Perspective: The Case Against Radioiodine Remnant Ablation in Patients with Well-Differentiated Thyroid Carcinoma

Ian D. Hay[1], I. Ross McDougall[2], and James C. Sisson[3]

[1]Division of Endocrinology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; [2]Division of Nuclear Medicine and Molecular Imaging, Stanford University Hospital and Clinics, Stanford, California; and [3]Division of Nuclear Medicine, Department of Radiology, University of Michigan Health System, Ann Arbor, Michigan

We take issue with the stance that postoperative radioiodine remnant ablation should be applied ubiquitously as adjuvant therapy in patients with well-differentiated thyroid carcinoma. In this article, we state the reasons that we believe a compelling case can be made against ablation in most patients.

Key Words: endocrinology; oncology; radionuclide therapy; ablation; radioiodine; thyroid carcinoma

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The application of postoperative radioiodine remnant ablation (RRA) as adjuvant therapy in the management of patients with well-differentiated thyroid carcinoma (WDTC) is presently ubiquitous (*1*). A recent North American survey of specialty physicians determined that "strong RRA recommendations were founded in opinions that RRA (i) decreases WDTC-related mortality and recurrence and (ii) facilitates WDTC follow-up at low risk of adverse effects" (*1*). We take issue with this stance and believe, for the reasons outlined in this article, that a compelling case against RRA in most patients with WDTC exists.

The first argument against RRA is that a foundation for adjuvant RRA has never been firmly established. To safeguard nerves and parathyroid tissues, surgeons frequently leave small portions of the thyroid gland during near-total and total thyroidectomies. The goal of ablation is to destroy these remnants in a belief that such therapy will be followed by a reduction in recurrences and mortality from the carcinoma. Twenty-five years ago, this tactic was described as "questionable pursuit of an ill-defined goal" (*2*); the appraisal remains apt.

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For correspondence or reprints contact: James C. Sisson, Division of Nuclear Medicine, Department of Radiology, Hospital B1 G505D, University of Michigan Health System, Ann Arbor, MI 48109-0028.
E-mail: jsisson@umich.edu

Nevertheless, adjuvant therapy has gained momentum in the 21st century (*1,3*). Modifications have primarily been aimed at administered activities of ^{131}I to improve short-range indices of success. Yet, whether activities should be 1.1 GBq (30 mCi) or larger is still not settled (*1,3*). In follow-up, negative diagnostic scanning serves as a major index of success; for the techniques of imaging, however, no standard protocol exists that includes the type of imaging instrument, collimation-detection of photons, duration of data acquisition, number of days of low-iodine diet, and whether stimulation of thyroid tissue should be obtained through withdrawal of thyroid hormone or by injections of recombinant TSH (rhTSH).

Nonetheless, 2 refinements in patient management have recently been superimposed: the administration of therapeutic ^{131}I without preceding scintigraphy to identify the target (*4,5*) and stimulation of thyroid tissue function by rhTSH. The rhTSH method has been approved in the European Union and recently by the Food and Drug Administration (*6*).

The *raison d'être* for adjuvant RRA rests on reaching 1 or more of the following 3 goals: an increased specificity in follow-up imaging using radioiodine (*1,4,5,7,8*), undetectable thyroglobulin levels (*4,5,7,8*), and elimination of microfoci of carcinoma in the remaining tissue in an attempt to decrease recurrences and increase disease-specific survival (*1,4,5,7,8*). Within these goals, adjuvant treatment is directed at residual thyroid tissue and not at imageable or biopsy-proven cancer.

Three obstacles have prevented attainment of these goals. First, scintigraphic images starting from a "blank slate" have not been shown to be more accurately interpreted than the postoperative patterns to which radioactivity has been added. Second, data have not been acquired to demonstrate that changes in serum thyroglobulin from an undetectable level are more predictive than those that rise from low levels. Third, the grouping of patients with all stages of well-differentiated carcinoma into results of ablation therapies has obscured any effects in patients with stage I disease.

The concept of ablation has become so attractive that knowledgeable thyroidologists have issued guidelines (*9,10*) that have entrenched ablation into everyday practice (*1*). These recommendations are commanding. As stated by 2 of us (*11*), "Guidelines produced by a committee appointed by a national organization [American Thyroid Association (ATA) (*10*)] have an aura of gravitas." Although experts at times contradict themselves (*11*), failure to adhere to such guidelines may invite litigation. Guidelines developed by a panel of experts from 13 European countries developed a hierarchy of indications for ablation (*9*), including those that may pertain to stage I disease: extensive lymph node involvement is a definite indication; no lymph node dissection, age less than 16 y, T1 greater than 1 cm and T2 are probable indications. The rationale is that "uncertainty persists concerning its [ablation's] benefit. . ." but "the consequences of administering 1.1 GBq or 3.7 GBq (30–100 mCi) of ^{131}I are minimal. . ." (*9*). The ATA management guidelines for patients with thyroid carcinoma recommend ablation for "selected patients with stage I disease, especially those with multifocal disease, nodal metastases. . ." (*10*). Included would be patients with stage I disease whose age was less than 45 y and who manifested classic papillary carcinoma with commonly occurring regional node metastases. The rationale is "fair evidence. . .but the strength of evidence is limited" (*10*).

Our second reason for finding a compelling case against RRA in most patients with WDTC is that data demonstrate an absence of benefit from adjuvant therapy in many patients. Papillary carcinoma, the most common thyroid malignancy, appears in a multifocal form in at least 17% of affected patients (*12,13*), and surgical extirpation of most tissue from both lobes of the thyroid has resulted in fewer local recurrences in patients with low-risk papillary carcinoma (*14*). But these findings do not translate into efficacy of adjuvant therapy. If small foci of carcinoma persisting after total thyroidectomy were eliminated by ^{131}I treatments, stage I patients receiving ablation should have fewer recurrences and perhaps fewer deaths from their carcinomas. Such outcomes have not been demonstrated. In a metaanalysis of the effectiveness of ablation, Sawka et al. (*15*) cited papers reporting that survival of patients was increased (*16*) and recurrences were fewer (*16–18*), but none of these reports dealt specifically with the stage I patients; all other publications discovered no significant association between ablation treatments and patient outcome. In a subsequent paper, successful ablations, when compared with unsuccessful ablations, were followed by statistically significant increases in disease-free intervals and cancer-specific survivals, but here too, patients were not categorized by stage of cancer (*19*).

A report from the Mayo Clinic (*20*) refuted the contention that RRA is beneficial to all cohorts with WDTC. When patients with stage I carcinoma, classified using several staging methods, were followed over years, no reduction was observed in either recurrence or cause-specific mortality rate (*21–23*). Because in many clinics patients with stage I disease compose half or more of the total (*18,21–23*), these results apply to a large proportion of individuals with WDTC. In addition, in the increasing number of cases of thyroid carcinoma, the increment has appeared primarily as small papillary tumors (*24*) in young patients (*25*), and thus, the percentage with stage I disease is likely to rise.

Our third reason for not favoring RRA concerns the risk from radiation. Although treatments with radioiodine have generally been safe, untoward effects, particularly in tissues that concentrate ^{131}I, are not uncommon. Sialadenitis developed in 3%−19% of patients receiving 1.1–4.8 GBq (30–130 mCi) (*26,27*), and after the larger activities, as many as 21% experienced stomatitis (*27*). Lacrimal gland injury (*26*) and epiphora from nasal lacrimal duct obstructions have been reported after 5.6 GBq (150 mCi) (*28*), an activity that may be cumulative from treatment of ablation failures. When patients not receiving ^{131}I were compared with treated patients, significantly increased risks of stomach cancer and leukemia (*29*) and of all second malignancies, particularly leukemia (*30,31*), were demonstrated.

Therapy with 3.7 GBq (100 mCi) of ^{131}I delivers about 0.28 Gy to the entire body (calculated from data reported by Thomas et al. (*32*) and Hanscheid et al. (*33*)). In a protocol that treated euthyroid patients after stimulation by rhTSH and without an identified target, absorbed blood doses were reduced by about 35% when compared with those in patients with hypothyroidism (*32*). Nevertheless, such ionizing radiation is certainly not insignificant. Although different forms of ionizing radiation incur different biologic effects, none can be considered trivial, a point adduced from the use of diagnostic CT (*34,35*).

Radioiodine therapy can benefit some patients with advanced thyroid carcinoma. For rare patients, ablation may be helpful in reducing a large postoperative residual of normal thyroid tissue. We freely admit that we ourselves have in the past prescribed ablation therapies. However, in a fair assessment of the data, we must conclude that the risks of ablation outweigh any discernable benefit. In the past, proposals for prospective studies on the effects of ablation therapy foundered on the magnitude of patients and the number of years required for meaningful assessment. Yet, a prospective multicenter controlled trial evaluating recurrences over 5–10 y may be feasible. In any case, we believe that a debate on the use of RRA is long overdue.

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