Radioiodine: The Classic Theranostic Agent

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Radioiodine has the distinction of being the first theranostic agent in our armamentarium. Millennia were required to discover that the agent in orally administered seaweed and its extracts, which had been shown to cure neck swelling due to thyromegaly, was iodine, first demonstrated to be a new element in 1813. Treatment of goiter with iodine began at once, but its prophylactic value to prevent a common form of goiter took another century. After Enrico Fermi produced the first radioiodine, 128I, in 1934, active experimentation in the United States and France delineated the crucial role of iodine in thyroid metabolism and disease. 129I and 131I were first employed to treat thyrotoxicosis by 1941, and thyroid cancer in 1943. After World War II, 131I became widely available at a reasonable price for diagnostic testing and therapy. The rectilinear scanner of Cassen and Curtis (Science 1949;110:94-95), and a dedicated gamma camera invented by Anger (Nature 1952;170:200-201), finally permitted the diagnostic imaging of thyroid disease, with 131I again the radioisotope of choice, although there were short-lived attempts to employ 129I and 132I for this purpose. 123I was first produced in 1949 but did not become widely available until about 1982, 10 years after a production technique eliminated high-energy 124I contamination. I continue to be the radioiodine of choice for the diagnosis of benign thyroid disease, whereas 123I and 131I are employed in the staging and detection of functioning thyroid cancer. 124I, a positron emitter, can produce excellent anatomically correlated images employing positron emission tomography/computed tomography equipment and has the potential to enhance heretofore imperfect dosimetric studies in determining the appropriate administered activity to ablate/treat thyroid cancer. Issues of acceptable measuring error in thyroid cancer dosimetry and the role in 131I therapy of tumor heterogeneity, tumor hypoxia, and kinetics must be overcome, and long-term outcome studies following 131I given based on this new dosimetry must be completed before the nuclear medicine community will be able to predictably cure our thyroid cancer patients with this technology.

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In the search for theranostic pairs, the spotlight of medical history shines first on iodine. A theranostic system integrates a form of diagnostic testing to detect the presence of a molecular target for which a specific therapeutic modality is intended.1 Theranostics involves the administration of a diagnostic agent:

- To determine localization in the site or disease state under study as a surrogate for a potential therapeutic agent with similar chemical properties;
- To examine its biodistribution as predictive of off-target (adverse) effects of the potential therapeutic agent;
- As an aid in determining the optimal therapeutic dosage or activity to be administered, based on the anticipated tumoricidal doses measured in the tumor site;
- To monitor the response to this treatment.2

This concept is not specific to radiopharmaceuticals but is easily transferable to this field by substituting a radionuclide with therapeutic potential, usually a beta emitter (alpha and Auger electron emitters have been used less often), for a gamma emitting diagnostic radionuclide.3

**Historical Perspective:**
**From Seaweed to Scinigraph**

The concept of examining the use of therapeutic botanicals (eg, seaweed) from which the curative principal is eventually extracted and purified after centuries (eg, iodine in the form...
Radioiodine: the classic theranostic agent

Radioiodine: Approaching a Theranostic Concept

The next phase of the history of iodine and thyroid disease began when Enrico Fermi (1901-1954) published a seminal article in 1934 using $^{238}\text{U}$ as a source of slow neutrons to produce 14 artificial elements, including the first radioisotope of iodine, $^{128}\text{I}$. There are actually 37 iodine isotopes, all radioactive except $^{127}\text{I}$, extending from $^{108}\text{I}$ to $^{144}\text{I}$. The following text and Table 1 discuss the important iodine radioisotopes that have been employed in the study of thyroid physiology, medical diagnosis, and therapy. The stage was now set for the development of radioiodine in medicine as the first theranostic pharmaceutical.

Iodine-128

Because Fermi had published his research in Nature, a journal read worldwide, it is difficult to understand why physicians at Boston's Massachusetts General Hospital (MGH), Saul Hertz (1905-1950) and J. Howard Means (1885-1967), only learned of the existence of radioiodine 2 years later, in 1936 at a Harvard symposium chaired by Massachusetts Institute of Technology's (MIT's) President, Karl Compton (1887-1954). At once, scientists and physicians at these collaborating institutions began exploring the value of radioiodine as a tracer for thyroid physiology and subsequently for diagnosis and therapy. For quantitation, the Geiger counter appeared to have been the instrument of choice. Robley Evans (1908-1996) and Arthur Roberts (1912-2004), physicists at MIT, working closely with MGH, made the short-lived $^{128}\text{I}$ (half-life 25 minutes) in 1937. In that year, Charles Leblond (1910-2007), in Paris, used $^{128}\text{I}$ to study thyroid uptake of rats and guinea pigs. A year later, $^{128}\text{I}$ uptake was found by Hertz, Roberts, and Evans to be rapid, with 35%-45% of the injected activity appearing in the rabbit thyroid in 15-30 minutes, a phenomenon blocked by stable iodine. The $^{128}\text{I}$ half-life (25 minutes) prevented any theranostic use of this radiotracer.

Iodine-130 and Iodine-131

In 1938, at the University of California, Berkeley, John Livingood and Glenn Seaborg, using Ernest Lawrence's cyclotron, bombarded tellurium targets and produced $^{129}\text{I}$, $^{130}\text{I}$, and $^{131}\text{I}$. These radioisotopes were sent back to the MIT/MGH scientists, astonishingly by first class mail, for extraction and experimentation. There Hertz and Roberts first derived the number of important observations on the role of iodine in thyroid disease, some of which would confuse thyroidologists for decades. He successfully treated cases of Graves' disease with $^{128}\text{I}$, the only stable iodine isotope, but achieved greatest renown for preventing endemic goiter by treating Akron schoolgirls with iodine. With these results, iodine seemed to be appropriate therapy for both hyperthyroidism and hypothyroidism. Marine also demonstrated that the canine thyroid gland concentrated iodine by feeding dogs large amounts of stable $^{128}\text{I}$ and then performing partial thyroidectomies.

Iodine determinations by Hertz, Roberts, and Evans in 1937 set the stage for the clinical development of radioiodine in medicine as the first theranostic pharmaceutical.
Table 1  Radioisotopes of Iodine with Medical Uses (Iodine-127 is the Only Stable Iodine Isotope)

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Principal Emissions/Energy (MeV)</th>
<th>Half-Life</th>
<th>Daughter</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-123</td>
<td>Gamma: 0.159</td>
<td>13.2 h</td>
<td>$^{129}$Te</td>
<td>Optimal for imaging nonmalignant thyroid tissue</td>
</tr>
<tr>
<td>I-124</td>
<td>$^{\beta_{max}}$: 2.14</td>
<td>4.2 d</td>
<td>$^{124}$Te</td>
<td>Employed for thyroid dosimetry with PET/CT</td>
</tr>
<tr>
<td></td>
<td>Annihilation: 0. 511</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gammas: 0.603, 0.723, 1.690</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-125</td>
<td>Gamma: 0.035</td>
<td>60.1 d</td>
<td>$^{125}$Te</td>
<td>Employed in brachytherapy</td>
</tr>
<tr>
<td></td>
<td>$^{\beta_{max}}$: 2.12</td>
<td>25.0 min</td>
<td>$^{129}$Xe</td>
<td>First radioisotope of iodine produced, 1934; employed to study thyroid uptake, 1937</td>
</tr>
<tr>
<td></td>
<td>Gamma: 0.441</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-130</td>
<td>$^{\beta_{max}}$: 1.04, 1.7</td>
<td>12.4 h</td>
<td>$^{130}$Xe</td>
<td>Thyrotoxicosis therapy, 1941</td>
</tr>
<tr>
<td></td>
<td>Gammas: 0.419, 0.538, 0.670, 0.743</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-131</td>
<td>$^{\beta_{max}}$: 0.608, 0.806</td>
<td>8.1 d</td>
<td>$^{131}$Xe</td>
<td>Discovered 1938 by Livingood, Seaborg; thyrotoxicosis therapy, 1941</td>
</tr>
<tr>
<td></td>
<td>Gammas: 0.364,0.637</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-132</td>
<td>$^{\beta_{max}}$: 2.12</td>
<td>2.3 h</td>
<td>$^{132}$Xe</td>
<td>Rarely used because of high energy emissions, short half-life</td>
</tr>
<tr>
<td></td>
<td>Gammas: 0.523 0.630, 0.668, 0.773, 0.954</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

quantitative radioactive iodine uptake concept from animal experiments. However, human studies, on 6 patients with a variety of thyroid disorders, were performed for the first time at Berkeley, using $^{131}$I. Unfortunately, the inclusion of 14 mg of stable $^{127}$I per dosage in these experiments clouded the results and hence any conclusions that could be made. The first human iodine uptake study was also attempted during these studies.\(^1\) In 1941, Hertz and Roberts at the MGH began using radioiodine therapy for thyrotoxicosis, treating their first patient on March 31, 1941, whereas Joseph Hamilton and John Lawrence at Berkeley treated their first patient on October 12, 1941.\(^3\) The output of the MIT cyclotron was such that 90% of the activity obtained was $^{130}$I, and 10% was $^{131}$I. Hertz and Roberts always felt that $^{130}$I produced faster results and was the radioisotope of choice. At MGH, J. Howard Means, required thyrotoxic patients to receive stable iodine after the radioiodine, as he felt that the blocking effect of excessive $^{127}$I explained a major part of the therapeutic effect. However, disagreement remained, and in 1942, at Columbia University, Bernard Brunstein, shed his anonymity when he appeared in a magazine article (October 31, 1949), detailing the remarkable cure of his cancer with the new radioactive iodine produced.\(^6\) The therapeutic use of $^{130}$I to treat thyrotoxicosis ceased as soon as the Atomic Energy Commission began distributing inexpensive, reactor-produced $^{131}$I at $1.70 per mCi (37 MBq).

Measurements of thyroidal function employing the gamma rays of $^{131}$I were quickly recognized as an important part of diagnosing and treating the overactive thyroid gland. In the late 1940s and early 1950s, there was a proliferation of thyroid function tests with $^{131}$I. Radioiodine uptake measurements were recognized as important, but agreement on issues such as when and by what route radioiodine activity should be measured required years, and many clinics still check both an early (about 6 hours) and late (24 hours) iodine uptake. This test, it was soon recognized, could be altered by a variety of medications, especially those that led to an expanded iodine pool. Although measurement of blood iodine clearance was felt to be the most reliable index of the thyroidal iodine accumulating function, it never became clinically valuable because the iodine dose had to be given intravenously and the study time consuming, also requiring a blood sample for counting.\(^7\) Urinary iodine collections were also employed but proved to be impractical because of patient cooperation issues. Measurements of the storage and release of iodine as protein-bound $^{131}$I have been employed to determine intrathyroidal exchangeable iodine,\(^8,9\) but neither approach has proved practical in diagnosing thyroid disorders.

The potential for radioiodine therapy of thyroid cancer was not overlooked, and in 1942, at Columbia University, Albert Keston et al first showed that a child’s thyroid cancer could concentrate radioiodine. The first adult to be cured of thyroid cancer by radioiodine, who had such a large volume of functioning tissue that he was thyrotoxic, was treated 4 times between 1943 and 1946 with a total of 109 mCi of $^{131}$I and 150 mCi of $^{131}$I by Samuel Seidlin et al.\(^10\) The patient, Bernard Brunstein, shed his anonymity when he appeared in a Life magazine article (October 31, 1949), detailing the remarkable cure of his cancer with the new radioactive iodine therapy, wherein the term “radioactive cocktail” was born.
All of these therapeutic efforts were performed without the benefit of true imaging until the Cassen and Curtis21 rectilinear scanner, functioning in 1949, replaced arduous point by point counting over the radioactive thyroid gland. In 1952, Anger’s first gamma camera, designed for thyroid imaging, appeared.22 Now radioiodine could take its place as the first theranostic radiopharmaceutical or pharmaceutical of any type. Thyroid scintigraphy employing 131I was at last possible for visualization of the structure and function of the gland as well as for therapy. 131I for diagnostic use has advantages of low cost and a long half-life, permitting it to be shipped considerable distances from the reactor in which it has been produced. However 131I is hardly an ideal diagnostic agent, especially for the evaluation of benign thyroid disease. The predominant gamma ray has a photopeak of 364 keV, which yields an intrinsic efficiency with the one-quarter inch crystal of an Anger gamma camera of only 25%, as compared with the much higher intrinsic efficiency with photopeaks of lower-energy radioisotopes, such as those of 125I and 99mTc, 79% and 83%, respectively. In addition, there are higher-energy, low-prevalence 131I photopeaks that are difficult to collimate and, therefore, degrade image quality. Finally, the predominant beta particle of 131I has maximum electron energy of 608 keV, and the emissions of 131I deliver a relatively high-radiation dose to the thyroid—1.3 rad/μCi (0.35 mGy/kBq) to a 20-g gland with 25% uptake. A better diagnostic agent was needed.

Iodine-125
125I was discovered by Reid and Keston in 1946 in a solution containing several radioisotopes separated from tellurium after bombardment with deuterons at MIT 6 months previously. The physical properties of 125I led to a consideration of its use as a biological tracer.23 With a gamma photopeak of 35 keV, the interaction with very thin (1-2 mm) sodium iodide scintillation crystals is efficient, and there is minimal septal collimator penetration. With no beta emission, the thyroid dose from 125I is less than that of 131I, even though the half-time of 125I, 60 days, is 7.5 times longer than that of 131I. This long half-time provides a shelf life convenient for storage, shipping, and synthesis. The decay scheme of 125I also leads to internally converted ejected electrons with maximum energy of 35 keV as well as slightly lower energy x-rays and 21 Auger electrons with energies of 0.07-30.1 keV. These emissions can damage the cell taking up this radioisotope but have little cytotoxic effect on nearby cells. This gives 125I a theoretical advantage in killing very small islands of widely separated thyroid cancer cells, whereas the energetic 608 and 806 keV (Emax) betas of 131I have a far greater range (0.6-2.0 mm from site of emission) but fewer interactions per emission than 125I within the iodine-concentrating cell, thus having greater therapeutic efficacy with larger, and relatively distant, masses of thyroid cancer.24 Diagnostic 125I scans appear to have no significant advantages over those performed with 99mTc-pertechnetate25 or 131I, and the latter radioisotope is better in characterizing superior mediastinal masses.26 125I has been used for protein iodination, in vitro diagnostic radioimmunoassay kits, and as a source for bone dosimetry devices and brachytherapy, the latter because of the long 125I half-life and the relatively short range of emitted gamma rays and still lower energy x-rays. It is reactor produced but is not available as a radiopharmaceutical for thyroid theranostic uses at this time, as it has no obvious advantages over the less expensive 131I.

Iodine-132
132I (half-life 2.3 hours, with beta decay, principal gamma photopeaks of 954, 773, 668, 630, and 523 keV) is mentioned here for completeness, because it has occasionally been used in the study of thyroid function, especially in repeated studies in the same individual where a series of pharmacological manipulations can be performed because of its short half-life.27 There have been a few European scintigraphic studies employing those 132I high-energy gammas,28 although there have been no peer-reviewed data employing 132I recorded in PubMed in 30 years.

Iodine-123
123I was first produced in 1949, but not until 1962 was there recognition of its diagnostic potential.29 123I, with a 159-keV gamma photopeak, has:

- More efficient interaction with sodium iodide crystals than 131I;
- No beta emission, so the radiation dose to the thyroid gland is a few percent of that from 131I;30
- An adequate 13.3-hour half-life allowing commercial shipping;
- More efficient collimation than 131I because of its lower energy;
- A requirement for less expensive shielding.

All these factors, resulting in superior images with fewer radiation safety issues, have led to a distinct preference for 123I for most diagnostic purposes. This author recalls that, ironically, in the first clinical comparison scan quality of 131I and 123I in Cincinnati, the 131I images were preferred because there were contaminating high-energy photons from the 123I product produced by the 122Te(4p,3n)123Xe reaction;30 123Xe, with a half-time of 2.1 hours, then decays to 123I.31 In 1972, pure, carrier-free 123I was produced using the 127I(p,5n)123Xe reaction, but more than a decade passed before it became widely available.32 Table 2 indicates the relative number of detectable photons per minute per rad in a 3 × 3-inch sodium iodide crystal 10 cm from the source and makes clear the advantage of 123I for diagnostic imaging of the thyroid.33 Radioiodine, first as 131I and currently with 123I, has been a remarkably useful diagnostic agent, proving invaluable in many clinical situations, including:

- The diagnosis of those cases of thyrotoxicosis where the distinction between unnnodular or multinodular toxic goiter and diffuse toxic goiter (Graves’ disease) cannot be made clinically, although thyroid ultrasonography...
and the assay for antithyrotropin antibodies can usually make this distinction;
- Determining the percentage iodine uptake and thus assisting the therapist in calculating the amount of administered activity of $^{131}\text{I}$ for nodular toxic goiter and Graves’ disease;
- Distinguishing thyrotoxicosis caused by destructive silent thyroiditis from hyperfunctioning thyroid tissue;
- Localization of functioning thyroid neoplasms;
- An aid in the differential diagnosis of superior mediastinal masses (although $^{131}\text{I}$, with a higher photopeak energy, is probably better for this purpose);
- The detection of accessory or ectopic thyroid tissue;
- Determining whether a solitary thyroid nodule is functioning or “cold.”

It must be acknowledged that there are fewer uses for the $^{123}\text{I}$ uptake and scan with the advent of newer diagnostic techniques.\(^{34}\)

### Iodine-124

Although $^{124}\text{I}$, with its energetic photons (511, 603, 723, 1690 keV), was once noted as an “undesirable contaminant” in the production of Iodine-123,$^{30,31,35}$ this radioisotope has the potential of becoming important in the theranostic approach to thyroid cancer. $^{124}\text{I}$, a cyclotron product ($^{124}\text{Te}^{[p,n]}^{124}\text{I}$), is the only long-lived (half-life 4.2 days) positron-emitting radioisotope of iodine, permitting functional imaging of many biological processes employing positron emission tomography/computed tomography (PET/CT). As an Auger electron emitter (9.2 per decay), there are potential therapeutic uses of this tracer as well.\(^{36}\) A source of error in counting $^{124}\text{I}$ coincidences occurs because the emission of its annihilation photons is accompanied by the high-energy prompt gammas noted previously, which can lead to invalid gamma ray coincidences and increased dead time. Several approaches have been attempted to reduce this potential source of error, including narrower windowing, sophisticated background subtraction, and dead time correction.\(^{37}\)

### Modern Theranostic Approaches

Activities of $^{131}\text{I}$ in excess of 2 mCi (74 MBq) employed for diagnostic scintigraphy in thyroid cancer may cause the phenomenon of stunning, reducing the uptake of higher, therapeutic dosages of this radioisotope.\(^{38,39}\) Therefore, the dual theranostic use of $^{131}\text{I}$ must be carefully designed to reduce the possibility of stunning.

The postthyroidectomy, preablative use of diagnostic scintigraphy is still somewhat controversial, as there are experienced clinicians who feel that this scan does not often change management, and an overall survival advantage from its use is difficult to document. However, those arguing for employing a diagnostic dose of radioiodine for scintigraphy before ablative therapy admit that, although this procedure has led to infrequent changes in patient care, nevertheless these management changes are so important that they cannot be overlooked. These include:

- Detection of heretofore unknown distant metastases in lung, bone, brain, etc, which require an increase in the administered $^{131}\text{I}$ activity;
- $^{131}\text{I}$ therapy of previously unrecognized brain metastases may require corticosteroids to reduce the possibility of posttherapy cerebral edema;
- A small percent of patients postthyroidectomy will have a very low or negative stimulated serum thyroglobulin assay, no antithyroglobulin antibody elevation, and a negative diagnostic radiiodine scan. These patients should not receive therapeutic $^{131}\text{I}$ when there is no evidence of tumor in the relevant preablative laboratory assays and diagnostic scan;
- Older patients and those with decreased renal function should receive a dosimetric assessment with diagnostic activities of radiiodine before aggressive empiric radiiodine therapy, to avoid both myelotoxicity and undertreatment;\(^{40,41}\)
- The advent of single-photon emission computed tomography (SPECT)/CT employing $^{123}\text{I}$ or low-activity $^{131}\text{I}$ should increase the use of imaging before $^{131}\text{I}$ radioablative or therapy of thyroid cancer, because the incremental diagnostic value of SPECT/CT for determining the true location of “hot spots” seen on planar imaging (eg, thyroid remnant vs nodal involvement) is at least 15%\(^{42}\) and as high as 74% in 1 study.\(^{43}\)

In the absence of $^{123}\text{I}$ for diagnostic imaging, $^{99m}\text{Tc}$-pertechnetate has been used for imaging the thyroid gland,\(^{44}\) as its gamma photopeak, 140 keV, has excellent efficiency in interacting with the sodium iodide crystal. Its theranostic value for pairing with therapeutic $^{131}\text{I}$, especially for functioning thyroid cancer, is limited by its short half-life and the lack of organization after uptake.\(^{45}\)

With a high therapeutic index (the ratio of therapeutic to toxic effects), empiric high activity $^{131}\text{I}$ therapy has been employed for many years\(^{46}\) because tumor doses from administered $^{131}\text{I}$ cannot be accurately calculated without:

<table>
<thead>
<tr>
<th>Iodine Radioisotope</th>
<th>Principal Photopeak (MeV)</th>
<th>Number of Detectable Photons/Min/ rad 24 h After Administration of Isotope Relative to $^{131}\text{I}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{123}\text{I}$</td>
<td>0.159</td>
<td>25.03</td>
</tr>
<tr>
<td>$^{124}\text{I}$</td>
<td>0.511</td>
<td>0.54</td>
</tr>
<tr>
<td>$^{125}\text{I}$</td>
<td>0.035</td>
<td>3.11</td>
</tr>
<tr>
<td>$^{126}\text{I}$</td>
<td>0.386</td>
<td>0.44</td>
</tr>
<tr>
<td>$^{128}\text{I}$</td>
<td>0.441</td>
<td>Half-life too short for 24-h uptake study</td>
</tr>
<tr>
<td>$^{130}\text{I}$</td>
<td>0.538</td>
<td>2.00</td>
</tr>
<tr>
<td>$^{131}\text{I}$</td>
<td>0.364</td>
<td>1.00</td>
</tr>
<tr>
<td>$^{132}\text{I}$</td>
<td>0.668</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Dosimetric studies of $^{131}$I therapy for thyroid cancer have been performed for well over 2 decades, but the results have not been fully consistent. For example, Maxon et al. using sequential planar scintigraphy, concluded that 300 Gy are required to ablate the thyroid gland. In contrast, O'Connell et al. employing PET equipment from the previous decade, found that 60 Gy were sufficient for ablation. Flux et al. employed SPECT with diagnostic activities of $^{131}$I and found complete ablation occurring from tissue doses ranging from 12 to 570 Gy, with failed ablations from tissue doses from 7 to 49 Gy. Better techniques, required to sort out these conflicting results, are becoming available.

The latest and most exciting application of the theranostic approach to thyroid disease involves the possibility of accurate dosimetry with the positron-emitting $^{124}$I, so that the appropriate amount of $^{131}$I can be administered to destroy the pathologic tissue. Phantom studies from 2002 confirmed that $^{124}$I activity concentration could be quantitated by PET with an error of <10%; volumetry was possible for nodules <13 mm with an error <20%.

Heterogeneity of tumor distribution, tumor oxygenation, and tumor cell kinetics is an important variable in assessing dose-response relationships. These are very difficult to measure in vivo, although currently available tracers, such as $^{99mTc}$-annexin V, $^{18}$F-fluoromisonidazole, and $^{18}$F-fluorothymidine, might be helpful to determine, respectively, the degree of tumor apoptosis, the intratumoral level of hypoxia, and rate of cell proliferation if these variables can be shown to have some predictive value for the response to $^{131}$I. Studies are also required to prove that the kinetics of low-dose $^{124}$I are identical with those of high-dose therapeutic $^{131}$I, because there could theoretically be unanticipated potential biological effects from therapeutic doses not predicted by the diagnostic study. Until there are a significant number of clinical studies with excellent follow-up of the tumor response to $^{131}$I activities administered based on $^{124}$I-based calculations, we will not know what an acceptable level of error in $^{124}$I dosimetric studies is. Certainly a 20% error could mean the difference between the presence and absence of a cytotoxic effect.

There is also no universally accepted model for predicting marrow toxicity, although the radiation dose threshold to the blood generally accepted to prevent myelotoxicity, manifested as pancytopenia, is 2 Gy. However, this assessment does not account for heterogeneity of marrow anatomy, attenuation of beta particles by bone spicules in the marrow, or previous therapy-related marrow damage.

The competing SPECT/CT quantitation approach employing $^{1-131}$I is also theoretically possible. SPECT quantitation techniques for low-energy radionuclides like $^{99mTc}$ appear to have overcome most of the issues presented by photon scatter, photon attenuation, and partial volume effects. A quantitation error <10% for $^{99mTc}$ sources has been reported with state-of-the-art SPECT equipment, but quantitative accuracy with higher-energy radionuclides like $^{131}$I is less than that with $^{99mTc}$, and there are currently no validated techniques for $^{131}$I SPECT quantitation in clinical situations.

**Conclusions**

Radioisotopic forms of sodium iodide represent the first molecule, which could be used for both diagnosis and therapy, depending on the emission of the chosen isotope. Table 1 lists the iodine radioisotopes that have found some use in the practice of nuclear medicine. However, in 2012, $^{123}$I is preferred for thyroid scintigraphy when the function and structure of benign disease must be determined, and also in many centers treating thyroid cancer for preablative scintigraphy, although $^{131}$I, in activities not to exceed 2 mCi (74 MBq), is also useful in this instance. For economic and logistic reasons, some centers employ $^{99mTc}$-pertechnetate to evaluate benign thyroid disease.

The combination of $^{124}$I and $^{131}$I with SPECT/CT or of $^{124}$I and $^{131}$I with PET/CT has led to the recognition that planar techniques for thyroid scintigraphy are not always adequate for correct localization of iodine-concentrating tissue and, hence, for staging and decisions on the amount of therapeutic $^{131}$I to be administered.

The nuclear medicine community now stands on the threshold of attaining dual goals of quantitating the functional volume of pathologic thyroid tissue and the in vivo pharmacokinetic data required for accurate $^{131}$I dosimetry. With this information, we should be able to determine the precise administered activity of $^{131}$I required to cure our patients’ functioning thyroid cancers, as well as appropriate cases of thyrotoxicosis, while simultaneously minimizing adverse events.

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**References**

1. Lee DY, King CP. Molecular theranostics: A primer for the imaging professional. Am J Roentgenol 2011;197:318-324
5. Sawin CT, Becker DV: Radioiodine and the treatment of hyperthyroidism: The early history. Thyroid 1997;7:163-176
10. Hertz S, Roberts A: Radioactive iodine as an indicator in thyroid physiology. Endocrinologist 1941;29:82-95
24. Maxon HR, Thomas SR, Samarutunga RC: Dosimetric considerations in the radioactive treatment of macrometastases and micrometastases from differentiated thyroid cancer. Thyroid 1997;7:183-187
28. Guntermann S, Mitterlechner E: Thyroid scintigraphy with 123I. Radiol Diagn (Baltimore) 1966;7:347-352
41. Kulkarni K, Van Nostrand J, Atkins F, et al: The relative frequency in which empiric dosages of radioiodine would potentially overtreat or undertreat patients who have metastatic well-differentiated thyroid cancer. Thyroid 2006;16:1019-1023