17 Role of Radioactive Iodine for Remnant Ablation in Patients with Papillary Thyroid Cancer

Nicole M. Iniguez-Ariza, Suneetha Kaggal, and Ian D. Hay

Introduction

The role of radioactive iodine (RAI) for remnant ablation in patients with papillary thyroid carcinoma has been a controversial topic for more than three decades [1–4]. In our chapter, we consider the implications of the recently published American Thyroid Association (ATA) Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (DTC) [2] and hope to clarify for our readers where we currently stand on their Recommendation 51, designed to answer the question of "What is the role of radioactive iodine (RAI) (including remnant ablation, adjuvant therapy or therapy for persistent disease) after thyroidectomy in the primary management of DTC?" Because there is a paucity of published studies specifically addressing the role of RAI and radioiodine remnant ablation (RRA) in patients who have either follicular thyroid cancer (FTC) or Hürthle cell cancer (HCC), we will be restricting our discussion in this chapter to the management of patients with papillary thyroid cancer (PTC), a tumor type which our institution has been carefully studying for more than 30 years [3].

We will plan to consider both low-risk and high-risk PTC patients in this chapter, and in attempting to define an appropriate role for post-surgical RAI in the management of patients presenting with PTC, we will plan to initially address three relevant questions:

1. How did RRA come to be an established part of PTC management?
2. Does RRA improve postoperative outcome in low-risk PTC (classified by tumor size) after complete tumor resection without gross residual disease?
3. If RRA is proven to be ineffective in reducing mortality and recurrence, not only in patients with small PTC tumors but also in all PTC patients with MACIS scores <6, should we be using RRA selectively to treat only the minority of patients with high-risk PTC who have MACIS 6+ disease?

After considering these questions, we will examine the main results from recently published meta-analyses of this controversial subject. Finally, we will carefully examine the evolution over the past two decades of thyroid

N.M. Iniguez-Ariza, M.D.
I.D. Hay, B.Sc., M.B. Ch.B., Ph.D, F.A.C.E., F.A.C.P., F.R.C.P. (✉)
Division of Endocrinology and Internal Medicine, Mayo Clinic and College of Medicine, 200 1st Street SW, Rochester, MN 55905, USA
e-mail: Ariza.Nicole@mayo.edu; hay.ian@mayo.edu

S. Kaggal, B.S.
Division of Biostatistics, Mayo Clinic and College of Medicine, 200 1st Street SW, Rochester, MN 55905, USA
e-mail: Kaggal.Suneetha@mayo.edu

A.T. Mancino, L.T. Kim (eds.), *Management of Differentiated Thyroid Cancer*,
DOI 10.1007/978-3-319-54493-9_17

cancer clinical management guidelines and clarify where we ourselves stand on Recommendation 51 of the 2015 ATA Guidelines [2].

Question 1: How Did RRA Come to Be an Established Part of PTC Management?

History of RAI During 1895 Through 1969

The foundation for the use of RAI in the treatment of thyroid diseases depended largely on advances in science and medicine made at the end of the nineteenth century and the beginning of twentieth century. During that period, it became more readily accepted that (1) the thyroid gland concentrated iodine, (2) tracer substances could be used to analyze biologic functions, and (3) radioactive isotopes could be artificially created.

By end of the nineteenth century, it was believed that the thyroid contained some substance capable of producing marked physiologic effects, and that iodine was a constant constituent of normal and pathologic glands. The German biochemist, Baumann, [5] found iodine in the thyroid gland in 1895 and Kendall, at the Mayo Clinic isolated "the" thyroid hormone (thyroxin) in 1914 using iodine as a marker for the hormone [6]. Joliot and Curie in 1934 discovered artificial radioactivity, [7] with the creation of a new radioactive element, radiophosphorus. Enrico Fermi [8] read the Joliot and Curie paper and tried their experiment, using neutrons instead of alpha particles as a radiation source. He described 22 new radioactive elements, including "radiated iodine," which showed an "intense effect" with a half-life of 30 min.

On November 12, 1936, Karl Compton from the Massachusetts Institute of Technology (MIT) spoke on the subject of "What physics can do for biology and medicine" at Harvard Medical School. He talked about how radioisotopes of many different elements could be made on demand and then used to trace metabolic events in living organisms. At the end of his talk, Saul Hertz from the Massachusetts General Hospital (MGH) apparently asked him whether there might be a radioactive isotope of iodine. Compton replied to Hertz that "yes, iodine can be made artificially radioactive." Soon thereafter, Hertz and Means arranged for physicists at MIT to make the short-lived ^{128}I, thereby permitting study at MGH of its physiology in rabbits. By 1938, they showed that the rabbit's thyroid gland [9] rapidly took up ^{128}I, but because of its short half-life (25 min), there was no hope for using ^{128}I as a potential treatment modality [10].

In 1939, Hamilton and Soley, working at University of California, San Francisco (UCSF), and in Berkeley, California, were able to make several other radioactive iodines, ^{130}I and ^{131}I, with half-lives of 12 h and 8 days, respectively. They were the first investigators to give these isotopes to humans for the study of thyroid physiology. Initially, RAI was used for the study of thyroid physiology, but soon thereafter, the possibility of using RAI as a treatment was considered in the management of both hyperthyroid and thyroid cancer patients.

The earliest study of the uptake of RAI in two cases of carcinoma was reported by Hamilton and colleagues [11] in 1940. In 1942, they described two other cases [12] in which tracer doses of radioactive iodine had been given to the patients prior to the removal of carcinomatous thyroids, but no significant deposition of the RAI in malignant areas was identified in either of these cases. Keston and colleagues [13] subsequently reported the first positive evidence of uptake of RAI by a femoral metastasis from a thyroid carcinoma. The patient was given 10 mCi of RAI, and the metastasis took up about 30%, while the thyroid gland itself took up only about 6% of the total amount administered. With this evidence, the possibility of the use of RAI as a therapeutic agent was suggested, because the metastasis in the femur had fixed such a large proportion of the radioactive material. Subsequently, from the autopsy of this patient, these authors reported that "the bulk of the metastatic tissue was undifferentiated" and the metastasis, which showed consistent uptake of iodine, was the only one which grossly resembled thyroid tissue and which, microscopically, showed well-differentiated tumor [14].

In 1946, Seidlin [15] published details of the successful treatment with RAI of a case of well-differentiated metastatic follicular thyroid cancer

(FTC) with functional metastases causing hyperthyroidism. In 1948, Rawon and coworkers [16] introduced the concept that, after thyroidectomy, there was increased capacity for thyroid metastases to concentrate ^{131}I. They demonstrated that eight patients had significant postoperative increase in RAI uptake in their metastatic lesions, which, prior to thyroidectomy, had shown minimal to no function.

Until 1949, the only counting device for external detection of radioactive substance was the Geiger-Müller (GM) tube, which was very insensitive to penetrating gamma rays from radionuclides such as ^{131}I. This problem was largely overcome by the first scintillation counters developed in 1949–1950 for medical use and constructed by Cassen [17, 18] and his colleagues at UCLA. In 1951, this UCLA group first used a scintillation detector to "scan" RAI distribution in the thyroid, and this made possible the subsequent era of thyroid gamma scans and whole-body radioiodine scanning. By 1951, a decade after the publication of Hamilton's pioneering work [11] with this isotope, the Food and Drug Administration (FDA) finally approved ^{131}I for thyroid patients; this represented the first radiopharmaceutical to be approved for human therapy.

In 1960, Blahd and associates [19] at UCLA published their experience since 1949 with the use of ^{131}I as postoperative therapy for thyroid cancer. Patients received on average therapeutic doses of 100 mCi, but the authors specified that smaller doses might be used to ablate postoperative thyroid remnants, depending upon the size of remnant tissue observed. All of the 26 patients who received ^{131}I therapy had undergone prior thyroid surgery. Fifteen patients in their series had proven metastatic lesions, and 11 patients were treated solely for the purpose of remnant ablation. Blahd's group at UCLA were likely the first to consider that RRA may be used to "complete the thyroidectomy" after an apparently complete surgical resection of primary tumor in localized differentiated thyroid cancer (DTC).

It should be noted that during the period of 1950–1969, only 3% of PTC patients, who had at the Mayo Clinic bilateral lobar resection (BLR) with curative intent, underwent within 6 postoperative months RRA, although during that time RAI therapy was routinely given to both patients who had incomplete primary tumor resection with gross residual disease and those demonstrated to have distant metastases at initial presentation. In other words, at Mayo, for the first two decades after the introduction of RAI as an approved therapy, 97% of PTC patients undergoing definitive, and potentially curative, BLR, typically near-total thyroidectomy (NT) or total thyroidectomy (TT), avoided RAI for remnant ablation.

Early Reports of RAI in Thyroid Cancer During 1970 Through 1981

In 1970, Varma and colleagues, [20] from Beierwaltes' group at Ann Arbor, claimed that ^{131}I administered postoperatively could reduce mortality from thyroid cancer. This study was based on the death rate analysis of 263 patients with PTC or follicular thyroid cancer (FTC) treated with ^{131}I after surgery (intervention group), when compared with the death rates in 50 patients with PTC or FTC treated surgically before the introduction of ^{131}I (control group). In the patients 40 years of age and older, the intervention group had a significantly lower death rate than the surgery-only group. The authors did acknowledge that one possible weakness of their data was that thyroid surgery at their institution may have become more radical since the introduction of ^{131}I in 1947, and a more aggressive operative approach, as directed by the surgical skills of Professor Norman Thompson, may have contributed, at least in part, to the better results observed in the intervention group.

In 1977, Krishnamurthy and Blahd [21] from UCLA again reported on the therapeutic value of postoperative ^{131}I therapy, this time in 54 patients (96% with well-differentiated thyroid cancers, WDTC) treated during a 25-year period. Twenty-four patients (44%) had metastases at the time of ^{131}I therapy, mainly to cervical and mediastinal lymph nodes and less frequently to the bone, brain, lung, and liver. The recurrence rate for

patients with metastases was 56% and in those without metastases was 25%. Seven deaths were attributed to thyroid cancer. The authors noted that no deaths from thyroid cancer occurred when "total ablation was achieved and maintained." They recommended that most patients with WDTC should be considered for postoperative RAI. In reviewing the contemporary management of thyroid cancer, they concluded that "there is as yet no unified single opinion in the medical community as to the best form of therapy for thyroid cancer. Personal philosophy, emotional factors, and the basic medical training play a significant role in the selection of therapy."

In that same year (1977) and again in 1981, Mazzaferri [22, 23] and colleagues reported on a cohort of 576 patients with histologically proven PTC that were treated at the USAF Hospital at Wilford Hall Air Force Base in Texas. In their initial 1977 paper, they described "highly variable" therapy provided to USAF personnel "treated in an individualized manner, reflecting the clinical situation, as well as the experience and bias of the attending physician." In total, 116 patients (20%) were given ^{131}I; 80 had residual nodal disease, 3 had presented with lung metastases, and only 33 (28%) were actually being treated for ablative purposes. In the 1977 report [23], they compared those treated postoperatively with thyroid hormone and ^{131}I to those receiving only thyroid hormone and demonstrated a significant reduction in cumulative percent recurrence in those receiving ^{131}I. Mazzaferri, on the basis of his initial study results, recommended that "ablative doses of I-131 should be employed postoperatively, especially in those with primary lesions that are multiple, locally invasive or larger than 1.5 cm and in those with local and/or distant metastases, provided adequate uptake of radionuclide can be demonstrated."

Clearly, at this point in the literature, the subtle distinctions between RAI therapy and RRA were not being adequately appreciated in this, the first real, study of the efficacy of RAI in a cohort of patients consisting only of pathologically confirmed PTC. In 1981, when his cohort [22] had now a median follow-up of 10 years, Mazzaferri concluded that "treatment with total thyroidectomy, postoperative RAI and thyroid hormone resulted in the lowest recurrence and mortality rates except in those patients with small primary tumors (less than 1.5 cm diameter) in whom less than total thyroidectomy and postoperative therapy with thyroid hormone alone gave results which did not differ statistically from those achieved with more aggressive therapy."

As noted above, at the Mayo Clinic, during the first 20 years (1950–1969) after the FDA approved ^{131}I for therapeutic purposes, RAI was regularly administered to patients either with gross residual disease or who had undergone distant spread, but was not employed in PTC patients undergoing potentially curative bilateral surgery for localized disease. During 1970–1974, only 6% of PTC patients underwent, within 6 postoperative months, RRA after potentially curative bilateral lobar resection (BLR), but by 1980–1989 there had been a tenfold increase in RRA rates [24, 25] to 59%, likely due to the influence of Mazzaferri's 1977 and 1981 reports [22, 23]. RRA in PTC should not be confused with RAI therapy, since, as defined initially by Harry Maxon and more recently by Anna Sawka, RRA "refers to the destruction of residual macroscopically normal thyroid tissue after complete gross surgical resection of cancer" [26, 27].

Question 2: Does RRA Improve Postoperative Outcome in Low-Risk PTC (Classified by Tumor Size) After Complete Tumor Resection Without Gross Residual Disease?

Assignment of PTC risk category at presentation is largely dependent on details readily derived from the contents of initial surgery and pathology reports and, where appropriate, preoperative radiologic imaging of chest and skeleton. Many different potential prognostic variables have been identified, and risk assessment systems developed

[28–36]. Detailed description of these systems is provided in Chap. 16. They can provide guidance on the need for postoperative treatment, including RRA.

Colum Gorman [37] was one of the first Mayo authors to question whether RRA possibly represented in PTC a "questionable pursuit of an unattainable goal," as locoregional recurrences occurred within the thyroid bed or neck nodes in 6 of 69 patients he followed up for up to 5 years. He emphasized the lack of a proven value of postsurgical RRA of presumed normal thyroid tissue and raised the future possibility of a more conservative or "selective" approach to RRA. In an accompanying Journal of Nuclear Medicine editorial entitled "Applying the Radioactive Eraser: I-131 to Ablate Normal Thyroid Tissue in Patients from Whom Thyroid Cancer Has Been Resected," Sisson [38] argued that "extinguishing evidence of thyroid cancer is beneficial, but ablation of normal thyroid tissue is another matter." He even suggested that "wiping the scintigraphic slate clean" did not necessarily eliminate the possibility of future recurrence. And he dared to question the importance of Mazzaferri's 1981 study, [22] in which fewer recurrences followed ^{131}I treatment of presumably normal thyroid residuals, emphasizing that the results were of marginal significance. He highlighted the possibility of second non-thyroid cancer risk following RAI treatment and ended his editorial with a very relevant observation: "to ablate or not to ablate is a question that will haunt us for some time to come."

In 1986, a study by McConahey, Hay, and colleagues [3] of 859 PTC patients treated at Mayo 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. These patients were conservatively treated, as only 16% underwent TT and 3% had postoperative RRA. They concluded their manuscript by stating "whether routine remnant ablation can substantially improve the already excellent results of surgical treatment remains, in our assessment, to be proved." In 1990, Hay [39] highlighted the influence of the studies from Michigan [21] and Ohio State [22, 23] on the worldwide use in follicular cell-derived cancer (FCDC) patients of RAI therapy and RRA. He found, however, that, in contrast to Mazzaferri's significantly improved recurrence rates after RAI in 153 ablated PTC patients, in a comparable outcome study of 946 similarly defined Mayo patients, he found no significant differences between bilateral potentially curative surgery ($n = 726$) and the same surgery plus RRA within 6 postop months ($n = 220$), with regard to tumor recurrence ($p = 0.06$), cause-specific mortality (CSM) ($p = 0.25$), or overall mortality ($p = 0.52$). Hay [39] concluded his review by stating 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 proved a satisfactory answer to Sisson's haunting question."

In 1994, DeGroot [40] summarized the then present status of RRA in the USA as follows: "Mazzaferri, Young and co-workers provided, nearly 2 decades ago, the first powerful support for the role of radioactive treatment in reducing recurrences and deaths in differentiated thyroid cancer….more recent studies by De Groot and colleagues, and Samaan and coworkers demonstrated, in a careful analysis stratifying patients by extent of diseases, that both more extensive surgery (lobectomy plus subtotal or near-total thyroidectomy) and radioactive iodine treatment reduce the numbers of recurrences and deaths. Hay and co-workers have thrown their support behind more extensive surgery, but have not yet supported routine radioactive remnant ablation." To which Grebe and Hay [41] responded in 1997 by stating that "it is still our stance that we remain unconvinced by the presently available retrospective data describing the efficacy of RAI remnant ablation in differentiated thyroid carcinoma."

In 1998 Wartofsky [42] wrote: "if we place ourselves in the shoes of even a "low risk" patient, would we not willingly accept the consequence of a 30–60 mCi ablative dose of ^{131}I in exchange for the certainty and peace of mind provided by a subsequent negative scan and

undetectable serum Tg level?" In the same article, [42] Schlumberger and Hay talked about a "selective approach" for the use of RAI in patients with PTC and FTC. They stated that RAI was clearly not indicated or not beneficial to patients with small intrathyroidal tumors and that RRA does not influence recurrence rates in patients with node-positive papillary thyroid microcarcinoma but for larger tumors, tumor multifocality, tumor extension beyond the thyroid capsule, or lymph node metastases, the beneficial effects of RAI continued to be debated. They concluded that RRA should be restricted to patients with poor prognostic indicators for relapse or death and representing only a small high-risk minority of DTC patients. In the same year, Morris and colleagues [43] published a survival analysis examining ^{131}I therapy in localized well-differentiated thyroid cancer, based on data from 1969 to 1993 on 1171 patients from the New Mexico Tumor Registry of whom 127 (37%) had received RRA. They concluded that there was no apparent survival benefit associated with RAI following "clinically appropriate" thyroidectomy.

As we have been updating outcome data of our eight-decade Mayo PTC cohort, it has become clear, as shown in Fig. 17.1, that throughout the 80-year period, a third of our

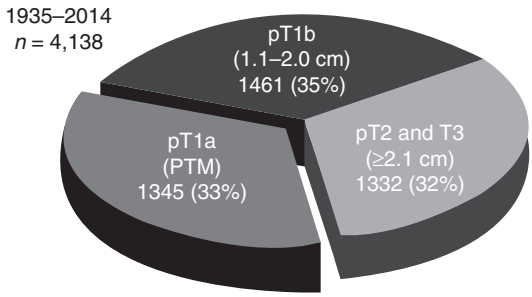

Fig. 17.1 Size distribution of maximal tumor diameter in 4138 adult PTC patients consecutively treated at Mayo during 1935–2014 and demonstrating that one-third of these patients during the eight decades presented with PTM and tumor diameters of 1 cm or less (pT1a)

PTC cases were at presentation 1 cm or less in greatest diameter and would be considered papillary thyroid microcarcinomas [44] (PTM) by the World Health Organization and categorized as pT1a in the current TNM classification approved by the ATA in the 2015 Guidelines [2]. pT1b tumors with 1.1–2.0 cm diameters accounted for a further 35%, while the largest tumors exceeding 2 cm in diameter made up the final 32%. For more than 24 years [44], our group has very carefully analyzed outcome details in pT1 tumors, accounting for almost 70% of our PTC cases. For the remainder of this section of our chapter, we will concentrate on trying to determine whether RRA does have any significant impact on outcome in more than 2/3 of all our PTC cases that are either pT1aM0 or pT1bM0 after complete tumor resection without gross residual disease.

In 2008 we presented and published [45] our experience of treating 900 pT1a tumors over a 60-year period (1945–2004). These patients were followed up for up to 54 years and on average for 17 postoperative years. At last follow-up, only three patients (0.3%) died of PTC. RRA was administered to 17% of the study group and, when reevaluated for efficacy, was found to be 99% successful in terms of negative neck and whole-body RAI scans. Expected and observed all-causes survival were near identical (p = 0.96). CSM rates at 20 and 40 years were 0.1 and 0.7%.

Of 758 patients without distant spread, undergoing BLR with complete tumor resection, 119 (16%) had RRA administered within 6 postoperative months. RRA did not impact tumor recurrence (TR) at local or distant sites, but postoperative ("recurrent") neck nodal metastases (NNM) were more frequently found after RRA, when compared to those treated by BLR only. These higher NNM rates were likely explained because node-positive patients were 10 times more likely to have received RRA. Four percent of node-negative

PTM patients got RRA, and at 20 years TR rates were 0.6% after BLR and 0% after BLR + RRA ($p = 0.79$). By contrast, 38% of node-positive cases got RRA, which did not decrease TR at either local ($p = 0.8$) or distant ($p = 0.7$) sites. Higher TR rates were seen with either multicentric tumors or patients who were node-positive at presentation. Accordingly, for our final analysis of the efficacy of RRA in PTM in our six-decade cohort, we elected to examine four subsets of patients divided according to the number of foci (unicentric vs. multicentric) and presence or absence of NNM at initial surgery.

With unifocal node-negative PTM, RRA did not decrease the <1% risk of nodal recurrence seen after BLR ($p = 0.8$). In multifocal node-negative cases, no recurrences at any site were seen in 101 patients, perhaps implying that multicentricity per se in PTM does not impart a higher risk of TR. In unifocal node-positive disease, RRA did not significantly reduce the 11% TR seen after BLR alone ($p = 0.2$). Finally, in the worst-case scenario of multifocal node-positive PTM, RRA did not in 100 cases significantly decrease the 22% TR rate (all sites) seen after BLR alone. Our 2008 conclusions [45] were that the extent of surgery did not affect TR rates, and RRA did not improve outcome in any subset of patients studied, including those with multicentric tumors or those presenting with NNM at initial surgery.

We recently presented [46] at the 2016 Meeting of the Endocrine Society the results from our experience in managing the 1345 PTM patients shown in Fig. 17.1. Of the 1281 potentially curable cases (no distant metastases and complete surgical resection after BLR), only 165 (13%) had RRA within 6 months of successful BLR. Interestingly, only 1% was ablated in the decade of 1965–1974, but in the decade of 1975–1984, when Mazzaferri's two initial PTC studies [22, 23] were published, this rate rose by more than 20-fold to 23%. However, in the subsequent three decades up to 2014, the rates of RRA dropped progressively from 20 to 16 during 1985–1994 and 1995–2004, respectively, and, most recently, 11% in the last decade of 2005–2014.

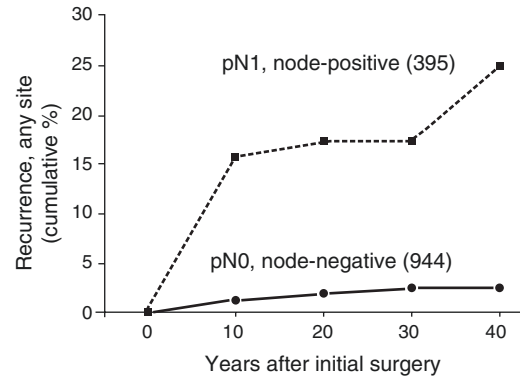

Fig. 17.2 Influence of neck nodal metastases at presentation on cumulative tumor recurrence rates over 40 postoperative years in 1339 patients with localized (M0) papillary microcancers, who had complete primary tumor excision at initial surgery and demonstrating a highly significant ($p < 0.001$) increase (almost tenfold) in those 395 patients who were node-positive (pN1)

Figure 17.2 illustrates, within the eight-decade PTM cohort, the very significant influence ($p < 0.001$) of NNM at presentation on subsequent discovery over 40 postoperative years of so-called "recurrent" NNM. In this recent study, we again concluded that PTM patients have normal life expectancy and typically are cured by adequate tumor resection. More than 99% of our PTM patients treated over eight decades were not at risk of either distant spread or mortality from cancer. The 20-year TR rates were only 7%, almost exclusively in regional (neck) nodes. The extent of initial surgery [46] did not affect locoregional recurrence rates ($p = 0.8$) and, most interestingly, the 30-year TR rates in node-positive cases after lobectomy alone were no different from those seen after BLR or even NT or TT

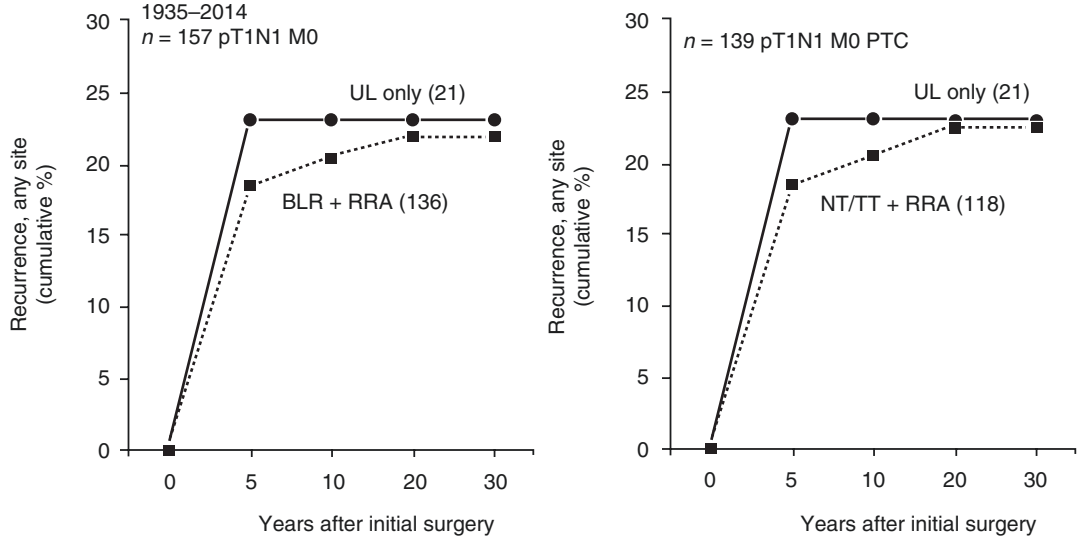

Fig. 17.3 Comparison, within patients with pT1aN1M0 microcarcinoma having potentially curative surgery at Mayo during eight decades (1935–2014), of cumulative tumor recurrence rates over 30 postoperative years and demonstrating that the recurrence risk (at any site, locoregional or distant) after unilateral lobectomy alone was no different (p = NS) from that seen after either bilateral lobar resection (BLR) and RRA (*left panel*) or near-total or total thyroidectomy (NT/TT) and RRA (*right panel*)

followed by RRA ($p = 0.99$). Figure 17.3 demonstrates that in node-positive PTM (pT1N1MO) the 30-year TR rate after UL was insignificantly different from the comparable rates seen after either (left panel) BLR + RRA or (right panel) NT or TT followed by RRA within 6 postoperative months.

In 2009, we had reported to the American Thyroid Association at their annual meeting that neither the 2006 ATA Cancer Guidelines [47] nor a more recently published report by Rosario [48] regarding adjuvant therapy in PTC tumors <2 cm diameter provided convincing data regarding a role for RRA in improving postoperative outcome in PTC patients with AJCC pT1 tumors, especially those pT1b tumors with diameters of 11–20 mm. We suggested [49] that if a prospective trial was to be designed to answer this question, it would likely involve "low risk" (e.g., with MACIS scores <6) tumors in patients aged 21 years or older, with surgically curable T1 disease (i.e., neither T4 nor M1) completely resected by initial successful BLR.

In the prospective retrospective study that we presented, [49] our aim was to define outcome in a cohort of 765 adult (aged 21 or older) patients with MACIS <6 pT1M0 PTC treated during the 35 years after the introduction of RRA and before the current era of ultrasound-guided neck nodal biopsies, recombinant human TSH-stimulated thyroglobulin (Tg) testing and near-routine central compartment neck nodal dissection. The 765 patients (545F; 220M) underwent BLR during 1950–1985 for tumors that were completely resected and were neither locally invasive at initial neck exploration nor distant spread at initial presentation.

Median patient age in this 1950–1985 cohort was 45 years (range 21–72), mean tumor size 12 mm (49% <11 mm); 24% were multicentric and 30% node-positive. Mean follow-up was 27 years (longest 55); 23% for >35 years. One hundred and seventy (22%) received RRA. 35-year occurrence rates for CSM, local recurrence (LR), regional nodal metastases (RNM),

and distant metastases (DM) were 1.1, 2.2, 5.0, and 1.6%, respectively. Comparable rates for Group A (n = 375 PTM with pT1a tumors <11 mm) were 0.6, 1.8, 4.5, and 0.5%. For Group B (n = 390 pT1b tumors of 11–20 mm diameter), rates were higher at 1.6, 4.3, 5.5, and 2.6%, respectively. RRA's impact was assessed by comparing survival to each of these four endpoints in patients undergoing BLR alone versus those receiving BLR + RRA within 18 postoperative months. The 35-year CSM rates in Groups A and B were after BLR 0.6 and 1.6% and after BLR + RRA insignificantly different ($p > 0.75$). Similarly, survival rates to LR, RNM, and DM were no different in ablated patients than after BLR alone in both Groups A ($p > 0.07$) and B ($p > 0.33$).

It was our principal conclusion [49] from this study that the results confirmed the excellent prognosis of AJCC pT1 tumors treated by BLR and did not identify a significant reduction in either mortality or recurrence rates in those patients with T1 PTC tumors selected for RRA.

Question 3: If RRA Is Ineffective in Reducing Mortality and Recurrence in PTC Patients with MACIS Scores <6, Should We Be Using RRA Selectively to Treat Only the Minority of Patients with High-Risk PTC, Who Have MACIS Scores of 6 or More?

In an attempt to quantify the influence of RRA on outcome in low-risk PTC after adequate initial surgery, we performed in 2002 [25] and again in 2006 [50] analyses on 1163 MACIS low-risk PTC (scores <6) patients, who had undergone NT or TT during 1970–2000 for tumors confined to the neck that were completely excised at initial neck exploration. 498 (43%) of these patients had RRA within 6 months of the initial surgery. Those who received RRA were more likely to have had NNM at presentation ($p < 0.001$). Of 636 node-negative patients, 195 (31%) received RRA. However, of 527 node-positive patients, 303 (57%) were ablated.

At 20 postoperative years, the CSM rate for the surgery alone patients was 0.4%, and for the NT/TT and RRA group, it was insignificantly different at 0.6% ($p = 0.64$). At 20 years, the TR rate was actually significantly higher in the ablated group (14% vs. 9%; $p = 0.008$), likely reflecting the tendency to more readily ablate node-positive patients. When the patients were divided into node-negative and node-positive groups, there were no statistically significant differences in outcome (CSM and TR) between those having surgery alone and those who also received postoperative RRA. Interestingly, there were no deaths from PTC in the 636 node-negative cases and only two in the node-positive group.

For the node-negative patients, the 20-year TR rates were 3.4% after surgery alone and 4.3% after surgery and RRA ($p = 0.80$). For the node-positive group, who clearly had much higher TR rates, the CSM rates at 20 years were 1.2% after surgery alone and 0.9% after RRA ($p = 0.99$). The 20-year TR rates only differed by 0.4%, being 19.5% for surgery alone and 19.9% for surgery and RRA ($p = 0.66$). Clearly, it was our 2006 conclusion [50] that RRA did not significantly improve the outcome (either CSM or TR) in low-risk (MACIS scores <6) PTC patients previously treated with initial NT or TT with curative intent. This conclusion obviously became a pivotal part of our Mayo policy [51] for managing patients with low-risk PTC published in 2007.

As we prepared for this chapter and were working on updated outcome results from our eight-decade Mayo PTC cohort, we considered it relevant to extend the years of our MACIS <6 cohort a further 14 years to encompass those low-risk PTC patients who were surgically treated definitively, with or without RRA, in the years of 2001–2014. This added a further 911 patients to

a new total cohort of 2074 adult MACIS <6 patients, of whom 760 (37%) underwent RRA within 6 months of NT or TT with curative intent. The principal details of the 20-year CSM and TR rates are included in the accompanying Table 17.1.

Table 17.1 Lack of influence of RRA on outcome in 2074 MACIS <6 low-risk PTC patients (without distant metastases) treated at Mayo during 1970–2014 by NT/TT with complete tumor excision

Low risk	20-Year mortality		20-Year recurrence	
(MACIS < 6) 1970–2014	NT/TT alone	NT/TT and RRA	NT/TT alone	NT/TT and RRA
All patients (%) (n = 2074)	0.3	0.7	8.7	18.2
	P = 0.09		P < 0.001	
Node-negative (%) (n = 1159)	0	0.5	3.9	4.6
	P = 0.11		P = 0.34	
Node-positive (%) (n = 915)	1.0	0.9	19.1	26.3
	P = 0.53		P = 0.08	

Figure 17.4 illustrates the differences in TR over 20 postoperative years between ablated and not ablated patients in the entire study cohort of 2074 low-risk PTC patients (left panel), the 1159 node-negative cases (middle panel) and the 915 node-positive patients (right panel). As expected, in the node-positive patients, most recurrences (83%) were situated in regional neck nodes. There were no significant differences between the ablated and the not ablated groups in terms of either local recurrences (p = 0.34) or distant metastases (p = 0.49), generally considered [3, 32] to be postoperative events associated with an increased risk of CSM. Interestingly, the recurrence rate in regional nodes was insignificantly higher (p = 0.05) in the 496 ablated patients, and this was felt to be attributable to significantly higher numbers of NNM found in those patients selected for RRA. The cumulative recurrence rates over 20 postoperative years in the 915 node-positive cases for all three anatomic locations

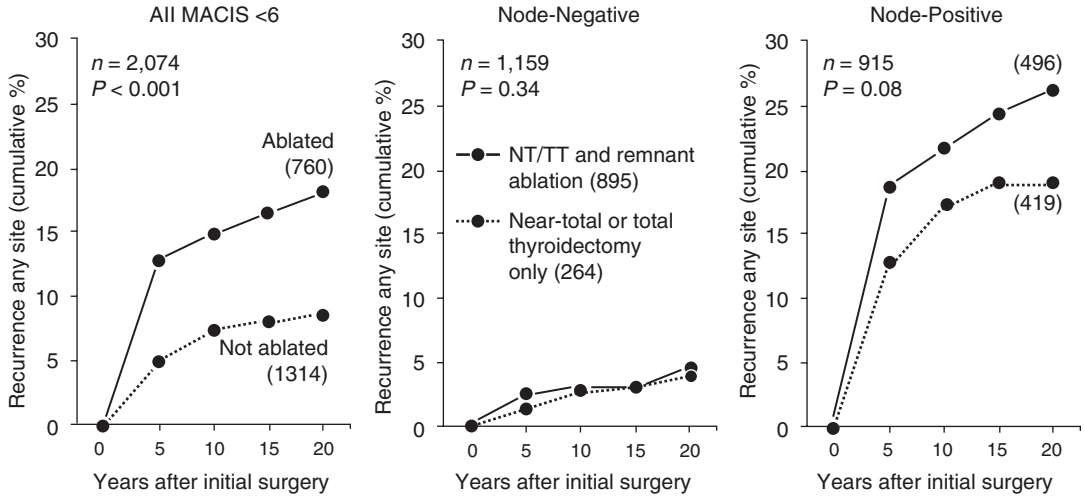

Fig. 17.4 Influence of RRA on tumor recurrence (any site) over 20 postoperative years in 2074 MACIS <6 PTC patients, who had no distant metastases and had undergone complete tumor resection after initial potentially curative surgery with NT/TT during the 35-year period of 1970–2014 (*left panel*), in 1159 pN0 node-negative patients (*middle panel*) and in 915 pN1 node-positive patients (*right panel*). Recurrence rates were higher (p < 0.001) in ablated patients (*left panel*), but were insignificantly different (p = NS) in either node-negative (*middle panel*) or node-positive patients (*right panel*)

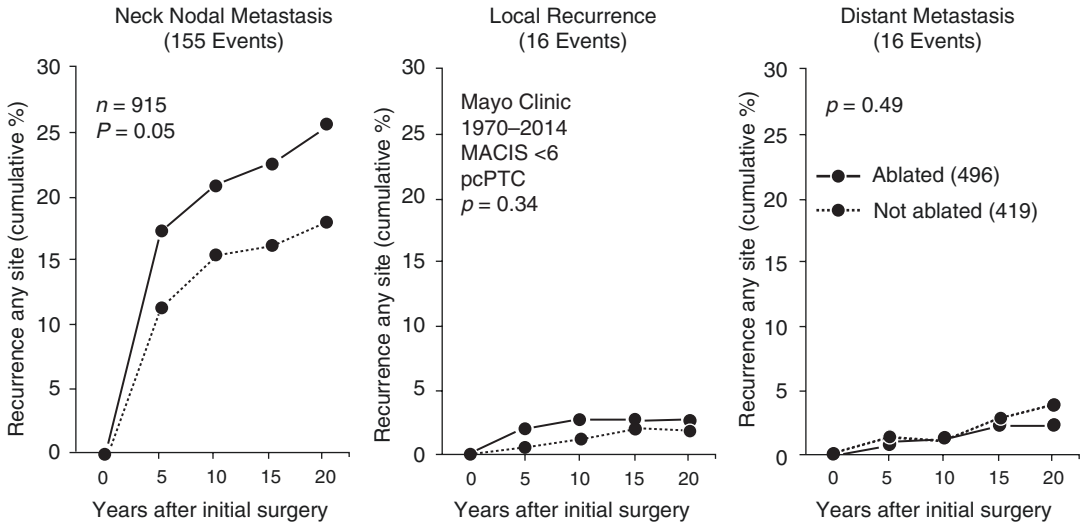

Fig. 17.5 Lack of influence of RRA administered within 6 postoperative months, when compared to NT/TT + RRA, in 915 potentially curable MACIS <6 node-positive PTC patients consecutively treated at Mayo during 1970–2014 on rates of cumulative tumor recurrence at regional (*left panel*), local (*middle panel*), and distant sites (*right panel*)

(regional, local, and distant) are illustrated in Fig. 17.5.

The results of these two studies defining the lack of impact of RRA on outcome in MACIS <6 low-risk PTC have helped convince us that RRA can probably be avoided in, not just the 68% of PTC patients who have pT1 tumors but also the 84% who have MACIS scores <6 and have tumors localized to the neck and having complete primary tumor excision at initial definitive surgery.

Era of Systematic Reviews and Meta-Analyses

That remarkable source of knowledge, Wikipedia, informs us that "conceptually, a meta-analysis uses a statistical approach to combine the results from multiple studies in an effort to increase power (over individual studies), improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree." Given the rancor expressed in the past 30 years over the vexed question of the efficacy of RRA in low-risk PTC, it is not perhaps surprising that multiple authors have jumped at the chance of "resolving uncertainty when reports disagree."

Mayo-trained Anna Sawka started this type of study in 2002–2003, while she was working at McMaster University in Hamilton, Ontario. She began by screening 1543 unique references and ended up by studying in great detail those 23 references [27] that "met all inclusion criteria," one of them from Mayo [25]. Her conclusion [27] from a systematic review of the 1966–2002 literature was that "the effectiveness of RAI ablation decreasing recurrence and possible mortality in low-risk patients with well differentiated thyroid carcinoma, although suspected, cannot be definitively verified by summarizing the current body of observational patient data." She expressed the opinion [27] that "only a long-term randomized controlled trial may definitely resolve this issue" and concluded that "in the meantime, the decision for RAI ablation must be individualized, based on the risk profile of the patient, as well as patient and physician preference, while balancing the risk and benefit of such therapy."

Four years later, Sawka published [26] an "updated systematic review" which included data from 20 studies from the original review [27], the original review itself, and seven newer studies from 2002 to 2007. Again, she was unable to identify any long-term randomized controlling trials examining outcomes after RRA; she therefore restricted her review to observational data. Her conclusion in 2007 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 WDTC." She observed [26] that "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. The current reality is that decision making about RRA in early stage thyroid carcinoma is a complex, evolving issue and long term higher quality evidence is needed to inform future clinical practice."

In a more recent systematic analysis of the 1966–2008 peer-reviewed literature, published in 2010, Sacks [52] from Cedars-Sinai 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 were less conclusive." On the basis of her analysis, she recommended the adoption of a risk group categorization, based on AJCC TNM staging and the MACIS score, and proposed a management guideline based on a patient's risk: very low, low, moderate, and high. Her 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 RAI treatment, and therefore we recommend against postoperative RAI in these cases."

Finally, in 2015, an Italian systematic review [53] by a group of investigators from Rome and led by Cooper, the lead author of the 2006 [47] and 2009 [54] ATA Guidelines, concluded that, when compared to earlier meta-analyses [26, 52] of literature until 2007–2008, "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." They expressed hope that the two presently ongoing European prospective randomized trials (the French Estimabl2 study and the British IoN study) will "provide valuable data to inform this issue." They recommended that "an undetectable serum Tg, especially in a high-sensitivity Tg assay, and negative neck US 6–12 months after surgery should enable many low risk and intermediate risk patients to be categorized as being 'free of disease', despite not having undergone RRA," thereby supporting a position remarkably close to that proposed in the 2007 description of the current Mayo management [51] of patients with low-risk PTC.

Evolution of Management Guidelines During 1997–2016

In the first AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma [55] published in 1997, it was stated that "RRA is used to complete the initial therapy in a patient whose FCDC has been completely resected—that is, when no gross residual disease is reported at the conclusion of the primary neck exploration. RRA is a procedure that is offered to patients who have undergone "potentially curative" surgical treatment and should not be confused with RAI therapy, in which larger administrated doses of I-131 are used in an attempt to destroy persistent neck disease or distant metastatic lesions." In the section under the heading of "adjuvant therapy," it was stated that "other investigators, however, have not advocated RRA in low-risk PTC patients because of lack of evidence of improved

outcome. The issue of RRA in low-risk patients remains unsettled; a case-by-case decision is recommended, guided by clinical judgement and experience."

In 2006, the ATA Taskforce stated in their management guidelines [47] that the reported advantage of reducing tumor recurrence and cause-specific mortality in PTC "appears to be restricted to patients with larger tumors (>1.5 cm) or with residual disease after surgery, while lower-risk patients do not show evidence for benefit". However, rather than advocating a selective use of RRA for only higher-risk patients, the ATA recommended [47] with a B rating that RRA be performed in "patients with stage III and IV disease (AJCC 6th edition), all patients with stage II disease younger than age 45 years (Any T Any N M1), most patients with stage II disease 45 years or older (T2NOM0) and selected patients with stage I disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion and/or more aggressive histologies."

Under these 2006 ATA Guidelines, of patients having an initial NT or TT with curative intent, it was estimated [56] that approximately 70% of PTC patients would be submitted to RRA "although all current staging and scoring systems would identify the high-risk minority, who could potentially benefit from RRA to be only about 15–20% of PTC cases." Hay [56] suggested that "since neither the Mayo [25, 50] nor the NTCTCSG [57] data can demonstrate improvement in either tumor recurrence or cause-specific mortality rates with RRA in low-risk patients, such an escalation of aggressive postoperative adjunctive therapy can hardly be justified. Indeed, one must seriously doubt whether the proposed increased use of RRA and the increasing evaluation of rhTSH-stimulated thyroglobulin levels will either be cost-effective or lead in future years to improved outcome results for patients with PTC, the commonest endocrine cancer."

Only 3 years later, Cooper and his ATA Taskforce issued Revised Guidelines [54] and here it was recognized that "the first dose of RAI may also be considered adjuvant therapy because of the potential tumoricidal effect on persistent thyroid cancer cells." In Recommendation 32, the strength of evidence for the efficacy of RRA in reducing CSM and TR, with the exception of M1 disease, varied from B to E. On the basis of reviewed contemporary data, the ATA advised that CSM and TR rates were likely after RRA to be reduced only in patients of 45 years or older with pT3 disease or in any patient with pT4 or M1 disease. They therefore recommended RRA "for all patients with known distant metastases, gross extrathyroid invasion of the tumor regardless of size, or primary tumor size >4 cm." For sure, they did not recommend RRA for either intrathyroidal PTM (pT1a) or patients without evidence of NNM at presentation. They advised, with a C recommendation rating, a "selective use" of RRA in patients "with 1–4 cm thyroid cancers confined to the thyroid who have documented lymph node metastases, or other high risk features when the combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer."

A novel feature of the 2009 Guidelines [54] was the description of a "three-level stratification" system for the assessment of the risk of recurrence. Using this risk adapted paradigm, [58] the ATA defined high-risk patients as those with distant metastases, incomplete tumor resection, or gross extrathyroid invasion (otherwise known to Mayo authors as the "MCI of MACIS" [33]) and leaving behind the continuous [33] variables of **A**ge and **S**ize to the AJCC/IUCC staging! ATA low-risk patients had complete tumor resection, no "local or distant metastases," and "no tumor invasion of locoregional tissues or structures." Also, low-risk tumors could not have aggressive histology, vascular invasion, or RAI uptake outside of the thyroid bed on a first post-treatment whole-body RAI scan: all in all, a rather complex definition for low-risk PTC! Those who were neither high nor low were termed intermediate and had to have "any of the following": (1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery, (2) cervical lymph node metastases or ^{131}I

uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation, or (3) tumor with aggressive histology or vascular invasion.

Citing the reference of Tuttle and Leboeuf [58] from 2008, the ATA Guidelines stated that "appropriate management requires an ongoing assessment of the risk of recurrence and the risk of disease-specific mortality as new data are obtained during follow-up." The 2009 Guidelines [54] did, however, during Dr. Mazzaferri's last term on the task force, stop short of including the risk adapted paradigm of Tuttle [58] into one of its 80 recommendations. Seven years later, the 2015 Guidelines [2] had now adopted the "three-level stratification" scheme; Recommendation 48 announced that "the 2009 ATA Initial Risk Stratification System is recommended for DTC patients treated with thyroidectomy, based on its utility in predicting risk of disease recurrence and/or persistence." In the Modified Initial Risk Stratification System outlined in Fig. 4 of the paper, the three tiers are somewhat simplified in that high risk implies gross invasion, incomplete resection and distant spread, low risk encompasses "intrathyroidal DTC," and intermediate risk includes "aggressive histology, minor extrathyroidal extension (MEE) and vascular invasion." A novel feature was the inclusion of the number and size of NNM in the risk classification. Thus, low risk was 5 or less NNM of <0.2 cm, intermediate risk was >5 involved NNM (0.2–3 cm), while high-risk included NNM with maximal diameters exceeding 3 cm. The ATA writing group did admit that "the incremental benefit of adding these specific prognostic variables to the 2009 Initial Risk Stratification system has not been established," perhaps implying that we will not have to wait another 7 years to see how these novel variables perform.

Current Role of RAI

In the Recommendation 51 of the 2015 Guidelines [2] which defined the role of RAI in the primary management of DTC, the recommendations depended largely on the novel ATA postoperative risk stratification. Thus, RAI adjuvant therapy was routinely recommended for ATA high risk, RRA was not routinely recommended for ATA low risk, and RAI adjuvant therapy "should be considered" for ATA intermediate risk. The ATA writers went on to clarify this position by stating that "given that the ATA risk classification is relatively new and the majority of studies examining therapeutic efficacy of postsurgical RAI remnant ablation or therapy (adjuvant or for persistent disease) have been performed with attention to traditional mortality risk stratification systems such as AJCC/TNM system, MACIS, NTCTCSG or others…we have also categorized some of the results of our evidence review according to the AJCC/TNM risk of mortality stratification system because this system has been in use longer in our field."

If one carefully examines Table 14 on page 56 of the 2015 Guidelines, [2] the most important columns relate to the bodies of evidence suggesting that RAI improves CSM or TR rates and the answer to the question: "Postsurgical RAI indicated?" Patients with tumors 1 cm or less (uni- or multifocal), who are pT1a N0 or NX M0 or MX, are the only subset with No No No, and patients with gross ETE or with distant metastases are the only examples of Yes Yes Yes. Patients with tumor size >1–4 cm (T1b or T2 N0 or NX M0 or MX) are not routinely advised to have RAI, but such therapy may be considered if microscopy reveals either aggressive histology or vascular invasion. With larger but node-negative tumors >4 cm diameter (T3N0MO), the data is conflicting and the ATA advises consideration of other adverse features. When it comes to MEE or T1-3 N1a or N1b disease, there is apparently no evidence that RAI reduces CSM and conflicting data regarding TR rates; thus, the ATA advises "Consider—Generally favored due to higher risk of recurrent disease." As if this situation was not complicated enough, the ATA writers state that "in addition to standard clinicopathologic features, local factors such as the quality of preoperative and postoperative US evaluations, availability and quality of Tg measurements, experience of the operating surgeon, and clinical concerns of the local disease management team may also be considerations in postoperative RAI decision-making."

Conclusions

So, having considered how RRA came to become an established part of PTC management, having looked at the results of multiple Mayo studies demonstrating the lack of efficacy of RRA in low-risk PTC, and having reviewed the meta-analyses of our international colleagues and the management guidelines of our specialist societies, where do we personally stand on the issue of RRA in the management of patients with PTC? As we stated in our introductory remarks, we are in no doubt that RAI therapy should be used regularly in the setting of patients who have incomplete tumor resection with gross residual disease and those who present with or subsequently develop distant spread with demonstrable uptake of RAI in metastatic lesions. We are convinced that RRA should not be employed in the management of PTM (pT1a) and indeed remain unconvinced that tumors between 11 and 20 mm, presently considered as pT1b, benefit from RRA after a potentially curative surgery.

Our recently published study of pT3 PTC [59] and the work of others seem likely to result in the AJCC in the near future downstaging PTC patients with "microscopic ETE" [2], and, therefore, such patients should not, in our minds, be given RRA. We worry somewhat about the ATA recommendation for routine RAI in PTC patients of any tumor size with gross ETE (ATA high-risk T4 AnyN AnyM). In that particular setting, we would think that application of the MACIS score could be highly relevant and that, in this circumstance, patients with local invasion, who have had complete surgery and lack distant spread, may not of necessity undergo RAI therapy.

We are in no doubt that the development of so-called recurrence in NNM is highly dependent on the nodal status of the patient at presentation, and it will be of interest in future years to see whether the neck nodal recurrence rate will significantly fall as nodal dissection [60] becomes a near routine part of the initial surgical approach to PTC. Our own experience with ultrasound-guided percutaneous ethanol ablation (UPEA) [61–63] of persistent or recurrent NNM has led us to believe that RRA rarely completely eliminates neck nodal burden, despite the "scintigraphic slate" being wiped clean [38]. Accordingly, in the setting [50, 51] of a young woman with stage I node-positive PTC who has had an initial surgery consisting of NT or TT with central compartment exploration [64, 65] and has at 3–6 postoperative months both a negative neck ultrasound scan and a near undetectable serum Tg on thyroxine suppressive therapy, one doubts whether such a patient would obtain further benefit from RRA. Clearly, the size and number [66] of NNM may prove to be relevant in this consideration and the role of extranodal extension [2] in the NNM of PTC requires much more study. However, the presence of NNM at presentation in a PTC patient would not, in our assessment, lead in 2017 at Mayo to RRA being "generally favored." Rather, such a patient would be followed up with regular neck US and serum Tg measurements, and if further NNM were to be found, surgery or UPEA at our institution would generally be favored over RAI therapy.

In general, we are delighted that successive ATA Management Guidelines are moving toward a more selective use of RRA in PTC management. As stated above, we favor RAI for distant metastases and persistent disease after incomplete primary tumor resection. We are enthusiasts for the MACIS prognostic scoring system and have now in our institution almost a quarter century of experience in staging and scoring PTC patients in the postoperative period and using such information to help make decisions as to the need, or not, for RRA. Currently, we typically consider RRA in the minority (about 15%) of PTC patients who have a MACIS score of 6 or more. Naturally, clinical experience, individual bias, prior medical training, and patient circumstances may lead us currently to be ablating a slightly larger fraction of our PTC patients, perhaps closer to 25–30%, in any 1 year. However, repeated

analysis of our eight-decade cohort data leads us to believe that as we have avoided RRA in the management of our MACIS <6 patients with low-risk PTC, we have not seen any worsening of either CSM or TR rates, and we have been encouraged by the improving outcome that we have seen in our high-risk PTC patients with MACIS scores of 6+. We optimistically hope that these trends continue and that the 2020 ATA Management Guidelines for treating adult PTC patients will be even more conservative.

Conflict of Interest None of the authors state that they have any conflicts of interest.

References

1. Ain KB. Radioiodine-remnant ablation in low-risk differentiated thyroid cancer: pros. Endocrine. 2015;50(1):61–6.
2. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133.
3. McConahey WM, Hay ID, Woolner LB, van Heerden JA, Taylor WF. Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. Mayo Clin Proc. 1986;61(12):978–96.
4. Sitges-Serra A. Low-risk papillary thyroid cancer: times are changing. Expert Rev Endocrinol Metab. 2014;9(1):9–18.
5. Baumann E. Ueber das normale Vorkommen von Jod im Thierkörper. Ztschr f Physiol Chem. 1895–1896; XXI(319).
6. Kendall EC. The isolation in crystalline form of the compound which occurs in the thyroid. Its chemical nature and physiologic activity. JAMA. 1915; LXIV(25):2042–3.
7. Joliot F, Curie I. Artificial production of a new kind of radio-element. Nature. 1934;133:201–2.
8. Fermi E. Radioactivity induced by neutron bombardment. Nature. 1934;133(3368):757.
9. Hertz S, Roberts A, Means JH, Evans RD. Radioactive iodine as an indicator in thyroid physiology. Iodine collection by normal and hyperplastic thyroids in rabbits. Am J Phys. 1940;128:565–76.
10. Sawin CT, Becker DV. Radioiodine and the treatment of hyperthyroidism: the early history. Thyroid. 1997; 7(2):163–76.
11. Hamilton JG, Soley MH, Eichorn KB. Deposition of radioactive iodine in human thyroid tissue. Univ Calif Publ Pharmacol. 1940;1:339–68.
12. Hamilton JG. The use of radioactive tracers in biology and medicine. Radiology. 1942;39:541–72.
13. Keston AS, Ball RP, Frantz VK, Palmer WW. Storage of radioactive iodine in a metastasis from thyroid carcinoma. Science. 1942;95(2466):362–3.
14. Frantz VK, Ball RP, Keston AS, Palmer WW. Thyroid carcinoma with metastases: studied with radioactive iodine. Ann Surg. 1944;119(5):668–89.
15. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. J Am Med Assoc. 1946;132(14):838–47.
16. Rawson RW, Marinelli LD, et al. The effect of total thyroidectomy on the function of metastatic thyroid cancer. J Clin Endocrinol Metab. 1948;8(10):826–41.
17. Cassen B, Reed CW, et al. Low-rate alpha scintillation counter. Nucleonics. 1949;5(4):55–9.
18. Cassen B, Reed CW, Curtis L. A sensitive directional gamma-ray detector. Nucleonics. 1950;78:5–6.
19. Blahd WH, Nordyke RA, Bauer FK. Radioactive iodine (I 131) in the postoperative treatment of thyroid cancer. Cancer. 1960;13:745–56.
20. Varma VM, Beierwaltes WH, Nofal MM, Nishiyama RH, Copp JE. Treatment of thyroid cancer. Death rates after surgery and after surgery followed by sodium iodide I-131. JAMA. 1970;214(8):1437–42.
21. Krishnamurthy GT, Blahd WH. Radioiodine I-131 therapy in the management of thyroid cancer. A prospective study. Cancer. 1977;40(1):195–202.
22. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med. 1981;70(3):511–8.
23. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. Medicine (Baltimore). 1977;56(3):171–96.
24. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery. 1987;102(6):1088–95.
25. Hay ID, McConahey WM, Goellner JR. Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. Trans Am Clin Climatol Assoc. 2002;113:241–60.
26. Sawka AM, Brierley JD, Tsang RW, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin N Am. 2008;37(2):457–80, x.
27. Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC. Clinical review 170: a systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation

for well-differentiated thyroid cancer. J Clin Endocrinol Metab. 2004;89(8):3668–76.
28. Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control. 2000;7(3):229–39.
29. Byar DP, Green SB, Dor P, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. Eur J Cancer. 1979;15(8):1033–41.
30. Hermanek P, Sobin LH. TNM classification of malignant tumours. 4th fully rev. ed. Berlin, New York: Springer; 1987. No. xviii.
31. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery. 1988;104(6):947–53.
32. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab. 1990;71(2):414–24.
33. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993;114(6):1050–7; discussion 1057–8.
34. http://www.thyroid.org/thyroid-cancer-staging-calculator/
35. British Thyroid Association, Royal College of Physicians. Guidelines for the management of thyroid cancer. In: Perros P, editor. 2nd ed. 2007. http://www.btf-thyroid.org/images/documents/thyroid_cancer_guidelines_2007.pdf
36. Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol. 2014;81(Suppl 1):1–122.
37. Snyder J, Gorman C, Scanlon P. Thyroid remnant ablation: questionable pursuit of an ill-defined goal. J Nucl Med. 1983;24(8):659–65.
38. Sisson JC. Applying the radioactive eraser: I-131 to ablate normal thyroid tissue in patients from whom thyroid cancer has been resected. J Nucl Med. 1983;24(8):743–5.
39. Hay ID. Papillary thyroid carcinoma. Endocrinol Metab Clin N Am. 1990;19(3):545–76.
40. DeGroot LJ. Long-term impact of initial and surgical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97(6):499–500.
41. Grebe SK, Hay ID. Follicular cell-derived thyroid carcinomas. Cancer Treat Res. 1997;89:91–140.
42. Wartofsky L, Sherman SI, Gopal J, Schlumberger M, Hay ID. The use of radioactive iodine in patients with papillary and follicular thyroid cancer. J Clin Endocrinol Metab. 1998;83(12):4195–203.
43. Morris DM, Boyle PJ, Stidley CA, Altobelli KK, Parnell T, Key C. Localized well-differentiated thyroid carcinoma: survival analysis of prognostic factors and (131)I therapy. Ann Surg Oncol. 1998;5(4):329–37.
44. Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery. 1992;112(6):1139–46; discussion 1146–37.
45. Hay ID, Hutchinson ME, Gonzalez-Losada T, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery. 2008;144(6):980–7; discussion 987–8.
46. Hay ID, Johnson TR, Kaggal S, Reinalda MS, et al. Papillary thyroid microcarcinoma in adult patients: how does outcome and morbidity after an initial unilateral thyroid lobectomy compare to a more conventional approach of near-Total or Total thyroidectomy and selective radioactive iodine remnant Abalation? Endocrine Society's 98th Annual Meeting and Expo. Boston: Endocrine Society; 2016:OR22-24.
47. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2006;16(2):109–42.
48. Rosario PW, Borges MA, Valadao MM, et al. Is adjuvant therapy useful in patients with papillary carcinoma smaller than 2 cm? Thyroid. 2007;17(12):1225–8.
49. Hay ID, Gonzalez-Losada T, Wiseman GA, et al. Radioiodine remnant ablation (RRA) did not improve postoperative outcome in 765 adult patients with surgically curable MACIS <6 AJCC T1 papillary thyroid carcinomas (PTC), whether they were microcarcinomas (0.1–1.0 cm) or with larger (1.1–2.0 cm) diameters. 80th Annual Meeting of the American Thyroid Association. Vol. 19. Palm Beach: Mary Ann Liebert; 2009:S-71.
50. Hay ID. Selective use of radioactive iodine in the postoperative management of patients with papillary and follicular thyroid carcinoma. J Surg Oncol. 2006;94(8):692–700.
51. Hay ID. Management of patients with low-risk papillary thyroid carcinoma. Endocr Pract. 2007;13(5):521–33.
52. Sacks W, Fung CH, Chang JT, Waxman A, Braunstein GD. The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. Thyroid. 2010;20(11):1235–45.
53. Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. J Clin Endocrinol Metab. 2015;100(5):1748–61.
54. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167–214.
55. Hay ID, Feld S, Garcia M, et al. AACE clinical practice guidelines for the management of thyroid carcinoma. Endocrinol Pract. 1997;3:60–71.
56. Hay ID. Papillary thyroid cancer in the twenty first century: a mid-Atlantic perspective one year after the publication of the 2006 ATA Clinical Management Guidelines. Hot Thyroidol. 2007;3:1–14.

57. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid. 2006;16(12):1229–42.
58. Tuttle RM, Leboeuf R. Follow up approaches in thyroid cancer: a risk adapted paradigm. Endocrinol Metab Clin N Am. 2008;37(2):419–35, ix-x.
59. Hay ID, Johnson TR, Thompson GB, Sebo TJ, Reinalda MS. Minimal extrathyroid extension in papillary thyroid carcinoma does not result in increased rates of either cause-specific mortality or postoperative tumor recurrence. Surgery. 2016;159(1):11–9.
60. Hay ID. Managing patients with a preoperative diagnosis of AJCC/UICC stage I (T1N0M0) papillary thyroid carcinoma: East versus West, whose policy is best? World J Surg. 2010;34(6):1291–3.
61. Hay ID, Charboneau JW. The coming of age of ultrasound-guided percutaneous ethanol ablation of selected neck nodal metastases in well-differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2011;96(9):2717–20.
62. Hay ID, Lee RA, Davidge-Pitts C, Reading CC, Charboneau JW. Long-term outcome of ultrasound-guided percutaneous ethanol ablation of selected "recurrent" neck nodal metastases in 25 patients with TNM stages III or IVA papillary thyroid carcinoma previously treated by surgery and 131I therapy. Surgery. 2013;154(6):1448–54; discussion 1454–45.
63. Lewis BD, Hay ID, Charboneau JW, McIver B, Reading CC, Goellner JR. Percutaneous ethanol injection for treatment of cervical lymph node metastases in patients with papillary thyroid carcinoma. AJR Am J Roentgenol. 2002;178(3):699–704.
64. Grant CS. Recurrence of papillary thyroid cancer after optimized surgery. Gland Surg. 2015;4(1):52–62.
65. Grant CS, Stulak JM, Thompson GB, Richards ML, Reading CC, Hay ID. Risks and adequacy of an optimized surgical approach to the primary surgical management of papillary thyroid carcinoma treated during 1999-2006. World J Surg. 2010;34(6):1239–46.
66. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22(11):1144–52.