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Changing Concepts in the Management of Differentiated Thyroid Cancer

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The management of patients with differentiated thyroid cancer has changed significantly over the last few decades. Mortality has decreased as the result of earlier detection, refined surgical approaches, subsequent radioiodine ablation, and the development of more sensitive methods for detecting and monitoring disease recurrence. The latter has been facilitated by serum thyroglobulin measurements, the use of recombinant human thyrotropin, and the use of ^{18}F-deoxyglucose/positron emission tomography in selected instances where radioiodine imaging fails to locate known or suspected recurrent or metastatic disease.
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Because differentiated thyroid cancer (DTC) is among the most curable of cancers yet the presence of incidental thyroid micrometastases (diameter 1 cm or smaller) is 5% to 36% of autopsied adults,[1] the management of DTC is one of the more debated topics in clinical medicine. Significant developments in monitoring and treatment during the past decade have changed many of the traditional approaches to the patient with DTC, some of which remain controversial. These developments and controversies are presented in this article, and include the initial surgical approach, the question of whether radioiodine ablation (RAI) is always necessary, the use of recombinant human thyrotropin (rhTSH) for both diagnosis and therapy, patient follow-up with serum thyroglobulin (Tg) levels with or without radioiodine imaging, and outpatient RAI. The highly debated issues are also covered, such as the preferred iodine isotope for imaging (I-131 versus I-123), the concept of thyroid stunning, and the handling of the difficult problem of the Tg-positive/radioiodine-negative patient.

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Current Approach After the Diagnosis of DTC

Extent of Surgery

Surgery is the primary mode of therapy for patients with differentiated thyroid carcinoma. Total thyroidectomy should be performed if the primary tumor is 1 cm or more in diameter or if extrathyroidal extension or metastases are present. This aggressive initial surgical approach is associated with lower rates of local and regional recurrences and overall morality.[2-5] If the tumor is less than 1 cm and confined to one lobe, then unilateral lobectomy and isthmectomy are appropriate. This operation should be performed by an experienced thyroid surgeon to minimize the postoperative risk of permanent hypoparathyroidism and recurrent laryngeal nerve injury.

RAI: Is It Always Indicated?

The most effective nonsurgical treatment for papillary thyroid carcinoma is radioiodine, in the form of I-131. Radioiodine has 3 main indications in the postoperative management of patients with thyroid cancer: ablation of residual thyroid tissue, imaging for possible recurrent disease, and treatment of residual or recurrent thyroid cancer.

The goals of RAI are: (1) to destroy any microscopic foci of disease remaining after the surgery and (2) to destroy any remaining normal thyroid tissue to (a) improve the value of serum Tg as a tumor marker, ie, if all normal thyroid cells are eliminated by RAI, then any increase in serum Tg in the follow-up of these patients becomes more specific and indicates recurrence of thyroid cancer, and (b) increase the spec-

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ificity of I-131 scanning for detection of recurrent or metastatic disease by eliminating uptake by residual normal tissue.

One should expect from the aforementioned goals that RAI can result in lower recurrence rates and possibly improved overall survival. Unfortunately, published data on this issue are retrospective and not randomized; there remains considerable disagreement about the role of I-131 ablation, especially in patients with low-risk disease (ie, no soft tissue invasion and no distant metastases).[6] Combining data from multiple retrospective studies, the relapse rate after RAI may be reduced by as much as 50%,[7] and decreased mortality has been demonstrated in several large retrospective studies among patients whose primary tumors were at least 1 to 1.5 cm in diameter or were muticentric, or who had soft tissue invasion at diagnosis.[3,5] At the Mayo Clinic, RAI did not improve mortality or recurrence rates in patients with low-risk papillary thyroid cancer who had undergone complete tumor excision.[8] It appears that there is less need for RAI in low-risk patients (tumor less than 1–1.5 cm and age younger than 40-45 years at diagnosis) who have had a true total thyroidectomy. RAI is recommended by many experts for any individual with a carcinoma >1 to 1.5 cm or of any size with obvious lymph node involvement, extrathyroidal extension, or multicentricity. Some also recommend RAI for any patient 40 to 45 years or older at diagnosis.[3,4,9]

Recombinant Thyrotropin Versus Thyroid Hormone Withdrawal for Monitoring and Treatment

Periodic diagnostic testing for disease recurrence most commonly includes serum Tg measurements and diagnostic radioiodine whole-body scanning (WBS). The former reflects the ability of the cells to produce Tg, and the latter is dependent on their ability to concentrate iodine. Because both of these processes are driven by thyroid-stimulating hormone (TSH), both tests are most sensitive during maximum TSH stimulation of both normal residual or neoplastic thyroid cells.[10] Traditionally, this was accomplished by temporary thyroid hormone withdrawal (THW) before testing, which would elevate the TSH level via negative feedback. However, 3 potential problems arise from THW: (1) the negative impact of the symptoms of prolonged hypothyroidism, such as fatigue, weight gain, and lack of productivity; (2) the theoretical stimulation and proliferation of DTC cells by the rising TSH (a particular problem with metastases in the vertebrae close to the spinal cord or located in the brain; and (3) the occasional patient whose TSH level cannot be elevated to the conventional cut-off level of 30 uIU/mL because of large thyroid hormone-producing metastases.[11] These drawbacks prompted interest in an alternative to THW, such as an exogenous form of TSH, whose administration is independent of the thyroid-pituitary axis, thereby allowing the patient to maintain the thyroid hormone regimen. This led to the development of a purified form of human TSH that maintains its biological activity, known as recombinant human TSH, or rhTSH.[11] After successful clinical trials, rhTSH was approved for use in diagnostic testing by the U.S. Food and Drug Administration (FDA). Subsequent reports in the literature comparing the use of rhTSH to THW for diagnostic testing in the surveillance of DTC patients found that testing using rhTSH was comparable to THW in terms of sensitivity and specificity, with no significant differences in the positive and negative predictive values.[12-14]

Administration of rhTSH is not indicated in the postoperative period after thyroidectomy because inevitably there will be remnant thyroid, which must be ablated to facilitate follow-up imaging and Tg measurements. Because postoperative RAI necessitates THW, that would defeat the purpose of rhTSH. Similarly, patients at high risk of disease recurrence, such as those with invasive or aggressive tumors and patients with known adenopathy or distant metastases, require THW for subsequent RAI. Instead, rhTSH-stimulated WBS and Tg measurements are appropriate for patients at low risk of harboring a thyroid remnant, disease recurrence, or metastatic disease. In our practice, an example of "low risk" would be a patient demonstrating a normal WBS and a serum Tg level of 2 μg/L or lower while under THW. Subsequent testing using rhTSH is indicated here because the need for future ablation is very unlikely. It should be noted, however, that there are no standard guidelines that distinguish "low-risk" from "high-risk" patients, or that dictate when rhTSH should be used in patient preparation for diagnostic testing. Such decisions should be agreed on by both the nuclear medicine physician and the referring endocrinologist, which requires both effective communication and mutual understanding.

Because rhTSH stimulation was found to be comparable with THW for diagnostic purposes, then theoretically it should be comparable with THW for RAI under clinical circumstances described above wherein THW needs to be circumvented. Numerous reports support the safety and efficacy of rhTSH summarized by Luster and coworkers;[15] from 1997 through 2004, reports published by 29 centers demonstrated the efficacy of using rhTSH in preparation for therapy in a total of 394 patients.

The use of rhTSH in DTC is FDA-approved for diagnostic testing only, and not for therapy. In the United States, therefore, in instances in which significant THW-induced hypothyroid complications are anticipated, or where THW cannot adequately elevate the endogenous TSH level, the use of rhTSH for RAI at present can only be achieved via "off-label" use of rhTSH, or by so-called compassionate clearance from the manufacturer (Fig. 1). In early 2005, the European Commission approved the use of rhTSH for therapeutic radioiodine preparation. This approval was based on a 9-center global randomized trial that found equivalent thyroid remnant ablation rates after treatment of 60 patients with 100 mCi I-131 (3700 MBq) postoperatively, prepared by either THW or by rhTSH stimulation.[16] The same data has been forwarded to the FDA for its regulatory approval for the use of rhTSH in RAI.

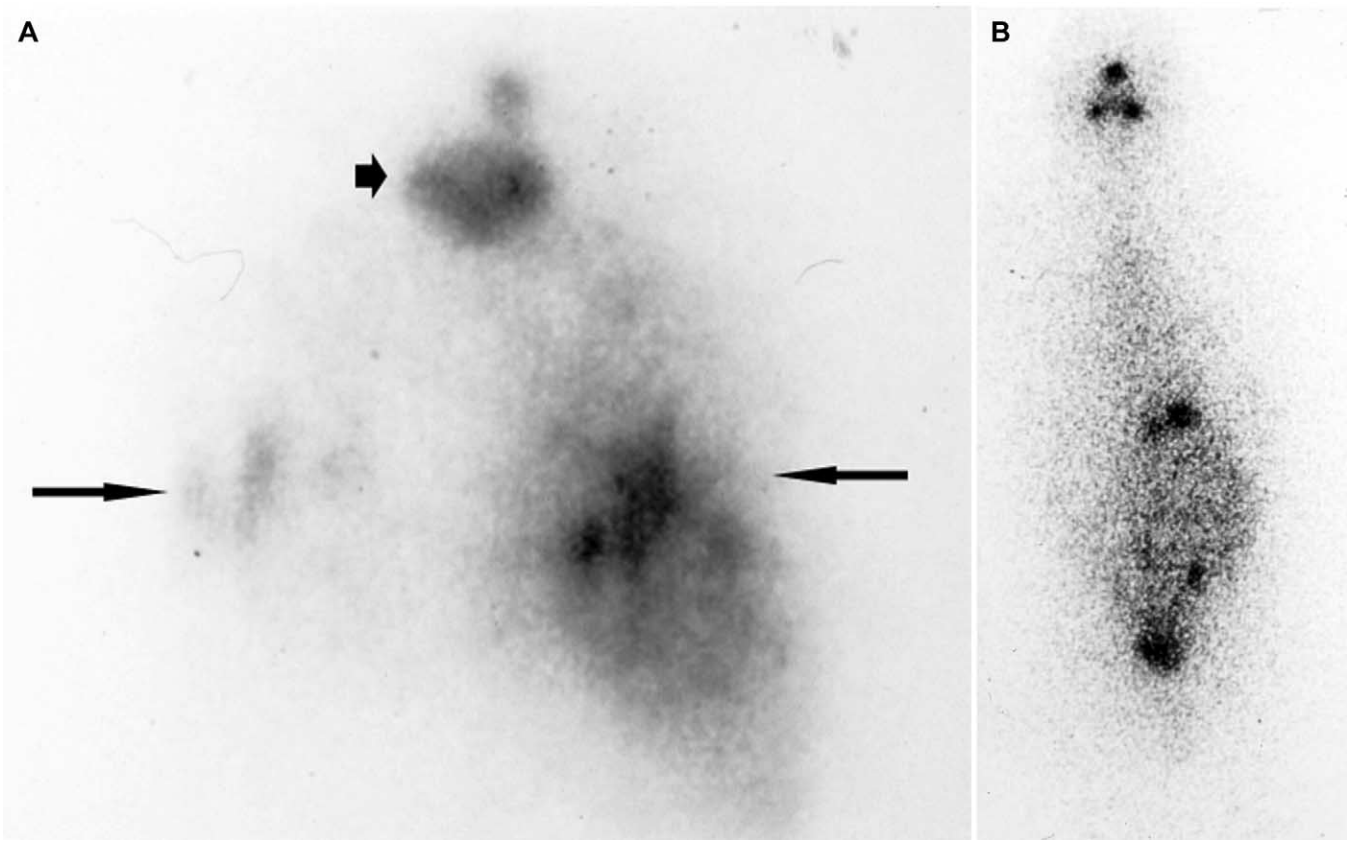

Figure 1 rhTSH-stimulated I-131 ablation. This 59-year-old man presented with a sternal mass, a biopsy of which revealed metastatic papillary-follicular DTC. Three months after total thyroidectomy and sternal resection, his Tg level was 50.7 μg/L, but a repeat TSH level was 11.72 IU/mL. He then underwent RAI with 200 mCi (7200 MBq) I-131 after 2 days of rhTSH stimulation. His 1-week postablation scan (A) reveals metastases in the manubrium (short arrow) and lung bases (long arrows). Nine months later, the Tg was 18 μg/L with a TSH of 16.43 IU/mL, on THW. A postablation scan 1 week after another 200 mCi (7200 MBq) with rhTSH stimulation revealed mild activity at the left lung base only (not shown). Six months later, via THW, the TSH level was 106.50 IU/mL, Tg $<$ 0.9 μg/L, and the diagnostic WBS was normal (B).

Thyroglobulin and Radioiodine Scanning for Long-Term Monitoring

Serum Tg

Serum Tg is very useful in the follow-up of patients with DTC who are treated with surgery and RAI. Tg is secreted by normal and neoplastic thyroid cells; if RAI eliminates all normal cells, the only remaining source of Tg production would be malignant thyroid cells. Therefore, measurements of serum Tg provide important information about the presence or absence of residual, recurrent, or metastatic disease in patients with DTC. Currently, serum Tg generally is measured by 2-antibody "sandwich" immunometric assays, which are quicker and more sensitive than the old radioimmunoassay.[17,18] The greatest limitation in interpreting Tg levels is the potential for interference by anti-Tg autoantibodies,[17] which can falsely lower serum Tg if measured by the immunometric assay and falsely increase serum Tg if measured by the radioimmunoassay. Therefore, for patients who have positive anti-Tg autoantibodies, measurement of serum Tg is not reliable and can be misleading. All laboratories that measure serum Tg should test for these antibodies in any serum submitted for Tg assay. As many as 25% of patients with DTC have anti-Tg autoantibodies after their initial surgery. Although the clinical significance of these antibodies is unclear, their persistence for more than 1 year after thyroidectomy and RAI probably indicates the presence of residual thyroid tissue and possibly an increased risk of recurrence.[19]

One important factor in the interpretation of serum Tg values is the concurrent serum TSH concentration, given that Tg production and secretion are TSH-dependent. Therefore, sensitivity of the serum Tg assay for detection of thyroid carcinoma increases when serum TSH levels rise after discontinuation of thyroxine therapy[20,21] or after administration of rhTSH.[12] A detectable serum Tg concentration during thyroxine therapy probably signifies the presence of carcinoma but not the absence of any normal thyroid tissue; in comparison, an undetectable serum Tg concentration during TSH stimulation suggests the absence of disease (and any normal thyroid tissue as well). In general, the sensitivity of detecting thyroid carcinoma by measurement of serum Tg after discon-

tinuation of thyroxine therapy is 85% to 95%,[20-22] but may be as low as 50% during therapy.[22] The results are most likely to be falsely negative during thyroxine therapy in patients with small nodal metastases of papillary carcinoma and in those with tumor dedifferentiation. Therefore, an undetectable serum Tg during thyroxine therapy can be misleading in a large proportion of patients with residual DTC and therefore a TSH-stimulated serum Tg level should be obtained in the follow-up of patients with DTC. Considerable evidence supports the notion that the 2 methods used to stimulate Tg (THW and rhTSH) are equally effective in detecting metastatic thyroid cancer when a cutoff of 2 μg/L is used.[13]

A formal set of recommendations[23] was published by an ad hoc consensus development group that advocated the use of rhTH-stimulated Tg testing without a diagnostic scan in low-risk patients with DTC; these are patients who have undergone total thyroidectomy and RAI at least 6 to 12 months ago, who have no clinical evidence of tumor, and who have undetectable serum Tg levels during thyroxine therapy; the majority will have had tumors smaller than 4 cm, not of a virulent subtype, which were completely resected with or without nodal metastases, but without distant metastases. In this consensus, there are 2 different scenarios: (1) If serum Tg is detectable on thyroxine therapy, further workup is needed to localize the residual cancer (neck ultrasound, chest x-ray; based on the results, either I-131 scanning/treatment or surgery would be considered). (2) If serum Tg is undetectable on thyroxine therapy 6 to 12 months after thyroidectomy and RAI, a rhTSH-stimulated Tg alone (without a diagnostic I-131 scan) is performed. A stimulated Tg level more than 2 μg/L needs immediate attention and further workup (same as above); A Tg level less than 2 μg/L could be followed with periodic Tg measurements (either on thyroxine therapy if rhTSH-Tg is undetectable or rhTSH-stimulated if rhTSH-Tg is detectable but less than 2 μg/L).

Radioiodine WBS

Classically, diagnostic radioiodine WBS are performed periodically (usually once a year) in the follow-up of patients with DTC. WBS are performed after thyroxin withdrawal or after the administration of rhTSH. Two negative annual successive WBS have very good predictive value for a lack of future recurrence.[24] Serum Tg concentrations less than 2 μg/L after rhTSH administration were rarely associated with evidence of disease in one study, suggesting that the diagnostic WBS could be eliminated in this clinical scenario.[25] Other studies had similar results.[23] However, in a study by Robbins and coworkers, 13% of patients with stimulated serum Tg concentrations less than 2 μg/L had evidence of residual thyroid cancer.[26]

The consensus[23] published in 2003 advocated that a rhTSH-stimulated Tg alone was sufficient for follow-up of low-risk patients with no clinical evidence of disease and suppressed serum Tg during thyroxine therapy. However, this approach is not followed by all physicians and many still perform diagnostic WBS in conjunction with stimulated serum Tg levels.

The Use of I-131 Vs I-123 for WBS

I-123 has a photon energy of 159 keV, which is optimal for imaging with conventional scintillation cameras and provides higher-quality images compared with the lower resolution images of I-131, due to the latter's high gamma photopeak of 364 keV. In the past, both the limited availability from suppliers and the higher cost compared with I-131 has prohibited wide use of I-123. However, recent improvements in the availability of the latter have lead to more reasonable and competitive pricing, allowing more access of I-123. Although some institutions are currently using I-123 with success, a few issues have remained controversial. First, the optimal dose for I-123 remains unresolved. As with most radiopharmaceuticals, including I-131, increasing the dose of I-123 provides images with the highest sensitivity but with the disadvantage of higher expense and radiation burdens. Second, a consensus has not been reached for optimal timing for whole-body acquisitions following I-123 administration. Third, more data are needed comparing the sensitivity of I-123 diagnostic WBS compared with I-131 diagnostic and postablation WBS.

In a small series, Berbano and coworkers[27] investigated the use of high dose 10 mCi (370 MBq) I-123 scans imaged at 4, 24, and 48 hours and compared the results to I-131 postablation scans and found a low discordance rate of 6%. Although both 4- and 24-hour images had good resolution, the background activity was higher with the 4-hour scans. The 48-hour scans provided no additional information. This same institution performed a repeat study at a lower dose of 5 mCi (185 MBq) I-123 scanned at 4 and 24 hours only and compared the scan to I-131 postablation scans.[28] They again showed a low discordance rate of 7.2% for 24-hour images, but the 4-hour scan demonstrated a higher discordance rate of 14.8%. In a much larger study of 238 patients, Alzahrani and coworkers compared 5 to 15 mCi (185-555 MBq) I-123 scans at 24 hours compared with I-131 postablation scans and revealed an overall concordance rate of 87.8%.[29] Furthermore, only 6.7% of the posttreatment scans showed new abnormal foci that may have changed management. In contrast, DeGeus-Oei and coworkers used 3 to 10 mCi (11-370 MBq) I-123 compared with postablation I-131 scans and found that postablation scans revealed an additional 13 lesions on 55 patients.[30]

A majority of the studies evaluating I-123 for differentiated thyroid carcinoma have compared I-123 scans to I-131 postablation scans and not to diagnostic I-131 scans. I-131 postablation scans are considered more sensitive than diagnostic I-131 scans, with a discordance rate ranging from 3% to 25%.[31-37] Because many researchers have found that I-123 diagnostic WBS have a comparable concordance rate with I-131 postablation WBS, can it be inferred that I-123 diagnostic WBS are more sensitive than I-131 diagnostic WBS? Several groups have investigated this question.

Park and coworkers[38] used very small doses of 300 uCi (11.1 MBq) I-123 scanned at 24 hours compared with 3 to 10 mCi (111-370 MBq) I-131 in 150 patients and found similar sensitivities for postthyroidectomy patients (90% versus

93%, respectively).[38] However, for patients with prior radioiodine ablation I-123 sensitivity was lower (70% versus 93%) but not significantly different ($P = 0.061$). Another group also used very low doses of 270 to 540 uCi (10-20 MBq) I-131 2-hour head and neck images compared with 48- to 72-hour 5 mCi (185 MBq) I-123 diagnostic WBS.[39] Although I-123 correctly identified 94% of thyroid remnants, the authors concluded that I-123 scans were less accurate than I-131 WBS.

Mandel and coworkers[40] compared 1.3 to 1.5 mCi (48.1-55.5 MBq) I-123 5-hour scans to both 3 mCi (111 MBq) I-131 diagnostic scans scanned at 42 to 44 hours and postablation scans on the same 14 patients. The quality of the I-123 5-hour images were superior to the I-131 diagnostic scans and there was also a 91% concordance rate between the two scans. Using higher doses of 2 to 3.5 mCi (74-130 MBq) I-123 imaged at 24 hours compared with 3 to 5 mCi (111-185 MBq) I-131 72- to 96-hour diagnostic scans, Sarkar and coworkers[41] demonstrated no differences in the detection of residual thyroid bed tissue but lower sensitivities with I-123 for detecting metastatic disease. In the setting of negative I-131 scans and elevated serum thyroglobulin, Siddiqi and coworkers demonstrated a concordance rate of 92%, including distant metastases, between 5 mCi (185 MBq) I-123 and I-131 postablation scans.[42]

The tremendous variation in protocols between all of these articles investigating I-123 complicates the review and comparison of their content. Actual scan imaging times, collimator differences (low-energy all purpose, high resolution, pinhole) for both I-123 and I-131 (high versus medium energy), the sporadic use of single-photon emission tomography (SPECT), scan speeds, postablation time intervals, and crystal thickness varies between the studies, or are not reported. Additionally, few authors performed quantitative analysis and the sample size was small in many series thereby reducing the statistical power.

In summary, the current data suggests that I-123 scans using 2 to 5 mCi (74-185 MBq) imaged at 24 hours are comparable but not superior to both I-131 diagnostic and postablation scans. The I-123 diagnostic scans provide an alternative for those who want to avoid the potential for so-called "stunning." Higher doses and longer scan times have not been sufficiently studied to draw any definite conclusions at this time.

The Stunning Effect: Fact or Fiction?

Thyroid stunning is generally defined as a phenomenon in which a diagnostic I-131 dose decreases the uptake of a subsequent ablative dose of I-131, thereby potentially lowering its therapeutic efficacy. Currently, there is evidence that stunning does exist at a cellular level. Postgard and coworkers[43] showed in vitro inhibition of iodide transport following I-131 exposure using porcine thyroid cells. However, the clinical impact of stunning remains controversial and there is a strong division among authors in the literature.

Proponents of stunning cite numerous qualitative studies based on visual assessment that have shown uptake on diagnostic scans that appears less apparent on post therapy scans implying stunning.[31,38,44-46] These observations have been supported by numerous quantitative series that have shown substantially decreased radioiodine uptake after I-131 therapy compared with after I-131 diagnostic doses as low as 1 mCi (37 MBq).[38,47-50] In a quantitative study evaluating absorbed dose, Jeevanram and coworkers found a higher reduction of therapeutic uptake with higher absorbed doses of diagnostic I-131.[51] Not all quantitative articles have demonstrated stunning, however. Dorn and coworkers[52] found no reduction in thyroid uptake after dosimetry with 10 mCi (370 MBq) I-131 test activity.

Those who have advocated stunning observe that stunning appears to follow a dose–response curve. With a higher diagnostic I-131 dose, the incidence of stunning increases.[45,53] As a result, many institutions have reduced the amount of I-131 given for the diagnostic dose but this may result in lower sensitivity for detecting thyroid tissue and metastatic disease.[54] Even though stunning may be more frequent at higher doses, Karam and coworkers[55] did not find worse outcomes in patients who received higher doses. Although the usual diagnostic I-131 doses are typically considered too low to achieve any significant therapeutic effect, the high end of the range of 2 to 10 mCi (74-370 MBq) often are used for hyperthyroid therapy, leading several authors to hypothesize that there is partial ablation from the diagnostic dose.[50,56,57] Other authors also have postulated that stunning is more pronounced in thyroid remnants compared with the metastases.[45,50] Distant metastases may trap iodine less effectively or have a shorter iodine half-life.

The opponents of stunning have performed qualitative studies citing no evidence of "visual" stunning.[32,58,59] They claim that if there is such a marked decrease in uptake after I-131 therapy compared with the I-131 diagnostic scan, that this difference would be easily detectable by experienced readers.[59] Supporters of stunning argue that visual analysis is not an accurate means for assessing for stunning and that quantitative measurements should be used.[47,57,60] However, even some quantitative studies have showed no reduction in thyroid uptakes.[52,61]

For most clinicians, the most important aspect of stunning is the possibility of negatively impacting clinical outcomes. If stunning occurs at a cellular level, can it also have clinical influence by requiring more therapeutic doses to achieve treatment success, or lead to adverse clinical outcomes? Several authors evaluated clinical outcomes and the results are mixed. Muratet investigated outcomes of 1 mCi (37 MBq) versus 3 mCi (111 MBq) I-131 and found lower success rates with the higher dose.[62] Studies by Park and colleagues have also shown lower outcomes.[38,45] However, Karam and coworkers found no association between diagnostic doses administered (2.5 mCi [92.5 MBq] and 5 mCi [185 MBq]) and ablation outcome.[55] Furthermore, both our previous series[63] and Nakada and coworkers[64] found no difference in outcomes between patients with visual stunning and those without (Fig. 2). In a quantitative study, Bajen and coworkers[61]

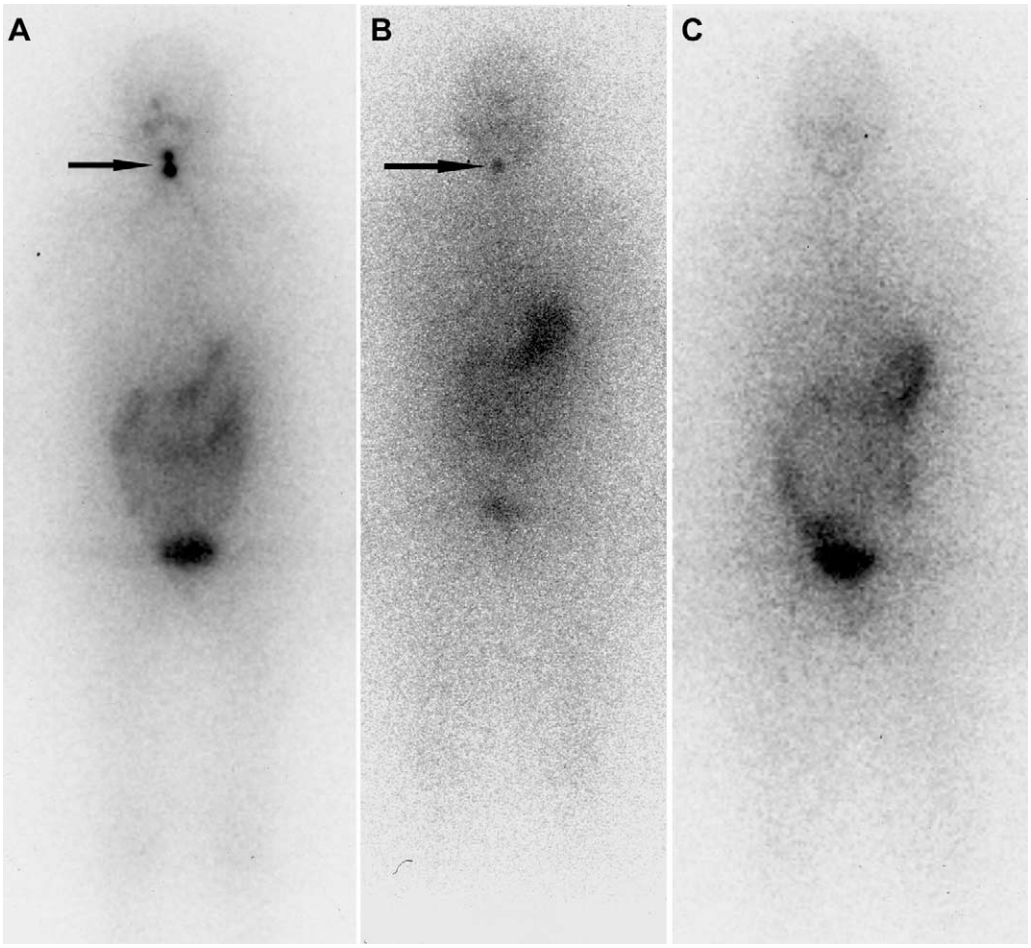

Figure 2 Thyroid stunning. Use of 48-hour 5 mCi (185 MBq) I-131 WBS (A) in a 38-year-old female with papillary-follicular DTC status post thyroidectomy reveals thyroid remnant (arrow). After ablation with 100 mCi (3700 MBq) I-131, a 1-week post ablation scan (B) indicates an interval decrease in thyroid bed activity. One-year follow-up 48-hour WBS after 5 mCi (185 MBq) I-131 is normal (C) with a Tg <0.9 μg/L with negative Tg-antibodies. Although demonstrated in this case, stunning had no clinical impact.

actually showed higher success rates in patients with stunning based on decreased I-131 uptakes.

To potentially avoid the possibility of stunning, some have advocated either substituting I-123 for the diagnostic WBS since it is a pure gamma emitter without any therapeutic effect, or eliminating completely the diagnostic WBS before ablation. However, not performing diagnostic scans has inherent pitfalls. First, it may lead to worse clinical outcomes by undertreating undetected disease. This concept is critical, as the first I-131 therapeutic dose has the highest therapeutic effect and subsequent doses are less effective.[52,65,66] Second, it may lead to administration of I-131 ablation in patients without significant thyroid remnant or noniodine avid thyroid cancer. Third, this strategy does not take into account the possibility that stunning may be caused by the therapy dose itself.

In summary, the concept of stunning remains controversial in the literature. Although there is evidence that stunning exists at a cellular level, investigations concerning its clinical significance are conflicting and no definitive conclusions can be made at this time. Both qualitative and quantitative analyses have their own pitfalls and both suffer from lack of standardization. Further systemic study will help clarify the impact of stunning from absorbed doses of I-131.

Management of the Tg–Positive/I-131–Negative Patient

An increased or persistently elevated Tg level indicates recurrent, persistent, or metastatic DTC, even if not visualized on the WBS. This results in a diagnostic dilemma. To date there is no single consensus regarding the management approach to patients in this situation.

False-Negative I-131 Scan

Under the suspicion of recurrent or metastatic DTC as evidenced by a Tg level greater than 2 μg/L,[23] a normal WBS can result from the following: inadequate TSH stimulation (ie, a TSH level less than 30 IU/mL at the time of imaging), small tumor size (below the resolution limits of the gamma cam-

era), iodine contamination (particularly from recent iodinated intravenous contrast), and tumor dedifferentiation. In the case of the latter, the DTC cells proliferate yet lose their ability to trap, organify, store, and metabolize iodine. The presumed mechanism is an acquired mutation of the sodium-iodine symporter (NIS) gene.[67] Without the NIS, the cells cannot incorporate iodine and theoretically, are not amenable to RAI. These DTC cells, however, still maintain the ability to synthesize Tg.

Localization

Regardless of the capability of the DTC cells to concentrate I-131, any potentially resectable local or metastatic lesion should be surgically removed before consideration for RAI. A tumor localization workup is therefore essential. Ultrasound scanning of the neck is the logical first step, which allows visualization of thyroid bed recurrence as well as cervical adenopathy. Anatomic imaging with computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent resolution, even for small lesions. Functional imaging with ^{18}F-fluorodeoxyglucose using positron emission tomography (FDG-PET) has been shown in numerous reports in the literature to accurately detect I-131-negative lesions.[68,69] Because rapidly growing recurrent and metastatic DTC cells consume more glucose than normal thyroid cells, they will concentrate radiolabeled glucose to a greater degree than normal cells. The faster the tumor growth, the more dedifferentiated the tumor cells, and the higher the glucose consumption. Consequently, FDG-PET is a sensitive tool for the detection of noniodine-avid DTC. Conversely, slow-growing iodine-avid DTC cells, although detectable on WBS, may not necessarily be detected on FDG-PET. The degree of FDG uptake is directly proportional to Tg synthesis (and the serum Tg level), the degree of tumor dedifferentiation, and also to the level of TSH stimulation.[70]

Role of FDG-PET

The largest series in the literature addressing the impact of FDG-PET on the management of patients with noniodine-avid DTC was undertaken by Schlutter and coworkers[71] in 2001. In their retrospective study, 118 FDG-PET scans were performed on 64 patients with DTC, 48 of whom had negative WBS. Forty-four patients had positive scans, 34 of which were proven true-positive, yielding a sensitivity of 77% and a positive predictive value of 83%. Of the 20 patients with normal FDG-PET scans, there were 15 false-negatives, giving a negative predictive value of only 25%. However, there was a change in management of 19 of the 34 patients (56%) with true-positive scans, a significant impact on patient care. The sensitivity of the scan increased as the serum Tg level increased; the true-positive rate was 11% with Tg levels less than 10, 50% with Tg levels 10 to 20, and 93% with Tg levels greater than 100 μg/L. This would be expected, because the higher the Tg level, the larger and more easily detectable the lesion. Another significant result from this study was the fact that the subset of patients who underwent further surgery on account of the FDG-PET scan results were free of recurrence on future follow-up. They conclude from this that although FDG uptake indicates tumor dedifferentiation, it does not necessarily indicate a poor prognosis with high mortality, as long as the tumor is completely removed. In general, however, FDG avidity of a DTC lesion is inversely proportional to the I-131 avidity, and in that sense, the degree of FDG uptake and prognosis are inversely related. In a series of 25 patients evaluated at the Memorial Sloan-Kettering Cancer Center, Wang and coworkers[72] found that high-dose RAI had no significant therapeutic impact on FDG-avid metastases.

Approach to the Patient With Localized But Nonresectable Metastases

If the metastatic lesions are not resectable, the Tg level is elevated, and the WBS is negative, some authors advocate empiric RAI, using doses of 100 to 300 mCi (3.7-11.1 GBq).[37,73] This approach is debatable, however, as others question the efficacy of such empiric therapy.[74,75] Fatourechi and Hay,[24] for example, showed that most patients in their series with negative WBS undergoing RAI did not demonstrate sufficient I-131 uptake on their postablation scans to warrant such empiric therapy. Instead, they advocate the use of external radiation therapy as being the treatment of choice for nonresectable, noniodine-avid DTC metastases.

Approach to the Patient With Nonlocalized Metastases

In this group of patients with suspected recurrence or metastases based on elevated Tg but which cannot be located radiographically, the question of empiric RAI has been evaluated by Fatourechi and Hay.[24] The theory behind this scenario is that the metastatic lesions are too small to be visualized radiographically; such "micrometastases" are below the resolution limit of any diagnostic imaging modality. These authors did a meta-analysis of 3 different series[37,76,77] in the literature. A total of 59 patients with micrometastases underwent empiric RAI, 50 of whom (85%) demonstrated uptake on postablation scans. The I-131 dose ranged from 75 to 300mCi. The authors postulated that I-131 activity within the small lesions was too low to be seen on the diagnostic I-131 scans, but sufficient enough to be detected on the postablation scans with the higher dose. Consequently, they recommend empiric RAI because there is a high likelihood of having a positive postablation scan after the therapy. Furthermore, the lack of any alternative treatments would justify empiric ablation. Schlumberger and coworkers[77] advocate repeating RAI until the postablation scan normalizes, up to a cumulative dose of 600 mCi (22.2 GBq) of I-131.

Inpatient Versus Outpatient RAI

Before 1997, patients with DTC undergoing RAI in the United States required hospital admission if they received more than 32 mCi of I-131 and were released when their exposure rates at 1 m fell to 7 mrem/hr or below, according to Regulatory Guide 10 CFR Part 35.75 of the Nuclear Regulatory Commission (NRC). After May 29, 1997, the NRC reg-

ulations were modified such that patients whose therapeutic doses exceeded 32 mCi need not be hospitalized, provided that their release does not expose the general public to a dose equal to or greater than 500 mrem.[78] This so-called "maximum likely dose" to an exposed individual is determined by patient-specific dose calculations that take into account the prescribed I-131 dose, whether or not the patient can transport himself/herself home alone, can function independently without the help of others in daily living, and maintains exclusive use of both sleeping and bathroom facilities for 1 or 2 nights. These are referred to as "occupancy factors." Under these criteria, for example, a patient may receive as much as 200 mCi (7.2 GBq) of I-131 and be released immediately, provided he/she can live alone for 2 nights. In our practice, this is not an unusual occurrence. Approximately three-fourths of our patients with DTC undergoing RAI are treated on an outpatient basis. By eliminating the requirement for hospitalization, the cost-savings are substantial.

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