

25th Annual Meeting of AACE, Orlando, Florida

Thursday, May 26, 2016: Meet the Experts T22 & T53

“Point/Counterpoint: Radioactive Iodine in PTC; To Use or Not to Use...That is the Question”

Why Prof. ID Hay has favored selective use of remnant ablation in PTC during 1986-2016

As a founding member of AACE, I look back warmly to my addressing the first AACE audience during a plenary session in Orlando at the 1962 annual meeting and, naturally, speaking on a similar theme to what we are now discussing at a new venue in the same city, some 25 years later! Also, I vividly remember being “invited” (or bullied) by Dr Felt two decades ago to single-handedly, and with these same two fingers on my keyboard, write the first AACE Guidelines for Thyroid Cancer Management (ref 14 in this syllabus contribution). And, naturally, how I vividly recall going with Stan (resplendent in his Texas Stetson!) to NYC, as I hit the NPR stations and Stan charmed the TV studios with his introduction of the Thyroid Awareness week and the importance of the “Neck Check”! And how could I possibly forget the attitudes of our academic colleagues in 1992, when they were very doubtful of any card-carrying endo doc who would wish to line up alongside the Floridian private practitioners and Mayo’s Hodgson and Gharib!! Perhaps the awarding of the FACE and the recognition of those worthy of a MACE made the difference in attitude...or was it the power of pharma?! But I digress...and you need your CME!

A. Historical Introduction: 1946-83

So, after the Hiroshima and Nagasaki bombs were dropped and the Manhattan Project curtailed, Seidlin (1) reported the uptake of radioiodine in a metastatic thyroid cancer and by 1970, Varma (2) from Michigan was claiming that I-131 administered postoperatively saved lives from thyroid cancer. In 1977, Bland’s group (3) from UCLA, reported that most patients worldwide, with follicular cell-derived thyroid cancer (FCDC), were being considered possibly eligible for postoperative radioactive iodine (RAI). His group may have been the first to consider radioiodine remnant ablation (RRA) to represent a ‘completion of thyroidectomy’. In 1977 and, again in 1981, Mazzaferri and colleagues (4,5) described outcome results on a USAF cohort treated at Wilford Hall AFB, where optimal outcomes, in terms of recurrence-free survival, were achieved when papillary thyroid cancer (PTC) patients postoperatively had both thyroid hormone suppressive therapy and RRA. The propagation of these results at national and international meetings resulted in millions of FCDC patients worldwide receiving, in a non-selective fashion, RRA. And few stood up in the first few years to question the efficacy of this novel therapy. At Mayo Clinic, where, for the first 20 years (1950-69) after the FDA approved I-131 for therapeutic purposes, only 3% of PTC patients had RRA, but by 1985-9 there had been a 20-fold increase in RRA rates (11, 17, 18).

B. Mayo Contributions: 1983-2009

In 1983, Colum Gorman (6) questioned whether RRA possibly represented in PTC a "questionable pursuit of an unattainable goal", as neck nodal 'recurrences' were not apparently prevented by RRA. In an accompanying Journal of Nuclear Medicine editorial, Sisson (7), who had worked closely at Michigan with Beierwaltes (2), dared to suggest that "wiping the scintigraphic slate clean" did not necessarily eliminate the possibility of future recurrence and advised that, in the absence of convincing improved outcome results, "to ablate or not to ablate is a question that will haunt us for some time to come". In 1986, in a study of 856 PTC patients conservatively treated during 1946-70, McConahey, Hay and colleagues (8) concluded with a statement: "whether routine remnant ablation can substantially improve the already excellent results of surgical treatment remains, in our assessment, to be proved."

By 1990, Hay (11) went ahead to directly criticize the results from Ohio State and Chicago (9, 10) but in 1994, deGroot (12) observed that "Mazzaferri and co-workers provided, nearly two decades ago, the first powerful support for the role of radioiodine treatment in reducing recurrences and deaths in differentiated thyroid cancer...more recent studies by DeGroot and colleagues, and Samaan and co-workers demonstrated, in a careful analysis, stratifying by extent of disease, that both more curative surgery (lobectomy plus subtotal or near-total thyroidectomy) and radioactive iodine treatment reduce the number of recurrences and deaths. Hay and co-workers have thrown their support behind more extensive surgery, but have not yet supported routine radioactive iodine ablation".

By 1997, Hay (13) again reported starkly contrasting outcome results from Mazzaferri, and raised concerns regarding efficacy of RRA in reducing locoregional recurrence rates (LRR) in most PTC patients. By 1998, Hay was writing with Schlumberger in JCEM on a "selective approach' to RAI use in FCDTC (16). In 2002 (17, 18) he described temporal trends at Mayo in initial therapy for PTC during 6 decades, and implied that increasing

RRA use was not leading to improved outcomes. In 2006 (21), he defined a program of selective use of RAI in managing patients with FCDTC, and, in 2007 (24), at the AAES Annual Meeting in Seattle, he described a comprehensive management program for patients with low-risk PTC (MACIS scores <6), that included an adequate initial surgery but avoided the use of RRA.

At Mayo, since 1935, 1/3 of PTC tumors have been 1 cm or less (pT1a microcancers) and a further 1/3 (pT1b) had tumor diameters between 11 and 20mm. In 2008, Hay described (27) a lack of efficacy of RRA in improving mortality and recurrence rates in papillary thyroid microcancers (PTM), and in 2009, he reported (29), at the Annual ATA Meeting in Palm Beach, a similar lack of influence of RRA after near-total/total thyroidectomy in improving outcome in patients with pT1b tumors between 11 and 20 mm in diameter. Since 2002 (17, 18, 22) he has repeatedly reported that patients with MACIS < 6 PTC, representing 84% of all papillary cancers, do not have reduced mortality or recurrence rates when RRA follows near-total or total thyroidectomy with complete tumor resection and without any evidence of postoperative gross residual disease.

Naturally, he was delighted to read in 2005 that our colleagues at Princess Margaret Hospital in Toronto, Canada (21) had found that, in a study of DTC patients seen at their institution over a 40 year period (1958-98) the use of RAI in low-risk patients was not associated with improved LRR. They had concluded that their findings were in contrast to those of Mazzaferri (4, 5), but were “in keeping with the reports from the Mayo Clinic in which Hay et al (17, 18) 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 PTC patients (defined as MACIS scores less than 6).”

In an expert review published in 2014 (38) and entitled “Low-risk papillary thyroid cancer: times are changing”, Sitges-Serra, an endocrine surgeon from Barcelona, noted that “even the MSK Center group (32, 37) -- that has fully supported the ATA Guidelines

-- has recently acknowledged that following appropriate surgical management, the majority of patients with low-risk disease, and even some patients with more advanced-stage (pT3) tumors or regional metastases, have low rates of recurrence and high rates of survival when managed without radioiodine ablation”.

C. Era of Systematic Reviews and Meta-Analyses

Sawka (19) started this type of study and concluded from the 1966-2002 literature 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”. In a second “updated systematic review” (27), she concluded 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”. In a more recent systematic analysis of the 1966-2008 peer-reviewed literature, published in 2010, Sacks (31) from Cedars-Sinai concluded “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.” Finally, in 2015, an Italian systematic review (40) led by Cooper, the lead author of the 2006 and 2009 ATA Guidelines (23, 29), concluded that, when compared to earlier meta-analyses (27, 31) of literature until 2007-8, “our review of the more recent literature (2008-14) 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.”

D. Evolution of Management Guidelines during 1997-2016

In the first AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma (14) published in 1997, RRA was defined as “the destruction of residual macroscopically normal thyroid tissue after surgical thyroidectomy” and it was stated that “RRA is used to complete the initial therapy in a patient whose FCDC had 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 with FCDC who have undergone “potentially curative” surgical treatment and should not be confused with RAI therapy, in which larger administered 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 (14) 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 (23) that the reported advantage of reducing tumor recurrence and cause-specific mortality in PTC “appears to be restricted to patients with larger tumors (>1.5cm) 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 with a B-rating (R32) that RRA be performed in “patients with stage II 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 (T2N0M)), and selected patients with stage I disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies (23).”

Under these 2006 guidelines, of patients having an initial near-total or total thyroidectomy with curative intent, it was estimated (24) 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 to 20% of PTC cases.” Hay suggested that “since neither the Mayo (18, 22) nor the NTCTCSG (39) 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.”

In the recently published ATA Management Guidelines (41) recommendation 51, on the basis of low-quality evidence, states that “RRA is not routinely recommended after thyroidectomy for ATA low-risk DTC patients” and “RAI adjuvant therapy should be considered after total thyroidectomy in ATA intermediate-risk level DTC patients.” A strong recommendation, based on moderate-quality evidence, was that “RAI adjuvant therapy is routinely recommended after total thyroidectomy for ATA high risk DTC patients.” These high risk patients, in whom post-surgical RAI would be indicated would be defined as either being “any size, gross ETE” (pT4 any N Any M) or with “distant metastases” (any T Any N M1). It was also recognized that “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.” Interesting times ahead!

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