The therapeutic use of radioisotopes in medicine as unsealed sources has a long history dating back to the 1930s. The established and continuing objectives are to provide radiation dose to the target tissue at the desired cytotoxic level while avoiding or minimizing toxic effects. Selected radionuclide therapy protocols including $^{32}$P for polycythemia vera, $^{131}$I for Graves’ disease, and $^{131}$I for postsurgical ablation of thyroid remnants in the management of differentiated thyroid cancer are presented for historical review with the focus on protocols for administering the radiopharmaceuticals and the role played by dosimetry. The discussion also includes consideration of complications and the assessment of outcome for these diseases. The vista for radionuclide therapy today is reviewed along with the options for determining the administered activity. Patient specific dosimetry encompasses a number of levels ranging from basic measurement of relevant biokinetic parameters and use of standard models to calculate (and extrapolate) radiation dose to sophisticated three-dimensional techniques employing fusion of physiologic and high-resolution anatomic images coupled with advanced 3-D voxel patient representation and Monte Carlo techniques for use in radiation dose calculation. The role of patient specific dosimetry in clinical trials (Phase I, II, III trials) along with its utility in treatment planning, follow-up evaluation, and elucidation of dose-response relationships is discussed. The challenge ahead for those who advocate patient specific dosimetry is to assemble the outcome data and perform the analysis to support this contention.

INTRODUCTION

The potential for expanding the horizons of the therapeutic use of radioisotopes as unsealed sources was recognized by the medical profession from the early days following the discovery of methods for creation of artificial radioactivity. Credit is given to Ernest O. Lawrence for construction of the cyclotron (1931) with the subsequent production of radiosodium and to Enrico Fermi for producing radioiodine by neutron bombardment of stable iodine (1934). Initial investigations focused on applications of phosphorus-32 and radioiodine. Iodine-131 took a commanding lead as the agent of choice in the treatment of thyroid disease after it was made readily available through action of the Atomic Energy Commission in 1946. Another radioisotope that appeared early on the scene was strontium-89 that has been used since 1941 for palliation of bone pain from metastatic cancer. An historical overview of the early use of selected radionuclides in therapy is provided in Table 1.

The fundamental objectives for radionuclide therapy remain steadfast, namely: 1.) To achieve appropriate treatment of the disease through delivery of a radiation dose at the desired cytotoxic level with the defined endpoints being cure, disease control (stabilization), or palliation, and 2.) To avoid or minimize toxic effects (spare normal organs), both in the acute time frame and as long term complications. The goal of radionuclide therapy is to maximize the therapeutic index as represented by the ratio of the radiation dose delivered to the tumor to that delivered to normal tissue.

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HISTORICAL REVIEW OF SELECTED RADIONUCLIDE THERAPY PROTOCOLS

The following radionuclide therapy protocols have been selected for historical review and discussion: 1.) \(^{32}\text{P}\) for polycythemia vera (PV), 2.) \(^{131}\text{I}\) for Graves’ disease, and 3.) \(^{131}\text{I}\) for postsurgical ablation of thyroid remnants in the management of differentiated thyroid cancer. The focus will be on options for administering the radiopharmaceuticals and the role played by dosimetry (if any). An additional emphasis will include considerations of negative events and the assessment of outcome.

A. \(^{32}\text{P}\) Orthophosphate in the Treatment of Polycythemia Vera

Polycythemia vera (PV) is a relatively rare disease characterized by an autonomous proliferation of marrow cells and may be treated by repeated phlebotomies, radiophosphorus or chemotherapy. The prognosis is poor if untreated (median survival 1.5 y). Both chemotherapy and \(^{32}\text{P}\) treatment protocols yield better results than phlebotomy alone. With phlebotomy, the average survival is 7.6 years (3.5 to 9.5 y) while with \(^{32}\text{P}\) including phlebotomies when needed, the survival period is extended from 11 to 15 years. Most common causes of death are: cardiovascular diseases including hemorrhage (30–50%), myelofibrosis with myeloid metaplasia (10–20%) and, in the case of \(^{32}\text{P}\) or chemotherapy management, acute myelogenous leukemia (10–20%).

With regard to the biological distribution of radiophosphorus, ionic \(^{32}\text{P}\) as orthophosphate is incorporated into proliferating and protein-synthesizing cells as well as into cortical bone (into hydroxyapatite crystal). The greatest radiation exposure is to bone marrow, liver, spleen, and to a lesser extent, to the gastrointestinal mucosa.

Administration protocols

\(^{32}\text{P}\) orthophosphate therapy regimens proposed and implemented were generally empirical as based on the response of the red blood cell volume (rbcv). Although \(^{32}\text{P}\) orthophosphate therapy for PV is limited today, it is still used in special circumstances (see outcomes section below). The following list summarizes the most common protocols utilized historically:

1.) Repeated small administrations until the desired reduction in rbcv is achieved.
2.) A single large administration based on patient weight.
3.) Administered activity based on an experimentally derived regression coefficient relating the reduction in rbcv to the activity of \(^{32}\text{P}\) administered regardless of weight. This protocol requires the actual and predicted rbcv’s to be known and, in that sense might be considered “patient specific.”
4.) Recommendation of the Polycythemia Vera Study Group (PVSG) 1976: An administered activity of 2–3 mCi (74–111 MBq) per meter squared body surface not to exceed an upper limit of 5 mCi (185 MBq). Alternatively, a fixed 3 mCi (111 MBq) might be given. Blood counts are monitored every 3 to 4 weeks. If no significant response is obtained by 12 weeks, the patient is re-treated with a 25% increase in activity. Augmentation is repeated every 12 weeks until an adequate response is observed; however, an upper limit of 7 mCi

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Disease Type (Specific Disease)</th>
<th>Date of Original Use (or early documentation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{32}\text{P})</td>
<td>Myeloproliferative disease (polycythemia vera)</td>
<td>1936</td>
</tr>
<tr>
<td>(^{32}\text{P})</td>
<td>Lymphoproliferative disease (leukemia)</td>
<td>1938</td>
</tr>
<tr>
<td>(^{32}\text{P})</td>
<td>Bone pain</td>
<td>1937</td>
</tr>
<tr>
<td>(^{89}\text{Sr})</td>
<td>Metastatic cancer to bone</td>
<td>1941</td>
</tr>
<tr>
<td>(^{131}\text{I})</td>
<td>Hyperthyroidism (Graves’ Disease)</td>
<td>1942</td>
</tr>
<tr>
<td>(^{131}\text{I})</td>
<td>Differentiated thyroid carcinoma (remnant ablation; tumor and metastases)</td>
<td>1944</td>
</tr>
</tbody>
</table>
(260 MBq) was specified for any administration.

**Radiation dosimetry**

The issue of radiation dose for intravenous administration of $^{32}$P was addressed in a preliminary manner by a number of investigators over the period 1952 to 1964. Somewhat more sophisticated recalculations were made by Edith Quimby (1968) based on existing data. Definitive work was provided by Spiers in 1976 who used a model that accounted for the relative contributions from the various marrow compartments. The recommendations of the PVSG allowed for a marrow dose of 100 rad from the initial administration of activity. However, the now classic difficulties in providing meaningful radiation dose estimates were clearly recognized:

“The variations in marrow and bone mass, $^{32}$P uptake, and its effective half-life make it impossible to predict the accurate radiation dose in each individual patient. Moreover the radiation sensitivity is another variable in the patient population” (Chaudhuri, 1987).

**Outcomes - complications and long term follow-up**

The primary concern is the induction of acute leukemia. The early analysis by Modan and Lilienfeld concluded that there was a relationship between the increased risk of acute leukemia and the $^{32}$P administered activity. In a study of 431 patients, the PVSG reported the incidence of leukemia to be more frequent after chemotherapy (chlorambucil) than $^{32}$P (11% vs 6%). Others quote the incidence of acute leukemia in PV patients receiving $^{32}$P to be in the 10 to 15% range – significantly more often than in patients not so treated. Additional complications specific to radiophosphorus treatment include vascular problems (bleeding and thromboembolism). The PVSG no longer exists as an operational entity (French and Italian groups have picked up the reigns on selected aspects). However, early on attempts made to find a replacement for $^{32}$P due to concerns over its leukemic risk led to the testing of hydroxyurea (HU) as a putative non-leukemogenic drug for treatment of PV. At the present time, $^{32}$P is used primarily for patients who might be allergic to HU and older patients who would otherwise forget to take the prescribed drug on a scheduled basis. A provocative concluding statement put forth by the PVSG and germane to the thesis of this presentation was: “With respect to the final question, the optimal treatment for polycythemia vera, it is apparent that the expectation of a single optimal therapy that would apply to all patients at all ages and stages of the disease was naïve.”

**B. $^{131}$I in the Treatment of Graves’ Disease**

In brief, in Graves’ disease (GD), the thyroid gland is generally hypertrophied and functions at an accelerated rate. Serum levels of thyroid hormones are increased while serum TSH (thyroid stimulating hormone) is depressed. Thyroid hormone and Tg (thyroglobulin) production are also increased. The metabolism and clearance of iodine is distinctly abnormal. Graves’ disease is 4 to 8 times more prevalent in women than men. The classic symptoms of hyperthyroidism include: weight loss (despite increase in appetite), weakness, dyspnea, palpitations, sweating, heat intolerance, tremor and irritability. Unique features of Graves’ disease include pretibial myxedema and exophthalmos.

**Administration protocols**

The treatment of Graves’ disease with $^{131}$I dates from the early 1940s. The following list summarizes the most common protocols:

1.) Repeated small administrations until a clinical cure was obtained (not widely used): 2 mCi (74 MBq) every 2 weeks.
2.) Fixed administered activity: 3 to 5 mCi (111 to 185 MBq) of $^{131}$I are given orally. Of patients so treated, 60% become euthyroid in 3 to 6 months. Those failing to respond are retreated with a second administration with the data showing that 85% of those patients become euthyroid or hypothyroid. Some practitioners modify the protocol by giving a larger administered activity to patients with larger thyroid glands.
3.) Activity per gram: The administered activity is based on the gland size and the radiiodine uptake and is designed to deliver a fixed activity per gram of thyroid tissue - generally 55 to 200 $\mu$Ci/g (~1.5 to 7 MBq/g).
4.) Radiation dose target levels: The administered activity is determined that will deliver a predetermined radiation dose to the thy-
roid. The classic Quimby-Marinelli formula is used. The effective half-time of $^{131}$I in the gland might be determined through serial measurements. Typical radiation dose target values might be 7000 rad (cGy).

The arguments expressed for or against a particular protocol follow a relatively standard format. The fixed activity procedure is logistically simple and the outcomes demonstrate reasonable success rates. On the other hand, since the administered activity has no relationship to biokinetics, gland size or severity of the disease, it disregards all of the variables that bear directly on the radiation dose delivered. It is also argued that this empirical treatment schedule will not lead toward a better understanding of the dose-response relationships – the latter being a desired objective. On the other side, there are those who argued that the radiation dose target level approach is no more effective than the fixed administration. Nevertheless, it was recognized that the dosimetry methodology provided a consistent framework that allowed standardized comparison of results.

**Radiation dosimetry**

The radiation dose delivered by the empirical fixed activity protocols (1 and 2 above) was not determined explicitly but was estimated to have been in the 3000 to 10,000 rad (cGy) range for typical biokinetics. Dose estimates for the microcurie per gram protocol are of the same magnitude. For the prescribed dose protocol, a common target dose is 7000 rad (cGy). Other investigators prefer higher dose values with 18,000 rad (cGy) delivered from a concentration of 200 $\mu$Ci/g. The traditional formula for dose calculation is:

$$D_{\gamma+\beta} = CT \ (73.8 \ E_{\beta} + 0.0346 \ g \ \Gamma)$$

where: C is the concentration ($\mu$Ci/g), $T$ is the effective half-time (days), $E_{\beta}$ is the average beta energy (MeV), g is a geometrical factor, and $\Gamma$ is the specific gamma ray constant (R/(h.mCi) at 1 cm. Use of this formula represents patient-specific methodology in that uptake and retention in the thyroid must be measured and the mass of the gland known (or estimated). Early on, the five variables recognized as being of importance for quantitative radiation dose calculations were: percentage uptake of the radiopharmaceutical, effective half-time, distribution of the radioisotope within the gland, weight and shape of the thyroid, and radiosensitivity of the thyroid cells. The greatest variable identified was in the estimation of the weight of the gland. This perspective has not changed in today’s era. In general, it has been observed that the probability of being cured of hyperthyroidism increases as the concentration of $^{131}$I in the gland increases over the range 50 to 180 $\mu$Ci/g. The Michigan group achieves a cure rate greater than 90% when the concentration is 200 $\mu$Ci/g. (Personal communication: J. Sisson, June 2001.)

**Outcomes - complications and long term follow-up**

An accepted fact is that, independent of the method of administration, long-term hyperthyroidism will be the outcome for patients treated with $^{131}$I for Graves’ disease. The statistics quoted are that the incidence of hypothyroidism is between 7 to 25% in the first year followed by an annual increment of 2 to 4%. Low administered activities do result in lower incidence of hypothyroidism in the first year as might be expected but the long term outcome for patients so treated still shows a significant probability of hypothyroidism (35 to 40% at 15 years).

The radiation dose to the blood (surrogate for the marrow) for $^{131}$I treatment of Graves’ disease was estimated to be in the range 8 to 16 rad (cGy). Although this figure was not particularly high, the possibility of induction of leukemia was evaluated by the initial Cooperative Thyrotoxicosis Therapy Follow-up Study Group (CTTFSG) and reported in 1968. The analysis of 18,000 patients treated by $^{131}$I compared with 1000 treated by surgery and antithyroid drugs, showed no difference in the rate of leukemia for a follow-up that totaled more than 100,000 patient years. With regard to the induction of thyroid cancer, a study of 16,000 patients treated by $^{131}$I indicated a lower incidence of cancer compared to a control group treated by surgery. A possible explanation is that the destruction of follicular cells effectively reduces or eliminates the capacity of the cells to respond to TSH. In the most recent follow-up (1998), the conclusions of the CTTFSG were: “Neither hyperthyroidism nor $^{131}$I treatment resulted in a significantly increased risk of total cancer mortality. While there was an elevated risk of thyroid cancer mortality following $^{131}$I treatment, in absolute terms the excess number of deaths was small, and the underlying thyroid disease appeared to play a role. Overall, $^{131}$I appears to be a safe therapy for hyperthyroidism.”
Differentiated thyroid carcinomas comprise approximately 80% of all malignant thyroid tumors. Of these, papillary carcinoma is the most common with a prevalence of about 71%. Papillary carcinomas are slow growing and, when confined to the neck and given appropriate treatment and follow-up, the prognosis for patients with this disease is excellent. Follicular carcinoma occurs in 10% to 40% of all thyroid cancers. Distant metastases occur more frequently with this cancer and thus prognosis is worse than for papillary thyroid cancer. Even when surgical total thyroidectomy is attempted, excision of the gland is seldom complete. Sufficient residual thyroid tissue may remain, and hypertrophy to maintain TSH levels within normal limits. The intent of radioactive iodine administration following surgery is to ablate remnant thyroid tissue and thus promote stimulated secretion of TSH to reveal the presence of functioning thyroid metastases, via subsequent tests, if they exist or should they develop.

Administration protocols

In William Blahd’s classic text on Nuclear Medicine, Rawson and Leeper made the colorful comment that “There are nearly as many therapeutic regimens for $^{131}$I in thyroid cancer as there are therapists.” Active debate continues in the field with regard to the most appropriate administration for radioactive iodine ablation therapy. The most common protocols are presented in the following list:

1.) High, fixed administered activity: 75–200 mCi (2.8–7.4 GBq) $^{131}$I. This protocol tends to be followed by most practitioners. Outcome statistics are quoted as achieving 85% success in eliminating all functioning thyroid activity in the thyroid bed.

2.) Low, fixed administered activity: 30 mCi (1.1 GBq) $^{131}$I.

3.) Administered activity calculated according to a predetermined radiation dose. In this protocol, the activity to be administered is determined according to a formula involving the desired radiation dose, remnant mass, effective half-time and 24-hour uptake (with the latter generally determined via uptake probe measurements). This approach may be considered patient specific to the extent that these patient parameters must be known.

4.) Quantitative Diagnostic Work-up. In this protocol, a tracer of $^{131}$I is administered to the patient and quantitative imaging techniques are employed over a period of days to establish patient specific bioenergetics. From this diagnostic data, utilizing appropriate calculation algorithms (typically following the MIRD schema involving residence time and S values), the radiation dose to the remnant is estimated. The radiation dose that would be delivered by a given therapeutic administration of $^{131}$I is extrapolated from the results of this tracer study.

For protocol 1 (high, fixed administered activity), the advantages include: obviating most need for reablitation, fewer laboratory visits and tests, less hospitalization (in the days prior to the revised NRC regulations on patient release), and fewer periods of debilitating hypothyroidism. With regard to the latter, it is noted that the advent of recombinant human TSH may alleviate this traditional disadvantage of TSH withdrawal protocols. The disadvantages lie in the logistics required for higher activities of radioactive iodine, radiation protection considerations, and the increased radiation dose to critical organs with the potential for complications.

With regard to protocol 2 (low, fixed administered activity), the advantages include: avoidance of hospitalization under the previous NRC regulations for patient release and reduced radiation dose to the whole body and critical organs. The chief disadvantage lies in the failure to achieve complete ablation in 17 to 40% of patients. This increases testing, inconvenience and expense. A theoretical but unproven possibility is that micrometastases may receive inadequate radiation. A final consideration is that residual thyroid tissue after low dose treatment may be more radioresistant because of a reduced biological half-time of $^{131}$I.

For protocol 3, the activity to be administered (AA) is calculated according to the formula:

$$\text{AA} = \frac{[\text{desired radiation dose (cGy)} \times \text{gland weight (g)} \times 6.7]}{[\text{effective half-time (d)} \times \%\text{uptake (24h)}]}.$$
remnant mass and 24-hour uptake and retention must be known. An additional decision must be made with regard to the desired radiation dose to be achieved. The original investigators\textsuperscript{30} selected 100,000 rad (cGy) as a conservative value in light of the 50,000 rad (cGy) found previously to ablate normal thyroid tissue with \(^{131}\text{I} \).\textsuperscript{31} More recently, a value of 30,000 rad (cGy) has been considered sufficient.\textsuperscript{32}

Finally, for protocol 4, sequential data acquisition provides patient specific biokinetics\textsuperscript{33,34} that are used in conjunction with now standard calculational models (e.g., the MIRD schema) to estimate the radiation dose to the remnant. Through this protocol, the administered activity may be tailored to provide the desired radiation dose for ablation (e.g., 30,000 rad (cGy)) while minimizing the radiation dose to other organs by not administering more activity than required. The fundamental assumption is that the biokinetics following therapeutic administration will be identical to those observed for the tracer. A complicating factor is the possibility of “stunning” whereby the therapeutic uptake is reduced relative to the prediction as a result of the effect of the tracer activity.\textsuperscript{35} However, another interpretation is that any apparent stunning observed is due to early effects of the therapeutic activity.\textsuperscript{36} Although the degree of stunning and its origin remain a matter of some controversy, a logical protocol would be to utilize the lowest possibly tracer activity while maintaining adequate statistics for quantitative imaging. A tracer activity commonly used is 2 mCi (74 MBq) with values generally found in the range from 1 to 10 mCi (37 to 370 MBq).

**Radiation dosimetry**

Direct consideration of the radiation dose to the remnant represents an integral component of protocols 3 and 4 above. Patient specific data (biokinetic information and remnant mass) are used in conjunction with the target radiation dose to determine the \(^{131}\text{I} \) administered activity (AA). For protocol 3, the activity to be administered (AA) is determined as:

\[
AA = \left[ \text{desired radiation dose (cGy)} \times \text{remnant mass (g)} \times 6.7 \right] / \left[ \text{effective half-time (d)} \times \% \text{uptake (24h)} \right]
\]

For protocol 4, the self-dose to the remnant per administered activity based on a single exponential decay is given as:\textsuperscript{32}

\[
D/A_0 = C_0 1.44 (T_{1/2})_\text{eff} [0.4135 + 0.8041\Phi_\gamma],
\]

where \( C_0 \) (\( \mu \text{Ci/g} \)) is the initial concentration, \((T_{1/2})_\text{eff} \) is the effective half-time in the remnant, and \( \Phi_\gamma \) is the self absorbed fraction for the gamma emission.

Of importance for both protocols is the fact that knowledge of the remnant mass is required as well as biokinetic characteristics. Typically, uncertainties in quantifying this mass introduce the largest potential source of error.

Radiation dosimetry involving quantitative data acquisition protocols has been used since the early 1960s to provide guidance as to “safe” \(^{131}\text{I} \) activities for administration in the attempt to reduce the risk of complications. As the classic example in 1962, Benua\textsuperscript{37} described quantitative techniques designed to avoid aplastic anemia or radiation pneumonitis. Following patient specific data acquisition and dosimetry calculations, the administered activity would be limited as a maximum to that activity that would deliver a radiation dose to the blood of 200 rad (cGy) with a whole-body retention of \(^{131}\text{I} \) at 48 hours not greater than 120 mCi (4.44 GBq) in the absence of pulmonary metastases or 80 mCi (2.96 GBq) if pulmonary metastases were present.

**Outcomes - complications and long term follow-up**

The prognosis for patients with differentiated thyroid cancer who undergo near-total thyroidectomy and radiodine therapy under any of the protocols above is generally excellent. The efficacy of \(^{131}\text{I} \) ablation therapy has been demonstrated through analysis of extensive patient studies.\textsuperscript{2,38} Exactly because the outcome for patients with differentiated thyroid cancer is so positive, it remains a challenge to demonstrate that the prognosis improves with \(^{131}\text{I} \) treatment. Part of the difficulty lies in ensuring that equivalent populations are compared since factors such as age, gender and size of tumor influence the outcome.\textsuperscript{39} The prospective randomized clinical trials that would be required to assess the effects of therapy would be excessively prolonged and highly expensive.\textsuperscript{40} However, a number of retrospective studies have shown conclusively that postsurgical treatment with \(^{131}\text{I} \) and thyroid hormone therapy reduces tumor recurrence and mortality.\textsuperscript{41,42,43}

Various complications following \(^{131}\text{I} \) therapy have been discussed in the literature.\textsuperscript{2,26,39} Short-term effects include: radiation thyroiditis (rare),
acute radiation sickness (rare), thyroid storm, bone marrow depression, and acute or chronic sialadenitis. Long-term effects include: leukemia (slight increase: prevalence 0.5%\textsuperscript{23}), pulmonary fibrosis, and azoospermia.

The value of quantitative radiation dosimetry studies to tailor the \textsuperscript{131}I administered activity to the amount just required for the desired therapeutic effect and not go above this level for the sake of minimizing toxicity to normal tissues and organs has been discussed.\textsuperscript{26,32} It is equally important that cytotoxic radiation dose levels are achieved through administration of sufficient activity levels, that is, to avoid “under-dosing” and missing the therapeutic effect. At the present time, proponents of the patient specific quantitative diagnostic work-up for \textsuperscript{131}I ablation of thyroid remnants are in the minority of practitioners. The primary reasons being that the quantitative approach is labor intensive (and thus expensive with commitment of both staff and patient extended over a period of days) and that a number of intrinsic factors introduce inaccuracies (e.g., mass estimation) that mitigate significance of the result in spite of all this work. Perhaps, most important, there has been no definitive study that has shown that quantitative work-up procedures are beneficial.\textsuperscript{39}

THE VISTA FOR RADIONUCLIDE THERAPY TODAY

At the present time, there is tremendous vitality in the field of radionuclide therapy both at the innovational level involving development of new agents and within the clinical application of established protocols. A recent volume of Seminars in Radiation Oncology was devoted to the topic of Systemic Radiation Therapy.\textsuperscript{39,44,45} Tables 2 and 3 provide a partial listing from this publication as an indication of the scope of the radioisotopes, carriers, and disease states showing potential or under investigation for systemic radionuclide therapy of unsealed sources and radioimmunotherapy (RIT) respectively.

ESTABLISHING THE ROLE FOR DOSIMETRY IN RADIONUCLIDE THERAPY TODAY

Fundamental Questions for Consideration

For those working in the field of radionuclide therapy, there are a number of fundamental questions that arise. The reaction to these questions and, indeed, whether some of them should be posed at all, evokes a wide range of response - often based upon one’s perspective as a basic scientist or practicing clinician. The present discussion is not intended to provide definitive answers but rather to offer a list worthy of consideration. It is important that scientists and physicians together engage in a dialogue that leads to consensus of approach.

1. Is there an optimal approach to the use of dosimetry in the delivery of any specific radionuclide therapy?
2. How might patient specific factors be used most appropriately in the optimization of radionuclide therapy?
3. For a specific disease, patient classification, and radionuclide therapy, should it be a goal that every treatment center follow the same standard protocol whether involving dosimetry or not?
4. Should it be an objective to establish consensus on a standard protocol within categories of patients.
5. For radionuclide therapies with an extensive history of patient treatment and clinical experience, are the outcome statistics in place that might support advocacy of a standard protocol?
6. Where outcome statistics are not available and/or developed, how might they be assembled?

Questions 3 and 4 above are generally considered provocative and raise a high degree of emotion among some clinicians. The point is made that basic scientists do not have an adequate appreciation of the variances involved in patient care. However, a more tempered response expressed in a personal communication has been offered by Gerald DeNardo (2001): “Monolithism leads to mediocrity at best. Medicine is both a science and an art. Practitioners should know the first and be good at the second. There is little in the way of non-controversial data that dictates that one approach fits all. However, we should be constantly developing new data through studies of high quality then use this information to educate and guide physicians to proceed within the range of better options. Dosimetry is a great asset in this quest . . . if kept practical yet optimal.” Worthy thoughts for contemplation by the advocates of patient specific dosimetry.
Today’s Options for the Delivery of Radionuclide Therapy - Determining the Administered Activity

The list below reviews the global possibilities for determining the administered activity to be given for the radionuclide therapy. It is recognized that some of the options may not be valid for a specific radionuclide therapy due to a number of considerations.

1. Fixed administered activity: single administration.
2. Fixed administered activity with multiple readministrations dependent upon patient response (follow-up) according to defined indicators.
3. Administered activity determined/constrained by rudimentary patient specific parameters such as body surface area, weight, target tissue mass, baseline platelet count, etc.
4. Administered activity determined/constrained by more extensive patient specific parameters including biokinetics (e.g., effective half-time, percentage uptake, target tissue mass) and the desired radiation dose to be delivered.
5. Administered activity determined by maximum radiation dose allowable to a critical organ or its surrogate (e.g., marrow, blood, whole body, lung) requiring knowledge of limited patient specific parameters.
6. Administered activity determined through a standard quantitative diagnostic work-up (tracer study) to assess biokinetic relevant parameters and anatomic information for target and critical organs. These data, in conjunction with the desired radiation dose to be delivered, are used to extrapolate from the tracer study to the therapeutic regimen.
7. Administered activity determined through a higher level quantitative diagnostic work-up involving three-dimensional imaging and voxel-based model calculations specific to the patient.

Options for the Role of Patient Specific Dosimetry in Radionuclide Therapy

Within the realm of patient specific dosimetry, there are a number of levels of sophistication with regard to protocols and calculational methodology:

a.) Level 1: Measurement of the relevant biokinetic parameters through tracer studies in the patient prior to therapeutic administration of the radiopharmaceutical. These data are used in conjunction with standard models (anatomic and mathematical) to calculate radiation dose for extrapolation from the tracer study to the therapeutic administration.

b.) Level 2: Extension of the database acquired through Level 1 by determination of additional relevant anatomic and/or tissue distribution characteristics specific to the patient. These latter data are used for minor adjustments to the standard anatomic models prior to calculation of radiation dose.

c.) Level 3 (and beyond): Definitive representation of the patient through three-dimen-

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### Table 2. Systemic radionuclide therapy - unsealed sources (Adapted from McDougall[39])

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>131I sodium iodine</td>
<td>Graves’ disease; single functioning nodule; toxic multinodular goiter; Nontoxic goiter</td>
</tr>
<tr>
<td>32P sodium phosphate</td>
<td>Polycythemia vera; thrombocytthemia</td>
</tr>
<tr>
<td>90Y silicate colloid</td>
<td>Severe arthritis</td>
</tr>
<tr>
<td>165Dy ferric hydroxide</td>
<td>Severe arthritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Malignant Disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>131I sodium iodine</td>
<td>Thyroid cancer; functioning metastases; ablation of residual tissue</td>
</tr>
<tr>
<td>131I MIBG</td>
<td>Metastatic neuroblastoma; metastatic pheochromocytoma</td>
</tr>
<tr>
<td>111In octreotide</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>32P chronic phosphate</td>
<td>Intracavitary therapy</td>
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<tr>
<td>89Sr strontium chloride</td>
<td>Painful skeletal metastases</td>
</tr>
<tr>
<td>153Sm EDTPA</td>
<td>Painful skeletal metastases</td>
</tr>
<tr>
<td>186Re HEDP</td>
<td>Painful skeletal metastases</td>
</tr>
</tbody>
</table>
sional techniques employing fusion of physiologic images (SPECT or PET) with high-resolution anatomic images (XCT or MRI). Account is taken of critical tissue distribution and status/viability (e.g., marrow). At the upper end, patient specific modeling would involve a 3-D voxel representation of the patient with point kernel or Monte Carlo techniques used to derive absorbed dose estimates.\textsuperscript{46,47,48}

Patient specific dosimetry has a role to play in the development of new agents. In Phase I trials, it is essential, and generally non-controversial, as human pharmacokinetics and dosimetry characteristics are documented in preparation for establishing the recommended starting administered activities for clinical trials. In Phase II trials, patient specific dosimetry is advised and generally applied in the limited patient clinical series designed to address efficacy aspects of the agent. At these two stages, it is essential to document any unexpected biodistribution and pharmacokinetic behavior that might impact patient safety. In addition, quantitative information is desired with regard to localization of the agent in both the target and non-target tissues leading toward estimates of radiation dose and eventual understanding of the expected toxicity/efficacy relationships.\textsuperscript{49} For Phase III trials, although a dosimetry component may be recommended, circumstances and the need for flexibility in practical implementation of the study protocol may preclude inclusion of a full patient specific dosimetry procedure.

The potential utility of patient specific dosimetry in the evaluation of radiopharmaceutical therapy extends into several different areas.\textsuperscript{45} All of them depend on the availability of reliable, accurate dosimetry calculations.

a.) Treatment Planning: To predict dose and minimize toxicity in order to increase the safety of therapy based on a tracer study for individual patients who may differ widely in retention and clearance of the agent.

<table>
<thead>
<tr>
<th>Table 3. Systemic radionuclide therapy – radioimmunotherapy (RIT). (Adapted from Knox and Meredith\textsuperscript{46})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Solid Tumors</strong></td>
</tr>
<tr>
<td><strong>Antibody Conjugate</strong> (from &gt;30 presented)</td>
</tr>
<tr>
<td>\textsuperscript{131}I-anti-EGFr</td>
</tr>
<tr>
<td>\textsuperscript{125}I-425</td>
</tr>
<tr>
<td>\textsuperscript{131}I-BC-2</td>
</tr>
<tr>
<td>\textsuperscript{90}Y-MUC-2-63</td>
</tr>
<tr>
<td>\textsuperscript{131}I-HMFG1</td>
</tr>
<tr>
<td>\textsuperscript{90}Y-HMFG1</td>
</tr>
<tr>
<td>\textsuperscript{186}Re-NR-LU-10</td>
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<tr>
<td>\textsuperscript{177}Lu-CC49</td>
</tr>
<tr>
<td>\textsuperscript{131}I-chL6</td>
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<tr>
<td>\textsuperscript{131}I-CC49</td>
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<tr>
<td>\textsuperscript{90}Y-anti-ferritin</td>
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<tr>
<td>\textsuperscript{131}I-anti-ferritin</td>
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<tr>
<td>\textsuperscript{125}I-17-IA</td>
</tr>
<tr>
<td>\textsuperscript{131}I-anti CEA</td>
</tr>
<tr>
<td>\textsuperscript{90}Y-ChT84.66 anti-CEA</td>
</tr>
<tr>
<td><strong>2. B Cell Lymphoma</strong></td>
</tr>
<tr>
<td><strong>Radionuclide</strong></td>
</tr>
<tr>
<td>\textsuperscript{131}I</td>
</tr>
<tr>
<td>\textsuperscript{90}Y</td>
</tr>
<tr>
<td><strong>Myeloablative</strong></td>
</tr>
<tr>
<td>\textsuperscript{131}I</td>
</tr>
<tr>
<td>\textsuperscript{90}Y</td>
</tr>
<tr>
<td>\textsuperscript{213}Bi</td>
</tr>
</tbody>
</table>
Arguments For and Against Patient Specific Dosimetry Protocols in the Clinical Setting

The advantages of utilizing patient specific dosimetry protocols in the general clinical setting focus primarily on the capability for providing a quantitative description of individual patient pharmacokinetics that allows specific estimation of radiation dose to target and normal tissues. This presents the opportunity for optimized delivery of the desired therapeutic radiation dose while minimizing toxicity. However, it must be recognized that realization of this advantage is predicated on a one-to-one correspondence between the biokinetics following therapeutic administration and those observed for the tracer study. An ancillary benefit is the ability to predict the hospitalization required and/or to define the appropriate safety protocols for attending personnel and family members. There is another aspect related to potential benefits that may of importance particularly to radiation oncologists. Namely, information available concerning the patient radiation dose history from prior nuclear medicine therapy may influence decisions regarding future treatment plans. This history would be on record for individuals who had undergone a patient specific dosimetry workup.

A principle disadvantage of patient specific dosimetry centers around logistical aspects. Quantitative data acquisition procedures are complex and demanding of both personnel and patient. Appropriate expertise must be available and care exercised to ensure the integrity of the data. Sequential studies entail time and expense on the part of the facility as well as representing an inconvenience to the patient. However, in addition, there are fundamental considerations such as the presence of inherent error components that lead to uncertainties in the calculated dose and their impact on interpretation of the end result. As one example mentioned previously, estimate of target mass represents a dominant source of error that must be recognized as being significant with regard to the accuracy of the dose calculation. Finally, if the goal were to establish a universal approach to acquisition of quantitative data, there are intrinsic practical difficulties to contend with in transporting protocols between institutions ranging from the equipment on site to the expertise available. Nevertheless, it should be recognized that these same considerations regarding precision of data analysis, time commitment to the work-up process, appreciation for sources of error, and universality of approach are an everyday fact of life in the world of external beam treatment planning within radiation oncology. External beam radiation therapy employs labor-intensive, quantitative approaches in concert with well-understood tissue tolerance characteristics. Translation of these approaches to nuclear medicine therapy, a desirable goal, would require well-documented toxicity and efficacy data for radiopharmaceutical dosimetry. Patient specific dosimetry would assist in achieving this goal.

Concluding Remarks

Through this discussion, we have reviewed the options for delivering radionuclide therapy. The stated objectives are to provide radiation dose to the target tissue at the desired cytotoxic level while avoiding or minimizing toxic effects. Patient specific dosimetry has the potential for contributing to this quest in a significant manner. Proponents look toward advances in data acquisition techniques and calculational models. Continuing investigations in this area and implementation of innovative protocols are encouraged. However there are other options that must be viewed as viable. This latter viewpoint is clearly expressed in the recent article by DeNardo, et. al. where they make the point that as long as simpler empirical methods provide safe and effective treatment, they should be considered valid—and perhaps preferable. For those who would like to claim that patient specific dosimetry methods are superior to empirical radionuclide administration protocols, “one has to demonstrate that the frequency of excess toxicities and/or tumor underdosing are significantly lower with the former than with the latter method when treating at the maximum tolerable dose with each approach.” Thus, the challenge ahead for the advocates of patient specific dosimetry is to assemble the outcome data and perform the analysis to support this contention.
REFERENCES

36. Benau RS, Cicala NR, Sonenberg M, et al. The relation...
of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. AJR 1962; 87: 171.


