Inability of Radioiodine Remnant Ablation to Improve Postoperative Outcome in Adult Patients with Low-Risk Papillary Thyroid Carcinoma

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Abstract

Objective: To determine whether radioiodine remnant ablation (RRA) reduces cause-specific mortality (CSM) or tumor recurrence (TR) rate after bilateral lobar resection (BLR).

Patients and Methods: There were 2952 low-risk adult papillary thyroid cancer (LRAPTC) patients (with MACIS scores <6) who underwent potentially curative BLR during 1955-2014. During 1955-1974, 1975-1994, and 1995-2014, RRA was administered in 3%, 49%, and 28%. Statistical analyses were performed using SAS software.

Results: During 1955-1974, the 20-year CSM and TR rates after BLR alone were 1.0% and 6.8%; rates after BLR+RRA were 0% (P=.63) and 5.9% (P=.82). During 1975-1994, post-BLR 20-year rates for CSM and TR were 0.3% and 7.5%; after BLR+RRA, rates were higher at 0.9% (P=.31) and 12.8% (P=.01). When TR rates were examined separately for 448 node-negative and 317 node-positive patients, differences were nonsignificant. In 1995-2014, post-BLR 20-year CSM and TR rates were 0% and 9.2%; rates after BLR+RRA were higher at 1.4% (P=.19) and 21.0% (P<.001). In 890 pN0 cases, 15-year locoregional recurrence rates were 3.4% after BLR and 3.7% after BLR+RRA (P=.99). In 740 pN1 patients, 15-year locoregional recurrence rates were 10% higher after BLR+RRA compared with BLR alone (P=.01). However, this difference became nonsignificant when stratified by numbers of metastatic nodes.

Conclusion: RRA administered to LRAPTC patients during 1955-2014 did not reduce either the CSM or TR rate. We would therefore not recommend RRA in LRAPTC patients undergoing BLR with curative intent.

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The year 2021 represents a significant milestone; not only does it commemorate the 80th year since Saul Hertz first administered radioactive iodine (RAI) to treat a hyperthyroid patient,[1] but it is now 70 years since the US Food and Drug Administration sanctioned the use of radioactive sodium iodide (^{131}I) in patients with thyroid disease, signifying the first approval of a radiopharmaceutical and, simultaneously, the birth of nuclear medicine.[2] By 1960, Blahd at UCLA was routinely using ^{131}I as postoperative therapy for metastatic thyroid cancer. In addition, his group pioneered the concept of radioiodine remnant ablation (RRA) to "complete the thyroidectomy" even after an apparently complete surgical resection of primary tumor in localized differentiated thyroid cancer (DTC) had been achieved.[3]

In 1970, the University of Michigan nuclear medicine group led by Beierwaltes was first to report that ^{131}I administered postoperatively could reduce mortality from DTC.[4] Specifically, they "showed for the first time statistically, that ablation of the ^{131}I uptake in the functioning remnant was associated with a 20-fold decrease in death

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rate."[1] In 1977, Mazzaferri et al[5] published their landmark US Air Force study, which reported a dramatically decreased tumor recurrence (TR) rate for papillary thyroid carcinoma (PTC) patients treated with surgery and postoperative ^{131}I compared with other therapeutic approaches. However, as recognized by Daniels and Kopp,[6] "there was no attempt to control for disease stage in the various therapy groups." By 1981, Mazzaferri[7] had recommended total or near-total thyroidectomy followed by RAI therapy for all patients with PTC of more than 1.5 cm in diameter and for those PTCs that were bilateral, metastatic, or locally invasive as well as for all patients with follicular thyroid cancer.

As is now more generally recognized,[8] "for the next several decades, the Mazzaferri approach was practiced in many centers throughout the United States for most DTC patients."[6] However, at Mayo Clinic, there has been doubt about the efficacy of RRA in the postoperative management of PTC since 1983,[9] and our multidisciplinary PTC management group[10,11] has pursued a policy of selective use of RRA,[12-14] starting soon after the MACIS (distant metastasis, patient's age, completeness of surgery, extrathyroid invasion, tumor size) prognostic scoring system for prediction of PTC-related mortality was described in 1993.[15]

In an analysis of outcome in 190 children and 4242 adults consecutively treated for PTC at Mayo Clinic during 8 decades (1936-2015), we reported that since 1976, both children and adults with MACIS scores below 6 had a less than 1% chance at 30 years of cause-specific mortality (CSM).[11] Because American Thyroid Association (ATA) management guidelines[16] for children with DTC and recommendations from the American Society of Pediatric Surgeons[17] have been directed specifically to children (aged 18 years or younger) and differ somewhat in RRA recommendations from the de-escalation[18-20] of aggressive ^{131}I therapy promoted in the 2015 ATA adult guidelines,[21] we elected in this study to restrict our study cohort to adult PTC patients who were 19 years of age or older at the time of initial pathologic diagnosis. The principal aim of this study was to determine whether postoperative RRA reduces CSM or TR rate in the 85% of adult PTC patients who have "low-risk" disease with postoperative MACIS prognostic scores below 6. We therefore chose to study all low-risk adult PTC (LRAPTC) patients who consecutively underwent during 6 decades (1955-2014) potentially curative bilateral lobar resection (BLR) at Mayo Clinic for localized disease (pM0) with surgically complete tumor resection.

PATIENTS AND METHODS

Mayo Rochester PTC Database

The Mayo Rochester PTC Database (MRPD) originated in 1980, when a comprehensive data-abstracting system was "designed by a team of clinical thyroidologists, surgeons, a pathologist, and a statistician."[22] Since 1983, it has been maintained by the senior author (I.D.H.). As reported in 1986, "the complete abstracting of medical records entailed several years, and the acquired information was coded and entered into a computer data bank for subsequent retrieval."[22] The initial paper[22] resulting from MRPD analysis described a cohort of 859 patients receiving their primary treatment at Mayo Clinic in Rochester during 1946-1970. In subsequent years, the data from patients treated during 1971 through 2019 were directly entered into the computer in a prospective fashion, and the scope of the questions posed significantly expanded. As of October 2020, the MRPD contained details of presentation, initial staging, surgery, pathologic examination, adjuvant therapy, and TR (local, regional, and distant) and the latest imaging, biochemistry, and status of 4765 APTC patients having primary treatment during 1935-2019 and observed for a median of 11.1 years and a mean of 15.2 postoperative years, now with a total experience of 72,402 patient-years of observation.

We had previously identified that at Mayo Clinic, the 4-decade period of

1976-2015 represented "the era of the rise and fall of remnant ablation."[11] As shown in Figure 1, in the first 4 years after the Food and Drug Administration approved the use of RAI, only 1% of LRAPTC patients who had undergone potentially curative BLR were given RRA. We therefore commenced this study in 1955, and to potentially have at least 5 years of follow-up after RRA, we concluded cohort recruitment with the patients treated during December 2014. Within these 60 years, we separately studied outcome in 3 time periods of 2 decades: 1955-1974, the era of Blahd[3] and Beierwaltes,[1,4] when only 3% were ablated; 1975-1994, the era of Mazzaferri,[5,7] when 49% were ablated and results were principally assessed by whole body ^{131}I scintigraphy; and 1995-2014, the post-MACIS era, when remnant ablation was more selective (28%) and tumor surveillance relied more on the extremely sensitive indicators of serum thyroglobulin assays and ultrasound-guided biopsy of suspicious neck masses.[17,23]

For purposes of this study, details for analysis were taken from the MRPD for all APTC patients with MACIS scores below 6 who were consecutively managed with potentially curative BLR (encompassing total or near-total thyroidectomy and bilateral subtotal thyroidectomy) between January 1, 1955, and December 31, 2014. These details included presenting features of the APTC patients (19 years of age or older at diagnosis); the extent of primary surgery; the findings at surgical pathologic examination; the details of RRA, if performed; and the postoperative course, encompassing local recurrence, regional and distant metastasis, and CSM. Where relevant, death certificates were obtained, as were details of any autopsies performed. The study protocol was approved by Mayo Clinic Institutional Review Board; each patient provided consent for inclusion in the MRPD. Follow-up information was obtained by Mayo Clinic reexamination, by review of outside medical records, or through correspondence with the home physician and patient or family members.

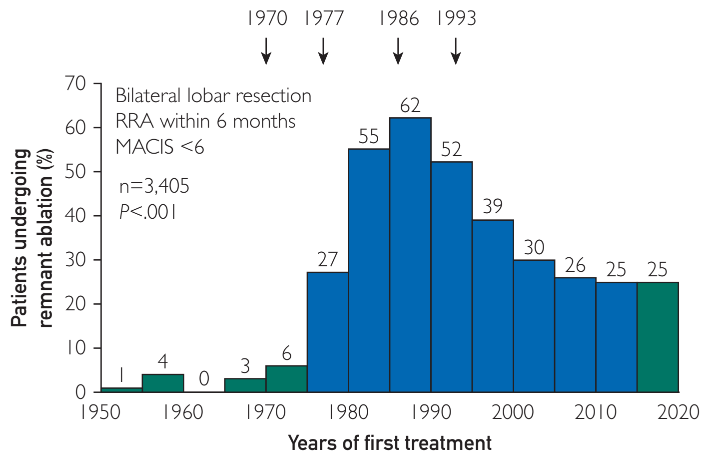

FIGURE 1. Trends during 7 decades (1950 through 2019) in the percentage of 3405 low-risk adult papillary thyroid carcinoma (LRAPTC) patients having potentially curative bilateral lobar resection for localized disease and also having postoperative radioiodine remnant ablation (RRA) administered within 6 postoperative months. Each column represents a 5-year period, and the numbers above the columns represent the actual percentage of LRAPTC patients undergoing RRA within 6 months. The 4-decade period of 1975-2014 represents what has been described as "the era of the rise and fall of remnant ablation."[11] The vertical arrows of 1970, 1977, 1986, and 1993 represent the publication dates of 4 manuscripts from the University of Michigan,[4] Ohio State University,[5] and Mayo Clinic[15,22] that greatly influenced the prescription of postoperative RRA for LRAPTC in Rochester, Minnesota.

Definition of Postoperative TR Events

The TR events at regional, local, and distant sites were identified per earlier publications[10,11,22,24,25] and, as in the National Thyroid Cancer Treatment Cooperative Study Group registry analysis,[26] characterized by "structural evidence of disease determined either radiologically or by pathology." Since 1986, we[22] and others[27] have recognized 3 types of TR with "differing prognostic implications."[10,24] These recurrent events were classified as postoperative regional nodal metastasis (RNM), local recurrence, and postoperative distant metastasis. A local recurrence was diagnosed "if biopsy-proven tumor was discovered in the anterior aspect of the neck, other than in the lymph nodes, at any time after apparently complete surgical removal of the original tumor."[22] Distant metastatic lesions diagnosed no later than

30 days after operation were considered to be present at the time of initial presentation; those diagnosed more than 30 days postoperatively were considered new distant metastatic lesions. None of our recurrent events were based solely on persistently elevated levels of serum thyroglobulin. The details of all recurrent events described in earlier reports[10,11,22,24,25] were reanalyzed before consideration of inclusion in this study. As the cohort of patients in the MRPD has expanded from the initial 1946-1970 cohort of 859 PTC patients[22] to the present total of 4953 patients of all ages from 1935-2019, follow-up details were continually updated and all new TR events added to the database.

Selection of Patients for the Study

We made a decision to study only those 2952 patients who had MACIS scores below 6 and who had potentially curative BLR performed for localized disease during the 6 decades of 1955 through 2014. At Mayo Clinic, the term BLR has been used in multiple published PTC management studies[10,11,14,25] to encompass 3 different types of bilateral surgical procedure and to denote surgery more extensive than ipsilateral thyroid lobectomy and isthmusectomy (hemithyroidectomy), which "after 1955 . . . was usually considered an inadequate thyroid cancer operation."[22] Historically, the bilateral procedure most frequently performed at Mayo Clinic for APTC[10,11] has been termed a near-total thyroidectomy, whereby the ipsilateral lobe and isthmus were totally removed and the lobe contralateral to the dominant tumor had a less than total lobectomy in an attempt to prevent postoperative hypoparathyroidism.[22] Bilateral subtotal thyroidectomy referred to patients who had an isthmusectomy and both lobes were subtotally resected, whereas a total thyroidectomy occurred when both thyroid lobes along with the isthmus were "totally" removed. Before embarking on this study, we had previously confirmed[10,11,22,24,25] that there were no meaningful differences in long-term outcome (CSM, local recurrences, and postoperative distant metastases) between the 3 bilateral surgical procedures, thereby justifying their being grouped together. As detailed in the earlier description of the MRPD, the 2952 patients were separately studied in 3 cohorts, each of 2 decades. As shown in Figure 1, the percentage of LRAPTC patients undergoing postoperative RRA within 6 postoperative months was 3% for 1955-1974, 49% for 1975-1994, and 28% for 1995-2014. During 1955-2014, the numbers of LRAPTC patients undergoing removal of neck nodes at the time of BLR almost doubled from 44% to 87%, and concomitantly, there was an increase in the numbers of confirmed RNM seen at surgical pathologic examination from 34% in 1955-1974 to 41% during 1975-1994 and 46% during the most recent period of 1995-2014.

Statistical Analyses

Survival rates from the date of initial surgery until death (cause specific) or TR were studied by standard life-table methods.[10,11] We used the Kaplan-Meier method[10,11,22] as available on our Statistical Analysis System (SAS) computer software. Studies of both CSM and TR involved all 2952 LRAPTC patients managed during 1955-2014 who did not have distant metastases at presentation and underwent complete tumor resection with BLR and who had no postoperative gross residual disease. Univariate comparisons of risk characteristics and trends across the decades were performed with the χ^2 test of proportion, the Fisher exact test, or the Kruskal-Wallis test, where indicated. Significance testing for differences in survival made use of the observed nature of the survival curves, which justified use of log-rank tests.[22] All tests were 2 sided, with an α level of .05. All calculations were performed using SAS software. SAS and all other SAS Institute Inc product or service names are registered trademarks of SAS Institute Inc.

RESULTS

Details of LRAPTC Patients Initially Managed by BLR During 1955 Through 2014

There were 2952 LRAPTC patients who had MACIS scores below 6 and underwent

TABLE. Presenting Variables Relevant to Selection of Postoperative RRA in 2952 APTC Patients With MACIS Scores Below 6 Managed With Potentially Curative BLR at Mayo Clinic, 1955-2014[a,b]

Variable present at time of initial definitive thyroidectomy	BLR alone (n=2096)	BLR+RRA (n=856)	Total (N=2952)	*P* value
Patient's age (y)				<.001[c]
Mean (SD)	45.1 (12.67)	42.3 (12.73)	44.3 (12.75)	
Median	46.0	43.0	45.0	
Range	19.0-73.0	19.0-72.0	19.0-73.0	
Patient's sex				<.001[d]
Male	574 (27.4)	308 (36.0)	882 (29.9)	
Female	1522 (72.6)	548 (64.0)	2070 (70.1)	
Extent of thyroidectomy				<.001[d]
Total thyroidectomy	770 (36.7)	375 (43.8)	1145 (38.8)	
Bilateral subtotal thyroidectomy or near-total thyroidectomy	1326 (63.3)	481 (56.2)	1807 (61.2)	
RNM resection performed				<.001[d]
Yes	1407 (67.1)	727 (84.9)	2134 (72.3)	
No	689 (32.9)	129 (15.1)	818 (27.7)	
Gross (macroscopic) invasion reported at surgery				<.001[d]
Yes	29 (1.4)	42 (4.9)	71 (2.4)	
No	2067 (98.6)	814 (95.1)	2881 (97.6)	
Largest PTC nodule (cm diameter)				<.001[c]
Mean (SD)	1.5 (1.01)	2.1 (1.27)	1.7 (1.13)	
Median	1.2	1.9	1.5	
Range	0.1-8.0	0.1-8.0	0.1-8.0	
Histologic grade				<.001[d]
Grade 1	2048 (97.7)	800 (93.5)	2848 (96.5)	
Grade 2	48 (2.3)	56 (6.5)	104 (3.5)	
No. of PTC foci				<.001[d]
Unifocal	1434 (68.4)	429 (50.1)	1863 (63.1)	
Multifocal	662 (31.6)	427 (49.9)	1089 (36.9)	
RNM confirmed at pathologic examination				<.001[d]
Node negative (pNX or pN0)	1422 (67.8)	286 (33.4)	1708 (57.9)	
Node positive (pN1a or N1b)	674 (32.2)	570 (66.6)	1244 (42.1)	

[a]APTC, adult papillary thyroid carcinoma; BLR, bilateral lobar resection; MACIS, metastasis, age, completeness of resection, invasion, size; PTC, papillary thyroid carcinoma; RNM, regional nodal metastasis; RRA, radioiodine remnant ablation.
[b]Categorical variables are presented as number (%).
[c]The Kruskal-Wallis test *P* value.
[d]The χ^2 test *P* value.

potentially curative BLR during 1955-2014. Their median age at diagnosis was 45 years (range, 19-73 years). There were 2070 women (70%) and 882 men (female-male ratio, 2.3:1). Mean tumor size was 1.7 cm (range, 0.1-8.0 cm); 1043 (35%) were microcancers (maximum diameter of ≤1 cm). Of the primary tumors, 71 (2%) were locally invasive to extrathyroidal soft tissues, and 1244 (42%) had RNM proven by surgical pathologic examination (pN1). There were 1145 (39%) patients who underwent a total thyroidectomy, whereas 1807 (61%) had either bilateral subtotal thyroidectomy (n=440) or near-total thyroidectomy (n=1367); 2134 (72%) had neck nodes removed at the time of initial BLR. In total, 957 (32%) had postoperative RRA. Ablation was performed within 6 postoperative months in 856 (29%); the median initial administered ^{131}I dose was 30 mCi (range, 26-200 mCi). All but 14 (1.6%) of the ^{131}I ablative doses were administered within 6 postoperative months at Mayo Clinic in Rochester, Minnesota. RRA was considered to have been successful if there was no visible evidence of RAI uptake at 24 hours or if uptake identified in the thyroid bed was quantitated at 1% or less. Such information was available in 68% of all 957 ablated patients, and ablations were found to have been successful in 94%. Median follow-up for the 2952 LRAPTC patients was 13.8 years, and the longest follow-up was 61.2 years. There were 50,903 patient-years of observation. At last follow-up, there had been 13 deaths due to PTC, 39 postoperative distant metastases, 44 local recurrences, and 237 postoperative RNMs.

The Table summarizes the differences in 9 presenting variables that may have influenced the decision to perform RRA within 6 months after potentially curative BLR. Ablation was performed significantly more often ($P<.001$) when patients were younger (median age of 43 years with BLR+RRA vs 46 years with BLR alone) or male (36% with BLR+RRA vs 27% with BLR alone). RRA was also more often performed ($P<.001$) when patients had been initially treated with total thyroidectomy or had undergone neck nodal resection. In addition, it was significantly more frequently performed ($P<.001$) in the presence at initial surgery of gross extrathyroid invasion, larger tumor size, grade 2 histologic features, multicentricity, or pathologically confirmed RNM (pN1). A difference in ablation rates was particularly obvious when RNM was confirmed by the surgical pathologist; 570 of 1244 (46%) of the node-positive (pN1) patients underwent RRA within 6 postoperative months, in contrast to 286 of 1708 (17%) of the node-negative (pN0/NX) patients.

Details of 1955-1974 Patients and Impact of RRA on CSM and TR

During the earliest 2-decade period of 1955-1974, we studied 557 consecutive LRAPTC patients with MACIS scores below 6 who had undergone potentially curative BLR. Median age was 44 years, and mean tumor size was 1.65 cm; 40% were microcancers. Gross extrathyroid extension was present in 3%, and 34% were node positive; 89% underwent near-total or total thyroidectomy (NT/TT), and 49% had neck nodes removed at the time of BLR. Only 17 patients (3%) were ablated within 6 postoperative months, and they were compared with the 540 patients who had undergone only BLR as primary therapy. The median follow-up of the 557 patients was 33.4 years, and the longest follow-up was 61.2 years. At last follow-up, there had been 7 deaths due to PTC, 11 postoperative distant metastases, 9 local recurrences, and 37 postoperative RNMs. At 20 postoperative years, 434 of 540 (80%) were being actively observed (remaining at risk), as were 14 of 17 (82%) of the BLR+RRA patients.

The same 9 clinicopathologic variables (as shown in the Table) that may have influenced the decision to perform RRA were examined for the patients treated during 1955-1974. Ablation was performed significantly more often ($P=.02$) when patients were younger (median age of 32 years with BLR+RRA vs 44 years with BLR alone) but not ($P=.11$) when the patients were male. RRA was more often performed when patients had initially undergone total thyroidectomy ($P<.001$) or had neck nodal resection ($P=.005$). It was not more frequently performed in the presence of gross extrathyroid invasion ($P=.53$) or grade 2 histologic features ($P=.41$). However, it was more often chosen in the presence of larger tumors ($P=.006$), multicentricity ($p=.001$), or pathologically confirmed RNM ($P<.001$). A difference in ablation rates was observed when RNM was confirmed by surgical pathologic examination as 14 of 17 (7.5%) of the pN1 patients underwent RRA in contrast to only 3 of 370 (0.8%) of the pN0/NX patients.

At 20 postoperative years, the BLR alone group had CSM and TR rates of 1.0% and 6.8%, respectively. The comparable rates for the BLR+RRA patients were 0% and

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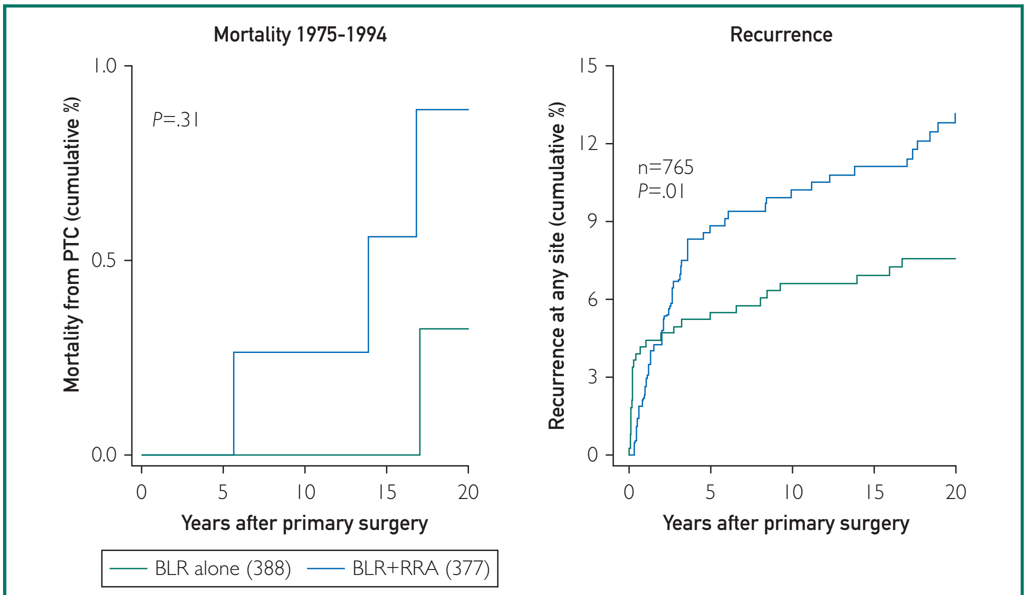

FIGURE 2. Postoperative cumulative occurrence rates through 20 years in 765 adult papillary thyroid carcinoma patients with MACIS scores below 6 managed during 1975 through 1994. The left panel demonstrates the nonsignificant difference in cause-specific mortality rates (*P*=.31) between the 388 having bilateral lobar resection (BLR) alone and the 377 having BLR plus radioiodine remnant ablation (RRA). The right panel shows the significant difference in the rates (*P*=.01) through 20 years for recurrence at any site between the BLR alone and the BLR+RRA groups. PTC, papillary thyroid carcinoma.

5.9%, respectively. The differences by log-rank testing between the groups were nonsignificant for either CSM (*P*=.63) or TR (*P*=.82). Moreover, there were nonsignificant differences seen between the groups with regard to recurrences identified at local (*P*=.59), regional (*P*=.98), or distant (*P*=.54) sites. It is of some interest that during this first time period, when neck ultrasound was not yet available and discovery of "nodal recurrence" depended on physical examination and scintigraphy, the 20-year occurrence rates of postoperative RNM for the BLR and BLR+RRA groups were nearly identical at 5.8% and 5.9%, respectively (*P*=.98).

Details of 1975-1994 patients and Impact of RRA on CSM and TR

During the 2-decade period of 1975-1994, we studied 765 consecutive patients with MACIS scores below 6 who had undergone potentially curative BLR. Median age was 43 years, and mean tumor size was 1.74 cm; 35% were microcancers. Gross extrathyroid invasion was present in 2%, and 41% were node positive; 93% underwent NT/TT, and 64% had neck nodes removed at the time of BLR. There were 377 patients (49%) ablated within 6 postoperative months; 80% of the ablated patients were rescanned, and 96% were judged to have had successful ablation. Values for the initial RAI doses administered were available for 369 (98%) of the BLR+RRA patients. The mean, median, and mode RAI dose values were 36.5 mCi, 29.9 mCi, and 29.9 mCi, respectively. The median follow-up of the 765 patients was 24.4 years, and the longest follow-up was 44.1 years. At last follow-up, there had been 4 deaths due to PTC, 16 postoperative distant metastases, 15 local recurrences, and 63 postoperative RNMs. At 20 postoperative years, 262 of 388 (68%) patients in the BLR alone group were still at risk, as were 269 of 377 (71%) patients of the BLR+RRA (ablated) group.

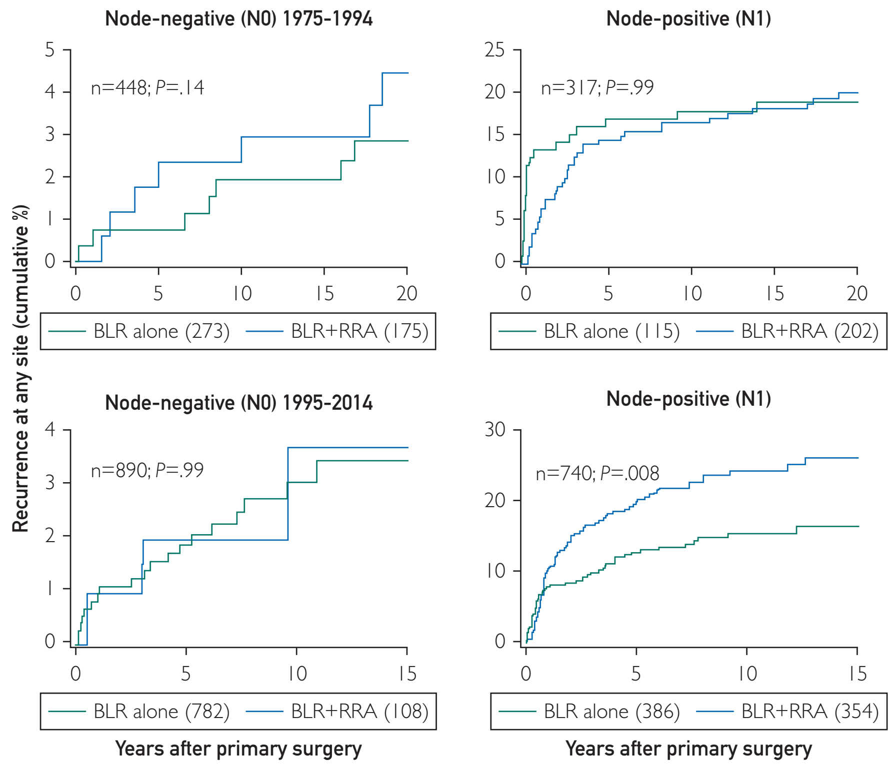

FIGURE 3. Postoperative cumulative rates of recurrence at any site through 20 years in 448 node-negative (pN0; left upper panel) and 317 node-positive (pN1; right upper panel) adult papillary thyroid carcinoma patients with MACIS score below 6 managed during 1975 through 1994 and in 890 node-negative patients (left lower panel) and 740 node-positive patients (right lower panel) managed during 1995 through 2014. The rates in pN1 patients were 4 to 6 times higher than in pN0 patients. Nonsignificant differences between bilateral lobar resection (BLR) alone and BLR plus radioiodine remnant ablation (RRA) were seen both in the 1338 node-negative patients treated during 1975-2014 (both left panels) and in the 317 node-positive patients (upper right panel) treated during 1975-1994. By contrast, in the 740 node-positive patients managed during the most recent 2 decades (1995-2014), the difference between the rate seen after BLR+RRA and that seen after BLR alone was significantly higher (P=.008).

The 9 clinicopathologic variables that may have influenced the decision to perform RRA were examined for the patients treated during 1975-1994. Ablation was performed significantly more often (P<.001) when patients were younger (median age of 40 years with BLR+RRA vs 46 years with BLR alone) but not (P=.26) when the patients were male. RRA was more often performed when patients had initially undergone neck nodal resection (P<.001) but not after total thyroidectomy (P=.69). It was not more frequently chosen in the presence of histologic grade 2 (P=.26) but was more frequently performed in the presence of gross extrathyroid invasion (P<.001), larger tumors (P<.001), multicentricity (P<.001), or pathologically confirmed RNM (P<.001). As in the 1955-1975 period, during 1975-1994, a difference in ablation rates was obvious when RNM was confirmed at surgical pathologic examination as 202 of 317 (64%) of the pN1 patients were ablated in contrast to 174 of 448 (39%) of the pN0/NX patients.

Figure 2 illustrates the cumulative occurrence rates through 20 postoperative years to end points of CSM (left panel) and TR at any site (right panel) and compares outcomes in the 388 patients having BLR alone with

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those seen in the 377 patients who had BLR+RRA. At 20 postoperative years, the BLR alone group had CSM and TR rates of 0.3% and 7.5%, respectively. The comparable rates for the BLR+RRA patients were higher at 0.9% and 12.8%, respectively. The statistical difference between the groups was nonsignificant for CSM (P=.31) but significant (P=.01) for TR at any site (local, regional, or distant).

As with the earlier 1955-1974 cohort's experience, there were no significant differences seen between the groups with regard to either local recurrences (P=.18) or postoperative distant metastases (P=.60), both events considered to be "more serious problems . . . which connote a bad prognosis"[27] and, in our experience,[10,11] associated with an increased risk of CSM.[22] For the BLR alone group treated during 1975-1994, the 20-year occurrence rate for postoperative RNM of 5.7% was similar to the 5.8% rate seen during 1955-1974. However, by contrast, the comparable rate for the BLR+RRA patients was more than twice as high at 11.7%, a highly significant difference (P=.006). When we looked at the clinical-pathologic variables that may have influenced the decision to perform RRA, we found that 39% of the node-negative patients were ablated, whereas 64% of the node-positive patients underwent BLR+RRA. We therefore decided to look at the postoperative outcomes separately for the 448 node-negative (pN0/NX) and the 317 node-positive (pN1) patients.

Figure 3 (upper panels) illustrates the cumulative occurrence rates of TR at any site through 20 postoperative years in 448 node-negative (pN0/NX; left upper panel) and 317 node-positive (pN1; right upper panel) patients with MACIS score below 6 managed with initial BLR during 1975-1994. The 20-year TR rates in the pN1 patients were more than 6 times higher than in pN0 patients (19% vs 3%). These rates were also slightly higher in the ablated patients in both pN0 (4.4% vs 2.8%) and pN1 (20.1% vs 18.9%) patients. However, the differences observed in TR at any site between the BLR and BLR+RRA groups were statistically nonsignificant in both node-negative (P=.14) and node-positive (P=.99) patients.

Details of 1995-2014 Patients and Impact of RRA on CSM and TR

During the most recent 2-decade period of 1995-2014, we studied 1630 consecutive patients with MACIS scores below 6 who had undergone potentially curative BLR. Median age was 45 years, and mean tumor size was 1.64 cm; 34% were microcancers. Gross extrathyroid invasion was present in 2%, and 45% were node positive; 80% underwent NT/TT, and 84% had neck nodes removed at time of BLR. There were 462 (28%) patients ablated within 6 postoperative months; 57% of the ablated patients were rescanned, and 94% were judged to have had successful ablation. Values for the initial RAI dose administered were available for 458 (99%) of the BLR+RRA patients. The mean, median, and mode RAI dose values were 63.4 mCi, 50.2 mCi, and 29.9 mCi, respectively. The median follow-up of the 1630 patients was 8.4 years, and the longest follow-up was 24.6 years. At last follow-up, there had been 2 deaths due to PTC, 11 postoperative distant metastases, 21 local recurrences, and 142 postoperative RNMs. At 15 postoperative years, 253 of 1630 (16%) patients remained at risk, but at 20 postoperative years, only 79 of 1630 (5%) were still being actively observed as of October 2020.

When we examined the clinicopathologic variables that may have influenced the decision to perform RRA for the most recent time period, we found that in contrast to 1955-1974 and 1975-1994, RRA was more frequently performed with male patients (P<.001) or with histologic grade 2 tumors (P<.001). Moreover, RRA was more often chosen (P<.001) with younger patients (median age of 44 years for BLR+RRA vs 46 years for BLR alone); when patients had undergone initial total thyroidectomy or neck nodal resection; or in the presence of gross extrathyroid invasion, larger tumors, multicentricity, or pathologically confirmed RNM. As in the 2 earlier time periods, a difference in ablation rates was obvious when RNM was confirmed

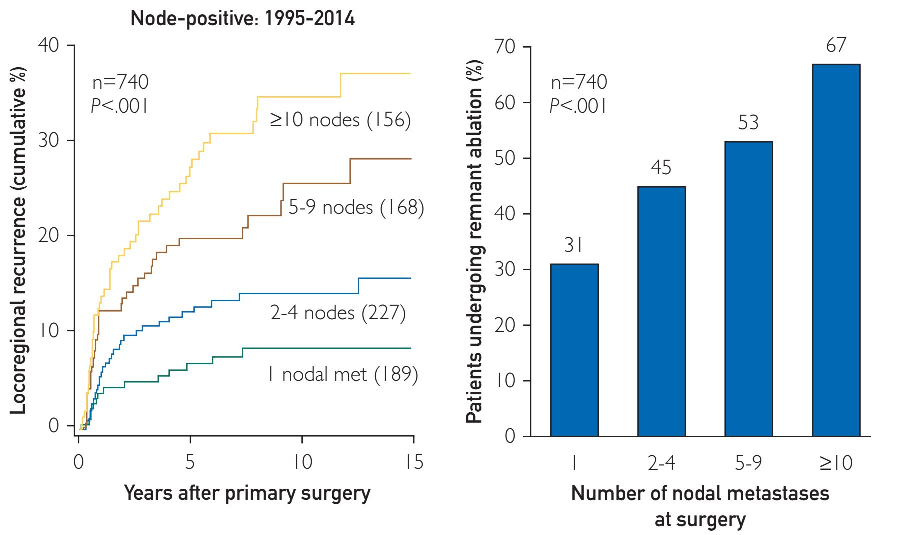

FIGURE 4. The left panel shows the cumulative rates of locoregional recurrence through 15 postoperative years for the 740 node-positive (pN1) adult papillary thyroid carcinoma patients with MACIS score below 6 managed during 1995-2014. The right panel illustrates the percentage of these 740 node-positive patients who underwent radioiodine remnant ablation (RRA) within 6 postoperative months. The data shown in the left panel demonstrate the highly significant correlation (*P*<.001) between the numbers of regional nodal metastases (RNMs) identified at surgical pathologic examination and the rates of locoregional recurrence, ranging from a 15-year rate for a single RNM of 8.5% through a comparable rate of 37.2% with 10 or more RNMs. The data shown in the right panel demonstrate the highly significant association (*P*<.001) between the numbers of RNMs found at surgery and the individual clinician's decision to give the patient RRA within 6 postoperative months, ranging from 31% given RRA with a solitary RNM to 67% receiving RRA when there were 10 or more RNMs at surgery.

by surgical pathologic examination as 354 of 740 (48%) pN1 patients underwent RRA in contrast to 108 of 890 (12%) pN0/NX patients.

At 20 postoperative years, the BLR alone group (n=1168) had CSM and TR (any site) rates of 0% and 9.2%, respectively. The comparable rates after BLR+RRA (n=462) were 1.4% and 21.0%, respectively. There was a nonsignificant difference in the CSM rates (*P*=.19) between the groups. However, the difference in TR (any site) was highly significant (*P*<.001), the ablated group having the much higher rate (21.0% vs 9.2%). RNM accounted for 92% of the total number of recurrent events (at any site). Moreover, as we had found in the 2 earlier time periods, the ablation rate for the node-negative patients was 12%, but for the node-positive patients, the rate was 4 times higher at 48%.

Figure 3 illustrates the postoperative cumulative occurrence rates of TR (any site) through 15 postoperative years in 890 node-negative (left lower panel) and 740 node-positive (right lower panel) APTC patients with MACIS scores below 6 managed during 1995 through 2014. The 15-year TR rate after BLR alone in 782 pN0 patients was 3.4%; it was nonsignificantly different (*P*=.99) in the 108 ablated patients at 3.7%. By contrast, the comparable rates for TR (any site) in the 740 pN1 patients were almost 7 times higher than in the 890 pN0 patients. Moreover, the difference in 15-year rates for TR (any site) between 26.5% in the 354 ablated patients and 16.7% in the 386 BLR alone patients was significantly higher (*P*=.008). This significant difference in TR (any site) within the node-positive (pN1) cases was certainly not explained by an increased number of distant metastases in the ablated patients because no significant difference (*P*=.26) existed within

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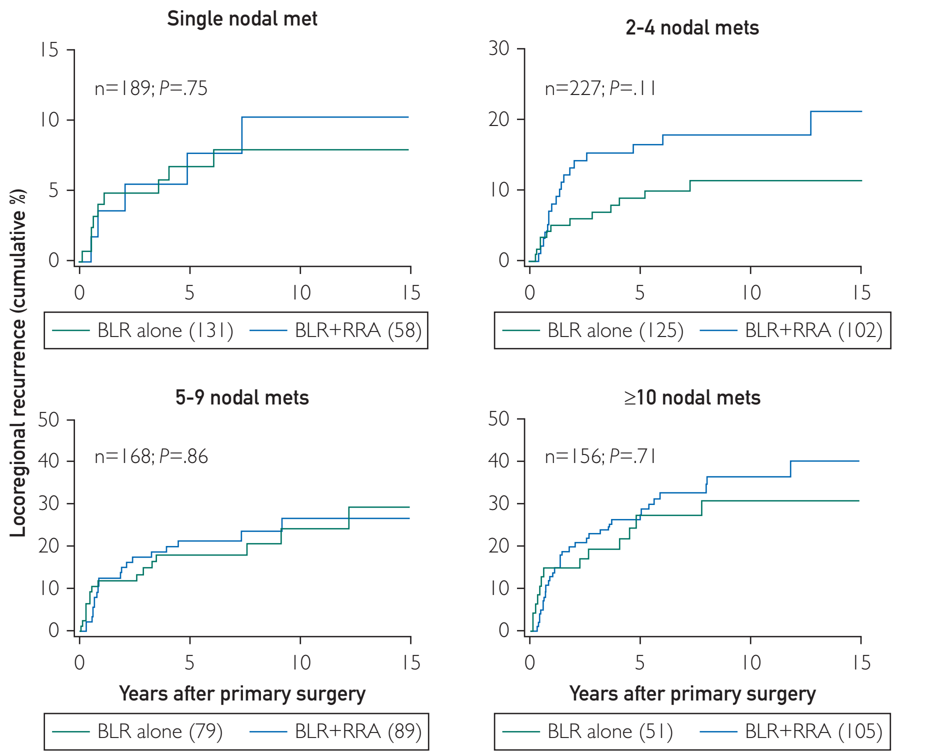

FIGURE 5. Cumulative locoregional recurrence (LRR) rates through 15 postoperative years comparing bilateral lobar resection (BLR) vs BLR plus radioiodine remnant ablation (RRA) in 189 patients (upper left panel) with a single RNM, 227 patients (upper right) with 2 to 4 RNMs, 168 patients (lower left) with 5 to 9 RNMs, and 156 patients (lower right) with 10 or more RNMs. In 3 of the 4 groups, the LRR rates were actually higher in the ablated patients; but in all 4 groups, the differences observed in LRR rates during 15 postoperative years between the BLR alone patients and the BLR+RRA patients were nonsignificant (P>.10).

the pN1 group between the 386 BLR alone and the 354 BLR+RRA patients with regard to the occurrence of postoperative distant metastases. By contrast, the 15-year locoregional recurrence (LRR) rate was significantly higher (P=.007) in the 354 ablated pN1 patients at 26% compared with the 16% rate seen in the 386 nonablated pN1 patients.

Increasing Burden of RNM and Impact of RRA on LRR

Within the 740 pN1 patients adequately treated by BLR, there were at initial surgical exploration 189 (25%) with a single pathologically confirmed RNM, 227 (31%) with 2 to 4 RNMs, 168 (23%) with 5 to 9 RNMs, and 156 (21%) with 10+ RNMs. Figure 4 (left panel) demonstrates that within the 740 node-positive patients, a highly significant correlation (P<.001) exists between the numbers of RNM at presentation and the rates of LRR through 15 postoperative years. The 15-year LRR rates found in association with 1, 2 to 4, 5 to 9, or 10+ RNMs were 8.5%, 16.0%, 28.4%, and 37.2%. Figure 4 (right panel) demonstrates a significant association (P<.001) between the numbers of RNM found at surgery and the individual clinician's decision to give RRA. The rates of RRA with 1, 2 to 4, 5 to 9, and 10+ RNMs at surgery were 31%, 45%, 53%, and 67%, respectively.

Figure 5 illustrates the 15-year cumulative LRR rates seen in patients with a single RNM at surgery (left upper panel), 2 to 4 RNMs (right upper panel), 5 to 9 RNMs (left lower panel), and 10+ RNMs (right lower panel). The rates during 15 postoperative years were compared between patients undergoing BLR only and those having BLR+RRA. With a single RNM, the 15-year LRR rate was 7.8% after BLR only and 10.1% after BLR+RRA (P=.75). With 2 to 4 RNMs (median, 3), the comparable rates were 11.4% and 21.1% (P=.11). With 5 to 9 RNMs (median, 6), the rates were much higher at 29.3% and 26.7% (P=.86). Finally, with 10+ RNMs (median, 15), the rates were 30.9% and 40.4% (P=.71). When one compares, within this node-positive LRAPTC population (as shown in Figure 5), the 740 patients stratified by their metastatic nodal burden (ranging from single to 10 or more RNMs), RRA did not in any of the 4 groups significantly reduce through 15 postoperative years the rates of LRR observed after BLR with curative intent (all P values >.10).

DISCUSSION

RRA has been defined as "the destruction of residual macroscopically normal thyroid tissue following surgical thyroidectomy."[28] James Sisson, a nuclear medical specialist from the University of Michigan, for at least 3 decades[29,30] held differing views from his departmental colleague, William Beierwaltes,[1,4,6] about its efficacy. In 1983, Sisson[29] argued that "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." Sisson[29] described the practice of using ^{131}I to ablate normal thyroid tissue in patients from whom thyroid cancer has been adequately resected as "applying the radioactive eraser," and he also reported that "in this milieu, scintigrams have come to be worshipped as portents and as arbiters of proper treatment." He concluded his teaching editorial by stating that "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."[29] Some 25 years later, Sisson[30] continued to take issue with the principal findings in 2008 of the Canadian-American Thyroid Cancer survey and a highly prevalent stance within North American specialty physicians[31] wherein "postoperative radioiodine remnant ablation should be applied ubiquitously as adjuvant therapy in well-differentiated thyroid carcinoma patients."[30]

In 1986, a study of 859 Mayo Clinic PTC patients consecutively treated during 1946-1970 found, after a median follow-up of 18 years, an overall mortality rate at 30 years of only 3% above that expected.[22] These 859 patients were conservatively treated as 16% underwent total thyroidectomy and only 3% had postoperative RRA. The authors concluded that "whether routine remnant ablation can substantially improve the already excellent results of surgical treatment remains, in our assessment, to be proved."[22] In 1990, one of these authors, after further reviewing the early experience at Mayo Clinic in Rochester, Minnesota, of RRA in PTC, concluded that "it is our expectation that further assessment of outcome in appropriately matched patients will permit a more rational use of remnant ablation, and we hope that such data will provide a satisfactory answer to Sisson's haunting question."[24]

In 1993, a novel prognostic scoring system[15] for predicting outcome in PTC was derived from Cox model analysis and stepwise variable selection in a study group of 1779 consecutive PTC patients surgically treated at Mayo Clinic during 1940-1989. The final model included 5 variables: metastasis, age, completeness of resection, invasion, and size (MACIS). A MACIS low-risk score of less than 6 accounted for 84% of the 50-year cohort and was associated with a 20-year CSM of less than 1%. Within 18 to 24 months of the publication of the MACIS prognostic system, the Mayo Thyroid Group committed to using the postoperative MACIS score, typically available before post-thyroidectomy discharge, to help identify the minority of PTC patients likely to benefit from RRA.[10,25] The intent of this "selective" policy[12-14] was to move toward omitting RRA from the management of low-risk PTC patients (score <6) while giving serious consideration to ^{131}I therapy in those with MACIS scores of 6 or more, who had a higher risk of PTC-related mortality. Thus, as long promoted by Blake Cady,[32] "the punishment would fit the crime," and as he so elegantly stated in 1997, "risk-group assignment would point the arrow to rational therapy selection in differentiated thyroid cancer patients."[33]

Snyder and his Mayo Clinic colleagues, as early as 1983, had emphasized that "numerous studies support the use of radioiodine in the treatment of metastatic disease; but extrapolation to the practice of remnant ablation does not follow."[9] After demonstrating, in PTC patients, that RRA directed to postsurgical remnants "reduced visible uptake to zero or nearly zero, but did not protect against tumor recurrence," they described the practice of RRA as "the questionable pursuit of an ill-defined goal."[9] Some 21 years later, when commenting on the first systematic review and meta-analysis[34] of the effectiveness of RRA, Mazzaferri[35] stated, "The benefit of remnant ablation remains unclear in low risk patients treated with bilateral thyroidectomy and thyroid hormone suppression of [thyroid-stimulating hormone]." He went on to advise within his editorial commentary that "it would be nice to think that a randomized trial might be done to settle once and for all the differences of opinion concerning the therapeutic efficacy of ^{131}I remnant ablation."[35] However, in their 2019 provocative editorial entitled "Guidelines are not gospels," Daniels and Kopp,[6] as they looked toward the future, stated, "We all eagerly await the results of ongoing appropriately powered randomized controlled trials of RAI for DTC. However, even these trials may not provide the final answers." Accordingly, there may still be a role for seeking answers to questions on RRA from painstaking analysis of outcome derived from institutional databases with large numbers of DTC patients observed for long postoperative periods.[11,26,36,37]

In the absence of "appropriately powered randomized controlled trials"[6] of RRA in low-risk PTC patients, the initial 2004 meta-analysis of Sawka et al[34] in turn prompted the publication since 2008 of 3 more systematic reviews and meta-analyses of peer-reviewed literature on this topic published from Canada,[38] the United States,[39] and Italy.[40] The updated systematic review of Sawka et al[38] published in 2008 included data from 20 studies from the original review[34] as well as 7 newer studies published during 2002-2007. Their conclusion was that "upon carefully examining the best existing long-term observational evidence, the authors could not confirm a significant, consistent benefit of RRA in decreasing cause-specific mortality or recurrence in early stage [well-differentiated thyroid cancer]."[38] In a 2010 systematic analysis of the 1966-2008 peer-reviewed literature, Sacks et al[39] from Cedars-Sinai in Los Angeles reported that "the preponderance of evidence suggests that RAI treatment is not associated with improved survival in patients with low-stage or low-risk DTC. The data concerning recurrence rates following RAI treatment in this group of patients are less conclusive." On the basis of their analysis, they recommended the adoption of a risk group categorization, based on the American Joint Committee on Cancer TNM staging and the MACIS score, and proposed a management guideline based on a patient's risk: very low, low, moderate, and high. Their final conclusion was that "a majority of very low-risk and low-risk patients, as well as select cases of patients with moderate risk, do not demonstrate survival or disease-free survival benefit from postoperative treatment, and therefore we recommend against postoperative RAI in these cases."[39]

More recently, Lamartina et al[40] conducted a systematic review concentrating on literature published on RAI and DTC since 2008 and concluded that "our review of the more recent literature (2008-2014) clearly shows no advantage of RRA in low-risk patients, but it was unable to provide conclusive data for or against RRA in preventing disease recurrence in intermediate-risk patients." They recommended from their analysis that "a careful evaluation of tumor pathological features and patient characteristics and preferences should guide RRA decision making."[40] Lamartina et al also[40] expressed hope that the two presently ongoing (and as yet unpublished) European prospective randomized trials (the French ESTIMABL2 study and the British IoN study) would "provide valuable data to inform this issue." In the ESTIMABL2 study, the primary end points are adverse events after 3 and 5 years, whereas the end point of the IoN study is progression-free survival after 5 years; in both trials, the study patients will randomly receive either 1.1 GBq (30 mCi) of ^{131}I or no RAI therapy. Foreseeable problems have already been identified with these trials, including the possibility that "the duration of follow-up may be too short to detect significant differences" because the meta-analyses of Sawka "found an improved recurrence-free and overall survival only in studies with follow-up of 10 years or more."[41] These critics were also uncertain "whether the aim of reducing morbidity and mortality can be realized" when only low activities of radioiodine, which they defined as 2 GBq (54 mCi) or less, were employed in the trials.[41]

Now, what can this study from the Mayo Clinic do to help clarify the situation for endocrinologists and oncologists who, while eagerly awaiting the latest ATA guidelines on managing DTC patients, are dealing in 2021 with the pros and cons of postoperative RRA, specifically as indicated for patients with the most common endocrine malignant neoplasm, PTC?

Our MACIS prognostic scoring system was introduced into our clinical practice 4 years before the publication of the first American Association of Clinical Endocrinology guidelines[42] and 13 years before the first ATA management guideline[43] and is still, 28 years later, used daily in our practice at Mayo Clinic. In addition, it has subsequently been adopted and used to aid in management decisions in medical centers in North America,[39] the United Kingdom,[44] Europe,[45,46] and Asia.[47] Like the prognostic scheme developed by the National Thyroid Cancer Treatment Cooperative Study Group,[26] the MACIS scheme, although designed to predict CSM, can also reliably predict TR in the setting of PTC patients with complete (potentially curative) surgical resection and no distant spread. We have always, in studying the impact of RRA on PTC outcome, tried to match "like with like,"[10,13,14,48] and in this regard, the MACIS scheme has provided us with a reliable way to categorize risk groups of patients (low risk with scores <6 and high risk with scores of 6+). However, because the MACIS scheme was designed to predict CSM, the presence or absence at initial presentation of RNM, which was not found to be an independent variable for CSM by our multivariate analyses,[15] is not taken into consideration within the MACIS prognostic score.

Like most previously reported studies[36,37] regarding the impact of RRA on outcome in APTC, this study is not randomized,[34,38-40] and it is from 1 institution and retrospective. However, our 2952 LRAPTC patients with a MACIS score of less than 6 were, during the years of our 6-decade study, managed by the same team of endocrinologists, surgeons, and nuclear medical specialists, and the patients who had BLR alone were compared with those having BLR+RRA within the same time frame. The decisions made about extent of surgery, intensity of thyroid hormone suppressive therapy, and indications for RRA were made in each time period by the same multidisciplinary team, who also observed at Mayo Clinic both groups of patients (BLR and BLR+RRA) in the same contemporaneous fashion and with the technology then available. We restricted our study to adult patients, and those who were included in the ablation group had to have their ^{131}I administered within 6 months of the primary surgical date. Thanks to the MRPD, we were able to study not only the end point of CSM but also TR at regional, local, and distant sites in patients who had undergone potentially curative surgery with no gross residual disease and with no evidence at presentation of distant metastases.

As in all retrospective studies, selection bias resulting from the physician's and patient's preference cannot be excluded. A

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survey of North American specialist physicians[31] found that strong physician recommendations for RAI were associated with the physician's beliefs that RRA decreases mortality and recurrence and facilitates follow-up. In this survey, physicians without strong convictions about RAI were more likely to incorporate the patient's preference.[49] However, as stated by Sawka et al,[38] "in an age of freely available information, patients themselves may have strong opinions about accepting or declining RRA and it is important for physicians to be sensitive to such concerns." In our study, as demonstrated by our comparisons of patient and tumor clinicopathologic features (Table) present at the time of initial thyroidectomy, Mayo Clinic physicians within all 3 time periods studied were significantly ($P<.001$) more likely to prescribe RRA when patients were younger, when tumors were grossly invasive and larger or multicentric, and particularly when RNM was pathologically confirmed. Perhaps, as recently observed, we (as physicians) "are all influenced by our mentors and tend to have faith in their teachings. We often prefer (or have faith in) research studies that support our point of view and practice habits, particularly when we have contributed to that research."[6]

In 2004, Mazzaferri[35] expressed the hope that "it would be nice to think that a randomized trial might be done to settle once and for all the differences of opinion concerning the therapeutic efficiency of ^{131}I remnant ablation." In 2008, it was suggested that a 5-year randomized controlled trial of RRA in LRAPTC would be feasible using TR or LRR as a primary treatment outcome, and assuming an event rate of 5% at 5 years and a hazard ratio of 0.60 after RRA, "a total of 528 patients would be needed for study."[38] In 2021, the European prospective randomized trials discussed by Lamartina et al[40] have not yet been completed, nor have preliminary results been reported. In the absence of such trials, management guidelines[21] have therefore been based on retrospective cohort studies from single institutions[36,37] or large cancer registries.[26]

In a review of controversies in the management of low-risk DTC, Haymart et al[49] defined a number of limitations that may afflict retrospective cohort studies of RRA in patients with LRAPTC. They considered that in many such studies, it was unclear whether RAI was being used for remnant ablation or "treatment of residual disease."[49] By excluding all patients with incomplete tumor resection and gross residual disease, we believe that this pitfall has been avoided in our study. They noted that many studies focus on overall survival, which they considered not to be "the optimal end point for a cancer with an excellent prognosis."[49] In this and all our previous studies[10,13,25] on this topic, we have preferred to study CSM. They noted that "recurrence is not captured by large cancer registries, and even when data on [disease-specific survival] and recurrence are available, the event rate is low, thus limiting the quality of many single-institution studies."[49] As we have discussed earlier in this manuscript, the MRPD permitted the identification of recurrent events at local, regional, and distant sites, and in the setting of pN1 patients with a tumor burden of 10 or more RNMs, our LRR rates at 15 postoperative years approached 40%. Last, they suggested that "single-institution studies are susceptible to ascertainment bias, as the patient cohort, treatment pattern, and follow-up may differ from the population at large."[49] We have since 2005 published 2 population-based studies[49,50] of long-term trends in thyroid carcinoma in Olmsted County, Minnesota, from 1935 to 2012 and can verify that the treatment pattern[51] and follow-up of LRAPTC in our present 6 decades of study were identical in our referral population and the local community.[52] Furthermore, the fact that 98% of our ablated patients returned to Rochester within 6 postoperative months to receive their ^{131}I dose and that some LRAPTC patients continue to be observed at Mayo Clinic up to 60 years after potentially curative surgery confirms that most LRAPTC patients managed at

Mayo Clinic come from the North Central (Upper Midwest) region of the United States and resemble the "population at large."

In an earlier study[10] of PTC patients with a MACIS score below 6 managed at Mayo Clinic during 1970-2000, we had noted that node-positive patients were twice as likely as node-negative patients to be given RRA. We had also demonstrated that TR (any site) after NT/TT+RRA significantly exceeded the rate seen after NT/TT alone. However, when the changes were analyzed separately for the 527 pN1 patients, the 20-year TR rates after NT/TT alone or NT/TT+RRA were nonsignificantly different at 19.5% and 19.9%, respectively (P=.66). More recently,[48] we extended this study to include patients with a MACIS score below 6 treated during 2001-2014 and found in the 915 node-positive patients that the 20-year TR (any site) rate in the ablated patients was nonsignificantly higher than that seen after surgery alone (26% vs 19%; P=.08). In addition, we demonstrated that this difference was not due to either local recurrence (P=.34) or distant metastasis (P=.49) but was likely related to the higher rate (P=.05) for postoperative RNM seen in the 496 ablated pN1 cases, which "was felt to be attributable to the significantly higher number of RNM found in those patients selected for RRA."[48]

In this study, in which only LRAPTC patients were considered, we further investigated the significant difference (P=.008) between BLR+RRA and BLR alone (Figure 3; right lower panel) seen during 1995-2014 in TR rates found in the 740 node-positive cases. We demonstrated (Figure 4) that increasing numbers of RNM at presentation led to a progressive rise in LRR rates as well as concomitantly increasing rates for clinicians prescribing RRA. However, when the impact of RRA on LLR rates was further studied and the extent of metastatic nodal burden stratified into 4 groups according to numbers of RNM (Figure 5), the differences seen between BLR alone and BLR+RRA became statistically nonsignificant (all 4 P values >.10).

In 1996, after an extensive review of relevant papers in the surgical oncologic literature, we concluded, "The primary treatment of nodal metastases in PTC is removal of macroscopically affected nodes at initial surgery, optionally supplemented with adjuvant radioiodine therapy in an attempt to reduce recurrence risk. The value, however, of postoperative radioiodine in preventing either nodal recurrence or cancer death in patients with PTC remains controversial."[53] The results of this study appear to be strong evidence against a beneficial effect in LRAPTC of RRA in preventing or even reducing "nodal recurrence."[53] In 2019, Daniels and Kopp[6] interpreted recommendations of the current (2015) ATA guidelines[21] as "generally not giving" RAI to low-risk of recurrence patients (including "low-volume nodal metastatic disease") but "considering RAI" for patients in the intermediate-risk group (including patients with "intermediate-size nodal metastases"). This contrasted with the attitudes of the European Thyroid Cancer Taskforce, whose high-risk group, for whom RAI would be definitely indicated, included those at high risk of recurrent disease, including "any lymph node metastases."[54] Indeed, European nuclear medical specialists,[55] in preparation for a "quadrilateral meeting of scientific societies involved in radioiodine treatment of DTC," stated as recently as 2020 that "literature published in the last decade offers data that support adjuvant postoperative radioiodine treatment in DTC patients with a tumor diameter exceeding 1 cm. Therefore, at least until randomized prospective studies prove otherwise, the prescription of adjuvant ^{131}I treatment to all DTC patients with a primary tumor diameter exceeding 1 cm remains a reasonable option."

We are convinced that in the 60 years of our study (1955-2014), our endocrinologist colleagues at Mayo Clinic in Rochester

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regularly made a decision that in LRAPTC patients (with an almost negligible risk of CSM), RRA was likely to be indicated in the presence of pathologically confirmed RNM, and as illustrated by Figure 4 (right panel), the more RNMs identified, the more frequently was RRA prescribed. If more studies in the future (including prospective controlled trials) also conclude that RRA does not diminish LRR and future practice guidelines should be modified to further influence practice, how should these patients with postoperative discovery of RNM be managed? In answering this question, Burman[56] suggested that the "deceptively simple options" would include observation, surgery, RAI therapy, and ethanol ablation. In this regard, we are proud that 2021 represents the 30th anniversary[57] since we were first in the world to eliminate postoperative nodes in PTC[58,59] with ethanol ablation. As Burman[56] in 2012 has said, "Percutaneous ethanol injection has been shown to be effective and should be used more frequently as it is a simple, effective, outpatient procedure." As our colleagues in Florida have more recently stated, "In properly selected patients with nodal metastases from DTC, compared with other locoregional therapy options, ethanol ablation has the greatest potential for applicability anywhere in the world."[60]

CONCLUSION

In this study, we demonstrated that during 60 consecutive years at Mayo Clinic, postoperative RRA given to LRAPTC patients who were treated with potentially curative BLR for disease confined to the neck did not significantly reduce either the CSM or TR rate, even in those LRAPTC patients with the highest metastatic nodal burden. We therefore strongly advise against the use of RRA in LRAPTC patients with MACIS scores below 6 undergoing BLR with curative intent. If such a policy were to be followed, at least 85% of PTC patients being presently diagnosed in the United States would not need to be exposed to RAI.

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Abbreviations and Acronyms: **APTC** = adult papillary thyroid carcinoma; **ATA** = American Thyroid Association; **BLR** = bilateral lobar resection; **CSM** = cause-specific mortality; **DTC** = differentiated thyroid cancer; **LRAPTC** = low-risk adult papillary thyroid carcinoma; **LRR** = locoregional recurrence; **MACIS** = metastasis, age, completeness of resection, invasion, size; **MRPD** = Mayo Rochester PTC Database; **NT/TT** = near-total or total thyroidectomy; **pN0** = no pathologic evidence of regional lymph node metastasis; **pN1** = pathologic evidence of metastasis to regional nodes; **PTC** = papillary thyroid carcinoma; **RAI** = radioactive iodine; **RNM** = regional nodal metastasis; **RRA** = radioiodine remnant ablation; **TR** = tumor recurrence

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