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Impact of Extent of Surgery on Tumor Recurrence and Survival for Papillary Thyroid Cancer Patients

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Abstract

Background—The extent of surgery for low-risk papillary thyroid cancer (PTC) has been the subject of debate among experts for decades.

Objective—In this paper, we aimed to systematically review whether thyroid lobectomy versus total thyroidectomy for PTC patients with tumors measuring 1.0–4.0 cm impacts tumor recurrence and survival.

Results—A systematic review of the literature from January 1990 to February 2018 yielded 13 relevant studies, including eight national cancer registry database studies, one multi-institutional thyroid cancer-specific database, three large-scale institutional series, and one meta-analysis. Data from these studies demonstrate that total thyroidectomy for the treatment of PTC measuring 1.0–4.0 cm does not confer a clinically significant improvement in disease-specific survival compared with thyroid lobectomy. Four of six studies also reported that total thyroidectomy is associated with a small but statistically significant improvement in disease-free survival, although it is argued whether this difference is clinically significant.

Conclusions—While the quality of the data limit the strength of our conclusions, and while tumor characteristics, patient risk factors, and preferences should be considered, most data support that lobectomy and total thyroidectomy yield comparable oncologic outcomes for PTC measuring 1.0–4.0 cm.

INTRODUCTION

Treatments for the majority of patients with papillary thyroid cancer (PTC) include surgery, radioactive iodine (RAI) therapy, and thyroid hormone suppression. Targeted molecular therapies are available for RAI-refractory disease, and the use of ablative techniques, including radiofrequency and ethanol ablation, has been described at specialized centers as part of research protocols for poor surgical candidates or as patient-preference options for low-burden disease. The extent of surgery for low-risk PTC has been the subject of debate among experts for decades. Given the cost, large sample size, and extended time required to

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obtain outcomes, prospective clinical trials have not been performed. Previously published guidelines and expert opinion have typically recommended total thyroidectomy for all patients with PTC (tumor >1 cm). This procedure allows for adjuvant treatment with RAI and surveillance with serum thyroglobulin level monitoring and whole body scanning. However, thyroid lobectomy is associated with lower rates of recurrent laryngeal nerve injury, hypoparathyroidism, and postoperative biochemical hypothyroidism necessitating thyroid hormone supplementation.[1] Given the excellent survival rate associated with PTC (98% at 5 years[2]), do patients who have PTC with tumor measuring 1.0–4.0 cm have similar oncological outcomes whether they undergo lobectomy or a total thyroidectomy?

Recent expert guidelines have addressed this question. The recommendation of the most recent National Comprehensive Cancer Network (NCCN) panel on thyroid cancer was for total thyroidectomy or thyroid lobectomy for patients without distant metastatic disease, cervical lymph node metastases, extrathyroidal extension, or prior radiation.[3] If lobectomy was performed and there were positive resection margins, macroscopic contralateral disease, or vascular invasion, the panel recommended completion thyroidectomy. This recommendation was based on lower-level evidence and consensus (non-uniform) that the intervention was appropriate (category 2B).

The 2009 American Thyroid Association (ATA) guidelines for patients with DTC recommended total thyroidectomy for all patients with PTC (tumor >1 cm).[4] Support for total thyroidectomy was based on the concept that the procedure allows optimal effectiveness of RAI therapy and based on contemporary data that suggested a recurrence and survival benefit with total thyroidectomy rather than lobectomy.[5] However, the indications for RAI therapy have become more selective, with no benefit seen for patients with American Joint Committee on Cancer tumor, node, metastasis classification stage I disease, as reported by the National Thyroid Cancer Treatment Cooperative Study (NTCTCS) group.[6] This practice change, along with new data suggesting minimal differences in disease-specific survival (DSS)[7,8] between total thyroidectomy and lobectomy, led to a ‘strong recommendation’ based on ‘moderate quality evidence’ in the revised 2015 ATA guidelines. The updated recommendation states that for tumors 1.0–4.0 cm without extrathyroidal extension or lymph node metastases, either procedure is acceptable. Patients in whom postoperative RAI is planned should undergo total thyroidectomy (i.e. familial PTC, bilateral disease, radiation exposure, or age >45 years). In this paper we aim to systematically review whether the extent of surgery for PTC patients (with tumor measuring 1.0–4.0 cm) impacts tumor recurrence and survival.

METHODS

A search of the MEDLINE, PubMed, Cochrane Library, Web of Science, EMBASE, and ClincialTrials.gov databases was performed with the assistance of a professional medical librarian. This study investigated adult patients (>18 years of age) who have biopsy-proven PTC with a dominant tumor measuring 1.0–4.0 cm and in whom the intervention was thyroid lobectomy versus total thyroidectomy. The outcomes of interest included overall survival (OS), disease free-survival (DFS) and DSS. We screened all articles from January 1990 to February 2018 restricted to the English language and human species using title,

abstract, keywords, and the following Medical Subject Heading (MeSH) terms: thyroidectomy, hemithyroidectomy, thyroid, lobectomy, mortality, treatment outcome, disease-free survival, survival analysis, survival rate, neoplasm recurrence, recurrence, mortality, oncological outcome, surgery, surgical procedures, operative, thyroid neoplasms, cancer, carcinoma, papillary, and PTC.

Our search revealed 3448 abstracts, of which 1689 were duplicates; 1759 titles and 63 abstracts were screened. Articles that had <100 patients per arm, lacked oncological outcomes, lacked a comparison group, or included a significant number of patients with a histological subtype other than PTC were excluded. No Cochrane reviews or enrolling randomized controlled trials were identified in our search. A hand search of references from published 2015 ATA guidelines for patients with DTC, as well as NCCN guidelines and included articles, was performed. Thirteen studies that were relevant to the study aim and met the inclusion criteria were included (Table 1).[5, 7, 9–19] When multiple analyses were performed in a study, the outcome most relevant to the key study aim and population was reported; adjusted analyses were preferred. Study evidence was graded as low, moderate, or high based on the American College of Physicians' Grading System for the Quality of Evidence and Strength of Recommendations[20] (Table 1).

RESULTS

Of the 13 full-text articles reviewed, there were eight national cancer registry database studies, one multi-institutional thyroid cancer-specific database, three large-scale institutional series, and one meta-analysis (Table 1).

Four of the eight registry studies utilized the Surveillance, Epidemiology, and End Results (SEER) Program database at different times and used different inclusion criteria and statistical methods. Barney et al.[9] found no statistical difference in OS ($p = 0.43$) or DSS ($p = 0.18$) between lobectomy and total thyroidectomy on adjusted analysis. When looking at a subset of patients with low-risk disease (evaluated by AMES criteria—age, metastasis, extent, and size), Haigh and colleagues[10] found no difference in 10-year OS ($p = 0.07$) on univariate analysis. Mendelsohn et al.[11] found similar results when extending the time frame and follow-up on adjusted survival analysis. Likewise, Adam et al.[12] found that extent of thyroidectomy in patients younger than 45 years of age was not an independent predictor of OS for 1.0–4.0 cm PTC tumors using both SEER and the American College of Surgeons National Cancer Data Base (NCDB) data. This group found the same result when expanding this analysis to include all adult patients ($N = 61,775$).[7] The unadjusted difference in survival at 10-year follow-up was 1.5 percentage points when comparing the lobectomy and total thyroidectomy groups (91.4% vs. 92.9%), but was not statistically significant on multivariable analysis. A previous study by Bilimoria et al.,[5] using earlier NCDB data, found that total thyroidectomy for PTC with tumors >1 cm was associated with a small but statistically significant improvement in unadjusted OS ($p = 0.027$), with an absolute difference of 1.3 percentage points (97.1% vs. 98.4%) at the 10-year follow-up, as well as improved DFS ($p = 0.001$).

To resolve the conflicting results found in the NCDB studies by Adam et al.[7] and Bilimoria et al.,[5] Rajjoub et al. also used the NCDB to determine whether OS was affected by extent of surgery, this time examining whether follicular variant PTC (FVPTC) had different OS compared with conventional PTC (cPTC), and then stratifying these results based on tumor size.[13] Adjusted OS for both FVPTC patients and cPTC patients with tumor sizes grouped from 1.0–3.9 cm did not show an OS advantage with total thyroidectomy compared with lobectomy. However, when these results were stratified by tumor size, grouped 1.0–1.9 cm and 2.0–3.9 cm, cPTC patients with tumors 1.0–1.9 cm did not show an OS advantage with total thyroidectomy compared with lobectomy, but patients with tumors 2.0–3.9 cm did ($p = 0.0226$). In contrast, FVPTC patients did not show an OS advantage with total thyroidectomy over lobectomy for tumors 1.0–1.9 cm or 2.0–3.9 cm. Lastly, a nested case-control study of thyroid cancer patients in the Swedish Cancer Registry found no advantage for total thyroidectomy on DSS for patients with stage I–II disease.[14]

A recent update by the NTCTCS registry of nearly 5000 patients used propensity score matching to balance disease severity in the subset of patients with stage I disease.[15] They found no difference in either OS or DFS when stratified by severity of disease at presentation based on extent of initial surgery. In a study of 1700 patients with AMES low-risk PTC, Hay et al.[16] found no difference in distant metastasis or DSS at 20 years ($p > 0.2$); however, recurrent disease was higher in patients undergoing lobectomy (14% vs. 2%, $p = 0.001$). Nixon and colleagues[17] reviewed 900 patients with tumors <4 cm over a 20-year period. No statistical difference was shown in OS or DSS based on extent of surgery. Kim et al.[18] demonstrated no difference in DFS in patients with PTC of 1.0–4.0 cm who underwent lobectomy compared with patients matched with baseline characteristics who underwent total thyroidectomy. Lastly, Guo and Wang[19] performed a meta-analysis of risk factors for disease recurrence, one of which was extent of surgery. While the degree of heterogeneity was high, they found double the risk of recurrence with thyroid lobectomy in the pooled analysis of seven studies.

DISCUSSION

Survival of patients with localized PTC is excellent. While no prospective, randomized trials exist, the best available retrospective data support similar DSS and OS outcomes for patients having thyroid lobectomy or total thyroidectomy. While Bilimoria et al.[5] found a statistically significant difference in OS by extent of surgery, there was a lack of available adjustment factors in this analysis, specifically data on comorbidity, multifocality, and extrathyroidal extension. Moreover, the clinical relevance of an improvement of 1.3 percentage points is debatable. More recently, after adjusting for the aforementioned factors using more recent data from the NCDB, Rajjoub et al. found that OS for cPTC patients (i.e. excluding FVPTC patients) with tumor sizes grouped from 1.0 to 3.9 cm did not show an OS advantage with total thyroidectomy compared with lobectomy.[13] Interesting, however, when these results were stratified by tumor size, cPTC patients with tumors 1.0–1.9 cm did not show an OS advantage with total thyroidectomy compared with lobectomy, but patients with tumors 2.0–3.9 cm did show an OS benefit, highlighting that the survival benefit of total thyroidectomy versus lobectomy for T2 tumors may differ based on tumor size. Future studies that also exclude FVPTC cases and stratify OS by tumor size will be instructive.

Three of the five included studies that reported DFS found that patients who had a thyroid lobectomy had a higher rate of recurrence, although it is argued that this difference is not clinically significant. Most recurrences are locoregional and can be treated without extensive morbidity with re-excision. Given the recent recommendations from the revised 2015 ATA and NCCN guidelines for localized disease that lobectomy for tumors 1.0–4.0 cm can be considered, more data from patients undergoing lobectomy alone will likely be forthcoming. As the literature in this area grows, a meta-analysis that estimates the effect of extent of surgery on DFS for these patients may be instructive.

While the quality of the data limit the strength of our conclusions, including the inability to retrospectively eliminate cases of noninvasive follicular tumor with papillary-like features, the current literature suggests that total thyroidectomy for the treatment of PTC measuring 1.0–4.0 cm does not confer a clinically significant improvement in DSS or OS compared with thyroid lobectomy. From the studies available, total thyroidectomy is associated with a small but statistically significant improvement in DFS. From an oncological standpoint, lobectomy and total thyroidectomy have similar rates of DSS and OS. Factors other than tumor size, including contralateral thyroid nodules, other coexistent thyroid pathology, and/or locoregional and/or distant metastasis, are relevant to decision making and each patient presents with a unique set of preferences and risk factors. Lastly, multidisciplinary care and communication are essential and beneficial to both the treating physicians and patients.

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SYNOPSIS

The optimal surgical strategy for 1.0–4.0 cm papillary thyroid cancer (PTC) is debated. While an individual patient's tumor characteristics, risk factors, and preferences should be considered, current literature suggests that for encapsulated PTC <4 cm, total thyroidectomy does not confer a clinically significant improvement in disease-specific or overall survival, thus either lobectomy or total thyroidectomy can be performed.

TABLE 1

Selected retrospective studies comparing total thyroidectomy and thyroid lobectomy outcomes

First author (year)	Data source	Control group – total thyroidectomy (*N*)	Study group – thyroid lobectomy (*N*)	Tumor size (cm)	Follow-up (years)	Outcome (95% CI)[a]	Grade of evidence[b]
Adam et al.[7] (1998–2006)	NCDB	54,926	6849	1.0–4.0	6.8	Multivariable OS HRR 0.96 (0.84–1.09)	++
Adam et al.[12] (1998–2006)	NCDB, SEER	<45 years of age NCDB = 26,371 SEER = 12,131	<45 years of age NCDB = 3151 SEER = 1379	1.0–4.0	14	Multivariable OS NCDB: HRR 1.45 (0.88–2.51) SEER: HRR 0.95 (0.70–1.29)	++
Barney et al.[9] (1983–2002)	SEER	12,598	3266	Any	6.7	Multivariable OS OS: $p = 0.43$ CSS: $p = 0.18$	++
Bilimoria et al.[5] (1985–1998)	NCDB	43,227	8946	>1.0	5.8	**DFS: HRR 1.15 (1.02–1.30)** **OS: HRR 1.31 (1.07–1.60)**	++
Carhill et al.[15] (1987–2012)	National Thyroid Cancer Treatment Cooperative Study Group	Stage I: 1492 Stage II: 975	Stage I: 296 Stage II: 129	<4.0	6	Stage I: DFS: HRR 1.52 (0.96–2.50) OS: HRR 2.04 (0.65–9.09) Stage II: DFS: HRR 0.92 (0.58–1.52) OS: HRR 0.64 (0.32–1.41)	++
Guo and Wang[19]	Meta-analysis of 13 studies	1998	618	All	2–6	**DFS: OR 2.38 (1.81–3.12)**	+
Haigh et al.[10] (1988–1995)	SEER	4612 AMES low-risk	820 AMES low-risk	93% <5.0	7.4	Univariate 10-year OS 89% (88–90.4%) vs. 91% (89–93%) [$p = 0.07$]	+
Hay et al.[16] (1940–1991)	Institutional database (Mayo Clinic)	1082 AMES low-risk without RAI	185 AMES low-risk without RAI	All	16	20-year DSS: 99.2% vs. 97.3% **DFS: 92.5% vs. 77.7% ($p < 0.001$)**	+
Kim et al.[18] (2004–2008)	Institutional database (Korea Cancer Center and Seoul National University Hospital)	298	147	1.0–4.0	7	10-year DFS: 94.1% vs. 89.1% ($p = 0.59$)	+
Lundgren et al.[14] (1958–1987)	Swedish cancer registry	Stage I, II: 193	Stage I, II: 212	<4.0	6.7	DSS: OR 1.0 (0.6–1.5)	++
Mendelsohn et al.[11] (1988–2001)	SEER	16,760	5964	All	9	Multivariable OS HRR 0.91 (0.71–1.15) 10-year DSS: 98.4% vs. 97.5%	++
Nixon et al.[17] (1986–2005)	Institutional database (Memorial Sloan Kettering Cancer Center)	528	361	<4.0	8.2	Multivariable OS: HRR 0.99 (0.6–1.6) 10-year DSS: 98% vs. 100% ($p = 0.246$)	++

First author (year)	Data source	Control group – total thyroidectomy (*N*)	Study group – thyroid lobectomy (*N*)	Tumor size (cm)	Follow-up (years)	Outcome (95% CI)[a]	Grade of evidence[b]
Rajjoub et al.[13] (2004–2008)	NCDB	21,589	1310	1.0–3.9, then stratified as 1.0–1.9 and 2.0–3.9	6.5	Multivariable OS: HRR 1.04 (0.80–1.36) [$p = 0.75$] 1.0–1.9 cm: HRR 0.76 (0.51–1.12) [$p = 0.1596$] **2.0–3.9 cm: HRR 1.53 (1.06–2.19) [$p = 0.0226$]**	++

NCDB National Cancer Data Base, *CI* confidence interval, *OS* overall survival, *HRR* hazard rate ratio, *SEER* Surveillance, Epidemiology, and End Results, *CSS* cancer-specific survival, *DFS* disease-free survival, *OR* odds ratio, *AMES* age, metastasis, extent, size; survival, *DSS* disease-specific survival, *RAI* radioactive iodine

[a] HRR values >1 favor total thyroidectomy. Values in boldface indicate statistical significance

[b] Grade of evidence:[20] + indicates low, ++ indicates moderate, +++ indicates high