THERAPEUTIC CONTROVERSY

The Use of Radioactive Iodine in Patients with Papillary and Follicular Thyroid Cancer

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*"Therapeutic Controversies" are an occasional feature of **The Journal of Clinical Endocrinology and Metabolism.** They present opposing views of invited contributors on a topic. All reprints must include the complete Therapeutic Controversy, so that each section can be read in context.*

Management of Patients with Scan Negative, Thyroglobulin Positive Differentiated Thyroid Carcinoma

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GENERAL aspects of the diagnosis and management of differentiated thyroid carcinoma (DTC) have been reviewed recently (1) and guidelines for management proposed (2). Yet controversy continues to plague our ability to develop specific evidence-based practice guidelines for issues related to initial radioiodine ablation and subsequent ^{131}I diagnostic and therapeutic interventions, due largely to the broad heterogeneity of the clinical characteristics of our patients and to the lack of sufficient data from well-controlled prospective studies. In our survey (3) of management practices by clinical thyroidologists for DTC, postoperative radioiodine ablation was recommended for a 2 cm well encapsulated lesion without evidence of tissue invasion by 61% of respondents. Sixty-nine percent of respondents obtained a pretreatment ^{131}I total body scan (TBS), and 87% obtained a post-treatment scan. Fifty-nine percent would obtain a subsequent follow-up scan, and 85% monitored serum thyroglobulin (Tg), whereas management varied widely on a number of other variations of the index case described.

In their respective sections of this *Therapeutic Controversy*, Sherman and Gopal and Schlumberger and Hay address different but related aspects of the management of patients with DTC. The respective authors are not engaged therefore in a debate. While DTC remains one of the most curable of all cancers, patients with aggressive disease are occasionally seen, and outcomes have been clearly related to a number of variables (4–6). Given the numerous variables existing in any single individual or in any group of patients, I believe the

design of and adherence to an algorithmic approach to the follow-up management of patients with DTC to be both treacherous and possibly overly simplistic. Rather, management of each case should be individualized. Having said that, let us examine some of the recommended approaches proposed by Sherman and Gopal and by Schlumberger and Hay.

Several series suggest that excellent prognosis with cure attends DTC of less than 1.5 cm diameter, even when treated with less than a near total thyroidectomy (5, 6). I would like to focus this discussion on higher risk lesions that are 2 cm or greater and that might have been associated with either regional node metastases or distant metastases. For such patients, the usual management would be total thyroidectomy followed by radioiodine ablation. This initial management has been almost universally adopted since the publication by Mazzaferri *et al.* (7) demonstrating that less aggressive surgery without radioiodine ablation is associated with higher rates of recurrence and death. Schlumberger and Hay would have us adopt a more "selective" approach to the use of radioiodine. They challenge whether ablation is actually of benefit and point out that the reduced recurrence rates seen in the Mazzaferri series after radioiodine ablation may have been the result of less than complete total thyroidectomies. This conclusion is based upon the finding of comparable recurrence rates with or without radioiodine ablation at the Mayo Clinic, where an ostensibly more complete thyroidectomy was regularly performed.

Schlumberger and Hay cite the results of Simpson *et al.* (8) as supporting this contention. These workers found that radioiodine ablation benefited survival only in patients with residual microscopic disease. Curiously, the Mayo group had previously published data indicating that frequency of local recurrence was no different between patients having total *vs.* bilateral subtotal thyroidectomy (9), and survival was not improved by total thyroidectomy in either minimal or higher risk patients with papillary carcinoma (10). Thus, the cited explanation for the variance of the Mayo results with those of Mazzaferri would appear unlikely or at least incomplete, and there must be other differences between the respective patient groups analyzed. I would infer a somewhat different conclusion from the observations of Simpson *et al.*, and that is a resultant clear benefit of radioiodine ablation. The issue

is related to the degree of certainty of the treating physician that there is no residual microscopic disease. Many of the reported series do not provide clear evidence of the extent of residual tissue as might be inferred from RAI uptakes or serum Tg levels. I would agree that a low-to-moderate risk patient with a baseline Tg level of less than 5 ng/mL and a postoperative RAI uptake of less than 0.5% would not require ablative therapy. However, if we place ourselves in the shoes of even a "low risk" patient, would we not willingly accept the consequence of a 30–60 mCi ablative dose of ^{131}I in exchange for the certainty and peace of mind provided by a subsequent negative scan and undetectable serum Tg level? That radioiodine therapy "wipes the slate clean" and provides the ability to more readily detect recurrence by either ^{131}I TBS or by monitoring serum Tg is not, apparently, a compelling argument to Schlumberger and Hay. They point out that Tg levels adequately monitor such patients, with 93% and 80% having immeasurably low levels while on and off levothyroxine suppression, respectively. These are impressive percentages on a statistical basis but not on an individual patient basis; I have difficulty settling for an 80–90% average if radioiodine ablation could bring my awareness of the presence or absence of residual disease closer to 100%. Schlumberger and Hay would simply catch those patients initially missed at a later time, several months later perhaps, as serum Tg began to rise, and they would then further evaluate and treat at that time. Such management would likely suffice and achieve a "cure" in most patients, but again I have concern for those who unpredictably may manifest more aggressive disease. In such patients, cure appears to be best achieved when their disease is caught and treated as early as possible. Mazzaferri and Jiang found that delays in treatment were associated with a higher mortality (4). Moreover, a serum Tg-based system of follow-up for detection of residual disease might be misleading due to false negatives; Schlumberger's group (11) reported patients with little elevation in Tg even in the face of pulmonary metastases, and in the last section of this *Controversy*, they cite that 20% of patients with known lymph node metastases may have low serum Tg. That Tg might be undetectable in the face of known metastatic disease while patients are on levothyroxine has been known for quite some time (12).

Schlumberger and Hay acknowledge that administering an ablative dose of radioiodine permits a follow-up scan that can detect the presence of unrecognized metastases. This fact also bears on our ability to achieve the salutary effects of treatment by earlier diagnosis. Casara *et al.* (13) realized remission rates of 78% in patients with negative chest x-rays but positive lung uptake on scan, in contrast to a remission rate of less than 4% in those patients who already had evidence of lung metastases on chest x-ray. Such studies confirm the reciprocal relationship between success of cancer therapy and size and duration of lesions.

Certainly few would argue with Schlumberger and Hay that one should always take advantage of the administration of a treatment dose of ^{131}I by performing a post-treatment scan [a position we share (3)], particularly with large (75–150 mCi) treatment doses that might disclose previously undetected metastases. But we can see patients with low serum Tg and significant metastatic disease even when no longer TSH suppressed (14). This phenomenon is related to the whole dilemma of false negative or low serum Tg levels in the face of known residual malignancy. The most likely explanations for this include the presence of interfering anti-Tg antibodies, which can be present in as many as 40% of patients with DTC (15), and the dedifferentiation of the tumor cells, such that they can still trap iodide but can no longer make and release Tg. It should be mandatory for laboratories to measure anti-Tg antibodies in every sample in which Tg is being measured. While assays for serum Tg are improving and becoming more standardized (albeit very slowly), Spencer *et al.* (15) point out that the presence of antibodies continues to be a problem, and can be associated with either falsely low or falsely high serum Tg measurements. Hence, a largely Tg-based strategy as suggested by Schlumberger and Hay may be problematic at times given the frequency of antibodies in the DTC population.

Schlumberger and Hay question the need for levothyroxine withdrawal for the purpose of a follow-up TBS a year after therapy. At present, this procedure requires allowing the patient to become sufficiently hypothyroid to raise serum TSH to more than 40 mU/L and thereby facilitate ^{131}I uptake and imaging of either residual thyroid bed tissue or malignancy. Such scans are done with doses of ^{131}I that range from 3–10 mCi. The larger doses are associated with better images and improved sensitivity of tumor detection but may also be associated with "stunning" or with a lower fractional uptake of ^{131}I with the subsequent treatment dose (16). Schlumberger and Hay would have us abandon these TBS doses as either unnecessary in the low risk patient with low serum Tg or problematic in the higher risk patient because of stunning. In the latter group, they would have us opt instead for a much larger dose that would suffice for both imaging and treatment. In this context, I am drawn again to the importance of individualizing management in the decision making process. I fully concur with the approach of Schlumberger and Hay to base the aggressiveness of further diagnostic and therapeutic approaches on the patient's risk factors, clinical situation, serum Tg on and off levothyroxine therapy, and other nonisotopic imaging techniques, such as ultrasonography or MRI, to identify residual or recurrent disease. With the imminent availability of recombinant human TSH (rhTSH) (17), we will be able to evaluate patients without having to render them hypothyroid. Indeed, in the absence of anti-Tg antibodies, failure of Tg to increase after rhTSH administration would be a compelling argument for the patient being free of malignancy and therefore having no indication for scanning or further isotope treatment. There will also likely be a role for rhTSH in facilitating the therapy of patients with metastatic disease. I have personally treated one patient with metastatic disease after rhTSH preparation, and another has been reported with salutary results (18). The ability to identify residual or recurrent disease by other scanning modalities that also would not require discontinuing TSH-suppressive levothyroxine therapy is discussed below.

Most endocrinologists dealing with thyroid cancer patients would agree with the therapeutic approach recommended by Schlumberger and Hay of combination ^{131}I and surgery. Their use of ^{131}I to identify lesions by an intraoperative detector probe is innovative. Many centers in the U.S.

would operate first on any palpable or otherwise accessible tumor recurrence and follow the surgery with radioiodine therapy. This has the benefit of "debulking" the tumor mass and rendering the radioiodine dose as more effective therapy. As pointed out by Schlumberger and Hay, "small neoplastic foci respond better to ^{131}I than larger ones." I think that it might be preferable to employ ^{123}I to guide the intraoperative gamma probe of the surgeon, an isotope that would be associated with less radiation exposure and less potential for stunning. Then, following surgery, the patient could be treated with a large dose of ^{131}I, particularly if serum Tg was still elevated (19). Surgical excision may not be warranted for the appearance of clinically detectable cervical lymph nodes in the presence of low serum Tg and negative anti-Tg antibodies. Rather, I would first want to demonstrate the presence of DTC metastases in the lymph nodes, which could be done by fine needle aspiration biopsy, with or without ultrasound guidance, and by subjecting the aspirate to either cytologic examination (20), PCR-based genetic analysis (21), or measurement of Tg (22).

Dr. Schlumberger was the first investigator to advocate empiric high dose ^{131}I therapy for patients who are "scan negative, thyroglobulin positive." Drs. Sherman and Gopal advise caution in applying high dose therapy in such patients in the absence of data confirming efficacy and an acceptable risk/benefit ratio, and I must agree with them. With this scenario, one should first attempt to uncover a cause for a possibly false negative scan or a false positive elevation of serum Tg. As mentioned above, the latter can be due to interfering anti-Tg antibodies (15). Explanations for a false negative radioiodine scan include inadequate TSH elevation, stable iodine contamination (*e.g.* history of recent iodine contrast radiography), dispersed microscopic metastases too small to visualize, or dedifferentiation of the tumor such that it can still produce Tg but has lost its iodide trapping ability. To rule out iodine contamination, serum or urinary iodide can be measured and a repeat TBS 4–6 weeks after an iodide depletion regimen can be considered (23).

In this setting faced with a decision as to how to proceed, I would again look at the patient in terms of risk factors, evidence of earlier metastatic or aggressive disease, and any arguments for employing other imaging tools such as MRI or ultrasound to visualize possibly occult disease. For example, given this scenario of "positive Tg and negative TBS" in a 58-yr-old man with a history of a 4 cm papillary or a 2 cm follicular lesion, I would consider the Schlumberger approach and treat with high dose radioiodine. On the other hand, with a history of a 2 cm papillary cancer with negative nodes and only marginally measurable or slightly elevated Tg (*e.g.* ~10 ng/mL), I might favor a more conservative approach. Significant to the decision making process is whether serum Tg levels are stable or rising. Of course, the patient must be brought into the decision-making process and informed fully of the extent of our collective knowledge, experience, and biases in regard to their specific situation. We would like to avoid treatment of patients with aggressive high dose radioiodine for uncertain indications and which might result in troubling sequelae such as xerostomia and/or azoospermia.

I agree with Sherman and Gopal that, absent evidence of progressive disease, the risks of aggressive radioiodine therapy may not be warranted given ill-defined goals. In addition to the experience of Schlumberger *et al.* (24), another oft-cited experience in support of empiric treatment of the thyroglobulin-positive, scan-negative patient is that of Pineda *et al.* (25). These workers reported 17 such patients, all of whom had had prior total thyroidectomy and radioiodine ablation. After treatment with 150–300 mCi of ^{131}I, 16/17 had visualization of metastases on their post-treatment scan. Tg levels decreased in 81% of patients after their first treatment dose, and in 90% and 100% of those patients who received second and third doses, respectively. While these results sound impressive as expressed, examination of the individual patient's Tg level responses is less so. Mean Tg decreased from 74 to 62 to 32 over 1–2 yr of follow-up, and only 6/29 positive scans became negative. The cogent issues raised by Sherman and Gopal, and previously by McDougall (26) and Mazzaferri (27), reflect the fact that many of these patients have minimal if any disease that would affect their life expectancy, and yet we are exposing them to unwarranted doses of radiation exposure, unwarranted at least until we obtain sufficient data from well-controlled studies that confirm efficacy of therapy. Certainly another important aspect of this empiric therapy is the cost to the patient in regard to the morbidity of hypothyroidism and its negative impact on productivity, as well as the cost in health care dollars related to hospitalization and the associated expensive technological procedures. Increasing scrutiny by watchdog agencies may challenge the indications for this therapy, and possible denial of reimbursement may cause additional problems for both the patients and their physicians.

Finally, I would mention the additional or alternative imaging procedures that are being developed and evaluated for patients with thyroid cancer. Given a negative ^{131}I TBS, are there other scanning modalities that might provide useful information? Drs. Sherman and Gopal have focussed on the dilemma facing us when confronted with a measurable or rising serum Tg and a negative ^{131}I TBS, generally considered the gold standard for detection of metastases. Once we have eliminated the various causes for false positive serum Tg or false negative TBS, what is the clinician to do? As reviewed above, many authorities question the risk benefit ratio of arbitrary high dose ^{131}I therapy as employed by Schlumberger and coworkers (24). Alternative therapeutic approaches to metastatic deposits of thyroid cancer include surgical excision or localized external radiation therapy (28), but the location of the metastases would need to be identified first. MRI and ultrasound have been employed for this purpose. In addition, I suggest that alternative scanning agents might play a very important role in this regard, for several recent reports have documented their potential usefulness in identifying lesions that are not visualized with traditional ^{131}I WBS.

One of the first to be employed was the [201]Thallium (^{201}Tl) (29). In one recent study of patients with bone metastases documented with positive ^{131}I scans, ^{201}Tl was compared to the bone agent, technetium-99 m hydroxymethylene diphosphonate (^{99m}Tc-HMDP). The two agents had a combined sensitivity of 93.5%. In a group of 14 patients with negative ^{131}I scans and other evidence of thyroid malignancy, [201]Tl

was positive in 10/14 and ^{99m}Tc-HMDP was positive in all 14. Carril *et al.* (30) found that ^{201}Tl enjoyed a sensitivity and specificity that was higher than that for ^{131}I for recurrent or persistent disease. Lesions were detected in 31/116 patients by ^{201}Tl but not by ^{131}I TBS. In patients who have been ablated and show no further ^{131}I uptake, the authors propose continuing management with no additional ^{131}I scans; as ^{201}Tl scanning does not require levothyroxine withdrawal, follow-up would be guided only by ^{201}Tl scanning and by monitoring serum Tg. Dadparvar *et al.* (31) compared ^{201}Tl and scanning with ^{99m}Tc-methoxyisobutyl isonitrile (^{99m}Tc-MIBI) and found that ^{131}I TBS alone was satisfactory as a preablation study, but that the addition of either alternative agent increased the diagnostic yield post-ablation, particularly when the ^{131}I TBS was negative. These results have not been universal, however, because Lorberboym *et al.* (32) found ^{131}I TBS to be both more sensitive and specific than ^{201}Tl, with the latter giving several false positive scans. Ugur *et al.* (33) noted a 70% overall concordance between ^{201}Tl, ^{99m}Tc-MIBI, and ^{131}I TBS, but observed false negatives with both alternative agents and concluded that they should not be used in lieu of ^{131}I TBS. Elser *et al.* (34) noted however a 94% sensitivity for the detection of positive lymph nodes and local recurrence with ^{99m}Tc-Sestamibi; they detected 32/40 metastases with Sestamibi compared with only 18/40 with ^{131}I TBS. More recently, investigators have attempted detection of thyroid cancer with ^{99m}Tc-tetrafosmin, a cationic agent employed previously for myocardial perfusion imaging (35–37). For 12 patients with elevated serum Tg (4 of whom had negative ^{131}I TBS), tetrafosmin was slightly superior to either ^{201}Tl or ^{99m}Tc-MIBI. This same group of workers (37) reported that tetrafosmin successfully identified 21/21 lesions that were positive by ^{131}I TBS, but an additional 17/23 lesions that were negative by ^{131}I TBS. The agent had 86% sensitivity for distant metastases, was positive in 4 patients with ^{131}I negative proven pulmonary metastases, and the findings correlated with other modalities identifying tumor such as computed tomography (CT) or ultrasound.

It is also significant that these alternative agents are logistically both more convenient and more expedient than scanning with ^{131}Iodine. In addition to being able to scan patients while they are still taking TSH-suppressive doses of levothyroxine, the time required for evaluation is much reduced. Instead of scanning 48–72 h after a dose of ^{131}I, the ^{99m}Tc-tetrafosmin planar scan is performed 20 min after injection of the isotope, with additional images taken by single-photon emission computed tomography (SPECT) of any suspicious lesions. ^{99m}Tc-tetrafosmin scans were negative in all 68 patients, studied by Lind *et al.* (37), who were free of disease on the basis of ^{131}I TBS and serum Tg.

Another agent, 18-fluorine fluorodeoxyglucose is employed with PET scanning (FDG-PET) with uptake of the agent related to glucose utilization by tumor tissue. The greatest uptake sensitivity has been noted with fastest growing undifferentiated tumors. Grunwald *et al.* (38) compared FDG-PET to ^{99m}Tc-Sestamibi and ^{131}I TBS. Of 29 studies, 11/29 had disease detected only with FDG-PET, 8/29 were detected only with ^{131}I TBS, and 10/29 were detected by both. Five sites were detected by FDG-PET and not by ^{99m}Tc-Sestamibi. FDG-PET may be useful in patients in whom ^{131}I TBS is not feasible due to a history of iodine exposure, and similarly, its use would not preclude scanning by CT with contrast if desired as an additional means of imaging tumor. A drawback is the lack of widespread availability of PET scanners due to their high cost.

Fridrich *et al.* (39) compared FDG-PET to ^{99m}Tc-MIBI and ^{131}I TBS and found both to be more sensitive than ^{131}I TBS with a slight edge in favor of ^{99m}Tc-MIBI. In addition to the benefit of having good uptake independent of the patients' serum TSH level, FDG-PET or MIBI did not have the propensity to have high background in the neck, mediastinum, and chest, as does ^{131}I, and could be employed more effectively to detect small metastases in these areas. On the other hand, liver and brain will demonstrate high uptake of FDG, and the ability to pick up metastases in these areas will be limited with this agent. Indeed, Feine *et al.* (40) were able to localize and identify positive neck metastases with FDG-PET in 6 patients with elevated serum Tg levels. A more conservative view to the utility of FDG-PET scanning has been proposed by Dietlein *et al.* (41). They observed positive FDG-PET images in 7/21 patients with positive lymph node metastases but negative ^{131}I TBS; sensitivity was 82% in patients with high serum Tg but negative TBS. They concluded that FDG-PET should not be used instead of ^{131}I-TBS but would serve as a useful complement to evaluation, particularly when the ^{131}I TBS was negative in the face of a rising or elevated level of serum Tg. Finally, imaging of DTC by somatostatin receptor scintigraphy (SRS) with octreotide has been reported by Baudin *et al.* (42). Of 25 patients with DTC and elevated serum Tg levels, 16/25 had negative ^{131}I TBS, and SRS was positive in 12 of these 16 patients and in 8/9 patients with positive ^{131}I TBS. While confirmatory studies will be required, SRS with labeled octreotide may represent another useful alternative to ^{131}I TBS, with the advantage of not having to withdraw TSH-suppressive levothyroxine therapy.

In conclusion, how should one manage the scan negative, thyroglobulin positive patient with no underlying reason to suspect either a false negative scan or a false positive serum Tg level? Schlumberger (1 and in this paper) would empirically treat with 100 mCi ^{131}I any patient with a Tg level of more than 10 ng/mL while off levothyroxine, and would only repeat the ^{131}I TBS every 2–5 yr when the Tg level is in the range of 1–10 ng/mL. Given clearly measurable Tg levels, I would encourage alternative imaging procedures. For papillary thyroid carcinoma with a propensity to regional recurrence, that could include ultrasound, CT, MRI, ^{99m}Tc-MIBI, or FDG-PET. For follicular thyroid cancer with its propensity for distant metastases (especially to bone and lung), ^{99m}Tc-tetrafosmin or ^{99m}Tc-HMDP or ^{201}Tl could be employed. Identification of isolated distant lesions by these methods would allow earlier intervention by surgical excision or external radiotherapy, rather than delaying further treatment until a subsequent ^{131}I TBS might become positive or until serum Tg levels might increase further as a result of further tumor growth. In patients with higher risk disease following early total thyroidectomy and high-dose radioiodine ablation, this approach should permit effective man-

agement until such time as more target-specific tumoricidal therapies become available.

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Thyroglobulin Positive, RAI Negative Thyroid Cancers:
The Role of Conservative Management

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Physicians who provide care for patients with endocrine neoplasms can often take advantage of the hormones and other secretory products that serve as sensitive and specific markers of diseases. Frequently, tumors that are smaller than the sensitivity limits of even the most state-of-the-art diagnostic imaging procedures are still capable of producing marked elevations of serum tumor markers. However, the ability to detect the presence of disease with a serum marker does not necessarily imply the need for or responsiveness to therapy. At one end of the spectrum, excessive ACTH levels in a patient with hypercortisolism often leads to an aggressive and sometimes invasive search for the source of the hormone, justified by the marked morbidity of untreated Cushing's syndrome and a reasonable frequency

of both biochemical and clinical improvement after therapy. In contrast, patients with medullary thyroid carcinoma commonly have minimally elevated serum levels of calcitonin after primary surgery, despite lack of demonstrable tumor on any radiographic or scintigraphic examination; however, the morbidity and mortality associated with this postoperative hypercalcitoninemia is fairly low, and even the most aggressive approaches to eradication of the sources of calcitonin are not commonly successful.

Thyroid follicular epithelial cells have two unique differentiated functions that allow the sensitive and specific detection of papillary and follicular thyroid carcinomas (DTC): the uptake and organification of iodine, and the production of thyroglobulin. Both of these functions are enhanced by increased serum levels of thyrotropin, another marker of thyrocyte differentiation. The ability to quantitate and image thyroid tissue, both normal and neoplastic, with tracer amounts of radioiodine also leads to a mode of specific therapy with higher quantities of radioiodine, usually in the form of [131]I. However, false negative results occur in up to 15% of diagnostic radioiodine scans in patients with detectable thyroglobulin levels after thyroid ablation. On the basis of a high frequency of post-therapy scans that demonstrate foci of radioiodine uptake combined with subsequent decrease in the serum thyroglobulin level, it has been proposed that patients with elevated serum thyroglobulins and negative diagnostic radioiodine scans after thyroidectomy and ablative treatment should receive empiric ^{131}I therapy with 100–300 mCi. Although such therapy can be administered and may be associated with a degree of response, as measured by both thyroglobulin levels and radioiodine uptake, it is far from clear that this approach to patient management should be widely adopted. Instead, the dictum of needing to balance evidence of potential benefit against the evidence of potential risk must be considered on a case-by-case basis, and empiric therapy may not be appropriate for most such patients.

First, it is necessary to consider the causes of morbidity and mortality due to DTC. Patients develop troubling symptoms due to disease affecting critical structures in the neck, bones, and central nervous system, and less commonly due to large tumor bulk in the lungs and mediastinum. Similarly, disease-related mortality is generally related to overwhelming tumor bulk, invasion into cervical structures, or central nervous system metastases (1). The risk for disease-related morbidity or mortality in patients with scan-negative, thyroglobulin-positive disease is not well defined. This may be particularly true for patients without evidence of tumor mass by other current imaging modalities such as high-resolution neck ultrasound or chest computed tomography. Patients with non-palpable locoregional recurrence of papillary carcinoma large enough to be detected by ultrasound have been reported to have survival rates similar to those with disease only detected scintigraphically. As the resolution of cervical ultrasound commonly approaches 2 mm, failure to demonstrate disease in the thyroid bed or paratracheal regions by this method, even if detectable by thyroglobulin measurements, likely indicates that conservative observation would not be deleterious. This consideration may be even more important for patients whose thyroglobulin level following thyroid hormone withdrawal is no more than 12 ng/mL,

which in the commonly cited NIH study was the cutoff that excluded extracervical uptake on post-therapy scanning (2). With time, mild thyroglobulin elevations may even diminish without specific intervention (3).

Second, there is no evidence whatsoever that either partial reductions in serum thyroglobulin levels or elimination of radioiodine uptake, visible only on post-therapy scans, are associated with improved patient outcome. Only a minority of patients in the NIH report achieved thyroglobulin (Tg) levels of less than 5 ng/mL, and radioiodine uptake rarely was completely ablated when present on post-treatment scans in extracervical sites. In fact, it has been argued that ^{131}I itself is not the most appropriate radioisotope to treat the micronodular foci of disease often found on post-therapy imaging (4). Instead, ^{125}I, with a shorter pathlength of radiation and greater delivery of effective radiation dose to small lesions, may be the more effective treatment.

Consistent with the philosophy of *primum non nocere*, the potential risks of empiric therapy must be considered as well. The decision to treat until all uptake has resolved on post-therapy imaging implies a need for at least two administrations of high-activity radioiodine, one to "treat" and one for a follow-up scan. Assuming that a patient has previously undergone radioiodine ablation, a total activity of at least 400–500 mCi will have been administered by this approach, likely increasing the risk of chronic sialoadenitis and xerostomia, and introducing the potential for impaired marrow function if careful blood dosimetry is not performed. Although the evidence for secondary malignancies from radioiodine administration is far from definitive, recent reports of increased rates of colorectal, bladder, breast, and salivary tumors should be taken into consideration as well, especially in younger patients who are otherwise more likely to live long enough to develop secondary malignancies (5, 6).

With these concerns in mind, it seems reasonable to consider empiric radioiodine therapy of Tg positive, scan negative disease as experimental and of unproven benefit. In that sense, prospective, randomized clinical trials should be undertaken to determine whether such therapy is beneficial. For those patients with evidence of progressive metastatic disease, it may be reasonable to consider a therapeutic trial of radioiodine before embarking on other treatment modalities. But, for younger patients with stable albeit elevated thyroglobulin levels and no radiographic evidence of disease otherwise, there does not appear to be sufficient evidence of benefit to warrant such therapy.

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Use of Radioactive Iodine in Patients with Papillary and Follicular Thyroid Cancer: Towards A Selective Approach

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Radioactive iodine (RAI) plays a major diagnostic and therapeutic role in the management of patients with follicular cell-derived thyroid cancer. It is used post-operatively to ablate normal thyroid remnants, during follow-up for whole body scanning and in patients with recurrent disease for treatment. RAI should, however, be used selectively in these three situations.

Radioactive iodine ablation

RAI ablation of thyroid remnants has been defined as "the destruction of residual macroscopically normal thyroid tissue following surgical thyroidectomy" (1). In theory, it is beneficial in three contexts:

1. By eradicating microscopic residual postoperative tumor foci, RAI may decrease the recurrence and mortality rates.
2. By ablating residual macroscopically normal thyroid tissue, RAI facilitates the early detection of recurrences by serum thyroglobulin (Tg) measurement and ^{131}I total body scan (^{131}I-TBS).
3. By administering a high dose of ^{131}I, it permits a highly sensitive TBS to be performed 4–7 days after the dose, which may uncover previously undetected foci of uptake outside the thyroid bed.

Each of these theoretical benefits should be carefully examined.

Does RAI ablation decrease the recurrence and death rates?

The available data demonstrating apparently beneficial effects of RAI ablation in terms of recurrence and mortality rates are not particularly convincing (2).

RAI ablation is clearly not beneficial to patients with small intrathyroid tumors (<1–1.5 cm) (3, 4) and does not influence recurrence rates in patients with node-positive papillary thyroid microcarcinoma (5).

In patients with larger tumors (≥1.5 cm) and multifocality, tumor extension beyond the thyroid capsule or lymph node metastases, the beneficial effects of RAI continue to be debated (2–10). Mazzaferri's studies showed in patients with a primary tumor at least 1.5 cm in diameter that the recurrence rate at 30 yr was 16% in his 138 RAI-treated patients, significantly less than the 38% rate observed in the 802 patients treated with T_4 alone. Even more remarkable were the reported mortality rates: no cancer-related death was observed in RAI-treated patients, significantly less than the 8% rate seen after 30 yr in the patients who did not receive such treatment (4). However, these favorable results were not confirmed in an analysis performed in an identical fashion on a series of 1542 patients with similar disease stages treated at the Mayo Clinic (2). At 30 yr, recurrence rates were comparable in the RAI group (16.6%) and in the no-RAI group (19.1%) ($P = 0.89$); the death rates, which were respectively 5.9% and 7.8%, were also similar ($P = 0.43$). Differences between these series may be related to the extent and completeness of surgical excision. This is suggested by the considerably lower 30-yr recurrence rate in the no-RAI group at the Mayo Clinic than those reported by other institutions. Other data support this conclusion. In patients with microscopic residual papillary or follicular carcinoma treated in 13 Canadian hospitals, local disease was controlled significantly more often, and survival at 20 years was better in patients treated postoperatively with either RAI ablation or external radiotherapy or both together than those treated with thyroid hormone alone ($P < 0.001$). In contrast, RAI ablation in patients without obvious residual disease did not significantly increase survival (9). Earlier studies at the Institut Gustave-Roussy (Villejuif, France) had led to the same conclusion (10).

Is Tg measurement and ^{131}I-TBS improved after RAI ablation?

In patients with nonablated normal thyroid remnants, either normal or neoplastic thyroid tissue may be responsible for Tg production. After total thyroid ablation by surgery and RAI, however, any detectable Tg level should signify the presence of neoplastic disease. Therefore, a potential advantage of RAI ablation is that Tg measurement may be rendered more specific for the detection of persistent or recurrent disease. However, experience has shown that, during the long-term follow-up in patients after total thyroidectomy, in whom thyroid uptake is low (<2%), the Tg level is undetectable in 93% during LT_4 treatment and in 80% after withdrawal of thyroid hormone therapy (11). Tg measurement can thus be used accurately to follow DTC patients treated by (near) total thyroidectomy, even if not RAI ablated. This also means in low-risk patients, that RAI ablation may simply be indicated in those with a detectable Tg level on T_4 treatment, some months after surgery. Of note, the Tg level remains detectable for some weeks after surgery in some patients, and then becomes undetectable.

On the other hand, ^{131}I-TBS is more sensitive after RAI ablation of normal thyroid remnants, because thyroid remnants with a high uptake may preclude the visualization of neoplastic foci in which the uptake is lower.

Is post-ablation ^{131}I-TBS worthwhile?

A number of studies have shown that the sensitivity of ^{131}I-TBS for detecting thyroid cancer is improved when the amount of radioactivity is increased.

As compared to diagnostic ^{131}I-TBS, post-therapy ^{131}I scans may detect new lesions in up to 50% of patients, with a significant proportion of the newly found lesions being distant metastases (12). During follow-up, in 80% of DTC patients with a detectable Tg level but no other evidence of disease, including a negative ^{131}I-TBS with a 2–5 mCi dose, a TBS performed with 100 mCi revealed neoplastic uptake in the neck or at distant sites (13–15).

These data clearly show that a TBS should be performed whenever a large amount of ^{131}I is administered. Post-ablation ^{131}I-TBS may reveal useful information, provided an adequate apparatus is used: it can demonstrate the completeness of surgical excision and may show foci of uptake outside the thyroid bed, in lymph node areas, or at distant sites. These findings may prompt further treatment and could have an impact on the ultimate outcome. Of interest, in high risk-patients after (near) total thyroidectomy, post-ablation ^{131}I-TBS results were closely related to Tg levels on the day of ^{131}I administration (16).

Conclusion

Despite reassuring data on long-term side effects, the persistent uncertainties regarding its effectiveness should dictate a selective use of adjuvant RAI. In fact, the cost and the inconvenience to the patient may be significant enough to outweigh its potential benefits (17–23).

In patients with a thyroid carcinoma of less than 1.0 to 1.5 cm in diameter, who represent one fifth to one third of all thyroid cancer patients, the prognosis is so favorable after surgery alone that other therapeutic procedures appear superfluous. Routine RAI ablation is clearly not indicated.

In patients with primary tumors exceeding 1.0–1.5 cm in diameter, the benefits of RAI ablation in terms of recurrence and survival rates are still controversial after what appears to be complete surgical excision. In low risk patients, the prognosis is so favorable after surgery alone that ^{131}I is not indicated. RAI ablation should be restricted to patients with poor prognostic indicators for relapse or death who represent only a small minority of DTC patients. Remnant ablation permits a highly sensitive ^{131}I-TBS to be performed, and relapses are readily detected at an earlier stage during follow-up.

At present, the benefits of RAI ablation in terms of recurrence and survival can only be demonstrated in patients with known or suspected residual neoplastic disease. These patients are selected for RAI ablation on the basis of well-established prognostic indicators that take into account both the initial extent of the disease and the surgeon's and pathologist's reports. With time, the number of these patients will decrease, as lesions are diagnosed earlier and as surgeons become more experienced with this type of procedure. If not given post-operatively, ^{131}I ablation therapy may be given some months later, in those with persistent elevated Tg levels.

Is follow-up diagnostic radioiodine scanning worthwhile?

Diagnostic radioiodine scans are the most commonly used imaging procedures during the follow-up of DTC patients, but the data yielded in unselected patients is low. Furthermore, patients may complain about the frequent withdrawal of thyroxine provoking morbid hypothyroidism, and the cumulative dose of radiation over many years can be significant. Recent trials have demonstrated that recombinant human TSH can stimulate uptake and Tg production similar to that obtained after withdrawal of thyroxine treatment and will probably be used routinely in the near future (24).

In many patients with papillary of follicular cancer a ^{131}I total body scan (TBS) with 2–5 mCi is performed within a year of initial treatment, either to check the completeness of RAI ablation or to visualize the thyroid remnants in patients who have not undergone RAI ablation. Furthermore, with the withdrawal of thyroxine, serum thyroglobulin (Tg) can be measured under the most sensitive conditions. However, the necessity for ^{131}I-TBS in such circumstances is not established for at least two reasons: first, almost all patients who have undergone (near) total thyroidectomy are totally ablated; second, a ^{131}I-TBS performed with 2–5 mCi has a much lower sensitivity for the detection of disease than that performed after ablation, with a much larger dose. In fact, in 200 patients followed at Institut Gustave-Roussy, from 1994 to 1996, such a TBS did not detect any unknown disease.

Subsequent follow-up should be based on patient and tumor-related risk factors, the clinical examination, ultrasonography of the neck, and the serum Tg level measured both while on T_4 treatment and after its withdrawal. There is an excellent correlation between the serum Tg level and the clinical status of patients without interfering auto-antibodies. However, it should be recognized that serum Tg is undetectable during T_4 treatment in about 20% of patients with isolated lymph node metastases in the neck, in about 5% of patients with lung metastases not visible on standard chest X-rays, and in less than 1% of patients with large distant metastases. Tg will increase to a high level in the majority of these patients, following T_4 withdrawal (11, 25). This has prompted several authors to advocate periodic T_4 withdrawal with Tg measurement and eventually a diagnostic ^{131}I-TBS. In reality, these patient categories are not frequently encountered: recurrent lymph node metastases occur in 10–15% of patients with papillary thyroid carcinoma and are frequently detected by clinical or ultrasonographic examination of the neck, while distant metastases occur during follow-up in less than 5–10% of patients. Most patients at risk of developing a relapse can be identified at the time of initial treatment simply by using prognostic factors and scoring systems (2, 25). Finally, most patients likely to relapse already have a detectable Tg level off T_4 treatment at the time of the first diagnostic ^{131}I-TBS.

Consequently, low-risk patients with no evidence of recurrence, and with an undetectable serum Tg level off T_4 treatment at the time of initial diagnostic ^{131}I-TBS, do not require any imaging procedure during subsequent follow-up. At Institut Gustave-Roussy, none of these patients developed a clinical recurrence with a follow-up of 20 years.

By contrast, high-risk patients with clinical or biochemical parameters suggestive of recurrence may require multiple imaging procedures, starting with a ^{131}I-TBS. As the sensitivity of ^{131}I-TBS is higher with a high amount of ^{131}I, consideration should be given to administration of a high dose of ^{131}I (100 mCi) in those patients with a Tg level either detectable during T_4 treatment or above 10 ng/mL following T_4 withdrawal. In these patients in whom the likelihood of recurrent disease is high, diagnostic ^{131}I-TBS should be discouraged as it will not preclude the subsequent administration of a high dose of ^{131}I and may stun the ^{131}I uptake by any thyroid tissue (26). If the high dose TBS is negative, it should not be repeated within a short interval of time.

In the near future, the availability of recombinant human

TSH will allow the omission of T_4 withdrawal during follow-up, while permitting the measurement of serum Tg in sensitive conditions (24). Also, this will allow selection of those patients with a detectable Tg level, who may benefit from ^{131}I-TBS.

Is ^{131}I therapy for recurrent disease worthwhile?

In these patients, high doses of ^{131}I are used both for the work-up (^{131}I-TBS) and for treatment. The efficacy of ^{131}I treatment depends upon the radiation dose delivered to the neoplastic foci, which is related to the ratio between ^{131}I uptake and the mass of the neoplastic foci (1). Experience has shown that small neoplastic foci respond better to ^{131}I than larger ones (27).

In most patients with small, nonpalpable neck recurrences, repeated ^{131}I treatments have led to complete remission, and only 16% of those patients underwent surgery for persistent uptake (28). However, recurrences that are either easily palpable or seen at ultrasonography, are best treated by a combination of ^{131}I and surgery. The following protocol is applied at the Institut Gustave-Roussy: 4–7 days after a large dose of [131]I (100 mCi), a highly sensitive TBS is performed; then surgery is undertaken. Its extent is guided by the TBS and with the help of an intraoperative probe; a post-surgical TBS, performed using residual ^{131}I activity, will then control for the completeness of surgical excision. This has led to cure in 92% of these patients (29).

[131]I therapy can achieve a complete remission in a third of patients with distant metastases. [131]I therapy is given after T_4 withdrawal every 3–6 months until the complete disappearance of ^{131}I uptake on post-therapy ^{131}I-TBS. Diagnostic ^{131}I scanning is of limited utility before planned therapy and, moreover, may stun the ^{131}I uptake by the neoplastic foci. Standard treatment doses range between 100 and 200 mCi. Significant prognostic indicators for complete remission include a young patient age, positive ^{131}I uptake, and small metastases. In patients with lung metastases, a complete remission was observed in 83% of lesions that were not visible on chest X-rays, in 53% of micronodular (<1 cm) and in only 14% of macronodular (>1 cm) metastases (27). Bone metastases are usually large when discovered, and only a few responses have been obtained after ^{131}I treatment.

In patients without ^{131}I uptake on the first high-dose ^{131}I-TBS, further ^{131}I treatments are pointless.

In conclusion, ^{131}I therapy is mostly effective in patients with small foci of recurrent disease. This underlines the prognostic significance of early detection, which is facilitated by an appropriate initial treatment and follow-up strategy, mainly based on knowledge of initial prognostic factors and periodic serum Tg measurement.

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