Survival after hemithyroidectomy versus total thyroidectomy in non-high-risk differentiated thyroid cancer: population-based analysis

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Abstract

Background: The extent of thyroid surgery remains controversial for differentiated thyroid cancers (DTCs) that measure more than 1 cm but are not considered high risk. This study aimed to compare survival outcomes between hemithyroidectomy (HT) and total thyroidectomy (TT) in non-high-risk DTCs.

Methods: A population-based retrospective cohort of patients with non-high-risk DTCs more than 1 cm undergoing HT or TT between 1997 and 2017 in a territory with 41 public hospitals and clinics serving a population of 7 million was analysed. Multivariable Cox proportional hazards regression models adjusted for patient demographics and clinical parameters were used to compare the overall, disease-specific, and recurrence-free survival between TT and HT. Risks of postoperative complications were compared between the two groups.

Results: A total of 4771 patients (HT, 1368; TT, 3403) underwent thyroid surgery as a primary treatment. Median (range) follow-up was 117 (range: 72–179) months. Patients in the TT and HT groups had comparable risks of overall survival (HR 0.87; 95 per cent c.i. 0.73 to 1.04; P = 0.119) and disease-specific survival (HR 0.85; 95 per cent c.i. 0.52 to 1.40; P = 0.518). The TT group had better recurrence-free survival (HR 0.37; 95 per cent c.i. 0.26 to 0.52; P < 0.001) than the HT group. The temporary and permanent hypoparathyroidism rates in TT group were 14.96 per cent and 7.49 per cent respectively; none were reported in the HT group.

Conclusions: Despite the comparable overall and disease-specific survivals, TT was associated with better recurrence-free survival than HT in a 10-year follow-up. This was at the expense of higher surgical morbidity rate in TT.

Introduction

The incidence of thyroid cancers has risen sharply in the past three decades1–3 driven mostly by the diagnosis of small, low-risk papillary thyroid cancers (PTCs) which is a predominant subtype of differentiated thyroid cancers (DTCs)4. This rising trend has raised concerns among clinicians about the over-diagnosis as well as overtreatment of ‘low-risk’ DTCs5–7. In response to these concerns, the 2009 and, to a greater extent, the 2015 revised American Thyroid Association (ATA) guidelines adopted a less aggressive approach for the management of low-risk DTCs8,9.

The most updated ATA guidelines recommended that patients with thyroid tumours more than 4 cm should perform near-total or total thyroidectomy (TT) as an initial procedure9. Tumours measuring 1–4 cm without minimal extrathyroidal extension and nodal metastasis can be offered either a hemithyroidectomy (HT) or TT9, whereas tumours measuring 1–4 cm with any one of the following features (microscopic invasion to the perithyroidal soft tissues, aggressive histology, vascular invasion, and/or nodal disease with more than five pathologically involved lymph nodes less than 3 cm in the largest dimension) would benefit from TT in the long term10,11; however, many of these histological features can be found in occult thyroid cancers during post-mortem examinations12, implying that these high-risk features may not actually translate into additional risk for recurrence12. Perhaps, a less aggressive surgical approach (HT) is more appropriate. We hypothesized that unless the DTCs measuring more than 1 cm had one of the high-risk features such as incomplete resection, gross extrathyroidal extension of the tumour, or the presence of distant metastases and/or clinical nodal disease, an HT would offer similar survival outcomes as TT.

To address this issue, this study aimed to compare the long-term survival outcomes between TT and HT for...
non-high-risk DTCs (tumours without high-risk features) using a population-based database.

Methods

Patient and data collection

The authorized approval of this study was obtained from the local institutional review board before commencement. Data of patients with DTC who underwent thyroid surgery from 1 January 1997 to 31 December 2017 were prospectively collected from the territory-wide coded database (the Hong Kong Hospital Authority Clinical Management System (CMS)). The CMS system links up all 41 public hospitals and clinics and covers a population of 7 million in the territory. This system was developed in 1994, providing clinicians with the chance to record and obtain data from an integrated platform. This system links up all major public hospitals, accounting for about 90 per cent of all in-hospital health services across the territory. The completeness rates of 100 per cent and 99.98 per cent in patients’ demographic and prescription records have been reported by previous evidence, validating the quality of the data set.

A high positive predictive value of the database also has been verified by recent studies. This database has been utilized in previous publications on thyroid disease.

To be eligible, patients who had a coded diagnosis of DTCs (PTCs or follicular thyroid carcinoma (FTC)), underwent either an HT or TT as a primary procedure, and had at least a 1-year follow-up after surgery were included in the study. PTCs and FTC accounted for about 85 per cent and 10 per cent respectively of all thyroid cancer incidences in Hong Kong. Small tumours (1 cm or less in diameter) that were found incidentally and had no metastasis, local invasion, or aggressive pathological features, were not included as they were categorized as benign in the territory-wide database. Those patients who had incomplete resection with or without gross extrathyroidal extension, who underwent neck dissection, or had evidence of clinical nodal disease, had a diagnosis of distant metastasis before surgery or within 1 year after surgery, had previous thyroid surgery or treatment for any thyroid disease or cancer, and those younger than 18 years old at the time of thyroid surgery were excluded.

Within a cohort of DTCs, ICD-9-CM codes were used to retrieve details of the surgical procedures (HT or TT). The cohort was then categorized into groups of TT and HT according to the extent of thyroidectomy. Those who underwent a completion thyroidectomy within 1 year of their initial HT were categorized into the TT group. Receiving a subsequent thyroidectomy beyond 1 year after initial HT was identified as recurrence. During the study interval, the decision for either HT or TT was at the discretion of the operating surgeon at that particular hospital; however, it should be noted that ATA guidelines have been the most recognized and adopted set of guidelines by surgeons in the territory. Therefore, the preference for HT or TT fluctuated during the study interval with HT being more frequently performed after the issuance of the 2015 ATA guidelines.

The index date of the study was defined as the date of thyroidectomy after the diagnosis of thyroid cancer. Data related to the demographics, laboratory tests, surgery types, history of co-morbidities, duration of thyroid cancer, and survival outcomes were collected for comparison analysis.

Outcomes

The outcomes of this study included overall survival, disease-specific survival, and recurrence-free survival. Recurrence was defined as an event that was followed by intervention such as a surgical biopsy, nodal excision, or neck dissection 12 months or more after the primary surgery. All patients were followed from the index date until the date of death, recurrence, or the date of data cut-off (31 December 2020), whichever came first. HT patients were censored as recurrence at the time when they had subsequent thyroidectomy more than 1 year after initial thyroid surgery. Reported surgical complications included neck hematoma, temporary or permanent (more than 12 months) hypoparathyroidism, and recurrent laryngeal nerve (RLN) injury. Permanent hypoparathyroidism was defined as postoperative albumin calcium (Ca) levels of less than 1.9 mmol/l with receiving Ca and/or vitamin D replacement therapy for more than 12 months after surgery. Transient hypoparathyroidism was defined as receiving replacement therapy of Ca and/or vitamin D for less than 12 months after surgery. Permanent unilateral RLN injury was identified if patients had a diagnosis of paralysis of vocal cords or larynx and/or received surgical treatment of repair larynx or speech therapy and management after 6 months from surgery, which were identified using the ICD-9-CM procedure codes. Bilateral damage to the larynx typically presented as dyspnoea with inspiratory stridor was not included in this study. All the disease diagnoses, treatment procedures, and surgical complication codes used in the study are listed in Table S1.

Statistical analyses

Baseline variables included age, sex, history of coronary heart diseases, heart failure, stroke, atrial fibrillation, diabetes, and hypertension, Charlson co-morbidity index (CCI) before the surgery date, and duration of DTC from date of diagnosis to date of thyroidectomy. An absolute standardized mean difference (ASMD) less than 0.2 was used to determine similarities between the two surgical groups.

Kaplan–Meier curves were plotted to assess the probabilities of survival outcomes, combined with the log rank test to estimate the difference between patients undergoing TT and HT. The multivariable Cox proportional hazards regression models adjusted with baseline variables were conducted to assess the relative risks of survival outcomes between the two surgical groups. The results estimated from the estimation models were reported as HR and their 95 per cent confidence interval (c.i.). Logistic regression was used to compare the incidence of postoperative complications after TT and HT.

Sensitivity analyses were performed to test the robustness of results by comparing survival outcomes between groups at different endpoints at the 5-year and 10-year follow-up; excluding patients receiving radioactive iodine therapy (RAI), which might be a confounding factor and associated with better survival outcomes. Subgroup analyses were conducted by categorizing patients into different subsets according to age at diagnosis (55 years or younger and older than 55), sex (female: male), and the date undergoing surgery (1997–2015 and 2016–2017 (interval after the issuance of the updated 2015 ATA guidelines)).

All statistical analyses were performed using STATA version 16.0. (Stata Corp, College Station, TX, USA). A two-tailed P value <0.05 was considered statistically significant.

Results

After excluding those who did not meet the inclusion criteria for DTCs that were larger than 1 cm but without true high-risk features, the study included 7532 patients, including 5741 patients undergoing HT and 1791 patients undergoing TT. The median age of patients was 55.8 years (IQR 41.4–70.9 years), and 73.7 per cent of patients were female. The most common histological type was PTC (79.0 per cent). The median follow-up time was 6.6 years (IQR 2.8–8.6 years), with 66.9 per cent of patients having more than 5 years of follow-up. The overall incidence of recurrence was 10.8 per cent (95 per cent c.i. 9.4–12.2 per cent) at 10 years, and the 10-year overall survival rate was 89.9 per cent (95 per cent c.i. 88.3–91.5 per cent). The most common cause of death was competing cause of death (28.9 per cent), followed by thyroid cancer (22.8 per cent).

In the univariable analysis, patients undergoing HT had a significantly lower risk of recurrence than patients undergoing TT (HR 0.72, 95 per cent c.i. 0.59–0.88, P = 0.0036) but a similar risk of death (HR 0.96, 95 per cent c.i. 0.80–1.14, P = 0.6398). In the multivariable analysis, patients undergoing HT had a significantly lower risk of recurrence than patients undergoing TT (HR 0.67, 95 per cent c.i. 0.55–0.81, P = 0.0002) and a similar risk of death (HR 0.98, 95 per cent c.i. 0.81–1.18, P = 0.8468).
features over the study interval, a total of 4771 patients were eligible for analysis (Fig. 1). TT was performed in 3403 (71.3 per cent), whereas HT was performed in 1368 (28.7 per cent) patients.

Table 1 compares the baseline characteristics of patients between the two groups. Of all patients, the mean(s.d.) age was 50.57(14.52) years, 3057 (64.07 per cent) were aged 55 years or younger, and 3812 (79.90 per cent) were female. Overall, 124 (2.60 per cent) had a history of coronary heart disease, 383 (8.03 per cent) had diabetes, 883 (18.51 per cent) had hypertension, and 1915 (40.14 per cent) had a CCI score of 4 or higher. All variables at baseline (all ASMDs less than 0.2) were similar between the TT and HT groups. The median (range) follow-up of the cohort was 117 (72–179) months (for TT, 120 (76–183) months; for HT, 106 (63–168) months).

Table 2 displays the cumulative incidence and incidence rates of survival outcomes of the two surgical cohorts. During the survey interval, patients in the TT and HT group had similar cumulative incidences of overall death (13.81 per cent versus 13.16 per cent) and disease-specific death (1.67 per cent versus 1.61 per cent). A total of 62 patients in the HT group were censored as recurrence when they performed subsequent thyroidectomy more than 1 year after the initial surgery. A lower cumulative incidence of recurrence (1.94 per cent versus 4.97 per cent) was observed in patients undergoing TT than in those treated with HT. Similar results were observed at different time points at the 5-year and 10-year follow-up (Table S2). The cumulative incidence of overall death was 4.38 per cent and 9.05 per cent, disease-specific death was 0.65 per cent and 1.32 per cent, and recurrence was 1.29 per cent and 1.79 per cent in the TT group at the 5-year and 10-year follow-up respectively. In HT group, the cumulative incidence of overall death was 4.90 per cent and 9.28 per cent, disease-specific death was 0.51 per cent and 0.95 per cent, and recurrence was 3.65 per cent and 4.53 per cent at the 5-year and 10-year follow-up respectively.

Despite patients undergoing TT and HT having similar incidence rates of overall death (12.54 versus 13.12 per 1000 person-years) and disease-specific death (1.52 versus 1.60 per 1000 person-years), the TT group had a lower incidence rate of recurrence (1.78 versus 5.06 per 1000 person-years) than the HT group at the end of follow-up.

Table 3 shows the results assessed by Cox proportional hazards models, which were adjusted for variables at baseline. No differences were found in patients treated with TT and HT in overall survival (HR 0.87; 95 per cent c.i. 0.73 to 1.04; P=0.119) and disease-specific survival (HR 0.85; 95 per cent c.i. 0.52 to 1.40; P=0.518). A better recurrence-free survival (HR 0.37; 95 per cent c.i. 0.26 to 0.52; P<0.001) was observed in patients who underwent TT. Figure 2 displays the 10-year survival curves for each outcome. The log rank tests showed no significant difference in overall survival and disease-specific survival between patients in the TT and HT group. Recurrence-free survival (P<0.001) was significantly increased in patients undergoing TT compared with HT.

Table 4 displays the comparison of surgical complication rates between the TT and HT groups. Patients following TT or HT were at risk of transient or permanent hypoparathyroidism and permanent unilateral RLN injury that was compared between groups. There was no significant difference in hematoma (0.85 per cent versus 0.95 per cent, P=0.743) and permanent unilateral RLN injury (1.79 per cent versus 1.02 per cent, P=0.057) in patients treated with TT and HT. The rates of transient and permanent hypoparathyroidism were 14.96 per cent and...
7.49 per cent respectively in the TT group. None resulted in the HT group.

The estimations from the sensitivity analyses were consistent with those in the primary analysis (Table S3). After excluding patients that received RAI after surgery (2157 (63.39 per cent) in TT and no case in the HT group), comparable overall survival and disease-specific survival were found between the two groups. A more favourable recurrence-free survival (HR 0.28; 95 per cent c.i. 0.17 to 0.44; P < 0.001) occurred in patients undergoing TT versus HT. Most results from the subgroup analyses by age and sex aligned with the primary analysis (Table S4). Notably, in patients aged 55 years or younger, TT had a favourable disease-specific survival compared with HT. In women, a better overall survival was found in TT than HT; however, TT was not associated with improved recurrence-free survival in men nor in patients who underwent surgery between 2016 and 2017.

**Discussion**

The optimal extent of thyroid surgery for DTCs that measure more than 1 cm and do not possess any high-risk factors, such as incomplete resection, gross extrathyroidal extension, clinically nodal disease, and distant metastasis, remains controversial. Ideally, initial treatment should offer the best disease control and survival outcomes without compromising safety concerns.
### Table 3 Hazard ratios of survival outcomes in patients undergoing hemithyroidectomy or total thyroidectomy for non-high-risk differentiated thyroid cancer at 5-year, 10-year, and the end of follow-up

| Outcomes | HR* | 95% c.i. | P   |
|----------|-----|----------|-----|
| Until end of follow-up† |     |          |     |
| Overall survival | 0.87 | (0.73,1.04) | 0.119 |
| Disease-specific survival | 0.85 | (0.52,1.40) | 0.518 |
| Recurrence-free survival | 0.37 | (0.26,0.52) | <0.001‡ |
| 5-year follow-up |     |          |     |
| Overall survival | 0.72 | (0.54,0.96) | 0.023‡ |
| Disease-specific survival | 1.10 | (0.46,2.58) | 0.834 |
| Recurrence-free survival | 0.35 | (0.23,0.53) | <0.001‡ |
| 10-year follow-up |     |          |     |
| Overall survival | 0.82 | (0.67,1.02) | 0.071 |
| Disease-specific survival | 1.22 | (0.66,2.28) | 0.524 |
| Recurrence-free survival | 0.38 | (0.27,0.55) | <0.001‡ |

*Adjusted for variables of age, sex, history of coronary heart disease, heart failure, stroke, atrial fibrillation, diabetes and hypertension, duration of thyroid cancer, and Charlson co-morbidity index. †Median 117 months (range 72–179).
‡Significant at 0.05 level by multivariable Cox proportional hazard regression.

Recurrence-free survival is an important survival outcome for deciding the extent of surgery. Aligning with the higher rate of recurrence-free survival in the TT than HT group of this cohort (10-year follow-up, 98.2 per cent versus 95.5 per cent), a previous meta-analysis showed a higher rate in patients who had TT than those treated with HT (95 per cent versus 92 per cent)31. Another meta-analysis by Zhang et al. suggested that HT increased the risk of recurrence in DTC for tumours 1.0 cm or smaller as well as tumours more than 1.0 cm12. In a study with 52,173 patients, Bilimoria et al. showed that TT was associated with a lower risk of recurrence and better survival compared with lobectomy for PTC more than 1.0 cm10. These findings agree with the assessment in this study that better recurrence-free survival was found in those undergoing TT for DTCs.

Despite the favourable recurrence-free survival in patients with TT versus HT in this study, some studies contested this indicating equivalent outcomes. From a study including patients with intra-thyroidal DTC, Nixon et al. showed no difference in local recurrence or regional recurrence between the lobectomy and TT group35. In an individual risk factor-matched cohort study with a median follow-up of 8.5 years, Kwon et al. reported similar performance in recurrence by extent of surgery34. The study by Kim et al. involving 8676 patients with papillary thyroid micro-carcinoma also showed no increased risk of locoregional recurrence outside of the contralateral remnant lobe in patients who underwent lobectomy compared with those treated with TT35. Differences in studies might be explained by the definitions of recurrence, which varied in the diagnosis of abnormality in imaging, cytological, and/or pathological analysis34,36,37. This present study used surgical biopsy, node excision, or neck dissection after primary thyroidectomy to define recurrence, which differed from other studies but provided a novel assessment. More studies are needed to explore the reasons for these differences, as well as the need for total or completion thyroidectomy.

Consistent with previously reported findings38,39, this study showed that transient and permanent hypoparathyroidism occurred in 14.96 per cent and 7.49 per cent of patients with TT respectively, compared with no case in those with HT. The incidence of transient and permanent hypoparathyroidism was relatively high in TT versus HT group. Postoperative hypoparathyroidism/hypocalcaemia poses a major challenge for patients undergoing TT (as opposed to HT34,40). Fortunately, the rate of RLN injury and haematoma did not differ significantly between the two groups. Similar to this study, Kwon et al. reported a higher hypoparathyroidism rate in the TT group34.

Using the nationwide inpatient sample database, Baldassarre et al. identified the independent risk factors of postoperative hypocalcaemia and showed that TT was associated with a significantly higher risk of hypocalcaemia compared with HT41. The study by Lo et al. also reported a higher incidence of RLN paralysis in TT patients than in HT patients42. With the application of extensive thyroid surgery to treat DTCs, the development of postoperative complications in patients after surgery should also be taken into consideration.

The main strengths of this study were the long-term follow-up and a large patient cohort. To estimate the survival outcomes over a long interval, patients who performed thyroid surgery between 1997 and 2017 and had a 12-month follow-up or longer were included in the analysis. This population-based study also provided more evidence from the real world to improve the management guideline for DTCs that were more than 1 cm and...
Fig. 2 Kaplan–Meier curves in patients undergoing hemithyroidectomy or total thyroidectomy for non-high-risk differentiated thyroid cancer

- **a** Overall survival
- **b** Disease-specific survival
- **c** Recurrence-free survival
without clear higher-risk factors. Another strength of this present study is that the impact of subsequent therapy of RAI on the survival outcomes was assessed by performing an analysis among patients who had no RAI after thyroid surgery. Adverse effects of thyroxine suppression may include the known increased risk for atrial fibrillation and osteoporosis\textsuperscript{33,34}; however, this study did not support the significant difference in these events between patients receiving a higher thyroxine dose and those receiving a relatively lower dose. This study also estimated major complications after thyroidectomy, showing that patients following TT would suffer excess surgical morbidity rate compared with those who underwent HT. This finding contributed to putting more considerations in the therapy decision for DTCs that TT might reduce recurrence rate but impose additional costs due to monitoring for and treating the surgical complications.

Nevertheless, some limitations of the study should be acknowledged. First, the retrospective study design may lead to bias in the outcome estimations; however, the data recorded in the CMS database have been validated and have a high positive predictive value\textsuperscript{46,47}. The current database management system has taken a series of measures to ensure the quality of data. Coding errors and implausible data have been avoided or corrected through reference range tables that enable one to categorize, classify, qualify, and constrain other data; provide a method of coding and decoding; and ensure that only valid values are entered into a database\textsuperscript{46}. The management system also provides methods that can check and ensure valid values, such as allowing the authorized users to manage, update, or delete those wrong records\textsuperscript{46}. Second, the information on PTCs such as allowing the authorized users to manage, update, or also provides methods that can check and ensure valid values, among patients who had no RAI after thyroid surgery. Adverse effects of thyroxine suppression may include the known increased risk for atrial fibrillation and osteoporosis\textsuperscript{33,34}; however, this study did not support the significant difference in these events between patients receiving a higher thyroxine dose and those receiving a relatively lower dose. This study also estimated major complications after thyroidectomy, showing that patients following TT would suffer excess surgical morbidity rate compared with those who underwent HT. This finding contributed to putting more considerations in the therapy decision for DTCs that TT might reduce recurrence rate but impose additional costs due to monitoring for and treating the surgical complications.

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**Disclosure**

The authors declare no conflict of interest.

**Supplementary material**

Supplementary material is available at BJS Open online.

**Data availability**

Due to ethical concerns, supporting data cannot be made openly available.

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