Association of Radioactive Iodine Administration After Reoperation With Outcomes Among Patients With Recurrent or Persistent Papillary Thyroid Cancer

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IMPORTANCE One-third of patients with papillary thyroid cancer (PTC) develop persistent or recurrent disease after initial therapy. Most patients with persistent or recurrent disease undergo reoperation, but the role of treatment with radioactive iodine (RAI) after reoperation is unclear.

OBJECTIVE To determine whether receipt of RAI after reoperation for recurrent PTC is associated with improved outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included electronic health record data from 102 patients who underwent neck reoperation for persistent or recurrent PTC at a tertiary referral center from April 2006 to January 2016; 50 patients received RAI after reoperation, and 52 did not receive RAI after reoperation. Data analysis was performed from September 1, 2017, to December 1, 2017.

MAIN OUTCOMES AND MEASURES Suppressed thyroglobulin (Tg) levels were compared between patients who underwent reoperation and received RAI and patients who underwent reoperation without receipt of RAI at the following time points: before reoperation (Tg0), after reoperation (Tg1), and after RAI or a comparable time interval among patients whose cases were managed without RAI (Tg2). Outcomes were biochemical response and structural recurrence after reoperation.

RESULTS The cohort comprised 102 patients who underwent neck reoperation for persistent or recurrent PTC (median age, 44 years [interquartile range, 33-54 years; SD, 14 years]; 67 [66%] female), 50 of whom received treatment with RAI after reoperation. Clinicopathologic characteristics of the patients at the time of the initial surgical procedure were similar between the reoperation with RAI group and the reoperation without RAI group with the exception of tumor (T) stage (T3 and T4, 28 of 50 [56%] vs 19 of 52 [37%]). Although median Tg levels were similar between the reoperation with RAI group and the reoperation without RAI group (Tg0, 3.3 ng/mL vs 2.4 ng/mL; Tg1, 0.6 ng/mL vs 0.2 ng/mL; and Tg2, 0.5 ng/mL vs 0.2 ng/mL; all differences were nonsignificant), the rate of excellent response at Tg1 was lower in the reoperation with RAI group (4 of 33 [12%] vs 24 of 51 [47%]; \( P = .007 \)). Structural recurrence after reoperation occurred in 18 of 50 patients (36%) in the reoperation with RAI group and 10 of 52 patients (19%) in the reoperation without RAI group. In multivariable analysis accounting for clinicopathologic characteristics and Tg0, receipt of RAI after reoperation was not associated with the rate of a second structural recurrence. In subset analyses limited to patients with incomplete response to reoperation and patients with T3 or T4 tumors, no association between receipt of RAI and the risk of a second recurrence was found.

CONCLUSIONS AND RELEVANCE Patients who received RAI after reoperation had outcomes similar to those in patients who underwent reoperation alone. RAI after reoperation was not associated with a significant clinical benefit in this limited series. Larger multicenter studies are required to determine whether receipt of RAI after reoperation improves outcomes among patients with recurrent PTC.

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Supplemental content

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Radioactive Iodine Administration After Reoperation for Recurrent or Persistent Papillary Thyroid Cancer

Original Investigation Research

The role of radioactive iodine (RAI) administration after reoperation for persistent or recurrent PTC is unclear. Current guidelines recommend RAI ablation after initial thyroidectomy for patients considered to have a high risk of recurrence, with the goals of ablating residual thyroid tissue to enhance surveillance and treating residual disease. Receipt of RAI has been shown to decrease the rate of locoregional recurrence among patients with intermediate and high risk of recurrence. However, data regarding the efficacy of RAI administered after reoperation for persistent or recurrent PTC are limited.

In this study, we analyzed the oncologic outcomes of reoperation for PTC in a tertiary referral center (Ronald Reagan UCLA [University of California, Los Angeles] Medical Center). The objective was to determine whether reoperation with administration of RAI was associated with improved biochemical markers or a lower rate of structural disease recurrence compared with reoperation without RAI.

Methods

Patient Population
Following approval by the UCLA Institutional Review Board, which waived the need for patient consent, patients were abstracted from UCLA Health System electronic medical records using the University of California Integrated Clinical and Research Data Repository. Data were deidentified. Patients who had potentially undergone reoperation for recurrent thyroid cancer between 2006 and 2016 were identified using International Classification of Diseases, Ninth Revision codes 193.0 (thyroid cancer) and Current Procedural Terminology codes 38724 (modified radical neck dissection) or 21552-21558 (excision procedures on the neck). This search yielded 1061 unique patient records. We then performed individual medical record review to identify patients with PTC who had undergone initial total thyroidectomy with or without subsequent RAI ablation and then had a reoperation for locoregional recurrence. Based on the data abstraction, 292 patients underwent reoperation for recurrent PTC between 2006 and 2016. We restricted the study to a single, high-volume surgeon who performed 156 of these reoperations to eliminate differences in surgical technique that could affect outcomes. We excluded 16 patients who had a history of reoperation before being evaluated at our hospital, 3 patients who were younger than 18 years, 4 patients who had no information available regarding their initial thyroidectomy and pathologic findings, and 31 patients who had insufficient follow-up after reoperation to determine whether they received RAI.

Structural and Biochemical Outcomes After Reoperation
We reviewed all postoperative thyroglobulin (Tg) levels, clinical notes, imaging studies, and pathologic findings. Structural recurrence was defined as malignant tissue confirmed by fine-needle aspiration biopsy or histopathologic findings after surgical resection. Suppressed Tg levels (associated with thyroid-stimulating hormone values <0.5 mU/L) were used to assess the biochemical response to treatment. The Tg levels were assessed just before reoperation (Tg0), within 6 months after reoperation (Tg1), and after RAI in the reoperation without RAI group or at a time point after Tg1 in the reoperation with RAI group. The shortest time between Tg1 and subsequent Tg measurement (Tg2) was 1 month. The Tg antibody level was measured with each Tg measurement, and Tg values were excluded from analysis for patients with Tg antibody levels greater than 20 IU/mL (the lower limit of detection). Those Tg values that were undetectable were assigned a value of 0.2 ng/mL (to convert to micrograms per liter, multiply by 1), which is the assay’s lower limit of detection at our institution.

Patient response to therapy was classified according to 2015 American Thyroid Association guidelines at the time of Tg1 measurement and at the last known follow-up examination. Disease status was categorized as excellent response (no clinical, biochemical, or structural evidence of disease; suppressed Tg level <0.2 ng/mL), biochemical incomplete response (suppressed Tg level >1 ng/mL), structural incomplete response (persistent or newly identified locoregional or distant metastases), or indeterminate response (suppressed

Key Points

Question Is receipt of radioactive iodine after reoperation associated with improved outcomes among patients with recurrent or persistent papillary thyroid cancer?

Findings In this cohort study of 102 patients who underwent reoperation for recurrent or persistent papillary thyroid cancer at a tertiary referral center, patients who received radioactive iodine after reoperation had similar or worse biochemical outcomes and recurrence-free survival compared with patients who underwent reoperation alone.

Meaning Receipt of radioactive iodine after reoperation may not be associated with improved outcomes or may be associated with only modest clinical benefit; larger multicenter studies are indicated to determine whether receipt of radioactive iodine after operation improves outcomes among patients with recurrent papillary thyroid cancer.

The final study cohort was separated into patients who underwent reoperation with RAI and patients who underwent reoperation without RAI. Of 50 patients in the reoperation with RAI group, 43 patients had undergone initial RAI ablation (median dose, 150 mCi; interquartile range [IQR], 105-160 mCi; SD, 48 mCi). Of 52 patients in the reoperation without RAI group, 50 patients had undergone RAI ablation (median dose, 151 mCi; IQR, 103-168 mCi; SD, 73 mCi).
Tg level of 0.2-1.0 ng/mL and/or nonspecific imaging abnormalities. Trends in Tg antibody levels were not considered in the assessment of disease status because they have been shown to be of no utility when measured with most commercially available assays.10

Statistical Analysis
The association between categorical variables was assessed using χ² tests or Fisher exact tests. Data were analyzed from September 1, 2017, to December 1, 2017. Univariable and multivariable Cox proportional hazards regression models were used to evaluate the association between patient and tumor characteristics and recurrent or persistent disease after reoperation. Multivariable regression analyses included adjustments for Tg0, age, sex, tumor stage at initial presentation, number of lymph nodes removed at reoperation, and number of nodes removed during reoperation that were shown to be malignant on pathologic examination. The associations between study variables and risk of second recurrence were reported as hazard ratios (HRs). Finally, we performed a power analysis with regard to our ability to detect a difference in second recurrences between patients who underwent reoperation with RAI vs patients who underwent reoperation without RAI. We used standardized differences instead of P values to evaluate imbalances in baseline covariates, 11 as recommended by Thomas and Pencina,12 Mark et al,13 and Cohn.14 Standardized differences of 0.2, 0.5, and 0.8 correspond to small, medium, and large effect sizes, respectively. In the context of hypothesis testing, P values <.05 were considered to be statistically significant. Bonferroni correction for multiple comparisons was performed when analyzing differences in Tg values between the reoperation with RAI group and the reoperation without RAI group. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Baseline Clinical Characteristics
The cohort consisted of 102 patients with PTC who had a reoperation for locoregional recurrence after initial total thyroidectomy. The median age was 44 years (IQR, 33-54 years; SD, 14 years), and 67 [66%] of the patients were female. Reoperation included central neck dissection (23 of 102 patients [22.5%]), modified radical neck dissection (37 of 102 [36.3%]), and combined central and modified radical neck dissection (42 of 102 [41.2%]). Of these, 50 patients underwent reoperation followed by RAI administration (median RAI dose, 155 mCi; IQR, 148-200 mCi; SD, 41 mCi), and 52 patients underwent operation without RAI (Figure 1). The clinicopathologic characteristics at initial operation were similar between the reoperation with RAI group and reoperation without RAI group with the exception of T stage, which was more advanced in the reoperation with RAI group than in the reoperation without RAI group (T3 or T4, 28 of 50 patients [56%] vs 19 of 52 patients [37%]; standardized difference, 0.48) (Table 1). In examining clinical characteristics at reoperation, the groups were similar with regard to total number of lymph nodes removed, number of malignant lymph nodes removed, and extent of reoperation (Table 2). On histopathologic review, microscopic extranodal extension was observed to be more prevalent in the reoperation with RAI group than in the reoperation without RAI group (29 of 50 patients [58%] vs 17 of 52 patients [33%]; standardized difference, 0.53).

Biochemical Response to Reoperation
The median (IQR) Tg level in the entire cohort decreased from 2.8 ng/mL (0.6-6.4 ng/mL) at Tg0 to 0.2 ng/mL (0.0-1.1 ng/mL) at Tg1 (median [IQR] of 2 months [1-3 months] after reoperation). Median Tg0 (2.4 ng/mL vs 3.3 ng/mL) and Tg1 (0.2 ng/mL vs 0.6 ng/mL) levels were similar between the
reoperation without RAI and reoperation with RAI groups (eFigure in the Supplement). In the reoperation without RAI group, 51 patients had Tg1 measured, and 24 patients had an excellent response (Table 3). The remainder included 10 patients with a biochemical incomplete response and 11 patients with an indeterminate response. Only 33 patients in the reoperation with RAI group had Tg1 measurements before receipt of RAI, including 4 patients with an excellent response (Table 3). The remainder included 10 patients with a biochemical incomplete response and 9 patients with an indeterminate response. Median Tg2 levels were similar between the reoperation without RAI and reoperation with RAI groups (0.2 [IQR, 0-0.9] vs 0.5 [IQR, 0-2.5] ng/mL, P = .08). The median time between Tg1 and Tg2 measurements was 4.7 months (IQR, 2.4-8.4 months).

Second Recurrence After Reoperation
After reoperation, 10 of 52 patients (19%) in the reoperation without RAI group had pathologic confirmation of recurrence compared with 18 of 50 patients (36%) in the reoperation with RAI group. The median (IQR) time to recurrence was 12 months (7-28 months) in the reoperation without RAI group and 11 months (6-72 months) in the reoperation with RAI group. There was no significant difference in recurrence-free survival after reoperation between the treatment groups (P = .24) (Figure 2). At the end of follow-
up, 2 patients in the reoperation with RAI group had died (one death was attributable to thyroid cancer, and the other was attributable to an unrelated cause). There was no mortality in the reoperation without RAI group.

All 10 patients in the reoperation without RAI group who had pathologic confirmation of recurrence had locoregional recurrences. Eight patients underwent a second reoperation, and 1 patient was treated with ethanol ablation. Of the 9 treated patients, 6 patients demonstrated no structural evidence of disease after a median (IQR) follow-up of 14 months (1-61 months) after the most recent treatment. Of the 18 patients in the reoperation with RAI group with pathologic confirmation of recurrence, 15 patients had locoregional disease and 3 patients had distant metastases (2 patients had metastases to the lung and 1 patient had metastases to the adrenal glands). Of the 15 patients with locoregional disease, 13 patients underwent a second reoperation and 2 patients underwent ethanol ablation.

**Response to Therapy Classification at Last Follow-up Examination**

At the end of follow-up, 28 of 52 patients (54%) in the reoperation without RAI group had an excellent response to the sum total of their therapy, whereas 8 patients (15%) had a structural incomplete response. In contrast, 13 of 50 patients (26%) in the reoperation with RAI group had an excellent response to therapy at the end of follow-up, and 13 patients (26%) had a structural incomplete response (Table 3).

**Table 3. Response to Therapy Classification**

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>No. (%) of Patients Reoperation Without RAI (n = 52)</th>
<th>Reoperation With RAI (n = 50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroglobulin level after reoperation*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent response</td>
<td>24 (47)</td>
<td>4 (12)</td>
<td>.007</td>
</tr>
<tr>
<td>Biochemical incomplete response</td>
<td>10 (20)</td>
<td>10 (30)</td>
<td></td>
</tr>
<tr>
<td>Structural incomplete response</td>
<td>6 (12)</td>
<td>10 (30)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate response</td>
<td>11 (22)</td>
<td>9 (27)</td>
<td></td>
</tr>
<tr>
<td>Last follow-up examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent response</td>
<td>28 (54)</td>
<td>13 (26)</td>
<td>.04</td>
</tr>
<tr>
<td>Biochemical incomplete response</td>
<td>6 (12)</td>
<td>8 (16)</td>
<td></td>
</tr>
<tr>
<td>Structural incomplete response</td>
<td>8 (15)</td>
<td>13 (26)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate response</td>
<td>10 (19)</td>
<td>16 (32)</td>
<td></td>
</tr>
</tbody>
</table>

**Cox Proportional Hazards Regression Analysis of Variables Associated With Second Recurrence**

In univariate analysis, RAI after reoperation was not associated with a decreased risk of a second structural recurrence (HR, 1.90; 95% CI, 0.88-4.14; P = .10). After controlling for clinicopathologic characteristics, including T stage at initial operation, Tg0, extent of reoperation, and extranodal extension on pathologic examination, RAI after reoperation was still not associated with the risk of a second recurrence (HR, 1.12; 95% CI, 0.43-2.98; P = .81) (eTable in the Supplement). After excluding patients with an excellent response at Tg1, thereby restricting the analysis to patients who had a detectable Tg level after reoperation, RAI after reoperation was still not associated with the risk of a second recurrence. We also tested for a possible relationship between Tg0 and the risk of a second recurrence. There was no association when Tg0 was treated as

Abbreviation: RAI, radioactive iodine ablation.

*One patient from the reoperation without RAI group and 17 patients from the reoperation with RAI group did not have a thyroglobulin level obtained after reoperation.

**Figure 2. Kaplan-Meier Curves Showing Structural Recurrence-Free Survival in the Reoperation Without Radioactive Iodine (RAI) Group and the Reoperation With RAI Group**

There was no significant between-group difference in structural recurrence-free survival after reoperation (P = .24 by log-rank test).
a continuous variable (HR, 1.12; 95% CI, 0.43-2.98; \( P = .81 \)) or dichotomized at a cutoff of 1 ng/mL (HR, 1.15; 95% CI, 0.46-2.89; \( P = .76 \)).

We also performed a subgroup analysis of patients with initial T3 and T4 tumors to investigate whether RAI after reoperation might selectively benefit patients at high risk of recurrence. In this subgroup, no differences in Tg0, Tg1, or Tg2 levels were found between patients who received RAI after reoperation and those who did not. Multivariable analysis that accounted for clinicopathologic characteristics, Tg0, and extent of reoperation showed that RAI after reoperation did not have a significant association with the risk of a second recurrence among this subgroup of patients with more advanced disease.

Discussion

Reoperation for recurrent or persistent PTC achieves initial biochemical complete response in up to two-thirds of patients, although 25% of patients ultimately develop a second recurrence.\(^\text{15}\) One-third (28) of the 85 patients in the series who were eligible to have disease status assessed at Tg1 had an excellent initial response, and 28 (27%) of 102 patients in the series developed a second recurrence. Receipt of RAI after reoperation did not improve outcomes in this study, although patients who received RAI may have had more aggressive disease compared with patients who underwent reoperation without RAI, given their higher initial T stage, lower rate of initial excellent response, and higher rate of extranodal extension at reoperation. After accounting for the possibility that patients who received RAI may have had more aggressive disease in multivariable and subgroup analyses, receipt of RAI after reoperation still was not associated with recurrence-free survival in this series.

Reoperation for PTC has been demonstrated to be an effective therapy for recurrent disease. Earlier analyses of reoperation for recurrent or persistent PTC found that 21% to 66% of patients achieved an excellent response after reoperation.\(^\text{16-19}\) A recent study of 157 patients with recurrent differentiated thyroid cancer demonstrated a 63% complete response rate (defined as suppressed or stimulated Tg <1 ng/mL with normal findings on neck imaging) at a median of 7 months after reoperation (range, 1-68 months).\(^\text{15}\) At a median follow-up of 5 years (range, 8 months to 33 years), 53% of patients still had a complete response without developing a second recurrence. In this study, the rate of excellent response (with a stricter definition of suppressed Tg <0.2 ng/mL) was 33.3% (28 of 85 patients who could have disease status assessed) at the first follow-up examination (median of 2 months [IQR, 1-3 months] after reoperation) and 40.2% at the last follow-up examination (median of 3 years [IQR, 1.2-5.4 years] after reoperation).

Biochemical and structural outcomes in this study were similar or worse among patients who underwent reoperation with RAI compared with those who underwent reoperation without RAI. However, this finding must be carefully interpreted because patients with more advanced disease may have been preferentially selected to receive RAI after reoperation. In that case, patients in the reoperation with RAI group would be expected to have worse outcomes, which could obscure a potential therapeutic benefit of RAI. The 2 groups were well matched with respect to most clinical factors, but patients in the reoperation with RAI group had a higher percentage of T3 and T4 disease at initial surgery, a higher rate of extranodal extension at reoperation, and a lower rate of excellent response immediately after reoperation compared with patients who underwent reoperation without RAI. We accounted for disease burden in multivariable regression analysis, adjusting for baseline Tg levels, tumor stage, and lymph node involvement, and receipt of RAI after reoperation still was not associated with a decrease in the risk of a second recurrence. Additional separate subgroup analyses of patients with locally advanced disease (stage T3 or T4) and patients with a detectable Tg level at Tg1 (after reoperation) also did not demonstrate an association between receipt of RAI after reoperation and outcomes.

Although receipt of RAI did not improve outcomes among the subset of patients at high risk for recurrence mentioned above, earlier limited studies have suggested that patients with an incomplete biochemical response to reoperation may benefit from RAI. A recent study of 50 patients with persistent locoregional differentiated thyroid cancer who underwent reoperation and received subsequent RAI found a decrease in Tg levels only among patients who had a biochemical incomplete response to reoperation.\(^\text{20}\) In another study that examined 113 patients with recurrent differentiated thyroid carcinoma who underwent reoperation with or without additional RAI treatment, receipt of RAI prolonged survival only among patients with a biochemical incomplete response after reoperation.\(^\text{21}\)

Limitations

This study has several limitations, the most important of which is nonrandom treatment selection arising from the retrospective design of the study. Patients who underwent reoperation with receipt of RAI were more likely to be selected on the basis of clinical features that were perceived to be associated with a higher risk of recurrence than were patients who underwent reoperation alone. Furthermore, this study was conducted at a referral center, which limits our knowledge of clinical events before surgery. Reoperation for PTC is rare, occurring in 2% of patients.\(^\text{22}\) Although our center aggregates patients in need of reoperation, the sample size yielded 80% power to detect a 22% difference in recurrence-free survival. With this caveat, after multivariable adjustment, we cautiously accept the null hypothesis that reoperation with receipt of RAI is not associated with a significant prolongation of recurrence-free survival. A difference of less than 22% remains possible. Further multicenter trials to assess the utility of RAI after reoperation for PTC are needed. Finally, this study is restricted to a single tertiary referral center, which may further limit the generalizability of these findings.
Conclusions

Despite these limitations, we revealed that reoperation for PTC may be associated with low morbidity and an excellent biochemical response. However, up to one-third of patients in this cohort developed a second recurrence. Receipt of RAI after reoperation was not associated with outcomes in this series. This single-institution study may not be adequately powered to detect a modest effect of treatment with RAI after reoperation. Thus, further multicenter studies will be needed.