IN THE JOURNALS **PERSPECTIVE**

Radioactive iodine does not have significant benefit for recurrent thyroid cancer

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Individuals who received radioactive iodine after reoperation for recurrent or persistent papillary thyroid carcinoma appeared to have similar or worse outcomes as patients who underwent reoperation alone, according to retrospective cohort study findings.

"Radioactive iodine has some important side effects," **Michael W. Yeh, MD,** medical director of the UCLA Endocrine Surgery Program, told *HemOnc Today.* "Patients with thyroid cancer and treating physicians may wish to avoid radioactive iodine after reoperation because there may not be a benefit to it."

Although long-term prognosis for patients with papillary thyroid cancer is good, up to 30% of patients experience persistent or recurrent locoregional disease after treatment.

Radioactive iodine ablation may decrease locoregional recurrence among patients at intermediate and high risk for recurrence.

"It is fairly common for patients with differentiated thyroid cancer to need a second operation to remove abnormal lymph nodes," Yeh said. "We commonly are asked the question: Is further treatment with radioactive iodine necessary/beneficial after reoperation?"

Current guidelines recommend radioactive iodine ablation after initial thyroidectomy for high-risk patients.

However, research on the efficacy of radioactive iodine ablation following reoperation for persistent or recurrent papillary thyroid carcinoma remains limited.

Yeh and colleagues evaluated electronic medical records from 102 patients (median age, 44 years; 66% women) who underwent reoperation for locoregional recurrence after initial total thyroidectomy at a tertiary referral center between April 2006 and

January 2016.

Reoperation procedures included central neck dissection (22.5%), modified radical neck dissection (36.3%), and a combined central and modified radical neck dissection (41.2%).

Fifty patients received radioactive iodine ablation following reoperation, and 52 patients underwent reoperation without radioactive iodine ablation.

Clinicopathologic characteristics at initial operation appeared similar between the two groups, with the exception of tumor stage, which appeared more advanced among patients who underwent reoperation with radioactive iodine ablation (T3-T4, 56% vs. 37%).

At reoperation, clinical characteristics — including total number of lymph nodes removed, number of malignant lymph nodes removed and extent of reoperation — appeared similar between the groups.

Investigators compared suppressed thyroglobulin (Tg) levels from patients who underwent reoperation with or without radioactive iodine ablation at three time intervals: prior to reoperation, within 6 months following reoperation, and after radioactive iodine ablation or at a comparable time for patients who did not receive radioactive iodine ablation.

Biochemical response and structural recurrence following reoperation served as the study's outcomes.

The median Tg level among the entire cohort decreased from 2.8 ng/mL (interquartile range [IQR], 0.6-6.4) before reoperation to 0.2 ng/mL (IQR, 0-1.1) following reoperation.

Median Tg levels before reoperation (2.4 ng/mL vs. 3.3 ng/mL) and following reoperation (0.2

ng/mL vs. 0.6 ng/mL) appeared similar between patients who underwent reoperation without and with radioactive iodine ablation.

Among patients who did not receive radioactive iodine ablation, 24 had an excellent response, 10 had a biochemical incomplete response, 11 had an indeterminate response, and one patient did not have Tg1 measured.

Thirty-three patients who received radioactive iodine ablation had Tg measured prior to reoperation. Four of these had an excellent response, whereas 10 had a biochemical incomplete response and nine had an indeterminate response.

The rate of excellent response at reoperation was lower in the radioactive iodine ablation group ($P = .007$).

The median Tg levels appeared similar after radioactive iodine ablation and at a comparable time interval for patients who did not receive radioactive iodine ablation (0.2 ng/mL vs. 0.5 ng/mL).

After reoperation, 10 patients (19%) in the reoperation without radioactive iodine ablation group had pathologic recurrence compared with 18 patients (36%) in the reoperation with radioactive iodine ablation group.

Multivariable analysis accounting for clinicopathologic characteristics and Tg prior to reoperation showed no association between receipt of radioactive iodine ablation after reoperation and second structural recurrence.

Subset analyses restricted to patients with incomplete response to reoperation and patients with T3 or T4 tumors also showed no association between radioactive iodine ablation and the risk for second recurrence.

Researchers acknowledged that patients who underwent reoperation with radioactive iodine ablation were more likely to be selected based on clinical features associated with a higher risk for recurrence than patients who underwent reoperation alone.

Yeh cited the retrospective design of the study as a limitation.

“In any retrospective study, the patients are not randomly assigned to different treatments,” Yeh said. “In this case, patients who had radioactive iodine after reoperation had more aggressive tumors than those who had reoperation alone. However, even when we used statistical methods to account for this difference, our conclusions remained the same.”

He added: “This question will require further investigation with a prospective randomized study design.” – *by Melinda Stevens*

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PERSPECTIVE

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Cristina P. Rodriguez

This report is an attempt to shed light on a common clinical dilemma in the treatment of differentiated thyroid cancer — the utility of RAI for patients who undergo re-resection for local or locoregionally recurrent disease. Researchers compared two cohorts that underwent surgical re-resection with or without RAI at a high-volume tertiary center. Unsurprisingly, patients with higher-risk disease were overrepresented in the RAI cohort. This retrospective analysis utilized statistical methods to control for potential confounders. They found no evidence of benefit with RAI, defined by biochemically (TG) or structurally (macroscopic biopsy proven) recurrent disease.

These observations are important, especially in light of the more selective use of RAI as a therapeutic modality in the adjuvant setting, reflected in the American Thyroid Association guideline changes over the past decade. This disease is compatible with a disease course measured in years despite the presence of hematogenous metastases; therefore, concerns about nontrivial short- and long-term toxicities of RAI give merit to appropriate patient selection.

The authors appropriately point out the pitfalls of a retrospective single-institution comparison. Although their statistical methods attempt to control for clinical factors such as T stage at re-resection, myriad other clinical features may influence the decision to treat with RAI after repeat surgical resection. Clinicians who treat this disease are familiar with the variability in clinical behavior, such as time to disease recurrence, presence of poorly differentiated histology, patient age, comorbidity and fitness. All of these factors are considered in therapeutic decision-making. These patients were all referred to a high-volume academic center, and the quality of the initial treatment was difficult to account for. It would be of interest to know what

proportion of these patients had persistent disease — and perhaps inadequate upfront surgical resection — compared with disease recurrence after adequate surgery, implying a more aggressive disease biology.

Although the authors focus on the endpoints of biochemical and structural recurrence, other endpoints such as time to development of distant metastases, disease-specific survival and OS estimates would be of significant clinical relevance. Similarly, the duration of follow-up is of importance when considering these observations. The authors do not explicitly state the median follow-up in the two cohorts, although analyzed patients underwent surgery between 2006-2016. Given the protracted natural history of this disease, one might question if more mature data might yield varying results in the two cohorts.

The authors concluded that a randomized clinical evaluation of RAI after re-resection of locoregionally recurrent disease is warranted. This challenging effort would involve the choice of the appropriate clinical endpoints, such as biochemical or structural PFS, disease-specific survival and OS, as well as patient-reported quality of life. It also would require stratification for factors such as quality of initial surgery, recurrent vs. persistent disease, and histologic evidence of aggressive features. An attempt to homogenize the surgical expertise during re-resection might mean surgical accreditation similar to the design of cooperative group surgical trials.

The observations in this paper help underscore the need for thoughtful trial design that hopefully will lead to evidence-based guidelines in locoregionally recurrent thyroid cancer.