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Isthmusectomy in selected patients with well-differentiated thyroid carcinoma

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Abstract

Background: Isthmusectomy in the treatment of well-differentiated thyroid carcinoma (WDTC) is controversial. In this study, we analyze the outcomes of WDTC managed by isthmusectomy alone.

Methods: Forty-three patients treated with isthmusectomy alone were identified from an institutional database of 6259 surgically treated patients with WDTC. Patient and tumor characteristics were analyzed. Disease-specific survival (DSS) and recurrence-free survival (RFS) were calculated using the Kaplan-Meier method.

Results: The pT classification was T1 for 41 and T2 for two patients. All were clinical N0, but 10 pts were pN1a. Using the American Thyroid Association risk stratification system, 9 patients were low-risk and 22 were intermediate-risk. One patient developed local recurrence, and two developed regional lymph node metastases; the 5- and 10-year DSS was 100.0%. The 5- and 10-year RFS was 93.1%.

Conclusions: Isthmusectomy alone is an acceptable procedure in selected patients with low- and intermediate-risk WDTC limited to the isthmus.

Keywords

isthmectomy; isthmus; isthmusectomy; low risk cancer; well-differentiated thyroid carcinoma

1 | INTRODUCTION

Well-differentiated thyroid carcinoma (WDTC) is generally known to have low biological aggressiveness and carries a good overall prognosis.^{1–3} However, WDTC of the isthmus has

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CONFLICT OF INTEREST
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been reported to have more aggressive features in comparison to WDTC of the lobes, including more frequent capsular invasion, lymph node (LN) metastasis and multifocality.⁴ There are no specific guidelines for the management of WDTC confined to the thyroid isthmus.⁵ Current guidelines do not support surgical management of thyroid cancer with procedures other than thyroid lobectomy or total thyroidectomy.^{6–9} The role of isthmusectomy in the treatment of WDTC is controversial. Treatment paradigm shifts, limited data, and differences in physician perceptions contribute to the controversy. The aim of this study is to assess the outcomes of patients with WDTC limited to the isthmus managed with isthmusectomy alone.

2 | PATIENTS AND METHODS

Following Institutional Review Board approval, 220 (3.5%) patients with WDTC limited to the isthmus, who were clinically N0, were identified from an institutional database of 6259 patients surgically managed from 1986 to 2015 at a tertiary care cancer center. Surgical treatment of the 220 isolated isthmus lesions was as follows: 14 (6.4%) patients had thyroid lobectomy with isthmusectomy, 161 (73.2%) patients had total thyroidectomy, 2 (0.9%) patients had subtotal thyroidectomy, and 43 (19.6%) patients had isthmusectomy alone. Three patients initially had an isthmusectomy but underwent a planned completion thyroidectomy. Completion thyroidectomy implies a secondary procedure within 12 months after initial isthmusectomy. One of these three requested a completion thyroidectomy, and the other two patients had tall cell variant of papillary thyroid carcinoma (PTC) with a primary tumor >1.5 cm on initial histology. The decision to proceed with a planned completion thyroidectomy was based on initial histology and done to facilitate radioactive iodine ablation. These three patients are included in the 161 patients who underwent total thyroidectomy. After excluding these patients who had a planned completion thyroidectomy, 43 patients met the inclusion criteria. This analysis included the 43 isthmusectomy alone patients.

Patient and tumor characteristics were recorded. Pathological details including tumor histology, primary tumor size, presence of extra thyroid extension (ETE), multifocality, and incidental perithyroidal LN metastasis (pN1a) on histopathology review of the specimen were recorded. Patients with clinically palpable or radiologically demonstrated LN metastases were excluded. Staging was assigned according to the eighth edition of the American Joint Committee on Cancer (AJCC)¹⁰ staging system and the American Thyroid Association (ATA) dynamic Risk-Stratification System⁶ was estimated within the first postoperative year.

Postoperative follow-up protocol involved physical examination with intermittent ultrasounds in the majority of patients during this study period. The use of serial thyroid ultrasound, thyroglobulin (Tg) and Tg antibody (Ab) measurements during postoperative monitoring were introduced in 2005. The presence of a subsequent WDTC in a lobe, or locoregional recurrence was based on findings “suspicious for” and “consistent with” WDTC on imaging and where possible, confirmed with cytology.

Statistical analysis was carried out using SPSS (version 25.0, IBM Corporation). Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were the main clinical endpoints of interest, calculated in months from date of initial surgery using the Kaplan-Meier method. For OS, the follow-up interval was until the date of last contact or death. For DSS, the follow-up interval was calculated to the date of last appointment with a member from the institution's disease management team or death with disease. For RFS, the follow-up interval was calculated similarly to the last appointment or first recurrence of any type.

3 | RESULTS

The patient and tumor characteristics of the cohort are shown in Table 1. The median age was 39 years (range 16–83). Eighteen patients were male and 25 were female. Prior to 2005, it was not a standard practice at our institution to perform preoperative ultrasounds on all patients. Decision as to the extent of surgery was made on clinical findings on physical examination and intraoperative exploration of the whole thyroid gland by bimanual palpation of the thyroid lobes. Preoperative fine-needle aspiration biopsy was performed on all nodules. Based on preoperative FNA, 22 patients (51.2%) had confirmed diagnosis of thyroid carcinoma, Bethesda category VI. Six had Bethesda category V, three had Bethesda category IV, two had Bethesda category III, and five had Bethesda category II.¹¹ In five patients, cytology was unsatisfactory or unknown. The primary tumors were classified as T1a (25), T1b (16), and T2 (2). PTC was the primary histology in 40 patients, and 3 had minimally invasive follicular cancer; 7 patients had tall cell variant of PTC, 9 patients had follicular variant of PTC, 8 patients had classical variant. In 16 patients, no specific subtype of PTC was reported. None of the patients experienced any postoperative complications, such as recurrent laryngeal nerve paralysis, hypocalcemia, hemorrhage, or wound sepsis. Forty-two patients (97.7%) were stage I, and one patient (2.3%) was stage II. The pathological T classification was pT1 in 41 patients (95.3%) and pT2 (4.7%) in 2 patients. The median size of lesion was 1.0 cm (range 0.3–3.0 cm). Microscopic ETE was present in 15 patients (34.9%), all of whom had invasion into the perithyroidal soft tissue, and 0 patients (0.0%) had microscopic positive margin (Table 1). Incidental multifocality in the surgical specimen was identified in five patients (11.7%).

On histopathology review, 10 patients (23.3%) had incidental nodal metastasis detected in perithyroidal LNs (pN1a; Table 2). These LNs were sub centimeter in size (range 0.1–1.2) and no patients had more than five positive LNs (range 1–3). No patients were diagnosed with distant disease. According to the ATA dynamic risk stratification, 9 patients (20.9%) were estimated as low-risk and 22 patients (51.2%) as intermediate-risk. For 12 patients, ATA risk stratification could not be assigned due to unavailability of complete information. The median follow-up was 68 months (range 1–360).

During the study period, one patient developed a unilateral lobe WDTC and two patients developed regional LN metastases. Five- and 10-year RFS were both 93.1% (Figure 1). The first patient developed a PTC in the right thyroid lobe at 123 months after initial surgery and was managed with a completion total thyroidectomy. The second patient had undergone an isthmusectomy and Sistrunk's procedure for a benign thyroglossal duct cyst at initial

surgery; a regional LN metastasis developed at 37 months and was managed with a completion total thyroidectomy and modified neck dissection. Following salvage surgery, both patients had no evidence of disease at final follow-up after a period of 173 and 108 months following salvage surgery, respectively. The third patient developed central compartment nodal metastases at 41 months and was recommended to have a completion total thyroidectomy and central neck dissection. However, the patient declined surgical management and therefore had persistent loco-regional disease at final follow-up with a structural incomplete response. He is alive and well with persistent disease, without any further progression of disease. No patient developed distant metastases and there were no disease-related deaths. The 5- and 10-year DSS were both 100.0% (Figure 2). The 5- and 10-year OS were 100.0% and 86.3%, respectively, in this study group. (Figure 2). However, 177 of the 220 patients with their primary tumors confined to the isthmus, who underwent a surgical procedure, more than isthmusectomy alone, had a 10-year RFS of 94.6% and DSS of 100.0%. These outcomes are very comparable to the outcomes of patients undergoing isthmusectomy alone.

4 | DISCUSSION

Generally at initial clinical presentation in most patients, thyroid nodules are present in the lateral thyroid lobes, while only a small minority of patients present with disease limited to the isthmus. The incidence of PTC presenting in the thyroid isthmus is reported to be between 1.0% and 9.2%.⁵ Several studies have shown isthmic PTCs to be associated with more aggressive histopathological features including a higher rate of capsular invasion,^{4,12,13} ETE,¹⁴ multifocality,^{4,13} and regional nodal metastases^{4,13,15,16} when compared to PTCs located in the lateral lobes.

At our institution, the extent of surgery, isthmusectomy vs total thyroidectomy or lobectomy has been guided by location of gross/macroscopic disease as well as tumor size, gross ETE, and extent of clinical nodal disease. Our study was designed to include patients with isthmic lesions only. Routine preoperative ultrasounds were uncommon at our institution prior to 2005. Decision as to the extent of surgery was made on clinical findings on physical examination and intraoperative exploration of the whole thyroid gland by bimanual palpation of the thyroid lobes. However, since that time we have performed preoperative Ultrasound whenever possible, to ensure there was no nodularity involving either lobe of the thyroid or enlarged central compartment LNs. Preoperative ultrasound findings and a fine-needle aspiration of the dominant thyroid nodule in the isthmus can accurately predict malignant thyroid disease and subsequently guide the extent of initial surgery.¹⁷ Therefore, in modern day practice, careful ultrasound evaluation of the thyroid gland should be performed on patients presenting with thyroid isthmus lesions.¹⁴ The median size of the isthmic lesion in our cohort was 1.0 cm (range 0.3–3.0 cm). We did not perform isthmusectomy in isthmic nodules larger than 3 cm. Although microscopic ETE was present in 15 patients (34.9%), it is no longer considered an adverse factor to upstage the pT classification of the primary tumor, according to the AJCC eighth edition revision of the staging system.¹⁰ In a previous study from our institution, we also reported that microscopic ETE had no significant impact on subsequent risk of recurrence or survival.¹⁸ On histopathology review, multifocal disease within the thyroid isthmus was found in 5 patients

(11.7%), whereas 35 patients (81.3%) had a solitary nodule confined to the thyroid isthmus with a unifocal carcinoma. In our study, patients with clinically apparent or grossly enlarged nodal disease were excluded. However, on histopathology review, 10 patients (23.3%) had LN metastasis detected in perithyroidal LNs (pN1a) found incidentally in the specimen of isthmusectomy. However, these metastatic LNs were consistently 5 (range 1–3) in number and the majority were sub centimeter in size (range 0.1–1.2 cm) in largest dimension.

Total thyroidectomy has been practiced for patients with WDTC located in the isthmus at many institutions.^{4,12–14,17,19} However, there are no specific data available in the literature for the management of WDTC confined to the thyroid isthmus with a long-term follow-up.⁵ Current guidelines, including the 2015 ATA guidelines,⁶ Korean Thyroid Association Guidelines,⁷ Korean Association of Thyroid and Endocrine Surgeons Guidelines,⁸ and British Thyroid Association guidelines⁹ do not mention isthmusectomy as an acceptable procedure in the management of WDTC.⁶ Therefore, the role of isthmusectomy in the treatment of WDTC has remained controversial.

Despite this, the use of isthmusectomies has been reported in the literature by some authors. Maser et al²⁰ and Skilbeck et al²¹ reported that an isthmusectomy in isolated isthmic lesions with benign or indeterminate cytology was an effective procedure, and had the advantage of minimizing surgical risk compared to thyroid lobectomy. When patients were diagnosed with malignancy on histopathology, all went on to receive a completion thyroidectomy, but the authors did not report on recurrence or survival for oncological outcomes.^{20,21}

Wang et al reported on 73 patients who underwent total thyroidectomy and bilateral prophylactic central neck dissection for solitary isthmic PTC and reported that the risk factors for paratracheal LN metastasis were age ≥ 38 years (odds ratio [OR]: 4.667; 95% confidence interval [CI]: 1.672–13.029), primary tumor size >0.6 cm (OR: 10.400; 95% CI: 2.199–49.184) and the risk factors for central LN metastasis were male sex (OR: 3.405; 95% CI: 1.121–10.345) and primary tumor size >0.7 cm (OR: 4.992; 95% CI: 1.756–14.190). As a result, they suggested an isthmusectomy may be insufficient in male patients, aged ≥ 38 years and with tumor larger than 0.6 cm.²² Huang et al studied 27 patients; 9 had an isthmusectomy, 14 received an extended isthmusectomy, and 4 received an isthmusectomy with unilateral lobectomy. They reported a 5-year RFS of 95.2% and suggested that an isthmusectomy or extended isthmusectomy is feasible for patients with WDTC arising in the isthmus.²³ We have previously reported on 19 patients who underwent isthmusectomy alone from 1986 to 2005 with satisfactory outcomes.²⁴ Our current study analyzes the outcomes of 43 patients treated with isthmusectomy alone for WDTC during a 30-year period. To our knowledge, this is the largest series reporting on the role of isthmusectomy alone for the management of WDTC confined to the isthmus, with up to 10 years of follow-up.

At our institution, an isthmusectomy is considered an oncologically safe procedure that encompasses all gross tumor and a surrounding portion of normal thyroid tissue.²⁴ Unlike other thyroid operations, including thyroid lobectomy, near-total or total thyroidectomy, an isthmusectomy does not require exploration of the tracheo-esophageal groove or formal identification of the recurrent laryngeal nerve and parathyroid glands. As a result, this procedure significantly reduces the risk of postoperative complications and morbidity. In our

cohort, none of the patients had any complications recorded in their medical records, such as recurrent laryngeal nerve injury, hypocalcemia, hematoma, or wound infection.

Recent studies of WDTC patients have reported an overall disease-related mortality rate of 1.0% to 2.6%.^{2,25–27} Following thyroid surgery for papillary thyroid microcarcinoma, with tumors ≤ 1 cm, disease-specific mortality rates have been reported to be $<1\%$, loco-regional recurrence rates approximately 2% to 6%, and distant recurrence rates 1% to 2%.^{28,29} Ghaznavi et al reported that the, “Integration of the AJCC stage, ATA risk, and age groups identified six subgroups with differing outcomes: (i) stage I/ATA low-risk, younger and older, 100.0% DSS; (ii) stage I/ATA intermediate-risk, younger and older, 98% DSS; (iii) stage I/ATA high-risk, younger, 95% DSS; (iv) stage I/ATA high-risk, older, 89% DSS; (v) stage II/ATA high-risk, younger, 78% DSS; and (vi) stage II/ATA high-risk, older, 61% DSS.”²⁵ The definition of low-risk WDTC was based on DSS. Other studies also report the 10-year DSS of the low-risk WDTC to be 95% to 100.0%.^{30,31} Lim et al reported that patients treated with a total thyroidectomy had an increased RFS when compared to those treated with lobectomy with isthmusectomy (hazard ratio: 0.355; 95% CI: 0.127–0.992).³² However, in another study of 27 patients with an isthmic WDTC managed with an isthmusectomy, extended isthmusectomy, or isthmusectomy and unilateral lobectomy, the 5-year RFS was 95.2%.²³ Sugeno et al.’s group studied 19 patients with WDTC isthmus malignancies. Four patients were treated with isthmusectomy alone and all were alive with no evidence of recurrence 20 years after initial surgery. This finding prompted the authors to recommend isthmusectomy as an appropriate treatment for malignant lesions of the thyroid isthmus.³³ In our study, the 5- and 10-year RFS were very similar to those who had only an isthmusectomy (93.1%), compared to those who had more aggressive thyroid gland surgery (94.6%); DSS were 100.0% in both groups at 10 years. Our results suggest that in properly selected patients, thyroid isthmusectomy alone is an effective treatment for WDTC. Finally, the 5- and 10-year outcomes according to the ATA risk stratification criteria were as follows. The 5- and 10-year RFS for low- and intermediate-risk groups were 100.0% and 87.5%, respectively. However, the DSS at 10 years was 100.0% for both groups. Another potential advantage of isthmusectomy alone is the avoidance for the need for postoperative thyroid hormone replacement, unless the TSH is elevated.

As with all retrospective studies, this study has several limitations that warrant discussion. Selection bias due to physician and patient preference cannot be ignored. Some patients with isthmic lesion alone may have been treated with total thyroidectomy or lobectomy as standard procedures in the management of WDTC patients. In addition, our approach to evaluating recurrence has evolved during the study period; in the first decade, most recurrences were detected on clinical examination. Since 2005, recurrent disease has been detected using serial ultrasounds and Tg measurements. As a result, our reported rate of recurrence, or appearance of new disease may be higher in the later time frame. However, this brings up an important and provocative question as to whether or not identification of subclinical disease with serial ultrasounds, Tg and TgAb determination improves long-term outcomes. Our findings of a 5- and 10-year DSS of 100.0% suggest this may not be clinically meaningful.

Based on our study, we feel isthmusectomy is considered adequate surgical treatment in low-risk patients with WDTC confined to the isthmus, without gross extrathyroid extension, or central compartment LN metastases, in the absence of any other nodules in the thyroid lobes.

5 | CONCLUSION

The role of isthmusectomy in the management of WDTC has been controversial. We report the outcomes of 43 consecutive patients treated with isthmusectomy alone for WDTC confined to the isthmus during a 30-year period. Our results show that isthmusectomy alone is an appropriate treatment option in selected patients with low- or intermediate-risk WDTC limited to the isthmus, and gives RFS and DSS similar to more extended thyroid operations.

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Abbreviations:

Ab	antibody
AJCC	American Joint Committee on Cancer
ATA	American Thyroid Association
CI	confidence interval
DSS	disease-specific survival
ETE	extra thyroid extension
LN	lymph node
OR	odds ratio
PTC	papillary thyroid carcinoma
RSS	recurrence-free survival
Tg	Thyroglobulin
WDTC	well-differentiated thyroid carcinoma

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FIGURE 1.

Kaplan-Meier estimates of recurrence-free survival (RFS) [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2.

Kaplan-Meier estimates of overall survival (OS) and disease specific survival (DSS) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1**Patient and tumor characteristics**

Patient and tumor characteristics	n (%) unless otherwise stated
Total	43 (100.0)
Sex	
Men	18 (41.9)
Women	25 (58.1)
Age	
Median (range)	39 (16–83)
<55 years old	34 (79.1)
55 years old	9 (20.9)
Histology	
Tall cell variant papillary thyroid carcinoma	7 (16.3)
Follicular variant papillary thyroid carcinoma	9 (20.9)
Classical variant papillary thyroid carcinoma	8 (18.6)
Unknown subtype papillary thyroid carcinoma	16 (37.2)
Follicular carcinoma: minimally invasive	3 (7.0)
Multifocality	
Not identified	35 (81.3)
Identified	5 (11.7)
Not reported	3 (7.0)
Margin	
Negative	35 (81.4)
Close	4 (9.3)
Positive	0 (0.0)
Not reported	4 (9.3)
Tumor size	
Median (range)	1.0 cm (0.3–3.0 cm)
Extrathyroidal extension	
Not Identified	27 (62.8)
Microscopic	15 (34.9)
Not reported	1 (2.3)

Note: Some columns may not equal 100.0 due to rounding.

TABLE 2**Staging and risk stratification**

	n (%)
Total	43 (100.0)
pT classification	
pT1a (≤ 1 cm)	25 (58.1)
pT1b (≤ 2 cm)	16 (37.2)
pT2 (≤ 4 cm)	2 (4.7)
pN classification	
pN0	33 (76.7)
pN1	10 (23.3)
M classification	
M0/MX	43 (100.0)
M1	0 (0.0)
AJCC stage (eighth edition)	
Stage I	42 (97.7)
Stage II	1 (2.3)
ATA risk	
Low	9 (20.9)
Intermediate	22 (51.2)
High	0 (0.0)
Unknown	12 (27.9)

Note: Some columns may not equal 100.0 due to rounding.

Abbreviations: AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association.