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Radioiodine remnant ablation in stage I adult papillary thyroid carcinoma: does it improve postoperative outcome?

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Abstract

Objective: To determine whether radioiodine remnant ablation (RRA) reduces cause-specific mortality (CSM) or tumor recurrence rates (TRR) after potentially curative bilateral thyroidectomy (BT) in low-risk adult papillary thyroid carcinoma (APTC) patients, we compared postoperative outcomes in 1836 pTNM stage I APTC patients having BT alone with 832 having BT+RRA during two consecutive 25-year periods.

Methods: The THEN cohort (consecutively managed during 1966–1990) comprised 809 patients (36% having BT+RRA) and the NOW cohort (1991–2015) comprised 1859 patients (29% BT+RRA). Analyses of differences in occurrence rates between BT alone and BT+RRA patients were performed with SAS software.

Results: During 1966–1990, when RRA rates rose ten-fold, 20-year CSM after BT alone was 0.6% and after BT+RRA was 1.2% ($P = 0.66$); during 1991–2015, when RRA rates progressively fell, no PTC deaths occurred in 1859 patients. In the THEN cohort, RRA did not significantly improve TRR at local, regional, or distant sites ($P > 0.1$), when compared to BT alone. RRA in NOW cohort was administered to 49% of node-positive (pN1) patients and 17% of node-negative (pN0/NX) patients ($P < 0.0001$); TRR therefore, were examined separately for pN0/NX and pN1 patients. In 1157 pN0/NX cases, 20-year locoregional TRR were 3.1% after BT and were higher ($P = 0.049$) at 8.6% after BT+RRA. In four pN1 groups, stratified by metastatic nodal burden, RRA did not significantly reduce the locoregional TRR observed after BT with curative intent ($P > 0.5$).

Conclusions: In a 5-decade experience, RRA administered postoperatively to stage I APTC patients did not reduce either CSM or TRR and should probably not be indicated when such patients undergo potentially curative BT.

Key Words

- ▶ remnant
- ▶ ablation
- ▶ low-risk PTC
- ▶ TNM stage I
- ▶ radioiodine
- ▶ tumor recurrence

Introduction

Adults with low-risk (1) papillary thyroid carcinoma (PTC) represent the commonest endocrine malignancy (2). In 2017, Pontius and colleagues (3) demonstrated, in a study of 244,040 PTC patients managed in USA during 2004–2012, that 89.8% of a Surveillance, Epidemiology, and End Results cohort and 89.3% of a National Cancer Database cohort had 8th edition TNM stage I disease (4, 5). Moreover, a 2021 multinational European study (6), designed to determine the optimal age cutoff for the TNM staging system, found that, with a 55-year age cutoff equivalent to the 8th edition TNM system, stage I disease was found in 84% of the 2355 PTC patients in their databases from Germany and the Netherlands.

Our multidisciplinary group are convinced that at our institution, radioiodine remnant ablation (RRA), when administered after potentially curative bilateral thyroidectomy (BT) to low-risk (MACIS scores <6) adult PTC (APTC) patients, has not reduced (7) either cause-specific mortality (CSM) or tumor recurrence rates (TRR). This present study represented our first attempt to apply the 8th edition TNM system to outcomes observed in patients within the Mayo Rochester PTC Database (MRPD). Since four of the presenting variables contained in the MACIS prognostic scoring system are also considered in the TNM system, we expected that our conclusions, with regards to the efficacy of RRA after potentially curative BT (pcBT), may well be similar. However, in order to increase the relevance of our findings to those many international centres now regularly using the latest pTNM system, we questioned whether our observation of an apparent inability of RRA to improve postoperative outcome in low-risk APTC (LRAPTC), as defined by MACIS scores <6, might also apply to those APTC patients treated at Mayo Clinic during 1966–2015 and now classifiable as having 8th edition pTNM stage I disease.

In this present study, we have looked at our 50-year experience of 2668 TNM stage I (4, 5) APTC patients treated at the Mayo Clinic with BT and have studied postoperative outcomes in 1836 patients treated with BT alone, compared to those 832 who had BT+RRA within 6 postoperative months. To further examine the previously documented ‘era of the rise and fall of remnant ablation’ (7, 8) observed at our institution and to more fairly compare the BT-alone group with those undergoing BT+RRA, we chose to separately study both CSM and TRR in two consecutive 25-year time periods when RRA selection rates, as well as radiological and biochemical methods available for tumor detection, were markedly different (7, 8, 9).

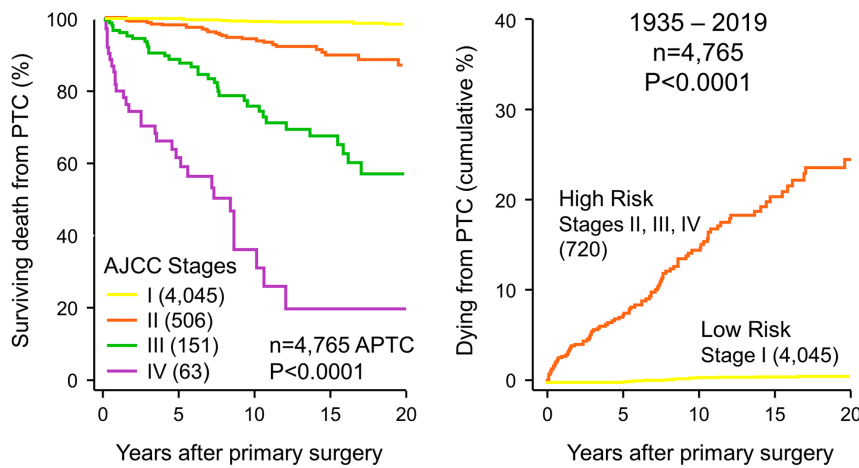
Subjects and methods

Application of 8th edition TNM staging to APTC patients within the MRPD

We used the previously described (7, 8) statistical resource of the MRPD to identify all adult (aged >18 years at diagnosis) PTC patients with TNM stage I disease, who were consecutively managed with BT between January 1, 1966, and December 31, 2015, at the Mayo Clinic in Rochester, Minnesota. The MRPD, as of May 2021, contained details of 4946 PTC patients (all ages) who have undergone primary surgical treatment at Mayo Rochester during 1935–2019 and were observed for a median of 16 years, encompassing a total experience of 77,549 patient-years of observation. The protocol for this present study was approved by the Mayo Clinic Institutional Review Board, and each patient provided consent for inclusion in the MRPD. Written consent was obtained from each patient or subject after full explanation of the purpose and nature of all procedures used. Follow-up information was obtained by Mayo Clinic reexamination, by review of outside medical records or through correspondence with home physicians and patients. To demonstrate the utility of the 8th edition TNM staging (4, 5) in our complete data set of APTC patients, Fig. 1 (left panel) illustrates the cause-specific survival rates through 20 postoperative years by TNM staging in the 4765 APTC patients (85% stage I) managed at Mayo during 1935–2019. At 10, 15, and 20 years, the numbers of stage I APTC patients being actively followed (remaining at risk) were, respectively, 2279 (56%), 1745 (43%), and 1333 (33%). Only 28 (0.7%) of 4217 stage I patients died due to PTC, and CSM at 20 postoperative years was 0.8%. Figure 1 (right panel) shows the comparison of CSM through 20 postoperative years in 4045 low-risk stage I APTC patients, when compared with 730 patients with high-risk stages (II, III, and IV); 20-year CSM (high risk to low risk) ratio (10, 11) was calculated as 31.4.

Selection of study patients from 1966 to 2015 and contemporary Mayo follow-up protocol

Figure 2 illustrates the ‘era of the rise and fall of remnant ablation’ (7, 8), as shown by changes in the percentage of 2668 stage I APTC patients consecutively treated during 1966–2015 and being initially managed by BT+RRA, the ablation being administered within 6 postoperative months. The first 25-year time period was represented by the THEN cohort of 809 stage I APTC patients managed with BT, encompassing both near-total or total

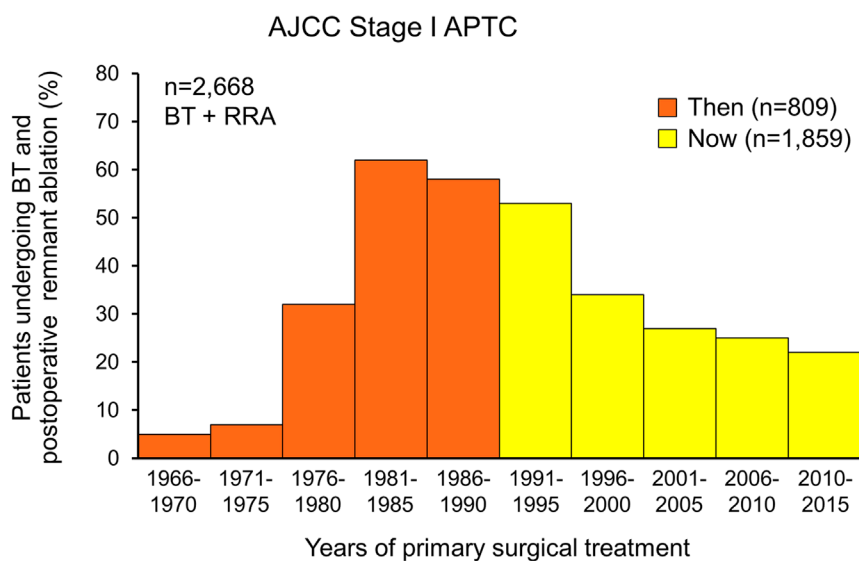


thyroidectomy (NTT) and bilateral subtotal thyroidectomy (BST) during 1966–1990. This was a period when RRA rates, as shown in Fig. 2, increased ten-fold, and throughout this time period, negative whole-body scanning (WBS) with radioactive iodine (RAI) and, in later years, non-stimulable TSH responses to thyrotropin-releasing hormone were considered as the ‘gold standards’ for adequate PTC treatment (8, 9, 10, 11).

The second time period was represented by the NOW cohort of 1859 stage I APTC patients managed between 1991 and 2015, during the time when RRA at the Mayo Clinic in Rochester, Minnesota, was being more selectively performed in higher risk (MACIS scores >6) patients (7, 8, 10, 12, 13), and the ultrasensitive indicators (14, 15) of serum Tg (basal and recombinant human TSH-stimulated),

ultrasound-guided biopsies of suspicious neck masses (16), and targeted high-resolution CT scans were typically employed (7, 8, 12, 13) in the recognition of tumor recurrence (TR).

Patients in the NOW cohort, who underwent potentially curative BT (pcBT) alone, were discharged from hospital with lifelong thyroxine therapy; serum TSH and Tg levels were measured and thyroxine dose adjustment typically was performed within the first 2–3 postoperative months. Those selected by clinicians for BT+RRA were sent home on tri-iodothyronine therapy for at least 6 weeks, and arrangements were typically made for these patients to return to Mayo Rochester after 2 weeks of hormone withdrawal for outpatient RRA, performed immediately after the completion of a ¹²³I WBS and followed, whenever



possible, by a later post-therapy WBS. All study patients typically had Tg measurements on thyroxine therapy, supplemented by neck exam and sonography at 1 postoperative year. Most clinicians would choose to check the completeness of ablation at 1 postoperative year with a further WBS (either after hormone withdrawal or recombinant human TSH stimulation), while in recent years, some would omit a WBS and depend more on ultrasensitive Tg measurements and sophisticated neck sonography to exclude locoregional disease. When postoperative recurrence was suspected due to rising Tg levels or the development of suspicious lesions on neck sonography, most patients returned to Mayo Rochester for US-guided biopsy, further imaging, and, when indicated, definitive therapy. Patients who had BT alone and had a satisfactory serum Tg and unremarkable neck sonography at 1 year would choose either to be followed annually to 5 postoperative years by Mayo or return to the care of their referring endocrinologist or primary care practitioner. Many patients who had undergone BT+RRA in Rochester returned there on an annual basis, while those having BT alone were more frequently followed up by their local practitioners. Follow-up reports were often available for such patients through shared electronic medical record systems, and this information was supplemented by phone calls and follow-up letters were sent to both patients and physicians.

Definition of postoperative TRR events

TRR events at regional, local, and distant sites were identified as per earlier publications (7, 8, 9, 10, 11, 17) and were characterized, as in the National Thyroid Cancer Treatment Cooperative Study group registry analysis, (18) by ‘structural evidence of disease determined either radiologically or by pathology’ and not based solely on persistently elevated levels of serum Tg. Since 1986, we (9) and others (19) have recognized three types of TR with ‘differing prognostic implications’ (9, 11) and have classified these events as postoperative regional nodal metastases (RNM), local recurrences (LR), and postoperative distant metastases (DM).

Statistical analyses

Survival rates from the date of initial surgery until death (cause-specific) or TR were studied by standard life-table methods (8, 10). We used the Kaplan–Meier method (8, 9, 10) as available on our Statistical Analysis System (SAS) computer software. Studies of both CSM and TRR involved

all 2668 TNM stage I (4, 5) APTC patients managed during 1966–2015, who did not have DM, either at diagnosis or first postoperative WBS, and had undergone complete tumor resection with BT and had no postoperative gross residual disease. Univariate comparisons of risk characteristics and trends across the decades were performed with chi-squared test of proportion, the Fisher’s 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 the use of log-rank tests (9). All tests were two-sided, with an alpha level of 0.05. 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, Cary, NC.

Results

Details of stage I PTC patients managed during 1966–2015

There were 2668 stage I APTC patients who, within 60 days of initial cytological or histologic diagnosis, underwent potentially pcBT during 1966–2015. Their median age at diagnosis was 44 years (range, 19–85 years) and 1865 (70%) were female. In total, 925 (35%) had postoperative RRA. Ablation was performed within 6 postoperative months in 832 (31%). The mean, median, and mode values of the initial administered ¹³¹I dose were, respectively, 51.1, 30, and 29.9 mCi (1890, 1110, and 1106 MBq). RRA was considered to have been successful if there was no visible evidence of RAI uptake at 24 h or if uptake identified in the thyroid bed was quantitated at 1% or less. Such information was available in 74% of all 832 ablated patients and ablations were found to have been successful in 94%.

Median follow-up for the 2668 stage 1 patients was 12.6 years; longest follow-up was 52.8 years; mean follow-up was 15.4 years and accounted for 41,188 patient-years of observation. At the time of last follow-up (LFU), a serum Tg on TSH-suppressive thyroxine therapy was retrievable from clinical records in 70% of the study patients; mean, median, and mode values were 2.3, 0.2, and <0.1 ng/mL, respectively. Comparable values in 1130 BT-alone patients were 2.2, 0.2, and <0.1 ng/mL and in 738 BT+RRA patients were 2.5, 0.1, and <0.1 ng/mL, respectively. The difference between the Tg values found at LFU between the BT alone and the BT+RRA patients was not statistically significant (Kruskal–Wallis *P*-value of 0.4459).

Nine presenting variables that may have influenced the clinician’s decision to perform RRA are summarized in

Table 1. Ablation was performed significantly more often ($P < 0.0001$) when patients were younger or male, and when patients underwent an initial NTT or had undergone a neck nodal resection. It was also significantly more frequently performed ($P < 0.0001$) at initial surgery in the presence of gross extrathyroid invasion, larger tumor size, grade 2 histology, multicentricity or pathologically confirmed RNM (pN1). The most striking difference in ablation rates was, however, seen when RNM were confirmed at pathology; 495/995 (50%) of node-positive (pN1) patients had BT+RRA, in contrast to 337/1673 (20%) of node-negative (pN0/NX) patients.

Details of the THEN cohort of stage I PTC patients managed during 1966–1990

During the earlier 25-year time period of 1966–1990, we studied 809 consecutive stage 1 patients who had

undergone pcBT. Median age was 43 years (range, 19–83) and mean tumor size was 1.75 cm (range, 0.1–8.0); 282 (35%) were microcancers. 83% had NTT; 60 (7%) underwent BST and 451 (56%) had neck nodes removed at the time of BT. At surgery, 19 (2%) had gross extrathyroid extension, 293 (36%) were node-positive (pN1), and 291 patients (36%) were ablated within 6 postoperative months; the mean, median, and mode values of the initial administered ^{131}I dose were, respectively, 40.7, 29.9, and 29.9 mCi (1505, 1106 and 1106 MBq).

The 291 BT+RRA patients were compared to the 518 patients who had undergone only BT as primary therapy. A significant difference ($P < 0.001$) in ablation rates was observed when RNM were confirmed by surgical pathology as 150/293 (51%) of the pN1 patients underwent RRA, in contrast to only 141/516 (27%) of the pN0/NX patients. Median follow-up for the 809 patients was 27.8 years, and the longest follow-up was 52.8 years. At LFU, there

Table 1 Presenting variables relevant to selection of postoperative RRA in 2668 patients with AJCC stage 1 disease managed with potentially curative BT at Mayo Clinic, 1966–2015.

Variables present at the time of initial definitive bilateral thyroidectomy	BT alone (n = 1836)	BT+RRA (n = 832)	Total (n = 2668)	P-value
Patient's age, years				<0.0001 ^a
Mean (s.d.)	46.0 (13.93)	42.1 (13.38)	44.8 (13.88)	
Median	46.0	42.0	44.0	
Range	19.0–85.0	19.0–82.0	19.0–85.0	
Patient's gender, n (%)				<0.0001 ^b
Male	502 (27.3)	301 (36.2)	803 (30.1)	
Female	1334 (72.7)	531 (63.8)	1865 (69.9)	
Extent of thyroidectomy, n (%)				<0.0001 ^b
Near-total or total	1509 (82.2)	744 (89.4)	2253 (84.4)	
Bilateral subtotal	327 (17.8)	88 (10.6)	415 (15.6)	
Nodal resection performed, n (%)				<0.0001 ^b
Yes	1261 (68.7)	674 (81.0)	1935 (72.5)	
No	575 (31.3)	158 (19.0)	733 (27.5)	
Gross (macroscopic) invasion reported at surgery, n (%)				<0.0001 ^b
Yes	19 (1.0)	46 (5.5)	65 (2.4)	
No	1817(99.0)	786 (94.5)	2603 (97.6)	
Largest PTC nodule (cm diameter)				<0.0001 ^a
Mean (s.d.)	1.5 (0.98)	2.2 (1.37)	1.7 (1.17)	
Median	1.2	2.0	1.5	
Range	0.1–8.0	0.1–8.7	0.1–8.7	
Histologic grade, n (%)				<0.0001 ^b
Grade 1	1794 (97.7)	772 (92.8)	2566 (96.2)	
Grade 2	42 (2.3)	60 (7.2)	102 (3.8)	
Number of PTC foci, n (%)				<0.0001 ^b
Unifocal	1233 (67.2)	443 (53.2)	1676 (62.8)	
Multifocal	603 (32.8)	389 (46.8)	992 (37.2)	
RNM confirmed at pathology, n (%)				<0.0001 ^b
Node-negative (pNX or pN0)	1336 (72.8)	337 (40.5)	1673 (62.7)	
Node-positive (pN1a or N1b)	500 (27.2)	495 (59.5)	995 (37.3)	

AJCC, American Joint Committee on Cancer; BT, bilateral thyroidectomy; PTC, papillary thyroid carcinoma; RNM, regional nodal metastases; RRA, radioiodine remnant ablation; Categorical variables are presented as number (%); ^aKruskal-Wallis test P -value; ^bChi-square test P -value.

had been 7 deaths from PTC, 10 postoperative DM, 17 LR, and 67 postoperative RNM. At 20 postoperative years, 76% of the BT-alone patients were being actively followed (remaining at risk), as were 74% of the BT+RRA patients.

Impact of RRA on CSM and TRR in stage I patients within the THEN cohort

At 20 postoperative years, the 518 patients in the BT-alone group had CSM and TRR (any site) of 0.6 and 7.9%, respectively. Comparable rates for the 291 BT+RRA patients were both higher at 1.2% ($P=0.66$) and 11.7% ($P=0.042$), respectively. When examined by site of recurrence, as shown in Fig. 3, non-significant differences in 20-year TRR were seen between the BT and BT+RRA patients with regards to local ($P=0.28$), regional ($P=0.07$), and distant ($P=0.76$) sites.

Details of the NOW cohort of stage I patients managed during 1991–2015

The NOW cohort comprised 1859 patients with stage I APTC who underwent pcBT. Median age was 45 years (range, 19–85) and mean tumor size was 1.7 cm (range, 0.1–8.7); 33% were microcancers. 81% underwent NTT; 19% had BST. At surgery, 80% had neck nodes removed, 2% had gross extrathyroid extension, and 38% were node-positive (pN1).

In total, 541 patients (29%) were ablated within 6 postoperative months and were compared to the 1318 patients (71%) who had undergone only pcBT as primary therapy. The mean, median and mode values of the initial administered ^{131}I dose were, respectively, 57.1, 49.9 and 29.9 mCi (2111, 1846 and 1106 MBq). As with the THEN cohort, a significant difference ($P < 0.0001$) in ablation rates was

obvious when RNM were confirmed at surgical pathology; 49% of the pN1 patients underwent RRA, in contrast to 17% of the pN0/NX patients.

Median follow-up was 9.3 years; longest follow-up was 29.1 years. At LFU, there had been no deaths from PTC, 10 postoperative DM, 20 LR, and 151 postoperative RNM. At 20 postoperative years, only 85/1318 (6%) of the BT-alone patients were being actively followed (remaining at risk), as were 89/541 (16%) of the BT+RRA patients, probably consistent with a greater intensity of postoperative tumor surveillance in those patients who had undergone RRA.

Impact of RRA on CSM and TRR in the NOW cohort managed during 1991–2015

After 19,408 patient-years of postoperative observation, none of the 1859 stage 1 APTC patients in the NOW cohort died from PTC. Figure 4 illustrates the cumulative TRR through 15 years at any site (left panel), locoregional sites (middle panel), and distant sites (right panel) in the NOW cohort. The 15-year TRR (any site) for BT alone and BT+RRA were 6.9 and 18.5%, respectively ($P < 0.0001$). The 15-year locoregional recurrence (LRR) rates after BT alone and BT+RRA were 6.9 and 18.4%, respectively ($P < 0.0001$). The 15-year occurrence rates for postoperative DM were 0.1% for BT alone and 1% after BT+RRA ($P < 0.0001$). RNM accounted for 151/166 (91%) of the total number of recurrent events at any site. Moreover, as we had found with the THEN cohort, the ablation rate for the 1157 node-negative patients was 17%; however, for the 702 node-positive patients, the rate was nearly three times higher at 49%. We therefore decided to further evaluate the TRR separately for the pN0/NX patients and pN1 patients. Within the pN0/NX group, at 15 postoperative years, 19% of the BT-alone patients and 39% of the BT+RRA patients were being actively followed.

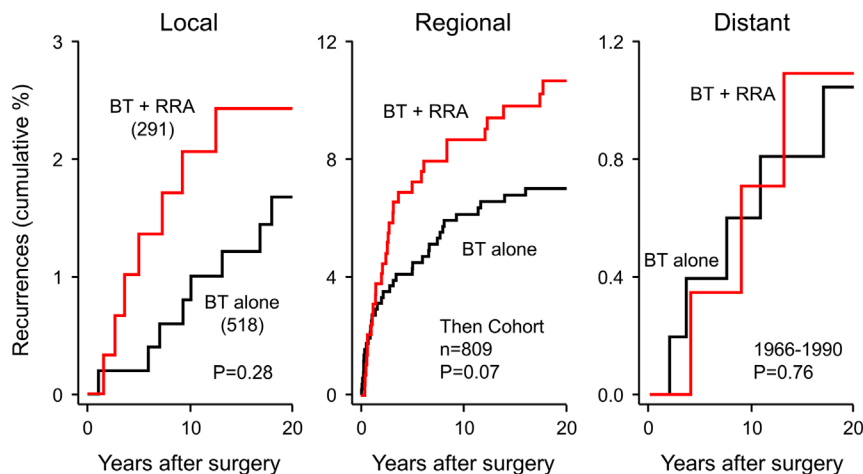


Figure 3

Postoperative cumulative recurrence rates through 20 years in 809 adult patients from the THEN cohort with stage I papillary thyroid carcinoma managed during 1966–1990. The left panel demonstrates the non-significant difference ($P = 0.28$) in the rates of local recurrence between 518 patients having bilateral thyroidectomy (BT) alone and 291 patients having BT plus radioiodine remnant ablation (RRA). The middle panel shows the non-significant difference ($P = 0.07$) in the occurrence of regional nodal metastases (RNM) between the BT alone and the BT+RRA patients. The right panel illustrates the non-significant difference ($P = 0.76$) in the rates of distant metastasis between the BT alone and the BT+RRA patients.

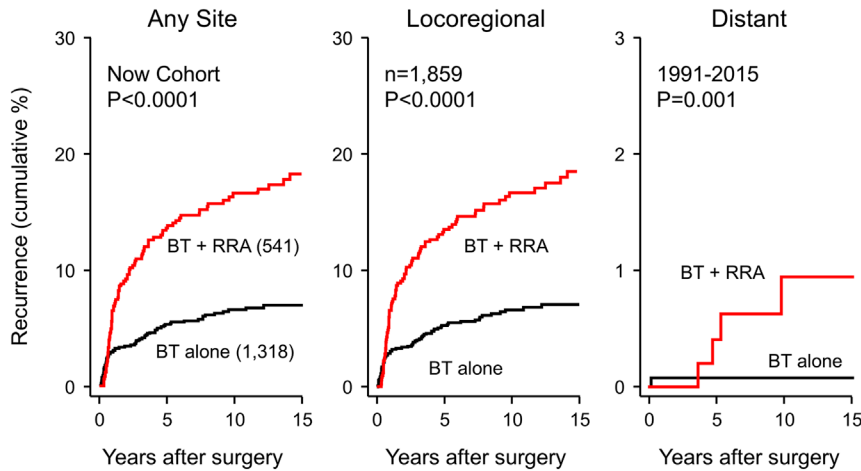


Figure 4

Postoperative cumulative recurrence rates through 15 years in 1859 adult patients from the NOW cohort with stage I papillary thyroid carcinoma managed during 1991–2015. The left panel demonstrates the significant difference in rates of recurrence at any site ($P < 0.0001$) between 1318 having BT alone and 541 having BT plus radioiodine remnant ablation (RRA). The middle panel shows the significant difference in the rates ($P < 0.0001$) of locoregional recurrence between the BT alone and the BT+RRA patients. The right panel illustrates the significant difference in the rates ($P < 0.0001$) of distant metastasis between the BT alone and the BT+RRA patients.

For the pN1 group, at 15 postoperative years, 15% of the BT-alone patients and 20% of the ablated patients were being actively followed.

Impact of RRA on TRR in the NOW cohort according to RNM status at presentation

The 15-year TRR after BT alone in 961 pN0/NX patients was 3.1%, as compared to 6.8% in the 196 ablated patients ($P = 0.003$). As illustrated in Fig. 5 (upper panels), no

postoperative DM were identified in those treated by BT alone, as compared to 1.9% ($P = 0.001$) after BT+RRA. The 15-year LRR rate for the BT-alone group was 3.1%, as compared to 6.8% after BT+RRA ($P = 0.005$). In total, 30/37 (81%) of the neck recurrences were in regional nodes; occurrence rate for RNM at 15 years was 2.3% for BT-alone patients, as compared to 6.8% for the ablated patients ($P = 0.001$). The significantly higher occurrence rates for RNM and DM in BT+RRA patients were thought likely to be related to the more frequent use (15, 16, 17, 18) of WBS,

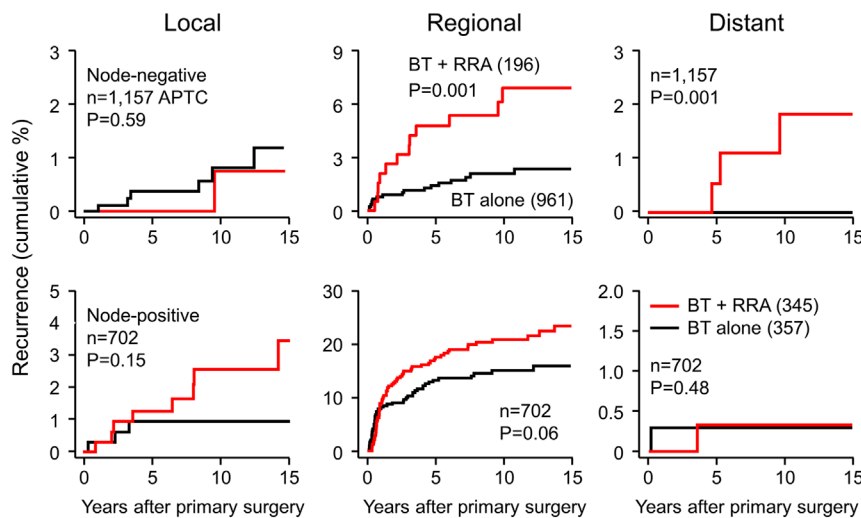


Figure 5

Postoperative cumulative recurrence rates through 15 years in the 1157 node-negative (upper 3 panels) and the 702 node-positive (lower 3 panels) stage I adult papillary thyroid carcinoma patients managed during 1991–2015. The left upper panel demonstrates the 1157 node-negative patients within the NOW cohort, and the non-significant ($P = 0.59$) difference in rates of local recurrence (LR) between the 961 patients having bilateral thyroidectomy (BT) alone and the 196 patients having BT+RRA. The upper middle panel shows the significant ($P < 0.001$) difference in rates of occurrence of regional nodal metastases (RNM) between the BT alone and the BT+RRA patients. The right upper panel illustrates the significant difference ($P = 0.001$) in rates of occurrence of distant metastases (DM) between the BT alone and the BT+RRA patients. The left lower panel demonstrates the 702 node-positive patients within the NOW cohort, and the non-significant ($P = 0.15$) difference in rates of LR between the 357 patients having BT alone and the 345 patients having BT+RRA. The lower middle panel shows the non-significant ($P = 0.06$) difference in rates of occurrence of RNM between the BT alone and the BT+RRA node-positive patients. The right lower panel illustrates the non-significant difference ($P = 0.48$) in rates of occurrence of DM between the BT alone and the BT+RRA patients.

neck sonography, high-resolution CT scans of the chest, and PET-CT scans in these ablated patients who were also being regularly followed with serial highly sensitive Tg measurements. The five node-negative BT+RRA patients who had distant spread between 4 and 20 years after successful RRA survived with their microscopic lung metastases.

Within the pN1 group, the difference in 15-year rates for TRR (any site) between 26% in the 345 ablated patients and 17% in the 357 BT-alone patients was of borderline significance ($P = 0.047$). However, as illustrated by the three lower panels of Fig. 5, no significant differences existed within the pN1 group between the BT alone and the BT+RRA patients with regards to the 15-year occurrence rates of postoperative LR ($P = 0.15$), RNM ($P = 0.06$), or DM ($P = 0.48$).

Increasing burden of RNM and impact of RRA on LRR

Within the 702 pN1 patients treated by pcBT, there were, at initial surgical exploration, 169 patients (24%) with a single pathologically confirmed RNM, 205 (29%) with 2–4 RNM, 162 (23%) with 5–9 RNM, and 166 (24%) with 10+ RNM. Figure 6 (left panel) demonstrates that, within these 702 node-positive patients, a highly significant correlation ($P < 0.0001$) existed 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, 2–4, 5–9, or 10+ RNM were 8.3, 14.6, 30.0, and 38.5%. Figure 6 (right panel) demonstrates a significant association ($P < 0.001$) between the numbers of RNM found at surgery and the individual clinician's decision to give RRA. The

rates of RRA with 1, 2–4, 5–9, and 10+ RNM at surgery were 30, 44, 59, and 65%, respectively.

The impact of RRA on 15-year cumulative LRR rates in patients with a single RNM at surgery, 2–4 RNM, 5–9 RNM, and 10+ RNM was carefully examined. As illustrated in Fig. 7, the rates over 15 postoperative years were compared between patients undergoing BT only and those having BT+RRA. With a single RNM, the 15-year LRR rate was 7.9% after BT only and 8.9% after BT+RRA ($P = 0.97$). With 2–4 RNM (median 3), the comparable rates were 12.5 and 16.6% ($P = 0.53$). With 5–9 RNM (median 6), the rates were 28.6 and 30.5% ($P = 0.72$). Finally, with 10+ RNM (median 15), the rates were 32.2 and 42.6% ($P = 0.98$). RRA did not, in any of the four groups, significantly reduce the 15-year rates of LRR observed after pcBT (all four P values > 0.5).

Discussion

In 2004, Ernest Mazzaferri (20) 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'. Some 15 years later, however, it was stated (21) that 'there are perhaps few controversies more heated in the thyroid cancer field than whether radioiodine should be used routinely following total thyroidectomy for patients with low-risk PTC'. The 2022 ETA consensus statement (22) recommended that 'in low-risk patients, the benefit of ^{131}I therapy is a matter of scientific debate and the decision on whether to perform RAI therapy should be based on the presence of individual risk modifiers'. Moreover, our

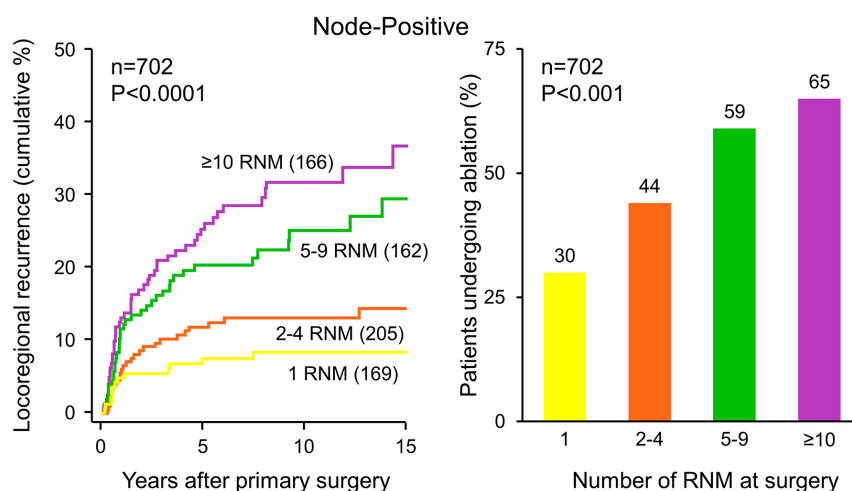
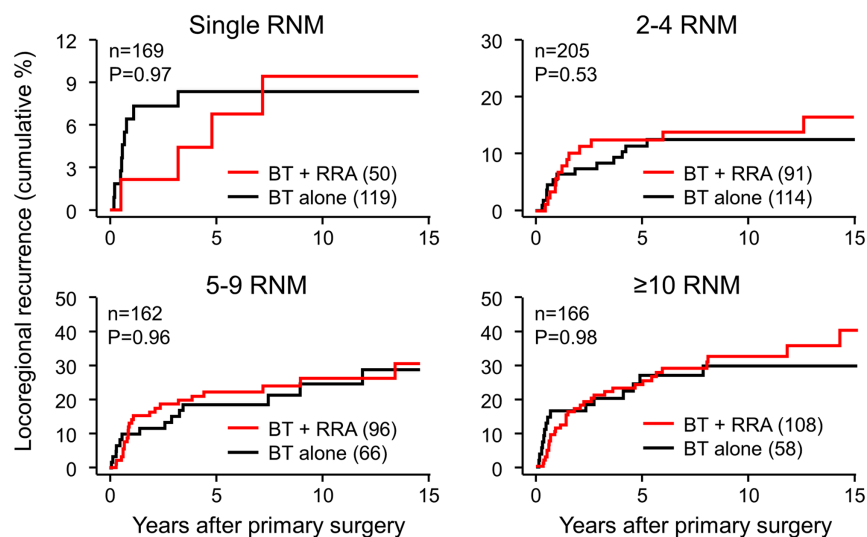


Figure 6

The left panel shows the cumulative rates of locoregional recurrence (LRR) through 15 postoperative years for the 702 stage I node-positive (pN1) adult papillary thyroid carcinoma patients in the NOW cohort managed during 1991–2015. The right panel illustrates the percentage of these 702 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 ($P < 0.0001$) between the number of regional nodal metastases (RNM) identified at surgical pathologic examination and the rates of LRR, ranging from a 15-year rate for a single RNM of 8.3% to a comparable rate of 38.5% with 10 or more RNM. The data shown in the right panel demonstrate the highly significant association ($P < 0.001$) between the numbers of RNM at surgery and the individual clinician's decision to give the patient RRA within 6 postoperative months.

**Figure 7**

Cumulative locoregional recurrence (LRR) rates through 15 years of comparing bilateral thyroidectomy (BT) to BT plus radioiodine remnant ablation (RRA) in 169 patients (upper left panel) with a single RNM and 205 patients (upper right) with 2–4 RNM. 162 patients (lower left) with 5–9 RNM, and 166 patients (lower right) with 10 or more RNM. In all 4 groups, the 15-year LRR rates were higher in the ablated patients, but in all 4 groups, the differences observed in LRR rates during 15 postoperative years between the BT alone patients and the BT+RRA patients were non-significant ($P > 0.5$).

European colleagues (22) stated that their consensus statement was ‘mostly based on retrospective studies and biases cannot be excluded, in particular, in the selection of patients. In fact, the only way to scientifically compare two treatment modalities and to exclude biases is to perform randomized prospective studies’, a statement with which both Dr Mazzaferri and the authors of this manuscript would agree, although our institutional reputations in this area of PTC research were largely based on such retrospective studies. At our institution, there has been doubt about the efficacy of RRA in the postoperative management of PTC since 1983 (23, 24), and our multidisciplinary team (8, 10), in the absence of available published randomized prospective studies, has pursued a policy of selective use of RRA (12, 13, 25) starting soon after the publication in 1993 of the MACIS prognostic scoring system (26) and aimed toward restricting the use of RRA to higher risk-patients (scores of 6 or more).

The recently reported randomized control trial (RCT) results (the first of its kind to be completed and published) by Leboulleux and the Tumeurs de la Thyroïde Refractaires Network (TUTHYREF) would suggest that node-negative (pNO/NX) APTC patients with either multifocal papillary microcancers or primary tumors between 11 and 20 mm in greatest dimension may not require postoperative RRA (27). What is the role of RRA in the postoperative management of low-risk PTC patients with similar-sized tumors but with pathologically confirmed RNM or larger tumors (>20 mm) with or without extrathyroid invasion? To date, there are as yet no results available for presently ongoing prospective randomized phase III trials to answer these questions, and since pTNM stage I represents a heterogeneous group of patients, it would be expected that future RCTs which

investigate the impact of RRA on postoperative tumor recurrence in low-risk APTC would involve homogeneous stage I patients selected more for their risk of recurrence, rather than the minimal risk of PTC death. Unfortunately, as has been the case since RAI therapy was first introduced, recent expert recommendations have been widely variable (22, 28, 29, 30, 31) and almost entirely based on retrospective analyses of outcome at specialist institutions, or in cancer registries or national patient cohorts. Even as recently as 2020, nuclear medical specialists (32) have stated that ‘literature published in the last decade offers data that support adjuvant postoperative radioiodine treatment in DTC patients with a tumor 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’.

As in all retrospective studies, selection bias resulting from the physicians’ and patients’ preferences cannot be excluded (7). In our study, as demonstrated by our comparisons of patient and tumor clinicopathologic features (Table 1) present at the time of initial BT, Mayo Clinic physicians were significantly ($P < 0.001$) more likely to prescribe RRA when patients were younger or male and when patients underwent an initial NTT or had undergone a neck nodal resection. It was also significantly more frequently performed ($P < 0.0001$) in the presence at initial BT of gross extrathyroid invasion, larger tumor size, grade 2 histology, and multicentricity. This preference for selecting RRA was particularly striking with pathologically confirmed RNM (pN1). Perhaps, as Daniels and Kopp (30) have recently observed, we (as physicians) ‘are all influenced by our mentors and tend to have faith in their

teachings, and 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'.

Our recently published 6-decade study (7) demonstrated to our satisfaction an inability of RRA to improve postoperative outcome in 2952 adult patients with LRAPTC (as defined by postoperative MACIS scores <6). The results of this present study also appear to provide further strong evidence against a beneficial effect on the postoperative occurrence rate of RNM in low-risk stage I APTC patients who have undergone BT with curative intent. In 2019, Daniels and Kopp (30) interpreted the recommendations of the current ATA guidelines (28) 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-sized nodal metastases'). By contrast, the 2006 consensus of the European Thyroid Cancer Taskforce (33) stated that RAI administration is definitely indicated in patients at high risk of recurrent disease, which, by their definition, included all APTC patients who had at initial surgery 'any lymph node metastases'. The 2022 ETA Consensus Statement (34) recommended, for the ATA intermediate risk category (with 5–20% risk of recurrence) including PTC patients with clinical N1 or >5 pathologic N1 with all N1 <3 cm in largest dimension, that 'RAI therapy may be indicated and should be tailored according to individual cases'. In this present study, 995 (37%) of our 2668 stage I patients had RNM proven by surgical pathology (pN1); in the NOW cohort managed during 1991–2015, during an era when sophisticated measures for recurrence detection were available, the 20-year postoperative recurrence rate after pcBT and RRA in pN1 patients was still 20%, 91% of the total number of recurrent events (at any site) were in RNM, and not one was associated with death due to PTC.

This study commenced in 1966, some 15 years after the Food and Drug Authority approved RAI for the management of thyroid cancer and concluded just 2 years before the publication of the 8th edition of the AJCC/UICC TNM system (4, 5). We are confident that, during the 50 years of the study, our endocrine colleagues at the Mayo Clinic were convinced (like some of our contemporary European colleagues) that in LRAPTC patients, RRA was warranted if the patient was proven to be node-positive at presentation. Indeed, the more RNM identified, the more frequently was RRA prescribed. From our recently published MACIS scores <6 study (7) and this present TNM stage I study, we would conclude that in node-positive patients, and even node-negative patients, it has been our experience that

RRA does not eliminate or even diminish the postoperative occurrence rates of RNM, considered now more often to be 'persistent' (35), rather than recurrent disease.

With the publication of these present results, we hopefully will move closer to providing answers for the late Jim Sisson (24) who almost 40 years ago suggested that in the treatment of APTC, 'to ablate or not to ablate is a question that will haunt us for some time to come'. In 2022, we hope that the results of our present studies will prompt the development of multinational prospective RCTs to further examine within stage I APTC the impact of RRA on the recurrence rates in carefully matched subsets of patients with tumors larger than those in the TUTHYREF study (27) and also in those younger than 55 years with extrathyroid invasion or pathologically confirmed RNM. Moreover, in a time when 'the use of radioactive iodine for low-risk thyroid cancer is common, despite the lack of benefit for low-risk disease and potential harms and costs' (36) we hope that our results may also satisfy what colleagues from Dr Sisson's former department (36) have identified as presently unmet educational needs for 'those physicians who are an important driver for the use of more intensive treatments for low-risk thyroid cancer'. Finally, we are encouraged to read in two recent reports that, following the publication of the de-escalating 'less is more' (37) ATA Management Guidelines (28), there is, derived from two different national databases, evidence to suggest that within the USA, there is now declining use of RAI in the management of low-risk adult PTC (37, 38), trends that we hope will continue.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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