TEACHING EDITORIAL

Applying the Radioactive Eraser: I-131 to Ablate Normal Thyroid Tissue in Patients from Whom Thyroid Cancer Has Been Resected

As a treatment for functioning thyroid cancer, radioiodine is compelling. Iodine-131 will destroy thyroid tissues, including well-differentiated cancers. However, the indolent nature of thyroid neoplasms obfuscates the effects of therapy; death rates of papillary carcinomas range from 1.0% to 11.5% in ten or more years of follow-up (*1-5*). Moreover, the use of thyroidectomy and thyroid hormone as well as radioiodine have confounded analyses of treatments. To determine the efficacy of any therapeutic protocol, one must negotiate a statistical labyrinth; proof is elusive even after years of study. No wonder that investigators have sought more readily available indices of therapeutic benefits. And in this milieu, scintigrams have come to be worshipped as portents and as arbiters of proper treatment.

As a method of determining residual functioning thyroid tissue, scintigraphy is certainly sensitive. In this issue of the *Journal*, Snyder et al. (*6*) point out that modern instruments will portray 0.5 μCi of I-131 in a gram of tissue, and suggest that a 1- or 2- mCi tracer dose will probably reveal all that is treatable by this radionuclide. Also, when treatments fail to obliterate the gamma images of thyroid cancer, obviously neoplasm remains. Such a pattern of persistence foretells of dire events (*3,7*). Extinguishing evidence of thyroid cancer is beneficial, but ablation of normal thyroid tissue is another matter. Although continued depiction of thyroid cancer is omnious, it does not necessarily follow that a blank scintigram is ideal. The menace of residual portions of normal thyroid glands has not been established, and their elimination must be controversial.

The issue is not trivial. Some normal thyroid cells are frequently and purposely preserved during a thyroidectomy. Indeed, surgical principles dictate protection of structures important to health during the excision of papillary and follicular carcinomas, and, to this end, fragments of thyroid tissue contiguous with laryngeal nerves and parathyroid glands are left in place. These thyroid remnants have been readily imaged. They have also been ablated by I-131 treatment to wipe the scintigraphic slate clean. And, as expected, arguments have arisen over how and why this should be done.

In describing how ablation can be attained efficiently, Snyder et al. (*6*) record that 30 mCi of I-131 eliminated all traces of postoperative normal thyroid remnants in 61% of 69 patients, but left another 20% with a minimal residual that was considered insignificant. Thus, radioiodine, in doses relatively small by oncologic standards, succeeded in 81% of the patients. However, as many as three doses of 30 mCi failed to erase evidence of functioning thyroid cells in four individuals. The authors could not explain these failures by the presence of tumor in association with normal tissue or by differences of rad doses imparted to the remnants. However, the larger the residual gland, the more likely was persistence of function after I-131 therapy. This relationship was statistically significant but was not deemed meaningful because the numbers in the comparison groups were few. The authors wisely hedged their conclusions, but evidence from other studies support a correlation between size of remnant and ease of ablation.

With 26-30 mCi, DeGroot and Reilly (*8*) destroyed thyroid remnants in 83% of 18 individuals, and a second treatment of 30-50 mCi removed the tissue in their remaining three patients (a small focus of functioning thyroid cancer remained in one). This greater success in ablation could have been achieved by treating only small amounts of tissue; the patients of DeGroot and Reilly had lower radioiodine uptake values (0.2-6%) than did those of Snyder et al. (1-23%). Ramacciotto et al. (*9*) also eradicated normal tissue more often when the tracer uptake was less than 5%: ablation occurred in 60% of patients in this category. Others have found that 30-mCi doses infrequently obliterate all traces of thyroid function (*10,11*), but the sizes of the remnants treated were not given. In fact, larger doses, 75-150 mCi of I-131 have not destroyed normal tissue in some patients

(*9*,*12*). When the thyroidal remnants—sometimes an entire lobe—are large, radioiodine treatments may reduce function to a low level, but when the results are examined by modern scintigraphic techniques, the criteria for ablation are not fulfilled.

Reasonable conclusions are: small quantities of normal tissue can be ablated by 30 mCi of I-131, but if the thyroid remnants are substantial in size (probably those that sequester more than 5% of the tracer dose), complete destruction may be difficult to achieve with any dose of radioiodine. It then follows that if ablation is incorporated into a therapeutic protocol, surgeons should anticipate this step by performing at least a near-total thyroidectomy. In addition, complete and detailed notes of what was seen, excised, and left in place during an operation are essential to the continuing care of the cancer patient.

But why should we ablate normal thyroid tissue as a part of the treatment of well-differentiated thyroid cancer? If the postthyroidectomy remnant is large, it may, through synthesis of thyroid hormone, inhibit secretion of thyrotropin. Conditions will then not be optimal for the stimulation of thyroid metastases, which usually require high levels of circulating thyrotropin to be detected and treated efficiently. Therefore, in patients who harbor substantial amounts of normal tissue and exhibit little or no elevation in serum thyrotropin concentrations, reduction of the remnant by I-131 treatment will permit a more sensitive search for metastatic disease. But complete destruction, i.e., ablation of all normal tissue, is not required to achieve profound hypothyroidism and high thyrotropin levels.

On the other hand, if the remnant of the thyroid gland is already small, showing perhaps less than 3% uptake of a tracer dose at 24 hr, benefits from its removal are not readily perceived. For example, when the concentration of I-131 portrayed by scintigraphy is (a) remote from the site where the primary tumor was excised, and (b) in a location where the surgeon purposely avoided a minute portion of normal gland to protect a laryngeal nerve, there is little logic in applying ablative therapy. Some have argued that since papillary carcinoma is often multifocal within the thyroid gland, every cluster of cells must be viewed as containing cancer. But as pointed out by Snyder et al. (*6*) in their review of the literature, the multicentricity of thyroid cancer, does not, per se, correlate with survival of patients.

In the Mazzaferri study, fewer recurrences of papillary (*1*) and follicular cancer (*13*) have followed I-131 treatment of presumably normal thyroid residuals, but these results were of marginal statistical significance. Moreover, the treated tissues, although presumably the remnants of near-total thyroidectomies, were of uncertain size (*13*). These data notwithstanding, the aggregate of evidence does not convincingly demonstrate that ablation of small remnants—and especially those remote from the primary tumor—lowers the rate of recurrent cancer. Although a national cooperative study proposes to evaluate ablation as a step in the therapy of well-differentiated thyroid cancers, recurrence rates for these neoplasms are so low [probably no more than 10% over 10 yr for those classified as at low risk, and thus for the majority of patients (*14*,*15*)] that the value of ablation, if any, will not be known for years.

Surely, I-131 has a long record of safety, but there can be little doubt that moderate to large doses of radiation will, when given to enough people, demonstrably increase the number of cancers, probably by increasing the incidence of leukemia (*16*). That cancers have not been detected in statistically significant numbers following I-131 therapy does not mean that radioiodine lacks carcinogenic properties, but only that its potential is of low magnitude. Bearing these concepts in mind, each physician who treats thyroid cancer must decide from incomplete knowledge whether to use I-131 as a radioactive eraser. To ablate or not to ablate is a question that will haunt us for some time to come.

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