



Postoperative Radioactive Iodine for Differentiated Thyroid Cancer: A Historical Perspective

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Abstract

Radioactive iodine has been used in differentiated thyroid cancer for postoperative thyroid remnant ablation for several decades, yet its indications remain controversial. Because the potential administration of postoperative RAI plays an important role in surgical decision-making, understanding the current indications for postoperative RAI is critical in the global management of differentiated thyroid cancer. This review examines the changing indications for postoperative radioiodine from its introduction to the current guidelines.

Introduction

The postoperative administration of Radioactive Iodine I-131 (RAI) has been an important component of therapy for Differentiated Thyroid Cancer (DTC) over the past several decades. Its uses include remnant ablation, adjuvant therapy, and therapy for persistent disease. Remnant ablation refers to the use of RAI to destroy any remaining normal thyroid tissue to improve the detection of recurrence using thyroglobulin measurement or whole-body RAI scanning. Adjuvant therapy refers to the use of RAI to destroy any microscopic deposits of disease that were not detected and removed surgically, with the goal of decreasing recurrence rates and improving overall survival [1]. For the purpose of this review, we will focus on postoperative RAI for these two indications, i.e. the use of postoperative RAI when all macroscopic evidence of disease has been removed surgically. RAI was introduced for the treatment of hyperthyroidism in 1941 and first used to treat metastatic thyroid cancer in 1948. By the 1960s, use of RAI for this purpose was well established [2]. In the 1970s, use of RAI for remnant ablation gained popularity after several studies demonstrated that it resulted in significant reduction in recurrence rates. However, the indications for postoperative RAI were (and remain) controversial [3]. Some centers used remnant ablation for all patients with DTC, while other centers used specific criteria to identify patients for ablation, such as tumors greater than a certain size, or any tumor with invasion or metastases. Because the ability to use postoperative RAI is dependent on the extent of surgery, it is often cited in the debate of lobectomy vs. total thyroidectomy for the surgical management of DTC. Therefore, understanding the current indications for postoperative RAI is crucial to the overall management of patients with DTC. The purpose of this review is to examine the historical indications for postoperative RAI and see how they have changed through time.

Initial Indications

Evaluation of the effectiveness of radioiodine ablation is dependent on accurate prediction of both the risk of death from thyroid cancer and the risk of recurrence. In the 1970s and 1980s many postoperative risk classifications of thyroid cancer patients were proposed, including TNM (American Joint Committee on Cancer and International Union Against Cancer), EORTC (European Organization for Research on Treatment of Cancer) [3], AMES (Lahey Clinic), AGES/MACIS (Mayo Clinic) and those from Mazzaferri (US Air Force) and DeGroot (University of Chicago). They used various combinations of risk factors including patient age, sex and size of the primary tumor plus the presence or absence of extra thyroidal invasion, multifocality, lymph node metastases and distant metastases to place patients in low and high risk categories [4]. In an analysis of 1,500 patients from the Mayo Clinic, Hay found that the percent of patients in the low risk category varied from 78% in the EORTC classification to 87.7% in the AMES classification [5]. This discrepancy may help explain the conflicting results of early large retrospective studies. Many groups supported the aggressive use of postoperative RAI after their data showed significant improvement in both recurrence and survival rates. In two influential papers, Mazzaferri used risk factors to analyze the

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effect of ablation on recurrence and death from thyroid cancer using data from the United States Air Force Central Tumor Registry. After an analysis of 576 patients in 1981, they advocated for a combination of total or near-total thyroidectomy, excision of metastatic lymph nodes, postoperative RAI, and lifelong TSH suppression for all papillary thyroid cancers >1.5cm and those with invasion of the thyroid capsule, multifocal cancer, or metastases [6]. That study was followed in 1994 with an analysis of a larger cohort of 1,355 patients with longer followup and found that postoperative treatment with radioiodine cut both the recurrence and death rates in half compared with thyroid hormone treatment alone [7]. However this benefit was not seen in their low risk category, defined as a primary tumor <1.5 cm and absence of any other risk factors. DeGroot et al. [6] analyzed 269 patients with papillary thyroid cancer over a twelve year follow up period. Their data showed decreased recurrence and mortality rates in Class I and II patients (intrathyroidal with positive cervical nodes, but no invasion or distant metastases) with tumors >1 cm when treated with subtotal thyroidectomy and postoperative RAI [8]. In contrast, other studies were skeptical about the efficacy of postoperative RAI. Its increasing use for papillary thyroid cancer was reported by Hay et al. [8]. at the Mayo Clinic in 2002 [9]. By the 1980s and 1990s, nearly half of papillary thyroid cancer patients at the Mayo Clinic were undergoing total or near-total thyroidectomy follow by RAI remnant ablation. However, this trend toward postoperative RAI did not result in any improvement in recurrence rates or cause-specific mortality in either their low risk or high risk patients. Nevertheless, Hay et al [10]. recommended RAI remnant ablation for high risk patients. As a result of these and similar studies, postoperative administration of radioiodine for ablation increased steadily. Data from the National Cancer Database documented that between 1990 and 2008, the use of postoperative RAI ablation increased from 40% to 56%. In the subset of patients with tumors <1.0 cm, ablation increased from 30% to 40% [10].

Evolution of Guidelines

Many changes have occurred in the population of papillary thyroid cancer patients over the last several decades. Increasingly sensitive diagnostic procedures such as ultrasound and ultrasound-guided fine needle aspiration of suspicious nodules have produced a large population of patients with small, low risk cancers. Improved surgical techniques are now capable of removing virtually all normal thyroid tissue. Pathologists have improved their reports to include more complete information about high-risk variants and risk factors such as the size of nodal metastases. Molecular studies have provided new insights into tumor behavior. Ultrasound, sensitive thyroglobulin assays, and recombinant human TSH have allowed us to detect tiny recurrences that might never become clinically apparent. Observational studies have questioned the need for surgery in papillary micro carcinomas and for total thyroidectomy in solitary papillary carcinomas in the 1-2 cm range. In response to these changes there has been significant evolution in the guidelines for postoperative management. Many guidelines have been published addressing the postoperative management of thyroid cancer. In 1996, the Standard of Care Committee of the American Thyroid Association (ATA) published their first set of guidelines for the management of DTC. The guidelines included recommendations on the use of surgery, radioiodine therapy, and levothyroxine therapy, based upon the current literature. Those guidelines were then updated in 2006, 2009, and 2015. We will concentrate our review on those published by the American Thyroid Association because they appear to be the

most influential and best show the evolution of treatment since the 1990s. The first set of guidelines published by the American Thyroid Association in 1996 consisted of only eight pages. It acknowledged the controversial use of postoperative RAI for low risk patients, but recommended only that "the decision to use radioiodine should be individualized and based on clinical experience" [11]. For the 2006 update, which had expanded to forty pages, the ATA Guidelines adopted the American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) TNM staging system as guidelines for RAI [12]. They recommended postoperative RAI for all patients <45 years with distant metastases (stage II) and all patients >45 years with tumors >2 cm, invasion beyond the thyroid capsule, metastatic lymph nodes, or distant metastases (stages II-IV). The 2009 ATA Guidelines acknowledged the fact the AJCC/UICC staging system was developed to predict mortality risk rather than recurrence and was less than ideal for guiding decisions regarding ablation. They therefore introduced a new staging system, the ATA Initial Risk Stratification System [13]. The new ATA Initial Risk Stratification System divided patients into three groups: low risk, intermediate risk, and high risk. They also cited a study done by the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) which prospectively followed 2936 patients in a multi-institutional registry for a median follow up of 3 years [14]. The results of the NTCTCSG study suggested that NTCTCSG stage I and stage II patients (patients <45 years without distant metastases and patients >45 years with primary tumor <4 cm, and without extra thyroidal extension or nodal metastases) showed no improvement in survival with postoperative RAI administration. Based upon the new risk stratification system and the NTCTCSG study, the 2009 ATA Guidelines did not recommend postoperative RAI for low risk patients (<1 cm without high risk features) and recommended selective use of postoperative RAI for intermediate risk patients (primary tumor 1-4cm, minimal extra thyroidal extension, and positive cervical lymph nodes).

The 2015 ATA Guidelines, now 133 pages in length, provide a more nuanced approach to postoperative management. Both the AJCC/UICC and ATA Initial Risk Stratification Systems are retained, including the categories of low, intermediate, and high risk, and they now include an estimate of the risk of structural recurrence for each individual risk factor and for combinations of risk factors. New risk factors included are the extent of lymph node involvement, mutational status, and/or the degree of vascular invasion in follicular thyroid cancer [1]. This was based upon newer studies that attempted to further characterize the role of primary tumor size, size and number of metastatic lymph nodes, and extent of extra nodal extension [15-18]. Reviewed the literature regarding the significance of size and number of metastatic lymph nodes on recurrence rates, with differentiation made between clinically positive nodes (cN1) and pathologically positive nodes (pN1). They concluded that patients with clinically positive nodes were associated with a higher recurrence rate, whereas pathologically positive nodes were associated with a higher recurrence rate if they numbered >5 or were >3cm in largest dimension. Extra nodal extension was also associated with increased recurrence rates. Based upon these new studies, the ATA concluded that postoperative RAI may not be indicated for tumors 1-4cm in size without high risk features, or those with microscopic lymph node metastases (pN1 <5 and <3 cm in largest dimension). Even with these latest guidelines considerable uncertainty remains. The table regarding decision making on postoperative RAI includes eight categories that are based on both the ATA and AJCC/UICC staging. Only for three are the recommendations definitive: patients with tumors <1 cm

(micro carcinomas) without any other risk factors should not receive postoperative RAI, and those with gross extra thyroidal extension or distant metastases should. For the rest, evidence on disease-specific survival and/or disease-free survival is felt to be conflicting, so the recommendation is to consider radioiodine, basing the decision on additional factors.

Conclusion

While the use of postoperative RAI has increased in popularity since its introduction, its benefits remain controversial. The initial large retrospective studies that looked at the use of postoperative RAI for thyroid remnant ablation indicated improvements in both disease recurrence and cause-specific mortality rates. This contributed to the widespread use of postoperative RAI. However, even the studies that showed the most promising results failed to demonstrate benefit in the low risk differentiated thyroid cancer. This may be in part due to the already very low rates of recurrence and mortality in this group. The features of DTC that constitute low risk are still being defined. Recent prospective studies have questioned the benefit of postoperative RAI in low risk and some intermediate risk patients, and as a result, the appropriate cutoff value for tumor size, the degree of invasion, and the size and number of nodal metastases are now being re-evaluated. We currently find ourselves in an era in which the indications for postoperative RAI are waning. Adding consideration for the risks and complications of RAI administration, the impetus toward using postoperative RAI less frequently may continue for the foreseeable future [19,20]. Postoperative RAI will continue to play an important role in the management of differentiated thyroid cancer. When used in combination with surgical removal of all detectable disease, postoperative RAI can destroy microscopic deposits of tumor and facilitate early recognition of recurrence. Given that the extent of surgery for DTC is often guided by the potential administration of postoperative RAI, the changing indications for postoperative RAI will have an important impact on our surgical management of DTC in the future.

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