Total thyroidectomy versus lobectomy for papillary thyroid cancer

A systematic review and meta-analysis

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Abstract

Background: This systematic review and meta-analysis collected data for evaluating the effect of surgical extent on overall survival (OS) and recurrence-free survival (RFS) in patients with papillary thyroid cancer (PTC).

Methods: We searched the PubMed, Embase, and Cochrane Library databases. The included studies compared two groups of patients with PTC: the total thyroidectomy (TT) group and the lobectomy (LT) group. The combined hazard ratio (HR) was calculated.

Results: Thirteen studies were included in the present study. The TT and LT groups had similar OS results (HR = 1.04; 95% CI: 0.90–1.21; \( P = .80 \)). In the subgroup analysis, the combined HR of the \( \leq 1 \) cm group and the 1.0 to 2.0 cm group showed that TT had no advantage with regard to OS compared to LT. In the 2.0 to 4.0 cm group, TT provided better OS than LT (HR = 0.88; 95% CI: 0.79–0.99; \( P = .03 \)). Patients who underwent TT had a better RFS outcome than those who underwent LT (HR = 0.56; 95% CI: 0.41–0.77; \( P < .0001 \)). In the subgroup analysis, both the \( \leq 1 \) cm group and >1 cm group that underwent TT were associated with better RFS.

Conclusions: Our meta-analysis suggested that LT increased the risk of recurrence in PTC patients with tumors \( \leq 1.0 \) cm and in PTC patients with tumors >1.0 cm. More importantly, LT was associated with higher mortality in PTC patients with 2.0 to 4.0 cm tumors. Caution is warranted when LT is performed in this group of patients.

Abbreviations: ATA = American Thyroid Association, CI = confidence interval, HR = hazard ratio, LT = lobectomy, NOS = Newcastle-Ottawa Scale, OS = overall survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PTC = papillary thyroid cancer, PTMC = papillary thyroid microcarcinoma, RFS = recurrence-free survival, TT = total thyroidectomy

Keywords: lobectomy, mortality, papillary thyroid cancer, recurrence, total thyroidectomy

1. Introduction

The incidence of thyroid cancer has increased greatly worldwide in the past few decades.\textsuperscript{[11–17]} This increase has been attributed mainly to papillary thyroid cancer (PTC),\textsuperscript{[16–19]} which is the most common histologic subtype of thyroid cancer, comprising up to 88% of all thyroid cancers.\textsuperscript{[11–14]}

Surgery is the mainstay treatment for PTC. The extent of the surgery can be categorized as total thyroidectomy (TT) or lobectomy (LT). There has been controversy regarding the optimal surgical extent of PTC for decades. TT provides advantages such as enabling the use of radioactive iodine as an adjuvant therapy, clearing microscopic cancer foci in the contralateral lobe, and allowing accurate postoperative thyroglobulin surveillance. LT decreases the risk of permanent hypoparathyroidism and recurrent laryngeal nerve injury.\textsuperscript{[14–16]} Furthermore, whether TT provides better overall survival (OS) or recurrence-free survival (RFS) than LT is unclear.

In general, patients with PTC have an excellent survival rate. There is no randomized clinical trial comparing the different surgical extent of PTC because it would require too many patients to be followed for a long time. The results of different retrospective studies addressing the surgical extent are inconsistent. Bilimoria’s study demonstrated that TT results in a lower recurrence rate and improved survival for PTC >1.0 cm compared to LT.\textsuperscript{[17]} The 2009 American Thyroid Association (ATA) guidelines recommended TT for PTC patients with tumors >1.0 cm.\textsuperscript{[18]} However, Adam’s study and Mendelsohn’s study contained many patients with tumors >1.0 cm and showed no difference in survival between TT and LT for patients with PTC.\textsuperscript{[19,20]} The 2015 updated ATA guidelines recommend that for tumors 1.0 to 4.0 cm without extrathyroidal extension and lymph node metastasis, both TT and LT are acceptable in patients with PTC.\textsuperscript{[21]}

Studies comparing TT and LT in patients with PTC have grown substantially since the 2015 ATA guidelines were...
published. In the current review, we performed a meta-analysis to collect data for evaluating the effect of surgical extent on OS and RFS in patients with PTC.

2. Materials and methods

2.1. Literature search strategy

We searched PubMed, Embase, and the Cochrane Library database using a combination of MeSH terms (“thyroid neoplasms”, “papillary thyroid cancer”, and “thyroidectomy”) and free text terms (“thyroid lobectomy” and “well-differentiated thyroid cancer”). Only articles published in English were selected. The search strategy is presented in Figure 1. Approval for this study was obtained from the Ethic Committee of Shandong Provincial Hospital Affiliated to Shandong University.

2.2. Study inclusion and exclusion criteria

The studies included in this review met the following criteria. First, the studied patients were diagnosed with PTC. Second, the studies included two groups: the TT group and LT group. Third, studies should compare the survival or recurrence of two different groups, and the hazard ratio (HR) and the 95% confidence interval (CI) should be obtained. Exclusion criteria included patients <18 years old, patients whose pathologic type was not PTC, and patients with recurrent or distant metastatic thyroid cancer. Letters, reviews, studies without full text, and non-English studies were also excluded.

2.3. Study quality assessment

The quality of the included studies was evaluated by the Newcastle-Ottawa Scale (NOS).[22] A maximum of nine points was assigned to each study, including the selection of the study groups, comparability of the groups, and outcomes. Studies with more than 6 points were considered to be of high quality. Otherwise, studies were excluded from the final meta-analysis.

2.4. Data extraction

The data were independently extracted by two reviewers and checked by other reviewers for accuracy. Discrepancies were resolved by consensus after discussion. Specific essential information was extracted, including first author, publication year, country of origin, number of patients, tumor size, median follow-up time, outcome of OS and/or RFS reported as HR and whether it was a multiple analysis.

2.5. Statistical analysis

The present study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] HRs and 95% CI for each comparison...
in the studies were extracted and pooled using the random-effects model in Review Manager (version 5.3; Cochrane Collaboration [http://www.cochrane.org]). An HR of less than one indicated a survival or recurrence benefit from TT. The heterogeneity of the studies was evaluated using the inconsistency statistic ($I^2$).[24] An $I^2$ of <25% represents low heterogeneity, 25–50% represents moderate heterogeneity, and >50% represents high heterogeneity.

3. Results

3.1. Characteristics of the included studies

Thirteen studies that met the inclusion criteria were analyzed in our meta-analysis.[17,19,20,25–28] Our search strategy is presented in Figure 1. The 13 studies were published between 2004 and 2018. Five studies were from the United States, and eight were from Korea. The characteristics of the 13 studies, including publication year, number of patients, patient age, sex, tumor size, follow-up time, multiple analyses, and outcomes assessed are listed in Table 1.

3.2. OS

Meta-analysis for OS included seven comparative studies. Among the seven studies, Haigh divided the patients into a high-risk group and a low-risk group, and Rajjoub also divided patients into two groups according to the tumor size. In these two studies, HR was reported separately according to two different groups of patients. The $I^2$ value was 72%, reflecting a high degree of HR heterogeneity among the included studies. Therefore, a random-effects model was used to estimate the combined HR. The combined HR was 1.04 (95% CI: 0.90–1.21; $P = 0.60$; Fig. 2A), showing that TT and LT had similar OS results.

We performed subgroup analysis according to different tumor sizes. In patients with tumors $\leq 1$ cm, the combined HR was 0.85 (95% CI: 0.66–1.09; $P = 0.21$; Fig. 2B) and showed similar OS for TT and LT. In patients with tumors between 1 cm and 2 cm, the combined HR was 0.99 (95% CI: 0.85–1.15; $P = 0.86$; Fig. 2C), showing that TT and LT had similar OS results. In patients with tumors between 2 cm and 4 cm, the combined HR was 0.88 (95% CI: 0.79–0.99; $P = 0.03$; Fig. 2D), indicating that TT provides better OS than LT.

3.3. RFS

Meta-analysis for RFS included nine comparative studies. The $I^2$ value was 78%, reflecting a high degree of HR heterogeneity among the included studies. Therefore, a random-effects model was used to estimate the combined HR, and the result was 0.56 (95% CI: 0.41–0.77; $P < 0.001$; Fig. 3A), showing that patients who underwent TT had a better RFS outcome than those who underwent LT.

Some studies have demonstrated that TT for PTC improves RFS only in patients with tumors $> 1$ cm. Whether TT for PTC improves RFS in patients with tumors $\leq 1$ cm is controversial. Therefore, we performed subgroup analysis according to different tumor sizes. We compared the RFS of TT with that of LT in patients with tumors $\leq 1$ cm. Five studies were included, and the combined HR was 0.51 (95% CI: 0.32–0.81; $P = 0.04$; Fig. 3B). This result indicated that TT can provide better RFS than LT in patients with tumors $\leq 1$ cm. In patients with tumors larger than 1 cm, the combined HR was 0.85 (95% CI: 0.76–0.96; $P = 0.009$; Fig. 3C). This result also showed that TT can provide better RFS than LT in patients with tumors $> 1$ cm.

Some studies revealed that most recurrence of PTC patients who underwent LT occurred in the contralateral lobe. We compared the RFS of TT with that of LT after exclusion of contralateral lobe recurrence. Two studies were included, and the combined HR was 0.66 (95% CI: 0.29–1.49; $P = 0.32$; Fig. 3D).

### Table 1

**Characteristics of the included studies.**

| First author | Publication year | Country of origin | Number of patients | Mean age (years) | Female | Tumor size | Mean follow-up time (years) | Multiple analysis | Outcomes assessed |
|--------------|-----------------|-------------------|--------------------|-----------------|--------|------------|--------------------------|-------------------|------------------|
| Haigh        | 2005            | USA               | 4612               | NA              | 4191   | $< 5 \text{ cm}$ 5027$^*$; $\geq 5 \text{ cm}$ 405$^*$ | 7.4             | Yes              | Mortality           |
| Bilmoria     | 2007            | USA               | 43,227             | 8946            | 39,426 | $< 1 \text{ cm}$ 10,247$^*$; $\geq 1 \text{ cm}$ 38,705$^*$ | 5.8             | Yes              | Recurrence, mortality |
| Mendelsohn   | 2010            | USA               | 16,760             | 5964            | 17,727 | $< 1 \text{ cm}$ 6542$^*$; $\geq 1 \text{ cm}$ 16,182$^*$ | 9.1             | Yes              | Recurrence, mortality |
| Lee          | 2013            | Korea             | 506                | 506             | 908    | $< 1 \text{ cm}$ | 11.8            | Yes              | Recurrence, mortality |
| Adam         | 2014            | USA               | 54,926             | 6849            | 48,788 | 1–4 cm | 6.8             |                   | Mortality |
| Lim          | 2015            | Korea             | 97                 | 126             | 201    | $< 4 \text{ cm}$ | 5.4             |                   | Recurrence |
| Hwangbo      | 2016            | Korea             | 2839              | 443             | 2897   | $< 2 \text{ cm}$ | 5.8             |                   | Recurrence, mortality |
| Kim SK       | 2016            | Korea             | 5387              | 3289            | 7057   | $< 1 \text{ cm}$ | 5.4             |                   | Recurrence |
| Kim MJ       | 2017            | Korea             | 298               | 147             | 368    | 1–4 cm | 7.0$^1$ | No              | Recurrence |
| Kwon         | 2017            | Korea             | 688               | 47              | 1216   | 0.5–0.8 cm | 8.5$^3$ | No              | Recurrence |
| Rajjoub      | 2018            | USA               | 21,589            | 1310            | 18,055 | 1.0–3.3 cm | 6.49            | Yes              | Mortality |
| Zhang        | 2018            | Korea             | 4262              | 968             | 4449   | $< 1 \text{ cm}$ 2934$^*$; $\geq 1 \text{ cm}$ 2131$^*$ | 10.2$^3$ | Yes              | Mortality |
| Song         | 2018            | Korea             | 381               | 381             | 644    | 1–4 cm | 9.8$^1$ | Yes              | Recurrence |

$^*$: Number of patients of corresponding tumor size.

$^1$: The median follow up time.
showing that there were no significant differences in RFS between TT and LT.

3.4. Quality of the included studies and publication bias

The quality of the 13 included studies was evaluated by NOS, and the scores were all ≥ 6 points (Table 2). This indicated that all the included studies were high quality.

To evaluate the publication bias of aggregated data in this meta-analysis, we generated funnel plots for OS and RFS (Fig. 4A and B). Overall, the included studies showed optimal symmetry, suggesting minimal publication bias.

4. Discussion

Thyroid cancer is the most rapidly increasing cancer in the past few decades in many countries. The incidence of thyroid cancer increased by 24.2% per year from 1999 to 2010.13 The American Cancer Society projected an incidence of 53,990 cases of thyroid cancer in 2018 in the United States.136 The estimated
The number of new cases of thyroid cancer in 2018 in 185 countries was 567,233.[37] The increasing incidence of thyroid cancer is largely because of the increased diagnosis of PTC through diagnostic changes.[37]

The debate on the appropriate extent of surgery for PTC has persisted for several decades. This controversy is mainly due to the positive prognosis of PTC patients and the questionable effect that TT has on patient OS and RFS. The 2006 ATA guidelines recommended TT for most patients with PTC.[38] As many studies revealed a positive prognosis of patients with tumors <1 cm, the 2009 ATA guidelines recommended TT for PTC patients with a tumor ≥1 cm,[18] and LT can be performed in low-risk patients with a tumor <1 cm. In 2015, ATA guidelines recommended that LT can be performed in selected patients with 1.0–4.0 cm tumors.[21] Recently, Gartland reviewed whether LT versus TT for PTC patients with tumors measuring 1.0 to 4.0 cm impacts tumor recurrence and survival.[39] They concluded that most data support that LT yields comparable oncologic outcomes for PTC patients with 1.0 to 4.0 cm tumors. Although the new ATA guideline has widened the group of patients with

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | IV | Random | 95% CI Year |
|------------------|------------------|----|--------|----|--------|-------------|
| Bilimoria        | -0.451           | 0.1368 | 14.4% | 0.64 | 0.40/0.84 | 2007        |
| Mendelsohn       | 0.0944           | 0.1266 | 16.5% | 1.10 | 0.86/1.41 | 2010        |
| Lee              | -1.1249          | 0.2228 | 12.4% | 0.32 | 0.21/0.50 | 2013        |
| Lim              | -1.1712          | 0.5333 | 5.9%  | 0.31 | 0.11/0.88 | 2015        |
| Hwangbo          | -0.5365          | 0.1834 | 13.3% | 0.58 | 0.41/0.84 | 2016        |
| Kim SK           | -0.9213          | 0.2075 | 12.7% | 0.40 | 0.27/0.60 | 2016        |
| Kim MJ           | -0.2151          | 0.4138 | 7.9%  | 0.81 | 0.36/1.81 | 2017        |
| Kwon             | -0.8916          | 0.3414 | 9.4%  | 0.41 | 0.21/0.80 | 2017        |
| Song             | -0.3577          | 0.3482 | 9.3%  | 0.70 | 0.35/1.38 | 2018        |

Total (95% CI) 100.0% 0.56 [0.41, 0.77]

Test for overall effect: Z = 3.56 (P = 0.0004)

Figure 3. Forest plot of studies comparing TT with LT for RFS in patients with PTC. (A) including all group of patients; (B) in patients with tumors ≤1.0 cm; (C) in patients with tumors >1 cm; (D) after exclusion of contralateral lobe recurrence. LT = lobectomy, RFS = recurrence-free survival, PTC = papillary thyroid cancer, TT = total thyroidectomy.
PTC who are suitable for LT, many low-risk patients with small
tumor sizes still received TT in many centers. The debate
regarding the proper surgical extent for PTC is still ongoing.
Macedo and his colleagues systematically evaluated the impact
of the surgical extent of thyroid resection on RFS and OS for
papillary thyroid microcarcinoma (PTMC).
They found that TT was associated with better RFS and could not
draw a conclusion about the correlation of surgical extent and OS due to
the small number of mortality events. A similar meta-analysis was
recently performed by Zheng and his colleagues. They drew a
similar conclusion with a previous meta-analysis by Macedo,
where patients who received TT had a decreased risk of
recurrence but not mortality compared to patients who had
LT for PTMC. In the current meta-analysis, tumor size was not
restricted, and several new published studies were included to
evaluate the effect of surgical extent on OS and RFS in patients
with PTC.

The combined HR of OS indicated that TT did not show an OS
advantage compared to LT. This result was similar to previous
two meta-analyses. All seven included comparative studies
underwent multiple analyses. Factors including age, sex, tumor
size, lymph node metastasis, and extrathyroidal extension were
adjusted in most of the multiple analyses. In Haigh’s study,
patients with low-risk PTC had worse OS after TT, which was an
unexpected finding. The authors attributed this result to the
strong section bias in favor of the use of TT. In Bilimoria’s
research, the results of multivariate analyses showed that LT was
associated with a 21% higher risk of death compared to TT. However,
potential influence factors in surgical type selection,
such as multifocality and extrathyroidal extension, were not
adjusted for in this study. The 10-year survival after TT was
98.4% compared with 97.1% after LT. The absolute benefit of
TT for OS is very low. In subgroup analysis, the corresponding
combined HR of the <1 cm group as well as the 1.0–2.0 cm group
indicated similar OS for TT and LT. In the 2.0–4.0 cm group, the
combined HR showed that TT was associated with improved OS.
This finding suggested that LT might be insufficient for PTC
patients with tumors larger than 2 cm. According to the 2015
ATA guidelines, LT can be performed in selected patients in this
group. To address this question, further study is needed.

ATA guidelines mainly focus on mortality. However, the most
important advantage conferred by TT was a decrease in the risk
of recurrence. In the present study, the combined HR indicated a
better RFS of patients who underwent TT compared with LT. In
the subgroup analysis, the combined HR in both the ≤1 cm group
and the >1 cm group suggested that TT was associated with

| Table 2 | Newcastle-Ottawa Scale for quality assessment. |
|--------|------------------------------------------------|
| Study  | Selection | Comparability | Outcome |
|        | Exposed cohort | Non-exposed cohort | Ascertainment of exposure | Outcome of interest | Control for factor | Assessment of outcome | Follow-up long enough | Adequacy of follow-up | Total score |
| Haigh  | * | * | * | * | * | * | * | * | * | 8 |
| Bilimoria | * | * | * | * | * | * | * | * | * | 8 |
| Mendelsohn | * | * | * | * | * | * | * | * | * | 8 |
| Lee | * | * | * | * | * | * | * | * | * | 9 |
| Adam | * | * | * | * | * | * | * | * | * | 8 |
| Lim | * | * | * | * | * | * | * | * | * | 8 |
| Hwangbo | * | * | * | * | * | * | * | * | * | 8 |
| Kim SK | * | * | * | * | * | * | * | * | * | 8 |
| Kim MJ | * | * | * | * | * | * | * | * | * | 8 |
| Kwon | * | * | * | * | * | * | * | * | * | 9 |
| Rajjoub | * | * | * | * | * | * | * | * | * | 8 |
| Zhang | * | * | * | * | * | * | * | * | * | 8 |
| Song | * | * | * | * | * | * | * | * | * | 9 |

Figure 4. Funnel plots used to assess the effects of publication bias on the OS and RFS. (A) funnel plot to assess publication bias effect on the OS; (B) funnel plot to assess publication bias on the RFS. Each dot represents a separate study. The funnel plots revealed no apparent evidence of publication bias. OS = overall survival, RFS = recurrence-free survival.
better RFS than LT. These results were similar to previous studies.\(^1\) Most recurrences in patients who received LT occurred in the contralateral lobe of the thyroid. Local recurrence in the remnant lobe after LT can be managed safely by a second operation. Therefore, recurrence in the contralateral lobe can also be regarded as a new developing disease instead of being considered a recurrence. Two studies focusing on PTMC included in the current meta-analysis compared the TT group with LT group for RFS after exclusion of contralateral lobe recurrence. The combined HR after exclusion of contralateral lobe recurrence showed TT had similar RFS with LT. This result suggested that the advantage of TT for RFS in PTMC was mainly due to a decrease in the risk of contralateral lobe recurrence.

We acknowledge that there are several limitations that should be considered when interpreting our current meta-analysis. First, all included studies were nonrandomized observational clinical studies classified as low quality studies in meta-analysis. Second, there are different patient selection criteria in different studies that could lead to heterogeneity. Third, different follow-up times and inadequate records of adverse events may lead to bias. Fourth, only studies published in English were included in the present study, which may lead to publication bias. Fifth, factors including lymph node metastasis and radioactive iodine treatment can affect the recurrence. Although most studies included in this meta-analysis performed multivariate or risk factor matched analyse in comparing the surgical extent, these factors may still lead to bias.

In conclusion, based on data of current meta-analysis, LT increased the risk of recurrence in both PTC patients with tumors \(\leq 1\) cm and in PTC patients with tumors \(>1\) cm. Most recurrences occurred in the contralateral lobe, which were thought to be managed safely by a second operation. More importantly, our meta-analysis suggests that LT was associated with higher mortality in PTC patients with 2.0 to 4.0 cm tumors. Caution is warranted when LT is performed in this group of patients.

**Author contributions**

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