

The Evolving Role of ^{131}I for the Treatment of Differentiated Thyroid Carcinoma

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The use of radioactive iodine (^{131}I) for the treatment of thyroid carcinoma has changed over the past 50 y. These changes are based on increasing awareness of the biophysical properties of ^{131}I and new discoveries concerning the biology of iodine handling by thyroid cells. The therapeutic administration of ^{131}I for thyroid remnant ablation and for metastases requires an appreciation of iodine clearance kinetics, of factors that can alter the occupancy time of ^{131}I within lesions, and of the role of thyroid-stimulating hormone in stimulating the sodium-iodide symporter. The potential complications and adverse events associated with ^{131}I are discussed. ^{131}I will continue to be a major weapon in the fight against metastatic thyroid carcinoma. Its future role will be modified by expanding knowledge of its relative risks and benefits.

Key Words: thyroid carcinoma; radioactive iodine; dosimetry; metastases; adverse effects; carcinogenesis

J Nucl Med 2005; 46:28S-37S

The first report of the use of radioactive iodine for the treatment of metastatic thyroid cancer was published by Seidlin et al. in 1948 (1). ^{131}I was administered to a patient who was clinically hyperthyroid despite having had a thyroidectomy for thyroid cancer. A scan after therapy revealed uptake in pulmonary metastases. This report was followed by many case reports that confirmed that metastatic thyroid cancer lesions could concentrate radioiodine.

Several groups in the United States and Europe began to formally evaluate the safety and efficacy of this approach in the 1950s (2-5). These early investigators discovered that increased iodine uptake occurred when the serum thyroid-stimulating hormone (TSH) was elevated and that this was most easily accomplished by withdrawing patients from thyroid hormone. Injections of exogenous bovine TSH (bTSH) were used to avoid prolonged hypothyroidism (6). However, the use of bTSH fell somewhat out of favor because of allergic reactions and the emergence of blocking antibodies that diminished the effectiveness of subsequent

administrations. By the 1960s, it became clear that ^{131}I could destroy metastatic lesions and increase survival of patients with metastatic thyroid carcinoma (7). However, complications of ^{131}I therapy began to emerge, including transient suppression of bone marrow function, rare cases of leukemia, salivary gland inflammation, and gonadal suppression.

In the 1970s, the concept of using ^{131}I to ablate thyroid remnants became popular. A report by Mazzaferri et al. (8) led to the growing use of ^{131}I for thyroid remnant ablation to complete the surgical removal of all normal thyroid tissue and to destroy microscopic deposits of thyroid cancer. Hay et al. (9) documented a rise in the use of ^{131}I therapy for thyroid cancer at the Mayo Clinic in the 1970s as the preparation became more available commercially. The use of bTSH ceased altogether in the mid-1980s with the discovery of Creutzfeldt-Jacob disease in some children who had received growth hormone extracted from human pituitaries, a discovery accompanied by the fear that other pituitary extracts contained the same agents. Schlumberger et al. (10) reported that ^{131}I could successfully destroy micronodular pulmonary lesions, especially in younger patients with well-differentiated thyroid carcinoma, but was relatively ineffective for large metastatic lesions, especially those in bone.

The use of ^{131}I has continued as a mainstay of therapy for thyroid cancer today. The growing awareness of subtle short- and long-term consequences of this therapy and its ineffectiveness in advanced metastatic thyroid carcinoma have led to a more cautious and conservative approach to its use. This review is intended to highlight the areas in which ^{131}I therapy has had its greatest achievements as well as those clinical situations in which its use is not supported by clinical experience or retrospective studies.

BIOPHYSICAL PROPERTIES OF ^{131}I

Physical Properties of ^{131}I

^{131}I is produced in nuclear reactors by neutron irradiation of tellurium dioxide and during the fissioning of uranium. The physical half-life of ^{131}I is 8.02 d. β -particles are emitted from ^{131}I atoms with various energies, with the maximal β -energy being 606 keV and the mean energy being 191 keV. After the emission of a β -particle, the ^{131}I

Received Nov. 8, 2004; revision accepted Nov. 24, 2004.
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atom undergoes further adjustment with emission of γ -rays. The major γ -radiations are at 364 and 637 keV. These β - and γ -radiations account for 90% of the radiation from ^{131}I . ^{131}I is available for oral ingestion as sodium iodine of high specific activity as a liquid solution or in capsules, for oral ingestion. It is rapidly and completely absorbed in the upper intestine, and the intravenous route is used only in patients who are unable to ingest the solution or capsules. Capsules are safer than liquid solutions, because less radioactivity is released into the air during handling. It is our experience that capsules also result in less oral mucosal irritation. Simultaneous ingestion of large amounts of water attenuates the radiation dose that may be emitted to the gastric wall before dissolution of the capsule.

Radiobiology

As ionizing radiation loses its energy, it disrupts chemical bonds throughout the cell, inflicting devastating damage on the DNA molecule and triggering cellular dysfunction and ultimately cell death. Most of the radiation dose is delivered by β -particles. β -particles do not penetrate deep into tissue (2 mm in depth, at most). The mean absorbed dose delivered by β -particles for a given radioactive concentration increases with the radius of tissue up to 10 mm and then remains constant. Because virtually no β -particles escape from large tumor deposits where ^{131}I is concentrated, large doses of ^{131}I may be given without damaging surrounding tissues. The inhomogeneity of radiation doses is a result of the spotty distribution of ^{131}I in neoplastic foci and the short path of β -particles. γ -radiation contributes only 10% of the total radiation dose, with a fraction of γ -rays being absorbed by the functioning tissue and the vast majority leaving the patient via the skin surface. This scattered radiation, which irradiates the patient and the environment, can be detected by a radiation detector.

Biologic Considerations

The metabolism of radioiodine in papillary and follicular carcinoma is profoundly altered. When compared with normal thyroid tissue, several defects are present in cancer tissue: (a) iodine uptake, via the sodium-iodide symporter (NIS), is always decreased and is undetectable in about a third of patients; (b) iodine organification is markedly reduced; (c) the effective half-life of iodine in tumor tissue is always shorter; and (d) response to TSH stimulation is usually present, even in the absence of clinically evident ^{131}I uptake.

In recent years, the expression of thyroid-specific genes has been studied at the mRNA and protein levels. The expression and targeting of NIS to the basal membrane is profoundly decreased (11), and this is associated with a decreased expression of thyroperoxidase and, to a lesser extent, of pendrin (the Pendred syndrome gene) and thyroglobulin (Tg) (12,13). The expression of Tg is decreased but remains detectable in almost all papillary and follicular thyroid carcinomas by immunohistochemistry and by serum measurement. The expression of the H_2O_2 generating sys-

tem, thyroid oxidase, may be normal, decreased or increased (14). As a result, organification is defective, Tg is poorly iodinated, and synthesis of thyroid hormone is rarely found. TSH receptors, however, continue to be expressed in most thyroid carcinomas. TSH stimulation will increase iodine uptake in tumors that express sufficient NIS and will increase Tg production by all tumor tissues, even by those unable to concentrate radioiodine (15). TSH stimulation, after withdrawal of thyroid hormone treatment or recombinant human thyrotropine (rhTSH), can increase the uptake of ^{18}F -FDG even in poorly differentiated carcinomas (16–18).

Iodine uptake is heterogeneous in both normal and tumoral thyroid tissues (19). This is mainly related to a heterogeneous expression of NIS. This heterogeneous expression and the short path of β -rays explain the heterogeneous dose distribution in neoplastic thyroid tissue that may be responsible for pitfalls in ^{131}I therapy, even when uptake is present in the tumor. The low expression levels of the thyroid genes that transport and organify iodine, which are basically all stimulated by TSH, underline the need for an intense TSH stimulation before any administration of ^{131}I .

DOSIMETRY: CONCEPTUAL FRAMEWORK AND METHODS

Clinical scientists working with ^{131}I for therapy in the 1950s observed several cases of severe bone marrow suppression after administering large activities of the isotope. They subsequently also noted several cases of aplastic anemia and leukemia as well as pulmonary fibrosis in those who had significant metastatic uptake in the lungs. They retrospectively analyzed the clinical data and decided that there were no significant adverse bone marrow sequelae when the dose to blood (or bone marrow) was <2 Gy from a single treatment. Similarly, they decided that no pulmonary fibrosis was evident in those with diffuse lung metastases who had <2.95 GBq (80 mCi) remaining in the body at 48 h after administration (3). Although these cutoffs were not rigorously confirmed, they have continued to be used as guidelines by generations of nuclear medicine physicians.

Studies by Maxon et al. (20,21) in the 1980s confirmed that radiation doses of $>8,500$ cGy were generally necessary to destroy most metastatic lesions. Unfortunately, although blood and whole-body dosimetry provides important safety cutoffs, it does not provide information as to the amount of radiation that will be delivered to the metastatic lesions. To determine the radiation dose to each lesion, one needs to define the concentration of radioiodine in the lesion (the ratio between total uptake in the lesion and the mass of the lesion) integrated over the time during which it remains in the lesion. The estimation of the mass of the lesions is often difficult and is impossible in small lesions not visible on radiography or CT scan. The determination of the uptake with time also requires multiple measurements. The goal of “lesion dosimetry” has been approximated by determining the percentage of the initial activity administered as determined by a region of interest from γ -camera images; how-

ever, many assumptions must be made to reach crude estimates.

The advent of PET imaging now provides the ability to accurately determine the concentration of a positron-emitting isotope within a specific volume (22). If the concentration is determined repeatedly over time, the “area under the curve” can be estimated for the entire dwell-time of the positron-emitting isotope. The increasing availability of the positron-emitting iodine isotope ^{124}I now enables much more exact in vivo determination of iodine concentration. This approach has been attempted by several groups. Eschmann et al. (23) found that volumes could be determined for lesions <13 mm in diameter and that ^{124}I concentration could be quantitated by PET. In a small group of thyroid cancer patients with metastases, who were treated with therapeutic amounts of ^{131}I , these authors predicted that radiation doses ranging between 70 and 170 Gy would be delivered to individual lesions. Sgouros et al. (19) developed a software program (3D-ID) to determine the concentration of radioisotopes within irregular volumes and applied this to PET images of ^{124}I in thyroid cancer metastases. Patients were treated with standard therapeutic doses of ^{131}I , and retrospective dosimetry was performed using registered ^{124}I PET images. Mean absorbed dose estimates were obtained for a total of 56 tumors and ranged from 1.2 to 540 Gy, with wide variations in the absorbed dose distribution between lesions and even within lesions. They concluded that ^{124}I PET-based, patient-specific lesion dosimetry is feasible and that sequential PET can be used to obtain cumulated activity images.

At present, whole-body and blood dosimetry is best reserved for therapy of widely metastatic thyroid carcinomas that exhibit radioiodine avidity. The goal is to deliver the highest radiation dose to all lesions without exceeding 2 Gy to the bone marrow. The suggestion that 3 Gy to blood may also be safe will need further confirmation (24). In the future, when the technical aspects of lesion dosimetry are finalized, it is possible that dosimetry will focus more on how much radiation is required to destroy metastatic lesions. It is likely that patients whose lesions would receive <10 Gy at the maximal tolerable activity (MTA) will not be offered ^{131}I , because the risks would outweigh the benefit. On the other hand, if one can deliver a lethal amount of radiation with ^{131}I by exceeding the MTA slightly, then the benefit may exceed the risk. It is likely that the use of ^{131}I will evolve as the practice of lesion dosimetry expands. However, no study has yet demonstrated that maximal activities based on dosimetry or high standard activities of ^{131}I are more effective than standard treatment with fixed activities of 3.8–5.6 GBq (100–150 mCi).

Studies have shown that during hypothyroidism there is a decrease in the renal clearance of radioiodine, resulting in a prolonged whole body retention (25,26). This will increase by a factor of 2 to 3 the radiation dose delivered to nonthyroidal tissues, including the blood and bone marrow (27). Moreover, colonic motility is decreased during hypothy-

roidism, and this may result in increased radiation to the colonic mucosa, which should be minimized by laxative treatment. Of note, the increased whole-body retention also increases the bioavailability of ^{131}I for thyroid lesions, and this may result in an increased fractional uptake. In comparison, the use of rhTSH in euthyroidism will decrease the body retention, resulting for a given activity in lower radiation exposure but possibly resulting in a lower uptake in thyroid tumor foci and lower radiation doses to the tumor. Further studies, such as that of Luster et al. (28), will be necessary to define the comparative lesional retention of radioiodine in the euthyroid and hypothyroid states.

^{131}I FOR THYROID REMNANT ABLATION

The administration of ^{131}I in the early postoperative period has been used for more than 40 y and is termed radioiodine remnant ablation (RRA). The goals of RRA are to destroy any microscopic deposits of thyroid carcinoma and to destroy any remaining normal thyroid tissue. In theory, if one could eliminate all normal thyroid cells, the only remaining source of Tg production would be malignant thyroid cells. This would then make the serum Tg a more specific tumor marker. Second, if all normal thyroid tissue is destroyed, any subsequent retention of radioiodine in the neck region would be the result of residual thyroid cancer. Finally, if microscopic deposits of differentiated thyroid cancer are destroyed, one should expect lower recurrence rates and possibly improved overall survival. The extent to which any or all of these goals have been achieved is a topic of considerable controversy because of the lack of well-controlled studies on which to draw firm conclusions. Unfortunately, published data on this issue are retrospective and not randomized. Although the practice of RRA has been widely adopted in the United States and Europe and is supported by several learned medical societies, its use should be based on risk of recurrence (29–31).

Preparation for RRA usually involves withholding thyroxine replacement after total thyroidectomy for 4–6 wk to increase endogenous TSH secretion, thereby stimulating iodine uptake by thyroid cells. Many centers considered the patients ready for treatment when the TSH level had risen to 25–30 mU/L. Many variations on this standard protocol have been introduced, including the use of triiodothyronine or low doses of thyroxine (e.g., two-thirds of the replacement dose) to minimize the hypothyroid symptoms while allowing the TSH to rise above 25 mU/L. A tracer dose of radioiodine is often used to determine the percentage uptake in the thyroid bed when the extent of surgery is uncertain, because large remnants will organify the radioiodine, resulting in much higher radiation doses to the remnant. The activities administered in the 1970s ranged from 0.9 to 5.5 GBq (25–150 mCi), with no rationale for using any of these activities. We strongly recommend obtaining a post-RRA whole-body scan to screen for any nonphysiologic uptake outside the thyroid bed region that would suggest metastatic

disease. Tissues that often take up iodine and can be misconstrued as metastases include the salivary glands in the mouth, the esophagus (as a result of swallowing radioactive saliva), the thymus gland, the breasts in some women, the liver, the stomach, the colon, and the bladder.

RRA success rates varied quite a bit and were generally accomplished by lower activities either after total thyroidectomy or in countries with endemic iodine deficiency. A recent large prospective trial from India found that the rate of successful remnant ablation in a hypothyroid cohort was maximal when 0.9 GBq (25 mCi) was used as a single dose (32). Many of these patients, however, had large thyroid remnants, which may have skewed the results to favor lower activities. Success rates in these patients were not higher for administered activities of up to 1.8 GBq (50 mCi). However, the number of patients included in each dose group was limited, and the generalizability of these findings remains uncertain. Randolph and Daniels (33) suggested that an entire lobe can be safely ablated with a single administration of ^{131}I . In certain circumstances in which the likelihood of residual thyroid carcinoma is high after a hemithyroidectomy, these authors found that a single administration of 1.1 GBq (29.9 mCi) of ^{131}I resulted in successful ablation in more than 80% of patients. However, their follow-up duration was too short to prove that ^{131}I lobe ablation has a similar long-term tumor control compared with completion thyroidectomy.

In a review of more than 2,500 patients at the Mayo Clinic, Hay et al. (34) reported that RRA did not improve mortality or recurrence rates in patients with low-risk papillary thyroid cancer (i.e., MACIS score <6) who had undergone complete tumor excision, and they discouraged the routine use of RRA in such patients. Sawka et al. (35) systematically reviewed published reports on RRA. The possibility that RRA may reduce recurrence rate or overall survival was examined. Although they found cohort studies to be inconsistently designed, in pooled analyses the evidence did support the reduction of relative risk of local and distant metastases (36). The studies were somewhat biased, however, in risk stratification, so that patients at higher risk were more likely to have had RRA. Only one study, which followed a cohort for more than 30 y, found that RRA resulted in a significant reduction in mortality (37). A comparison with similar patients treated at the Mayo Clinic suggested that these benefits may reflect differences in completeness of surgical excision (38). It appears that there is less need for RRA in low-risk patients who have had a true total thyroidectomy and, conversely, a greater need when large remnants are present or in patients who are at high risk for recurrence, based on histology, age, or extrathyroidal extension.

In the past, the achievement of a negative diagnostic whole-body scan was a standard goal (20). However, it has become clear that diagnostic whole-body scans have very low sensitivity in most patients, and are much less sensitive than whole-body scans after therapy, provided that uptake in

thyroid remnants is low (39). More recent retrospective studies have found that the lack of rise in serum Tg in response to TSH elevation is a more reliable test, with a higher negative predictive value of residual or recurrent cancer, and can be used reliably as a criterion for ablation (40,41).

Numerous reports suggest that diagnostic scanning with low amounts of ^{131}I (to estimate the mass of the thyroid remnant) may diminish the subsequent uptake of a therapeutic dose (termed “stunning”). The exact nature of the reduced uptake after therapy is the subject of some debate. Hilditch et al. (42) reported that both ^{131}I and ^{123}I are associated with stunning, even though ^{123}I does not give off any β -particles. Recently, Lassmann et al. (43) have found that administration of as little as 74 MBq (2 mCi) of ^{131}I could reduce subsequent thyroid remnant uptake by more than 50%. We suggest that, in general, if a total thyroidectomy has been performed by an experienced surgeon, then no pre-RRA scanning is necessary. We recommend that a standard empiric activity in the 0.9–3.7 GBq (30–100 mCi) range is reasonable for patients, as long as the TSH level is above 30 mU/L.

The recent availability of recombinant human TSH for diagnostic testing led several investigators to explore its value in preparing for RRA. A preliminary report in 2001 suggested that this approach was feasible, administering a mean activity of 4 GBq (110 mCi) (44). A retrospective study from Memorial Sloan–Kettering found comparable RRA success rates whether patients were prepared by thyroid hormone withdrawal or by rhTSH (45). A randomized phase II study has been completed, and the preliminary report also finds that preparation with rhTSH and administration of 3.7 GBq (100 mCi) results in ablation rates comparable with thyroid hormone withdrawal, with significantly less whole-body irradiation (46).

In general, we suggest that RRA can be omitted in low-risk patients who have well-differentiated solitary carcinomas <1.5 cm in greatest diameter without lymph node involvement and who have undergone a complete resection of the tumor. We recommend RRA for any individual with a carcinoma >1.5 cm or with a thyroid carcinoma of any size with obvious lymph node involvement, extrathyroidal extension, or multicentricity. We also recommend RRA for all individuals who have undergone incomplete surgical resection. All individuals who have RRA should have a whole-body scan after therapy to screen for unexpected metastatic lesions.

We recommend that all patients who have had a total thyroidectomy for papillary thyroid carcinoma, whether followed by RRA or not, be placed on doses of thyroxine sufficient to keep the TSH level below the lower limit of normal, unless medically contraindicated. Furthermore, all patients should be evaluated at 3–6 mo after surgery with a neck ultrasound and a serum Tg level while the TSH is suppressed. The absence of metastatic disease on the initial scan after therapy associated with negative ultrasound find-

ings and a suppressed Tg that is undetectable are very favorable but cannot exclude totally persistent disease. In this setting, 2 consensus statements recommend an rhTSH stimulation test at 1 y to expose occult disease (39,47). If the stimulated Tg is undetectable after rhTSH, the risk of recurrence is <0.5%, and the level of TSH could be allowed to rise to the normal range (0.5–2.5 mU/L) by decreasing the thyroxine dose. Yearly follow-up for such patients can consist of a clinical examination with TSH and Tg determinations. If TSH stimulation is not performed, persistent disease cannot be excluded, and LT4 treatment should be maintained at suppressive doses. Of note, there is no need for subsequent ¹³¹I whole-body scans in patients with an undetectable serum Tg after rhTSH, because virtually all patients with distant metastases had detectable serum Tg in that situation (48). Exceptions include patients with small lymph node metastases, which can be detected with neck sonography.

In 15%–20% of patients, the serum Tg becomes detectable after rhTSH stimulation. The significance of these low detectable Tg levels remains a subject of debate. Follow-up of such patients has shown that the rhTSH-stimulated Tg levels will decrease some months or years later and become undetectable in two-thirds of such patients, who will then be considered cured. It is likely in these patients that Tg was produced by irradiated cells that died between the 2 challenges; in the other third, serum Tg will gradually increase and the majority of these patients will experience a recurrence (49,50). Thus the trend of serum Tg is much more informative than any single measurement alone.

The use of supersensitive Tg assays cannot replace, at present, stimulation by TSH, because the number of patients with low but detectable suppressed Tg values in supersensitive assays is extremely high, but their clinical course is yet to be determined.

¹³¹I THERAPY FOR LOCOREGIONAL RECURRENCES

Locoregional lymph node recurrences are usually discovered by neck sonography or by physical examination. They occur in 15%–20% of all patients with differentiated thyroid carcinoma. When enlarged nodes are confirmed to be malignant by fine-needle aspiration biopsy, the therapy of choice is usually surgical resection. However, increasingly sensitive power Doppler sonography can lead to the discovery of small masses or nodes that may be amenable to radioiodine therapy. At Memorial Sloan–Kettering, we found that a single dose of radioiodine can abolish subsequent locoregional uptake of radioiodine in approximately 65% of patients (51). Selected centers will use dosimetry in such patients to administer the maximal safe dose; however, most centers will administer an empiric activity, such as 3.7 or 5.5 GBq (100 or 150 mCi).

At the Institut Gustave Roussy (IGR), we find that small lymph node metastases (<1 cm in diameter) can be treated with ¹³¹I alone, and if any abnormality (such as ¹³¹I uptake

or abnormalities on neck sonography) persists after 2 or 3 treatment courses, surgery may be warranted. Large lymph node metastases (>1 cm in diameter) are usually only partially responsive to ¹³¹I treatment, and surgery can be undertaken as a first-line treatment.

¹³¹I THERAPY FOR DISTANT METASTASES

¹³¹I therapy has been used to control distant metastases from differentiated thyroid carcinoma for more than 50 y. It was clear early on that metastatic lesions only had a small fraction of the iodine avidity that normal thyroid tissue exhibited. The most common distant metastatic sites are lungs, spine, and appendicular bone. The standard preparation for radioiodine therapy of distant metastases involves withdrawal of thyroid hormone to elevate the TSH level. There is no evidence that higher TSH levels provide any better outcomes than those just above 25–30 mU/L. Occasionally, widespread differentiated thyroid carcinoma can produce thyroid hormone, which prevents a significant elevation of TSH. The activity administered may be empiric, ranging from 3.7 to 11.1 GBq (100–300 mCi), or may be tailored according to dosimetric studies. At the present time there is no evidence that one approach results in a better outcome than the other.

At IGR, Schlumberger et al. (52) reported a retrospective follow-up of 394 patients with distant metastases who were treated with radioactive iodine. Forty-six percent of the patients had complete resolution of uptake and excellent long-term survival. Factors that predicted a good response included young age and small volume disease, especially diffuse micronodular lung disease, and this was confirmed by subsequent studies (53–56). At Memorial Sloan–Kettering, we found that at 1 y after a single high dose of radioiodine complete resolution of radioiodine uptake could be achieved in 33% of those with lung metastases and in 7% of those with bone metastases (51). Many anecdotal reports and several series on the use of radioactive iodine therapy for bone metastases are in agreement that bone metastases are generally resistant to commonly used activities of ¹³¹I, which may be related primarily to the usual large mass of bone metastases at their discovery (57–60).

A retrospective report from the Mayo Clinic described 85 patients with metastatic differentiated thyroid carcinoma (61). At 10 y, 75% of the patients had died. Univariate analysis found that radioiodine uptake by lesions was associated with a better prognosis; however, this did not hold up under multivariate analysis, which found that older age and multiple organ sites were the only significant predictors of cancer mortality.

We have recently found that metastatic lesions that show high avidity for ¹⁸F-FDG on PET appear to be resistant to high-dose radioiodine therapy (62). We caution against repeated administrations of high-dose ¹³¹I in such patients, unless there is progressive evidence of favorable response to the therapy. We also caution that resolution of radioiodine

uptake in metastatic lesions on subsequent whole-body scan may lead to a false sense of achievement while less differentiated components that can only be imaged by ^{18}F -FDG PET are progressing (63).

A new approach that may shed light on the unpredictable response of metastatic lesions to radioiodine therapy is emerging. PET has the ability to precisely determine the concentration of a positron emitter in an individual lesion in vivo. As noted previously, recent developments with ^{124}I PET-based lesion dosimetry may enable more educated decisions on which patients to treat, based on the likelihood of delivering sufficient radiation to individual lesions (19).

There has been a trend toward using radioiodine therapy for thyroid cancer survivors who have elevated serum Tg levels, even in the absence of identifiable lesions (64–66). Several small series have reported that lesions can often be seen on scans after therapy and that subsequent serum Tg levels are often lower. Other investigators also find that this strategy occasionally helps localize occult disease. However, they recommend against widespread use of radioiodine therapy in all patients who have mild elevations of serum Tg in the absence of radiologically identifiable disease (67,68). It is likely that patients seen at different stages of follow-up have been mixed in these studies, and more recent studies have shed light on this issue. Two-thirds of patients who have detectable serum Tg after TSH stimulation and no other evidence of disease at 1 y after initial therapy will normalize their serum Tg at the subsequent control TSH stimulation, in the absence of any further treatment. This is the result of the disappearance of benign or malignant thyroid cells that have been irradiated and disappear slowly. In patients with persistent cancer, the serum Tg will gradually increase, and this trend will define a group needing additional treatment (49,69).

^{131}I TO ASSIST IN SURGICAL LOCALIZATION OF RESIDUAL DISEASE

A local or regional recurrence that is palpable or easily visualized with sonography or CT scan or that persists after 2 to 3 courses of ^{131}I therapy should be surgically removed. A report by Travagli et al. (70) suggested that total excision can be facilitated by a whole-body scan performed 4 d after administration of 3.7 GBq (100 mCi) of ^{131}I , because additional tissue that should be excised may be identified. Surgery is performed 1 d later, preferably using an intraoperative probe. The completeness of resection is verified 1 to 2 d after surgery by another total-body scan. At IGR, the intraoperative probe was useful or decisive in the majority of patients, because it permitted the excision of neoplastic foci embedded in sclerosis resulting from previous surgery or located in unusual sites and permitted evaluation of the completeness of surgical excision. This protocol permitted total excision in 92% of cases. The dose to the surgeon's hands remained within the authorized safety range.

STRATEGIES TO AUGMENT RADIATION DELIVERED BY ^{131}I

The limited success rate of radioiodine at destroying metastatic lesions has been assumed, probably correctly, to be the result of low occupancy of the isotope in thyroid cancer cells and, therefore, low radiation doses. Several groups have attempted strategies to increase the intracellular occupancy time.

The value of a strict low-iodine diet as preparation for radioiodine therapy of metastatic disease has been debated for years. There are no evidence-based prospective studies that have clearly shown a benefit from this practice. However, there is general acceptance of this approach, based on the observations that high levels of exogenous iodine (such as after iodinated contrast agents for CT scans) can block the uptake of radioactive iodine. This is why iodine contamination should be avoided by instructing patients to follow a low-iodine diet for 1–2 wk and to discontinue pharmaceutical or “alternative medicine” products, such as health or multivitamin pills. Moreover, when in doubt about iodine contamination or, even better, as routine practice, urinary iodine should be measured. Patients with elevated urine iodine ($>200\ \mu\text{g/L}$) should be postponed from receiving ^{131}I therapy until levels revert to normal. It should be noted that maintaining LT4 treatment when rhTSH is used for stimulation slightly increases the urinary iodine excretion, but that will remain far below $200\ \mu\text{g/L}$.

Lithium had been shown to reduce the exit of iodine from normal thyroid cells. Because this is a clinically available drug for the treatment of psychiatric disorders, several groups have explored its potential use at increasing the effective radiation dose to metastatic lesions. Koong et al. (71) summarized the experience from the National Institutes of Health group in 15 patients. They found that lithium pretreatment increased retention in 24 of 31 individual lesions. The lengthening of the half-life of radioiodine resulted in a doubling of radiation to the lesions on average. No long-term outcomes were reported from this cohort.

Other agents that have been explored as potential adjuvants to increase the effectiveness of radioactive iodine are based on increasing NIS expression in thyroid cancer cells. Furuya et al. (72) found that histone deacetylase inhibitors could restore radioiodine accumulation in poorly differentiated thyroid cancer cells in vitro. Our preliminary experience with the histone deacetylase inhibitor, suberoylanilide hydroxamic acid, found that increased radioiodine uptake was present in 1 of 3 evaluable patients (73). Demethylating agents may also be used in this context.

Several groups have investigated the redifferentiating properties of retinoic acid derivatives. An early report in 1 patient documented that retinoids could apparently redifferentiate thyroid cancer cells leading to enhanced radioiodine uptake (74). Many anecdotal reports have followed that support or reject this approach. This subject has been reviewed extensively by Schmutzler (75). Re-

cently, Haugen et al. (76) reported that 2 retinoid receptors, RAR β and RXR γ , are differentially expressed in thyroid cancer cell lines and that application of the amyloid precursor protein ligand suppressed proliferation in cell lines that expressed both of these isoforms. In the largest study to date, Jarzab et al. (77) found that isotretinoin appeared to stimulate radioiodine accumulation in only 2 of 23 treated patients. No significant effect on tumor progression has been reported.

SIDE EFFECTS OF ^{131}I THERAPY

The most clinically evident side effects of ^{131}I treatment are usually minimal and transient. Nausea and gastric pain often occur after ^{131}I treatment and typically last a few days. Sialadenitis is not uncommon in the first few days after therapy, with pain and enlargement of salivary glands but rarely progressing to chronic xerostomia (78). Prophylaxis usually takes the form of ingestion of large quantities of fluids and sialogogues, such as lemon juice or chewing gum. There is no evidence that these maneuvers reduce the incidence or severity of sialadenitis, but they are commonly used. Subsequent obstruction of salivary gland ducts may occur weeks to years later, resulting in sudden swelling, tenderness, and rarely infection of the salivary glands, most commonly the parotid gland. Loss of taste or dysgeusia is a regular feature, but this usually lasts only a few days. Ocular dryness and nasolacrimal drainage system obstruction have recently been reported in thyroid cancer patients treated with ^{131}I (79). In cases of large thyroid remnants, neck edema may be prevented by short-term corticosteroid therapy. It is noteworthy that no respiratory sequelae were observed after ^{131}I treatments of diffuse lung metastases (52).

Infertility, Gonadal Failure, and Genetic Effects

Administration of ^{131}I is strictly contraindicated in pregnant and lactating women. The primary sources of radiation to the gonads from ^{131}I therapy are circulating iodoproteins in the blood and ^{131}I in the bladder and gut. After the administration of 37 MBq (1 mCi) of ^{131}I to a euthyroid subject, doses to the ovaries are 1.4 mGy (0.038 mGy/MBq) and doses to the testes are 0.85 mGy (0.023 mGy/MBq) (based on MIRD). These doses are in the same order of magnitude as doses delivered by a pelvic radiograph. In males, repeated radioiodine administration is associated with an impairment of spermatogenesis, increased levels of follicular-stimulating hormone, and decreased levels of inhibin B (80,81). There is typically no significant decrease in the serum testosterone concentration after ^{131}I treatment. In females, a transient ovarian failure, mainly in older premenopausal women (82), and an earlier onset of menopause have been observed after ^{131}I treatments (83).

The notion that radiation is mutagenic and may affect germ cells (thereby resulting in genetic damage to offspring) has raised concern regarding the use of ^{131}I in the management of thyroid disorders in patients of childbearing

ages. An extensive study of Japanese atomic bomb survivors demonstrated no statistically significant genetic effects (84). Moreover, no evidence of any significant genetic effect was found in 2 large studies of pregnancy outcomes and offspring of cancer patients who had undergone abdominal or pelvic irradiation during childhood or adolescence (85,86). In these studies, the increased prevalence of miscarriages was attributed to radiation-induced pelvic fibrosis. The study of the outcomes of 290 pregnancies that occurred after treatment of thyroid carcinoma when compared with those of 2,181 pregnancies that occurred before treatment of differentiated thyroid carcinoma revealed an increased frequency of miscarriages after thyroid surgery and after ^{131}I treatment. The prevalence did not vary with cumulative exposure to ^{131}I , but the prevalence was maximal in women who became pregnant within 1 y of treatment with ^{131}I . Exposure to ^{131}I did not alter the likelihood of preterm birth, low birth weight, stillbirth, congenital malformations, death during the first year of life, thyroid disease, or nonthyroidal malignancies in offspring. On the basis of these data, there is no reason for patients exposed to radioiodine to avoid pregnancy. It is recommended that conception be delayed for 1 y after therapeutic administrations of ^{131}I and until control of thyroid hormonal status has been achieved (87). Indeed, thyroid hormonal status should be carefully monitored (before conception and during pregnancy) by TSH measurements every 2 or 3 mo, because pregnancy frequently requires increases in the daily thyroxine dosage (88).

Carcinogenic Effects

Studies of large cohorts of thyroid cancer survivors treated with radioiodine have been monitored for an increased risk of solid tumors or leukemias. Because these tumors may occur only in a minority of patients treated with the largest cumulative activities of ^{131}I , discrepant results have been reported, and this issue remains controversial.

The risk of leukemia is significantly increased for cumulative activities higher than 18.5 GBq (500 mCi), especially when associated with external radiation therapy. For cumulative activities below 18.5 GBq (500 mCi), it is suggested that the relationship between the cumulative activity and the risk is linear, and from these data it was inferred that exposure to 3.7 GBq (100mCi) may double the risk. Fortunately, because of the very low incidence of acute leukemia in the general population, this increased risk results in only a very few cases (89). On the other hand, several studies did not find any increased risk of second malignancies related to radioiodine therapy (90–93). A large European study found an increased risk of all solid tumors in ^{131}I -treated thyroid cancer patients, and a site-by-site analysis found a relationship between ^{131}I exposure and the occurrence of bone and soft tissue, colorectal, and salivary gland cancers (88). An excess risk of breast cancer has been reported in females treated for a thyroid carcinoma (94). However, this risk was not related to previous radiation exposure with ^{131}I or ex-

ternal radiation exposure (95). Although the risks are not considerable, these data support a selective use of radioiodine only in patients in whom clinical benefits are expected. When treated with ^{131}I , simple measures such as abundant hydration and laxative treatment should be used to reduce tissue radiation doses.

Radiation Safety

The general strategy is that radiation exposure should remain as low as reasonably achievable for all persons concerned. The safety factors for external exposure are time, distance, and shielding. Exposure is directly proportional to the time an individual is in the vicinity of the source; therefore, time should be minimized. Exposure decreases with the square of the distance from the source; therefore, the distance should be maximized. Shielding may be used in specific circumstances. Considerable measures should be used to avoid contamination of the skin with radioactive material, and even greater care should be taken to prevent internal contamination by swallowing or breathing or by absorbing radioactive material through the skin.

Written and oral information should be provided to patients before ^{131}I treatment to increase compliance and to decrease uncertainty. Hospital personnel should be regularly educated, and written treatment procedures should be readily available to increase safety.

Notable differences are found in regulations between countries. In many countries, such as the United States, France, and Italy, patients are hospitalized in special units for administrations of $>0.7\text{--}1\text{ GBq}$ (20–30 mCi). Typical recommendations suggest that patients can be discharged when the dose rate at 1 m is $<40\text{ }\mu\text{Sv/h}$, which corresponds to an activity of $0.7\text{--}1\text{ GBq}$ (20–30 mCi). These patients are requested to avoid contact with children and pregnant women and to avoid public transportation for a few days. In other countries, such as Germany, regulations are even more stringent.

Although initially high, the risk of external radiation is short lived in thyroid cancer patients, because uptake is low in thyroid tissues (typically $<2\%$) and the biologic and resulting effective half-life in thyroid tumors and the total body is short (typically 12–15 h in hypothyroid patients). Patients can usually be discharged from the hospital 2 or 3 d after ^{131}I administration. Simple measures, such as abundant oral hydration ($>2\text{ L/24 h}$), lemon juice, and laxative treatment, may reduce radiation concentration in the patient's body.

CONCLUSION

^{131}I has had a major impact on the progressive control and cure of thyroid carcinoma. However, we have learned over the years that it is not a panacea. It has significant side effects that must be considered in determining the risk-to-benefit ratio for each patient. There is agreement that ^{131}I remnant ablation reduces local recurrence rates after total or near-total thyroidectomy, in those at higher risk for recur-

rence. It is very useful for iodine-avid disease that is not surgically accessible, especially diffuse lung metastases in younger individuals. Its efficacy in older individuals with large metastases is considerably lower but still poorly defined. More epidemiologic studies on the incidence and prevalence of complications of ^{131}I are needed to enable us to better define the risks and benefits of this therapy. The growing knowledge of how ^{131}I is incorporated into metastatic lesions, of the factors which can prolong its occupancy time, and of the development of lesion dosimetry methods will undoubtedly alter its usage pattern in the future.

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J Nucl Med. 2005;46:28S-37S.

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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AND MOLECULAR IMAGING