Radioiodine for Thyroid Cancer — Is Less More?

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In this issue of the Journal, Schlumberger et al. and Mallick et al. describe the administration of radioiodine (iodine-131) after total thyroidectomy in patients with low-risk thyroid cancer. Postsurgical treatment has long played an important role in the management of this increasingly common cancer. In the United States, the incidence nearly tripled (from 2.7 to 7.7 cases per 100,000) from 1973 through 2002. Similar increases have been reported in Europe. Such increases appear to result largely from more frequent radiologic detection and subsequent fine-needle aspiration of small thyroid nodules, leading to the diagnosis of low-risk thyroid cancer.

Guidelines of the American Thyroid Association conclude that data are too conflicting to support a recommendation for or against the routine use of radioiodine postoperatively in patients with low-risk thyroid cancer, whereas guidelines of the European Thyroid Cancer Taskforce are more favorable toward its use. Despite this uncertainty, the use of radioiodine for low-risk thyroid cancer in the United States has increased substantially during the past 35 years but without changes in outcomes. The goal of such treatment is to ablate residual thyroid, thereby improving the specificity of thyroglobulin assays and permitting detection of persistent disease by subsequent whole-body scanning.

In the two carefully performed, randomized, prospective studies by Schlumberger et al. and Mallick et al., a low dose of radioiodine (1.1 GBq [30 mCi]) was shown to be as effective as a high dose (3.7 GBq [100 mCi]) in reducing thyroglobulin to a very low level and eliminating residual thyroid tissue, as seen on ultrasonography. Thyroid ablation occurred even in patients with pathologically confirmed local lymph-node involvement.

These results should change standard practice, although they also raise the question of whether any radioiodine therapy is required for low-risk patients, since 21 to 59% of the patients in these two studies had already met the goal of a low thyroglobulin level after thyroidectomy alone. The use of radioiodine to achieve effective ablation in the remainder of patients must be weighed against increasing the risk of second primary cancers through exposure to radiation and the expense and logistics of radioiodine administration. In addition, in a recent 10-year follow-up study, the use of radioiodine did not prolong overall or disease-free survival in low-risk patients. However, the omission of radioiodine therapy also precludes post-treatment whole-body scanning, which can disclose unsuspected persistent or distant metastatic disease, as was found in 3% of these patients. Distant metastatic thyroid cancer, especially in patients over the age of 45 years, can be a more dangerous disease. For clinicians and patients, treatment poses a difficult question: How can the standard of care be improved for the majority without sacrificing the standard care for the minority? Many observers would argue that persistent local or metastatic disease would probably be identified by elevations in serum thyroglobulin levels during the initial assessment or subsequent follow-up, allowing for treatment modification.

These studies also compared strategies for preparing patients for radioiodine administration. Since thyrotropin is required to stimulate the uptake of radioiodine, two options exist: allow levels of endogenous thyrotropin to rise in re-
sponse to thyroid hormone withdrawal or administer exogenous recombinant human thyrotropin (thyrotropin alfa). Both studies emphasize the convenience and lack of hypothyroid symptoms with the use of thyrotropin alfa, as compared with hormone withdrawal. Nonetheless, both investigations were noninferiority trials and ultimately proved the equivalence of thyrotropin alfa and thyroid hormone withdrawal with respect to the primary end point. No significant differences in treatment-related adverse events were reported in the cohorts. Although a minority of patients undergoing thyroid hormone withdrawal reported having short-term symptoms of hypothyroidism, all symptoms had resolved by 3 months. Notably, these studies were not placebo-controlled, and patients who stop taking levothyroxine are typically advised to expect hypothyroid symptoms, whereas those receiving thyrotropin alfa are not.

Do these data clearly indicate that thyrotropin alfa should be preferred over thyroid hormone withdrawal in the preparation of patients for radioiodine treatment? They do not. One must consider that the use of thyrotropin alfa costs between $2,000 and $8,000 and requires two extra clinic visits for intramuscular administration with the associated costs of travel and time. In our clinic, we often use thyroid hormone withdrawal to increase thyrotropin levels for higher-risk patients in whom mild hypothyroidism is not contraindicated. The duration of the withdrawal period and the likelihood of major symptoms of hypothyroidism can be minimized by initiating thyroid hormone withdrawal when the thyrotropin level is normal and then monitoring it weekly and administering radioiodine after the level reaches 25 mU per liter.

Defining optimal therapy for patients with low-risk thyroid cancer is challenging because of the slow growth of such tumors and the high success rate of initial surgery. As suggested, an appropriate next step might be to randomly assign low-risk patients to receive either low-dose radioiodine or no radioiodine and monitor them for recurrence. Ideally, though, the identification of a pattern of gene expression or of a patient characteristic associated with a higher risk of recurrence would allow us to focus more aggressive treatment appropriately. Until then, less can indeed be more.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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