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Radioactive iodine remnant uptake after completion thyroidectomy – Not such a complete cancer operation

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Abstract

Background—Given limitations in preoperative diagnostics, thyroid lobectomy followed by completion thyroidectomy (CT) for differentiated thyroid cancer (DTC) may be required. It is unclear if resection quality by CT differs from total thyroidectomy (TT). Additional surgeon or patient factors may also influence "completeness" of resection. This study evaluates how CT and surgeon volume influence the adequacy of resection as measured by radioactive iodine (RAI) remnant uptake.

Methods—A retrospective review of a prospectively collected thyroid database was queried for patients treated for DTC with TT or CT followed by RAI ablation. CT patients were matched 1:2 by age, gender and tumor size, to TT patients. Surgeon volume, time to completion, and continuity of surgeon care were reviewed.

Results—Over 18 years, 45 patients with DTC had CT and RAI. Mean age 48±2 years. 76% were female, with a tumor size of 2.7±0.3cm. CT had higher remnant uptake than TT (0.07 vs. 0.04, p=0.04). CT performed by a high volume surgeon had much lower remnant uptakes (0.06% vs. 0.22%, p=0.04). Remnant uptake followed a step-wise decrease with involvement of a high volume surgeon for part or all of the surgical management (p=0.11). Multiple regression analysis found CT (p=0.02) and surgeon volume (p=0.04) to significantly influence uptake after controlling for other factors.

Conclusion—Single stage TT provides a better resection based on smaller thyroid remnant uptakes than CT for patients with thyroid cancer. If a staged operation for cancer is necessary, surgeon volume may impact the completeness of resection.

Keywords

Papillary Thyroid Cancer; Radioactive Iodine Ablation; Completion Thyroidectomy; Remnant Uptake; Well Differentiated Thyroid Cancer; Surgeon Volume; Surgical Outcomes

Introduction

When faced with a thyroid nodule with an indeterminate result after fine needle aspiration (FNA), thyroid lobectomy is indicated for definitive diagnosis (1, 2). For lobectomy

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specimens revealing a diagnosis of thyroid cancer, completion thyroidectomy (CT) is frequently required (1–9). While complications associated with CT have been studied, less is known about oncologic outcomes (10). Although thyroid procedures are starting to shift towards high volume surgeons, still a large portion of thyroid procedures are being performed by low volume surgeons (11). Radioactive iodine (RAI) remnant uptake and remnant uptake to dose ratio (UDR) have been proposed as a quality measure in thyroid resection for both benign and malignant thyroid disease (12, 13).

The aim of this study was to evaluate the extent of surgical resection, as measured by RAI remnant uptake percentage, with CT compared to total thyroidectomy (TT). Secondary aims included evaluating surgeon volume and continuity of surgeon care as they influenced RAI remnant uptake percentage after CT.

Methods

With IRB approval, a prospectively collected thyroid database was retrospectively queried for patients treated for differentiated thyroid cancer (DTC) at a tertiary referral, academic center. The study period spanned from 1994 to 2012. Patients who underwent CT followed by RAI were identified, and matched 1: 2 based on patient age, gender and tumor size with patients treated with TT followed by RAI ablation during the same time period. Patients without complete records of remnant uptake data were excluded.

Patient demographics, pathology reports, radioactive iodine treatment records, surgeon volume, time to CT, and continuity of surgeon care were reviewed. High volume was defined as >20 thyroid cases per year (14). For patients with initial surgery performed outside of our system, information regarding the initial surgeon, hospital and/or city was not completely available. In instances where only geographical location or hospital was known, assumptions were made based on location and hospital size to determine likely degree of surgeon volume. When surgeon identity was known, classification was based on known practice habits. For completion patients, surgeon volume for who performed the first operation as well as the surgeon volume for who ultimately performed the completion was noted. Patients were grouped by either low volume surgeon to low volume surgeon, low volume surgeon to high volume surgeon, or high volume surgeon to high volume surgeon. In instances of low volume surgeon to low volume surgeon, some patients were referred from a community low volume surgeon to our institutional low volume surgeons, while some were performed by the same low volume surgeons at our institution. Patients in the low volume to high volume surgeon group may have had their initial surgery either within the community or by our institutional low volume surgeons. Patients in the high volume to high volume group had both surgeries performed by the same surgeon. Radioactive iodine dosing and remnant uptake percentage was recorded from the whole body scan at time of initial ablative dose. Remnant UDR was then calculated (12).

Statistical analysis was performed using IBM SPSS Statistics, version 21.0. Fisher's Exact Test, Mann-Whitney U, Kruskal-Wallis, Pearson Chi-Square, and unpaired t-test were used as appropriate for data analysis. Multiple linear regression to evaluate surgeon volume and surgery performed (CT vs. TT) and their influence on remnant uptake was performed, while accounting for additional patient factors. A p-value of < 0.05 was determined to be significant. Data are expressed as mean ± standard error of the mean (SEM) when normally distributed, and as median with inter-quartile range when non-normal in distribution (radioactive iodine dosing, remnant uptake percentage and UDR).

Results

From 1994 to 2012, 45 patients were identified who met the inclusion criteria of undergoing CT followed by RAI ablation for DTC. As the matched controls were selected to control for age, gender and tumor size, no difference was noted in these parameters between those patients who underwent CT and those who had a single staged, TT (Table 1). The CT group was noted to have a greater incidence of Follicular Carcinoma and Hurthle Cell Carcinoma. Patients were treated with an equal amount of RAI for ablation. However, patients treated with CT were noted to have both a higher median remnant uptake (0.07% vs. 0.04%, p=0.04) as well as a higher median UDR (0.0008 vs. 0.0004, p=0.04) in comparison to the TT group.

Over the study period, patients were cared for by a total of five surgeons within the study institution. Of these, two surgeons were defined as low volume and three surgeons were defined as high volume (14). Patient age and gender was equivalent between all groups. Surgeon volume for the initial operation and CT were noted. Tumor size, dose of RAI, remnant uptake and UDR did not differ (Table 2). Time to CT was quicker when a high volume surgeon performed both initial lobectomy and CT at 4 weeks, compared to 9.5 weeks when both procedures were done by a low volume surgeon, or 1 year when the patient switched to a high volume surgeon for completion thyroidectomy(p <0.01).

In addition to surgeon volume, other factors such as continuity of surgeon care and timing of CT were analyzed. Patients were determined to either have the same surgeon perform both stages of the operation, or to switch to another surgeon for the CT, regardless of surgeon volume. This did not impact median remnant uptake (0.07% vs. 0.08%, p= 0.36) nor median UDR (0.0007 vs. 0.0017, p=0.20). To see if time between initial thyroid resection and ultimate CT was associated with any change in remnant uptake or UDR, patients were categorize as either having less than 6 weeks or greater than 6 weeks between surgeries. This did not result in any difference in median remnant uptake (0.06% vs. 0.08%, p=0.26) or in median UDR (0.0007 vs. 0.0013, p=0.20).

Further comparison was made looking at volume status of the surgeon who performed the CT, and how that compared to surgeon volume status in TT (Table3). CT patients managed by a high volume surgeon had lower remnant uptake (0.06% vs. 0.22%, p=0.04) and UDR (0.0005 vs. 0.006, p=0.03) than the CT patients managed by low volume surgeons. This trend was also seen with the TT patients, as previously reported (12). High volume surgeons performing CT still had twice the remnant uptake (0.06% vs. 0.03%) and UDR (0.0005 vs. 0.0003) compared to TT, indicating that even in the hands of a high volume surgeon, a more complete resection is performed with a TT opposed to a staged lobectomy followed by CT. Given the very small difference between these two values the significance of this is unclear. CT performed by a high volume surgeon still had lower remnant uptake when compared to a TT performed by a low volume surgeon (0.06% vs. 0.3%).

Multiple linear regression was performed to evaluate factors influencing remnant uptake. Patient age, gender, surgery performed (CT or TT), surgeon volume, and tumor size were all included. Performance of a CT was found to increase the remnant uptake (p=0.02), while high surgeon volume was found to decrease the remnant uptake (p=0.04) after controlling for other factors.

Discussion

This study has demonstrated that remnant uptake after CT is greater than after TT. This group has previously shown that increased remnant uptake, or uptake dose ratio, after TT is associated with an increased risk for thyroid cancer recurrence (12). Thus, the increased

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remnant uptake seen with CT implies that there is in an increased risk for thyroid cancer recurrence when compared to patients undergoing an initial TT.

The work up of a thyroid nodule is largely dependent on the results of the fine needle aspiration (1). 25–30% of nodules will have indeterminate FNA results, with variable associated underlying risk of malignancy which requires surgical lobectomy to establish a definitive diagnosis (1, 2, 15). While the Bethesda System for reporting thyroid cytopathology on FNA has helped provide a consistent framework for which results can be classified, institutional variation may exist (2, 16). Ongoing research on molecular testing of FNA samples suggests that if any mutations exist within the sample, the risk of malignancy is much higher and patients can be managed with TT instead of a diagnostic lobectomy (15, 17). However, molecular testing is only helpful in those patients with indeterminate cytology and positive mutation results, as the sensitivity of the tests are still low (15, 17). Gene expression panels have also been developed to help clarify diagnosis in instances of indeterminate FNA samples, however they have utility in only identifying benign nodules with a high negative predictive value, and not identifying those patients with malignancy (18). Until a more sensitive and specific test is developed for the diagnosis of DTC, diagnostic lobectomy followed by CT will still be required in a subset of patients (5). At present time, molecular testing is not routinely utilized at our institution. It is not surprising that CT group had a greater percentage of Follicular Carcinoma and Hurthle Cell Carcinoma, due to the limitation of FNA to distinguish benign from malignant within these lesions (Table 1). While papillary thyroid cancer has characteristics which are diagnostic on cytology, Follicular and Hurthle Cell Carcinomas still require histologic evaluation.

Across general surgery, surgeon volume has been shown to be associated with improved patient outcomes (19). This is no different for thyroid surgery (11, 14, 20, 21). Gourin et al looked at where and by whom thyroid surgery was performed in the state of Maryland over a 19 year period (11). There was a significant trend in thyroid procedures moving to high volume surgeons during this study. The high volume surgeons were found to perform a more extensive surgery, with lower rates of recurrent laryngeal nerve injury or hypocalcemia. A European study demonstrated that surgeons at the extreme ends of their career were more likely to have complications after thyroidectomy (21). Looking at the field of endocrine surgery as a whole, Stravrakis et al found that surgeons performing more than 100 endocrine cases a year, encompassing thyroid, parathyroid and adrenal, maintain the lowest complication rates, while surgeons performing 4 or fewer endocrine cases were responsible for a disproportionally high complication rate (20). Sosa et al found that high volume surgeons, even after correcting for case mix variability, had significantly lower complication rates and length of stay (14). Hospital volume was not found to be independently associated with patient outcomes.

While the multiple linear regression demonstrated that surgery performed was an independent factor influencing remnant uptake, looking at the data in Table 3, even though surgeon volume was adjusted for in the multiple variable model, it is possible that the differences between overall remnant uptake in the CT compared to TT may have been influenced by the number of high volume surgeons making up the completion group (73%) versus the total group (88%). This would further support CT for cancer being referred to a high volume surgeon.

With our current pre-operative diagnostic abilities, some patients will still need to undergo a diagnostic lobectomy to definitively make the diagnosis of cancer. As a large portion of thyroid surgery is still being performed by low volume surgeons, it is very likely these initial lobectomies will be performed by a low volume surgeon (11). Based on the data presented in this study, however, patients identified to need CT for thyroid cancer are best served, from an oncologic standpoint, by referral to a high volume surgeon (12). Previous studies have shown repeatedly that complication rates for thyroid surgery are much lower with high volume surgeons as well (11, 14, 20).

As this study is retrospective in nature, it has inherent limitations. We have no instances of patients going from a high volume surgeon for initial surgery to a low volume surgeon for completion to complete the assessment on all possible combinations. Due to the small sample size, certain findings did not reach statistical significance. Specifically, patients in the completion thyroidectomy group who were treated by a high volume surgeon for either completion thyroidectomy alone or for both surgeries did not have statistically significant differences in tumor size, RAI dose, remnant uptake or UDR. Upon looking at the data presented in Table 2, it is possible significance between these variables may be found upon further study in a larger population.

In conclusion, remnant uptake after CT is greater than after TT suggesting that a greater amount of thyroid tissue is left behind. This has been previously shown to be associated with a higher rate of thyroid cancer recurrence (12). When patients are in need of a CT, high volume surgeons will perform a much more “complete” resection than low volume surgeons as suggested by lower remnant uptake. It is the recommendation of the authors that patients requiring CT for thyroid cancer be referred to a high volume surgeon to optimize oncologic outcomes.

Acknowledgments

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Synopsis

Since a diagnosis of thyroid cancer is not always established based on fine needle aspiration, some patients require completion thyroidectomy after an initial thyroid lobectomy for thyroid cancer. Radioactive iodine remnant uptake scans after completion thyroidectomy demonstrate more tissue left behind compared to patients undergoing an initial total thyroidectomy. Surgeon volume also influences remnant uptake after completion, suggesting if a completion thyroidectomy is necessary, patients will undergo a more complete resection with a high volume surgeon.

Table 1

Demographic information of completion thyroidectomy patients versus matched control total thyroidectomy patients.

	Completion Thyroidectomy	Total Thyroidectomy	P-Value
N	45	90	
Age (Years)	48 ± 2	48 ± 2	0.89
Female	34 (76%)	64 (71%)	0.68
Tumor Size (cm)	2.7 ± 0.3	2.2 ± 0.2	0.08
Tumor Pathology			**<0.01**
Papillary	28 (62%)	77 (86%)	
Follicular	11 (24%)	9 (10%)	
Hurthle Cell	6 (13%)	4 (4%)	
Median Radioactive Iodine Dose (mCi)	78 (32–145)	82 (50–146)	0.27
Median Remnant Uptake (%)	0.07 (0.02–0.32)	0.04 (0.01–0.16)	**0.04**
Median Uptake to Dose Ratio	0.0008 (0.0003–0.0103)	0.0004 (0.0001–0.0023)	**0.04**

Data are expressed as mean ± standard error of the mean, number (%) or median (inter-quartile range) as appropriate.

Table 2

Surgeon volume at time of lobectomy and at time of completion.

	Low Volume to Low Volume Surgeon	Low Volume to High Volume Surgeon	High Volume to High Volume Surgeon	P-Value
N	12	13	20	
Age (Years)	48 ± 6	52 ± 3	45 ± 3	0.38
Female	75%	85%	70%	0.65
Tumor Size (cm)	2.3 ± 0.6	2.0 ± 0.4	3.3 ± 0.5	0.17
Radioactive Iodine Dose (mCi)	32 (30–115)	52 (32–144)	100 (51–150)	0.12
Remnant Uptake (%)	0.22 (0.06–1.11)	0.06 (0.04–0.09)	0.06 (0.01–0.26)	0.11
Uptake to Dose Ratio	0.006 (0.001–0.032)	0.0007 (0.0003–0.0020)	0.0005 (0.0001–0.0046)	0.06
Time to Completion	9.5 weeks (6 weeks – 8.5 years)	1 year (15 weeks – 3 years)	4 weeks (1 week – 7 weeks)	**<0.01**

Data are expressed as mean ± standard error of the mean, number (%) or median (inter-quartile range) as appropriate.

Table 3

Impact of surgeon volume for completion thyroidectomy and total thyroidectomy.

	Completion Thyroidectomy			Total Thyroidectomy		
	Low Volume Surgeon	**High Volume Surgeon**	**P-Value**	**Low Volume Surgeon**	**High Volume Surgeon**	**P-Value**
N	12	33		11	79	
Age (Years)	48 ± 6	48 ± 2	0.98	37 ± 5	49 ± 2	**0.01**
Female	75%	76%	0.96	64%	72%	0.56
Tumor Size (cm)	2.3 ± 0.6	2.8 ± 0.4	0.52	2.3 ± 0.5	2.2 ± 0.2	0.72
Radioactive Iodine Dose (mCi)	32 (30–115)	80 (50–146)	0.06	33 (31–102)	84 (52–147)	0.09
Remnant Uptake (%)	0.22 (0.06–1.11)	0.06 (0.02–0.18)	**0.04**	0.3 (0.07–0.61)	0.03 (0.009–0.094)	**<0.01**
Uptake to Dose Ratio	0.006 (0.001–0.032)	0.0005 (0.0002–0.0026)	**0.03**	0.007 (0.002–0.014)	0.0003 (0.0001–0.0019)	**<0.01**

Data expressed as mean ± standard error of the mean, number (%) or median (inter-quartile range) as appropriate.