Selective Use of Radioactive Iodine in the Postoperative Management of Patients With Papillary and Follicular Thyroid Carcinoma

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Radioiodine remnant ablation (RRA) was developed in the 1960s to “complete a thyroidectomy” in the initial management of papillary and follicular thyroid cancer. By the 1990s, it was claimed that RRA diminished recurrence rates in follicular cell-derived cancer (FCDC) patients and decreased the cause-specific mortality (CSM) in patients more than 40 years old at initial surgery. The international trend for the past decade has been towards routine RRA in most FCDC patients. Clinical guidelines have been produced by many societies, promoting such an aggressive stance. Since 1997, many papers have reported improved outcome in FCDC, when patients were subjected to RRA after bilateral lobar resection. However, during the same time-period, it has been recognized that most FCDC patients are truly at “low-risk” of developing life-threatening recurrences. Accordingly, it has been suggested that rational therapy selection should lead to restricting aggressive therapy to those “high-risk” FCDC patients, more predisposed to CSM. To date, no prospective controlled trials exist. Presently available outcome data is based on single institutional or multicenter retrospective studies. This article summarizes the available relevant reported data, and concludes that a selective use of RRA in the postoperative management of FCDC patients is rational, and should actually be encouraged.


Key Words: remnant ablation; differentiated thyroid cancer; postoperative radioiodine; cause-specific mortality; tumor recurrence; outcome prediction

INTRODUCTION

In the United States, papillary thyroid carcinoma (PTC) during the past three decades has accounted for between 80% [1] and 88% [2] of patients with thyroid malignancy. PTC is associated typically with a 20-year cause-specific mortality of only 5%, whereas in most recent studies, the less common follicular thyroid cancer (FTC) and Hurthle cell cancer (HCC) have higher 20-year mortality rates in the 15%–25% range [3]. Radioactive iodine (RAI) was first used to treat metastatic follicular cell-derived cancer (FCDC) in 1940 [1]. The concept of remnant ablation to “complete thyroidectomy” derives from the early 1960s, and by the late 1980s, it was reported to decrease postoperative recurrences, when compared with surgery and thyroid hormone suppression alone [4]. During 1997–2001, it was further claimed that radiiodine remnant ablation (RRA) effectively reduces recurrences of FCDC in all patients and decreases the mortality rate in patients more than age 40 years at the time of diagnosis [5,6].

During the past two decades, it has been increasingly recognized that between 70% and 88% of PTC patients may be classified at presentation as “low-risk” on the basis of prognostic factors established by multivariate analyses of large cohorts of treated patients [7–10]. PTC patients who are, at presentation, pTNM stages I or II, AMES low-risk, or have MACIS scores less than 6, enjoy a 1% cause-specific mortality (CSM) at 20 postoperative

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years. By contrast, the 12%–30% of patients classified as “high-risk” by pTNM, AMES, or MACIS, have CSM rates 25–40 times higher than the “low-risk” patients [7–10]. A logical extension of a belief in risk-group assignment in FCDC would naturally lead to an application of “rational therapy selection” in this commonest of endocrine malignancies [9,11–13]. Indeed, as Blake Cady has repeatedly emphasized, in the management of patients with low-risk PTC, the “punishment should fit the crime” [7,9]. Unfortunately, in the past decade this has not been the therapeutic trend.

Sadly, since 1996, many specialist societies in the United States and in Europe have published guidelines for the treatment of DTC, where it is recommended that almost all patients with FCDC more than 1 cm in diameter will receive radioactive iodine-131 for postoperative RRA [14–16]. It is claimed that such an aggressive management program will eliminate mortality and further reduce recurrence at local and distant sites. During this same time-period, it is noteworthy that few surgical centers in the United States have had the opportunity of comparing eras, where surgery and thyroid hormone therapy alone was usual (1950–1974), as opposed to the last quarter of the past century (1975–2000), where RRA was increasingly employed for FCDC therapy.

In the past 5 years, analysis has been completed on the outcome results of 2,512 PTC patients consecutively treated at the Mayo Clinic during the period from 1940 to 2000 [11,12]. During that period, encompassing more than six decades, there were two significant therapeutic trends (Fig. 1). The first was a change in surgical practice during 1940–1969 from unilateral lobectomy to bilateral lobar resection. The second trend was the increased use of radioactive iodine-131 for postoperative RRA [1]. It is claimed that such an aggressive management program will eliminate mortality and further reduce recurrence at local and distant sites. During this same time-period, it is noteworthy that few surgical centers in the United States have had the opportunity of comparing eras, where surgery and thyroid hormone therapy alone was usual (1950–1974), as opposed to the last quarter of the past century (1975–2000), where RRA was increasingly employed for FCDC therapy.

![Fig. 1. Trends in the (left panel) extent of initial surgery, and (right panel) the proportion of PTC patients having radiiodine remnant ablation after initial bilateral lobar resection at Mayo Clinic during 1940–2000.](image)

In this contribution for Seminars in Surgical Oncology the early history and more recent claims for efficacy of RRA will be described. A typical case of low-risk PTC will be presented, and the questions raised in the postoperative management will be addressed by evidence-based answers, derived from the results of recently completed Mayo outcome analyses. Thereafter, the recent results of large national and multicenter studies from Canada and the USA will be briefly discussed and placed in perspective.

**ORIGINS, EARLY CLAIMS, AND LATER DISCLAIMERS FOR REMNANT ABLATION**

In 1940, Hamilton and his UCSF associates first reported the uptake of RAI in a thyroid carcinoma [18], and by 1942 Keston described the first treatment of a patient’s iodophilic femoral metastasis with a 10 mCi therapeutic dose [19]. By 1960, Blahd and his UCLA colleagues had given 11 FCDC patients RAI to ablate postoperative remnant tissue in an attempt to “complete the thyroidectomy” [20]. At the Mayo Clinic, during 1950–1969, patients with PTC, who had either gross residual disease or initial distant metastases, regularly received postoperative RAI in therapeutic doses. However, of 568 PTC patients having initial potentially curative bilateral surgery during that 20-year period, only 19 (3%) received within 6 postoperative months a dose of RAI aimed at ablating the residual thyroid remnant [1]. In 1970, a group from the University of Michigan reported that 84 patients with FCDC, who were aged 40 years and older, and were treated with surgery followed by RAI, experienced a significantly lower mortality rate than 32 controls who had surgery alone [21]. However, in this report the extent of disease was not controlled and the so-called control group came from an earlier period (1933–1947) marked by less aggressive surgery [3].

Although RAI therapy is clearly indicated and often beneficial for patients with local or distant residual disease [22,23], the use of RRA, which has been defined as “the destruction of residual macroscopically normal thyroid tissue following surgical thyroidectomy” [24] in low-risk patients remains highly controversial. Less controversial is RRA in patients with high-risk PTC, who are more likely to benefit from RRA in terms of decreased disease progression and mortality [25]. The goals of RRA are said to be threefold: (1) to destroy any occult microscopic carcinoma cells within the thyroid remnant, (2) to facilitate RAI scanning for detection of recurrent or metastatic disease by destruction of remaining normal tissue, and (3) to improve the value of serum Tg as a tumor marker in follow-up [14]. In addition, the
use of a large amount of RAI for therapy allows for obtaining a postablative whole body scan (WBS) with increased sensitivity for persistent disease detection [26]. Mazzaferri and his US Air Force study of 1977 significantly influenced the worldwide treatment of PTC, and the implications of his message are still widely debated today. In 1977, he reported lower recurrence rates in 114 PTC patients receiving thyroid hormone and RAI therapy, when compared to 414 operated patients who received thyroid hormone alone [27]. However, on closer scrutiny of the data, in only 33 patients was RAI given merely to ablate residual thyroid tissue. The majority of the patients had either residual neck nodal disease after primary surgery or lung metastases. Yet, on the basis of the encouraging results reported in these 33 patients, postoperative management for thousands of PTC patients treated in the USA during the late 1970s was forever changed [1], leading to a dramatic upsurge in use of a large amount of RAI for therapy allows for obtaining a postablative whole body scan (WBS) with increased sensitivity for persistent disease detection [26].

In 1981, Mazzaferri reported no improvement in recurrence rates after RAI in 153 patients with small (<1.5 cm) primary tumors [28]. His 1987 report [29] showed significant differences in recurrence rates between those treated with RRA and thyroxine (9%) when compared to thyroxine only (17%). He reported in 1994 that 138 of his Ohio State University (OSU) stage 2 (intermediate-risk) or 3 (high-risk) patients with FCDC, treated by RRA, had a reduction in recurrence rates, when compared to patients treated with surgery and T4 only (30-year rates of 16% versus 38%), and had not one cancer-related death after RRA, significantly less than the 8% mortality rate seen in 802 patients not given RRA [30]. However, in only 138 of the 350 patients reported as treated with RAI, could this treatment be classified properly as remnant ablation [3]. These patients were combined for recurrence data, but the 138 RRA patients were analyzed separately for mortality.

In 1997, Mazzaferri further reported on 151 patients with FCDC, who had received RRA, and compared them to 755 who received thyroid hormone alone, and 98 who were given no postoperative therapy. All 1,004 patients had no apparent residual tumor after surgery. He reported that RRA “is effective in reducing recurrence of FCDC in patients of all ages and reduces the risk of death from thyroid carcinoma in patients > age 40 at the time of diagnosis.” This effect was not apparent in patients with isolated tumors smaller than 1.5 cm with no nodal metastases or extrathyroidal invasion [31]. He most recently reported on 230 FCDC patients who had received RRA, and found RRA was an independent variable that reduced cancer recurrence and death [32].

DeGroot et al. from the University of Chicago merely found a non-significant trend towards reduced recurrence for patients with tumors more than 1 cm in size, either confined to the thyroid or node-positive. Using a Cox model, they were unable to confirm any survival advantage for patients who received RRA. Using a chi square test, which is less rigorous, (since it only considers final outcome and does not factor in duration of observation), they found that patients with >1 cm intrathyroidal or node-positive tumors had a significantly reduced risk of recurrence and death, if treated with RRA [33]. Samaan and colleagues have also reported that RAI therapy is the most powerful prognostic indicator for increased disease-free interval and an important predictor of CSM [34]. A group from UCSF also reported improved recurrence rates after RRA, but could not demonstrate improved CSM rates in patients with PTNM stage greater than T1N0M0 [35].

By contrast, Simpson and his colleagues from Toronto in 1988 found no significant difference in recurrence rates or long-term cause-specific survival between patients who received RRA and those who did not, provided that the patients lacked microscopic or gross residual disease after surgical therapy [36]. Schlumberger and colleagues at the Institut Gustave-Roussy found similar results [37]. Sanders and Cady also reported from the Lahey Clinic that RAI therapy did not significantly improve survival in their AMES low-risk or high-risk FCDC patients [38]. A number of other studies published in the 1990s have also failed to confirm a survival benefit for patients treated with adjuvant RAI [3,39].

Overall, the presently available retrospective data describing the efficacy of RRA in PTC, especially in low-risk prognostic groups, is not convincing. Even a meta-analysis published in 2004 by Sawka and colleagues from Canada [40], attempting to define from currently published reports the effectiveness (or not) of RRA for well-differentiated FCDC, concluded that “the effectiveness of RAI ablation in decreasing recurrence and possible mortality in low-risk patients

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Fig. 2. Changing frequency of remnant ablation at Mayo Clinic during 1970–2000 in 1,423 PTC patients, without initial distant metastases, who underwent RRA within 6 months of potentially curative bilateral resection.
with well-differentiated thyroid carcinoma, although suspected, cannot be definitively verified by summarizing the current body of observational patient data.”

Data from 1990 to 2002 Mayo-derived PTC studies certainly do not lend support to an enthusiasm for routine RRA in most patients with FCDC. In 1990, it was reported that, of 946 Mayo patients similar in stage to Mazzaferri 1987 reported patients, 220 had received RRA within 6 months of bilateral potentially curative surgery. The recurrence rate was 9.6% after surgery alone and 13.3% in those who were ablated (P = 0.06). CSM rates at 10 years were insignificantly different at 2% for the surgery alone group and 3% for the ablated patients [1]. Both groups received similar T4 therapy and were of similar age (mean age 43 vs. 41). In 1997, Grebe and Hay reported that 439 ablated OSU stages 2 or 3 FCDC patients, having their initial treatment at Mayo, had comparable recurrence (17% vs. 19%; P = 0.89) and CSM rates (5.9% vs. 7.8%; P = 0.43), when compared to 1,103 matched patients treated with only surgery and T4 [3]. These results markedly disagreed with the results of Mazzaferri 1987 PTC report [29] and his 1994 FCDC report [30]. It is very probable that the Mayo recurrence rates, which are considerably lower than those reported by other institutions, may be related to the extent and completeness of surgical excision typically performed at the Mayo Clinic [11–13].

Additionally, Mayo authors [41] have shown that in papillary thyroid microcarcinoma (tumor size 1 cm or less), 45 ablated node-positive patients did not have significantly fewer locoregional recurrences than 108 non-ablated node-positive cases, the 10-year rates being 9% and 12%, respectively (P = 0.99). Also, in 1992 it was reported to the Endocrine Society that 92 ablated node-positive PTC patients with small tumors (1.5 cm or less) had near-identical locoregional recurrence rates (P = 0.59) to 194 non-ablated cases [42]. More recently, we reported identical recurrence and cause-specific mortality rates in 371 ablated AMES low-risk PTC cases and in 1,267 non-ablated cases [43].

In 2002 we presented to the Society of Nuclear Medicine the results of a study of 1,205 PTC patients with primary tumors smaller than 16 mm diameter (mean age 45 years, median tumor size 1 cm), consecutively treated at Mayo during 1940–2000, and followed for up to 56 years, median 14 years. After bilateral lobar resection (BLR), the risks of local or distant spread were not decreased by RRA, and the 227 ablated patients actually had higher rates of nodal recurrence (NR) than the 833 non-ablated (P < 0.001). When NR rates were studied in the 367 node-positive patients, the 20-year rate of 15% after RRA and BLR was insignificantly different (P = 0.23) from the 13% seen after only BLR. For node-negative patients treated by BLR, the 20-year NR rate of 1% was not improved by RRA. We concluded that routine RRA, after BLR with apparently complete tumor excision, is no longer justifiable in the management of patients who present with small (<16 mm diameter) PTC [44].

It should also be recognized that RRA has the potential for significant side effects. Short-term side effects include radiation thyroiditis (up to 70%), sialadenitis (up to 10%) which may become chronic, odynophagia, herpes zoster, leukopenia, endocrine and reproductive testicular and ovarian failure (mostly reversible), and radiation cystitis. Long-term carcinogenic risks may theoretically include leukemia, stomach, breast, and bladder cancer [3]. Aldinger and associates from M. D. Anderson in 1978 reported an incidence of undifferentiated thyroid cancer in 4% of 243 patients treated with RAI [45]. More recent concerns have been raised in both Europe and the United States regarding the possibility of RAI-treated patients later developing radiation-induced second malignancies, potentially resulting in increased overall non-thyroid cancer-related mortality [46–48]. Another additional consideration, particularly in an under-insured young PTC patient, could be that the financial cost and inconvenience may also outweigh any potential benefit in a low-risk patient.

CHALLENGES POSED IN THE POSTOP MANAGEMENT OF LOW-RISK PTC

Consider the example of a 25-year-old female presenting in the postpartum period with a 1.5 cm palpable nodule in her right thyroid lobe. A fine needle aspiration biopsy reveals cells that are highly suspicious for a PTC. A preoperative ultrasound scan reveals no suspicious lateral adenopathy, but does show tiny microcalcified hypervascular nodules (3–6 mm) in the left lobe, as well as a second smaller (7 mm) non-palpable suspicious nodule within the right lobe. Neck exploration is advised. A near-total thyroidectomy and central compartment exploration is performed. Careful examination of the thyroid and the level VI nodes reveals a bilateral multicentric histologic grade 1 PTC, which has involved two of five removed right central nodes. There was at surgery no evidence of extrathyroidal invasion of adjacent tissues, and tumor excision was complete, with no evidence of gross residual disease at the end of the surgical procedure. The patient is at the time of surgery both clinically and biochemically euthyroid, with a sensitive TSH of 1.5 mU/L, and a preoperative basal thyroglobulin of 22 ng/ml.

The patient recognizes that she will have to take thyroid hormone daily for the rest of her life. She is prepared to put up with that minor hardship, and also is willing to be followed annually by a local endocrinologist.
in future years. She has, however, significant misgivings about being given a dose of RAI for postoperative remnant ablation. In counseling this young woman, what data can a clinician turn to, in an attempt to allow her to make a proper decision about adjunctive RAI? She wants to know what will be her likely outcome, and whether the proposed RRA can really reduce her chance of dying from PTC or having her cancer recur in future years.

Before providing advice to such a young woman with low-risk PTC, it might be relevant to give consideration to the likely “natural history” of her operated disease. This patient with PTC is 25 years old (<45 years) and has no evidence of distant spread to our knowledge. She has a 1.5 cm (T1) tumor and has evidence of regional nodal involvement (N1) in the central compartment (level VI). Her tumor does not exhibit local (extra-thyroid) invasion, and the tumor was apparently completely excised, with negative postoperative margins obtained. Her pTNM stage would be stage I (T1N1aMx) by the most recent AJCC classification [49]. By the criteria of AGES, AMES, and MACIS [50], she would be classified with an AGES score of <4, as an AMES low-risk category, and with a MACIS score of <6. It would be predicted that she would likely enjoy a 99% 20-year cause-specific survival from her PTC [1], and one might estimate that her chance of having a recurrent neck node discovered within 20 years of primary surgery would approximate 20% [51]. Conventionally, she would be treated postoperatively with thyroid hormone suppressive therapy. The mainstay of her postoperative imaging over the years would likely be high-resolution ultrasound examination of her neck [52]. Any recurrent tumor would likely arise in the neck, particularly on the side of her dominant nodule, perhaps related to the already known involvement of the right central compartment [1]. The controversy in this case relates to the role of postoperative radioiodine remnant ablation (RRA) in preventing the development of loco regionally recurrent PTC [1,12].

The concept of using remnant ablation with RAI to ‘complete a thyroidectomy’ has existed since at least 1960, when Blahd and his colleagues at UCLA [20] described their first decade’s experience with radioisotope therapy and concluded that “a realistic appraisal of the I-131 treatment of thyroid cancer is extremely difficult. The unfortunate muddling of therapeutic modalities and the remarkable longevity of many of these patients for the most part frustrates any forthright analysis.” By 1984, Beierwaltes from Michigan stated, based on their institutional experience of ablating 511 patients with I-131, that “there is no question today that we should ablate normal thyroid tissue as a part of the treatment of well-differentiated thyroid cancer” [53].

By contrast, Gorman from Mayo Clinic in 1983 emphasized that “numerous studies support the use of radioiodine in the treatment of metastatic disease; but extrapolation to the practice of remnant ablation does not follow” [54]. After he demonstrated that, in patients with PTC, ablative therapy directed to postsurgical remnants “reduced visible I-131 uptake to zero or nearly zero, but did not protect against tumor recurrence,” he described the practice of RRA as “the questionable pursuit of an ill-defined goal” [54]. In the same issue of that journal, Sisson [4] from Ann Arbor observed that “scintigrams have come to be worshiped as portents and as arbiters of proper treatment.” From a review of the then available literature, which he described as “a statistical labyrinth,” he concluded that “the aggregate of evidence does not convincingly demonstrate that ablation of small remnants—and especially those remote from the primary tumor—lowers the rate of recurrent cancer. Bearing these concepts in mind, each physician must decide from incomplete knowledge whether to use I-131 as a radioactive eraser.” Sisson proposed [4] in 1983 that “to ablate or not to ablate is a question that will haunt us for some time to come.” Even a recently published meta-analysis could not find convincing evidence for routine RRA in low-risk PTC and suggested that only a full-scale prospective controlled trial would truly establish answers to Sisson haunting question [40].

If one were to design a prospective controlled trial to evaluate the role of RRA, one would wish to exclude patients with initial distant metastases and those who had undergone incomplete surgical resection of primary tumor, that is, restrict entry to patients undergoing potentially curative surgery. One would wish the patients to be matched for age, sex, extent of initial disease, and histology. Ideally, both groups should have a standard primary operation, preferably near-total (NT) or total thyroidectomy (TT), performed by specialist surgeons. To qualify as ablative therapy, the RAI would have to be administered for uptake confined to the thyroid bed soon after the operation, typically within 3–6 months. Those patients, who would be randomly allocated to the surgery-only group, should be treated identically with regards to thyroxine suppressive therapy and followed in a similar manner to the ablated group by the same group of physicians. Follow-up data would require scrupulous evaluation with multivariate analyses. Obviously, such a prospective trial has not yet been planned. Indeed, Wong and colleagues [55] have suggested that for 45-year-old women “each arm of the trial would require nearly 4,000 patients to detect a 10% reduction in mortality after 25 years... If one in every ten patients was enrolled in such a study, enrollment would take 10 years, and results would be available after 35 years.” A more recent Dutch study would suggest that the number of patients needed to show a 30% reduction in disease recurrence would be less than 600 [56].
In the absence of such prospective data, the best available published data relates to retrospective studies of operated patients, who have comparable risk factors at presentation. The Mayo-derived AGES [57], and MACIS classifications [3,8] and Cady AMES risk-group categories [7] have, in our opinion, allowed us to make some conclusions in PTC patient cohorts about the impact of initial extent of surgical resection in outcome results. In an attempt to quantify the influence of RRA on outcome after adequate initial surgery, we recently performed analyses on 1,163 MACIS low-risk (scores <6) patients, who had undergone NT or TT during 1970–2000 for tumors confined to the neck and completely excised at initial neck exploration. These 1,163 patients were operated in a standard manner by a small group of specialized Mayo surgeons, who had recognized expertise in endocrine surgery. The preoperative investigations and the postoperative care were provided by Mayo staff endocrinologists, who also prescribed and monitored the patients’ postoperative thyroxine therapy [12].

During 1970–2000, 875 PTC patients at Mayo-Rochester underwent initial NT, while 502 had TT. Of these, 848 (97%) of the NT group and 472 (94%) of the TT group had no distant spread at presentation and had complete tumor excision at initial surgery. Of these 1,320 patients in the potentially curable NT/TT group, 1,163 (88%) were at presentation classified as having MACIS scores of <6. Four hundred ninety eight (43%) of these low-risk patients had RRA within 6 months of the initial surgery. Those who received RRA were more likely to have had positive neck nodes at presentation (P < 0.001). Of 636 node-negative patients, 195 (31%) additionally had RRA performed. However, of 527 node-positive patients, 303 (57%) were ablated.

Looking carefully at the 1,163 MACIS <6 PTC patients undergoing NT/TT at Mayo-Rochester, the majority (57%) had only surgery, but 498 (43%) had RRA within 6 postoperative months. At 20 postoperative years the cause-specific mortality (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 tumor recurrence (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 (Table I). Interestingly, there were no deaths from PTC in the 636 node-negative cases and only 2 in the node-positive group. For the node-negative patients (Fig. 3), 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 (Fig. 4) only differed by 0.4%, being 19.5% for surgery alone and 19.9% for surgery and RRA (P = 0.66). Thus, we have concluded that RRA did not significantly improve the outcome (either CSM or TR) in low-risk (MACIS <6) patients previously treated with initial NT or TT.

### Table I. Lack of Influence of RRA on Outcome in 1,163 MACIS Low-Risk (Scores <6) Patients (Without Distant Metastases) Treated During 1970–2000 at Mayo by Near-Total (NT) or Total Thyroidectomy (TT)

<table>
<thead>
<tr>
<th>Low-risk (MACIS &lt;6)</th>
<th>20-year mortality</th>
<th>20-year recurrence</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>NT/T alone</td>
<td>NT/TT and RRA</td>
</tr>
<tr>
<td>All patients (1,163)</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>P-value</td>
<td>P = 0.64</td>
<td></td>
</tr>
<tr>
<td>Node-negative (636)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-positive (527)</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>P-value</td>
<td>P = 0.99</td>
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Fig. 3. Survival to first tumor recurrence during 20 postoperative years in 636 node-negative MACIS low-risk (scores <6) patients treated during 1970–2000. All 636 initially underwent either near-total or total thyroidectomy; 195 (31%) additionally had RRA performed.
In August 2004, commenting on the meta-analysis of Sawka [40], Mazzaferri stated that “the benefit of remnant ablation remains unclear in low-risk patients treated with bilateral thyroidectomy and thyroid hormone suppression of TSH” [58]. Sawka herself concluded that “the incremental benefit of remnant ablation in low-risk patients treated with bilateral thyroidectomy and thyroid hormone suppressive therapy is unclear” [40].

Moving from the general to the particular, should one be recommending RRA for this young woman? Because of the compelling data from Mayo just presented, wherein RRA was not efficacious in reducing recurrence rates in PTC patients who had tumors 1 cm or less [41], or diameter <16 mm [44], or classified as AMES low-risk [43] or with MACIS scores <6 [12], I for one would not be recommending that this patient be submitted to RRA.

**FURTHER DOUBT AND INCREASINGLY AGGRESSIVE CLINICAL GUIDELINES**

Of relevance, a recently completed study from Toronto of 729 FCDC patients, treated at Princess Margaret Hospital during 1958–1998, found in a multivariate analysis that there was no significant improvement in cause-specific survival with “more aggressive treatment (administration of RAI and/or RT).” Moreover, in low-risk patients (AJCC stage I <45 yrs) there was no apparent benefit from RAI. They therefore concluded that “RAI may not be required in young patients under the age of 45 years without distant metastases” [59]. In their discussion they stated [58] that “the results of this study are in contrast to the findings of Mazzaferri and Jhiang...but are, however, more in keeping with the reports from the Mayo Clinic in which Hay et al. were unable to demonstrate any improvement in recurrence or cause-specific mortality rates after RAI ablation in either the 636 node-positive or the 527 node-negative low-risk papillary thyroid cancer patients (defined as MACIS scores less than 6).”

The National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) was founded in 1986 and has for the past 20 years maintained a registry contributed to by 11 North American institutions, and prospectively following a large non-randomized cohort of patients with FCDC, with the object of assessing the effects of initial and longitudinal management on their outcomes. By June 2001 2,936 patients were registered and the results of outcome following initial therapy were presented to the 2nd Annual Spring Meeting (2005) of the American Thyroid Association. After two decades of data entry and very detailed analysis, the NTCTCSG has now come to the remarkable conclusion that “no treatment modality, including lack of radioactive iodine, was associated with altered survival in stage I patients”! Moreover, Jonklaas and colleagues [60] “were unable to show any impact, positive or negative, of specific therapies in stage I patients.” They have concluded that “postoperative RAI therapy does not provide significant benefit in stage I patients, and could even be harmful,” and have suggested that “further evaluation of the potential risks and benefits of treatment in stage I patients is, therefore, indicated.”

Recently, a European consensus report recommended that “postsurgical use of RAI should be selective, given that uncertainty persists concerning the benefits in decreasing recurrence rates and cause-specific mortality” [61]. This group, derived from 12 European countries, also advised that “remnant ablation should be restricted to patients with incomplete surgical excision or poor prognostic factors for recurrence or death.” This European consensus report, perhaps leading in the future to a more selective use on the Continent for remnant ablation, contrasts with the recommendations of the National Thyroid Cancer Guidelines Group, formed during 2000 under the auspices of the British Thyroid Association (BTA). This group advised in 2002 that “for most patients with tumors greater than 1 cm in diameter, radioactive iodine ablation of the thyroid remnant should be carried out following total thyroidectomy” [15].

The recently published American Thyroid Association (ATA) Guidelines have recommended RRA for stages III and IV disease, all patients with stage II disease 45 years or older, and selected patients with stage I disease, “especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies” [16]. This relative lack of selection, advised by both the BTA and the ATA is, I believe, unfortunate, and will likely in future years subject many young stage I PTC patients on both sides of the Atlantic to I-131 therapy, that is unlikely either to
improve their already excellent prognosis or completely eliminate persistent neck nodal metastases.

In contrast to other leading endocrine centers, we at Mayo have since 1994 adopted a selective approach to RRA, and tend to restrict its use to patients with high-risk (MACIS score 6+) PTC or those, now rare, patients with FTC or HCC. Additionally, rather that routinely favoring ‘blind’ I-131 administration of large doses with subsequent post-therapy whole body scans, we at Mayo still prefer to perform in selected high-risk patients quantification of uptake with a postoperative whole body I-123 scan, to customize the administered dose, and to follow with further diagnostic scanning usually at 3–6 months.

We have not been impressed that the information obtained from post-therapy scans regularly provides data that influences subsequent therapy or results in a reassignment of tumor TNM stage [62]. We are, however, very impressed that patients with typical (low-risk) PTC have a very high chance of ‘cure’ after adequate initial surgery and only levothyroxine therapy, and we would caution others that our 25-year cause-specific survival rate of 100% for 636 node-negative MACIS <6 PTC patients treated by near-total or total thyroidectomy alone cannot be improved by remnant ablation [12].

REFERENCES

2. Davies L, Welch HG: Increasing incidence of thyroid cancer is due to an increase in detection of small papillary thyroid carcinomas. JAMA 2006;295:2164–2167.

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