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Radioactive iodine ablation post differentiated thyroid cancer surgery: an analysis of use and impact of the American Thyroid Association guidelines

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Abstract

Background

The 2009 American Thyroid Association (ATA) three-tiered risk stratification, and its updated version in 2015, provided clearer guidance on the use of radioactive iodine (RAI) ablation in differentiated thyroid cancer (DTC) patients. This study examines the impact of these guidelines on RAI use in our institution.

Methods

Patients diagnosed with DTC during three different time periods (group 1:2002-2006, group 2:2010-2014, and group 3:2017-18) were identified and risk stratified according to the ATA guidelines. RAI use and extent of surgery was compared between the three groups. Categorical variables were analysed using Fisher's exact (2x2) and Chi-square (>2x2) tests.

Results

A total of 415 patients were included (group 1=88, group 2=215, group 3=112). The proportion of patients having total thyroidectomy were 84.6%, 84.7 % and 69.6% in groups 1, 2 and 3, respectively (p=0.003). Central lymph node dissection was significantly higher in the more contemporary groups compared to group 1 (9.1% vs 41.9% vs 64.3%, p<0.001). Overall, fewer patients received RAI in more recent times (76.6% vs 54.8% vs 26.8%, p<0.001), most evident in the low risk patients (70% vs 29.1% vs 5.1%, p<0.001). In the high risk group, the majority received RAI, with no difference between the groups.

Conclusion

Comparing DTC patients treated in our unit before and after publications of the 2009 and 2015 ATA guidelines, more nodal surgery was performed with less RAI administered in the latter groups. Better risk stratification according to the ATA guidelines has allowed more judicious use of RAI ablation.

Introduction

Differentiated thyroid carcinoma (DTC) encompasses both papillary and follicular variants and comprises the vast majority (90%) of all thyroid cancers.[1] Of the differentiated cancers, papillary thyroid cancer (PTC) and its variants account for approximately 85% of cases compared to 10% of follicular thyroid cancer (FTC). In recent decades, DTC has become increasingly prevalent, largely attributable to the increasing use of neck ultrasonography and fine needle aspiration resulting in increased diagnosis.[1]

The mainstay of treatment for DTC is surgical resection, with either total thyroidectomy or lobectomy. Although the prognosis of treated DTC is generally excellent, with 10-year survival rate exceeding 90%,[2] recurrence is recognised as an important contributor to increased morbidity and mortality. Metastatic involvement of cervical lymph nodes increases the risk of local recurrence.[3,4] As such, therapeutic central lymph node dissection (CLND) should accompany total thyroidectomy in patients with clinically involved central nodes.[5,6] The role of prophylactic CLND is more controversial but can be considered for patients with clinically uninvolved nodes with higher risk primary tumours.

In addition to surgery, radioactive iodine (RAI) administration may be indicated for remnant ablation, adjuvant therapy (to destroy suspected but unproven metastatic disease), or to target known persistent disease. RAI is associated with a reduced rate of disease recurrence and improved survival in high risk patients after total thyroidectomy.[7,8] RAI ablation is recommended in patients with any DTC >4cm, extrathyroidal or extranodal extension, and distant metastatic disease, with some studies suggesting its benefit in patients with other high risk factors such as aggressive tumor histology (such as tall cell, columnar or insular variants).[9]

It is generally accepted that RAI is not beneficial in low risk patients with tumor size <1cm.[10] In patients with 1-4cm DTC and no other worrisome features, the guidelines on adjuvant RAI ablation is less clear due to conflicting evidence on the benefit of recurrence. As RAI ablation is not without complications, there has been an increasing shift away from its routine use in low to intermediate risk patients. More and more, studies have also shown that the use of high dose RAI ablation (i.e. 100mCi) has no advantage over a lower dose of 30mCi,[11-13] hence leading to the guidelines recommending the use of the lower dose especially in low and intermediate risk disease.[6]

The 2009 American Thyroid Association (ATA) risk stratification system provided a useful guide in determining which DTC patients should be considered for post-thyroidectomy RAI ablation. Patients are categorised as having low, intermediate or high risk tumors according to the tumor characteristics exhibited (Table 1).[5] These ATA guidelines were updated in 2015 and published in 2016. The risk stratification system remained largely the same but was modified to include the number and size of involved lymph nodes, and also stratified FTC with extensive vascular invasion to the high risk group.[6]

We aimed to examine the change in practice at our institution after publication of the ATA 2009 and 2015 guidelines, in particular, the use of post-thyroidectomy RAI ablation and lymph node dissection. We hypothesised that with the improvement in evidence-based risk stratification, there should be a trend towards a decrease in the usage of RAI ablation for low risk patients. Furthermore, we hypothesised an increase in the use of prophylactic central lymph node dissection to facilitate better staging and allow more accurate risk stratification.

Methods

This study is a retrospective review of a prospectively maintained database of consecutive patients undergoing thyroid surgery for DTC. Patients were allocated into three treatment groups based on the time period of surgery; group 1 (between 2002-2006, group 2 (2010-2014), and group 3 (2017-2018). The five-year time periods of group 1 and 2 were selected to represent the cohort of patients who were treated before and after the release of the 2009 ATA guidelines, respectively. Group 2 was intentionally chosen a year after the release of the new guidelines to allow practitioners to become familiar with implementing any change in practice accordingly. However, as practice had already been well-established prior to the 2009 guidelines, the authors did not feel that it was necessary to select patients that fell immediately within the 5 years prior to 2009. Group 3 represents a contemporary cohort treated following the release of the current 2015 ATA guidelines. Information regarding patients' demographic factors and clinical variables were obtained from medical records. Patients whom have been lost to follow-up or have had their medical records destroyed were omitted from the study.

All patients in this study diagnosed in 2010 and later were discussed at a multi-disciplinary team (MDT) meeting involving surgeons, endocrinologists, nuclear medicine physicians, radiologists, pathologists, and specialist nurses. As the MDT meeting was implemented at our institution in 2009, the first cohort of patients did not have MDT discussions but were stratified into risk categories according to the 2009 ATA guidelines as described above. Patients in the second and third groups were discussed at MDT meetings at which point they were stratified into the 2009 and 2015 risk classifications, respectively. The MDT recommendations for further treatment were recorded in the case notes, and these were available for review during data collection.

The extent of surgery was compared between the three periods. Patients were identified as having had a total thyroidectomy, hemithyroidectomy, subtotal thyroidectomy or isthmusectomy. Thyroid lobectomy followed by completion thyroidectomy was recorded as total thyroidectomy for the purpose of this study. The use of central or lateral lymph node dissection was also recorded. Therapeutic central neck dissection was always performed, whereas prophylactic central neck dissection was up to the individual surgeon and assessed on a case-by-case basis, taking into account risk factors such as patient age, gender, and size of primary. The number of patients who received RAI ablation was compared between the three groups. All data analysed was categorical. Analysis using Fisher's exact (2x2) and Chi-square (>2x2) tests was performed using IBM® SPSS® Statistics ver. 24.0 software for Mac (IBM Corp, 2016). The p value for statistical significance was set at $p<0.05$.

Results

Surgery performed

There were 415 patients included in this study, of which 88 (21.2%) were treated between 2002-2006 (group 1), 215 (51.8%) between 2010-2014 (group 2) and 112 (27%) between 2017-2018 (group 3). The majority of patients were female (71.6% in group 1, 77.2% in group 2, and 73.2% in group 3) and the majority had PTC (73.9% in group 1, 78.1% in group 2 and 88.4% in group 3). In group 1, 76/88 (86.4%) had total thyroidectomy compared to 182/215 (84.7%) in group 2 and 78/112 (69.6%) in group 3 (p=0.003). In addition to this, 8/88 (9.1%) had central lymph node dissection (CLND) in group 1 vs 90/215 (41.9%) and 72/112 (64.3%) in groups 2 and 3, respectively (p<0.001). In group 1, 6/88 (6.8%) had lateral lymph node dissection (LLND) vs 37/215 (17.2%) in group 2 and 15/112 (13.4%) in group 3 (p=0.147). Demographic information, surgery performed, and histopathology are displayed in Table 2.

Risk stratification

There was no difference in tumor size (see table 2) or aggressiveness of histology (e.g. tall cell, oncocytic variants) across the three groups (3.4% vs 1.9% vs 0%, p=0.171). There was also no difference in vascular invasion (15.9% vs 20% vs 13.4%, p=0.493) or the occurrence of metastatic disease at the time of data collection (5.7% vs 4.7% vs 0.9%, p=0.117).

RAI use

Overall, fewer patients received RAI in the more recent cohorts; 76.6% in group 1 vs 54.8% in group 2 and 26.8% in group 3 (p<0.001). This difference was most evident in the low risk patients, where 35/50 (70%) patients in group 1 received RAI compared to 30/103 (29.1%) in group 2 and 4/78 (5.1%) in group 3 (p<0.001). In the high risk group, the majority of patients received RAI (group 1 vs group 2 vs group 3; 100% vs 89.3% vs 100%, p=0.302) (see Figure 1). In the intermediate risk group, 14/27 (82.4%) received RAI in group 1, compared to 60/79 (75.9%) in group 2 and 15/23 (65.2%) in group 3 (p=0.430).

Discussion

RAI treatment in DTC aims to ablate the postsurgical thyroid remnant to facilitate early detection of recurrence based on serum thyroglobulin measurement, eliminate suspected microscopic disease, and to treat known persistent disease.[6,7] RAI ablation is no longer considered a routine "one size fits all" adjuvant treatment for patients following total thyroidectomy for DTC.[14] Although there is demonstrated improvement in disease-specific survival and reduced risk of recurrence, particularly in high risk patients, RAI is not without complications, such as cumulative-dose related dysfunction of salivary and nasolacrimal glands,[15] and an increased risk of secondary malignancies.[16] The 2009 ATA guidelines provided formal recommendations for post-thyroidectomy RAI use, and this was subsequently superseded by the updated 2015 version. This newest edition encompasses a few important additions to the risk categories, such as the de-escalation of patients with small lymph node metastases from intermediate risk to the low risk category. As these patients are now deemed low risk, RAI ablation is therefore not recommended.

In recent years, there has been an increase in workload for the endocrine surgeons involved in this study which is reflected in the almost 2.5 times more patients in group 2 compared to group 1. Our data reveals more selective use of RAI ablation in more recent times, with significantly fewer patients in the contemporary groups receiving RAI compared to the historical group. With the implementation of the 2009 and subsequent 2015 ATA risk stratification system, progressively less RAI was used in the low and intermediate risk groups, with this difference being statistically significant in the low risk patients. No difference was observed in the high risk groups between the three time periods – it is generally accepted that RAI therapy in the high risk patients reduces both the risk of recurrence as well as disease-specific mortality.[17] The small proportion of high risk patients (10.7%) in group 2 who did not receive RAI can be explained by either patient's refusal or the patient's care being transferred to another institution.

In our institution, adjuvant therapy decisions post thyroidectomy are made in the context of a multi-disciplinary team (MDT) meeting, which was first implemented in 2009.[18,19] Along with the published guidelines, and the expertise offered by this multi-disciplinary group, carefully-considered decisions are made regarding thyroid cancer treatment; both surgical (completion thyroidectomy, lymph node dissection) and non-surgical (TSH suppression, RAI use). This approach has also led to our adherence to guidelines, as has been reported by Moore *et al*. in New York, where a similar change in RAI usage was reported following publication of the 2009 guidelines, with management decisions made within a multi-disciplinary environment.[20]

The reduction in the use of RAI was accompanied by more aggressive surgery in our study, in particular, central lymph node dissection. The indications for and the extent of lymph node dissection in DTC patients have always been controversial. Whilst there is consensus that therapeutic lymph node dissection is indicated in patients with clinical or biopsy-proven lymph node metastases, the indication for prophylactic central lymph node dissection is a subject of debate,[21] and attempts have been made to develop nomograms to predict involvement of central compartment lymph nodes.[22,23] The central neck compartment is the primary zone of lymphatic involvement for PTC.[1,24] It is commonly accepted that regional lymph node involvement is associated with increased tumor recurrence, and recurrence rates have been shown to be higher in node positive patients over the age of 45 years.[25,26] Lymphadenectomy can therefore not only prevent future recurrence, but also play an important role in staging. Ultra-sensitive thyroglobulin assays have also raised the bar for classifying response to therapy. In our patient cohort, there was significantly more central lymph node dissection carried out in the later groups. We postulate that the increase in the number of prophylactic central lymph node dissections has led to more accurate staging, allowing greater confidence in the risk stratification and hence omission of RAI ablation. However, due to the retrospective nature of this study, we are cognisant of the fact that we cannot accurately ascertain whether the CLND performed were therapeutic or prophylactic. In addition, data was not collected on hypoparathyroidism (or other complications) in patients undergoing CLND, but it is noted that this group may have a higher risk of hypoparathyroidism.[27]

In our cohort, there was a marginal decrease in the number of patients undergoing total thyroidectomy in the most recent group. This may reflect the 2015 ATA guidelines which suggest that thyroid lobectomy alone may be sufficient in the management of DTC that are >1cm but <4cm, without ETE or lymph node metastases. As a result, this may have consequently also influenced the more selective use of RAI.

Our study is limited by its use of retrospective data and associated potential bias. The period of follow-up in our study would be too short to accurately address whether changes in RAI usage and lymph node dissection have resulted in a change in recurrence, and hence this data was not collected, and indeed larger numbers would be required to draw strong conclusions from recurrence data, due to its infrequency. During our data collection, there did not appear to be a standardised time at which post-operative thyroglobulin (Tg) levels were taken, with some patients having had their first Tg levels checked 9 to 12 months after surgery, therefore this information was also omitted. This study could be further expanded to include data on the trends of RAI dosage used, but is currently beyond the scope of this paper.

After publication of the 2009 and 2015 ATA guidelines for the management of differentiated thyroid cancer, a higher proportion of patients have undergone central lymph node dissection, and fewer have received radioactive iodine. Evidence-based risk stratification guidelines have influenced our practice in caring for patients with DTC.

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Table 1: The 2009 American Thyroid Association (ATA) three-level risk stratification system[5], with additional characteristics updated in the 2015 guidelines[6]

Risk category	Characteristics included in 2009 Guidelines	Additional characteristics expanded in 2015 Guidelines
Low risk	• No local or distant metastases • All macroscopic tumour has been resected • No tumour invasion of locoregional tissues or structures • The tumour does not have aggressive histology (e.g. tall cell, insular, columnar cell carcinoma) or vascular invasion • If ^{131}I is given, there is no ^{131}I uptake outside thyroid bed on first posttreatment whole-body RAI scan (RxWBS)	• Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2cm in largest dimension) • Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer • Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion • Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $BRAF^{V600E}$ mutated (if known)
Intermediate risk	• Microscopic invasion of tumour into perithyroidal soft tissues • Cervical lymph node metastases or ^{131}I uptake outside thyroid bed on the RxWBS done after remnant ablation • Tumour with aggressive histology or vascular invasion	• Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension • Multifocal papillary microcarcinoma with ETE and $BRAF^{V600E}$ mutated (if known)
High risk	• Macroscopic tumour invasion (gross ETE) • Incomplete tumour resection • Distant metastases • Thyroglobulinemia out of proportion to what is seen on posttreatment scan	• Pathologic N1 with any metastatic lymph node ≥ 3 cm in largest dimension • Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)

Table 2. Patient characteristics and treatment modalities

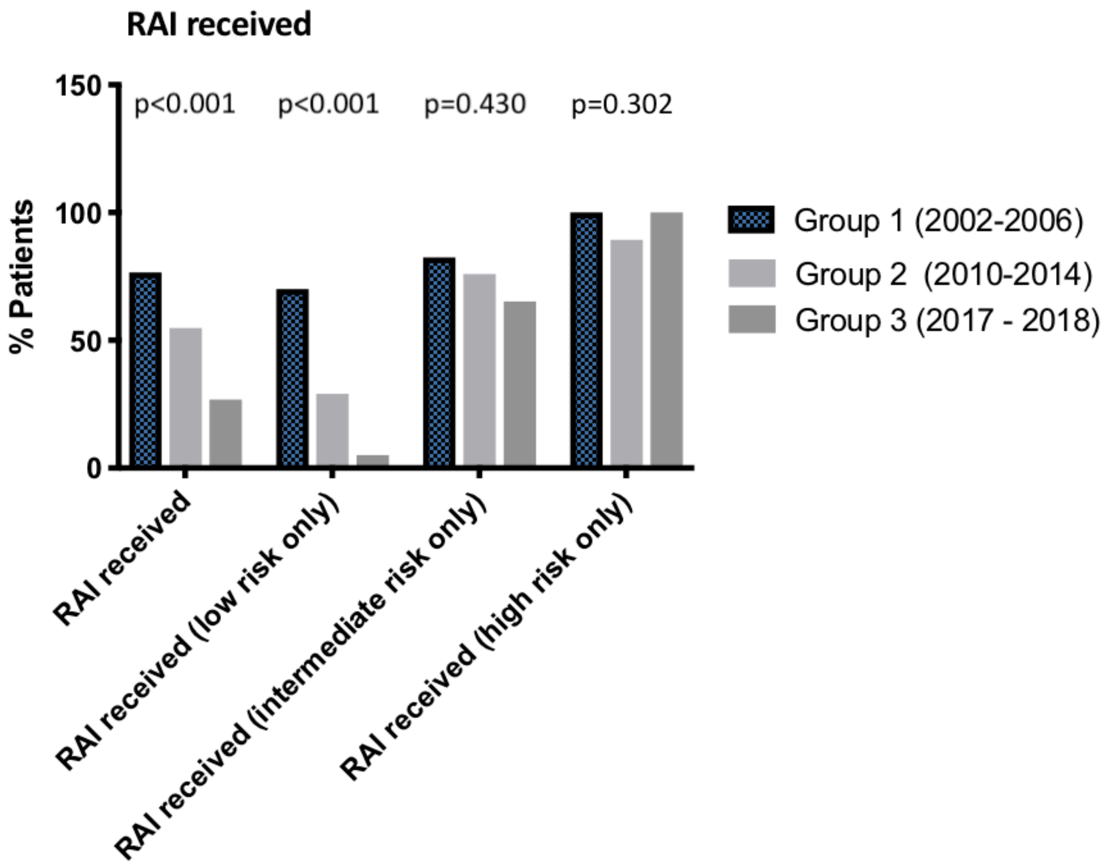
	Group 1 (2002-2006) N (%)	Group 2 (2010-2014) N (%)	Group 3 (2017-2018) N (%)	p-value
Age (mean +/-SEM)	47.23 +/- 1.61	49.57 +/- 1.03	48.61 +/- 1.45	0.470
Gender:				
Female	63 (71.6)	166 (77.2)	82 (73.2%)	0.524
Tumour size (median + IQR)	19mm (10-25)	15mm (8-30)	15mm (8–25)	0.333
Tumour Size:				
T1	49 (59.0%)	130 (61.7%)	75 (67%)	0.190
T2	27 (32.5%)	56 (26.2%)	31 (27.7%)	
T3	7 (8.4%)	28 (13.1%)	6 (5.4%)	
Nodal Status:				
Central nodes involved*	12 (13.6%)	54 (25.2%)	45 (40.2%)	<0.001
Lateral nodes involved	6 (6.8%)	30 (14.0%)	15 (12.3%)	<0.001
Histopathology:				
Papillary thyroid cancer	65 (73.9%)	168 (78.5%)	99 (88.4%)	0.030
Follicular thyroid cancer	21 (23.9%)	44 (20.6%)	10 (8.9%)	
Both papillary and Follicular	2 (2.3%)	2 (0.9%)	3 (2.7%)	
Surgery performed:				
Total thyroidectomy	76 (86.4%)	182 (84.7%)	78 (69.6%)	0.003
Hemithyroidectomy	10 (11.4%)	32 (14.9%)	34 (30.4%)	
Subtotal thyroidectomy	1 (1.1%)	0	0	
Isthmusectomy	1 (1.1%)	1 (0.5%)	0	
Central neck dissection:				
Performed	8 (9.1%)	90 (41.9%)	72 (64.3%)	<0.001
Not performed	79 (89.8%)	123 (57.2%)	40 (35.7%)	
Unknown/missing data	1 (1.1%)	2 (0.9%)	0	

Lateral neck dissection:				
Performed	6 (6.8%)	37 (17.2%)	15 (13.4%)	0.147
Not performed	81 (92%)	176 (81.9%)	97 (86.6%)	
Unknown/missing data	1 (1.1%)	2 (0.9%)	0	

* In Group 1 only 8 patients underwent a central neck dissection, however, central lymph node metastases were identified in 12 patients. This is most likely due to metastases to incidental perithyroidal lymph nodes removed with the thyroid specimen in patients that did not undergo a formal central neck dissection.

Figure Legends

Figure 1. Comparative use of RAI in groups 1, 2 and 3 stratified according to risk category (low, intermediate and high)



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