant metastases. It occurs in elderly patients (18).

Columnar cell variant: This is a more rare tumor. It is characterized histologically by prominent nuclear stratification of elongated cells.

Hurthle cell variant: This is another rare tumor type. It is characterized by papillary structures lined with histologically distinct oxyphilic cells.

In general, the tall and columnar cell variants are more aggressive forms of thyroid papillary cancer.

According to the World Health Organization (WHO) classification, a PTC measuring 1.0 cm or less in diameter is identified as a microcarcinoma. It has a very good prognosis and grows very slowly (19). It may present as a small classic papillary carcinoma or may appear as an unencapsulated sclerotic nodule of a few millimeters in diameter that infiltrates the thyroid tissue ("occult carcinoma"). The microcarcinoma is usually detected as an incidental nodule at ultrasonography or by surgical histopathology in the thyroid resection specimen.

Follicular Thyroid Cancer

Common Histologic Type

Follicular thyroid cancer is an "epithelial carcinoma showing evidence of follicular cell differentiation but lacking the diagnostic features of papillary carcinoma" (11). It tends to be more common in regions with iodine deficiency and in patients older than 50 years. Ten-year survival rates are lower than in PTC ranging from 60% to 70%.

It usually presents as a solitary thyroid tumor. The diagnosis of malignancy depends on the presence of blood vessel and/or capsular invasion. Histologic

diagnosis is divided into two categories according to the degree of invasiveness. This aspect confers prognostic significance.

Encapsulated or minimally invasive FTC is an encapsulated tumor whose growth pattern resembles that of a microcarcinoma. Blood vessel invasion is almost never seen. It has a better prognosis than the widely invasive variant.

Widely invasive FTC may be partially encapsulated but the tumor margins are infiltrative and vascular invasion is often extensive. It always has a follicular element but when follicular differentiation is poor or absent the tumor is classified as a poorly differentiated carcinoma.

It invades blood vessels, and metastasizes to lungs and bone. Brain and lymphatic metastases are rare. Metastases are frequent in the widely invasive variant and rare in the minimally invasive one.

Follicular Thyroid Cancer Variants

Clear cell carcinoma: This is a rare follicular cancer variant with clinic characteristics similar to those of classic FTC. Tumor cells show glycogen accumulation or dilatation of the granular endoplasmic reticulum with a clear cell appearance.

Hurthle Cell Carcinoma (Oncocytic Carcinoma or Oxyphilic Variant Follicular Thyroid Cancer)

The precise classification of this tumor is controversial. The WHO considers this carcinoma as an oxyphilic variant of FTC (20). Other institutions consider that this tumor has different microscopic, behavioral, and etiopathogenic features that set it apart from all others (21). Hurthle cell carcinoma is composed of greater than 75% of cells with oncocytic features. It is a usually solitary tumor with complete or partial encapsulation. Malignant behavior is predicted by vascular or capsular invasion (as in FTC) (22). It is more frequently associated with extrathyroid extension and distant and lymph-node metastases than the common FTC. Although Hurthle cell carcinomas usually produce Tg they mostly lack radioiodine uptake in comparison with standard DTC.

Pathogenesis

Radiation

The major known risk factor for DTC is prior exposure to radiation. A history of radiation exposure has two major clinical implications: (*i*) increased risk of developing thyroid nodules and (*ii*) increased risk of a thyroid nodule being malignant.

Risk factors associated with radiation-induced thyroid tumors:

- Amount of radiation exposure
- Young age at exposure to radiation
- High serum Tg concentration
- Other radiation-related tumors
- First-degree relative with radiation-related tumor.

The most significant sources of radiation exposure are therapeutic irradiation and environment disasters. Radiation is known to induce DNA strand breaks (23,24). Recently, an increased incidence of childhood thyroid cancer was observed in heavily contaminated territories after the Chernobyl accident. Children aged less than five years at the time of the accident were more likely to develop thyroid cancer (25).

Studies of adult iodine-131 (I-131) exposure for therapeutic and diagnostic purposes continue to be reassuring with respect to addition of radiation risks. However, there is a suggestion of a small effect of I-131 on increased thyroid nodularity, carcinoma incidence, and thyroid carcinoma mortality, although this increased thyroid condition could be also related to the underlying thyroid condition or an increase in surveillance or diagnosis (26).

Oncogenes

The most frequent genetic alterations in DTC are somatic rearrangements of the RET proto-oncogene, which generate several chimeric RET\PTC in PTC.

Pre-existing Thyroid Disease

Thyroid carcinoma is often preceded by other thyroid diseases. Goiter, benign thyroid nodules, lymphocytic thyroiditis, and Graves' disease, all are common processes. Whether patients with these abnormalities are at higher risk for developing thyroid carcinoma is uncertain (27,28).

Hormonal and Reproductive Factors

Thyroid carcinoma, like most thyroid diseases, occurs more frequently in women than in men, suggesting that hormonal factors are involved in its pathogenesis. More studies need to be performed to conclude if puberty, parity, or exogenous estrogens are associated with thyroid cancer.

Dietary Factors

Iodine: Some decades ago, a study showed the relationship between iodine-deficient endemic goiter and thyroid carcinoma (29). Since then, other studies demonstrated that iodine supplementation failed to reduce the incidence of thyroid cancer (30–32). However, the effects of iodine intake on development

of specific histologic types of thyroid carcinoma are clearer. In endemic goiter areas, follicular and anaplastic carcinomas predominate. In areas with iodine supplementation, the proportion of follicular carcinoma declines and that of PTC increases (33,34). The role of other dietary factors on DTC pathogenesis remains very controversial.

DIAGNOSIS

Patients with DTC typically present with a solitary thyroid nodule or with enlarged lymph nodes of the neck. The diagnosis of thyroid cancer usually begins with the palpation of an asymptomatic thyroid nodule. In about half of the patients, a doctor discovers the nodule during a routine physical examination. In the other half of the situations, it is the patient who first notices a thyroid asymmetry.

Ultrasound and thyroid scintigrams are the first-line diagnostic tools in the case of suspected carcinoma. Ultrasound features that indicate cancers are a solid hypoechoic tumor with irregular borders. A thyroid scan shows a nonfunctioning or cold lesion. Fine-needle aspiration (FNA) for cytologic diagnosis is the initial invasive evaluation in most patients (35). FNA can make the diagnosis of PTC but it cannot be used to distinguish between follicular adenoma and carcinoma. The diagnosis of micro- or occult carcinoma is usually made during pathologic examination of a multinodular goiter or after the FNA biopsy of an incidental nodule found on ultrasonography.

Prognostic Factors

There are some controversies in the treatment of DTC with respect to the extent of surgery, use of I-131 and thyroxine suppression. Recognition of prognostic factors facilitated the development of a selective approach to therapy and follow-up (36–39).

Factors Influencing Prognosis and Outcome

The prognosis of DTC may be determined by an interaction of three factors:

Patient variables
- Age
- Gender
- Other thyroid diseases
- Family history

Tumor variables
- Histology

Multifocality
Lymph-node metastases
Capsular invasion
Extrathyroid extension
Distant metastases
Irradiation-induced carcinoma
Oncogenes
Therapy variables
Extent of resection
Radioiodine therapy

Patient Variables

Age: Age over 40 years at the beginning of the therapy is the most important adverse prognostic factor. Prognosis becomes progressively worse thereafter, particularly after 60 years of age (40,41). Children usually have more advanced tumors, with local and distant metastases and higher recurrence rates; however, their prognosis is excellent (42). An exception is children under age 10 who have very high mortality rates (43–45).

Gender: Thyroid cancer recurrence and mortality rates are higher in men. Although estrogen and progesterone receptors are expressed in up to 50% of PTCs, this does not explain the risk imposed by male gender (41,46).

Other thyroid diseases: One study of PTC associated with Graves' disease found that the tumors were more often multifocal with distant metastases (47). Serum from patients with Graves' disease has been shown to stimulate the progression of follicular cells to carcinoma in vitro (48).

PTC appears to carry a better prognosis when Hashimoto's thyroiditis or lymphocyte infiltration are associated (49,50). Hashimoto's thyroiditis itself, however, is considered a risk factor for DTC.

Family history: About 5% of PTCs are familial tumors inherited as an autosomal dominant trait although the responsible gene is still unknown. Familial PTC seems to have a worse prognosis. It can be inherited with other diseases, such as familial adenomatous polyposis (Gardner's syndrome), Cowden disease (a very rare familial syndrome of multiple hamartomas and breast carcinoma), or Carney complex (a familial syndrome of hypercortisolism and pigmented adrenal nodules, spotty skin pigmentation, myxomas, schwannomas, pituitary adenomas, and testicular endocrine tumors).

Tumor Variables

Histology: Outcome is more favorable with PTC than with FTC. The poorer prognosis in FTC patients is also related to an older age and to a more extensive tumor burden at initial diagnosis. Within these two histological entities the outcome may be different for their respective variants (Table 2). Hurthle cell carcinoma (oncocytic carcinoma or oxyphilic variant FTC) may have a worse prognosis than FTC (51) although some studies show that overall mortality is similar. Older age, greater tumor size, and extensive disease predict poor outcome in Hurthle cell carcinoma (52,53).

Multifocality: Multifocal disease is frequently found in PTC and much less frequently in FTC. Multifocality in one lobe is almost always associated with bilateral thyroid cancer when complete thyroidectomy is performed. It has been associated with higher rates of lymph-node metastases, persistent local disease, regional recurrences, and distant metastases (54,55).

Table 2 Prognostic Factors Associated with Poor Outcome

Patient variables	Older age
	Male gender
	DTC and Graves' disease
	Familial PTC
Tumor variables	PTC variants: tall cells; columnar cells; diffuse sclerosing subtypes
	FTC variants: widely invasive
	Multifocality and bilaterality
	Lymph-node extension
	Capsular invasion
	Extension beyond the thyroid capsule
	Distant metastases
	Irradiation-induced PTC
	RET/PTC oncogenes. Initial lack of radioiodine uptake or loss during the course of the disease
Therapy	Time of treatment is more than one year
	Incomplete tumor resection
	No postoperative iodine-131 therapy when other poor prognostic factors exist

Abbreviations: DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; PTC, papillary thyroid cancer.

Lymph-node metastases: They are frequent in PTC—from 35% to 70% in different series, and in up to 80% in children—depending on the extent of lymph-node surgery, and much less frequent (less than 20%) in FTC (7,56).

Even in papillary microcarcinoma local nodes may be involved (57). The prognostic impact of lymph-node metastases is still controversial. Some report that the presence of lymph-node metastases has no predictive value for recurrence or survival (58). Others find an increased risk for local tumor recurrence (40,59). Persistent or recurrent lymph-node metastases are also considered a risk factor for developing lung metastases.

Capsular invasion and extrathyroidal extension: Tumor extension beyond the thyroid capsule is present in 8% to 32% of PTC and is frequently observed in widely invasive follicular carcinoma. It is an independent risk factor, exposing patients to higher local recurrence rates, distant metastases, and mortality (11,60,61).

Distant metastases: Distant metastases at the time of initial diagnosis signal a poor prognosis in patients with both PTC and FTC. They are initially present in 1% to 3% of PTC and in 7% to 15% of FTC. Bone metastases are sometimes the first clinical manifestation of thyroid cancers. Distant metastases of differentiated thyroid cancer are usually localized in the lungs and bones; less common sites include the brain, liver, and skin. They are the main cause of death from DTC. Children and young adults with pulmonary metastases have a more favorable prognosis when their distant metastases are discovered early, are small, and concentrate I-131 (62).

Irradiation-induced carcinoma: Papillary thyroid cancers associated with radiation are usually large and multicentric. They have high recurrence rates, although no higher mortality rate (63).

Oncogenes: RET/PTC rearrangements are present in about 40% of PTCs and may play a role in metastatic behavior. In Chernobyl children, RET/PTC3 oncogenes were found and PTC3 may be present in more aggressive tumors, however, the importance of tumor genetics remains controversial (41,64).

Therapy Variables

Tumor staging systems and prognostic scoring systems: Several staging and prognostic scoring systems have been used to discriminate between low-risk patients with favorable outcome, who require less aggressive therapy and higher risk patients at risk for greater morbidity and mortality from thyroid carcinoma and require aggressive therapy regimens. The most frequently used system is tumor node metastases (TNM).

Tumor node	Metastases scoring system
T0	No evidence of primary tumor
T1	Tumor $\leq$2 cm limited to the thyroid
T2	Tumor $>$2 cm $\leq$4 cm limited to the thyroid
T3	Tumor $>$4 cm limited to the thyroid or with minimal extrathyroid extension
T4a	Invasion of any: subcutaneous soft tissue, larynx, trachea, esophagus, and recurrent laryngeal nerve
T4b	Invasion of any: prevertebral fascia, mediastinal vessels, and carotid artery
N0	No regional lymph node metastasis
N1a	Metastases in pretracheal and paratracheal nodes
N1b	Metastases in other unilateral, bilateral, or contralateral cervical or upper mediastinal lymph nodes
M0	No distant metastases
M1	Distant metastases

Tumor node	Metastases scoring system
Age $<$45 years	
Stage I	Any T, any N, M0
Stage II	Any T, any N, M1
Age $\geq$45 years	
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0 or any T1-3, N1a, M0
Stage IVa	T1-3, N1b, M0 or T4a, any N, M0
Stage IVb	T4b, any N, M0
Stage IVc	Any T, any N, M1

SURGERY

Whether a patient with DTC should undergo total thyroidectomy or thyroid lobectomy is a controversial treatment issue. Proponents of total thyroidectomy for all patients with DTC defend the need based on the following reasons: (*i*) high incidence of microscopic multifocal disease, (*ii*) to facilitate radioactive iodine for the detection and treatment of residual disease, (*iii*) to allow the use of Tg as a marker for recurrent disease, and (*iv*) possibility of anaplastic transformation of any microscopic foci of carcinoma (65).

Those who propose limited thyroid resection (lobectomy with isthmus resection) argue that without documented benefit of total thyroidectomy in

low-risk patients, even the small increased risk of permanent hypoparathyroidism (4% to 9%) and recurrent nerve damage (1% to 8%) is not justifiable and may avoid life-long thyroid hormone replacement (61).

POSTOPERATIVE MANAGEMENT

After surgery, the risk factors of the tumor should be reanalyzed, mainly concerning the status of cervical lymph nodes and multifocal disease.

A whole-body I-131 scan is usually performed after thyroidectomy. Although some authors recommend that diagnostic I-131 scans be avoided completely, others argue a whole-body I-131 scan should be performed to determine the amount of residual tissue remaining, the radioiodine avidity of residual tissue, and the appropriate I-131 dosimetry (66–68).

Owing to follicular cell damage induced by large scanning doses of I-131, however, a "stunning" effect may occur. Stunning may decrease uptake in the thyroid remnant or in tumor for several weeks, thus impairing the therapeutic efficacy of I-131 (69).

Some authors point out that the diagnostic benefit of a 74 MBq or lower dose is far smaller than that of a 111 to 370-MBq dose (70). The value of such small diagnostic doses is further called into question by studies indicating that as many as 19% of patients who have no thyroid tumor visualized in diagnostic scans are identified with tumor tissue in 3700-MBq post-therapy scans (71). However, small doses (74 MBq) of I-131 may be recommended to avoid the stunning effect.

The diagnostic whole-body I-131 scan is usually performed four to six weeks after thyroidectomy without any thyroid hormone replacement in the interval. This period mainly allows time for circulating T4 to fall to undetectable levels with a corresponding rise of serum thyroid-stimulating hormone (TSH). This time period also allows for any iodine used during surgery to be excreted. Iodine restriction and TSH levels of more than 30 mU/L guarantee ideal conditions for radioiodine uptake and treatment efficacy.

RADIOIODINE TREATMENT

Iodine-131 has been used for over 60 years in the treatment of patients with DTC, to destroy both remaining thyroid cells and carcinoma foci. However, the indications for radioiodine therapy continue to be debated (9,72).

Radioiodine therapy of DTC is based on the ability of tumor cells to accumulate iodine, leading to in intensive, selective, and tumoricidal irradiation (73).

Iodine-131 has a physical half-life of 8.05 days. It decays by high-energy gamma photon (364 keV) and particulate emissions (beta particle). The beta emission has an average energy of 192 keV [max energy = 607 keV (90%), and 810 keV (7%)] and the beta particle will deposit its energy within 2.2 mm (90%) and 3.1 mm (7%), respectively of its site of origin (74) with a mean tissue range of only 0.8 mm.

The success of thyroid ablation with I-131 depends mainly on the mass of remaining thyroid tissue in the neck and the initial dose rate to this tissue.

ABLATION

Ablation with radioiodine should be used selectively. In low-risk patients (younger than 40 years, with a tumor less than 1 to 1.5 cm, without extracapsular extension or vascular invasion, submitted to total thyroidectomy) (75), the long-term prognosis after surgery alone is so favorable that I-131 ablation is not recommended in general (76,77).

Ablation with I-131 is performed when the patient has a tumor with the potential for recurrence, because it decreases both recurrence and death rates (50). Retrospective data from multiple studies show that radioiodine ablation is associated with a 50% reduction in locoregional relapse and the long-term disease-specific mortality is probably reduced in primary tumors that are at least 1 to 1.5 cm in diameter, are multicentric, or have soft-tissue invasion at presentation (40,77,78). Although debate about ablating the thyroid bed with I-131 after total thyroidectomy continues (9,79), there are some compelling reasons to do this (78): (*i*) to destroy any residual microscopic foci of residual disease, (*ii*) to increase the sensitivity of subsequent I-131 scanning for detection of recurrent or metastatic disease by eliminating uptake by residual normal tissue, (*iii*) high circulating TSH levels, necessary to enhance tumor I-131 uptake, cannot be achieved with a large thyroid remnant, and (*iv*) to improve the value of measurements of serum Tg as a tumor marker.

Adjuvant radioiodine should be administered to all patients with differentiated carcinoma, when the primary tumor is likely to relapse or cause death, and to patients who have evidence of extrathyroidal disease, either by direct invasion outside of the gland or locoregional metastases. In patients with residual disease following surgery, including extracervical metastases, therapy with I-131 should be performed.

Therapy with I-131 is performed by either administering an empiric fixed dose or using dosimetry-guided activities. Quantitative dosimetry methods are used to determine the activity for the therapeutic dose, based on the individual patient's radioiodine pharmacokinetics. Some authors advocate this approach (80) because radiation exposure from arbitrarily fixed doses of I-131 can vary considerably. Using dosimetry methods, the

therapeutic dose may be adjusted to compensate for patient-to-patient variability in the rate of iodine clearance (67,81). If the calculated dose to the tumor is less than 35 Gy, it is unlikely that the cancer will respond to radioiodine therapy (82). Radioiodine activities that deliver 500 to 600 Gy to the residual normal tissue and 40 to 50 Gy to metastatic foci are likely to be effective. Dosimetry for diffuse lung metastases may be difficult to estimate because of the need to estimate tumor size.

Although the clinical merits of dosimetry-guided radioiodine therapy have been demonstrated, most centers have adapted the fixed-dose technique using 3.7 to 7.4 GBq (100 to 200 mCi) I-131 owing to the technical and logistic difficulties of dosimetry studies. Tumor/remnant tissue volume estimates are often the greatest challenge for individual assessment of radioiodine dosages based on dosimetry. Patients who show I-131 uptake and have no metastatic disease are treated with 2960 to 3700 MBq (80 to 100 mCi). Lymph-node metastases that are not large enough to excise are treated with approximately 5550 MBq (150 mCi).

In recent years, lower activities of radioiodine (e.g., 1200 MBq) have been used, mainly in the United States, allowing outpatient treatment. The literature reports conflicting results with this practice. Some studies show a similar efficacy for both types of doses, principally with lower radioiodine uptake and small remnants of residual thyroid tissue (83–85). There are however other reports suggesting less efficacy for lower doses (86,87). Nonetheless, this practice is not widely implemented, and further studies are required before such low dose regimens can be generally recommended (88). More recently, in the United States, newer guidelines from the Nuclear Regulatory Commission provide greater flexibility in the dosing and management of outpatients treated with I-131. They also allow outpatient treatment with higher doses of radio-iodine (89).

The efficacy of radioiodine depends on patient preparation, tumor-specific characteristics, sites of disease, and administered radioiodine activity. Iodide uptake by thyroid tissue is stimulated by TSH and is suppressed by increased endogenous iodide stores. Following thyroidectomy, the patient's thyroid hormone levels must decline sufficiently to allow the TSH concentration to rise to above 25 to 30 mU/L. This period of hormone withdrawal typically lasts four to five weeks. Patients should avoid foods with high iodine content for at least one week prior treatment (90).

DIETARY SOURCES OF IODINE

Iodized salt
Milk/dairy products
Eggs
Seafood and fish
Seaweed and kelp products

Bread made with iodide conditioners
Iodide-containing multivitamins

Also, medication containing iodine or drugs that can alter iodine uptake and utilization should be avoided before treatment for an adequate period of weeks or months, based on their effect on iodine metabolism (e.g., radiographic contrast agents, amiodarone, and so on).

DRUG INTERACTIONS

Type of medication	Recommended time of withdrawal
Antithyroid medication	Three to seven days
Synthetic thyroid hormone	Two weeks for triiodothyronine; four to six weeks for thyroxine
Expectorants, vitamins, kelp	Two to three weeks, depending on iodide content
Topical and oral (Lugol) iodine (e.g., surgical skin preparation)	Two to three weeks
Radiographic contrast agents	
Water-soluble	More than three to four weeks (assuming normal renal function)
Lipophilic agents	More than one month
Amiodarone	Three to six months or longer

Recently, the use of recombinant human thyroid-stimulating hormone (rhTSH) has been advocated to increase TSH level before radioiodine ablation, and some studies have shown this method to be as effective as levothyroxine withdrawal (91). However, more studies are needed on this issue. The current role for rhTSH ablation is perhaps for patients at high risk of severe hypothyroidism complications such as cardiovascular or psychiatric side effects including depression and the risk of suicide.

Other potential advantage of rhTSH radioiodine ablation/treatment is decreased radiation exposure (and perhaps, a short in-hospital period) as dosimetry data suggest that whole-body and whole-blood radioiodine clearance may be faster in euthyroid patients after administration of rhTSH (92).

Some drugs can increase iodine uptake by thyroid cells and may be useful in patients with certain histological subtypes of thyroid carcinoma that concentrate iodine less well (e.g., Hurthle cell carcinoma). Some studies suggest that adjuvant treatment with lithium increases radioiodine uptake and retention in thyroid cells (93).

Patient preparation for treatment with I-131 includes a written informed consent before treatment; ideally patients should be physically able to take

care of themselves. Pregnancy and breastfeeding are absolute contraindications for radioiodine treatment and a pregnancy test must be performed in all women of childbearing age. A thorough explanation of the whole procedure should be made (including potential complications and side effects as well as explanation of the measures to reduce radiation exposure to family members or to the general public). Women of childbearing age should be advised against pregnancy in the first 6 to 12 months after treatment.

RADIATION SAFETY

As a general rule, it is prudent to keep radiation exposures at the lowest possible levels. This is the principle underlying the phrase "As low as reasonably achievable," or ALARA. As national radiation safety regulations may vary, the following recommendations should be considered as suggestions only.

Patients who receive more than 1100 MBq (30 mCi) of I-131 should be admitted to an individual hospital room with a private bathroom. Appropriate radioactive trash disposal containers should be placed in the room. A radiation sign should be placed on the patient's door, and public access should be restricted.

Although patients may wear their personal clothes, disposable articles (e.g., cutlery, food trays) should be used. Abundant liquid ingestion should be encouraged to reduce radiation exposure to the urinary bladder and salivary glands and to improve renal clearance of radioiodine during the first two days.

All staff should be familiar with methods of minimizing radiation exposure. All persons involved in radioiodine therapy should wear monitor badges. Badges must be processed on a periodic basis; the frequency is to be determined by the local Radiation Safety Division. Members of the staff directly involved in the administration of radioiodine therapy, mainly in the liquid form, should obtain a thyroid burden measurement within one week following administration of the therapy dose.

Usually, patients submitted to treatment with I-131 do not need special nursing assistance. For the very special patient whose clinical status requires close nursing procedures, personnel rotation is advised. Protective gloves and shoe covers should be worn on entering the patient's room and hands should be washed after leaving the room. As a general rule, the time spent close to the patients should be limited to a minimum.

Therapy with iodine-131—radiation safety: general guidelines for the staff
Time spent close to patients should be limited to a minimum
Use of monitoring badges
Thyroid burden measurement for members of the staff directly involved in the administration of radioiodine therapy (especially when administered in liquid form)
Use of protective gloves and shoe covers whenever entering the patient's room

Threrapy with iodine-131—radiation safety: general guidelines for the patient
Abundant liquid ingestion
Lemon juice ingestion; chewing lemon drops

Patients may be released when activity levels within the patient drop below 1110 MBq (30 mCi) or when the dose rate at 1 m is less than 0.07 mSv/hr (7.0 mrem/hr) (94). However, national regulations may vary and have to be considered by the practitioner.

After discharge, the entire room should be monitored for the presence of radioactive contamination. Disposable gloves and shoe covers should be used when changing bed linens, washing the floor, and the like. After discharge from the hospital and up to one week after treatment, a simple set of measures usually is enough to reduce radiation exposure of the family members or to the general public. The general principle is to avoid prolonged, close contact with other people during this period. Patients with infants at home should arrange for care to be provided by another person for the first days after treatment.

Therapy with iodine-131—radiation safety: general guidelines after discharge (up to one week after treatment)
Limit the time spent in public places
Limit traveling by public transportation and prolonged automobile trips with others
Delay returning to work if there is close contact with others
Use private bathroom and flush toilet twice after each use
Use disposable eating utensils, linen, towels, and clothes, and wash separately
Sleep alone and avoid prolonged intimate contact (mainly with children and pregnant women)
Do not prepare food for others or use gloves to do so

Approximately three to seven days after the administration of the ablative dose of radioiodine, a post-therapy whole-body scan should be performed to confirm irradiation of functional thyroid tissue. Because of its greater sensitivity than the diagnostic scan it can be used as a sensitive survey for the presence of radioiodine avid metastases.

RADIOIODINE COMPLICATIONS

Acute complications of therapy with I-131 are mostly nonsevere and usually short-lived. The more usual symptoms include sialoadenitis, radiation thyroiditis,

neck edema, nausea, and gastritis (95). The salivary glands concentrate iodine and sialoadenitis may occur in about 30% of patients treated with radioiodine (96). It is characterized by pain, tenderness, and swelling of the salivary glands. Some patients suffer from reduced salivary gland function for more than one year after therapy with I-131. The use of lemon juice or lemon candies and abundant water ingestion reduces the incidence and severity of sialoadenitis and reduces absorbed radiation dose to the salivary glands. Recently, a study indicated that an early start of sucking lemon candy may provoke an increase in salivary gland damage suggesting that lemon candy should not be given until 24 hours after therapy with I-131 (97). The use of amifostine may reduce significantly the damage to salivary glands, mainly when high doses are administered (98). Radiation thyroiditis and neck edema (99), when symptomatic, are usually treated with nonsteroidal anti-inflammatory drugs, or with steroids in the rare patient with more severe symptoms. Abundant liquid ingestion should always be encouraged; this augments the urinary flow output and decreases the radiation burden to the urinary bladder and the whole body. Gastrointestinal symptoms may be treated with antiemetics (nausea) and antacids (gastritis). Thyroid storm due to the release of large amounts of thyroid hormones occurs rarely in patients with extensive follicular metastases, usually within 10 days after treatment (76). Rarely, patients with brain metastases may develop edema and hemorrhage. Late effects include transitory decreased white blood cells, oligospermia, and transient ovarian failure. Infertility is rare except after high doses. There is no evidence of increased risk of congenital abnormalities (100). Patients with diffuse pulmonary metastases may rarely develop pulmonary fibrosis after radioiodine treatment.

Over the long-term, radioiodine therapy may be associated with development of secondary malignancies, such as acute myelocytic leukemia, usually occurring between 2 and 10 years after therapy. The risk increases in patients above the age of 50 who have received a dose of 37 GBq (1 Ci) of I-131 or more and is greater when this dose had been given over a short period of time (6 to 12 weeks). The risk is considerably lower when the total blood dose per treatment is less than 2 Gy (101). Increased prevalence of cancers of the urinary bladder, salivary gland, colon, and female breast has also been reported in patients, but with little agreement on the degree of absolute risk (101,102). Cumulated activities of more than 37 GBq (1 Ci) can also result in myelodepression with a decrease in blood cell components, the risk increasing with the administered activity.

FOLLOW-UP

Patients who have undergone thyroidectomy and radioiodine ablation require lifelong thyroid hormone replacement to prevent hypothyroidism and to

minimize TSH stimulation, which promotes tumor growth. However, controversies remain regarding the level of thyrotropin suppression. It seems reasonable to adjust the level of TSH suppression based on the patient's initial clinicopathologic features (103). Thyroid-stimulating hormone levels of 0.1 mU/L or less are usually recommended to minimize the risk of tumor growth; however, treatment with higher doses of thyroid hormone is associated with greater risk of osteoporosis, especially in postmenopausal women. In patients with an undetectable serum Tg concentration and negative neck ultrasound during follow-up, the risk of recurrence is so low that thyroxine doses which maintain TSH levels between 0.1 and 0.5 mU/L are recommended.

The follow-up of thyroid cancer is based on the detection of residual and recurrent thyroid carcinoma. This is traditionally performed by routine palpation and ultrasonography of the thyroid bed and locoregional lymph-node areas, and measurements of serum Tg combined with I-131 whole-body scans after thyroid hormone withdrawal or administration of recombinant TSH (104,105). A low-iodine diet is generally recommended for 7 to 10 days before I-131 administration to enhance the sensitivity for lesion detection. The I-131 whole-body scan may be repeated every year until at least two negative whole-body scans are obtained. The predictive value for 10-year relapse-free survival of one negative I-131 scan is about 90%, whereas two consecutive negative scans have a predictive value greater than 95% (106).

Recently some authors advocate that scanning with I-131 may be discouraged in patients who underwent total thyroidectomy and radioiodine ablation and do not show any clinical evidence of residual tumor or elevated levels of Tg during TSH suppression (107,108). The surveillance of these patients can be performed by using rhTSH-stimulated Tg levels as diagnostic parameter. This is still a matter of debate, because it does not seem valid for all risk groups and not all patients undergo the same clinical management.

Medical Follow-Up—Low-Risk Patients with No Thyroglobulin Antibodies and No Clinical Evidence of Disease

These patients were submitted to total thyroidectomy and I-131 ablation. There was no evidence of disease on postablation whole-body scintigraphy (WBS).

Six months to one year after therapy with I-131, the use of sensitive Tg assays can separate the patients with persistent disease from those free of disease that are unlikely to have recurrent disease, without the need for repeated whole-body radioiodine scans (Fig. 1).

Medical Follow-Up—High-Risk Patients and Metastatic Disease

After the administration of an ablative dose of I-131, further treatment is warranted (surgery and/or I-131 therapy) if the post-therapy whole-body scan

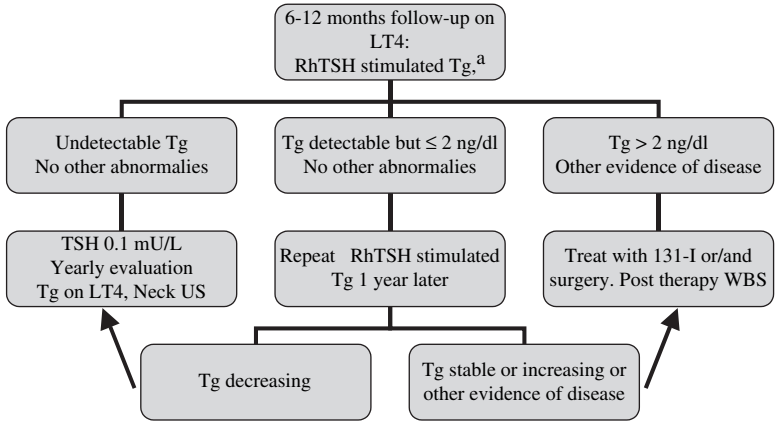

Figure 1 Medical follow-up after initial treatment–low risk patients. [a]Thyroid-stimulating hormone (TSH) stimulation can be achieved using either thyroid hormone (LT_4) withdrawal or recombinant human TSH (rhTSH). *Abbreviations*: Tg, thyroglobulin; WBS, whole-body scintigraphy. *Source*: From Ref. 109.

shows uptake outside the thyroid bed. If no uptake is seen outside the thyroid bed, the combination of a diagnostic I-131 whole-body scan, with 74 MBq (2 mCi) of I-131, and serum Tg measurement, is recommended by many authors 6 to 12 months after thyroid ablation under withdrawal of L-thyroxin or under rhTSH (Fig. 2).

The serum Tg measurement seems to be a sensitive predictor of complete remission or persistent disease (provided that anti-Tg autoantibodies are negative). Nearly all patients with local or distant disease have detectable or elevated

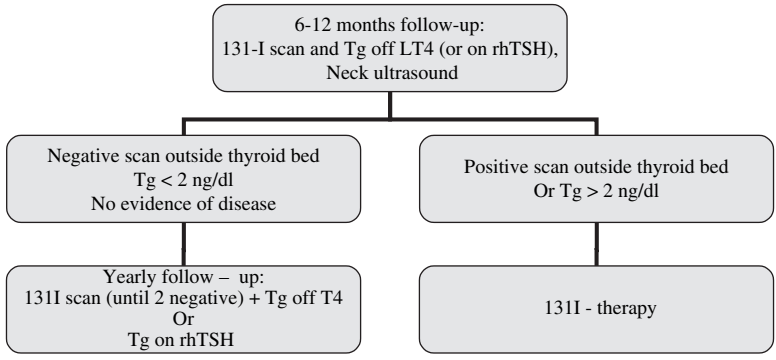

Figure 2 Medical follow-up after initial treatment–high risk patients. *Abbreviations:* LT_4, thyroid hormone; Tg, thyroglobulin.

serum Tg levels, while patients in stable remission have undetectable serum Tg concentrations. Compared with serum Tg measurement, the yield of the diagnostic I-131 whole-body scan is lower. A significant proportion of patients may have elevation of serum Tg in the presence of falsely negative diagnostic I-131 whole-body scans.

If during the follow-up an elevated Tg is found, ultrasonography of the thyroid bed and cervical node compartments may be used to accurately identify suspected locoregional metastases or local tumor recurrences and facilitate FNA of such lesions. This technique should be considered in the routine follow-up of patients with extrathyroidal invasion or locoregional nodal metastases (110).

In patients with evidence of metastatic disease, treatment should be continued until Tg levels remain below 2 to 5 ng/mL. When retreatment with I-131 is necessary, it is best to wait 6 to 12 months to administer the dose to allow for time for effects from the preceding dose to be completed, unless rapidly progressive disease develops. In patients with radioiodine-concentrating metastases, outcome may not be favorable (111,112).

Patients with metastases in the regional lymph nodes are treated with high activities of I-131, usually 5550 MBq (150 mCi). In case of locoregional recurrence, surgery may be an option.

In patients with lung metastases (usually not present on the X-ray but seen on chest computed tomography and/or on the whole-body scan), a micronodular (miliary) pattern of metastases is usually associated with a good I-131 uptake and a better prognosis. Macronodular lesions (over 0.5 cm) frequently show poor I-131 uptake and have an associated worse prognosis. Patients with pulmonary metastases concentrating iodine have a five-year survival rate of 60%, compared with 30% for those whose tumors do not take up iodine (62). Iodine-131 activities of 5550 to 6475 MBq (150 to 175 mCi) and higher are recommended for empiric treatment of pulmonary metastases.

Skeletal metastases often do not concentrate I-131 and complete resolution of disease occurs in few patients only. Patients may benefit from external radiotherapy, after I-131 therapy (113). In patients with single bone or pulmonary lesions and no evidence of other distant metastases, surgical treatment might be considered alternatively. Recently, embolization in combination with I-131 therapy has been shown to be useful in the treatment of patients with DTC and bone metastases (114).

Fluor desoxy glucose-positron emission tomography (FDG-PET) has been proven useful to identify metastases in patients with persistently elevated Tg levels and negative whole-body scans (115). These patients may be retreated with I-131 as some studies have shown that there may be abnormal uptake in the post-therapy scan and/or decline in Tg values (116,117).

Some thyroid carcinomas lose their capability for I-131 concentration owing to a dedifferentiation of tumor cells. Various studies provide evidence

that the differentiated function of iodine metabolism may be reinduced in these tumors by retinoic acid administration (118,119) although this procedure has not proven to be as reliable as expected so far.

Finally, gene therapy in preclinical studies is a novel and exciting avenue for the future treatment of advanced differentiated and anaplastic tumors of the thyroid. These encompass a range of approaches, such as corrective gene therapy, cytoreductive gene therapy, and immunomodulatory gene therapy (120).

THERAPY WITH IODINE-131: INDICATIONS

After surgery:
- Ablation of functional thyroid tissue
- Treatment of functional metastases

During follow-up:
- Treatment of functional metastases
- Potential treatment of patients with elevated Tg levels and a negative diagnostic radioiodine scan

THERAPY WITH IODINE-131: CONTRAINDICATIONS

- Pregnancy
- Breastfeeding

THERAPY WITH IODINE-131: SIDE EFFECTS

Acute side effects
- Sialoadenitis
- Radiation thyroiditis
- Neck edema
- Nause
- Gastritis
- Thyroid storm
- Edema and acute cerebral hemorrhage

Long-term side effects
- Decreased white blood cells, myelodepression
- Oligospermia
- Transient ovarian failure
- Long-term xerostomia
- Infertility
- Pulmonary fibrosis
- Secondary malignancies, acute myelocytic leukemia

REFERENCES

1. National Cancer Institute—SEER Cancer Statistics Review, 1975–2002.
2. Parkin DM, Whelan SJ, Ferlay J. Cancer incidence in five continents, Vol. 8 IARC Scientific Publication 143, International Agency for Research on Cancer, Lyon 1997.
3. Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993; 114:1050–1058.
4. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma: a population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973–1991. Cancer 1997; 79:564–573.
5. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993; 328:553–559.
6. AACE Guidelines. Endocrine practice. Vol. 7 no. 3, May–Jun 2001.
7. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. CA 1998; 48:6–30.
8. Mazzaferri EL. Thyroid carcinoma: papillary and follicular. In: Mazzaferri EL, Samaan N, eds. Endocrine Tumors Cambridge, MA: Blackwell Scientific Publications, 1993:278–333.
9. Hay ID. Papillary thyroid carcinoma. Endocr Metab Clin North Am 1990; 19: 545–576.
10. Schneider AB, Ron E. Carcinoma of follicular epithelium. In: Braverman LE, Utiger RD, eds. The Thyroid. 8th ed. Philadelphia: Lipincott, Williams, Wilkins, 2000:vii. Thyroid diseases: tumors.
11. Schlumberger M, Pacini F. Thyroid Tumors. 2nd ed. Nucléon, Paris, France.
12. Katoh R, Sasaki J, Kurihara H, et al. Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma: a clinico-pathologic study of 105 consecutive patients. Cancer 1992; 70:1585–1590.
13. Zidan J, Karen D, Stein M, et al. Pure versus follicular variant of papillary thyroid carcinoma. Clinical features, prognostic factors, treatment, and survival. Cancer 2003; 97:1181–1185.
14. Passer C, Prager G, Scheuba C, et al. Follicular variant of papillary thyroid carcinoma: a log-term follow-up. Arch Surg 2003; 138(12):1362–1366.
15. Tielens ET, Sherman SI, Hruban RH, et al. Follicular variant of papillary thyroid carcinoma. A clinicopathologic study. Cancer 1994; 73:424–431.

16. Sobrinho-Simões M, Soares J, Carneiro F, et al. Follicular variant of papillary carcinoma of the thyroid: report of eight cases of a distinct aggressive type of thyroid tumor. Surg Pathol 1990; 3:189–203.
17. Soares J, Limbert E, Sobrinho-Simões M. Diffuse sclerosing variant of papillary thyroid carcinoma: a clinicopathologic study of ten cases. Pathol Res Pract 1989; 185:200–206.
18. Johnson TL, Lloyd RV, Thompson NW, et al. Prognostic implications of the tall cell variant of papillary thyroid carcinoma. Am J Surg Pathol 1988; 12:22–27.
19. ItoY, Urano T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 2003; 13:381–387.
20. Hedinger C, Williams ED, Sobin LH. Histological typing of thyroid tumours. International Histological Classification of Tumors. WHO Vol. 11. 2nd ed. Berlin: Springer-Verlag, 1988.
21. Rosai J, Carcangiu ML, De Lellis RA. Tumors of the thyroid gland. Atlas of Tumor Pathology. 3rd series. Washington DC: AFIP, 1992:Fascicle 5.
22. Stojadinovic A, Ghossein RA, Hoos A, et al. Hurthle cell carcinomas: a critical histopathologic appraisal. J Clin Oncol 2001; 19:2616–2625.
23. Schneider AB, Fogelfeld L. Radiation induced endocrine tumors. Cancer Treat Res 1997; 89:141.
24. Schneider AB, Ron E, Lubin J, et al. Dose-response relationships for radiation induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on thyroid. J Clin Endocrinol Metab 1993; 77:362.
25. Hindie E, Leenhardt L, Vitaux F, et al. Non-medical exposure to radioiodines and thyroid cancer. Review. Eur J Nucl Med Mol Imaging 2002; 29(suppl 2):S497–S512.
26. VII Thyroid diseases: tumors. In: Braverman LE, Utiger RD, eds. The Thyroid. 8th ed. Philadelphia: Lipincott, Williams, Wilkins, 2000:879, 880.
27. Ron E, Kleinerman R, Boice JD Jr., et al. A population-based case-control study of thyroid cancer. J Natl Cancer Inst 1987; 79:1.
28. Levi F, Franceschi S, Lavecchia C, et al. Previous thyroid disease and risk of thyroid cancer in Switzerland. Eur J Cancer 1991; 27:85.
29. Wegelin C. Malignant disease of the thyroid and its relation in goiter in men and animals. Cancer Rev 1928; 3:297.
30. Franceschi S, Talamini R, Fassina A, et al. Diet and epithelial cancer of the thyroid gland. Tumori 1990; 76:331.

31. Pettersson B, Coleman MP, Ron E, et al. Iodine supplementation in Sweden and regional trends in thyroid cancer incidence by histopathologic type. Int J Cancer 1996; 65:73.
32. Pendergrast WJ, MilmoreBK, Maecus SC. Thyroid cancer and thyrotoxicosis in the United States: their relation to endemic goiter. J Chronic Dis 1961; 13:22.
33. Williams ED. TSH and thyroid cancer. Horm Metab Res Suppl 1990; 23:72.
34. Gyory F, Lukacs G, Nagy EV, et al. Differentiated thyroid carcinoma: prognostic factors. Magy Seb 2001; 54(2):69–74.
35. Gharib H. Thyroid nodules and multinodular Goiter. In: Cooper DS, ed. medical management of thyroid disease. New York: Marcel Dekker 2001:187–225.
36. Kuriakose MA, Hicks WL Jr, Loree TR, Yee H. Risk group-based management of differentiated thyroid carcinoma. J R Coll Surg Edinb 2001; 46(4):216–223.
37. Eichhorn W, Tabler H, Lippold R, et al. Prognostic factors determining long-term survival in well-differentiated thyroid cancer: an analysis of four hundred eighty-four patients undergoing therapy and aftercare at the same institution. Thyroid 2003; 13:949–958.
38. Shaha AR, Shaha JP, Loree TR. Risk group stratification and prognostic factors in papillary carcinoma of thyroid. Ann Surg Oncol 1996; 3:534–538.
39. Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control 2000; 7(3):229–239.
40. Mazzaferri EL, Jhian SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994; 97:418–428.
41. Kloos RT, Mazzaferri EL. Thyroid carcinoma. In: Cooper DS, ed. medical management of thyroid disease. New York: Marcel Dekker 2001:187–225.
42. Chow SM, Law SC, Mendenhall WM. Differentiated thyroid carcinomas in childhood and adolescence-clinical course and role of radioiodine. Pediatr Blood Cancer 2004; 42(2):176–183.
43. Harach HR, Williams ED. Children thyroid cancer in England and Wales. Br J Cancer 1995; 72:777–783.
44. Hung W. Well-differentiated thyroid carcinomas in children and adolescents: a review. Endocrinologist 1994; 4:117–126.
45. Samuel AM, Rajashekharrao B, Shah DH. Pulmonary metastases in children and adolescents with well-differentiated thyroid cancer. J Nucl Med 1998; 39:1531–1536.

46. Vini L, Hyer SL, Marshall J, et al. Long-term results in elderly patients with differentiated thyroid carcinoma. Cancer 2003; 97:2736–2742.

47. Belfiore A, Garofalo MR, Giuffrida D, et al. Increased aggressiveness of thyroid cancer in patients with Graves' disease. J Clin Endocrinol Metab 1990; 70:830–835.

48. Filetti S, Belfiore A, Amir SM, et al. The role of thyroid-stimulating antibodies of Graves' disease in differentiated thyroid cancer. N Engl J Med 1988; 318:753–779.

49. Matsubayashi S, Kawai K, Matsumoto Y, et al. The correlation between papillary thyroid carcinoma and lymphocytic infiltration in the thyroid gland. J Clin Endocrinol Metab 1995; 80:3421–3424.

50. Stocker DJ, Burch HB. Thyroid cancer yield in patients with Graves' disease. Minerva Endocrinol 2003; 28(3):205–212.

51. Samaan NA, Schultz PN, Hickey RC, et al. Well-differentiated thyroid carcinoma and the results of various modalities of treatment: a retrospective review of 1599 patients. J Clin Endocrinol Metab 1992; 75:714–720.

52. Lopez-Penabad L, Chiu AC, Hoff AO, et al. Prognostic factors in patients with Hurthle cell neoplasms of the thyroid. Cancer 2003, 97:1186–1194.

53. Bhattacharyya N. Survival and prognosis in Hurthle cell carcinoma of the thyroid gland. Arch Otolarygngol Head Neck Surg 2003; 129:207–210.

54. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001; 86:1447–1463.

55. Pasieka JL, Thompson NW, McLeod MK, et al. The incidence of bilateral well-differentiated thyroid cancer found at completion thyroidectomy. World J Surg 1992; 16:711–716.

56. Wang TS, Dubner S, Sznyter LA, et al. Incidence of metastatic well-differentiated thyroid cancer in cervical lymph nodes. Arch Otolarygngol Head Neck Surg 2004; 130(1):110–113.

57. Baudin E, Travagli JP, Ropers J, et al. Microcarcinoma of the thyroid gland: The Gustave-Roussy Institute experience. Cancer 1998; 83:553–559.

58. Cady B. Staging in thyroid carcinoma. Cancer 1998; 83:844–847.

59. Tsang TW, Brierley JD, Simpson WJ, et al. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 1998; 82:375–388.

60. American Joint Committee on Cancer: Chapter 8: Thyroid. AJCC Cancer Staging Handbook. 6th ed. New York: Springer, 2002:89–98.

61. Cady B. Pappilary carcinoma of the thyroid gland: treatment based on risk group definition. Surg Oncol Clin N Am 1998; 7:633–644.

62. Sisson JC, Giordano TJ, Jamadar DA, et al. 131I treatment of micronodular pulmonary metastases from papillary thyroid carcinoma. Cancer 1996; 78:2184–2192.

63. Viswanathan K, Gierlowski TC, Schneider AB. Childhood thyroid cancer: characteristics and long-term outcome in children irradiated for benign conditions of the head and neck. Am J Dis Child 1994; 148:260–265.

64. Nikiforov YE, Nikiforova M, Fagin JA. Radiation-induced post-Chernobyl pediatric thyroid carcinomas. Oncogene 1998; 125:46–52.

65. Silveberg SG, Hutter RVP, Foote FW Jr. Fatal carcinoma of the thyroid: histology, metastases, and causes of death. Cancer 1970; 25:792–902.

66. Mazzaferri EL. Carcinoma of follicular epithelium: radioiodine and other treatment outcomes. In: Braverman LE, Utiger RD, eds. Thyroid: A Fundamental and Clinical Text. Philadelphia: Lippincott-Raven, 1996: 922–945.

67. Maxon HR, Englaro EE, Thomas SR, et al. Radioiodine-131 therapy for well-differentiated thyroid cancer—a quantitative radiation dosimetric approach: outcome and validation in 85 patients. J Nucl Med 1992; 33:1132–1136.

68. Hodgson DC, Brierly JD, Tsang RW, et al. Prescribing 131iodine based on neck uptake produces effective thyroid ablation and reduced hospital stay. Radiother Oncol 1998; 47:325–330.

69. Leger FA, Izembart M, Dagousset F, et al. Decreased uptake of therapeutic doses of iodine-131 after 185-MBq iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. Eur J Nucl Med 1998; 25:242–246.

70. Waxman A, Ramanna L, Chapman N, et al. The significance of I-131 scan dose in patients with thyroid cancer: determination of ablation: concise communication. J Nucl Med 1981; 22:861–865.

71. Nemec J, Svatoplyk R, Zamrazil V, Pohunkova D. Comparison of the distribution of diagnostic and thyroablative I-131 in the evaluation of differentiated thyroid cancers. J Nucl Med 1979; 20:92–97.

72. Voutilainen PE, Siironen P, Franssila KO, et al. AMES, MACIS and TNM prognostic classifications in papillary thyroid carcinoma. Anticancer Res 2003; 23(5b):4283–4288.

73. Haldemann AR. The basis for radioiodine therapy in differentiated thyroid cancer. Ther Umsch 1999; 56(7):403–407. General Principles.

74. Bender JM, Dworkin HJ. Iodine-131 as an oncology agent. J Nucl Med Technol 1993; 21:140–150.

75. Sanders LE, Cady B. Differentiated thyroid cancer: reexamination of risk groups and outcome of treatment. Arch Surg 1998; 133(4):419–425.

76. Samuel AM, Rajashekharra BI. Radioiodine therapy for well-differentiated thyroid cancer: a quantitative dosimetric evaluation for remnant thyroid ablation after surgery. J Nucl Med 1994; 35:1944–1950.

77. DeGroot LJ, Kaplan EL, McCormick M, et al. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990; 71:414–424.

78. Mazzaferri EL. Thyroid remnant 131I ablation for papillary and follicular thyroid carcinoma. Thyroid 1997; 7:265–271.

79. Taylor T, Specker B, Robbins J, et al. Outcome after treatment of high-risk papillary and non-Hürthle-cell follicular thyroid carcinoma. Ann Intern Med 1998; 129: 622–627.

80. Maxon HR, Thomas SR, Hertzberg VS. Relationship between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. N Eng Jour Med 1983; 209:937–941.

81. Leeper RD, Shimaoka K. Treatment of metastatic thyroid cancer. Clin Endocrinol Metabol 1980; 9:383–404.

82. Bushnell DL, Boles MA, Kaufman GE. Complications, sequela and dosimetry of iodine-131 therapy for thyroid carcinoma. J Nucl Med 1992; 33:2214–2221.

83. Johansen K, Woodhouse NJ, Odugbesan O. Comparison of 1073 MBq and 3700 MBq iodine-131 in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid cancer. J Nucl Med 1991; 32(2):252–254.

84. Rosario PW, Reis JS, Barroso AL, et al. Efficacy of low and high 131I doses for thyroid remnant ablation in patients with differentiated thyroid carcinoma based on post-operative cervical uptake. Nucl Med Commun 2004; 25(11): 1077–1081.

85. Logue JP, Tsang RW, Brierley JD, et al. Radioiodine ablation of residual tissue in thyroid cancer: relationship between administered activity, neck uptake and outcome. Br J Radiol 1995; 67:1127–1131.

86. Doi SA, Woodhouse NJ. Ablation of the thyroid remnant and 131I dose in differentiated thyroid cancer. Clin Endocrinol (Oxf) 2000; 52(6):765–773.

87. Sherman SI. Optimizing the outcomes of adjuvant radioiodine therapy in differentiated thyroid carcinoma. J Clin Endocrinol Metab 2002; 87(9): 4059–4062.

88. Bal C, Padhy AK, Jana S, et al. Prospective randomized clinical trial to evaluate the optimal dose of 131I for remnant ablation in patients with differentiated thyroid carcinoma. Cancer 1996; 77: 2574–2580.

89. Coover LR, Silberstein EB, Kuhn PJ, et al. Therapeutic 131I in outpatients: a simplified method conforming to the Code of Federal Regulations, title 10, part 35.75. J Nucl Med 2000; 41(11):1868–1875.

90. Lakshmanan M, Schaffer A, Robbins J, et al. A simplified low iodine diet in I-131 scanning and therapy of thyroid cancer. Clin Nucl Med 1988; 13:866–868.

91. Cooper DS, Specker B, Ho M, et al. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid 1998; 8(9):737–744.

92. Luster M, Francesco Lippi F, Jarzab B, et al. rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: a comprehensive review. Endocr Relat Cancer 2005; 12:49–64.

93. Kong SS, Reynolds JC, Movis EG, Lithium as a potential adjuvant to 131I therapy of metastatic, well differentiated thyroid carcinoma. J Clin Endocrinol Metab 1997; 82:273.

94. Office of Nuclear Regulatory Research. U.S. Nuclear Regulatory Commission Regulatory Guide 8.39—Release of Patients Administered Radioactive Materials.

95. Solans R, Bosch JA, Galofre P, et al. Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy. J Nucl Med 2001; 42:738–743.

96. Alexander C, Bader JB, Schaefer A, et al. Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. J Nucl Med 1998; 39(9):1551–1554.

97. Nakada K, Ishibashi T, Takei T, et al. Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? J Nucl Med 2005; 46(2):261–266.

98. Bohuslavizki KH, Brenner W, Klutmann S, et al. Radioprotection of salivary glands by amifostine in high-dose radioiodine therapy. J Nucl Med 1998; 39(7):1237–1242.

99. Maxxon HR, Thomas SR, Saenger EL, et al. Ionizing radiation and the induction of clinically significant disease in the human thyroid gland. Am J Med 1977; 63:967.

100. Sarkar SD, Beierwaltes WH, Gill SP, et al Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. J Nucl Med 1976; 17(6):460–464.

101. Vathaire F, Schlumberger M, Delisle MJ, et al. Leukaemias and cancers following iodine-131 administration for thyroid cancer. Br J Cancer 1997; 75:734–739.

102. Vassilopoulou-Sellin R, Palmer L, Taylor S, Cooksley CS. Incidence of breast carcinoma in women with thyroid carcinoma. Cancer 1999; 85:696–705.

103. Robbins RJ, Voelker E, Wang W, et al. Compassionate use of recombinant human thyrotropin to facilitate radioiodine therapy: case report and review of literature. Endocr Pract 2000; 6(6):460–464.

104. Haugen BR, Lin EC. Isotope imaging for metastatic thyroid cancer. Endocrinol Metab Clin North Am 2001; 30: 469–492.

105. Kohlfuerst S, Igerc I, Lind P. Recombinant human thyrotropin is helpful in the follow-up and 131I therapy of patients with thyroid cancer: a report of the results and benefits using recombinant human thyrotropin in clinical routine. Thyroid 2005; 15(4):371–376.

106. Grigsby PW, Baglan K, Siegel BA. Surveillance of patients to detect recurrent thyroid carcinoma. Cancer 1999; 85:945–951.

107. Bombardieri E, Seregni E, Villano C, et al. Recombinant human thyrotropin (rhTSH) in the follow-up and treatment of patients with thyroid cancer. Tumori 2003; 89(5):533–536.

108. Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma.

109. Schlumberger M, Pacini F, Wiersinga WM, et al. Follow-up and management of differentiated thyroid carcinoma: a European perspective in clinical practice. Eur J Endocrinol 2004; 151:539–548.

110. Antonelli A, Miccoli P, Fedeghini M, et al. Role of neck ultrasound in the follow-up of patients operated on for thyroid cancer. Thyroid 1995; 5:25–28.

111. Brow AP, Greening WP, Mcready VR. Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden Hospital experience. Br J Radiology 1984; 57:323–327.

112. Maxon HR, Smith HS. Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. Endocrinol Metab Clin North Am 1990; 19:685–718.

113. Schlumberger M, Challeton C, De Vathaire F, et al. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. J Nucl Med 1996; 37:598–605.

114. Van Tol KM, Hew JM, Jager PL, et al. Embolization in combination with radioiodine therapy for bone metastases from differentiated thyroid carcinoma. Clin Endocrinol 2000; 52:653–659.

115. Caplan RH, Wickus GG, Manske BR. Long-term follow-up of a patient with papillary thyroid carcinoma, elevated thyroglobulin levels, and negative imaging studies. Endocr Pract 2005; 11(1):43–48.

116. Pineda JD, Lee T, Ain K, et al. Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. J Clin Endocrinol Metab 1995; 80(5):1488–1492.

117. Koh JM, Kim ES, Ryu JS, et al. Effects of therapeutic doses of 131I in thyroid papillary carcinoma patients with elevated thyroglobulin level and negative 131I whole-body scan: comparative study. Clin Endocrinol (Oxf) 2003; 58(4):421–427.

118. Simon D, Koehrle J, Reiners C, et al. Redifferentiation therapy with retinoids: therapeutic option for advanced follicular and papillary thyroid carcinoma. World J Surg 1998; 22:569–574.

119. Simon D, Korber C, Krausch M, et al. Clinical impact of retinoids in redifferentiation therapy of advanced thyroid cancer: final results of a pilot study. Eur J Nucl Med Mol Imaging 2002; 29(6):775–782.

120. Spitzweg C, Morris JC. Gene therapy for thyroid cancer: current status and future prospects. Thyroid 2004; 14(6):424–434.

5

Palliation of Bone Pain from Osteoblastic Metastases

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INTRODUCTION: THE PROBLEM

The incidence of cancer in the United States is over a million new cases a year (excluding cancers of the skin), of which over 100,000, perhaps up to 150,000 patients a year, develop bone metastases. The frequently occurring tumors that spread to the bone are prostate, breast, and lung cancer. The presence of bone metastases obviously signals reduced survival but also heralds a number of clinically significant complications, including bone pain which will afflict up to two-thirds of those with bone metastases. Other complications include fracture, hypercalcemia, and spinal cord compression. This chapter will discuss the role of nuclear medicine in pain control of these painful osseous metastases.

MECHANISMS OF PAIN

The mechanisms of bone pain are not easy to investigate. A patient may present with multiple osseous metastases only one of which is painful, for no obvious reason. Mechanical expansion of the periosteum and microfracture are two probable mechanisms of bone pain, but there may be multiple cytokines involved in pain modulation, such as substance P, prostaglandin E_1 (PGE_1) and PGE_2, and bradykinin, some of which may be secreted by radiosensitive peritumoral lymphocytes. Evidence for this is indirect in that pain may diminish after only 2–4 Gy from teletherapy, before there has been significant tumor cell killing but at a time when lymphocytes exposed to these levels of radiation will die in large numbers.

DIAGNOSTIC MODALITIES

In approaching the diagnosis of the etiology of apparent skeletal pain in a patient with cancer, the history and physical examination are important but insufficiently sensitive and specific. Skeletal radiography of the painful site is the fastest and least expensive approach, but a whole-body bone scan will provide a complete picture of the extent and severity of the disease. It is important to know the degree of osteolysis in a painful site of bone metastasis, as this will determine which therapeutic modality is employed, as will be detailed next. These two imaging modalities complement each other in important ways in diagnosing and treating the pain of osseous metastases.

THERAPY OF BONE PAIN DUE TO OSTEOBLASTIC METASTASES

The treatment of cancer-induced bone pain involves analgesics, with or without radiation and chemotherapy. The pattern of analgesic use is generally based on the World Health Organization's (WHO's) three-step approach to pain relief, beginning with nonsteroidal inflammatory medications, followed, if necessary, by level II drugs (relatively weak opiates). If these are insufficient, more potent opiate analgesics such as morphine are employed. Opiates have often distressing side effects, including sedation, nausea, and constipation, so that the dose of these should be as low as possible to maintain the patient's overall quality of life. In an attempt to lower these doses of analgesics, radiation and chemotherapy are employed. Radiation is usually given with teletherapy, either in a single dosage of 8 Gy or in fractionated dosages of about 30 Gy. These two radiotherapeutic approaches have equal initial efficacy, but the latter has a longer lasting effect in most patients. This form of treatment is often employed for a single painful site but cannot be repeated if the pain recurs. Hemibody radiation has been successfully employed in the past and has a success rate for pain palliation equal to that of other radiation modalities. Recognition of its gastrointestinal and hematologic side effects has reduced hemibody or wide field radiation utilization significantly in the United States.

An effect of appropriate chemotherapy can be to reduce bone pain, as has been documented for mitoxantrone in prostate cancer and the taxanes in breast cancer in up to 30% of patients. Another sort of "chemotherapy" is the use of the bisphosphonates to treat bone pain. Oral and intravenous bisphosphonates have been shown to reduce bone pain, especially in osteolytic cancers, as well as to reduce the risk of pathologic fracture and treat hypercalcemia. Nitrogen-containing bisphosphonates inhibit farnesyl diphosphate synthase, an enzyme involved in osteoclast cholesterol biosynthesis. This leads to a reduction in the lipid geranylgeranyldisphosphate which prenylates guanosine triphosphatases (GTPases) required for normal cytoskeletal organization and vesicular traffic in the osteoclast. In addition, bisphosphonates modulate the expression of bcl-2, leading to caspase-dependent osteoclast apoptosis. This multifaceted osteoclast inhibition and destruction lead to reduced bone turnover, and increased bone mass and mineralization. As

bisphosphonates are not radioactive, and therefore require no special licensure or handling, and one infusion of the newer bisphosphonates is effective for up to four weeks, medical oncologists often favor these drugs which can be given in the office. For at least one of these bisphosphonates, pamidronate, no inhibition of subsequent skeletal uptake by the therapeutic tetraphosphonate samarium-153 (Sm-153) lexidronam (to be discussed next) has been found.

RADIOPHARMACEUTICAL THERAPY

Particle-emitting bone-seeking radiopharmaceuticals have attracted the attention of the nuclear medicine community over the last three decades for the treatment of the pain of osteoblastic metastases. For the eight pharmaceuticals appearing in Table 1 there are published data on clinical trials in humans. All are reactor produced, and all emit a beta particle except for tin (Sn)-117 pentetate and strontium-85 (Sr-85) which produce low energy conversion electrons. Sr-85 also yields low energy X-rays. The radiopharmaceutcials in Table 1 are listed in descending order by the progressively longer half-lives of the radionuclide involved. The maximum and mean energy of the emitted particle, with the corresponding maximum and mean particle ranges in millimeters, and the energy of any emitted gamma photons, are also tabulated. Of these eight, only phosphorus-32 (P-32) as sodium phosphate, Sm-153 lexidronam (EDTMP), and Sr-89 chloride are commercially available in the United States, although rhenium-186 (Re-186) etidronate (HEDP) is widely employed in Europe.

Table 1 Beta or Electron-Emitting Radiopharmaceuticals for Painful Metastases

Radiopharmaceutical	$t_{1/2}$ (d.)	Maximum E_B (MeV)	Mean E_B (MeV)	Max range (mm)	Mean range (mm)	Gamma MeV (% abundance) half-life
^{188}Re(Sn)HEDP	0.7	2.12	0.73	11.0	2.7	0.155 (10%)
			0.79		3.1	
^{153}Sm-EDTMP	1.9	0.81	0.23	2.5	0.6	0.103 (28%)
						0.070 (5%)
^{90}Y-citrate	2.7	2.27	0.94	11.1	2.5	—
^{186}Re(Sn)HEDP	3.8	1.07	0.33	4.5	1.1	0.137 (9%)
^{117m}Sn-DTPA	13.6	0.127[a]	n.a.	0.27	0.2	0.159 (86%)
		0.152[a]	n.a.		0.3	
^{32}P-phosphate	14.3	1.71	0.70	7.9	3.0	—
^{89}Sr-chloride	50.5	1.46	0.58	7.0	2.4	0.909 (0.10%)
^{85}Sr-chloride	64	0.025[a]	n.a.	—	10	0.514
		0.040[a]	n.a.			plus 10-15 keV x-rays

[a]Conversion electrons

Abbreviation: n.a., not available.

MECHANISMS OF RADIOPHARMACEUTICAL LOCALIZATION

Bone metastases may be radiographically osteolytic, reflecting the loss of adjacent bone, or osteoblastic when there is more new bone produced than is lost. The radiographic appearance of a bone metastasis is therefore the net result of the balance of osteoclast activity, direct resorption of bone caused by tumor-secreted factors, and production of new reactive or "woven" bone by adjacent osteoblasts. In the great majority of these metastases there is an osteoblastic component. This leads to localization of these radiopharmaceuticals listed in the table, which bind rather selectively to reactive bone [as does the bone scanning agent technetium-99m methylene diphosphonate (MDP)] because of specific interactions with the dominant bone mineral, hydroxyapatite. In reactive bone surrounding osteoblastic metastases there is a large surface area of amorphous hydroxyapatite which appears prior to crystallization, leading to an excess of bone-seeking radiopharmaceutical deposition relative to normal bone, in ratios ranging between 2 and 15:1, although the usual abnormal-to-normal bone ratio is in the range of 3 to 5:1. Specific mechanisms of deposition will be discussed with each radiopharmaceutical, but all require adequate blood flow to the metastasis. It is an as yet unexplained fact that many, if not all, of these radiopharmaceuticals are retained longer in woven or reactive than in normal bone, further enhancing the abnormal-to-normal bone ratios, and, presumably, their therapeutic effectiveness. These radiotracers all have a significant element of renal excretion; Sr-89 and P-32 will also appear in the feces to some extent. None of the organs of either system (genitourinary, gastrointestinal) receive a significant radiation dose if the patient is well hydrated and defecates daily. The marrow always receives a biologically significant dose, which may lead to mild to moderate, reversible myelosuppression. No other organ receives a significant radiation dose. Whole-body retention of these compounds ranges from about 30% to 40% in a nearly normal skeleton to close to 90% in the presence of widespread metastatic disease.

RADIOPHARMACEUTICAL PROPERTIES

Shown in Table 1, the bone palliation radiopharmaceuticals differ considerably in physical half-life, and dose rate (by a factor of 90), the energy of their emission, effective range (by a factor of 40), presence or absence of a gamma emission, mechanism of skeletal retention, and the degree to which the radiopharmaceutical is incorporated on the surface of, or throughout, the bone. With all of these physical and physiological differences between them, it is surprising that there are no unequivocal data that there is any real difference between them in their reported efficacy for reducing the pain of osteoblastic metastases. The few comparative studies in print also show no significant differences in this effect. The reported range of success in pain relief varies widely between authors, even for the same radiopharmaceutical. This fact raises several methodologic issues which must be addressed before considering the data on each radiopharmaceutical.

METHODOLOGIC ISSUES IN DETERMINING DOSE–EFFECT RELATIONSHIPS

In radiobiologic studies of tumor, dose–response curves are frequently constructed based on the conditions of the study. For in vitro studies of cell survival this is not a difficult task, but in human studies of these radiopharmaceuticals (called "unsealed sources" of radiation by the U.S. Nuclear Regulatory Commission) for pain relief, the production of a dose–response relationship is difficult. Tumor and marrow doses are difficult to calculate for several reasons. Intraosseous trabecular distribution and thickness are both variable in and around tumors. The thicker the trabeculae, as in osteoblastic lesions, the greater the chance of beta particle absorption, reducing the average distance that the particle can travel. The anatomic distribution of tumor throughout the bone, especially trabecular bone where the largest proportion of any radiopharmaceutical is deposited, is also variable. The biologic half-life of Sr-89, Sm-153 lexidronam, Re-186 etidronate, and Sn-117 m pentetate, for which data are available, and by extrapolation for P-32, is prolonged on reactive versus normal bone, and inevitably a mixture of these will occur in any osseous metastatic lesion. The target bone-to-nontarget ratios will differ between different metastatic sites in the same patient. Thus, a number of assumptions are required before radiation dose estimation, and these can lead to quite different results. For example, the published range of dose estimates from Sr-89 to bone metastases has been reported to range between 59 and 611 mGy/MBq (220–2260 rads/mCi). These questions raise the issue of the need for individual lesion dosimetry, if a dose–response curve could be established.

The other part of this conundrum, measurement of response, is perhaps more difficult, as it is rooted in human subjective perceptions of pain. Pain thresholds differ between individuals, making generalizations about a radiation dose which relieves pain not easily reproducible. The crucial question of objective pain measurement has been approached in many ways. Semiquantitative scales, patient diaries, the use of descriptor adjectives, and the visual analog scale (VAS) (a 10-cm line on which the patient is asked to point to where his degree of pain lies, between 0 cm for no pain and 10 cm for the worst pain imaginable) have all been tried. The VAS has a reproducibility of $\pm 20\%$, but has nevertheless proven to be a reliable tool. The amelioration of pain may occur if the patient reduces his activities of daily living (ADL), for example, going to bed, or if the patient increases his analgesic dose. Therefore measurements of the efficacy of a drug in reducing pain must also take into account changes in ADL and medication. In most studies employing the radiopharmaceuticals of Table 1, this important methodologic approach has not been taken. The Utrecht group has demonstrated the value of a tripartite scale which requires an examination not only of pain reduction, but also ADL, and medication changes. This approach should be applied to all future research in the area.

PHOSPHORUS-32-SODIUM PHOSPHATE

This radiopharmaceutical was the most widely employed agent for the treatment of bone pain from osseous metastases between 1950 and approximately 1980. It is usually administered intravenously, but there are studies showing equal efficacy with oral administration, where absorption varies between 40% and 80%. Oral P-32, which is much less expensive than any of the radiotracers to be discussed (and therefore suitable for developing countries) was compared in 1999 with intravenous Sr-89 in an study sponsored by the International Atomic Energy Agency (IAEA). There was no significant difference found in response rates from P-32 or Sr-89 treatment; both were about 90% efficacious. In the early years of P-32 utilization, it was employed after a week of androgen therapy in the belief that tumor and bone uptake would be stimulated. However, the data on which this supposition was made were flawed. Androgen administration can lead to severe side effects, such as spinal cord compression in the presence of bone metastases. Clinical results without administered androgens were as good as with this hormone preparation (or with the use of parathyroid hormone). P-32 not only distributes throughout bone hydroxyapatite as a substitute for the stable phosphate, but it also is incorporated into nucleic acids, compounds with high-energy phosphate bonds such as adenosine triphospate (ATP) and creatine phosphate, and in kinases signaling receptor activation. In fact, P-32 was first used for its myelosuppressive properties by John Lawrence in 1939, when studies on P-32 treatment of myeloproliferative and lymphoproliferative diseases began. Its use for reduction of bone pain started in about 1950, and the fears some have had for the dangers of P-32 myelosuppression were never realized. In fact, only one death and one intracerebral hemorrhage from P-32-induced myelosuppression have been reported. Response rates for pain reduction have ranged between 60% and 90%, with earlier studies especially lacking in rigorous methodology to measure the factors surrounding pain reduction. In the recent IAEA-sponsored study noted before, P-32 caused grade 2 marrow toxicity (platelets 50,000–74,999/ul; leukocytes 2000–2999/ul) in a minority of patients, with no clinical sequelae. A comparative study of P-32 with hemibody radiation detected equivalent therapeutic responses, although hemibody radiation yielded faster clinical responses and more toxicity. Responses to P-32 in the form of pain palliation are generally seen between days 5 and 14 after injection, a time range rather similar to all the other radiopharmaceuticals under discussion. Metastatic breast and prostate carcinoma do not differ in their response rates.

STRONTIUM-89

Strontium and calcium are both in Family 2 of the Periodic Table, with the former atom slightly larger than the latter. The body does not distinguish between these two elements with the result that Sr-89 is distributed throughout bone as it can substitute for calcium in hydroxyapatite. First suggested for therapeutic efficacy

in the 1940s, Sr-89 came into wider use after the successful alleviation of bone pain by several German groups of investigators who reported response rates of up to 90%, using dosages from 1 to 3 mCi. A number of dose escalation studies have indicated that 40 to 60 uCi/kg body weight produce response rates which do not increase with higher dosages, although more toxicity is seen at higher administered activities with this, and all other, radiopharmaceuticals used for this purpose. Response rates have been reported from 40% to 90%, depending on the criteria used. Some, but not all, investigators have found a better response to Sr-89 in patients with higher performance scores. For example, in a study of patients with a mean survival of 23 weeks, only 29% experienced any pain relief.

Pain palliation response duration from Sr-89 has ranged between 6 and 12 weeks. A review of 18 articles describing treatment of 715 patients with dosages of Sr-89 from 1 to 12 mCi yielded response rates of 65%. Most investigators do not see a clear dose–response rate with this, or the other radiotracers under discussion employing further dose escalation once a threshold for pain relief has been reached. Most of these studies were performed on patients with metastatic prostate carcinoma, but equivalent effects have been reported for metastases from breast and other carcinomas. When a drop in prostate specific antigen (PSA) levels has been used as a marker of cytotoxicity, there seems to be no correlation between this phenomenon and pain relief.

Several placebo-controlled studies have been performed employing Sr-89, with response rates ranging between 59% and 67% in the treated groups and 21% and 34% in the placebo groups. In a study comparing Sr-89, teletherapy, and hemibody radiation the response rates were similar, ranging from 61% to 66%. Platelet and leukocyte counts of the Sr-89-treated patients showed decrements of 30–50% without clinical sequelae. On follow-up, the Sr-89-treated group had fewer new sites of metastatic disease than the other two groups.

As an adjuvant to teletherapy given for a solitary painful site, Sr-89, given at a rather high dosage of 10.8 mCi delayed the need for further radiotherapy to the previously treated site and also the appearance of pain at new sites when compared with the patients who received teletherapy with placebo. This has also been demonstrated with a dosage of 5.4 mCi, closer to the usual dosage of 4 mCi employed in the United States. As a result, less pain medication and a higher quality of life were recorded for the patients receiving teletherapy plus adjuvant Sr-89, although there was no difference shown in survival. Only grade 1 myelotoxicity was seen with Sr-89 in this study.

Only Sr-89 has been shown to delay the time until recurrent or new sites of pain requiring teletherapy appear. This effect has not been sought, or at least published, in research on the other radiopharmaceuticals in the table. The success of Sr-89 in providing this benefit probably relates to the long effective half-life of the radiopharmaceutical in bone.

In a retrospective study of patients with progressive bone pain, spinal cord compression was completely prevented in those receiving palliative teletherapy, and occurred in only 4% of those receiving Sr-89, but in 21% of the patients

treated with a nitrogen-containing bisphosphonate, olpadronate, and in 50% of historical controls. This research needs to be repeated in a prospective study because of its important implications for patient care.

SAMARIUM-153 LEXIDRONAM (EDTMP, ETHYLENEDIAMINETETRAMETHYLPHOSPHONATE)

This radiopharmaceutical is a chelate holding the Sm-153 atom. At the hydroxyapatite surface, an oxygen atom on a phosphonate moiety may coordinate with a calcium atom on the bone mineral surface. There is some evidence that samarium atoms may also be hydrolytically released at the hydroxyapatite surface because of a higher affinity of Sm-153 for oxygen atoms of the hydroxyapatite, forming samarium oxide. It is a gamma emitter but is far too expensive to be used to detect osteoblastic activity prior to administration of a larger therapeutic dose. Technetium (Tc)-99m-medronate or oxidronate is employed for this purpose. As with the other radiopharmaceuticals under consideration, skeletal retention is related to the extent of increased osteoblastic lesions throughout the skeleton. With a much shorter half-life than Sr-89, its dose rate is higher and much of the dose is delivered over the first two half-lives. Skeletal retention is complete by about six hours, with very little Sm-153 found in the urine thereafter. Reported response rates range from 55% to 80%, generally do not increase with dose escalation (although, predictably, myelotoxicity does), and are also independent of the tumor type treated.

There have been several placebo-controlled studies using Sm-153 lexidronam.The response rate from 1.0 mCi/kg was more rapid than that from 0.5 mCi/kg, in one of these, but the clinical response was equivalent between the two groups after five weeks, and both were better than the placebo. There was myelotoxicity up to grade 3 or 4 in 10% of the patients, with recovery of depressed blood counts by about eight weeks. Marrow suppression was more severe in the presence of widespread metastases, previous chemotherapy or teletherapy, or with significant marrow involvement two other controlled studies have confirmed the efficacy of this treatment, with the higher dose (1.0 mCi/kg) showing a response greater than 0.5 mCi/kg in each of the first four weeks after injection. Response rates ranged between 55% and 70% and were not significantly different. The reduction in pain has been reported to last between 2 and 17 weeks, with one study claiming that 50% of responses lasted 16 weeks. In the blinded studies noted before, response duration averaged six weeks. Multiple dosages have been successfully given with repeated responses. In one study, a multiple dose regimen (two to four doses, separated by three-month intervals) led to a higher overall response than a single dosage. Because of the shorter half-life of Sm-153 (given as the lexidronman chelate) compared with Sr-89, there is a widespread belief that myelotoxicity resolves more quickly with Sm-153 lexidronam, but there are no studies directly comparing the two radiopharmaceuticals to provide confirmation of this.

RHENIUM-186 ETIDRONATE (HEDP, HYDROXYETHYLIDENEDIPHOSPHONATE)

Rhenium is a member of the same Family VIIA of the Periodic Table as Tc, and their chemical properties are predictably quite similar, although Re is more easily oxidized to the perrhenate than Tc is to pertechnetate. To take advantage of the beta-emitting characteristics of Re-186 (and Re-188, described in Table 1), Re-186 etidronate was synthesized. This compound has the same affinity for bone as the Tc-99m etidronate analog, as well as all the other radiopharmaceuticals under discussion. Because Re-186 is more easily reoxidized, one finds this radionuclide in the urine of patients receiving it for a longer period than with Sm-153-lexidronam. Similar to Sm-153 lexidronam, this compound appears to chemisorb to bone, through coordination with the oxygen atoms, and also forms a rhenium oxide compound on the hydroxyapatite surface. While not approved for use in the United States, it is widely employed in Europe. The early studies on Re-186 etidronate suggested response rates as high as 77%, but with more rigorous criteria, the Utrecht group has published response rates closer to 55% for both painful metastatic breast and prostate cancer. Using the tridimensional analysis referred to before, the Utrecht group found a response rate of 6/18 at 35 mCi, 7/9 at 50–60 mCi, and 7/10 at 80–95 mCi. Pain reduction was counted as significant only if it lasted at least two weeks. Fifty-four percent of the patients met this criterion, but only 35% of responses lasted four weeks. As with the rest of the radiopharmaceuticals under discussion, there is a threshold of efficacy beyond which higher doses lead only to greater toxicity but not to greater pain relief. Thirteen studies of Re-186 etidronate which have been analyzed reveal response rates ranging between a low of 54% and a high of 87%, close to the 90% found in the IAEA study of P-32 and Sr-89. It is clear that the stricter the criteria one employs, especially taking into account the changes in activities of daily living and medication for each patient following injection, the lower the response rate observed.

A small double-blind crossover study established that Re-186 etidronate is more active than placebo. A more recent published comparison of Sr-89 and Re-186 etidronate found no difference in response rates, 84% for the former, 92% for the latter, with no difference found also in the mean duration of pain relief, 125 days with Sr-89 and 107 days with Re-186 etidronate. Myelotoxicity was also similar, but platelet and leukocyte counts returned to baseline by six weeks after Re-186 etidronate and 12 weeks after Sr-89, a statistically significant difference.

OTHER RADIOPHARMACEUTICALS FOR THE PAIN OF OSTEOBLASTIC METASTASES

The other radiopharmaceuticals listed in the table have shown efficacy in one or more clinical studies but have not been made available to practicing nuclear medicine physicians after early trials, usually because of economic and/or

regulatory issues. Re-188 etidronate has been given to patients but little clinical data is available. As it has the highest dose rate of any of these radiotracers, it remains of interest. Yttrium (Y)-90 citrate has the most energetic beta emission of the materials listed but only limited clinical data have come forth. Sn-117m is of particular interest because its emissions, low-energy electrons, have very short path lengths and would be predicted to cause the least myelosuppression. This limited marrow toxicity has been confirmed in several studies, with a response rate in the range published for the other radiopharmaceuticals discussed. Sr-85 emits extremely low energy conversion electrons and 10–15 keV X-rays and has been described as yielding 75 to 80% patient responses, with pain relief less likely in patients with poorer performance status, similar to the findings in some, but not all of the Sr-89 studies noted before.

TREATMENT INDICATIONS

While these radiopharmaceuticals are capable of reducing or relieving the pain of any bone metastasis with an osteoblastic component causing increased uptake on a bone scan, most patients with a single painful site will receive teletherapy, avoiding the mild to moderate myelosuppression of these radiopharmaceuticals. Multiple painful metastases with an osteoblastic component (documented on bone scan) represent the chief indication for the use of the commercially available beta emitters in the table. After teletherapy to the spine and other sites for metastatic disease with recurrent pain, these radiopharmaceuticals may be safely employed when additional external beam radiotherapy is contraindicated because of the concern of radiogenic necrosis.

While there exist data that patients with poorer performance status do not respond well to these radiopharmaceuticals, there is no humane reason for excluding these patients from a treatment which can reduce the detrimental effects of high doses of narcotic analgesics. The belief that a patient may die in a month or so is also no reason to deny such treatment if there is a chance it can make any contribution to the patient's quality of life in his final weeks. Persistent radiation in a patient who has died can be handled with simple radiation safety precautions.

PREDICTORS OF RESPONSE

It is difficult to determine what patient characteristics, other than the presence of a pathologic fracture, indicate a poor chance of responding to treatment of bone pain with radiopharmaceuticals. Cytopenias and a decrease in tumor markers caused by these radiopharmaceuticals do not correlate well with response. The presence of narcotic tolerance does not indicate the likelihood of response. Higher dosages than those which have been empirically determined to be effective do not yield greater response rates.

Recent studies have again suggested that a larger tumor burden may indicate a lower chance for successful outcome, perhaps because there are fewer

radioactive molecules then to be distributed over a relatively larger bone tumor mass. A related Chinese study noted a statistically significant relationship between bone uptake of radiopharmaceutical (Sm-153 lexidronam) and therapeutic effect, again suggesting that dosimetric considerations may improve patient selection and the amount of activity injected.

CONTRAINDICATIONS TO THE USE OF RADIOPHARMACEUTICALS FOR PAIN RELIEF

A single site of bone pain should receive teletherapy. Metastatic disease detected radiographically where there is no osteoblastic response (i.e., a bone scan showing no abnormality in the painful site) as, for example, in about half of the myeloma patients, should not be treated with these agents, as there will be no localization where the Tc-99m medronate or oxidronate bone scan shows no increased uptake. In painful sites where marked osteolysis (over 50% of the cortex destroyed by tumor) is radiographically apparent, teletherapy is required, often accompanied by prophylactic orthopedic intervention, to avoid pathologic fracture. A pathologic fracture is quite painful and will, of course, not respond to radiopharmaceutical therapy despite the abnormal bone scan at the site. Cord compression and epidural metastases should be dealt by employing teletherapy and/or surgery but not with beta emitters. Nonosseous sources for pain referred to bony sites must be carefully excluded, as clearly these radiopharmaceuticals will be ineffective in this clinical setting.

There are also hematologic contraindications to the use of these radiopharmaceuticals. Significant cytopenias (pretreatment leukocyte count below about 2500–3000/ul, absolute neutrophil count below 1000/ul, platelet count below 60,000–100,000/ul) raise the risks for infection and bleeding. It should be recalled that there are other reasons for pancytopenia in cancer patients, including recent or concurrent chemotherapy or radiotherapy, marrow involvement by tumor, and disseminated intravascular coagulation.

Disseminated intravascular coagulation (DIC) is usually subclinical and has been reported in up to 10% to 20% of prostate cancer patients. In this entity, megakaryocyte production and turnover are greatly increased to provide the maximum platelet supply possible, and these platelets have very short half-lives as they participate in the ongoing clotting process. In this disorder, suppression of megakaryocyte production by these beta emitters can lead to precipitous and life-threatening thrombocytopenia, so very active DIC is a relative contraindication to the use of these radiopharmaceuticals. A search for fibrin split products is a far more sensitive test for DIC than the platelet count.

ADVERSE REACTIONS

There are only two significant adverse reactions related to treatment with these radiopharmaceuticals. Myelosuppression is expected from irradiation of the

marrow by beta particles localized in the bone which surrounds the marrow. The resulting decrease in leukocyte and platelet counts may not even result in leukopenia and thrombocyopenia if the patient has a normal pretreatment leukocyte and platelet count and no evidence of DIC. The drop in leukocytes and platelets is usually in the range of 30% to 50% of the preinfusion count with these radiopharmaceuticals. The nadir is between four and six weeks, and recovery occurs by eight to twelve weeks; both nadir and recovery may be at the earlier end of this range with the more short-lived radionuclides.

The flare phenomenon, an increase in pain in the sites being treated, is the other side effect. This is usually seen within 72 hours of administration, lasts a few days at most, and occurs in from about 5% to 60% of patients, depending, among other issues, on the degree of carefulness of follow-up, the asking of leading questions about pain, and the actual definition of the flare phenomenon employed. For example, a patient may assume that one day after infusion he is capable of more activity, tries to perform an act that is painful, and thus reports increased pain. This area has not been carefully studied.

TREATMENT APPROACHES

The preparation of a patient for therapy with a beta-emitting radiopharmaceutical begins several days before the actual infusion. Fully informed written consent is necessary, and the patient must be told that there are rare deaths from this therapy, almost all in patients with unrecognized DIC. This author has found it useful to give the patient a consent form to take home and share with family and other concerned parties before he signs it. A bone scan is necessary before treatment if one has not been done for several months and must be abnormal in the painful sites to be treated. Correlative radiographs of the painful sites should be reviewed. A complete blood count and assay of fibrin split products a day before treatment are necessary. These radiopharmaceuticals are very expensive, and one does not want to order them if they will not be used when a contraindication appears in the form of an abnormal laboratory test on the day of treatment.

DOSIMETRIC CONSIDERATIONS

For the reasons described in an earlier section of this text, accurate, reproducible lesion dosimetry is not yet possible. When the substantial technical issues around this measurement have been solved, the threshold dose below which pain relief rarely occurs can be determined. Then the information from a bone scan may be used to decide if administration of one of these radiopharmaceuticals will have any analgesic effect. With reliable marrow dosimetry, the nuclear medicine physician will also have a better idea of the degree of myelosuppression to expect. Currently, the clinician can only deal with these considerations empirically.

TREATMENT MONITORING AND OUTCOME

The nuclear medicine physician should follow the treated patient closely with the referring physician, in order to advise him of the patient preparation and workup, as well as alerting him to the possible adverse reactions and their time course, as noted before. The informed consent process requires an empathetic physician who is prepared to answer sophisticated questions from a well-informed patient. The nuclear medicine physician should be available for further consultation with both the patient and the referring physician.

REPEAT TREATMENTS

All of these radiopharmaceuticals have been successfully given a second time, or even up to 5 to 10 times, if there has been a response to the first treatment. The response rate to the second treatment is usually in the 50% range, often slightly less than with the first therapy. Myelotoxicity appears to be cumulative, so that the blood counts may not return to the same levels after two or more treatments that were seen after the first injection.

RADIATION SAFETY CONSIDERATIONS

Under current regulations of the U.S. Nuclear Regulatory Commission all these radiopharmaceuticals may be administered in the outpatient setting and hospitalization is not required. A special treatment room is advisable to avoid even the perception of exposure of other patients and staff unnecessarily, but there are no data indicating any radiation hazard to the personnel of the nuclear medicine facility as long as appropriate shielding measures are taken for the radiopharmaceutical during storage and administration. As P-32 and Sr-89 emit no significant photons, and the bremsstrahlung they produce are not of any clinical significance, no precautions need to be taken when these patients are released, except for good hygiene, that is, handwashing and avoidance of urine contamination, and not conceiving a child for several months. Measurements of radiation coming from patients who have received gamma-emitting Sm-153 lexidronam and Re-186 etidronate indicate that no stringent home precautions are required other than those noted before. Separate utensils and toilet facilities are unnecessary. The time required for a couple to sleep apart is 24 to 72 hours for the two gamma-emitting radiotracers.

RADIOPHARMACEUTICAL–CHEMOTHERAPY COMBINATIONS

There are a number of studies in patients with bone metastases which have combined a beta-emitting radiopharmaceutical, usually Sr-89, with a variety of chemotherapeutic drugs, including gemcitabine, estramustine, mitoxantrone, paclitaxel, carboplatin, cisplatin, and doxorubicin, with only a very few truly

controlled for response with or without the radiopharmaceutical. Some of these have been used in combination, as with Sr-89, estramustine, and vinblastine. The response rates in these studies have ranged from 55% to 80%, a range seen in multiple investigations that did not include chemotherapeutic agents.

Sr-89 followed by carboplatin yielded superior pain relief compared with Sr-89 in one study, with no difference in survival. In a study of hormone refractory prostate cancer with painful bone metastases, induction therapy with ketocononazole, doxorubicin, estramustine, and vinblastine was followed by randomization to receive doxorubicin with or without subsequent Sr-89. The median survival time for the combination was 27.7 months and for doxorubicin alone was 16.8 months. If confirmed, this would be one of the first studies showing that a beta-emitting radiopharmaceutical conveyed a survival advantage. On the other hand, the addition of Sr-89 to gemcitabine in painful prostate cancer metastatic to bone yielded no response at all.

ECONOMIC VALUE OF RADIOPHARMACEUTICAL THERAPY FOR PAINFUL BONE METASTASES

There have been careful studies of the economic benefits of using beta-emitting radiopharmaceuticals. For example, Sr-89 palliative therapy has been demonstrated to reduce the lifetime healthcare costs of patients with painful bone metastases by decreasing the need for teletherapy, narcotic analgesics, and hospitalization.

PROCEDURE FOR ADMINISTERING RADIOPHARMACEUTICALS TO TREAT THE BONE PAIN OF OSTEOBLASTIC METASTASES

1. *Patient evaluation and data required for treatment of painful bone metastases*
   a. A bone scan performed within the previous six to eight weeks must show abnormally increased uptake at the painful site(s).
   b. Platelet and leukocyte counts must be adequate. The platelet count should exceed 100,000 μL and leukocyte count should exceed 2500–3500/μL.
   c. Significant disseminated intravascular coagulation must be excluded with an assay of fibrin split products.
   d. Fully informed, written consent, including an explanation of home precautions, should be accomplished, preferably twice, once several days before the treatment. This should include the risks of pancytopenia, the flare phenomenon, and remote risk of death.
   e. The painful site should not be treated with radiopharmaceuticals if there is any risk of vertebral compression, epidural metastasis, osteolytic disease destroying 50% or more of the cortex, or evidence of pathologic fracture.

   f. Teletherapy is preferred for treatment of single painful lesion.
2. *Dosimetric considerations*
   a. Our dosimetric techniques are currently inadequate to have these data be a part of the decision-making process on therapeutic dosage.
3. *Choice of radiopharmaceutical*
   a. Sr-89 has been shown to delay the need for repeat therapy and the onset of new painful metastases.
   b. Re-186 etidronate has been demonstrated to cause a shorter period of cytopenia than Sr-89, and the same is probably true for Sm-153 lexidronam.
   c. P-32 is far less expensive than the other radiopharmaceuticals, can be given orally, and has equal efficacy with no greater risk of death than with Sr-89, Re-186 etidronate, and Sm-153 lexidronam.
   d. Thus, there are benefits to the use of any of these radiopharmaceuticals.
4. *Special patient preparation*
   a. No premedication or fasting is required.
   b. The patient should be well hydrated at home, and should receive about 0.5–1.0 l of any liquid orally or intravenously before treatment to ensure rapid renal excretion.
   c. Constipation must be avoided in order to clear Sr-89 and P-32 from the bowel. These agents are not themselves constipating.
5. *Dosage administration*
   a. A running intravenous line should be in place. Make sure it works well by infusion of some 50–100 mL of saline solution.
   b. A plastic syringe shield should be used, as the production of bremsstrahlung from beta particle interactions with shielding material increases as the atomic weight of the shielding material rises.
   c. Gloves and a finger badge should be worn by the individual performing the injection.
   d. These radiopharmaceuticals should be given slowly into the intravenous line over two to three minutes, as the mass of the radiopharmaceutical injected may be sufficient to have physiologic effects. Etidronate and lexidronam may chelate calcium and magnesium, acutely but briefly lowering the blood levels of these cations. A bolus of Sr-89 may have calcium-like effects on cardiac physiology. A vial of calcium gluconate should be on hand for rapid administration if cardiac arrhythmias occur.
6. *Treatment monitoring*
   a. The patient may return home after the radiation safety officer monitors the patient.

b. The patient should be told that changes in bone pain usually are seen within 7 to 14 days after treatment but may become even more evident over three to four weeks.

7. *Side effects*
   a. The patient should be instructed to report any (cytopenia-induced) bleeding episodes, petechiae, sore throat, or fever at once.
   b. The patient should be told there is some chance of an increase in discomfort at the painful sites being treated and instructed on what medication he may take to deal with this. He must also be informed that this is not a discouraging sign.
8. *Follow-up plans*
   a. The patient should be told to follow-up either with the referring physician or the nuclear medicine physician, if the referring doctor has so indicated, at least every two weeks up to twelve weeks.
   b. Platelet and leukocyte counts may be monitored after two weeks.
   c. If there is a response to treatment the patient must be told that this is rarely permanent but that more treatments can be given.
9. *Instructions to the patient/radiation safety*
   a. The patient may return home.
   b. For P-32 and Sr-89 treatments, there is no need to avoid proximity to one's spouse, children, or pregnant women.
   c. For the gamma-emitting Re-186 and Sm-153 there are no convincing data that the patient represents a radiation hazard to anyone, but local radiation safety office precautions should be followed. There should be little reason for couples to sleep apart for more than a day or so.
   d. Men should urinate sitting down for several days after therapy, although urinary Sm-153 lexidronam excretion is generally complete well within 24 hours after injection. There is no need for the use of separate toilets.
   e. Handwashing for 20 seconds after urination or defecation is suggested.
   f. Separate utensils are not needed.
   g. Stringent birth control measures should be undertaken for at least six months.

ANNOTATED BIBLIOGRAPHY

Atkins HL. Radiopharmaceuticals for bone malignancy. J Nucl Med Technol 1998; 26:80–83. *A concise review of available radiotracers.*

Ben-Josef E. Radiotherapeutic management of osseous metastases: a survey of current patterns of care. Int J Radiat Oncol Biol Phys 1998; 40:915–921. *A wide variety of effective regimens are analyzed.*

Dearnaley DP. Palliation of bone metastases in prostate cancer. Hemi-irradiation or strontium-89. Clin Oncol 1992; 4:101–107. *Good review of efficacy and adverse reactions of both techniques.*

McEwan AJ. Palliation therapy with bone seeking radiopharmaceuticals. Cancer Biother Radiopharm 1998; 13:413–426. *A critical literature review.*

McEwan AJ. Unsealed source therapy of painful bone metastases. Semin Nucl Med 1997; 27:165–182. *A review of indications, contraindications and utilization of the various radioisotopes available.*

Poulson HS, Nielsen OS, Klee M, et al. Palliative irradiation of bone metastases. Cancer Treat Rev 1989; 16:41–48. *A survey of the results of teletherapy palliation for bone pain.*

Salazar OM, Rubin P. Hendrickson FR, et al. Single dose half-body irradiation for palliation of multiple bone metastases from solid tumors. Final Radiation Therapy Oncology Group Report. Cancer 1986; 58:29–36. *The use of hemibody irradiation is effective in bone pain palliation.*

Silberstein EB. Dosage and response in radiopharmaceutical therapy of painful osseous metastases. J Nucl Med 1996; 37:249–252. *A summary of the controversy in determining if an increase in dosage of injected radiotracer yields a better response rate.*

Phosphorus-32

Aziz H, Choi, K, Sohn C, et al. Comparison of ^{32}P therapy and sequential hemibody irradiation (HBI) for bony metastases as methods of whole body irradiation. Am J Clin Oncol 1986; 9:264–268. *Pain palliation with P-32 in 80% with response within a week. Hemibody radiation provided similar but faster responses and more toxicity.*

Friedell HL, Storaasli JP. The use of radioactive phosphorus in the treatment of carcinoma of the breast with widespread metastases to bone. Am J Roentgenol 1950; 64:559–575. *The first study of P-32 efficacy, with biodistribution and toxicity data well displayed. Ten of 12 responded.*

Silberstein EB. The treatment of painful osseous metastases with phosphorus-32-labeled phosphates. Sem Oncol 1993; 20(suppl 2):10–21. *Comprehensive review of thirty studies of P-32 therapy.*

Strontium-89

Ben-Josef E, Lucas DR, Vasan S, et al. Selective accumulation of strontium-89 in metastatic deposits in bone; radio-histological correlation. Nucl Med Commun 1995; 16:457–463. *Strontium deposition occurs in areas of significant osteoblastic activity, mostly in areas adjacent to metastatic deposits but also in subchondral and endosteal locations.*

Berna L, Carrio I, Alonso C, et al. Bone pain palliation with strontium-89 in breast cancer patients with bone metastases and refractory bone pain. Eur J Nucl Med 1995; 22:1101–1104. *A 47% response rate is reported in breast cancer patients.*

Blake GM, Zivanovic MA, McEwan AJ, et al. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. Eur J Nucl Med 1986; 12:447–454. *Description of Sr-89 kinetics in normal and involved bone showing that the latter retains Sr-89 much longer than normal bone.*

Brundage MD, Crook JM, Lukka H. Use of strontium-89 in endocrine-refractory prostate cancer metastatic to bone. Provincial Genitourinary Cancer Disease Site Group. Cancer Prev Control 1998; 2:79–87. *Clinical guidelines and literature review. Survival is not prolonged by Sr-89.*

Charron M, Brown M, Rowland P, et al. Pain palliation with strontium-89 in children with metastatic disease. Med Pediatr Oncol 1996; 26:393–396. *Two children were studied in this report, one of the few with pediatric data. Sr-89 is only effective if the bone scan is abnormal.*

Cipriani C, Atzei G, Argirδ G, et al. Gamma camera imaging of osseous metastatic lesions by strontium-89 bremsstrahlung. Eur J Nucl Med 1997; 24:1356–1361. *Techniques for imaging patients who have received Sr-89 are provided.*

Guerrieri P, Modoni S, Parisi S, et al. Bone formation markers and pain palliation from bone metastases treated with strontium-89. Am J Clin Oncol 1994; 17:77–79. *Procollagen I and III levels were markedly elevated in patients who had no response to Sr-89 but were normal or slightly elevated in responders.*

Leong C, Mckenzie MR, Coupland DB, et al. (1994) Disseminated intravascular coagulation in patients with metastatic prostate cancer: fatal outcome following strontium-89 therapy. J Nucl Med 1994; 35:1662–1664. *Description of a rare but dangerous contraindication to therapy with unsealed sources.*

Malmberg I, Persson U, Ask A, et al. Painful bone metastases in hormone-refractory prostate cancer: economic costs of strontium-89 and/or external radiotherapy. Urology 1997; 50:747–753. *Adjuvant Sr-89 added to teletherapy was found to yield potential cost savings as compared to teletherapy initially and at relapse, since Sr-89 prolonged the time to relapse or to new sites of bone pain.*

McEwan AJ, Amyotte GA, McGowan DG, et al. A retrospective analysis of the cost effectiveness of treatment with Metastron in patients with prostate cancer

metastatic to bone. Eur Urol 1994; 26(suppl 1):26–31. *Sr-89 can reduce management costs for patients with advanced prostate carcinoma.*

McEwan AJB, Porter AT, Venner PM, et al. An evaluation of the safety and efficacy of treatment with strontium-89 in patients who have previously received wide field radiotherapy. Antibody, Immunoconjugates, Radiopharm 1990; 3:91–98. *The response rates and toxicity of Sr-89 are not different between patients who have previously received wide field radiotherapy and teletherapy*.

Mertens WC, Stitt L, Porter AT. Strontium-89 therapy and relief of pain in patients with prostate carcinoma metastatic to bone; a dose response relationship? Am J Clin Oncol 1993; 16:238–242. *There was a statistically significant relationship between increasing dosages of Sr-89 and complete, but not partial, pain relief.*

Nair N. Relative efficacy of ^{32}P and ^{89}Sr in palliation in skeletal metastases. J Nucl Med 1999; 40:256–261. *Intravenous Sr-89 and oral P-32 were equal in efficacy and no significant toxicity occurred with either radionuclide.*

Pine F, Herranz R, Garcia A, et al. Strontium-89 for palliation of pain from bone metastases in patients with prostate and breast cancer. Eur J Nucl Med 1997; 24:1210–1214. *Fifty patients with prostate cancer, 26 with breast cancer showed good response to Sr-89 measured by activities of daily living scales on pain scores.*

Porter AT, McEwan AJB, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int J Radiat Oncol Biol Phys 1993; 25:805–813. *The Trans-Canada study showed that Sr-89 could prolong the time until appearance of new or recurrent painful metastases*.

Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. Radiother Oncol 1994; 31:33–40. *Hemibody radiation, teletherapy and Sr-89 are equivalent in pain palliation.*

Robinson RG, Preston DF, Spicer JA, et al. Radionuclide therapy of intractable bone pain. Emphasis on strontium-89. Sem Nucl Med 1992; 22:28–30. *A review of the largest series of patients treated with Sr-89, although patients not surviving 3 months are excluded.*

Schmeler K, Bastin K. Strontium-89 for symptomatic metastatic prostate cancer to bone: recommendations for hospice patients. Hospice J 1996; 11:1–10. *Response rates for patients with Karnofsky performance scores of 60 or less were about 40% while patients with scores over 60 were around 70%.*

Schmidt CG, Firusian N. ^{89}Sr for the treatment of incurable pain in patients with neoplastic osseous infiltration. Int J Clinical Pharmacol 1974; 9:199–205. *Early recognition of the value of Sr-89 for pain palliation after this tracer has been little used since description of its use in 1942.*

Schraml FV, Parr LF, Ghuroni S, et al. Autopsy of a cadaver containing strontium-89-chloride. J Nucl Med 1997; 38:380–382. *From an autopsy performed*

4 days after 4.4 mCi of Sr-89, no participant received a measurable radiation dose. A calculated hand dose of 15 mrem is below the dosimeter detection rate.

Scioto R, Maini CL, Tofani A, et al. Radiosensitization with low-dose carboplatin enhances pain palliation in radioisotope therapy with strontim-89. Nucl Med Commun 1996; 17:799–804. *Carboplatin plus Sr-89 yielded a higher rate of pain control than Sr-89 alone.*

Silberstein EB, Taylor A Jr. Procedure guideline for bone pain treatment: 1.0. J Nucl Med 1995; 37:881–884. *Society of Nuclear Medicine endorsed document on how to use unsealed sources for bone pain treatment.*

Silberstein EB, Williams C. Strontium-89 therapy for the pain of osseous metastases. J Nucl Med 1985; 26:345–348. *First English language description of Sr-89 use with a dose-escalation trial showing no value in increasing dosage.*

Rhenium-186

Collins C, Eary JF, Donaldson G, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a Phase I/II trial. J Nucl Med 1993; 34:1839–1844. *Grade 3 (of 4) hematologic toxicity occurred in 35–40% of patients at dosages of 2.5–3.0 mCi/kg. No dosage response relationship was statistically significant.*

deKlerk JMH, van Dieren EB, van het Schip AD, et al. Bone marrow absorbed dose of rhenium-186-HEDP and the relationship with decreased platelet counts. J Nucl Med 1996; 37:38–41. *Myelotoxicity correlated well with mean marrow absorbed dose.*

deKlerk JMH, van het Schip AD, Zonnenberg BA, et al. Dose escalation study of rhenium-186 hydroxyethylidene diphosphonate in patients with metastatic prostate cancer. Eur J Nucl Med 1994; 21:1114–1120. *Well designed study using dimensions of pain response, medication index, activity scale to describe responses to Re-186 etidronate.*

deKlerk JMH, van het Schip AD, Zonnenberg BA, et al. Evaluation of thrombocytopenia in patients treated with rhenium-186-HEDP. Guidelines for individual dosage recommendations. J Nucl Med 1994; 35:1423–1428. *Careful examination of radiotoxicity of Re-186 etidronate which is greater with more bone involvement.*

deKlerk JMH, van het Schip, Zonnenberg BA, et al. Phase I study of rhenium-186-HEDP in patients with bone metastases originating from breast cancer. J Nucl Med 1996; 37:244–249. *Thrombocytopenia was the dose-limiting toxicity with maximum tolerated administered activity 65 mCi (2405 MBq).*

deKlerk JMH, Zonnenberg BA, Krouwer HGJ, et al. Transient cranial neuropathy in prostatic cancer with bone metastases after rhenium-186-HEDP treatment. J Nucl Med 1996; 37:465–467. *Transient cranial neuropathy is possible if metastases occur to the sites of foramina through which cranial nerves pass.*

Deutsch E, Libson K, Vanderheyden JL, et al. The chemistry of rhenium and technetium as related to the use of isotopes of these elements in therapeutic and diagnostic nuclear medicine. Nucl Med Biol 1986; 13:465–477. *Excellent chemical review of Re-186 and Tc-99m chemistry.*

Eary JF, Durack L, Williams D, et al. Consideration for imaging Re-188 and Re-186 isotopes. Clin Nucl Med 1990; 15:1911–1916. *Medium energy collimator recommended.*

Englaro E, Schroder, LE, Thomas SR, et al. Safety and efficacy of repeated sequential administrations of Re-186(Sn)HEDP as palliative therapy for painful skeletal metastases. Clin Nucl Med 1992; 17:41–44. *Two patients received 5 and 7 injections of Re-186 etidronate for pain with a good clinical response. The platelet count slowly fell to 40–50% of initial levels.*

Mathieu L, Chevalier P, Galy G, et al. Preparation of rhemium-186 labeled HEDP and its possible use in the treatment of osseous neoplasms. Int J Appl Rad

Isotopes 1979; 20:725–727. *The earliest description of Re-186 etidronate preparation for therapy.*

Maxon HR, Schroder LF, Washburn LC, et al. Rhenium-186(Sn)-HEDP for treatment of osseous metastases. J Nucl Med 1998; 39:659–663. *Biodistribution and dosimetry of Re-188 etidronate is similar to that of Re-186 etidronate. A wolfram-188/rhenium-188 generator may be used.*

Maxon HR, Thomas SR, Herzberg VS, et al. Rhenium-186 hydroxyethylidene diphosphonate for the treatment of painful osseous metastases. Sem Nucl Med 1992; 22:33–40. *Summary of Re-186 etidronate efficacy in the first site to use this therapy.*

Quirijen JMSP, Han SH, Zonnenberg BA, et al. Efficacy of rhenium-186 etidronate in prostate cancer patients with metastatic bone pain. J Nucl Med 1996; 37:1511–1515. *Sophisticated study of Re-186 etidronate efficacy in prostate cancer showed 55 responses (lower than usual) when stringent criteria are applied.*

Samartunga RC, Thomas SR, Hinnefeld JD, et al. A Monte Carlo simulation model for radiation dose to metastatic skeletal tumor from rhenium-186(Sn)-HEDP. J Nucl Med 1995; 36:336–350. *Uniform lesion model calculations underestimate the radiation dose to blastic lesions by a factor as high as 1.8.*

Samarium-153 EDTMP

Collins C, Eary JF, Donaldson G, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a Phase I/II trial. J Nucl Med 1993; 34:1839–1844. *Grade 3 (of 4) hematologic toxicity occurred in 35–40% of patients at dosages of 2.5–3.0 mCi/kg. No dosage response relationship was statistically significant.*

Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. J Nucl Med 1993; 34:1031–1036. *Detailed biokinetic and biodosimetry data.*

Goeckeler WF, Troutner DE, Volkert WA, et al. ^{153}Sm radiotherapeutic bone agents. Nucl Med Biol 1986; 13:479–482. *Excellent paper on Sm-153 chemistry.*

Ketring AR, ^{153}Sm-EDTMP and ^{186}Re-HEDP as bone therapeutic radiopharmaceuticals. Nucl Med Biol 1987; 14:223–232. *Comparative radiopharmacy of Re-186 and Sm-153. Re-186 etidronate elutes from bone while Sm-153 lexidronam does not.*

Logan KW, Volkert WA, Holmes RA. Radiation dose calculations in persons receiving injections of samarium-153 EDTMP. J Nucl Med 1987; 28:505–509. *Sm-153 lexidronam dosimetry—a preliminary approach.*

Resche I, Chatal JF, Pecking A, et al. A dose-controlled study of ^{153}Sm-ethylenediaminetetramethylenephosphate (EDTMP) in the treatment of patients with painful bone metastases. Eur J Cancer 1997; 33:1583–1591. *There was no significant difference between the percent pain relief or analgesic dosage when comparing 0.5 mCi/kg and 1.0 mCi/kg dosages of Sm-153 lexidronam.*

Sandeman TF, Budd RS, Martin JJ. Samarium-153-labeled EDTMP for bone metastases from cancer of the prostate. Clin Oncol 1992; 4:160–164. *At high activities (3.0–4.5 mCi/kg) thrombocytopenia proved lethal in 4 of 8 patients. In this dose escalation study there was a high degree of pain reduction but this lasted 4–6 weeks in most.*

Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. J Clin Oncol 1998; 16:1574–1581. *The 1.0 mCi/kg dosage acts slightly more quickly than the 0.5 mCi/kg dose: a large cooperative trial.*

van Rensburg AJ, Albert AS, Louw WKA. Quantifying the radiation dosage to individual skeletal lesions treated with samarium-153-EDTMP. J Nucl Med 1998; 39:2110–2115. *A gamma camera-based quantitation technique found the activity concentration of Sm-153 in trabecular bone to be twice that of cortical bone, while lesion concentrations were 3–7 times higher than in normal bone.*

Tin 117m Pentetate

Atkins HL, Mausner LF, Srivastava SC, et al. Tin-117 m(4+) for palliation of pain from osseous metastases: a pilot study. J Nucl Med 1995; 36:725–729. *One of the early publications on tin-117 m efficacy.*

Krishnamurthy GT, Swailen FM, Srivastava SC, et al. Tin-117 m(4+) DTPA: pharmacokinetics and imaging characteristics in patients with metastatic bone pain. J Nucl Med 1997; 38:230–237. *Soft tissue and osseous components of biokinetics are quantitated.*

Srivastava SC, Atkins HL, Krishnamurthy GT, et al. Treatment of metastatic bone pain with tin-117 m stannic diethylenetriaminepentaacetic acid. A phase I/II clinical study. Clin Cancer Res 1998; 4:61–68. *Comparative dosimetry and toxicity with other unsealed sources favor Sn-177m DPTA; good efficacy study.*

6

^{224}RaCl Therapy for Treatment of Ankylosing Spondylitis

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TOPIC AND BACKGROUND

Ankylosing spondylitis (AS) is a common inflammatory rheumatic disease, leading to severe pain, disability, and impaired quality of life in at least one-third of all patients (1). Moreover, the disease has a relevant socioeconomic impact, because it frequently affects men and women during their third life decade.

In the United States, the incidence of AS is 7.3 per 100,000 patient years (2), and the frequency is supposed to be similar to rheumatoid arthritis. Today, approximately 350,000 U.S. citizens suffer from AS.

The treatment is based on both physiotherapy and nonsteroidal anti-inflammatory agents, including selective cyclooxygenase-2 (COX_2) inhibitors. Therapeutic effects are additionally discussed for several "disease-modifying drugs," like sulfasalazine or methotrexate. None of these drugs is Food and Drug Administration (FDA) approved for AS. However, methotrexate, in particular, is frequently used in the United States (3), although its therapeutic efficacy is limited (4). The recently introduced "biologicals," infliximab and etanercept, have shown to be effective in AS by blocking the proinflammatory cytokine tumor necrosis factor (TNF)-α (5). Etanercept was approved for the treatment of AS by the FDA in July 2003. Owing to some well-known, severe side effects, very high costs, and the lack of long-term experience with these new

substances, it is important to re-emphasize the α-emitter ^{224}RaCl (radium chloride) for treatment of AS, which was used for therapy of different bone and joint diseases in Europe from the mid-1940s until 1990. After being off the market for economic reasons, a new ^{224}RaCl preparation was reapproved by the German Federal Institute for Drugs and Medical Devices (BfArM) in 2000.

Pathophysiology of Ankylosing Spondylitis

The first description of two patients suffering from complete inflammatory ankylosis of the spine and peripheral joints was presented by Adolf Struempell in 1884, followed by reports by Wladimir von Bechterew and Pierre Marie (6).

The etiology of this rheumatoid-inflammatory disease is still unknown. Owing to the frequent association with the human leukocyte antigen HLA-B27 in more than 90% of all AS patients, a genetic predisposition is highly assumed. However, only 10% of all HLA-B27-positive persons develop AS during their life time; thus, proof of HLA-B27 is not sufficient for the diagnosis of AS. The genetic aspect is additionally emphasized by a higher incidence of the disease of approximately 30% in first-grade relatives of patients with AS (7). In particular, HLA-B27-positive patients with reactive arthritis, chronic-inflammatory bowel disease, and psoriatic disease, frequently suffer from clinically severe AS (6).

The main function of HLA-B27, which belongs to class-1 HLA molecules, is the presentation of peptide antigens to CD8-positive T-cells (8). The origin of these peptide antigens from different bacteria and its trigger function is known in case of reactive arthritis, and thus, it is also discussed for the pathogenesis of AS. Both a direct induction of an autoimmune response or a cross reaction between bacterial peptides and autoantigens may trigger the development of AS. It is known from both magnetic resonance imaging (MRI) and immunohistochemical studies that the transition zone between bone and cartilage is the primary localization of the inflammatory process (9,10). This holds especially true for the sacroiliac joint, chondro-apophyseal insertion zones of tendons, ligaments, and joint capsules, and the border zone between the vertebral body and the intervertebral disc. The G1-domain of aggrecan, which is the most abundant proteoglycan in cartilage, is discussed as a potential autoantigen (11).

Clinical Course of Ankylosing Spondylitis

Low back pain and stiffness in the sacroiliac region in the early morning are often the only symptoms in the beginning of the disease. If the pain lasts for more than three months, especially in patients below the age of 40, the diagnosis of AS should be taken into account. Typically, pain and stiffness decrease during exercise. Another possible symptom is an alternating and transient pain in the anterior chest wall, the neck, in the knee joints or the heels. These complaints may be triggered by sudden movements like sneezing or stumbling. In addition to these articular and spinal symptoms, an iridocyclitis is a frequent early sign.

The clinical examination may demonstrate decreased mobility of the spine and the chest in this phase of AS. Measurements should at least contain the Ott and Schober sign as parameters of thoracic and lumbar mobility, the Flèche sign for the cervical spine, the fingertips–floor distance for anteversion of the whole spine, the Mennell sign for verifying sacroiliac involvement and thoracic excursion during breathing, as summarized in Table 1. The measurements of spinal mobility are especially important for follow-up examinations in the same patient because of interindividual differences, for example, a fingertip–floor distance of 3 cm is not pathologic per se. An increment to 10 cm, six months later, however, should be noticed very seriously.

In the later course of the disease, radiological signs of sacroiliits and increasing mineralization of ligaments and tendons are seen as a part of the modified New York criteria (12), thus leading to the final diagnosis of AS in many patients. In each patient, the diagnosis is based on both clinical signs and radiological criteria, shown in Table 2. However, the mean delay between the onset of first symptoms and the diagnosis of AS is between five and seven years (13), which is obviously too late, considering the fact that the most severe harm and loss of mobility happens during the first decade of the disease (14). Thus, approximately one-third of all AS patients are significantly impaired at the time of diagnosis (13).

The further course of the disease may be mild with only slow progress and long periods without subjective complaints. Other patients suffer from rapid

Table 1 Clinical Tests for Measuring Spine Mobility in Ankylosing Spondylitis

Sign	Afflicted area	Examination
Ott	Thoracic spine	Mark C7 and a 30-cm line in caudal direction ⇒ Measure extension in maximum anteversion
Schober	Lumbar spine	Mark S1 and a 10-cm line in cranial direction ⇒ Measure extension in maximum anteversion
Flèche	Cervical spine	Patient leaning against the wall in upright position ⇒ Measure distance between occiput and wall
Mennell	Sacroiliac joint (SIJ)	Patient lying on his left side, fix the SIJ with your left hand ⇒ Shear stress on the SIJ by extension of the right leg ⇒ Other side vice versa

Table 2 The Modified New York Criteria for the Diagnosis of Ankylosing Spondylitis

Criteria:
Low back pain and stiffness for at least three months, not eased by resting, alleviated by exercise
Limited mobility of the lumbar spine in both sagittal and frontal plane
Limited thoracic excursion, adapted to age and gender
Bilateral sacroiliitis stages 2–4[a]
Unilateral sacroiliitis stages 3–4
True diagnosis of ankylosing spondylitis if
Unilateral sacroiliitis stages 3–4 or
Bilateral sacroiliitis stages 2–4 combined with any clinical sign

[a]Radiological stages of sacroiliitis following the New York criteria: 0 = normal; 1 = suspected sacroiliitis with blurred joint space; 2 = minimal sacroiliitis with osteolytic areas and increasing subchondral osseous thickening; 3 = intermediate sacroiliitis with sclerosis on both sides of the articular surface and partial osseous bridging; 4 = total bony ankylosis with/without bony sclerosis.
Source: From Ref. 12.

and painful progressive ossifications, leading to early and severe disability. Approximately 20% of all patients with AS are at risk for severe disability and a premature withdrawal from employment (15). However, a spontaneous remission of the inflammatory and osteogenic activity is also possible in every condition of AS.

Several clinical indices were proposed to assess the disease activity during the time course of AS or for the evaluation of treatment response, as the correlation with laboratory parameters of inflammation is only weak. The most important and widely accepted indices were developed by a group of rheumatologists in Bath, England. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) mainly refers to both pain and stiffness of the spine and peripheral joints. The degree of functional impairment during the patient's daily activities is evaluated by the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Metrology Index (BASMI), which consist of several parameters for spinal and hip joint mobility (16).

Indications and Contraindications for ^{224}RaCl Therapy in Ankylosing Spondylitis

The decision for treatment with ^{224}RaCl always should be made in close collaboration of the nuclear medicine specialist and the rheumatologist. Diagnosis of AS and a failure of conservative pharmacotherapy with both nonsteroidal antiinflammatories and analgesics, or the presence of specific contraindications against these drugs are a prerequisite. The patients frequently complain of lower back pain, severe morning stiffness in the back and spine, and of breathing impairment owing to progressive inflammation and stiffening of their chests.

Table 3 Indications for ^{224}RaCl (Radium Chloride) Treatment

Diagnosis of ankylosing spondylitis by a rheumatologist
Failure of conservative pharmacotherapy
Active mineralization processes in the axial skeleton (referring to stages 2 and 3)

Only patients with active mineralization processes in the axis skeleton should be selected for ^{224}RaCl therapy. Following the clinical and radiological classifications, those are particularly patients showing areas of progressive ossification in the sacroiliac joints and in at least two spine regions referring to the historical illness stages II and III of AS (17,18).

In later stages, presenting with an almost complete spinal ankylosis (so-called "bamboo stick spine"), ^{224}RaCl therapy is no longer reasonable. Furthermore, in these patients, the pain is frequently regressive. Active mineralization zones, into which the calcium analog, ^{224}RaCl, is firmly incorporated, can be easily proven by bone scintigraphy, showing local accumulation of the bone-seeking ^{99m}Tc-HDP (99 m technetium-hydroxy-methylene-phosphonate) on the delayed images 3-h postinjection. Evidence of an increased mineralization, for example, in the chest or the spine, is an indication for radionuclide therapy with ^{224}RaCl (Table 3). Figure 1 shows an example of active multifocal mineralization processes on the delayed images of a whole-body bone scan in a patient with AS (Fig. 1).

Contraindications are pregnancy and breastfeeding; adolescents with still-active metaphyseal growth plates; history of hematopoietic diseases or cancer; recent bone fractures; impaired liver function; acute infections; and preceeding treatment with drugs toxic to the bone marrow (Table 4).

The Radiopharmaceutical

After intravenous injection, the calcium analog, ^{224}Ra, is incorporated into areas of active bone mineralization. The degree of uptake correlates strongly with the

Table 4 Contraindications for ^{224}RaCl (Radium Chloride) Treatment

Absolute contraindications
Pregnancy, lactation
Adolescents with still-active metaphyseal growth plates
Recent bone fractures
Relative contraindications
History of hematopoietic diseases
Preceeding treatment with radiation or drugs toxic to the bone marrow
Impaired liver function
Acute infections
Renal impairment

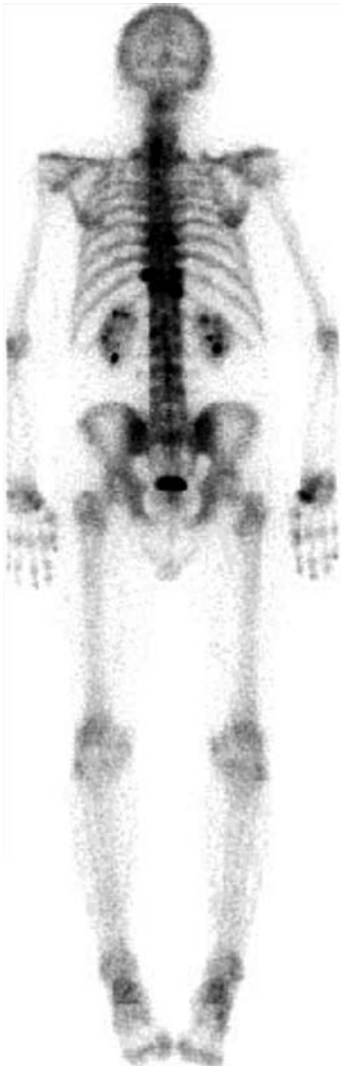

Figure 1 Posterior view of a whole-body bone scan of a 54-year-old male patient with ankylosing spondylitis, acquired three hours after injection of 600 MBq of ^{99m}Tc-HDP (99m technetium-hydroxy-methylene-phosphonate). Multifocal areas of enhanced bone metabolism are prominent in the entire spine, which is consistent with clinical symptoms of pain and impaired mobility.

intensity of calcium metabolism, which is elevated in areas of pathological ossification during AS. In an adult, approximately 25% of the injected dose is incorporated in the skeleton, 55% in a 10-year-old child and 75% in an infant (19). The radionuclide is mainly deposited on the surface area of the bone, that is, under the

endosteum, the periosteum, and in the zones of compact bone undergoing bone remodeling.

^{224}Ra is both an α- and a γ-emitter. It decays with a physical half-life of 3.64 days into further daughter nuclides, which send out not only α particles, but also β particles and γ radiation to some extent. The final product of this radioactive decay is ^{208}Pb, which is stable, inert, and unobjectionable in the given dose from both a toxicological and a pharmacological point of view. Owing to its high osteotrope affinity, ^{224}Ra is enriched in sites of active bone formation in the skeleton, and blocks the secretion of proinflammatory cytokines in the course of activated autoimmune processes. Depending on the short range of the α particles in the tissue of approximately 50 μm, for example, only a few cell diameters, the radiation dose to other tissues, especially to the bone marrow, is acceptably low. A direct inhibition of pain-mediating nerve fibers is not an assumed mechanism of action, as the nervous system is generally thought to be relatively resistant to radiation. By blocking the inflammatory cytokines, ongoing mineralization processes are inhibited in addition to the anti-inflammatory and analgetic results. Antiosteoblastic effects were frequently discussed for ^{224}RaCl, but have not been proven to date. Whole-body skeletal uptake of ^{99m}Tc-HDP is unchanged after treatment of AS with ^{224}RaCl compared with the uptake values prior to therapy, suggesting no significant changes in bone metabolism in general (20).

Uptake of ^{224}Ra into the bone is very fast with only 8% of the injected dose remaining in the circulating blood after 15 minutes. Eight hours after injection, only 1.5% is still found in the blood. This unbound ^{224}RaCl is excreted up to 95% via the feces, and up to 5% via the urine.

The industrial production of ^{224}RaCl from highly pure ^{228}Th today is safe and reproducible. Highly developed quality controls assure the absence of significant contaminations with long-lasting radionuclides. ^{224}RaCl must not be mixed with other drugs. In particular, any comedication with calcium or phosphate should be discontinued because of the decreasing bone uptake of ^{224}Ra due to competitive binding effects.

Side Effects

Acute side effects from ^{224}RaCl are rare, and allergic reactions are not likely because of the absence of additives, the high purity, and the nonimmunogenic nature of the product itself as an ion. An undesirable but frequent effect is an increase in pain during the first days of therapy. Prior to the beginning of a treatment course, the patient should be informed in detail about this harmless and transient, but inconvenient, side effect, which can be treated with analgesics in nearly all cases.

Occasionally, an iridocyclitis may occur during the treatment with ^{224}RaCl. This may be induced by the underlying disease, and is not proven to be triggered by the radionuclide. Nevertheless, treatment with ^{224}RaCl should be discontinued

in these patients until the iridocyclitis, which is usually treated symptomatically by an ophthalmologist, has stopped.

In rare cases, a mild depression of the bone marrow with a slight and transient decrease of blood counts is seen, although no case of agranulocytosis has been documented so far. In individual cases, lesions of the liver and colicky discomforts in pre-existing urolithiasis were reported for former ^{224}RaCl formulations.

As ionizing radiation may cause chromosomal damage, the long-term compatibility and the evaluation of any risk of cancer induction is of great interest. In this respect, it is very important to differentiate between the former high-dose ^{224}RaCl treatment regimen using less purified drug formulations between the 1940s and the 1970s and the "modern" therapy. There are two major studies performed by the Institute of Radiation Hygiene, Federal Office for Radiation Protection (BfS) in Germany on a long-term follow up of patients who had received these two different treatment schedules.

In the early years of ^{224}RaCl therapy, an aqueous mixture of ^{224}Ra with traces of eosin and colloidal platinum, called "Petheostor" was used not only to treat AS, but also tuberculosis. Many patients were younger than 21 years, and received higher cumulative doses over a longer time course than would be used today. In a total of 899 patients treated in Germany from 1945 to 1964 with high activities of at least 15 MBq "Petheostor," malignant bone tumors, mostly osteosarcomas, were seen in 56 cases (6.2%). Seventy-six percent of those tumors were seen in a subgroup of patients aged 21 years and younger (21,22).

In a second study, 1577 patients, treated between 1948 and 1975 with a cumulative activity of 10 MBq of ^{224}RaCl, 1 MBq per week, were followed (23) and compared with a control group of 1462 patients with AS, who had not been treated with ^{224}RaCl. The total percentage of malignant tumors was 9.4% in the treated versus 11.0% in the control group. No osteosarcoma was seen; however, there were four other malignant bone tumors (0.25%) observed after ^{224}RaCl treatment—one fibrous sarcoma, one malignant fibrous histiocytoma, one malignant lymphoma, and one malignant myeloma. Of these four tumors, only the first two were possibly induced by ionizing radiation (15). There was only one malignant myeloma in the control group. Eight cases of myeloid leukemia were observed in the ^{224}RaCl group versus three cases in the nontreated patients; this additional risk of 0.4% for leukemia is significantly increased compared with the controls ($P < 0.01$). This is consistent with the data obtained from animal studies (24), which demonstrated an increase in the incidence of leukemia with a decrease in the number of malignant bone tumors, by lowering the cumulative activity of ^{224}RaCl. Other animal experiments showed an increasing risk for the development of an osteosarcoma with an organ dose of at least 9 Gy to the bone surface (25)—a value which is not reached by current treatment regimens with a cumulative activity of 10 MBq ^{224}RaCl. According to the data known today, the risk of leukemia induction seems to be slightly increased after the treatment of AS with ^{224}RaCl. This

should be considered if an indication for ^{224}RaCl therapy is discussed. However, this risk must be balanced against the well-known risks of long-term intake of nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, or even the still unknown risks of the new group of "biological" TNF-α-blockers. An elevated risk for malignant bone tumors, however, has not been proven after low-dose treatment with 10 MBq ^{224}RaCl in adults. A meta-analysis of the available literature, ordered by the German Federal Institute for Drugs and Medical Devices, covered 7064 treatments from 1969 to 1983, and showed a nonsignificant increase of 0.1% of the total mortality rate after therapy with ^{224}RaCl in patients with AS (26).

Radiation Safety Considerations

The effective whole body dose from a cumulative standard application of 10 MBq ^{224}RaCl is approximately 2.5 Sv (27). This dose is slightly above the value obtained by high-dose radioiodine treatment in thyroid cancer. However, owing to the different linear energy transfer (LET) factors of α and β particles and γ radiation, the data are difficult to be compared with each other. α radiation from ^{224}RaCl has a higher emission rate, a much higher energy, and leads to a more localized, intense radiation load compared with β or γ radiation. The dose estimates for several organs are shown in Table 5. Owing to the mechanism and sites of incorporation, the bone surface and the red bone marrow have the highest dose coefficients with 88 and 8.5 Sv per 10 MBq ^{224}RaCl, respectively. The dose-limiting organ is the bone surface with a cumulative absorbed dose of 4.4 Gy.

Considering the radiation load to other persons, such as medical personnel, family members or coworkers of a patient treated with ^{224}RaCl, both the α and β

Table 5 Effective Organ Doses Owing to Cumulative Application of 10 MBq ^{224}RaCl (Radium Chloride)

Organ	Effective organ dose (Sv/10 MBq ^{224}RaCl)
Bone surface	88.0
Red bone marrow	8.50
Liver	2.60
Colon	1.40
Kidneys	1.50
Lung	0.45
Ovaries	0.56
Uterus	0.45
Testes	0.55
Whole body	2.5

Source: From Ref. 27.

particles have a range too short to exert any significant effects. Only the additional γ radiation should be taken into account. However, this radiation dose is very low. With the assumption of continuous residence after injection of 1 MBq ^{224}RaCl at a distance of 1 m, 32 μSv would be the maximum total effective dose for a noninvolved person, for example, a total maximum of 320 μSv from 10 MBq ^{224}RaCl [expertise from the Federal Office for Radiation Protection (BfS), Germany, concerning the radiation load for uninvolved persons during ^{224}RaCl (data of patients with AS, 6/20/1997)]. This dose is comparable with one mammogram, and lower than the dose from a single conventional X-ray of the spine. Emission of activity from ^{224}RaCl by exhalation is negligible. Oral incorporation of patient excretions by insufficient hygienics of others during patient care would be the only way to receive a significant radiation load.

Treatment Outcome, Clinical Studies

A large number of studies on the clinical efficacy of ^{224}RaCl treatment for AS have been published in recent decades. Many of them do not fulfill the strict criteria for scientific studies as demanded today; some are only qualitative descriptions, partly lacking a control group, and others are only retrospective evaluations. However, in a total of 2700 patients described by these historical studies, an overall response was demonstrated in about 75% (15). Table 6 summarizes the 11 most reliably controlled studies, covering a total of 986 patients (27). Therapeutic success lasting at

Table 6 Clinical Studies on the Efficacy of ^{224}RaCl (Radium Chloride) Treatment for Ankylosing Spondylitis

	Number of ^{224}RaCl treatments		Number of control cases	
Reference	Improvement	Total	Improvement	Total
Schneller (30)	12	15	9	15
Ruett (31)	17	18	—	—
Uibe (32)	219	240	—	—
Kutz (33)	86	92	—	—
Laschner (34)	75	91	—	—
Koch (35)	290	297	44	73
Schmitt (36)	62	78	14	70
Liska (37)	14	16	—	—
Redeker et al. (38)	44	53	—	—
Biskop et al. (39)	54	60	—	—
Mueller (40)	22	26	5	20
Total	895 = 91%	986	72 = 40%	178

Source: From Refs. 15, 27.

least five years was noted in 91% of patients treated with ^{224}RaCl. Forty percent in the control group, treated with conventional anti-inflammatory drugs, experienced significant pain relief. Regarding the effects on spinal ossification, Rudolph et al. (28) reported on a significantly retarded progression following treatment with ^{224}RaCl. Their radiological analysis of the kyphotic angle, number and size of syndesmophytes, and degree of sacroiliac ankylosis in a total of 181 patients revealed a marked effect of ^{224}RaCl therapy compared with a control group of patients who did not receive the radiopharmaceutical. Interestingly, these effects were still detectable 11 to 15 years after treatment. A dose reduction in anti-inflammatory pharmacotherapy in 65% of patients with AS, following treatment with ^{224}RaCl, was reported by Seyfarth in 1987 (29).

In conclusion, a large number of historical studies demonstrate a good clinical efficacy of treatment with ^{224}RaCl in patients with AS. However, due to the lack of controlled prospective studies, approval by the German Federal Institute for Drugs and Medical Devices is coupled with the charge to conduct a prospective long-term phase IV study. In this clinical trial, all the patients treated with ^{224}RaCl must be followed up for at least 10 years to document any long-term side effects.

224-Ra TREATMENT GUIDELINES

Dosage and Method of Administration

^{224}RaCl is meant for intravenous use only. Currently, 10 injections at weekly intervals are administered with an activity of 1 MBq each (low-dose regimen). The drug is calibrated by the manufacturer at delivery. ^{224}RaCl should be administered within three hours of the calibration time as indicated on the package (in Europe, normally Thursday or Friday at 12.00 hours). A dose adaptation for elderly patients is not required. The total activity of 10 MBq must not be exceeded. The shelf life of ^{224}RaCl is three hours after calibration time.

Owing to possible tissue damage and necrosis, particular care has to be taken that the drug is not administered paravenously or leak out of the vessel and infiltrate the surrounding tissue. Before and after the injection of ^{224}RaCl, rinsing the needle with isotonic saline solution is recommended to document intravenous free flow. An inline catheter with a short-running infusion of 100 ml NaCl, for example, may be used to assure safe intravenous administration of the radiopharmaceutical.

Contamination of people and objects by radioactivity excreted by the patients should be avoided. In case of surface contamination, the area should be washed off thoroughly. Any contamination can be detected by a small amount of secondary radiation (β and γ radiation) induced by ^{224}RaCl. Owing to insufficient knowledge about possible subsequent harms and side effects of repeated therapies, a therapy with a total activity of 10 MBq ^{224}RaCl may be performed only once.

Instructions for Use/Handling

According to national radiation safety regulations, ^{224}RaCl can only be delivered to, handled, and administered by authorized persons in defined clinical settings. Handling, administration, and disposal of waste are submitted to the regulations of the local supervising authority and/or to the corresponding licenses.

The radiopharmaceutical has to be administered under aseptic conditions. The administration of radioactive drugs, in general, includes a risk for third persons owing to the radiation and possible contaminations by ingestation. In case of ^{224}RaCl, the risk of third persons is very low, because the α particles have a range of only 50 μm and the portion of β and γ radiation is very low. Therefore, in Germany, ^{224}RaCl can be administered on an out-patient basis. Nevertheless, the directives of radiation protection and the respective radiation protection guidelines in medicine are to be respected. After application, all materials that have been used for preparation and application of the treatment dose must be decontaminated or treated as radioactive waste. Radioactive waste and leftovers of the radioactive drug and excretions of patients have to be treated as radioactive waste according to regulations.

Special Warnings, Precautions, and Follow-Up

^{224}RaCl may only be administered to women of childbearing age or to patients with increased infectious susceptibility (e.g., chronic obstructive diseases) in justified cases (Table 7).

Table 7 Patient Preparation and Treatment Procedure

Obtain history of pretreatment and drug history; review results of previous imaging and confirm appropriateness of indication for ^{224}Ra therapy
You should also check
Blood parameters (leukocytes, erythrocytes, platelets)
History of administration of drugs toxic to the bone marrow or bone marrow radiation
Liver function
Renal function
Hematopoietic diseases
Add missing imaging procedures, such as radiographs of the axis skeleton, three-phase bone scanning, MRI if necessary
Obtain written informed consent; provide written and verbal information on ^{224}RaCl treatment
Pregnancy testing in women of childbearing age
Vein puncture and intravenous administration (inline catheter) according to the rules of asepsis in a dedicated room for the use of radionuclides according to national law and local regulations
Before injection of the radiopharmaceutical, check for the correct radionuclide and activity
After injection of ^{224}RaCl flush the needle with 0.9% saline

Table 8 Treatment Monitoring and Patient Follow-Up

Before, during, and after treatment, blood counts of leukocytes, erythrocytes, and platelets are required weekly
A check-up for side effects or other complications is recommended at every time point of weekly administration
Clinical follow-up examinations to assess treatment response and blood counts are recommended 3, 6, and 12 months after therapy, and then in annual intervals thereafter for 25 years

A relative contraindication exists for women of childbearing age. Contraception during and up to six months after the end of the therapy with ^{224}RaCl must be planned. The reason is that ^{224}RaCl crosses the placenta and deposits in the skeleton of the unborn child. In cases in which radioactive drug treatment of women in childbearing age is necessary, pregnancy must be excluded. Data concerning the transmission to breast milk are not available. Breastfeeding must be discontinued in cases where the drug is to be administered to a breastfeeding mother.

Fluid intake and frequent voiding should be encouraged for the first 24 hours following treatment. Owing to the excretion of ^{224}RaCl in urine and feces, patients should be instructed to empty their bladder and colon at least once during the 24 hours following treatment. The toilet should be flushed two or three times. Handwashing should be performed routinely and frequently (Table 9). Sharing food and eating utensils is prohibited.

Before, during, and after the treatment, peripheral blood counts (leukocytes, erythrocytes, and platelets) are required. The counts must be performed weekly before each administration during the total period of treatment. If leukocyte counts decrease below 4.000/μl, lymphocyte counts below 500/μl, or neutrophil granulocyte counts below 1000/μl, the therapy has to be stopped. Treatment must be stopped also in the case of a decrease in thrombocytes below 50,000/μl or hemoglobin value below 9.0 g/dl.

Owing to the potential damage to the bone marrow and the potentially long latent period between treatment with ^{224}RaCl and myelotoxic effects or possible induction of leukemia, regular complete blood counts (three months, six months, and one year after the end of treatment, and then in one-year intervals, up to 25 years) have to be performed. After administration of ^{224}RaCl, no effects on the ability to drive or handle machines are to be expected.

Overdose

The risk of an overdose consists of an undesired high radiation exposure with the potential of acute toxic radiation effects. In this case, further treatment with ^{224}RaCl has to be stopped immediately. The blood counts must be controlled in short-term intervals, because of a possible impairment of hematopoiesis.

Table 9 Patient Instructions, Side Effects, and Radiation Safety Considerations

Patients should receive written and verbal information about the procedure and side effects
Mobilization of the patient and physical therapy is necessary for treatment efficacy
Patients benefit from the treatment in about 65% to 90% of cases
Treatment response may be delayed by several months
Risk of a temporary increase of pain during the first days of therapy (treat with over-the-counter anti-inflammatory drugs)
Iridocyclitis may occur in rare cases; ^{224}RaCl-treatment should be discontinued until the iridocyclitis has stopped
Risks associated with intravenous administration of ^{224}RaCl are local tissue necrosis and radiation exposure and risk of leukemia
Patients should be advised to report any worsening or other unusual changes in health, and the patient should be given a phone number for contact he can reach at any time
Information about radiation safety considerations should be provided
^{224}RaCl therapy should not be performed in pregnant or breastfeeding women
Pregnancy should be avoided after treatment with ^{224}RaCl by effective contraception for four to six months
Urinary contamination should be avoided by flushing the toilet two or three times and handwashing after every toilet use; men should urinate sitting down
No additional home precautions are required

Abbreviation: RaCl, radium chloride.

Methods to reduce the radiation exposure after administration are not known. However, this is a rather theoretical consideration, as each vial contains only 1 MBq ^{224}RaCl at calibration time.

REFERENCES

1. Zink A, Listing J, Wollenhaupt J. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis—results from the German rheumatological database. German collaborative arthritis centers. J Rheumatol 2000; 27:613–622.
2. Carbone LD, Cooper C, Michet CJ, Atkinson EJ, ÓFallon WM, Melton LJ III. Ankylosing spondylitis in Rochester, Minnesota, 1935–1989. Is the epidemiology changing? Arthritis Rheum 1992; 35:1476–1582.
3. Ward MM. Quality of life in patients with ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res 1999; 12:247–255.
4. Biasi D, Carletto A, Caramaschi P, Pacor ML, Maleknia T, Bambara LM. Efficacy of methotrexate in the treatment of ankylosing spondylitis: a three-year open study. Clin Rheumatol 2000; 19:114–117.
5. Brandt J, Sieper J, Braun J. Treatment of ankylosing spondylitis and undifferentiated spondyloarthritis with TNFα-antagonists. Z Rheumatol 2003; 62:218–227.
6. Braun J, Sieper J. Spondylitis Ankylosans. Bremen, Boston: UNI-MED International Medical Publishers, 2002.
7. Linden S van der, Valkenburg HA, de Jong BM, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals: a comparison of relatives of spondylitis patients with the general population. Arthritis Rheum 1984; 27:241–249.
8. Sieper J, Braun J. Pathogenesis of spondylarthropathies. Persistent bacterial antigen, autoimmunity or both? Arthritis Rheum 1995; 38:1547–1554.
9. Bollow M, Fischer T, Reisshauer H, et al. Quantitative analyses of sacroiliac biopsies in spondylarthropathies: T cells and macrophages predominate in early and active sacroiliitis—cellularity correlates with the degree of enhancement detected by magnetic resonance imaging. Ann Rheum Dis 2000; 59:135–140.
10. Maksymowych WP. Ankylosing spondylitis—at the interface of bone and cartilage. J Rheumatol 2000; 27:2295–2301.
11. Zhang Y, Guerassimow A, Leroux JY, et al. Arthritis induced by proteoglycan aggrecan G1 domaine in BALB/c mice. Evidence for T-cell involvement and the immunosuppressive influence of keratan sulfate on recognition of t and b cell epitopes. J Clin Invest 1998; 101: 1678–1686.
12. Linden S van der, Valkenburg A, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984b; 27:361–368.

13. Zink A, Listing J, Klindworth C, Zeidler H. The national database of the German Collaborative Arthritis centres: I. Structure, aims and patients. Ann Rheum Dis 2001; 60:199–603.

14. Gran JT, Skomsvoll JF. The outcome of ankylosing spondylitis: a study of 100 patients. Br J Rheumatol 1997; 36:766–771.

15. Reiners C, Braun J. Treatment of ankylosing spondylitis with 224Ra-Radium chloride. Der Nuklearmed 2001; 2:105–112.

16. Jones SD, Steiner A, Garrett SL, et al. The bath ankylosing spondylitis patient global score (BAS-G). Br J Rheumatol 1996; 35:66–71.

17. Ott VR. Klinik und Therapie der ankylosierenden Spondylitis (Morbus Strümpell-Marie-Bechterew). In: Brügel H (Hrsg) Fortschritte auf dem Gebiet der rheumatischen Erkrankungen und der degenerativen Gelenkerkrankungen. Stuttgart, New York: Schattauer, 1972:92–104.

18. Schilling F. Spondylitis ankylopoetica: Die sogenannte Bechterewsche Krankheit und ihre Differentialdiagnose (einschliesslich Spondylitis hyperostotica, Spondylitis psoriatica und chronischem Reiter Syndrom). In: Diethelm L (Hrsg) Handbuch der medizinischen Radiologie, Bd. IV, Teil 2. Berlin, Heidelberg, New York: Springer, 1964:452–689.

19. ICRP publication 67. Age-dependant doses to members of the public from intake of radionuclides. Part 2: Ingestion dose coefficients. International Committee on Radiological Protection. Oxford: Pergamon Press, 1993.

20. Kampen WU, Prause J, Brenner W, Czech N, Muhle C, Henze E. Skeletal uptake of 99mTc-HDP remains unaltered after treatment of ankylosing spondylitis with the alpha-emitter 224-Ra. Eur J Nucl Med 2001; 28:995.

21. Spiess H. The Ra-224 study: past, presence and future. In: van Kaick G, Karaoglu A, Kellerer AM, eds. Health effects of internally deposited radionuclides: emphasis on radium and thorium. Proceedings of an International Seminar held in Heidelberg, Germany, April 18–2, 1994. Singapore: World Scientific, 1995:157–159.

22. Nekolla EA, Keisheimer M, Kellerer AM, Kruse-Isingschulte M, Goessner W, Spiess H. Induction of malignant bone tumors in radium-224 patients: risk estimates based on the improved dosimetry. Radiat Res 2000; 153:93–103.

23. Wick RR, Nekolla EA, Goessner W, Kellerer AM. Late effects in ankylosing spondylitis patients treated with ^{224}Ra. Radiat Res 1999; 152:8–11.

24. Humphreys ER, Isaacs KR, Raine TA, Saunders J, Stones VA, Wood DL. Myeloid leukemia and osteosarcoma in CBA/H mice given ^{224}Ra. Int J Radiat Biol 1993; 64:231–235.

25. Muggenburg BA, Hahn FF, Griffith WC Jr, Lloyd RD, Boecker BB. The biological effects of Ra-224 injected into dogs. Radiat Res 1996; 146:171–186.

26. Gloebel B. Ra-224 for internal radiotherapy of ankylosing spondylitis (M. Bechterew)—an alternative to chemotherapy? NUC Compact 1985; 16:272–277.

27. Lassmann M, Noske D, Reiners C. Therapy of ankylosing spondylitis with ^{224}Ra-radium chloride: dosimetry and risk calculations. Radiat Environ Biophys 2002; 41:173–178.

28. Rudolph F, Salewski H, Franke J. Late results of throrium-X treatment in Bechterew's disease (a 15-year study). Beitr Orthop Traumatol 1980; 27:29–37.

29. Seyfarth H. Experiences with treatment of ankylosing spondylitis in the GDR with respect to Radium-224 therapy. Akt Rheumatol 1987; 12:26–29.

30. Schneller H. Experiences with the Peteosthor-treatment of Bechterew's disease. Med Klin 1951; 5:142–144.

31. Ruett A. Treatment of Bechterew's disease. Dtsch Med Wochenschr 1952; 77:649–652.

32. Uibe P. Treatment of Bechterew's disease with Thorium X. Z Orthop Traumatol 1958; 272–275.

33. Kutz G. Delayed damages from treatment with Th-X. Z Orthop 1963; 97:474.

34. Laschner W. Results and complications of the treatment of Bechterew's disease with Thorium-X. Z Orthop Ihre Grenzgeb 1973; 111:743–748.

35. Koch W. Indication and results of Radium-224-(Thorium X)-therapy of ankylosing spondylitis. Z Orthop 1978; 116:608–616.

36. Schmitt E. Long-term study on the therapeutic effect of Radium-224 in Bechterew's disease. Z Orthop Ihre Grenzgeb 1978; 116:608–616.

37. Liska G. Spondylarthritis ankylopoetica and its therapy with Thorium X. A follow-up study on patients of the University Clinic of Orthopedics in Wuerzburg. Doctoral thesis 1980; University of Wuerzburg, Germany.

38. Redeker S, Crone-Muenzebrock W, Weh L, Montz R. Scintigraphic, radiologic and clinical results after Radium-224 therapy in 53 patients with ankylosing spondylitis. Beitr Orthop Traumatol 1982; 29:218–223.

39. Biskop M, Arnold W, Weber C, Reinwald AK, Reinwald H. Can Radium-224 (Thorium-X) effect the progression of Bechterew's disease. Beitr Orthop Traumatol 1983; 30:374–381.

40. Mueller D. Five year follow-up control of Radium-treatment (^{224}Ra) in patients with spondylarthritis ankylopoetika with respect to scintigraphy. Doctoral thesis 1993; University of Leipzig, Germany.

7

Radioimmunotherapy of Solid Tumors

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INTRODUCTION

Radioimmunotherapy (RIT) has been the subject of investigations since the early 1970s. A tumor antigen-binding protein is labeled with a therapeutic radionuclide and administered systemically—the radionuclide decay results in lethal radiation that putatively destroys cancer cells. RIT of lymphoma has shown great promise (1–5), and two anti-CD20 agents are approved by the Food and Drug Administration (FDA) for clinical use. There are no pivotal or phase 3 trials in solid tumor RIT, partly because the need for nonimmunogenic proteins necessitated the development of chimeric and humanized antibodies, and also because tumor radiation-absorbed dose with radiolabeled intact immunoglobulin has been inadequate in most of the systems studied.

Solid tumor RIT has been studied in various cancers: breast, ovarian, colorectal, renal, prostate, and brain. The only positive outcome in most of these studies has been disease stabilization in many patients. No outcome indicators have yet been sufficiently promising to warrant phase 2 or other development with nonmyeloablative RIT. These initial clinical trials have been very instructive in the development of "optimal" strategies, including antigen-binding construct design, optimal radionuclides for tumors of various sizes, and treatment delivery systems.

Immunogenicity of the antigen-binding construct is not the only constraint facing RIT for solid tumors. Antigenic modulation and heterogeneity, barriers to

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penetration of protein into tumor, and adequate relative tumor uptake and residence time are some of the other factors (6,7) that are still problematic for successful therapy. Bone marrow toxicity without treatment response has been a serious constraint as well.

Understanding RIT requires the understanding of therapeutic radionuclides and antigen-binding constructs. The unique biology of solid tumors necessitates the development of strategies for rational treatment designs that address the biological complexity of solid tumors.

ANTIBODY CONSTRUCTS

The earliest clinical trial with a radiolabeled antibody was carried out in solid tumors with polyclonal antibodies (8). Development of the hybridoma technique (9) allowed monoclonal antibody production with reproducible characteristics. Initial production of these antibodies was in murine systems, and the inherent immunogenicity of xenogeneic proteins became apparent in the initial studies. Most humans who receive murine antibodies develop human antimouse antibodies (HAMA) that preclude effective multiple dosing regimens (10). The search for nonimmunogenic molecules led to the use of chimeric antibodies (11), with the murine Fv, grafted genetically to a human constant region, and to humanized antibodies where only the complementarity-determining region (CDR) remains of murine origin (12). Development of suitable nonimmunogenic antibodies would be essential to regimens that require multiple administrations. However, genetically engineered proteins have sometimes been immunogenic as well.

An obvious initial strategy to increase antibody tumor delivery was to decrease the size of the labeled protein. The resulting more rapid clearance would decrease the levels of circulating species, and therefore decrease the absorbed dose to marrow. Deletion of whole antibody constant regions, either by digestion or by genetic modification, resulted in bivalent $F(ab)'_2$ fragments (no CH_2 and CH_3 domains) and monovalent Fab fragments. However, the resulting faster blood clearance has not improved relative tumor to bone marrow dose significantly (13). There is also increased renal retention of these smaller molecules (Fab $>$ $F(ab)'_2$). Single-chain antigen binding proteins (sFv) are linear constructs of light and heavy Fv fragments that clear rapidly from the blood and may have lower renal retention compared with the Fab' fragments (the lack of CH1/CL domains results in a molecule of approximately 26 kDa) (14,15). Other constructs with rapid clearance are minibodies, which consist of two sFv fragments linked by a component of the heavy-chain region (e.g., CH_3), and diabodies, which comprise two sFv fragments joined chemically by disulfide bonds or by genetic engineering of the sequences (16).

RADIONUCLIDES

Physical and chemical properties, fate after antibody metabolism in vivo, and the nature of the emitted radiation, are all factors that must be taken into account

when deciding a radionuclide for RIT. Cytotoxic radionuclides may be divided into three groups of radiochemicals: halogens (Iodine, ^{211}At); metals (^{90}Y, ^{67}Cu, ^{213}Bi, ^{212}Bi); and transitional elements (^{186}Re). Radionuclides can be further categorized into four types of cytotoxic agents: pure beta emitters (^{67}Cu and ^{90}Y); alpha emitters (^{213}Bi, ^{211}At); beta emitters that emit gamma radiation (^{177}Lu, ^{186}Re, ^{131}I); and Auger emitters and radionuclides that decay by internal conversion, including ^{125}I and ^{67}Ga.

A variety of thyroid disorders have been treated effectively for decades with ^{131}I (iodine), and its biologic behavior is well understood. ^{131}I has gamma emissions suitable for imaging, though a radiation safety liability sometimes requires hospitalization after therapy (17). Its long half-life is probably ideal for therapy with intact immunoglobulins, and the labeling process is relatively straightforward (18).

^{131}I is not the optimal nuclide when conjugated with antibodies that are internalized into tumor cells via clathrin-coated pits following antibody–antigen interaction (19). This leads to dehalogenation of the complex and release of the radionuclide, thus decreasing tumor radiation-absorbed dose. The use of residualizing linkers that provide stronger binding of the halide to the antibody has been explored to overcome this limitation (20).

Radiometals, unlike radioiodine are usually attached to antibodies by chelates, and do not detach from the antibody following internalization. ^{90}Y (yttrium), a pure beta-emitting radiometal, has been widely studied in RIT (21). ^{90}Y is an attractive choice for several reasons. The high-energy beta-minus emission of Y-90 can be effective in bulky tumors, and its pure beta emission allows for outpatient therapy. A limitation of yttrium, however, is its affinity for bone. When ^{90}Y is detached from the chelating agent after metabolism of the radiolabeled construct, the bone marrow can receive unacceptably high levels of radioactivity. Lutitium-177 (^{177}Lu) may be a suitable alternative in this regard as its half-life and other physical characteristics are similar to ^{131}I, and its gamma emission allows for external imaging (22).

Rhenium is a transitional element, and both ^{186}Re (rhenium) and ^{188}Re have been linked to antibodies. Developments in radiochemistry have made possible stable attachment of these isotopes to proteins. ^{188}Re is produced from a Tungsten-188 generator (permitting elution on site) (23), and its 17-hour half-life holds promise for locoregional therapies or for therapies with rapidly clearing molecules. Because of its physical properties, including longer half-life, ^{186}Re has been more extensively studied. Rhenium nuclides emit photons that allow for external imaging with conventional nuclear medicine equipment. Early clinical trials have exploited the ^{186}Re gamma emissions to provide dosimetry analyses of absorbed doses to tumors and normal organs, and have demonstrated its safety for use in RIT for solid tumors (24).

Alpha particles are high-energy helium nuclei with high linear energy transfer (LET). In addition to having short half-lives, the range of energy deposition is only 50–80 μm. Alpha particles hold interest for RIT, as their high linear-energy deposition can deliver lethal radiation to small tumor clusters. However, the recoil

energy of alpha decay has precluded stable attachment of these radionuclides to proteins. Advances in radiochemistry addressing this problem have led to a renewed interest in alpha particles. Cyclotron-produced astatine (At-211) is under investigation as therapy for several tumor types. Clinical trials have been reported using ^{211}At-labeled chimeric anti-tenascin antibody 81C6 for gliomas (25). Bismuth-213 [^{213}Bi—eluted from a actinium-225 (Ac-225) generator] has a short (46 minutes) half-life and is being studied in hematologic neoplasms (26).

In vivo generators of alpha particles are being investigated for their ability to deliver cytotoxic particles to micrometastases. These "nanogenerators" overcome the limitations posed by the short half-lives of most alpha particles (27), though the problems associated with recoil following alpha decay and the production of nonmetal daughters, francium and astatine (which then may not remain attached to the chelate), are significant.

Auger emitters deposit high LET over extremely short distances, and are therefore most effective when the decay occurs in the nucleus, and less so when the decay occurs in the cytoplasm (28). ^{125}I is the prototypical radionuclide, but its long decay half time renders it less than optimal for therapy. Other similar radionuclides that have been studied, although not with antibodies, have included ^{111}In (indium). In both cases, the amount of radioactivity necessary is economically prohibitive. A radionuclide that is gaining increasing attention in this category is ^{67}Ga (gallium). Improvements in chelation chemistry have resulted in stable radioimmunoconjugates with ^{67}Ga, and clinical trials are planned.

RADIOIMMUNOTHERAPY FOR SOLID TUMORS

Colon Cancer

The large majority of clinical solid tumor RIT studies have been carried out in colon cancer. The first clinical trial with radiolabeled antibodies was with anti–carcinoembryonic antigen (CEA) antibodies (8). Colon cancer antigen systems may be divided into secreted, for example, CEA and TAG-72 (sialyl Tn), cell surface receptors, including 17-1A, Lewis-y, and A33, and stromal antigens, notably fibroblast activation-protein-alpha. Antibodies against other solid tumor components, particularly vascular endothelial growth factors, have been developed, and are being prepared for preclinical and clinical RIT studies.

Carcinoembryonic Antigen

Goldenberg et al. pioneered the use of antibodies in the detection and therapy of cancer (8), and his group has subsequently carried out RIT studies with ^{131}I-labeled murine and humanized anti-CEA antibodies (29–32). A phase 2 trial of 21 patients treated with ^{131}I labeled humanized anti-CEA Ab (hMN-14; Immunomedics, Inc., Morris Plains, New Jersey, U.S.A.) studied the response to RIT in patients with small volume metastasis refractory to treatment and in patients who had undergone surgical resection of metachronous liver metastases (33). Both

groups of patients received a single dose of 2220 MBq/m^2 (60 mCi/m^2) I-131 antibody, previously demonstrated to be the maximum nonmyeloablative tolerated dose. Among both groups of patients, the study demonstrated an overall response rate of 58%, with a mean duration of response of nine months. Of the nine patients receiving RIT in an adjuvant setting following surgery, seven remained disease free at 36 months post-treatment, considerably longer than historical controls. These results underscore the suitability of current methods of RIT for small-volume disease rather than bulky disease.

Nonimmunogenic antigen-binding constructs against CEA have also been studied. The initial dose-finding study with a chimeric antibody established no mass dependence upon tumor targeting and no evidence of immunogenicity (34). Subsequent RIT studies with ^{90}Y-labeled antibody (35) demonstrated that the observed toxicity was radionuclide dependent. The maximum tolerated dose (MTD) for a radiolabeled intact immunoglobulin is dependent upon the radionuclide, and is independent of the antigen or solid tumor type. The lack of responses in this nonmyeloablative trial prompted the initiation of an ongoing myeloablative trial (36). At this time, review of available data suggests that nonmyeloablative RIT with intact immunoglobulin (Ig) G is unlikely to result in major responses. This finding has spurred development of various specific radiolabeled protein constructs, which are now being produced for clinical study (16,37).

Some of the results of clinical studies using other specific antigen binding labeled proteins are now available for review. Begent et al. have carried out studies using ^{131}I-labeled antigen-binding constructs [whole IgG, F(ab)'$_2$ fragments, cross-linked divalent (DFM) and trivalent (TFM) versions]. Although there was selective targeting of iodinated sFv to tumor, the degree of uptake was not adequate to result in treatment responses (38). Begent et al. have continued their studies by developing a single-chain Fv fragment of their anti-CEA antibody. This sFv construct is grown in *Escherichia coli* and exhibits specific targeting abilities (39).

TAG-72

Monoclonal antibody (MAb) CC49, a murine IgG targeting a heterogeneously expressed antigen (Tn/sialylTn) on a tumor-associated mucin, TAG-72, expressed in most colorectum, ovary, breast, stomach, and pancreas adenocarcinomas (40), has been explored as a potential RIT for several solid tumors. An initial study comparing CC49 with its lower affinity counterpart B72.3 showed that CC49 had better relative uptake in colorectal cancer (41). Phase 1 RIT studies with ^{131}I-CC49 in colorectal cancer demonstrated excellent tumor targeting, and a nonmyeloablative MTD of 2775 Mbq/m^2 (75 mCi/m^2) (10). Further clinical trials, however, have demonstrated no objective responses with tumor doses of 0.19–6.67 Gy (19–667 rads) (42). Dose-limiting toxicity in these studies was hematopoietic. Moreover, immunogenicity, manifest by the production in the host of HAMA, was invariable.

The administration of an immunosuppressive agent, deoxyspergualine (DSG) has failed to satisfactorily reduce the immunogenicity of the radiolabeled murine protein products (43); hence, humanization of antibody has been carried out. In order to ensure that the clearance of the humanized antibody was as close as possible to that of the murine-intact IgG, the CH_2 domain of the chimeric antibody was deleted. Initial clinical trials (44) have shown that clearance and targeting characteristics for these chimeric species are indeed comparable with murine derivatives and that the novel protein is nonimmunogenic.

Initial studies in colon cancer were followed by phase 1 and phase 2 studies in a variety of other solid tumors, notably breast and prostate cancers (44–48). A phase 1/2 trial of intraperitoneal ^{177}Lu-CC49 Ab in 27 patients with recurrent ovarian cancer (49) defined MTD (again, hematopoietic) as 1665 MBq/m^2 (45 mCi/m^2); most patients progressed after therapy with prolonged disease-free survival observed only in patients with microscopic disease. Since then, intraperitoneal RIT with ^{131}I-CC49 has also been carried out in ovarian cancer (50) and combination therapy is being investigated (51).

In all these studies, there has been excellent tumor targeting, but no significant clinical responses. As is the case with most antigen–antibody systems in solid tumors, the limitations in the clinical application of radiolabeled CC49 IgG are primarily attributed to normal tissue toxicity, immunogenicity, and relatively poor penetration into tumor. Genetically engineered single-chain antibody fragments (sFvs) may potentially overcome some of these limitations. The data in animal models using *E. coli*-produced sFvs demonstrated more rapid systemic clearance with better tumor penetration of these agents with consequent higher tumor: background ratios than the corresponding IgG, $F(ab')_2$ or Fab' fragments in animal models (52–55); their small size may reduce their immunogenic potential. Early studies at Memorial Sloan–Kettering Cancer Center (MSKCC) (56) of a ^{123}I-labeled sFv CC49 in human metastatic colorectal carcinoma demonstrated the potential of these agents to target tumor; renal retention was low, but this may be a function of dehalogenation. Their small size and monovalency may be less than ideal for successful RIT (although radiolabeled peptides, with comparable affinity characteristics and putative renal retention have shown promise). The first generation of sFvs were produced in bacterial systems, and may not have been stable in vivo. Newer production methodologies in yeast systems may confer glycosylation advantages (bacteria do not glycosylate proteins) that result in a more stable product in vivo. Other methodologies include the use of radiometal–chelate–sFv immunoconjugates, as the halogenation of sFv using current methods may result in radioactivity binding to tyrosine residues in the receptor; the radioiodinated sFv may therefore be subject to dehalogenation in vivo.

Antibody A33

Antibody A33 binds to an antigen expressed on normal colonic and distal small-bowel epithelium and colon cancers. The antigen is a member of the

immunoglobulin superfamily. A33 has been shown to undergo rapid internalization, without significant dehalogenation, after binding to antigen on the cell membrane. Moreover, antigen distribution in colon cancers has been homogeneous. Phase 1/2 studies of ^{131}I-mAb A33 RIT carried out in patients with colon cancer (57) demonstrated (as expected) that dose-limiting hematologic toxicity was radionuclide dependent and the MTD was determined to be 2775 MBq/m^2 (75 mCi/m^2) ^{131}I. Gastrointestinal symptoms were not dose limiting, presumably because of relatively rapid turnover of the target cell in the base of the colonic crypt.

Our data (58) suggested that the radioiodinated antibody does not appear to undergo catabolism following internalization (probably via the macropinosome); we thus carried out a trial with ^{125}I-murine A33, taking advantage of the high LET of I-125 (Fig. 1). This phase 1/2 study did not result in dose-limiting toxicity at doses as high as 350 mCi/m^2 of ^{125}I. There were only modest response rates (59). One of the 21 patients had a mixed response based on imaging studies and two patients had stable disease with decreased serum CEA levels. Interestingly, the patients who received RIT had higher levels of response with further chemotherapy [carmustine (BCNU), vincristine, fluorouracil, and streptozocin (BOF-Strep)], suggesting a potential role of combined RIT and chemotherapy. Humanized A33 has been investigated by Welt's group at MSKCC (60). It has targeting abilities comparable with the murine protein, with significant immunobiologic effector function. Studies comparing the efficacy of combined radiosensitizing chemotherapy (capecitabine) and RIT with ^{131}I-huA33 are currently underway.

Other Antigenic Systems Studied

Antibody 17-1A (murine IgG_{2a}), which reacts against the surface epithelial antigen (KSA), and internalizes subsequent to interaction, has also been studied with both ^{131}I and ^{125}I. A pilot dose-escalation clinical trial of ^{125}I-chimeric 17-1A in patients

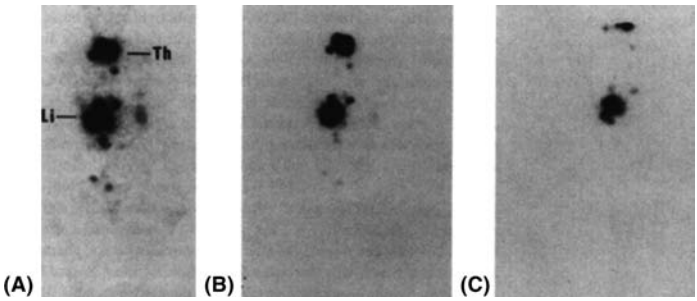

Figure 1 Anterior whole body images one (**A**), two (**B**), and six (**C**) weeks after 125-iodine-murine A33 radioimmunotherapy (RIT) in a patient with colon cancer metastatic to liver (Li)—thyroid uptake of radioactivity is also visualized.

with metastatic colorectal cancer was conducted (61) at the University of Alabama in Birmingham. The results of this study corroborated our clinical trial results that high-dose outpatient RIT with a ^{125}I-labeled internalizing antibody could be achieved without significant patient toxicity or radiation hazard.

The team at MSKCC and at the Ludwig Institute for Cancer Research has attempted to identify targets not only on cancer cell surfaces, but also on other components of the tumor, including stroma and vasculature. We developed a novel targeting approach to colon cancer therapy by developing an antibody, F19, against fibroblast activation protein-alpha (FAP-α). FAP-α is highly expressed by activated fibroblasts abundant in most solid tumors, including more than 95% of primary and metastatic colorectal carcinomas, but is not expressed by normal tissue (other than healing scar).

^{131}I-mAb F19 was studied in a mass escalation study at MSKCC. Lesions as small as 1 cm could be visualized by scintigraphy (62). The easy accessibility of the FAP-positive tumor stromal fibroblasts to circulating monoclonal antibodies prompted the humanization of this antibody, now named sibrotuzumab (BIBH 1). Phase 1 mass dose-finding studies have not shown a mass dependence (63), and RIT studies with ^{131}I-labeled antibody have shown a toxicity profile comparable with other ^{131}I-labeled humanized antibodies.

Ovarian Carcinoma

Ovarian carcinoma is an attractive target for RIT, both because the antigen systems have been well defined and because the disease is confined to the peritoneal cavity for most of its course, allowing the possibility of locoregional intraperitoneal therapy. In addition to CC49 antibodies, various other antibody–antigen systems have been studied in ovarian cancer. MX 35, expressed homogeneously in most nonmucinous ovarian cancers, with minimal normal tissue cross-reactivity (64), has been studied at MSKCC and elsewhere. Several studies utilizing ^{131}I- and ^{125}I-labeled Ab MX35 showed excellent localization to sites of ovarian tumors, including micrometastases in the peritoneal wall (65). MOv18, targeting the membrane folate receptor, again fairly ubiquitous in nonmucinous ovarian cancers and with limited normal tissue cross-reactivity, is another promising agent. ^{131}I chimeric MOv18 showed moderate visualization of tumor sites with tumor absorbed doses of 600–3800 cGy, and stable disease for two to more than six months (66), with no evidence of immunogenicity [measured as development of human antichimeric antibodies (HACA)]. Intraperitoneal RIT using ^{90}Y-labeled murine anti-human milk fat globulin-1 ($HMFG_1$) (analogous to the *muc-1* antigen) as an adjuvant to chemotherapy, compared with chemotherapy alone, have shown increased overall survival in patients who received the RIT, compared with those who received chemotherapy alone (67). Ovarian cancer is limited to the peritoneal cavity for most of its natural progression, and therefore, intraperitoneal therapies have always held promise for a disease with limited treatment options. A randomized phase 3 adjuvant study with intraperitoneal ^{90}Y-labeled murine anti-$HMFG_1$ has just been concluded in the United States, and results are awaited.

Systemic RIT studies with anti-*muc1* antibodies have been carried out largely in breast cancer. Unlike most of the aforementioned studies, which employed radioiodine initially and then studied other radionuclides, the studies with a novel humanized anti-*muc1* antibody, BrE3, were initially carried out with ^{90}Y (68). This antibody may be a "second generation" anti-*muc1* antibody as it appears to react with the deglycosylated antigen alone, which may be more preferentially expressed in tumors, with minimal secretion into interstitium and serum. Targeting (using ^{111}In as a surrogate) has been shown to be excellent (69)—RIT therefore appears justified.

Limited studies with intrathecal RIT have also shown promise. Intrathecal RIT has potential, as radiation in the closed compartment is more likely to have efficacy when its retention can be enhanced by conjugation to a large molecule that will transit slowly into the systemic compartment. Beta-emitting nuclides, utilized in most studies (70–77), may be less than ideal as most of the energy is probably deposited outside the intrathecal space. In this respect, alpha emitters may be ideal as they deposit high LET radiation over submillimeter distances (78). No studies have progressed to phase 2 or higher; however, this is more a function of radionuclide availability and patient characteristics than a lack of promise.

The Lewis Y (Le^y) antigen is a blood group–related antigen that is, expressed in a high proportion of epithelial cancers, including breast, colon, ovarian, and lung cancer, and therefore, is an attractive target for monoclonal antibody-directed therapy. Early studies with anti-Le^y antibodies carried out using chemoimmunoconjugates demonstrated significant GI toxicity without significant efficacy (79). An anti-Le^y antibody, B3, developed at the National Institutes of Health (NIH), labeled either with ^{111}In, to study biodistribution, or ^{90}Y for therapy (80), demonstrated a favorable biodistribution profile and acceptable hematologic toxicity, with no dose-limiting GI side effects (probably because the mass of antibody was low, and the antigen distribution in the GI tract is largely on the luminal surface). The MTD was found to be 740 MBq of ^{90}Y. The Le^y antigen is abundantly expressed in both gastric and ovarian cancers—diseases that are limited to the peritoneal cavity for much of their natural course. A phase 1 intraperitoneal RIT study using ^{90}Y labeled to humanized anti-Le^y antibody hu3S193, initially generated at MSKCC (81), in patients with minimal residual disease ovarian cancer (Fig. 2), could not be completed owing to inadequate accrual. We had hoped to take advantage of the immunobiologic effector function of the humanized IgG_1 and the decreased marrow radiation resulting from increased residence time of radioactivity in the peritoneal cavity and therefore outside the vascular space.

Carbonic Anhydrase IX

Carbonic anhydrase IX (a product of the Von Hippel Lindau gene) is expressed in the vast majority of clear cell renal carcinomas, and therefore, is an excellent

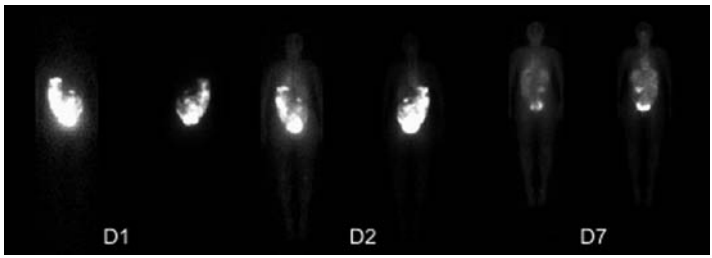

Figure 2 Anterior and posterior 111-indium whole-body images after intraperitoneal radioimmunotherapy (RIT) with 90-yttrium-humanized 3S193 (the indium was colabeled with the yttrium).

therapeutic target for a cancer refractory to chemotherapy whose five-year survival rate is less than 10%. Antibody G250, developed by Oosterwijk et al., recognizes carbonic anhydrase-IX with normal tissue cross-reactivity, limited only to biliary epithelium (82). Our initial study with murine G250 demonstrated excellent targeting to renal tumors with probably the highest absolute solid tumor uptakes documented by biopsy. Repeat treatment was obviated by HAMA (83). Multiple administrations may be crucial for the treatment of heterogeneous, bulky solid tumors. Chimeric G250 (IgG_1) was therefore produced and studied in phase 1 studies with ^{131}I.

A study has been carried out with a single large RIT dose. This has demonstrated a decrease in HACA formation (84,85), and the ability to predict HACA by carrying out "scout" dose imaging. In order to evaluate the effect of treatment dose fractionation upon safety and efficacy, we simultaneously started a single large-dose RIT study based on escalating amounts of ^{131}I and a study of fractionated cG250 using 1110-MBq (30 mCi) ^{131}I-cG250 doses in a whole body radiation-absorbed dose-based schema (85) (Fig. 3). In this study, the MTD of ^{131}I was found to be 0.75 Gy, and dose-limiting toxicity was hematologic. Preliminary calculations suggest that dose-limiting whole body radiation-absorbed dose is not different in "rapidly" fractionated and single large dose treatment schema (86). However, differential distribution of radioactivity in tumor may vary following each fraction, therefore, putatively allowing better delivery of cytotoxic radiation. These data are currently being analyzed.

As the G250 antibody binds to epithelial cells of the large bile duct and gall bladder, and as biliary cancers are sensitive to radiation, RIT with WX-G250 RIT may have clinical benefits in the treatment of biliary cancer patients. These cancers are particularly difficult to treat owing to the late stage at diagnosis. The ^{131}I-labeled antibody WX-G250 RIT is designed to identify the tumor cells and deliver doses of radiation directly to the tumor cells. Clinical phase 1/2 trials with WX-G250 RIT in biliary cancer patients appear promising. As the antigen is expressed on both normal biliary tissue and biliary cancers, the evaluation of

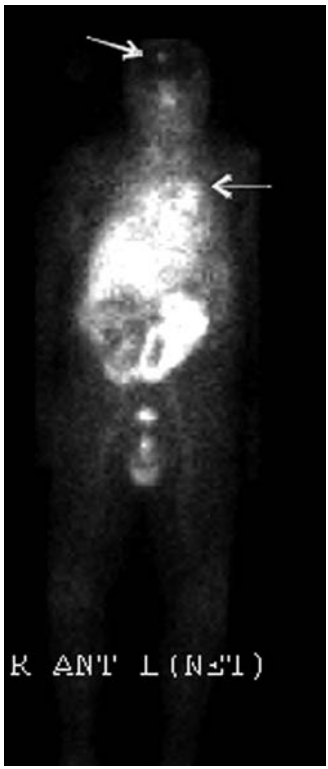

Figure 3 Anterior whole-body images after 131-iodine-cG250. Note the excellent targeting to metastases (*arrows*).

differential expression is important to the selection of an appropriate RIT model, and we are therefore evaluating differential in vivo expression of tumor antigen using quantitative positron emission tomography (PET) and ^{124}I-cG250.

Prostate Specific Membrane Antigen

Although prostate cancer has received much attention because of the success of diagnostic biomarkers, the success of RIT for the disease has lagged behind. Studies of ^{131}I-murine CC49 did not show objective response (87) in patients with prostate cancer. Subsequent attempts to increase antigen expression using interferon pretreatment also did not result in objective treatment responses (88). Fourteen patients received seven doses of interferon, followed by 2775 MBq/m^2 (75 mCi/m^2) 131I-CC49 treatment. Although antigen (TAG-72) expression seemed to be upregulated, evidenced by increased tumor localization, no significant response was achieved. The immunogenicity of the murine protein remained a problem.

Prostate-specific membrane antigen (PSMA) is a nonsecreted internalizing antigen, and therefore an excellent target for RIT. Humanized mAb J591 targets the external domain of PSMA (89). Phase 1 studies of ^{90}Y and ^{177}Lu labeled humanized J591 have been completed, and have shown an excellent safety profile with dose-limiting toxicity being, as expected, hematopoietic (90,91).

PRETARGETING STRATEGIES

In order to enhance the efficacy of RIT, multistep targeting strategies have been under development. These methods are designed to minimize the radiation to normal tissue that is attributed to prolonged residence time in the body. One approach utilizes the interaction of avidin and biotin. The pretargeting tumor-specific antibody/avidin fusion protein is administered. After the circulating antibody has been cleared with a clearing agent, radiolabeled biotin is injected. This process attaches to the streptavidin on the tumor surface (Fig. 4).

Early studies of pretargeted RIT, designed to evaluate its safety and therapeutic ratio, demonstrated a mean tumor to marrow absorbed dose ratio of 63:1, which is an order of magnitude greater than the 6:1 ratio, usually seen in conventional RIT (92). Studies of pretargeted treatment with monoclonal antibody NR-LU-10-streptavidin (constructed as a tetrameric sFv bound to streptavidin) and ^{90}Y-biotin in refractory colorectal adenocarcinoma demonstrated mean tumor absorbed dose of 0.5 ± 0.2 cGy/MBq, which was significantly higher than the dose estimate to the kidney 0.3 ± 0.1 cGy/MBq and to the bone marrow (0.1 mGy/MBq). Despite these impressive ratios, only 8% of the patients showed a major response to therapy. Although hematologic toxicity was not dose limiting, nonhematologic toxicities were significant (93), underscoring that this technique will not spare normal tissues that express antigen. It is

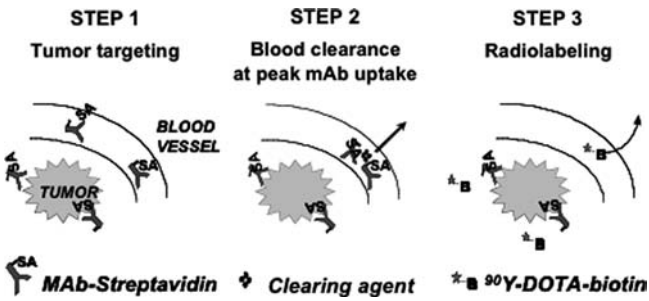

Figure 4 Tumor pretargeting with bispecific construct: a bispecific agent (e.g., bispecific antibody or an antibody/streptavidin fusion) is administered, which saturates the antigen on the tumor. Subsequently, a small radionuclide carrier is administered, which binds to the tumor-localizing bispecific agent.

anticipated that dose-limiting toxicity with these multistep techniques will likely be renal. This poses additional issues as nephropathy is usually not evident until several years after renal insult, and it is thus difficult to evaluate nephrotoxicity in the treatment setting. Finally, avidin and streptavidin are immunogenic. This limits the administration of the initial agent to single use. Such multistep targeting methods are therefore analogous to external beam therapy in that they can be used over one course with no possibility for retreatment.

Promising results using the pretargeting approach have been shown in gliomas. Studies of biotinylated anti-tenascin monoclonal antibody, with ^{90}Y-dodecane tetraacetic acid (DOTA) biotin as the radionuclide, have demonstrated response as sole therapy for recurrent disease and in the adjuvant setting (94).

Bispecific constructs that react against a radiometal–chelate complex, on the other hand, are unlikely to be immunogenic, and therefore hold promise as therapeutic agents (95,96). These novel systems should be able to deliver higher amounts of relative tumor radiation-absorbed dose than would be possible with single-step radiolabeled antibody methods. They may have the added advantage of less immunogenicity of avidin-based systems, allowing multiple/repeat therapies.

STRATEGIES FOR FUTURE STUDIES

Early lack of success in solid tumor RIT, combined with the encouraging results in RIT of lymphoma, has provided impetus for the development of a plethora of treatment approaches for solid tumors. Constructs linked to radionuclides with varying radiobiologic characteristics, patient-specific therapy, fractionated therapy and pretargeting are some methods currently being investigated. A new generation of clinical trials are either being initiated or in planning stages to try to maximize therapeutic efficacy of RIT for solid tumors. These trials share some similar characteristics:

1. *Advances in radiochemistry*: Auger and alpha emitters have been labeled without loss of immunoreactivity to a variety of antigen-binding constructs. Positron emitters like ^{64}Cu, ^{86}Y, and ^{124}I are now available for PET-based dosimetry. These will permit the calculation of tumor and critical organ radiation-absorbed doses and optimize accurate dose delivery. Although ^{131}I, ^{186}Re, ^{188}Re, and ^{177}Lu are ideal radionuclides for external single-photon imaging, surrogate gamma emitters must be used to evaluate the distribution and clearance of pure beta emitters. ^{111}In has been considered to be an appropriate surrogate for ^{90}Y. Their half-lives are almost identical, and both are readily incorporated into the same metal-chelating agents. A recent study using PET imaging to compare ^{86}Y and ^{111}In as surrogates for ^{90}Y showed that, although ^{111}In and ^{86}Y have similar biodistribution, ^{86}Y remained in organs, such as bone for a longer period of time (97). ^{86}Y is a more suitable surrogate for ^{90}Y, and the short $T_{1/2}$ of

^{86}Y may not be a limitation, given the inherent sensitivity of PET. This feature has been used to obtain extremely accurate dosimetry in bone-seeking radiopharmaceuticals (97) and with radiolabeled peptides (98).

2. *Genetic engineering*: Putatively nonimmunogenic antibody constructs, pretargeting strategies, affinity-enhancement systems, and other methods will lead to enhanced tumor uptake and/or improved tumor-to-nontumor ratios, leading to an increase in tumor radiation dose. Pretargeting studies, first described by Goodwin et al. several decades ago (99), demonstrate the great potential of this strategy, realized only now by appropriate genetic engineering. Genetic modification of antigen-binding constructs has included exploration of their production not only in bacterial systems, but also in yeast and mammalian cells. Univalent sFv proteins may be more stable when grown in yeast or mammalian cells. Bivalent diabodies have the advantage of improved affinity, but are retained to a great degree in the kidney (100), thus raising the specter of unacceptable nephrotoxicity. It may be possible to retain bivalency and minimize renal accumulation by adding other moieties, notably the CH_3 domain (101), or adding cytotoxic agents, such as tumor necrosis factor (TNF) dimers (102).
3. *Understanding radiobiology*: Utilizing radionuclides with physical characteristics tailored to the individual disease condition, bulky tumors, minimal residual disease, and adjuvant therapy, will improve our ability to treat tumors appropriately. Successful systemic-targeted radiotherapy depends not only on careful selection of appropriate antigen targets and antibody constructs, but also on the choice of radionuclides appropriate for the extent and type of disease. Alpha emitters will be more suitable for microscopic disease, energetic beta emitters for bulky disease, low-energy beta emitters in a system that permits adequate distribution of radioactivity throughout tumor will limit the side effects to normal tissue. Toxicity is always the prime concern of therapy. The physical and biologic characteristics of radionuclides will need to be combined with the pharmacodynamic properties of the antigen-binding constructs for combination therapies. Sequential therapies with different nuclides based on tumor burden and other characteristics will be critical in multinuclide therapy selection. Combination RIT will likely be as important to successful therapy as combination chemotherapy has been.
4. *Combination multimodality therapy*: Using chemotherapy or external beam radiotherapy in conjunction with RIT, earlier in the treatment of solid tumors, may maximize the promise of RIT. Complementary modalities have great potential. Chemotherapeutic agents, such as paclitaxel and gemcitabine, may not only have independent cytotoxicity, but also act as radiosensitizers, and enhance the efficacy of RIT (though it is as yet unclear whether normal tissue toxicity will be

similarly enhanced). We are investigating the potential of small molecule inhibitors that can cause downstream metabolic effects that will change tumor uptake of and the susceptibility of tumor cells to, RIT. Agents, such as tirapazamine, which affect the hypoxic fraction of tumors may also enhance RIT efficacy. Agents that cause changes in the permeability and vascularity of tumors will permit radioimmunoconjugate access to tumor regions that may otherwise not be reached. The use of antiangiogenic agents, in particular, is of great interest as it appears clear that these agents may decrease the tumor uptake of radioimmunoconjugate (if RIT is instituted after antiangiogenic therapy), and conversely decrease egress of radioimmunoconjugate if the antiangiogenic agent is administered at an as yet undetermined time after RIT. These exciting studies are currently being designed in preclinical models and will soon be applied in the clinic.

5. *Administration schedule*: The use of fractionated multidose RIT instead of single larger dose RIT may result in a slower rate of tumor cell repopulation. Theoretical models have compared the effects of large single-dose administration and rapid fractionation (103). Although a large single dose may have a large rate of cell killing, fractionated therapy may offer the advantages of lower toxicity and prolonged tumor response. In addition, similar to the rationale behind multimodality therapy, preceding doses may cause architectural changes in the tumor that may allow subsequent doses to target previously inaccessible regions. However, studies with fractionated and single large-dose RIT have shown no advantage in safety or total tumor radiation-absorbed dose. We are currently analyzing the data to determine whether changes in intratumoral distribution of radioactivity (86) occur with fractionated RIT. Nevertheless, RIT dose fractionation may have promise when combined in a multimodality therapeutic strategy.

These and other as yet undetermined strategies will lead to a new era of tailored RIT for solid tumors that is safe and effective. The success of RIT for hematologic cancers has led to an expectation that RIT will find its niche in solid tumor cancer therapy, both in the adjuvant situation and in bulky disease. Combination RIT, either given in sequence or simultaneously, will soon be a crucial player in the era of molecular therapeutics, as cancer therapy must target both isolated cancer cells and bulky tumors. It is heartening that the FDA has been very receptive to the idea of multimodality therapy with RIT and biologic/chemotherapeutic agents.

SUMMARY

As with chemotherapy, RIT has had its initial successes in the hematologic neoplasms. Two radiolabeled antibodies have been approved by the FDA—one labeled with ^{90}Y, the other with ^{131}I, both against the CD20 receptor present in

most B-cell lymphomas. Significant response rate and duration improvements with these agents, both in the myeloablative and nonmyeloablative setting, have led to a resurgence of interest in RIT. Effective RIT of solid tumors is however far from FDA approval, with no agents currently in phase 3 trials.

Unlike B-cell lymphoma, where the host human does not readily mount an immune response against xenogeneic protein, solid tumor RIT cannot be undertaken with murine antibodies, and the clearance kinetics of less immunogenic chimeric and humanized antibodies probably do not allow the delivery of large-enough amounts of radiation to tumor, even at myeloablative doses. Humanized intact immunoglobulins have been approved for a variety of solid tumors, including breast and colon cancer; radiolabeled antibodies have however not shown great promise in solid tumors. This has spurred the development of antigen-binding constructs and other strategies, including multistep targeting to increase relative tumor radiation-absorbed dose.

Genetic engineering has provided not only smaller proteins, for example, single-chain fragments, but also bispecific antibodies that can attach to tumor cells and provide a site for attachment of radionuclide-carrying molecules. An increasing number of radionuclides with therapeutic potential are now being produced, and can be stably attached to antigen-binding proteins, thanks to considerable advances in linker chemistry. Optimized radiolabeled antigen-binding constructs and multistep targeting systems are now being studied in clinical trials, and it appears that the goal of achieving adequate tumor radiation-absorbed dose may be at hand. Multimodality therapy is commonplace in cancer, and the rationale for combining radioimmunotherapy with other biologic therapy or chemotherapy is strong. These types of clinical trials are also being initiated. In this chapter, major antigen systems were highlighted after a brief discussion on radionuclides of therapeutic potential. There was also an overview of dosimetry methodology. Possible future directions for this promising therapy have also been discussed.

REFERENCES

1. Witzig TE, White CA, Gordon LI, et al. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-hodgkin's lymphoma. J Clin Oncol 2003; 21:1263–1270.
2. Horning SJ. Future directions in radioimmunotherapy for B-cell lymphoma. Semin Oncol 2003; 30(suppl):29–34.
3. Press OW. Radioimmunotherapy for non-Hodgkin's lymphomas: a historical perspective. Semin Oncol 2003; (suppl):10–21.
4. Press OW, Unger JM, Braziel RM, et al. A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin lymphoma: Southwest Oncology Group Protocol S9911. Blood 2003; 102:1606–1612.
5. Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005; 352:441–449.
6. O'Donoghue, J.A. The implications of non-uniform tumor doses for radioimmunotherapy. J Nucl Med 1999; 40:1337–1341.
7. Padera TP, Stoll BR, Tooredman JB, Capen D, di Tomaso E, Jain RK. Pathology: cancer cells compress intratumour vessels. Nature 2004; 427:695.
8. Goldenberg DM, DeLand F, Kim E, et al. Use of radiolabeled antibodies to carcinoembryonic antigen for the detection and localization of diverse cancers by external photoscanning. N Engl J Med 1978; 298: 1384–1386.
9. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975; 256:495–497.
10. Divgi CR, Scott AM, Dantis L, et al. Phase I radioimmunotherapy trial with iodine-131-CC49 in metastatic colon carcinoma. J Nucl Med 1995; 36:586–592.
11. Billetta R, Lobuglio AF. Chimeric antibodies. Int Rev Immunol 1993; 10:165–176.
12. Caron PC, Schwartz MA, Co MS, et al. Murine and humanized constructs of monoclonal antibody M195 (anti-CD33) for the therapy of acute myelogenous leukemia. Cancer 1994; 73(suppl):1049–1056.
13. Delaloye B, Bischof-Delaloye A, Buchegger F, et al. Detection of colorectal carcinoma by emission-computerized tomography after injection of 123I-labeled Fab or F(ab')2 fragments from monoclonal anti-carcinoembryonic antigen antibodies. J Clin Invest 1986; 77:301–311.
14. Chang CN, Landolfi NF, Queen C. Expression of antibody Fab domains on bacteriophage surfaces. Potential use for antibody selection. J Immunol 1991; 147:3610–3614.

15. Zaccolo M, Griffiths AP, Prospero TD, Winter G, Gherardi E. Dimerization of Fab fragments enables ready screening of phage antibodies that affect hepatocyte growth factor/scatter factor activity on target cells. Eur J Immunol 1997; 27:618–623.

16. Webber KO, Reiter Y, Brinkmann U, Kreitman R, Pastan I. Preparation and characterization of a disulfide-stabilized Fv fragment of the anti-Tac antibody: comparison with its single-chain analog. Mol Immunol 1995; 32:249–258.

17. Tuttle WK III, Brown PH. Applying Nuclear Regulatory Commission guidelines to the release of patients treated with sodium iodine-131. J Nucl Med Technol 2000; 28:275–279.

18. Press OW, Eary JF, Appelbaum FR, et al. Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. N Engl J Med 1993; 329:1219–1224.

19. Carrasquillo JA, Mulshine JL, Bunn PA Jr., et al. Indium-111 T101 monoclonal antibody is superior to iodine-131 T101 in imaging of cutaneous T-cell lymphoma. J Nucl Med 1987; 28:281–287.

20. Garg PK, Alston KL, Welsh PC, Zalutsky MR. Enhanced binding and inertness to dehalogenation of alpha-melanotropic peptides labeled using N-succinimidyl 3-iodobenzoate. Bioconjug Chem 1996; 7:233–239.

21. Wiseman GA, Witzig TE. Yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin) induces long-term durable responses in patients with relapsed or refractory B-Cell non-Hodgkin's lymphoma. Cancer Biother Radiopharm 2005; 20:185–188.

22. Smith-Jones PM. Radioimmunotherapy of prostate cancer. Q J Nucl Med Mol Imaging 2004; 48:297–304.

23. Guhlke S, Beets AL, Oetjen K, Mirzadeh S, Biersack HJ, Knapp FF Jr. Simple new method for effective concentration of 188Re solutions from alumina-based 188W-188Re generator. J Nucl Med 2000; 41:1271–1278.

24. Postema EJ, Borjesson PK, Buijs WC, et al. Dosimetric analysis of radioimmunotherapy with 186Re-labeled bivatuzumab in patients with head and neck cancer. J Nucl Med 2003; 44(10):1690–1699.

25. Zalutsky M, Reardon D, Akabani G, et al. Astatine-211 labeled human/mouse chimeric anti-tenascin monoclonal antibody via surgically created resection cavities for patients with recurrent gliomas: phase I study. Neurooncology 2002; 4:S103 (Abstr).

26. Jurcic JG, Larson SM, Sgouros G, et al. Targeted alpha particle immunotherapy for myeloid leukemia. Blood 2002; 100:1233–1239.

27. Miederer M, McDevitt MR, Sgouros G, Kramer K, Cheung NK, Scheinberg DA. Pharmacokinetics, dosimetry, and toxicity of the targetable atomic

generator, 225Ac-HuM195, in nonhuman primates. J Nucl Med 2004; 45:129–137.

28. Adelstein SJ, Kassis AI, Bodei L, Mariani G. Radiotoxicity of iodine-125 and other auger-electron-emitting radionuclides: background to therapy. Cancer Biother Radiopharm 2003; 18:301–316.
29. Behr TM, Sharkey RM, Juweid ME, et al. Phase I/II clinical radioimmunotherapy with an iodine-131-labeled anti-carcinoembryonic antigen murine monoclonal antibody IgG. J Nucl Med 1997; 38:858–870.
30. Juweid ME, Sharkey RM, Behr T, et al. Radioimmunotherapy of patients with small-volume tumors using iodine-131-labeled anti-CEA monoclonal antibody NP-4 F(ab')2. J Nucl Med 1996; 37:1504–1510.
31. Juweid M, Sharkey RM, Behr TM, et al. Clinical evaluation of tumor targeting with the anticarcinoembryonic antigen murine monoclonal antibody fragment, MN-14 F(ab)2. Cancer 1996; 78:157–168.
32. Behr TM, Liersch T, Greiner-Bechert L, et al. Radioimmunotherapy of small-volume disease of metastatic colorectal cancer. Cancer 2002; 94(suppl):1373–81.
33. Hajjar G, Sharkey RM, Burton J, et al. Phase I radioimmunotherapy trial with iodine-131-labeled humanized MN-14 anti-carcinoembryonic antigen monoclonal antibody in patients with metastatic gastrointestinal and colorectal cancer. Clin Colorectal Cancer 2002; 2:31–42.
34. Wong JY, Chu DZ, Yamauchi D, et al. Dose escalation trial of indium-111-labeled anti-carcinoembryonic antigen chimeric monoclonal antibody (chimeric T84.66) in presurgical colorectal cancer patients. J Nucl Med 1998; 39:2097–2104.
35. Wong JYC, Chu DZ, Yamauchi DM, et al. A phase I radioimmunotherapy trial evaluating 90yttrium-labeled anti-carcinoembryonic antigen (CEA) chimeric T84.66 in patients with metastatic CEA-producing malignancies. Clin Cancer Res 2000; 6:3855–3863.
36. Koppe MJ, Soede AC, Pels W, et al. Experimental radioimmunotherapy of small peritoneal metastases of colorectal origin. Int J Cancer 2003 Oct 10; 106(6): 965–972.
37. Winter G. Synthetic human antibodies and a strategy for protein engineering. FEBS Lett 1998; 430:92–94. Review.
38. Begent RH, Ledermann JA, Green AJ, et al. Antibody distribution and dosimetry in patients receiving radiolabelled antibody therapy for colorectal cancer. Br J Cancer 1989; 60:406–412.
39. Begent RH, Verhaar MJ, Chester KA, et al. Clinical evidence of efficient tumor targeting based on single-chain Fv antibody selected from a combinatorial library. Nat Med 1996; 2:979–984.

40. Molinolo A, Simpson JF, Thor A, Schlom J. Enhanced tumor binding using immunohistochemical analyses by second generation anti-tumor-associated glycoprotein 72 monoclonal antibodies versus monoclonal antibody B72.3 in human tissue. Cancer Res 1990; 50:1291–1298.

41. Divgi CR, Scott AM, McDermott K, et al. Clinical comparison of radiolocalization of two monoclonal antibodies (mAbs) against the TAG-72 antigen. Nucl Med Biol 1994; 21:9–15.

42. Murray JL, Macey DJ, Kasi LP, et al. Phase II radioimmunotherapy trial with 131I-CC49 in colorectal cancer. Cancer 1994; 73(suppl): 1057–1066.

43. Divgi CR, Scott AM, Gulec S, et al. Pilot radioimmunotherapy trial with 131I-labeled murine monoclonal antibody CC49 and deoxyspergualin in metastatic colon carcinoma. Clin Cancer Res 1995; 1: 1503–1510.

44. Rogers BE, Roberson PL, Shen S, et al. Intraperitoneal radioimmunotherapy with a humanized anti-TAG-72 (CC49) antibody with a deleted CH2 region. Cancer Biother Radiopharm 2005; 20:502–13.

45. Macey DJ, Grant EJ, Kasi L, et al. Effect of recombinant alpha-interferon on pharmacokinetics, biodistribution, toxicity, and efficacy of 131I-labeled monoclonal antibody CC49 in breast cancer: a phase II trial. Clin Cancer Res 1997; 3:1547–1555.

46. Meredith RF, Khazaeli MB, Macey DJ, et al. Phase II study of interferon-enhanced 131I-labeled high affinity CC49 monoclonal antibody therapy in patients with metastatic prostate cancer. Clin Cancer Res 1999; 5(suppl):3254s–3258s.

47. Meredith RF, Khazaeli MB, Plott WE, et al. Phase II study of dual 131I-labeled monoclonal antibody therapy with interferon in patients with metastatic colorectal cancer. Clin Cancer Res 1996; 2:1811–1818.

48. Mulligan T, Carrasquillo JA, Chung Y, et al. Phase I study of intravenous Lu-labeled CC49 murine monoclonal antibody in patients with advanced adenocarcinoma. Clin Cancer Res 1995; 1:1447–1454.

49. Alvarez RD, Partridge EE, Khazaeli MB, et al. Intraperitoneal radioimmunotherapy of ovarian cancer with 177Lu-CC49: a phase I/II study. Gynecol Oncol 1997; 65:94–101.

50. Meredith RF, Alvarez RD, Partridge EE, et al. Intraperitoneal radioimmunochemotherapy of ovarian cancer: a phase I study. Cancer Biother Radiopharm 2001; 16:305–315.

51. Alvarez RD, Huh WK, Khazaeli MB, et al. A phase I study of combined modality (90)Yttrium-CC49 intraperitoneal radioimmunotherapy for ovarian cancer. Clin Cancer Res 2002; 8:2806–2811.

52. Colcher D, Bird R, Roselli M, et al. In vivo tumor targeting of a recombinant single-chain antigen-binding protein. J Natl Cancer Inst 1990; 82:1191–1197.
53. Milenic DE, Yokota T, Filpula DR, et al. Construction, binding properties, metabolism, and tumor targeting of a single-chain Fv derived from the pan carcinoma monoclonal antibody CC49. Cancer Res 1991; 51:6363–6371.
54. Adams GP, McCartney JE, Tai MS, et al. Highly specific in vivo tumor targeting by monovalent and divalent forms of 741F8 anti-c-erbB-2 single-chain Fv. Cancer Res 1993; 53:4026–4034.
55. Yokota T, Milenic DE, Whitlow M, Wood JF, Hubert SL, Schlom J. Micro autoradiographic analysis of the normal organ distribution of radioiodinated single-chain Fv and other immunoglobulin forms. Cancer Res 1993; 53:3776–3783.
56. Larson SM, El-Shirbiny AM, Divgi CR, et al. Single chain antigen binding protein (scFv CC49): first human studies in colorectal carcinoma metastatic to liver. Cancer 1997; 80:2458–2468.
57. Welt S, Divgi CR, Kemeny N, et al. Phase I/II study of iodine 131-labeled monoclonal antibody A33 in patients with advanced colon cancer. J Clin Oncol 1994; 12:1561–1571.
58. Daghighian F, Barendswaard E, Welt S, et al. Enhancement of radiation dose to the nucleus by vesicular internalization of iodine-125-labeled A33 monoclonal antibody. J Nucl Med 1996; 37:1052–1057.
59. Welt S, Scott AM, Divgi CR, et al. Phase I/II study of iodine 125-labeled monoclonal antibody A33 in patients with advanced colon cancer. J Clin Oncol 1996; 14:1787–1797.
60. Barendswaard EC, Scott AM, Divgi CR, et al. Rapid and specific targeting of monoclonal antibody A33 to a colon cancer xenograft in nude mice. Int J Oncol 1998; 12:45–53.
61. Meredith RF, Khazaeli MB, Plott WE, et al. Initial clinical evaluation of iodine-125-labeled chimeric 17-1A for metastatic colon cancer. J Nucl Med 1995; 36:2229–2233.
62. Welt S, Divgi CR, Scott AM, et al. Antibody targeting in metastatic colon cancer: a phase I study of monoclonal antibody F19 against a cell-surface protein of reactive tumor stromal fibroblasts. J Clin Oncol 1994; 12:1193–1203.
63. Scott AM, Wiseman G, Welt S, et al. A phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res 2003; 9:1639–1647.

64. Rubin SC, Kostakoglu L, Divgi C, et al. Biodistribution and intraoperative evaluation of radiolabeled monoclonal antibody MX35 in patients with epithelial ovarian cancer. Gynecol Oncol 1993; 51:61–66.

65. Finstad CL, Lloyd KO, Federici MG, et al. Distribution of radiolabeled monoclonal antibody MX35 F(ab')2 in tissue samples by storage phosphor screen image analysis: evaluation of antibody localization to micrometastatic disease in epithelial ovarian cancer Clin Cancer Res 1997; 8:1433–1442.

66. van Zanten-Przybysz I, Molthoff CF, Roos JC, et al. Radioimmunotherapy with intravenously administered 131I-labeled chimeric monoclonal antibody MOv18 in patients with ovarian cancer. J Nucl Med 2000; 41:1168–1176.

67. Nicholson S, Gooden CS, Hird V, et al. Radioimmunotherapy after chemotherapy compared to chemotherapy alone in the treatment of advanced ovarian cancer: a matched analysis. Oncol Rep 1998; 5:223–226.

68. DeNardo SJ, Kramer EL, O'Donnell RT, et al. Radioimmunotherapy for breast cancer using indium-111/yttrium-90 BrE-3: results of a phase I clinical trial. J Nucl Med 1997; 38:1180–1185.

69. Kramer EL, Liebes L, Wasserheit C, et al. Initial clinical evaluation of radiolabeled MX-DTPA humanized BrE-3 antibody in patients with advanced breast cancer. Clin Cancer Res 1998; 4:1679–1688.

70. Richardson RB, Kemshead JT, Davies AG, et al. Dosimetry of intrathecal iodine131 monoclonal antibody in cases of neoplastic meningitis. Eur J Nucl Med 1990; 17:42–48.

71. Moseley RP, Davies AG, Richardson RB, et al. Intrathecal administration of 131I radiolabelled monoclonal antibody as a treatment for neoplastic meningitis. Br J Cancer 1990; 62:637–642.

72. Hopkins K, Kemshead JT. Progress review: intrathecal and intratumoral injection of radiolabeled monoclonal antibodies (MoAbs) for the treatment of central nervous system (CNS) malignancies. J Drug Target 1993; 1:175–183.

73. Bigner DD, Brown M, Coleman RE, et al. Phase I studies of treatment of malignant gliomas and neoplastic meningitis with 131I-radiolabeled monoclonal antibodies anti-tenascin 81C6 and anti-chondroitin proteoglycan sulfate Me1-14 F (ab')2—a preliminary report. J Neurooncol 1995; 24:109–122.

74. Papanastassiou V, Pizer BL, Chandler CL, Zananiri TF, Kemshead JT, Hopkins KI. Pharmacokinetics and dose estimates following intrathecal administration of 131I-monoclonal antibodies for the treatment of central nervous system malignancies. Int J Radiat Oncol Biol Phys 1995; 31:541–552.

75. Kemshead JT, Hopkins KI, Chandler CL. Treatment of diffuse leptomeningeal malignancy by intrathecal injection of 131I radioimmunoconjugates. Recent Results. *Cancer Res* 1996; 141:145–158.

76. Brown MT, Coleman RE, Friedman AH, et al. Intrathecal 131I-labeled antitenascin monoclonal antibody 81C6 treatment of patients with leptomeningeal neoplasms or primary brain tumor resection cavities with subarachnoid communication: phase I trial results. Clin Cancer Res 1996;2:963–972.

77. Kramer K, Cheung NK, Humm JL, et al. Targeted radioimmunotherapy for leptomeningeal cancer using (131)I-3F8. Med Pediatr Oncol 2000; 35:716–718.

78. Zalutsky MR, Stabin MG, Larsen RH, Bigner DD. Tissue distribution and radiation dosimetry of astatine-211-labeled chimeric 81C6, an alpha-particle-emitting immunoconjugate. Nucl Med Biol 1997; 24: 255–261.

79. Saleh MN, Sugarman S, Murray J, et al. Phase I trial of the anti-Lewis Y drug immunoconjugate BR96-doxorubicin in patients with lewis Y-expressing epithelial tumors. J Clin Oncol 2000; 18:2282–2292.

80. Pai-Scherf LH, Carrasquillo JA, Paik C, et al. Imaging and phase I study of 111In- and 90Y-labeled anti-LewisY B3. Clin Cancer Res 2000; 6: 1720–1730.

81. Kitamura K, Stockert E, Garin-Chesa P, et al. Specificity analysis of blood group Lewis-y (Le(y)) antibodies generated against synthetic and natural Le(y) determinants. Proc Natl Acad Sci 1994; 91:12957–12961.

82. Oosterwijk E, Bander NH, Divgi CR, et al. Antibody localization in human renal cell carcinoma: a phase I study of monoclonal antibody G250. J Clin Oncol 1993; 11:738–750.

83. Divgi CR, Bander NH, Scott AM, et al. Phase I/II radioimmunotherapy trial with iodine-131-labeled monoclonal antibody G250 in metastatic renal cell carcinoma. Clin Cancer Res 1998; 4:2729–2739.

84. Steffens MG, Boerman OC, de Mulder PH, et al. Phase I radioimmunotherapy of metastatic renal cell carcinoma with 131I-labeled chimeric monoclonal antibody G250. Clin Cancer Res 1999; 5:3268s–3274s.

85. Divgi CR, O'Donoghue JA, Welt S, et al. Phase I clinical trial with fractionated radioimmunotherapy using 131I-labeled chimeric G250 in metastatic renal cancer. J Nucl Med 2004 Aug; 45(8):1412–1421.

86. O'Donoghue JA, Sgouros G, Divgi CR, Humm JL. Single-dose versus fractionated radioimmunotherapy: model comparisons for uniform tumor dosimetry. J Nucl Med 2000; 41:538–547.

87. Meredith RF, Bueschen AJ, Khazaeli MB, et al. Treatment of metastatic prostate carcinoma with radiolabeled antibody CC49. J Nucl Med 1994; 35:1017–1022.

88. Slovin SF, Scher HI, Divgi CR, et al. Interferon-gamma and monoclonal antibody 131I-labeled CC49: outcomes in patients with androgen-independent prostate cancer. Clin Cancer Res 1998; 4:643–651.

89. Nanus DM, Milowsky MI, Kostakoglu L, et al. Clinical use of monoclonal antibody HuJ591 therapy: targeting prostate specific membrane antigen. J Urol 2003; 170:S84–S88.

90. Bander NH, Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ. Phase I trial of 177lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. J Clin Oncol 2005; 23:4591–4601.

91. Vallabhajosula S, Goldsmith SJ, Hamacher KA, et al. Prediction of myelotoxicity based on bone marrow radiation-absorbed dose: radioimmunotherapy studies using 90Y- and 177Lu-labeled J591 antibodies specific for prostate-specific membrane antigen. J Nucl Med 2005; 46:850–858.

92. Breitz HB, Weiden PL, Beaumier PL, et al. Clinical optimization of pretargeted radioimmunotherapy with antibody-streptavidin conjugate and 90Y-DOTA-biotin. J Nucl Med 2000; 41:131–140.

93. Breitz H, Knox S, Widen P, et al. Pretargeted radioimmunotherapy with antibody-streptavidin and Y-90 DOTA-biotin (Avicidin): result of a dose escalation study. J Nucl Med 1998; 39:71P.

94. Paganelli G, Bartolomei M, Ferrari M, et al. Pre-targeted locoregional radioimmunotherapy with 90Y-biotin in glioma patients: phase I study and preliminary therapeutic results. Cancer Biother Radiopharm 2001; 16:227–235.

95. Sharkey RM, McBride WJ, Karacay H, et al. A universal pretargeting system for cancer detection and therapy using bispecific antibody. Cancer Res 2003; 63:354–363.

96. Bardies M, Bardet S, Faivre-Chauvet A, et al. Bispecific antibody and iodine-131-labeled bivalent hapten dosimetry in patients with medullary thyroid or small-cell lung cancer. J Nucl Med 1996; 37:1853–1859.

97. Rosch F, Herzog H, Plag C, et al. Radiation doses of yttrium-90 citrate and yttrium-90 EDTMP as determined via analogous yttrium-86 complexes and positron emission tomography. Eur J Nucl Med 1996; 23:958–966.

98. Jamar F, Barone R, Mathieu I, et al. 86Y-DOTA0)-D-Phe1-Tyr3-octreotide (SMT487)—a phase 1 clinical study: pharmacokinetics, biodistribution and

renal protective effect of different regimens of amino acid co-infusion. Eur J Nucl Med Mol Imaging 2003; 30:510–518.

99. Goodwin DA, Meares CF. Advances in pretargeting biotechnology. Biotechnol Adv 2001; 19:435–450.
100. Yoo TM, Chang HK, Choi CW, et al. Technetium-99 m labeling and biodistribution of anti-TAC disulfide-stabilized Fv fragment. J Nucl Med 1997; 38:294–300.
101. Wu AM. Engineering multivalent antibody fragments for in vivo targeting. Methods Mol Biol 2004; 248:209–225.
102. Bauer S, Adrian N, Williamson B, et al. Targeted bioactivity of membrane-anchored TNF by an antibody-derived TNF fusion protein. J Immunol 2004; 172:3930–3939.
103. DeNardo GL, Schlom J, Buchsbaum DJ, et al. Rationales, evidence, and design considerations for fractionated radioimmunotherapy. Cancer 2002; 94(4 suppl): 1332–1348.

8

Radioimmunotherapy of Lymphomas

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INTRODUCTION

Lymphomas represent the fifth most common malignancy in the western world in incidence, accounting for approximately 5% of new cancer diagnoses amounting to approximately 60,000 new diagnoses each year in the United States (1). Patients with this group of disorders typically present with symptoms related to lymphadenopathy, as well as constitutional symptoms such as fevers, night sweats, or weight loss. Diagnosis is ideally made by excisional biopsy of an involved lymph node. This is followed by the standard initial evaluation that includes staging by physical examination, computerized tomography and bone marrow studies to determine the extent of the disease, as these factors are important in determining the most appropriate therapy. The other major factor that influences the chosen therapy is the histological subtype. In general, patients with Hodgkin's disease are treated with curative intent. In contrast, patients with non-Hodgkin's lymphoma can be divided into two broad groups. The first group is the group of patients with "aggressive" histology with the prototypic subtype being diffuse large B-cell lymphoma, the most common non-Hodgkin's lymphoma (NHL) (2). Patients with aggressive histologies are also treated with curative intent, typically with combination chemotherapy for patients with advanced stage disease, and with short-course combination chemotherapy followed by involved field radiation therapy for patients with early-stage disease. With this approach, approximately 30% to 60% of patients can achieve long-term remissions (3). Unfortunately, the majority of patients with aggressive

lymphomas will not be cured by primary therapy. For these patients, high-dose chemotherapy with hematopoietic stem cell transplantation has been shown to improve outcomes compared with further standard chemotherapy, though only 30% to 50% of such patients with responsive disease have the possibility of long-term remission with this approach (4). For such patients who have relapse following a hematopoietic stem cell transplant, the options for prolonged disease-free survival are limited to investigational therapies.

The second major clinical subgroup of non-Hodgkin's lymphoma is the cohort of patients with indolent lymphoid malignancy, with the prototypic subtype being follicular non-Hodgkin's lymphoma. Though patients with this group of malignancies generally experience a longer median survival, there appears to be no clear-cut evidence that these types of lymphoma can be cured with standard therapies (5). Typically, remission durations become shorter over time and tumors become resistant to any therapeutic venture, eventually resulting in death either from infectious complications, cytopenias, or direct lymphomatous progression. In addition, aggressive therapies in asymptomatic patients do not appear to impact the overall survival despite the fact that responses can be achieved (6). For this reason, many clinicians have opted to treat patients with indolent diseases that are asymptomatic with a "watch-and-wait" approach until they develop complications that can be attributed to their lymphoma (7). Once treatment is required, the specific choice of therapy can range from low toxicity approaches such as oral alkylating agents to aggressive treatments such as high-dose therapy and stem cell transplantation. Despite the variety of therapeutic approaches for indolent NHL, the vast majority of patients will eventually succumb to their disease and proven approaches to prolong survival have yet to be developed.

The field of non-Hodgkin's lymphoma therapy, however, has achieved many advances in the last decade, particularly in the area of monoclonal antibody therapy. This has been possible, in part, owing to readily accessible tissue from lymph nodes and bone marrow biopsies, well-characterized lymphoma cell lines, as well as well defined and consistently expressed antigens. Unlabeled monoclonal antibodies are thought to kill target tumors via multiple mechanisms including induction of apoptosis, activation of complement, and recruitment of immune effector cells involved with antibody-dependent cellular cytotoxicity. A variety of antibodies and target antigens have been evaluated for this purpose as summarized in Table 1. The first monoclonal antibody to be approved for the treatment of cancer was rituximab, which targets the CD20 antigen. Initial studies demonstrated response rates approximately 50% with a minority of patients achieving complete response (8). CD20 has proven to be an ideal target owing to its only known expression on normal and malignant B-cells, its lack of modulation or internalization as well as its inability to be significantly shed from the cell surface. Despite the activity of agents such as rituximab, most patients treated with this agent alone do not attain complete responses. Limitations to the efficacy of unconjugated antibodies in lymphoma patients

Table 1 Summary of Selected Clinically Evaluated Anti-lymphoma Monoclonal Antibodies

Antibody	Target antigen	Target cell
1F5	CD20	B-cell NHL
Rituximab	CD20	B-cell NHL
Tositumomab	CD20	B-cell NHL
Ibritumomab	CD20	B-cell NHL
Campath 1H	CD52	CLL
Epratuzumab	CD22	B-cell NHL
Anti-idiotype	Surface Ig	B-cell NHL
Lym-1	HLA-DR	B-cell NHL
Denileukin-diftitox	IL-2 receptor	T-cell NHL
Anti-ferritin	Ferritin	Hodgkin's disease

Abbreviations: CLL, chronic lymphocytic leukemia; HLA, human leukocyte antigen; NHL, non-Hodgkin's lymphoma.

include inherent apoptosis resistance mechanisms of malignant cells, the lack of adequate immune effector capability, and the requirement that each individual lymphoma cell must be targeted to be killed. The addition of a radionuclide payload to such antibodies can overcome some of these limitations.

Radioiummunotherapy (RIT) does not rely exclusively on immune effector mechanisms or direct induction of apotosis to effect target cells. RIT can also target unbound malignant cells that are within the path length of the emitted particle via the "crossfire" or "bystander effect" further enhancing the ability of this modality to fully eradicate tumor. The development of such lymphoma-specific monoclonal antibodies along with the known radiosensitivity of NHL made this an ideal system to evaluate the efficacy of RIT.

A variety of radioisotopes have been evaluated over the last two decades including iodine 131 (I-131), yttrium 90 (Y-90), copper 67 (Cu-67), rhenium 186 (Re-186), and bismuth 212 (Bi-212). Despite the variety of isotopes used, the vast majority of experience has been with isotopes with I-131 and Y-90. The properties of these isotopes are summarized in Table 2 (9). I-131 has both a high-energy gamma emission as well as beta emissions which

Table 2 Comparison of Iodine-131 (^{131}I) and Yttrium-90 (^{90}Y)

	^{131}I	^{90}Y
Emission	Beta, gamma	Beta
Average beta energy	0.192 MeV	0.934 MeV
Average path length	0.8 mm	5.3 mm
Nonspecific retention	Thyroid	Bone, liver
Half-life	8 days	2.7 days

allows I-131-based conjugates to be used both for imaging and dosimetry as well as therapy. In contrast, Y-90, which has only a beta emission requires a surrogate isotope, which is indium-111 (In-111) to be used for dosimetry and imaging purposes. The absence of a gamma emission with Y-90, however, does afford a potentially reduced risk of radiation exposure to family members and healthcare providers once the therapeutic dose is administered.

CLINICAL TRIALS UTILIZING ANTI-CD20 IN THERAPY

Investigators have taken two broad approaches with the use of anti-CD20 radioimmunoconjugates. First approach limits the dose of radioisotopes by its myelosuppressive effect. This nonmyeloablative therapy has been evaluated both with I-131 and Y-90 radioconjugates. Some of the earliest experience with this approach comes from the University of Michigan. Dr. Kaminsky et al. (10) utilized whole-body dosimetry to determine the maximal safe dose of I-131 tositumomab (anti-CD20) therapy. The initial phase I studies used trace-labeled (5–10 mCi) antibody to evaluate the whole-body biodistribution. The therapeutic dose was then delivered in a dose-escalation schema ranging from 25 to 85 cGy whole-body dose with dose escalation occurring in 10 cGy increments. The dose-limiting toxicity was hematologic and 75 cGy was established as the maximally tolerated dose for patients with normal platelet counts and 65 cGy for patients with platelet counts between 100 and 150,000/μl. Hematologic nadirs typically occurred six to eight weeks after treatment, though patients experienced a few other toxicities associated with this therapy in contrast to what one would expect with traditional chemotherapeutic approaches. Finally, though response was a secondary endpoint 22 of the 28 patients achieved objective responses. Since these initial studies, numerous phase II trials have been carried out both by the University of Michigan group as well as other sites evaluating the efficacy of nonablative I-131 tositumomab in a variety of clinical settings of patients with indolent B-cell lymphomas that has continued to demonstrate clinical activity and safety.

Another approach to nonablative anti-CD20 RIT utilizing Y-90 has also been investigated. Instead of a patient-specific cGy approach, most of these studies were carried out utilizing a mCi/kg dose escalation schema. Patients were first pretreated with the chimeric anti-CD20 antibody rituximab to optimize the biodistribution. Patients then received ibritumomab tiuxetan trace-labeled with ^{111}In. Serial whole-body gamma camera images were then taken to ensure that aberrant biodistribution did not occur. Approximately one week later, patients were then treated with the therapeutic dose of rituximab followed by the therapeutic dose of Y-90-labeled ibritumomab tiuxietan. Patients were initially treated at 0.2 mCi/kg of Y-90 (11). The maximally tolerated doses was determined based on hematological toxicity and was found to be 0.4 mCi/kg in patients with platelet counts above 150,000 and normal white blood counts and 0.3 mCi/kg in patients with platelet counts of 100,000 to

149,000/mL. As with the I-131 tositumomab therapy, the nonhematologic toxicities were minimal with the exception of infusion-related toxicities primarily associated with the infusion of the chimeric anti-CD20 antibody rituximab. Responses were seen in 67% of the treated patients, the majority of which had indolent lymphoma. Selected trials evaluating nonmyeloablative RIT are summarized in Table 3.

Both the I-131 and Y-90 investigators have also shown that the addition of the radionuclide improves response rates over the radiolabeled antibody alone for patients with relapsed indolent lymphomas. These were demonstrated in two separate randomized phases III trials. In the first trial, I-131 tositumomab was compared with tositumomab alone. Patients receiving I-131 tositumomab had complete and overall response rates of 33% and 55%, respectively, as compared with patients receiving unlabeled tositumomab who had complete and overall response rates of 8% and 19%, respectively ($P = 0.002$). Similarly, a randomized trial was carried out comparing Y-90 ibritumomab tiuxetan-based RIT at the 0.4 mCi/kg dose with unlabeled rituximab at 375 mg/m^2 four times a week. The overall response rate in the Y-90 group was 80% as compared with 56% for the rituximab group ($P = 0.002$). The duration of responses however was nonstatistically significantly different, though this study was not powered to show differences in response duration. Nevertheless, these studies do confirm the principle that the addition of a radioisotope can improve the response rates as compared with unlabeled CD-20 antibodies.

HIGH-DOSE RADIOIMMUNOTHERAPY

In contrast to the aforementioned studies whereby the radioisotope dose was limited by marrow suppression, other investigators have evaluated the use of further escalating the dose of RIT and providing hematologic support with autologous hematopoetic stem cell infusions. This strategy was pioneered at the University of Washington in Seattle. These investigators used organ-specific dosimetry as it was hypothesized that specific normal organs may encounter toxicity as doses were escalated beyond the level of myeloablation and that a mCi/kg approach could not accurately predict the radiaton dose to normal organs (12). The initial phase I trials escalated the dose, based on the dose to the highest normal organ starting at 10 Gy and escalating through 30.75 Gy (13). This dose escalation schema established the maximally tolerated dose with autologous hematopoetic support to be approximately 27 Gy to the highest normal organ. The dose-limiting toxicity was cardiopulmonary toxicity reflecting the fact that the normal organ receiving the highest dose was typically the lung. As with the nonablative RIT, the nonhematopoietic toxicities under the maximally tolerated dose were mild to moderate with toxicities considerably less than what one would expect with traditional transplant regimens. The escalation of the radiation dose did translate into improved responses with an overall response rate of 95% and complete response rate of 84% (13). Long-term follow-up of the cohort of

Table 3 Summary of Selected Nonmyeloablative Anti-lymphoma Radioimmunoconjugates

Drug	Isotope	Target	Lymphoma type/ disease setting	n	Response	References
Tositumomab	I-131	CD20	Indolent NHL/relapsed	9	67% (44% CR)	(10)
Tositumomab	I-131	CD20	Indolent NHL/ chemotherapy refractory	60	65% (20% CR)	(17)
Ibritumomab Tiuxetan	Y-90	CD20	Indolent NHL/ relapsed-refractory	34	82% (26% CR)	(11)
Ibritumomab Tiuxetan	Y-90	CD20	Indolent NHL/ rituximab-refractory	54	74% (15% CR)	(16)
LL2	I-131/Y-90	CD22	NHL/relapsed	22	15–29%	(18)
Lym-1	Cu-67	HLA-DR	NHL/relapsed	12	58%	(19)
Anti-ferritin	Y-90	Ferritin	Hodgkin's disease/ relapsed	39	51%	(20)

Abbreviations: CR, complete remission; Cu-67, copper-67; I-131, iodine-131; NHL, non-Hodgkin's lymphoma; Y-90, yttrium-90.

these patients with follicular lymphoma estimated that 67% would be alive and 48% alive without disease progression at five years (14). Patients did, however, experience expected periods of cytopenias, which one would expect to see with autologous transplant patients in general. Another general finding was that in spite of protection of the thyroid gland with oral iodine solution over 60% of the patients eventually developed an elevated thyroid-stimulating hormone (TSH) (15). More recently, this myeloablative approach has been evaluated with alternative radioimmunoconjugates as well as in combination with high-dose chemotherapy. Selected myeloabltive anti-CD20 RIT trials are summarized in Table 4.

TREATMENT INDICATIONS AND ALTERNATIVES

Most patients with lymphoid malignancies have a wide variety of therapeutic options available, thus, the resulting challenge of determining the appropriateness of using RIT for a given patient. This decision is to be carefully considered and a hematologist or medical oncologist should be involved to place this decision in its clinical context. At the present time, there are only two Food and Drug Administration (FDA)-approved radioimmunoconjugates in the United States, Y-90-ibritumomab-tiuxetan (Zevalin®) and I-131-tositumomab (Bexxar®). These are most appropriate for patients with relapsed or refractory low-grade or follicular lymphoma expressing CD20. It is also required that patients have less than 25% bone marrow involvement by bilateral bone marrow biopsy, a platelet count greater than 100,000/μL, and a neutrophil count greater than 1500/μL. Treatment alternatives to RIT include standard chemotherapy, unlabeled antibody therapy, external beam radiation, and high-dose therapy approaches and stem cell transplantation.

TREATMENT SIDE EFFECTS

Both Y-90-ibritumomab tiuxetan and I-131-tositumomab have comparable side effect profiles when given at the FDA-approved nonmyeloablative doses. In the series by Dr. Witzig, summarizing the safety of Y-90-ibritumomab tiuxetan in a series of 349 patients treated with this approach, 80% of the patients were noted to have had at least one adverse event. Patients experienced additional toxicities such as chills, fever, or flushing 21%, 13%, or 5% of the time, respectively (16). Many of these events were related to the unlabeled rituximab infusion, which is known to cause such reactions. The most important toxicity however is the hematologic toxicity. Unlike traditional chemotherapy, the hematologic nadir of platelets and neutrophils typically occurs six to eight weeks after therapy. In this series of 349 patients, 129 (37%) experienced grade I or II thrombocytopenia, whereas 63% experienced grade III or IV cytopenia. In addition, 40% of patients experienced grade I or II neutropenia, whereas 60% of the patients experienced grade III or IV neutropenia. Infection or fever associated

Table 4 Selected Trials Evaluating Myeloablative Anti-CD20 Radioimmunotherapy for Relapsed B-cell NHL

Drug	Isotope	Radiation dose[a] (Gy)	Chemotherapy	Phase	N	CR/PR	Follow-up	Reference
1F5, tositumomab	I-131	15–37.5	No	I	13	77%/15%	Median OS > 26 months	(13)
Tositumomab	I-131	25–31	No	II	21	76%/10%	2-year OS/PFS = 93%/62%	(21)
Tositumomab	I-131	20–27	VP-16, CY	I/II	52	77%/10%	2-year OS/PFS = 83%/68%	(22)
Rituximab	I-131	≤ 27	No	II	7	86%/14%	5 of 6 in CR at 25 months	(23)
Ibritumomab	Y-90	≤ 10	VP-16, CY	I	18	100%/0%	1-year OS and DFS = 92%	(24)

[a]Dose to highest critical normal organ.

Abbreviations: CR, complete remission; DFS, disease free survival; I-131, iodine-131; OS, overall survival; PFS, progressive free survival; Y-90, yttrium-90.

with neutropenia occurred in 29% of the patients, resulting in 7% of the patients requiring hospitalization. Increased hematologic toxicity was found to be associated with a higher percentage of bone marrow involvement at study entry, and prior fludarabine therapy.

Similar toxicity profiles have been observed for I-131-tositumomab. Dr. Kaminsky reported in the pivotal trial of I-131-tositumomab, that 42% of the patients experienced infusional toxicity during the dosimetry infusion, as compared with 24% during the therapeutic dose. These toxicities were predominantly in the grade I–II category, with only 2% of the patients having grade III or IV toxicity (17). One explanation for the lower rates of infusional toxicity with Bexxar may be the lack of a chimeric monoclonal antibody such as rituximab, that is used as predosing for Zevalin® therapy and can more actively fix complement. As with yttrium-based RIT, the dose-limiting toxicity was hematologic, with a median time to nadir of approximately 35 to 45 days following therapy. Eighteen percent of patients experienced grade IV neutropenia, and 22% experienced grade IV thrombocytopenia. Finally, 1 of 56 evaluable patients developed hypothyroidism, 8.3 months after therapy. In summary, the acute toxicities associated with nonablative anti-CD20 RIT are rather mild as compared with traditional chemotherapeutic agents, with some degree of infusional toxicities and delayed cytopenias, most of which do not result in infections, bleeding, or hospitalization.

DOSIMETRY CONSIDERATIONS

Y-90-Ibritumomab Tiuxetan

The use of Y-90-ibritumomab tiuxetan does not require formal dosimetry calculations when used according to FDA-approved guidelines. This approach uses a mCi/kg therapeutic dose, but does require In-111 imaging to ensure that an altered biodistribution does not occur. To evaluate for such an altered biodistribution, patients are given trace-labeled In-111-ibritumomab tiuxetan following the rituximab cold infusion. They then undergo serial whole-body gamma camera imaging over several following days to ensure that early postinfusion of the majority of the radioimmunoconjugate remains within the blood pool and over time localizes to target tumor sites. If there is no evidence for an altered biodistribution, patients can then be treated with 0.4 mCi/kg of Y-90 up to a maximum of 32 mCi with this approach. Patients with platelet counts between 100,000 and 150,000 should be treated with 0.3 mci/kg of Y-90-ibritumomab.

In contrast, the use of I-131-tositumomab requires whole-body dosimetry. Patients receive a cold dose of 450 mg of tositumomab, followed by a trace-labeled hot dose of approximately 35 mg of tositumomab labeled with 5 mCi of I-131. Patients then undergo serial whole-body gamma counts on days 0, 2, 3, or 4, and days 6 or 7 following trace infusion. From these results, a calculation as to the appropriate mCi dose of I-131 can be achieved to deliver 75 cGy whole-body

radiation dose to patients with normal platelet counts and 65 cGy whole-body dose to patients with platelet counts between 100,000 and 150,000.

Calculation of therapeutic dose of I-131-tositumomab is given in Equation 1. [Activity hours are derived from patient mass and reference table. Residence time represents 37% of residual whole body activity as derived from a semi-log plot of percent injected whole body activity. Desired total body dose (TBD) is either 75 cGY or 65 cGy depending on platelet count.]

$$\text{Therapeutic dose (mCi)} = \frac{\text{Activity hours (mCi)}}{\text{Residence time (hr)}} \times \frac{\text{Desired TBD (cGy)}}{75\ \text{cGy}} \quad (1)$$

Patients are then infused with the therapeutic dose in the same algorithm consisting of a cold 450 mg unlabeled anti-CD20 antibody dose followed by the labeled 35 mg dose.

EVALUATING THE PATIENT FOR TREATMENT

In order to ensure that the patients are most appropriately treated with the approved radioimmunoconjugates, collaboration with a hematologist or medical oncologist who is experienced in the treatment of lymphoma should be employed. Importantly, one should ensure that patients have the appropriate diagnosis of a B-cell lymphoma. This should include confirmation of target antigen expression, CD20, in the lymphoma tissue, either by immunocytochemistry or flow cytometry. A review of pathology reports should be sufficient to satisfy this requirement. Second, one should ensure that patients have less than 25% bone marrow involvement in the lymphoma by bilateral bone marrow biopsies. Again, this can be satisfied by the review of a pathology or hematology report from patient's recent bone marrow studies. Finally, patients should have platelet counts above 100,000/μL and neutrophil counts above 1500/μL, which can be determined by a routine complete blood count with differential. Ideally, patients would also have relatively normal hepatic and renal function as well as cardiopulmonary reserve, though this is not an absolute requirement.

DATA NEEDED FOR TREATMENT/DOSIMETRY CONSIDERATIONS

Yttrium-90-Ibritumomab Tiuxetan

In order to treat patients with this Y-90-labeled radioimmunoconjugate, an In-labeled test dose must be administered to ensure appropriate biodistribution (as described previously). Patients should be premedicated with diphenhydramine and acetaminophen, and then infused with 250 mg/m^2 of rituximab. Patients should be closely monitored during the rituximab infusion, as infusional

reactions such as hypotension and chills can occur. Immediately following the rituximab dose, patients should be infused with approximately 5 mg of In-111-labeled ibritumomab tiuxetan. Patients should then undergo serial whole-body imaging within the first 24 hours, within 48 to 72 hours, and optional imaging between 90 and 120 hours. This should be performed with whole anterior and posterior images to ensure that there is not an altered biodistribution such as a rapid clearance from the blood pool early postinfusion, or an abnormal localization to a nontarget site.

Approximately one week after the test dose of In-111-ibritumomab tiuxetan, patients should be treated with the appropriate mCi/kg dose of Y-90-ibritumomab tiuxetan. This should be carried out using 0.4 mCi/kg in patients with normal platelet counts and 0.3 mCi/kg in patients with platelet counts between 100,000 and 150,000/μL. It is important to note that the maximal dose to any patient is 32 mCi. Patients again should be premedicated with Benadryl and Tylenol and infused with the 250 mg/m^2 dose of rituximab. This is then followed by the therapeutic dose of Y-90-labeled ibritumomab tiuxetan. Further details regarding the appropriate use of ibritumomab tiuxetan-based RIT can be obtained from the package insert of this drug.

Iodine-131-Tositumomab

I-131-tositumomab also requires a trace-labeled infusion prior to the therapeutic dose. Unlike the Y-90-ibritumomab tiuxetan, I-131-tositumomab trace infusion is used to calculate the therapeutic dose. For this purpose, 450 mg of unlabeled tositumomab is infused over 60 minutes. This is then immediately followed by an intravenous infusion of 35 mg of tositumomab radioiodinated with 5 mCi of I-131 given over 20 minutes. Patients then undergo total body gamma counts within one hour of the dosimetry infusion and then two to four days and six to seven days after infusion of the dosimetric dose. If the biodistribution is altered, such as the absence of predominance of the blood pool early postinfusion or localization to nontarget sites, the therapeutic infusion should not be administered. Importantly, the determination of the total body residence time is derived from the total body gamma counts. The appropriate mCi dose of I-131 is determined to deliver the desired TBD of either 75 cGy or 65 cGy, depending on the patient's platelet count as described in Equation 1. For the therapeutic dose, again 450 mCi of unlabeled tositumomab is infused over 60 minutes. This is then immediately followed by 35 mg of tositumomab radioiodinated with the desired dose of I-131 to deliver the appropriate TBD. Following infusion, one must note that appropriate restrictions on patient contact and discharge from the hospital must follow local, federal, and state guidelines. Finally, all infusions should be premedicated with acetaminophen and diphenhydramine and patients should be prophylaxed with a thyroid protective agent such as super saturated potassium iodide (SSKI) or Lugol's solution for at least 24 hours prior to

administration of the first dose of I-131-tositumomab, and continued until two weeks after the last administration of I-131-tositumomab.

TREATMENT MONITORING

Patients should be monitored for infusional toxicities with frequent vital sign measurements as well as clinical assessment by a trained healthcare provider. Common toxicities associated with monoclonal antibody therapy, particularly chimeric or humanized antibodies such as rituximab, include chills and hypotension. These side effects are most associated with the first infusion of monoclonal antibody and particularly common in patients who have high tumor burdens or evidence of circulating malignant cells. Such patients with high tumor burdens may be additionally prophylaxed with allopurinol and vigorous hydration as needed to prevent tumor lysis syndrome.

Once the patient has successfully completed the therapeutic infusion, the primary toxicity to monitor is hematologic and the secondary sequellae of pancytopenia. Patients should at the minimum receive a weekly blood count with differential and platelet count from the time of the treatment dose through the patient's nadir and recovery of hematopoietic function. This nadir typically occurs six to eight weeks after the treatment dose and may require over 12 weeks to recover to the patient's baseline counts. Finally, the patients should be cautioned that if they develop fevers, chills, or other signs of infection, as well as signs of bleeding prior to recovery of their hematopoietic function, these should be immediately reported to their primary healthcare provider as neutropenic sepsis or serious bleeding complications hypothetically may occur. Additional supportive measures also may be needed in selected patients at the discretion of the patient's primary clinician, such as hematopoietic growth factor support and/or blood product transfusion.

In addition to monitoring the toxicities of the aforementioned approach, the patient's primary clinician will also routinely monitor the efficacy of the therapy either by physical examination and/or radiographic imaging. It is important to note that the maximal effect of RIT, unlike chemotherapy, may occur beyond six months after the therapeutic dose.

SUMMARY

Radioimmunotherapy represents a promising new treatment modality for patients with lymphoma. When used appropriately, RIT can induce responses in the majority of patients with limited nonhematopoietic toxicity, particularly when compared with standard chemotherapeutic regimens. Future studies will be required to better define the optimal place of RIT in the hematologist/oncologist's armamentarium as well as the ideal dose, schedule, and potential for combination with other drugs. More importantly, randomized trials will be needed to determine whether RIT can truly alter the natural history of this group of diseases.

REFERENCES

1. Eltom MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. J Natl Cancer Inst 2002; 94(16):1204–1210.
2. Shipp MA, Abeloff MD, Antman KH, et al. International Consensus Conference on High-Dose Therapy with Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas: report of the jury. J Clin Oncol 1999; 17(1):423–429.
3. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: eastern cooperative oncology group study 1484. J Clin Oncol 2004; 22(15):3032–3038.
4. Baldissera RC, Nucci M, Vigorito AC, et al. Frontline therapy with early intensification and autologous stem cell transplantation versus conventional chemotherapy in unselected high-risk, aggressive non-Hodgkin's lymphoma patients: a prospective randomized GEMOH report. Acta Haematol 2006; 115(1–2):15–21.
5. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 1995; 13(7):1726–1733.
6. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol 1993; 20(5 suppl 5):75–88.
7. Horning SJ. Treatment approaches to the low-grade lymphomas. Blood 1994; 83(4):881–884.
8. Maloney DG. Preclinical and phase I and II trials of rituximab. Semin Oncol 1999; 26(5 suppl 14):74–78.
9. Leonard JP, Siegel JA, Goldsmith SJ. Comparative physical and pharmacologic characteristics of iodine-131 and yttrium-90: implications for radioimmunotherapy for patients with non-Hodgkin's lymphoma. Cancer Invest 2003; 21(2):241–252.
10. Kaminski MS, Zasadny KR, Francis IR, et al. Radioimmunotherapy of B-cell lymphoma with [131I]anti-B1 (anti-CD20) antibody. N Engl J Med 1993; 329(7):459–465.
11. Witzig TE, White CA, Wiseman GA, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. J Clin Oncol 1999; 17(12):3793–3803.
12. Eary JF, Krohn KA, Press OW, Durack L, Bernstein ID. Importance of pretreatment radiation absorbed dose estimation for radioimmunotherapy of non-Hodgkin's lymphoma. Nucl Med Biol 1997; 24(7):635–638.

13. Press OW, Eary JF, Appelbaum FR, et al. Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. N Engl J Med 1993; 329(17):1219–1224.

14. Gopal AK, Gooley TA, Maloney DG, et al. High-dose radioimmunotherapy versus conventional high-dose therapy and autologous hematopoietic stem cell transplantation for relapsed follicular non-Hodgkin lymphoma: a multivariable cohort analysis. Blood 2003; 102(7):2351–2357.

15. Liu SY, Eary JF, Petersdorf SH, et al. Follow-up of relapsed B-cell lymphoma patients treated with iodine-131-labeled anti-CD20 antibody and autologous stem-cell rescue. J Clin Oncol 1998; 16(10):3270–3278.

16. Witzig TE, White CA, Gordon LI, et al. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-hodgkin's lymphoma. J Clin Oncol 2003; 21(7):1263–1270.

17. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001; 19:3918–3928.

18. Juweid ME, Stadtmauer E, Hajjar G, et al. Pharmacokinetics, dosimetry, and initial therapeutic results with 131I- and (111)In-/90Y-labeled humanized LL2 anti-CD22 monoclonal antibody in patients with relapsed, refractory non-Hodgkin's lymphoma. Clin Cancer Res 1999; 5(10 suppl):3292s–3303s.

19. O'Donnell RT, DeNardo GL, Kukis DL, et al. 67 Copper-2-iminothiolane-6-[p-(bromoacetamido)benzyl-TETA-Lym-1 for radio immunotherapy of non-Hodgkin's lymphoma. Clin Cancer Res 1999; 5(10 Suppl):3330S–3336S.

20. Herpst JM, Klein JL, Leichner PK, et al. Survival of Patients with resistant Hodgkin's disease after polyclonal Yttrium 90-labeled antiferritin treatment. J Clin Oncol 1995; 13(9):2394–2400.

21. Press OW, Eary JF, Appelbaum FR, et al. Phase II trial of 131I-B1 (anti-CD20) antibody therapy with autologous stem cell transplantation for relapsed B cell lymphomas. Lancet 1995; 346(8971):336–340.

22. Press OW, Eary JF, Gooley T, et al. A phase I/II trial of iodine-131-tositumomab (anti-CD20), etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsed B-cell lymphomas. Blood 2000; 96(9):2934–2942.

23. Behr TM, Griesinger F, Riggert J, et al. High-dose myeloablative radioimmunotherapy of mantle cell non-Hodgkin lymphoma with the iodine-131-labeled chimeric anti-CD20 antibody C2B8 and autologous stem cell support. Results of a pilot study. Cancer 2002; 94(suppl 4):1363–1372.

24. Winter JN. Combining yttrium 90-labeled ibritumomab tiuxetan with high-dose chemotherapy and stem cell support in patients with relapsed non-Hodgkin's lymphoma. Clin Lymphoma 2004; (5 suppl 1):S22–S26.

9

Polycythemia Vera and Therapy with Phosphorus-32

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INTRODUCTION

Radioactive isotopes of phosphorus (Greek: "lightbringing") were among the first artificially produced radioisotopes in the pioneering experiments by Frédéric Joliot and Iréne Curie in 1934, and by Enrico Fermi and his group in the same year. In 1935, George Hevesy, after having seen the results of Fermi, was the first to produce microcurie quantities of phosphorus-32 (P-32) in Copenhagen by using a strong Ra/Be source given to Niels Bohr, and applying P-32 in a biological experiment to study the bio-distribution in rats (1). Soon, millicurie quantities were being produced by Ernest O. Lawrence in the cyclotron at Berkeley, California, and Lawrence started periodically sending Hevesy a few millicuries of P-32 (2). Later, in 1937, Hevesy was possibly the first to give a dose of a man-made radioactive substance to a human being in a study of the excretion of P-32 in a hospital patient (3). Later work by Hevesy focused on the possible use of P-32 as a red blood cell (RBC) label, which did not turn out to be satisfactory, owing to insufficient stable RBC binding.

In the meantime, Ernest O. Lawrence's brother, John H. Lawrence, a physician, developed an interest in the application of radiation for the treatment of

cancer, after having seen his mother being cured of pelvic cancer by the application of a new therapy—external high voltage radiation. By this time, it was common knowledge that overexposure to radiation would lead to a reduction in the formed elements of the blood, thought of as "killing" of the formed elements, and is still not perceived as a suppression of the production by the bone marrow. To hypothesize that radiation might be useful in diseases characterized by too many blood cells, like leukemias and polycythemia, was but a short step. After several experiments in leukemic mice, in 1938, John H. Lawrence applied P-32 in the treatment of chronic myeloid leukemia in a 29-year-old student, and by 1940, he published a report on a total of five patients (4). A coworker of John H. Lawrence was to expand on the use of P-32 in polycythemia vera (PV) (5), and explain that it did not kill the excess RBC, but that it reduced the production of RBC by the bone marrow with a delayed effect of about six weeks to three months, thus necessitating the use of phlebotomy for immediate relief.

DEFINITION, DIAGNOSIS, AND SELECTION OF PATIENTS FOR TREATMENT

PV or Vaquez–Osler disease is a chronic progressive myeloproliferative disorder, characterized by splenomegaly and an increased production of all the myeloid elements. The disease is dominated by an elevated hemoglobin concentration.

The onset of PV is gradual and the disease has a slowly progressive course. PV is an uncommon disorder with an annual incidence of about five new cases per million population. In general, PV begins in late middle life, and occurs slightly more often in males. It is a rare disease in children. Without treatment, the median survival of PV is less than two years, although exceeding 10 years with the existing treatment options.

In general, there is still no consensus as to the optimal approach to either the diagnosis or management of PV. The three main forms of therapy are phlebotomy, chemotherapy, and treatment with P-32. Before the therapy is initiated, the diagnosis of PV must be confirmed to exclude secondary causes of polycythemia, in which an elevated level of hemoglobin results from high levels of erythropoietin production as a result of hypoxia (high altitude, pulmonary disease, cardiac right-to-left shunt) or in certain neoplasias.

Disease manifestations in PV that require treatment fall into two major categories: life threatening and non-life threatening. Life-threatening manifestations of PV include increased hematocrit, vascular events (thrombosis and bleeding), and evolution into myelofibrosis with myeloid metaplasia and acute leukemia. Non-life-threatening complications of PV include constitutional symptoms, such as microvascular disturbances and pruritus (6).

Reducing the red cell mass and maintaining it at a safe level (hematocrit, 42–47%) by phlebotomy is the first principle of therapy in PV. The reduction

Table 1 Selection Criteria for Treating Polycythemia Vera Patients with Phosphorus-32

Age of the patient—reserved for elderly patients (>70 years)
Poor treatment compliance
Life expectancy <10 years (e.g., longstanding history of PV).

Abbreviation: PV, polycythemia vera.

of the red cell mass removes a major source of complications. For many patients, no other therapy may be necessary for many years (7), although this treatment has been associated with a higher risk of thrombosis, whereas early treatment with chemotherapy (hydroxyurea, chlorambucil) or P-32 substantially reduces the risk of thrombotic complications (8).

Treatment with P-32, however, appears to reduce survival (median survival 10.9 years versus 12 years with phlebotomy alone), as P-32 may increase the incidence of acute leukemia when compared with phlebotomy alone (1.5% with phlebotomy alone and 9.6% with P-32). [Summary of trial data by the Polycythemia Vera Study Group as cited in Ref. 8.]

Because P-32-associated leukemia in PV peaks after seven years of treatment, P-32 therapy is best reserved for elderly patients over the age of 70 years, and for patients with issues of treatment compliance or if life expectancy is less than 10 years, as is the case in patients with longstanding history of PV (Table 1). The therapy with P-32 should be preceded by repeated phlebotomies in order to reduce the hematocrit to 42% to 47%.

CONTRAINDICATIONS

Absolute contraindications are pregnancy and continued breastfeeding. The use of P-32 is not recommended in women of childbearing age. Given the selection criteria of age or life expectancy of the patient in general, these contraindications are only theoretical.

To avoid bone marrow toxicity, the administration of P-32 is contraindicated in patients with total white cell count $<2.0 \times 10^9\ l^{-1}$, or in patients with rapidly deteriorating renal function (9).

PHYSICAL ASPECTS OF PHOSPHORUS-32

P-32 is a reactor produced radionuclide, with a physical half-life of 14.29 days. It decays solely by beta-minus emission to S-32. The beta particles (electrons) emitted have a maximum energy of 1700 keV (average 694.7 keV). The beta particle loses its energy largely via collision with orbital electrons, leading to ionization or excitation. Only a small fraction of energy loss (0.4% in

water) comes from direct reactions with the nuclei, leading to deflection and rapid deceleration of the beta particle, accompanied by the emission of the lost energy in the form of photon radiation ["braking radiation," Bremsstrahlung, (10)]. This becomes important when adequate shielding needs to be chosen for the handling of this isotope. The maximum range for the beta particle in air is 607 cm, in water 0.785 cm, with an average range in air of about 152 cm and in water of about 0.198 cm. The distances traveled in tissue are approximately equal to those traveled in water—average is 3 mm with a maximum range of 8 mm.

RADIATION PROTECTION ASPECTS

Handling Sources

As the prodution of bremsstrahlung is linearly dependent on the atomic number Z, low Z materials, like glass, plastic, and lucite, are the preferred shielding materials for P-32 electrons. The beta particles travel a maximum of 3.1 mm in glass and 6.7 mm in lucite. Although no gamma radiation is produced in the decay process, larger amounts (over 100 MBq) of P-32 will produce sufficient photon radiation (bremsstrahlung) to warrant extra safety measures in the form of 2- to 3-mm lead shielding around a primary shield of glass or plastic. As the distances traveled in air by the emitted beta particles are large, sources containing P-32 should always be shielded appropriately. Direct contact with vials, and the like, should be avoided. The skin and the lens of the eye of the operator are at greatest risk (Table 2).

Estimates of dose rates after skin contaminations with P-32 vary from 1.8 to 2.0 Gy/h per MBq/cm^2 (11). As the threshold erythema dose is estimated to be 10 Gy for P-32 (12), even small spills of the commercially provided injection solution or extravasations could presumably lead to local skin effects.

Spills

Wash skin thoroughly with water and soap. Several online sources suggest using white vinegar for cleaning of spills on workbenches and other surfaces.

Table 2 Radiation Protection Aspects of Phosphorus-32

Prefer shielding materials, such as glass, plastic, or lucite
Extra shield with 2- to 3-mm lead, if activity $>$ 100 MBq
Avoid direct contact with vials, syringes
Protect skin (use two pairs of gloves) and eyes of the operator (goggles)

RADIOPHARMACEUTICAL ASPECTS

P-32 is provided as a sterile, nonpyrogenic solution for intravenous (IV) injection. Prior to administration, the patient dose should be measured in a suitable dose-calibration system. Specialist physicist advice and/or calibration of ordinary dose calibrators, used for photon-emitting radiopharmaceuticals (as usually present in Nuclear Medicine departments), might be needed to ensure that correct activity readings are obtained for this beta emitter.

Injection

In view of the aforementioned aspects, it seems reasonable to suggest the following measures during the injection procedure (Tables 2 and 3):

- appropriate shielding of injection barrel (plastic + lead);
- two pairs of gloves;
- goggles for the person injecting the radiopharmaceutical;
- protection of the skin of the patient around the venipuncture site (drape);
- establishment of an IV line (preferably not located in the antecubital fossa, to avoid damage to local important anatomic structures), with a three-way stopcock, checked for proper placement with saline flush.

Proper procedure is important as it is difficult to confirm extravasation of P-32, given that the detection of P-32 outside the body is difficult (beta particles do not penetrate skin, with very little photon production for imaging).

As for any other therapy with radiopharmaceuticals or chemotherapy, the patient should have detailed information about the therapy before receiving it. Written informed consent from the patient must be obtained.

Biodistribution

Following IV administration, the radiopharmaceutical clears rapidly from whole blood and plasma, and is incorporated into the nucleic acids of proliferating cells and into the cortical bone. The agent is incorportated into the hydroxyapatite molecule. The ratio of phosphorus uptake in tumorous bone relative to normal bone is about 2:1. It was, and, in some countries, is still in use for the palliation of painful

Table 3 Administration of Phosphorus-32

Obtain written informed consent
Protection of the skin of the patient around the venipuncture
Place an intravenous line
Check placement with saline flush

Table 4 Instructions to the Patient

Give instructions concerning hygiene in written form
If possible, use a separate toilet; men should urinate sitting down; double flushing of the toilet; proper hand washing
Give advice to follow instructions for at least the first two days

bone metastases. The main effect of the radiopharmaceutical in PV is to suppress hyperproliferative cell lines. The biological half-life of the radiopharmaceutical in bone marrow is seven to nine days, corresponding to a red marrow absorbed dose of 11.0 mGy/MBq.

Patient as a Radioactive Source

External radiation from the patient in terms of beta radiation or bremsstrahlung is negligible (Table 4). As 20%–50% of the injected dose appears in the urine during the first week, contamination with urine presents a hazard. Adequate hygiene must be advised (men should urinate sitting down, double flushing of the toilet, proper hand washing, have other persons in household use other toilet) for at least the first two days after injection.

Pregnancy

According to the European Association of Nuclear Medicine (EANM) Procedure Guideline, pregnancy should be avoided for four months after therapy. The fact that it is unlikely that women of childbearing age will be eligible for P-32 therapy is emphasized.

TREATMENT APPROACHES

Two treatment approaches are used:

- Fixed approach: initially 74–111 MBq (2–3 mCi) per m^2 body surface area is administered with an upper limit of 185 MBq (5 mCi). This may be repeated at three monthly intervals.
- Sliding scale approach: using the sliding scale approach, a fixed dose of 111 MBq (3 mCi) is first administered. In the absence of response, a second treatment may be given after three months with a 25% increment in dose. Treatment may be repeated with continuing dose incrementation until an adequate response is obtained. The upper limit of a single treatment dose is 260 MBq (7 mCi).

FOLLOW-UP

Full blood counts should be monitored at monthly intervals to assess response, or the need for a new therapy if no response is seen by three months (hematocrit remains above 47%, or continued phlebotomy is required).

The majority of patients show a decline in red cell counts by four to six weeks, to a maximum effect at around three months. If the patient does not respond to P-32 (as mentioned earlier), another mode of therapy should be instituted. The remission may last for six months to two years.

Acute side effects are possible: early side effects are leucopenia and thrombocytopenia (9), and may need transfusional support. The increased risk of the development of acute leukemia by treated patients should be taken into consideration during follow-up.

REFERENCES

1. Chievitz O, Hevesy G. Nature 1935; 136:754. In: Brucer M. A Chronology of Nuclear Medicine. St. Louis: Heritage Publications, 1990:222.
2. Brucer M. A Chronology of Nuclear Medicine. St. Louis: Heritage Publications, 1990:222.
3. Hevesy G, et al. Kgl Danske V Selsk 1937; 13:9. In: Brucer M. A Chronology of Nuclear Medicine. St. Louis: Heritage Publications, 1990:222.
4. Lawrence JH, et al. Radium 1940; 35:51. In: Brucer M. A Chronology of Nuclear Medicine. St. Louis: Heritage Publications, 1990:226.
5. Erf L, et al. Ann Int Med 1941; 15:487. In: Brucer M. A Chronology of Nuclear Medicine. St. Louis: Heritage Publications, 1990:258.
6. Tefferi A. Polycythemia vera: a comprehensive review and clinical recommendations. Mayo Clin Proc 2003; 78:174–194.
7. Spivak JL. Polycythemia vera: myths, mechanisms, and management. Blood 2002; 100(13):4272–4290.
8. Tefferi A, Solberg LA Jr, Silverstein MN. A clinical update in polycythemia vera and essential thrombocythemia. Am J Med 2000; 109:141–149.
9. EANM Procedure Guidelines for ^{32}P therapy. Eur J Nucl Med 2003; 30:BP17–BP19.
10. Cember H. Section on Bremsstrahlung in Chapter 5: Interaction of radiation with matter. In: Cember, H. Introduction to Health Physics. 3rd ed. New York: McGraw-Hill, 1996:129–131.
11. Batchelor S. Section 15.6.3 Special techniques for specific radionuclides: Phophorus-32. In: Martin CJ, Sutton DG, eds. Practical Radiation Protection in Health Care. New York: Oxford University Press, 2002:253.
12. Castronovo FP Jr, McKusick KA, Strauss HW. The infiltrated radiopharmaceutical injection: Dosimetric considerations. Eur J Nucl Med 1988; 14:93–97.

10

Iodine-131 Radiotherapy for Benign Thyroid Disease

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INTRODUCTION

Radiotherapy with radioactive iodine-131 (RAI) has been used to treat benign thyroid diseases for over 50 years (1). Diseases of thyroid hyperfunction that can be treated with RAI include Graves' disease (GD), solitary hyperfunctioning nodule, and toxic multinodular goiter. RAI may also benefit patients with subclinical hyperthyroidism, particularly patients at risk for cardiac or systemic complications. RAI is used less frequently for the treatment of euthyroid goiters. The information in this chapter pertains only to the use of RAI in doses that are typical for the treatment of benign thyroid disease. Information regarding the use of RAI for malignant thyroid disease is available in Chapter 5.

The preferred method for treating hyperthyroidism varies in different countries. In a survey of American Thyroid Association (ATA), European Thyroid Association (ETA), and Japanese Thyroid Association (JTA) members,

69%, 22%, and 11% of respondents, respectively, chose RAI as the therapy of choice for an index patient with GD (2). In the same survey, antithyroid drugs were regarded as initial therapy in 30.5%, 77%, and 88% of ATA, ETA, and JTA respondents, respectively. Such variation likely stem from differences in perceived risks of prescribing radioactive treatments, differences in cost, local requirements for hospitalization during treatment, patient compliance, response to antithyroid medications, and natural history of autoimmune thyroid disease in different populations. Differences in dietary iodine content may also significantly affect treatment response in various populations (3).

Most jurisdictions have specific regulations for possession and use of iodine-131 and other radionuclides. Physicians who use radioisotopes must be knowledgeable and in compliance with all applicable laws. Therapeutic decisions should always be made with consideration for the population from which the patient originates and to local standards of practice.

BIOLOGICAL BASIS OF IODINE ACCUMULATION IN THYROID TISSUE

The sodium iodide symporter (NIS) is responsible for the specificity of RAI for thyroid tissue. This transmembrane protein transports iodide against an electrochemical gradient via a sodium-dependent active transport mechanism by which two sodium ions are transported along with one iodide ion (4). Synthesis of this protein is regulated by activation at the thyrotropin receptor (5). Following the characterization of the NIS gene in 1996, much research has been directed toward understanding the role of the NIS in autoimmune and malignant thyroid disease.

The NIS protein is most abundantly expressed in thyroid tissue, although it is also present in glandular and mucosal tissue, choroid plexus, ciliary body of the eye, and placenta. Normal NIS protein expression is limited to the basolateral membrane in a small percentage of thyroid follicular cells at any one time (6). However, in autoimmune thyroid disease, thyrotropin receptor-mediated activation by stimulating auto-antibodies increases the NIS protein expression to the point that it is expressed on both basolateral and apical surfaces in the majority of thyroid follicular cells. Synthetic mechanisms responsible for iodine organification and incorporation into colloid matrix are also increased, leading to enhanced thyroid hormone turnover, resulting in the manifestations of hyperthyroidism.

Radiotherapy of thyroid disease using iodine-131 relies on the emission of high-energy beta particles to cause damage to thyroid gland tissue. Iodine-131 has a physical half-life of 8.1 days, a principal gamma-ray energy of 364 keV, and beta-particle emission with an average energy of 0.192 MeV. With a tissue range of 0.8 mm, beta-particle emission is responsible for the majority of local therapeutic effect. The ensuing inflammation caused by radiation is followed by fibrosis, resulting in the reduction of the synthetic capacity of the thyroid gland. For this type of therapy to be effective, thyroid tissues must accumulate and retain iodine-131 long enough for adequate amounts of radiation to be

delivered. With increased iodine turnover in hyperthyroid disease states, such as GD, the effective biological half-life is shortened to an estimated four to six days. It is important to keep in mind that although hyperthyroidism related to GD may be eliminated by RAI, the underlying autoimmune disease may persist indefinitely, and that continued follow-up is necessary to monitor associated autoimmune syndromes, such as ophthalmopathy.

CONTRAINDICATIONS TO RADIOACTIVE IODINE THERAPY

A patient who is pregnant should not be treated with RAI (7). RAI crosses freely into the placenta, and the fetal thyroid tissue is capable of accumulating iodine after the 12th week of gestation. Administration of RAI during this period may result in severe neonatal hypothyroidism. Fetal and neonatal thyroid irradiation may also increase the risk of developing thyroid cancer later. Retained activity in the maternal bladder may also increase the risk of malignancy by direct radiation exposure to the fetus.

Women who are actively lactating or nursing also should not receive RAI. Iodine is excreted in breast milk. NIS protein expression is also increased significantly in mammary tissue during lactation, thus increasing the radiation exposure to the breast. Nursing should not be resumed until the birth of the next child.

RAI has no role for the treatment of hyperthyroid conditions that are self-limited or when thyroid tissue is not hyperfunctioning. These conditions include silent, subacute, and postpartum thyroiditis in addition to factitious thyroid disease.

PRETREATMENT STUDIES

Thyroid function tests should confirm results that are consistent with the disease to be treated. Women of childbearing age should have documentation that they are not pregnant at the time of treatment. Routine pregnancy testing should be offered prior to RAI therapy (7).

Traditionally, RAI uptake measurements have been used to determine the amount of radioactivity to administer for treatment. However, this amount may also be empirically determined. Regardless of the method for dose selection, routine thyroid uptake measurements are useful for confirming increased thyroid gland function prior to treatment. This helps avoid inappropriate treatment of hyperthyroid conditions not associated with increased thyroid function, such as silent thyroiditis or factitious hyperthyroidism. RAI uptake measurements can also help exclude a hyperfunctioning gland with "blocked" uptake. This condition, which will significantly reduce the effectiveness of RAI treatment, may follow exogenous iodine exposure, such as from intravenous contrast agents. Other substances which may contain large amounts of iodine include expectorants, kelp, agar, carageenan, Lugol's solution, potassium iodide solutions, and drugs, such as amiodarone. RAI uptake measurements should be performed following the withdrawal of such interfering materials in the same manner as done for treatment.

Typically, thyroid gland uptake measurements are acquired at four to six hours and 24 hours following the ingestion of a test capsule of 0.15–0.37 MBq (4–10 μCi) of iodine-131. Alternatively, 3.7–7.4 MBq (100–200 μCi) of iodine-123 may be used. An estimate of the 24-hour iodine-131 uptake measurement may be also be derived from the early measurement, allowing for testing and treatment to be completed in one day (8).

Scanning is useful for the confirmation of hyperfunctioning nodules and the exclusion of cold nodules which need to be further evaluated. Although it is debatable whether a thyroid scan adds information that would alter the management of GD, scanning does provide confirmation of the diagnosis of GD while excluding the rare possibility of incidental thyroid cancer, which may manifest as a hypofunctioning nodule. Such nodules should be evaluated for possible malignancy prior to treatment with RAI.

DOSE FOR GRAVES' DISEASE

The amount of RAI to be administered for treating hyperthyroidism related to GD may be selected empirically or determined by a dose calculation based on the assessments of thyroid mass and function (Table 1). Standard treatment usually involves a single administration of RAI. The administration of small amounts of activity (e.g., 2 mCi) at frequent intervals is not recommended, because it allows patients to remain hyperthyroid for longer periods of time, and has not been proven superior at preventing iatrogenic hypothyroidism.

To deliver a specific dose to the thyroid, it is necessary to know the gland size, maximal uptake, and effective half-life of iodine in the targeted thyroid tissue. It may be assumed that the effective biological half-life of RAI is four to six days in the majority of patients with GD. For dosimetry calculation,

Table 1 Calculation of Administered Activities for Treatment of Benign Thyroid Diseases

Use the following equation to correct for 24-hour RAI uptake in target thyroid tissue:
Administered activity = Thyroid tissue mass (g) × Activity per g tissue/RAI uptake at 24 hours
with RAI uptake expressed as a fraction of 100% uptake. (e.g., 30% uptake is 0.30)
Typical activities per gram for various hyperthyroid diseases:
Graves' disease: 2.96–7.4 Mbq
Graves' disease with "rapid turnover": 5.55–7.4 MBq
Solitary hyperfunctioning nodule: 7.4 MBq
Toxic multinodular goiter: 3.7–7.4 MBq
Euthyroid goiter: 3.7–4.625 MBq

Retreatments may require larger amounts of administered activity.
Abbreviation: RAI, radioactive iodine.

most physicians use a formula prescribing an activity per estimated gram of thyroid, corrected for the 24-hour uptake. A simple, commonly used formula for treating GD prescribes 2.96–7.4 MBq (80–200 μCi) per estimated mass of thyroid tissue in grams (9):

$$\text{Administered activity} = \text{Thyroid tissue mass (g)} \times \text{Activity per g tissue/RAI uptake at 24 hours}$$

with RAI uptake expressed as a fraction of 100% uptake. (e.g., 30% uptake is 0.30)

Although it may be possible to estimate thyroid mass by palpation, it is difficult to estimate the degree of thyroid hyperfunction (i.e., thyroid uptake) on the basis of clinical findings alone. Thus, most methods for calculating administered activity will require thyroid RAI uptake measurements, typically at 24 hours. A more complicated, but potentially efficacious approach has been the use of late RAI uptake measurements to allow the estimation of physiologic half-life of RAI (10).

Most recommended administered activities range between 3.7 and 7.4 MBq (100–200 μCi) per gram, corrected for percentage thyroid uptake. Administration of 2.96–4.44 MBq (80–120 μCi) per gram will generally deliver doses of 50–100 Gy to the thyroid (9). Lower doses may reduce the incidence of hypothyroidism following treatment, but will increase the likelihood that a second treatment will be needed. Administration of 5.5 MBq (150 μCi) per gram will yield a dose of approximately 120 Gy to the thyroid. Larger doses can increase the likelihood of developing hypothyroidism in the post-treatment period, but should reduce morbidity related to prolonged hyperthyroidism. If a high success rate is the primary goal, doses between 200 and 300 Gy may be used.

Occasionally, patients with GD may demonstrate RAI uptake more at four to six hours than at 24 hours. This condition of "rapid turnover" may necessitate the administration of larger amounts of radioactivity (5.5–7.4 MBq/g), owing to the shorter physiologic half-life of iodine in this situation. Larger amounts of radioactivity may also be reasonable in patients with relatively low iodine uptake (9).

Patients with persistent hyperthyroidism following a first treatment with RAI may benefit from additional treatments. Higher doses are often used for retreatments, which are typically given three to six months after the initial treatment. Previous RAI treatment failure does not lessen the chance of a successful retreatment (11).

Although treatments based on dose calculations appear efficacious, they have not proven superior to the use of empirically selected administered activities. The advantages of using a fixed administered activity for treating hyperthyroidism are its simplicity and successful outcome in an acceptable number of patients. The effectiveness of such an approach appears comparable to a dose calculation method. In one prospective trial, patients with GD, hyperfunctioning solitary nodules and multinodular goiters, were randomized to receive a fixed radioiodine dose (5, 10, or 15 mCi, based on palpable gland size), versus a

calculated dose based on thyroid gland size and 24-hour radioiodine uptake (12). Comparable rates of euthyroidism, hypothyroidism, and persistent hyperthyroidism were seen in both groups. There were also comparable reductions in gland size. A number of other studies have also supported the equivalence of using several fixed administered activities versus a calculated activity for the treatment of GD or toxic multinodular goiter (13,14).

If a fixed amount of activity is chosen, it is still important to keep in mind that the effectiveness of therapy remains dependent on the total radiation dose to the target tissue. In a randomized trial comparing the administration of a standard activity (15 mCi) to an administered activity, calculated to give a target dose of 100 Gy, it was shown that the success rate of the treatment in either arm was dependent on both the thyroid volume and target dose (15). If the estimated dose to the thyroid exceeded 200 Gy in patients receiving a standardized treatment with 15 mCi, a success rate of 80% was obtained.

DOSE FOR TOXIC NODULAR GOITER

In addition to GD, thyrotoxicosis can also result from a single hyperfunctioning nodule, or multiple hyperfunctioning nodules (i.e., toxic multinodular goiter). Although antithyroid drugs can ameliorate hyperthyroidism, definitive treatment is more commonly accomplished with RAI or surgery. Less commonly, percutaneous ethanol injection has also been used for large solitary nodules (16,17). Compared with treatment with RAI, hypothyroidism is a more common sequel of surgery (18). The choice of surgery versus radiation for nodular goiters is beyond the scope of this chapter, although surgery should be considered strongly in patients with goiters causing significant airway obstruction or an increased risk of harboring thyroid cancer. Treatment decisions for these patients should be made in consultation with a surgeon with expertise in thyroid surgery.

Most patients with toxic nodular goiters will remain hyperthyroid until definitively treated. Occasionally, central necrosis may occur in a single hyperfunctioning nodule with spontaneous resolution of hyperthyroidism, although this should not be anticipated in lieu of more definitive treatment. An initial course of antithyroid drugs may be considered in order to render the patient euthyroid before surgical or radioiodine treatment.

Nodular goiters are believed to be more radio resistant than the diffuse goiter of GD. Large doses, between 150 and 300 Gy, have frequently been used for toxic adenomas (19). A calculated administered activity of 7.4 MBq (200 μCi) per gram to the nodule, corrected for 24-hour uptake, has been used successfully. Standardized administered activities at appropriate doses (e.g., 740–1110 MBq) may also prove effective. With administered activities of less than 370 MBq (10 milliCuries), treatment failures are common (20).

Radiation exposure to normal thyroid tissue in the setting of solitary toxic nodules has never been shown to increase the incidence of thyroid cancer. This is likely because uptake in the normal thyroid tissue is suppressed. Nevertheless,

suppressed thyroid tissue may still receive a dose as high as 23 Gy (19). However, hypothyroidism following RAI treatment does seem to occur less frequently for solitary hyperfunctioning nodules compared with GD or multinodular goiter. In order to minimize the risk of hypothyroidism following treatment, a suppressed thyroid-stimulating hormone (TSH) level should be present, and a thyroid scan should be performed to exclude significant extranodular uptake (21). A reduction in the nodule size can be expected following RAI treatment (22).

For toxic multinodular goiters, doses of 150 Gy may be adequate to resolve hyperthyroidism. Administered activities between 3.7 and 7.4 MBq (100–200 μCi) per gram have been shown to be effective (18). Fixed administered activities (e.g., 1110 MBq) have also been used. Not uncommonly, patients with toxic multinodular goiters may have large glands and 24-hour RAI uptake measurements that are not significantly elevated. This may necessitate the administration of relatively large amounts of radioactivity. In the United States, higher administered activities may be used for nonhospitalized patients, if it can be documented that radiation exposure to the public is not likely to exceed 5 mSv (0.5 rem) (23).

EUTHYROID MULTINODULAR GOITERS

Although surgery may be the first-line treatment of significantly enlarged euthyroid multinodular goiters, RAI has also been used. In the setting of nonhyperfunctional thyroid tissue, there are greater concerns that nonablative therapy with RAI would predispose residual thyroid tissue to develop thyroid cancer. The actual risk of cancer from RAI, used to treat euthyroid goiters, is not known. RAI may be more preferable in patients older than 65 years, in whom contraindications to surgery are more common, and the risk of developing fatal and nonfatal cancer from RAI may be negligible (24).

Doses of 3.7 to 4.625 MBq (100–125 μCi) per gram of estimated thyroid tissue have been used for the treatment of euthyroid goiters. More than 90% of patients can be expected to demonstrate a decrease in goiter size with an average reduction of 40% at one year (25). Tracheal compression may also improve significantly, both symptomatically and radiographically (26). However, caution should be exercised in patients with significant or impending compression, as RAI may conceivably cause transient swelling owing to inflammation, potentially threatening airway patency. A small percentage of patients may have transient hyperthyroidism, and approximately 4% of patients may develop autoimmune thyroid disease following the treatment of euthyroid goiter with RAI (27). The latter may be attributed to the release of thyroid antigens following radiation-induced tissue necrosis. A significant number of patients may also become hypothyroid following treatment. In one randomized trial, comparing RAI to levothyroxine suppression for the treatment of nontoxic goiter, RAI was more effective than levothyroxine suppression for reducing the size of nontoxic goiter; however, 44% of RAI-treated patients subsequently became

hypothyroid (28). In contrast, 35% of the levothyroxine-treated patients experienced clinical hyperthyroidism. Given the differing risks and benefits of the various treatments, these options should be discussed with patients in consultation with clinicians experienced in the management of sporadic goiters.

CAPSULE VERSUS LIQUID

Radioiodine is available in a liquid solution or capsule. Capsules are more convenient, but have generally been more expensive. Liquid formulations may require extra measures to minimize radiation contamination at the time of administration. RAI in capsules and liquid are generally believed to be equivalent in efficacy, although there has been some concern regarding a reduction in RAI bioavailability from capsules, because of incomplete dissolution related to the amount of magnesium stearate in the capsule (29).

GOALS AND EXPECTED OUTCOMES OF TREATMENT

With adequate doses of radioactivity, an 80% response rate should be expected. A primary goal of treatment is to resolve hyperthyroidism in as short a time as possible. However, with RAI doses calculated to achieve this goal in the majority of patients, a significant number of patients will ultimately become hypothyroid. The incidence of hypothyroidism was first estimated at 20% to 40% of patients one year after RAI therapy (30). With more conservative doses of RAI, the incidence of hypothyroidism may be lower, although, often at the expense of higher rates of persistent hyperthyroidism. Patient preferences, the availability of close follow-up, and potential risks from persistent hyperthyroidism should be considered when deciding between more definitive treatment with higher doses and the use of more conservative doses.

Some authorities have maintained that hypothyroidism, which is easily and inexpensively treated with thyroid hormone supplementation, is preferable to persistent hyperthyroidism, which, if not optimally treated, may produce significant morbidity. It is also commonly believed that hypothyroidism may be a frequent long-term consequence of autoimmune thyroid disease. This has led to the recommendation for higher treatment doses to reduce the need for additional treatments in patients who do not respond to initial treatments. If hypothyroidism is regarded as a potential therapeutic endpoint, patients should be given the understanding that they will likely require life-long thyroid hormone supplementation to maintain normal function in the future.

Hypothyroidism tends to occur more frequently in patients with small thyroid glands and lower 24-hour uptake measurements (31). Other independent predictors of hypothyroidism following RAI treatment include a diagnosis of GD, the level of thyroid autoantibodies, no antithyroid treatment given prior to RAI, nonpalpable goiter, and high RAI dose. In one series, the absence of

these risk factors was associated with a 12% probability of developing hypothyroidism, whereas with all factors, the probability increases to 96% (32). Hypothyroidism may occur several years following RAI treatment, and may be more likely in patients who have had multiple RAI treatments (33). Regardless of whether the goal is to achieve euthyroidism or acceptable rates of hypothyroidism, all patients who have been treated with RAI should receive longitudinal clinical follow-up along with thyroid function studies. Patients with autoimmune thyroid disease should also be monitored for complications, such as Graves' opthalmopathy.

In addition to abolishing hyperthyroidism, treatment with radioiodine should significantly reduce thyroid gland size in patients with GD. A 50% to 80% reduction in gland volume may be seen in proportion to the radiation dose given (34).

PATIENT PREPARATION AND ADJUNCTS TO TREATMENT

Clinical exacerbations of hyperthyroidism caused by RAI treatment are relatively uncommon. Pretreatment with antithyroid drugs have been shown to attenuate transient increases in thyroid hormone levels following treatment (35). They may also lower the baseline hormone levels, reducing the clinical significance of any transient increase in these levels (36). Beta blockers may reduce symptoms related to hyperthyroidism, although it should not be solely relied upon to prevent impending thyroid storm. To reduce symptoms which may occur during treatment, beta-blocker medications, such as propranolol, 80–160 mg/day, or atenolol, 50–150 mg/day, can be considered in patients without significant contraindications to this class of medication. Beta blockers may be continued during RAI treatment.

To reduce morbidity from hyperthyroidism and prevent worsening of symptoms before the effects of radioiodine are realized, patients may also be given antithyroid medications several days before or after RAI treatment. If given, such medications should be discontinued three to five days prior to RAI administration. These drugs generally can be resumed 3 to 10 days following treatment, or earlier, if clinically necessary (Table 2).

Pretreatment with propylthiouracil (PTU), with discontinuation up to one week prior to treatment, may increase the failure rate of radioiodine treatment (37). PTU interferes not only with iodine organification, but also may cause an iodide diuresis (38). For this reason, some have advocated higher doses (e.g., increase by 25%) for patients receiving antithyroid medications shortly before or after RAI treatment (39). Compared with PTU, pretreatment with methimazole may have a lesser effect on the failure rate of RAI treatment (40). Several prospective studies, where patients were randomized to no pretreatment with antithyroid drugs versus pretreatment with methimazole up to four to six days prior to RAI administration, found no significant differences in the success rate or the time to therapeutic response (41,42). The adverse effect of antithyroid

Table 2 Preparing Hyperthyroid Patients for Radioactive Iodine Treatment

Withdraw drugs which may interfere with RAI treatment: antithyroid medications for at least three days, multivitamins for one week, over-the-counter medications (expectorants, topical iodine, kelp, agar, potassium iodide solutions) for 2–3 weeks or longer depending on the iodine content, radiographic contrast agents for 4 weeks, and amiodarone for at least three to six months.
Review results from previous biochemical tests, RAI uptake measurements, and thyroid scintiscans. Confirm the appropriateness of treatment and treatment dose.
Obtain written informed consent. Provide verbal and written instructions.
Consider pretreatment with beta blockers for symptomatic control. Beta blockers may be continued during treatment.
Patients who have the potential to become pregnant should undergo pregnancy testing. If history indicates pregnancy is impossible, testing may be omitted at physician's discretion.
Breastfeeding patients should be instructed to stop for at least two days prior to treatment. Patients must be instructed not to resume breastfeeding until the birth of their next child.
Patient identity must be confirmed immediately before treatment in accordance with institutional requirements.

Abbreviation: RAI, radioactive iodine.

medications on RAI treatment efficacy may be more significant for toxic nodular goiters than for GD (43).

Patients should not eat solid foods or drink dairy products for at least two hours before and after treatment. Water is advised, however, to reduce radiation exposure to the genitourinary tract. Multivitamins should be discontinued seven days prior to treatment. Low iodine diets for about one week prior to RAI treatment have also been advocated, although this has not been convincingly shown to improve response when RAI is used for the treatment of hyperthyroidism. Written informed consent should be obtained at the time of treatment. Informed consent should include a review of the disease, the rationale for treatment, treatment alternatives, potential side effects and outcomes, and the need for follow-up, in addition to radiation precautions, which should be provided both verbally and in written form. Patients with GD should be counseled regarding the risks of ophthalmopathy. The prescribed activity should be verified in a dose calibrator and the patient's identity should be confirmed immediately prior to treatment.

SIDE EFFECTS

Side effects of RAI given at doses to treat benign thyroid disease are generally mild, infrequent, and self-limiting. These include thyroid tenderness, salivary gland swelling, and nausea. In addition to permanent hypothyroidism, transient

hypothyroidism may also occur (44,45). Transient hypoparathyroidism has also been reported (46). Thyroid tenderness and swelling may respond to nonsteroidal anti-inflammatory agents. Exacerbation of hyperthyroidism may also occur, but thyroid storm, although potentially fatal, is considered uncommon (47). Severe side effects appear more likely in patients with large goiters, who may also be at risk of tracheal compression on very rare occasions (48). Vocal cord paresis has also been reported as an extremely rare complication of RAI therapy (49).

Ophthalmopathy

Ophthalmopathy may be particularly severe in 3% to 5% of patients with GD. The ocular manifestations of GD appear more frequently in women than men. Although it usually presents concomitantly with hyperthyroidism, it may precede or follow clinical hyperthyroidism (50). An area of controversy is whether treatment with radioiodine is associated with the onset or worsening of Graves' ophthalmopathy. Exacerbation of ophthalmopathy has been attributed to radioiodine-induced release of antigens shared by the thyroid and orbit. Conflicting results from studies of ophthalmopathy and RAI may be attributed to the retrospective and nonrandomized nature of most studies, inadequate control groups, and the nonstandardized assessment of ocular changes. Progression of ophthalmopathy may occur in approximately 15% of patients, especially those who smoke, have pre-existing eye disease, high levels of TSH-receptor antibody, or severe manifestations of thyroid disease (51). Cigarette smoking has been associated with an increased risk for progression of ophthalmopathy following radioiodine therapy, and a decreased efficacy of orbital radiation and glucocorticoid therapy (52).

Concomitant treatment with glucocorticoids can protect against the progression of opthalmopathy in patients with nonsevere ophthalmopathy (53,54). As worsening of pre-existing eye disease is more frequent than new ophthalmopathy following RAI treatment, patients most likely to benefit from corticosteroids are those with clinically evident eye disease, especially if they continue smoking. Prednisone, 0.4–0.5 mg/kg per day, beginning immediately after radioiodine treatment, continued for one month, and then tapered over three months, has been shown to be effective in a randomized controlled trial (53). As both hyperthyroidism and corticosteroids may increase bone turnover, patients receiving long-term corticosteroids should be considered for evaluation of bone density and therapies to prevent osteoporosis. Pretreatment with methimazole does not appear to prevent the development or exacerbation of ophthalmopathy after RAI treatment (55). Patients with more severe ophthalmopathy should receive prompt evaluation and treatment independent of RAI. Treatment for significant ocular disease includes high-dose glucocorticoids, orbital radiotherapy, orbital decompression, or a combination thereof. Patients with Graves' ophthalmopathy should be strongly encouraged not to smoke.

Cancer Risk from Radioactive Iodine Therapy

The possibility of an increased risk of cancer following radioiodine therapy for hyperthyroidism remains controversial despite numerous studies supporting the safety of RAI for this indication. A multicenter retrospective cohort study examined cancer mortality in over 35,000 patients after three treatment modalities for hyperthyroidism (56). The total number of cancer deaths was not increased for this group as a whole. Interestingly, an increased risk of cancer mortality was seen in patients treated exclusively with antithyroid drugs. Radioiodine treatment was not associated with excess total cancer deaths, or to any particular cancer, with the exception of thyroid cancer, where there was a slight increase in thyroid cancer mortality following radioiodine therapy, although the underlying thyroid disease was suggested to have played a role. Another study found that the incidence of thyroid cancer in radioiodine-treated patients over a 27-year period was not significantly different from its incidence in the general population (57). One population-based study actually found a small decrease in the risk of several types of cancer following radioiodine therapy (58). It is important to note that the number of children treated with RAI is small in the majority of these studies.

Genetic Effects to Offspring

There is no evidence that exposure to radioiodine affects the long-term outcomes of subsequent pregnancies and offspring (59). A 370-MBq (10 mCi) dose of iodine-131 is estimated to deliver a dose of approximately 0.01–0.03 Gy to the ovaries, mostly from excreted RAI in the bladder. Radiation dose can be minimized with hydration and frequent voiding following treatment. Women of childbearing age should be counseled to refrain from becoming pregnant for at least six months following therapy. This is primarily to confirm treatment response, given that there are significant perinatal risks related to thyrotoxicosis.

TREATMENT OF CHILDREN WITH HYPERTHYROIDISM

Graves' disease is the most common cause of hyperthyroidism in childhood. As in adults, there are a number of options regarding the treatment of hyperthyroidism in children. The three most common treatment options are medical therapy with antithyroid drugs, treatment with RAI, and surgery.

Medical therapy with antithyroid drugs carries a small risk of serious adverse reactions, which include hepatic failure and agranulocytosis. Upon discontinuation of antithyroid drugs, relapse can be expected in the majority of pediatric patients (60). With medical therapy, prepubertal children may require many more years of treatment compared with adolescents before antithyroid drugs can be discontinued (61). Surgery for hyperthyroidism may have the highest cure rates of all the treatment modalities. Patients with large glands (>80 g), severe ophthalmopathy, and poor response to other treatments may benefit most from surgery. Surgery may also be preferred for single toxic adenomas to avoid

exposure of nonablated thyroid tissue to radiation. However, thyroidectomy carries a small risk of hypoparathyroidism and recurrent laryngeal nerve damage. The success of surgery depends on the experience of the surgeon.

Although RAI is effective, the potential risks related to radiation exposure need to be carefully discussed with the parents or guardians of pediatric patients. Common concerns that may need to be addressed include genetic and oncogenic effects of administering radioactivity, and the potential for radiation exposure to others by young patients in whom proper hygiene may be difficult to maintain.

With external radiation exposure, there is a known risk of thyroid cancer in children that may decrease with increasing age at exposure (62). Studies of radiation exposure related to fallout from nuclear weapon testing in the Marshall Islands and the Chernobyl disaster have also shown higher rates of thyroid cancer in children (63). However, less is known regarding the risk of thyroid cancer following the medical use of RAI in children, and a comprehensive study of thyroid and nonthyroid cancer risks in this setting has not been performed. At prescribed activities of 3.7–7.4 MBq (100–200 μCi) per gram of thyroid tissue, one study did not detect an increased incidence of thyroid cancer in children (64). However, definitive long-term data on the oncogenic effects of therapeutic doses of RAI in children is lacking.

Because of radiation concerns, RAI therapy is often considered as second-line therapy in children. RAI remains efficacious in treating patients who have not responded to other therapies. Second-line indications include failure of antithyroid drug therapy, adverse reactions to antithyroid drugs, contraindications or refusal of surgery, and permanent prevention of hyperthyroidism.

Because of the theoretical risk of thyroid cancer after thyroid irradiation in individuals less than 20 years of age, one approach has been to advocate RAI doses sufficient enough to ablate all residual thyroid tissue (65). Such doses also reduce the need for retreatment, thus decreasing the morbidity related to prolonged hyperthyroidism. To achieve ablation in the majority of children with GD, thyroid tissue dose of at least >270 Gy (i.e., 11.1 Mbq/g) may be needed, especially when the gland is large (66). Radiation safety precautions need to be carefully explained to both patients and family members to prevent contamination and unnecessary radiation exposure to others. RAI treatment may not be appropriate in patients who are unable to comply with instructions.

PATIENT INSTRUCTIONS, PRECAUTIONS, AND FOLLOW-UP

Following the administration of therapeutic doses of RAI, contamination from excretion of RAI in urine, perspiration, breastmilk, and saliva, can be associated with internal accumulation of RAI by others who come in contact with the patient. Potential avenues of radiation exposure to others include ingestion of iodine-131 excreted by the patient, and from emitted gamma rays from iodine-131 (Table 3). Although there is little evidence to suggest that small amounts of radiation from iodine-131 treated patients can cause significant problems to

Table 3 Instructions for Patients Receiving Radioactive Iodine Treatment and Follow-Up

Before treatment:
If there is a possibility that you are pregnant, inform the physician. RAI treatment should not be given to pregnant women.
If you are breastfeeding, you must stop for several days before treatment. After treatment, you cannot restart breastfeeding for that child. You may breastfeed with the birth of your next child.
Do not eat for two hours before or after receiving treatment
For the first 72 hours after treatment:
Drink plenty of fluids to help flush any extra radioactive iodine from your body.
Do not spend prolonged periods of time closer than 3 feet to any adult, or within the same room as any child.
For 4–7 days after treatment, including the first 72 hours:
Void as often as possible. Flush toilet twice after use.
Wash hands thoroughly and routinely.
Do not share eating utensils or towels. Use separate or disposable eating utensils.
Wash utensils separately or before placing in dishwasher.
Avoid close contact with children and pregnant women (not closer than 2 feet) for long periods of time. Sleep in a separate bed. If you are caring for a child, brief contact is acceptable, but avoid prolonged close contact, such as sitting in your lap.
Avoid kissing and sexual intercourse.
Occasionally, there may be temporary neck or gland soreness. This can be treated with over-the-counter pain relievers like acetominophen.
Follow-up:
Follow-up with your primary physician in four to six weeks and at regular intervals thereafter. Occasionally, a second treatment may be necessary. You may require long-term thyroid hormone supplementation. Eye problems from Graves' disease may also occur or worsen after treatment.
Do not get pregnant for at least six months, and not until your medical condition has resolved. Consult your physician before getting pregnant.

Abbreviation: RAI, radioactive iodine.

others, guidelines have provided simple recommendations to reduce unnecessary radiation exposure, especially to pregnant women, infants, and children. It is a requirement of the United States Nuclear Regulatory Commission to give patients verbal and written instructions prior to treatment with RAI.

The Society of Nuclear Medicine has recommended that patients sleep alone for the first few days after treatment. For the first 72 hours, patients should not spend prolonged periods of time closer than three feet to any adult, or within the same room as any child. An easy to follow guideline is to maintain a distance of one arm's length between treated persons and others. Short periods of contact are acceptable. If caring for an infant, patients should minimize the amount of time spent in close proximity with the infant during this time.

Specifically, infants should not be held for prolonged periods because of proximity to the thyroid or bladder. It is also recommended that time spent with pregnant women and young children be minimized for four to seven days after treatment. Work restrictions should be given to patients who may potentially expose pregnant women or children when performing their occupation.

Fluid intake and frequent voiding should be encouraged for at least the first 24 hours following treatment. Patients should be instructed to wake up at least once the night following treatment to empty their bladder. The toilet should be flushed two or three times. Handwashing should be performed routinely and frequently. If patients perspire heavily, clothing should be washed separately. Because of contamination concerns, it is not recommended to treat women during their menses. Sharing food and eating utensils should be prohibited. Patients should wash their utensils separately or use disposable utensils.

Lactating women who wish to be treated should be instructed to discontinue breastfeeding. Treatment should be withheld until lactation ceases. It may be possible to detect radioactivity in breast milk for several months following treatment. Patients should be instructed not to resume breastfeeding until the birth of another child.

Women capable of childbearing should be asked to avoid pregnancy for at least six months following treatment, in order to confirm resolution of hyperthyroidism in addition to minimizing risks from radiation.

Patients should be told that symptoms would resolve over several weeks, and that they would require close follow-up, as hyperthyroidism may worsen during the intervening time. Symptoms of uncontrolled hyperthyroidism should be described, and patients should be informed to seek medical attention if such symptoms occur. They should also be made aware of the probable need for thyroid hormone supplementation in the future. The risk of persistent hyperthyroidism and myxedema following treatment necessitates close follow-up that includes clinical examination and thyroid function tests. Patients with GD should be made aware that ophthalmopathy may occur or worsen. Patients should follow-up with their physician in four to six weeks. One study suggests that the assessment of treatment response may be most reliable at 12 to 14 weeks after therapy, although it may be possible to identify nonoptimal responders as early as six to eight weeks (68). Instructions for patients are summarized in Table 3. In the United States, the most current regulations for RAI therapy may be obtained from the U.S. Nuclear Regulatory Commission.

REFERENCES

1. Becker DV, Sawin CT. Radioiodine and thyroid disease: the beginning. Semin Nucl Med 1996; 26(3):155–164.
2. Wartofsky L, Glinoer D, Solomon B, et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. Thyroid 1991; 1(2):129–135.
3. Solomon BL, Evaul JE, Burman KD, Wartofsky L. Remission rates with antithyroid drug therapy: continuing influence of iodine intake? Ann Intern Med 1987; 107(4):510–512.
4. Spitzweg C, Heufelder AE, Morris JC. Thyroid iodine transport. Thyroid 2000; 10(4):321–330.
5. Saito T, Endo T, Kawaguchi A, et al. Increased expression of the Na + /I- symporter in cultured human thyroid cells exposed to thyrotropin and in Graves' thyroid tissue. J Clin Endocrinol Metab 1997; 82(10):3331–3336.
6. Jhiang SM, Cho JY, Ryu KY, et al. An immunohistochemical study of Na + / I- symporter in human thyroid tissues and salivary gland tissues. Endocrinology 1998; 139(10):4416–4419.
7. Stoffer SS, Hamburger JI. Inadvertent 131I therapy for hyperthyroidism in the first trimester of pregnancy. J Nucl Med 1976; 17(02):146–149.
8. Hayes AA, Akre CM, Gorman CA. Iodine-131 treatment of Graves' disease using modified early iodine-131 uptake measurements in therapy dose calculations. J Nucl Med 1990; 31(4):519–522.
9. Cooper DS. Treatment of thyrotoxicosis. In: Braverman LE UR, eds. The thyroid: a fundamental and clinical text. 7th ed. Philadelphia: Lippincott, 1996:708–734.
10. Bajnok L, Mezosi E, Nagy E, et al. Calculation of the radioiodine dose for the treatment of Graves' hyperthyroidism: is more than seven-thousand rad target dose necessary? Thyroid 1999; 9(9):865–869.
11. Leslie WD, Peterdy AE, Dupont JO. Radioiodine treatment outcomes in thyroid glands previously irradiated for Graves' hyperthyroidism. J Nucl Med 1998; 39(4):712–716.
12. Jarlov AE, Hegedus L, Kristensen LO, Nygaard B, Hansen JM. Is calculation of the dose in radioiodine therapy of hyperthyroidism worth while? Clin Endocrinol (Oxf) 1995; 43(3):325–329.
13. Kok SW, Smit JW, de Craen AJ, Goslings BM, van Eck-Smit BL, Romijn JA. Clinical outcome after standardized versus dosimetric radioiodine treatment of hyperthyroidism: an equivalence study. Nucl Med Commun 2000; 21(11):1071–1078.

14. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab 2003; 88(3):978–983.
15. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H. Treatment of Graves' hyperthyroidism with radioiodine: results of a prospective randomized study. Thyroid 1997; 7(2):247–251.
16. Del Prete S, Caraglia M, Russo D, et al. Percutaneous ethanol injection efficacy in the treatment of large symptomatic thyroid cystic nodules: ten-year follow-up of a large series. Thyroid 2002; 12(9):815–821.
17. Del Prete S, Russo D, Caraglia M, et al. Percutaneous ethanol injection of autonomous thyroid nodules with a volume larger than 40 ml: three years of follow-up. Clin Radiol 2001; 56(11):895–901.
18. Erickson D, Gharib H, Li H, van Heerden JA. Treatment of patients with toxic multinodular goiter. Thyroid 1998; 8(4):277–282.
19. Gorman CA, Robertson JS. Radiation dose in the selection of 131I or surgical treatment for toxic thyroid adenoma. Ann Intern Med 1978; 89(1):85–90.
20. Estour B, Millot L, Vergely N, et al. Efficacy of low doses of radioiodine in the treatment of autonomous thyroid nodules: importance of dose/area ratio. Thyroid 1997; 7(3):357–361.
21. Huysmans DA, Corstens FH, Kloppenborg PW. Long-term follow-up in toxic solitary autonomous thyroid nodules treated with radioactive iodine. J Nucl Med 1991; 32(1):27–30.
22. Nygaard B, Hegedus L, Nielsen KG, Ulriksen P, Hansen JM. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. Clin Endocrinol (Oxf) 1999; 50(2):197–202.
23. US Nuclear Regulatory Commission N. 1997 criteria for release of individuals administered radioactive materials. Federal Register 1997; 62:4120.
24. Manders JM, Corstens FH. Radioiodine therapy of euthyroid multinodular goitres. Eur J Nucl Med Mol Imaging 2002; 29(suppl 2):S466–S470.
25. Freitas JE. Therapeutic options in the management of toxic and nontoxic nodular goiter. Semin Nucl Med 2000; 30(2):88–97.
26. Huysmans DA, de Haas MM, van den Broek WJ, et al. Magnetic resonance imaging for volume estimation of large multinodular goitres: a comparison with scintigraphy. Br J Radiol 1994; 67(798):519–523.
27. Huysmans AK, Hermus RM, Edelbroek MA, et al. Autoimmune hyperthyroidism occurring late after radioiodine treatment for volume reduction of large multinodular goiters. Thyroid 1997; 7(4):535–539.

28. Wesche MF, Tiel VBMM, Lips P, Smits NJ, Wiersinga WM. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metab 2001; 86(3):998–1005.

29. Yu MD, Huang WS, Cherng CC, Shaw SM. The effect of formulation on reduced radioiodide thyroid uptake. J Nucl Med 2002; 43(1):56–60.

30. Hagen GA, Ouellette RP, Chapman EM. Comparison of high and low dosage levels of 131-I in the treatment of thyrotoxicosis. N Engl J Med 1967; 277(11):559–562.

31. de Bruin TW, Croon CD, de Klerk JM, van Isselt JW. Standardized radioiodine therapy in Graves' disease: the persistent effect of thyroid weight and radioiodine uptake on outcome. J Intern Med 1994; 236(5):507–513.

32. Ahmad AM, Ahmad M, Young ET. Objective estimates of the probability of developing hypothyroidism following radioactive iodine treatment of thyrotoxicosis. Eur J Endocrinol 2002; 146(6):767–775.

33. Holm LE, Lundell G, Israelsson A, Dahlqvist I. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. J Nucl Med 1982; 23(2):103–107.

34. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H. Reduction in thyroid volume after radioiodine therapy of Graves' hyperthyroidism: results of a prospective, randomized, multicentre study. Eur J Clin Invest 1996; 26(1):59–63.

35. Koornstra JJ, Kerstens MN, Hoving J, et al. Clinical and biochemical changes following 131I therapy for hyperthyroidism in patients not pretreated with antithyroid drugs. Neth J Med 1999; 55(5):215–221.

36. Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R. The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after (131)I ablation for Graves' disease. J Clin Endocrinol Metab 2001; 86(7):3016–3021.

37. Hancock LD, Tuttle RM, LeMar H, Bauman J, Patience T. The effect of propylthiouracil on subsequent radioactive iodine therapy in Graves' disease. Clin Endocrinol (Oxf) 1997; 47(4):425–430.

38. Matty AJ, Pye RG. The effect of acute doses of propylthiouracil on the renal excretion of iodide and other electrolytes in the rat. Experientia 1968; 24(12):1213–1214.

39. Crooks J BW, Wayne EJ, MacDonald E. Effect of pretreatment with methylthiouracil on results of 131-I therapy. British Medical Journal 1960; 1:151.

40. Imseis RE, Vanmiddlesworth L, Massie JD, Bush AJ, Vanmiddlesworth NR. Pretreatment with propylthiouracil but not methimazole reduces the

therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab 1998; 83(2):685–687.

41. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab 2001; 86(8):3488–3493.
42. Braga M, Walpert N, Burch HB, Solomon BL, Cooper DS. The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. Thyroid 2002; 12(2):135–139.
43. Korber C, Schneider P, Korber-Hafner N, Hanscheid H, Reiners C. Antithyroid drugs as a factor influencing the outcome of radioiodine therapy in Graves' disease and toxic nodular goitre? Eur J Nucl Med 2001; 28(9):1360–1364.
44. Sawers JS, Toft AD, Irvine WJ, Brown NS, Seth J. Transient hypothyroidism after iodine-131 treatment of thyrotoxicosis. J Clin Endocrinol Metab 1980; 50(2):226–229.
45. Connell JM, Hilditch TE, McCruden DC, Alexander WD. Transient hypothyroidism following radioiodine therapy for thyrotoxicosis. Br J Radiol 1983; 56(665):309–313.
46. Burch WM, Posillico JT. Hypoparathyroidism after I-131 therapy with subsequent return of parathyroid function. J Clin Endocrinol Metab 1983; 57(2):398–401.
47. McDermott MT, Kidd GS, Dodson LE, Jr., Hofeldt FD. Radioiodine-induced thyroid storm. Case report and literature review. Am J Med 1983; 75(2):353–359.
48. Becker DV, Hurley JR. Complications of radioiodine treatment of hyperthyroidism. Semin Nucl Med 1971; 1(4):442–460.
49. Snyder S. Vocal cord paralysis after radioiodine therapy. J Nucl Med 1978; 19(8):975–976.
50. Marcocci C, Bartalena L, Bogazzi F, Panicucci M, Pinchera A. Studies on the occurrence of ophthalmopathy in Graves' disease. Acta Endocrinol (Copenh) 1989; 120(4):473–478.
51. Wiersinga WM, Bartalena L. Epidemiology and prevention of graves' ophthalmopathy. Thyroid 2002; 12(10):855–860.
52. Bartalena L, Marcocci C, Tanda ML, et al. Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Ann Intern Med 1998; 129(8):632–635.
53. Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after

radioiodine therapy for hyperthyroidism. N Engl J Med 1989; 321(20): 1349–1352.

54. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998; 338(2):73–78.
55. Kung AW, Yau CC, Cheng A. The incidence of ophthalmopathy after radioiodine therapy for Graves' disease: prognostic factors and the role of methimazole. J Clin Endocrinol Metab 1994; 79(2):542–546.
56. Bartalena L, Marcocci C, Pinchera A. Treating severe Graves' opthalmopathy. In Balliere's Clinical Endocrinology and Metabolism. London: Harcourt Publishers, Ltd., 1997:521–536.
57. Ron E, Doody MM, Becker DV, et al. Cancer mortality following treatment for adult hyperthyroidism. Cooperative Thyrotoxicosis Therapy Follow-up Study Group. Jama 1998; 280(4):347–355.
58. Angusti T, Codegone A, Pellerito R, Favero A. Thyroid cancer prevalence after radioiodine treatment of hyperthyroidism. J Nucl Med 2000; 41(6): 1006–1009.
59. Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P. Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. Lancet 1999; 353(9170):2111–2115.
60. Schlumberger M, De Vathaire F, Ceccarelli C, et al. Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. J Nucl Med 1996; 37(4):606–612.
61. Dotsch J, Rascher W, Dorr HG. Graves disease in childhood: a review of the options for diagnosis and treatment. Paediatr Drugs 2003; 5(2):95–102.
62. Shulman DI, Muhar I, Jorgensen EV, Diamond FB, Bercu BB, Root AW. Autoimmune hyperthyroidism in prepubertal children and adolescents: comparison of clinical and biochemical features at diagnosis and responses to medical therapy. Thyroid 1997; 7(5):755–760.
63. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995; 141(3):259–277.
64. Robbins J, Schneider AB. Thyroid cancer following exposure to radioactive iodine. Rev Endocr Metab Disord 2000; 1(3):197–203.
65. Dobyns BM, Sheline GE, Workman JB, Tompkins EA, McConahey WM, Becker DV. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy follow-up study. J Clin Endocrinol Metab 1974; 38(6):976–998.

66. Rivkees SA, Sklar C, Freemark M. Clinical review 99: The management of Graves' disease in children, with special emphasis on radioiodine treatment. J Clin Endocrinol Metab 1998; 83:3767–3776.

67. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. Pediatrics 2003; 111(4 Pt 1):745–749.

68. Daae LN, Solheim DM. The early follow-up of 131I-treatment of thyrotoxicosis. Eur J Nucl Med 1980; 5(3):199–203.

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about the book...

One in three of the 30 million Americans who are hospitalized is diagnosed or treated with nuclear medicine techniques. This text provides a succinct overview and detailed set of procedures and considerations for patient therapy with unsealed radioactivity sources. Serving as a complete literature reference for therapy with radiopharmaceuticals currently utilized in practice, this source covers the role of the physician in radionuclide therapy, and essential procedures and protocols required by health care personnel.

A detailed and user-friendly outline of considerations and recommendations for effective patient care, this source contains a series of tables and charts for efficient decision-making in therapy planning and patient treatment...offers contributions from experts seasoned in the utilization of nuclear medicine in clinical practice...supplies comprehensive discussions on the use of radiolabeled antibodies in lymphoma therapy...contains procedures for unusual radiopharmaceutical therapies such as Ra-224...and discusses principles of therapy with unsealed sources.

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