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Complication Rates of Total Thyroidectomy vs Hemithyroidectomy for Treatment of Papillary Thyroid Microcarcinoma
A Systematic Review and Meta-analysis

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Supplemental content

IMPORTANCE Papillary thyroid microcarcinomas (PTMCs) have been associated with increased thyroid cancer incidence in recent decades. Total thyroidectomy (TT) has historically been the primary treatment, but current guidelines recommend hemithyroidectomy (HT) for select low-risk cancers; however, the risk-benefit ratio of the 2 operations is incompletely characterized.

OBJECTIVE To compare surgical complication rates between TT and HT for PTMC treatment.

DATA SOURCES SCOPUS, Medline via the PubMed interface, and the Cochrane Central Register of Controlled Trials (CENTRAL); through January 1, 2021, with no starting date restriction. Terms related to papillary thyroid carcinoma and its treatment were used for article retrieval. This meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline and was written according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.

STUDY SELECTION Original investigations of adults reporting primary surgical treatment outcomes in PTMC and at least 1 complication of interest were included. Articles evaluating only secondary operations or non–open surgical approaches were excluded. Study selection, data extraction, and risk of bias assessment were performed by 2 independent reviewers and conflicts resolved by a senior reviewer.

DATA EXTRACTION AND SYNTHESIS Pooled effect estimates were calculated using a random-effects inverse-variance weighting model.

MAIN OUTCOMES AND MEASURES Cancer recurrence and site, mortality (all-cause and disease-specific), vocal fold paralysis, hypoparathyroidism, and hemorrhage/hematoma. Risk of bias was assessed using the McMaster Quality Assessment Scale of Harms scale.

RESULTS In this systematic review and meta-analysis, 17 studies were analyzed and included 1416 patients undergoing HT and 2411 patients undergoing TT (HT: pooled mean [SD] age, 47.0 [10.0] years; 1139 [84.6%] were female; and TT: pooled mean [SD] age, 48.8 [10.0] years; 1671 [77.4%] were female). Patients undergoing HT had significantly lower risk of temporary vocal fold paralysis compared with patients undergoing TT (3.3% vs 4.5%) (weighted risk ratio [RR], 0.4; 95% CI, 0.2-0.7), temporary hypoparathyroidism (2.2% vs 21.3%) (weighted RR, 0.1; 95% CI, 0.0-0.4), and permanent hypoparathyroidism (0% vs 1.8%) (weighted RR, 0.2; 95% CI, 0.0-0.8). Contralateral lobe malignant neoplasm recurrence was 2.3% in the HT group, while no such events occurred in the TT group. Hemithyroidectomy was associated with a higher overall recurrence rate (3.8% vs 1.0%) (weighted RR, 2.6; 95% CI, 1.3-5.4), but there was no difference in recurrence in the thyroid bed or neck.

CONCLUSIONS AND RELEVANCE The results of this systematic review and meta-analysis help characterize current knowledge of the risk-benefit ratio of HT vs TT for treatment of PTMC and provide data that may have utility for patient counseling surrounding treatment decisions.

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Papillary thyroid microcarcinomas (PTMCs), defined as papillary thyroid cancer measuring less than or equal to 1.0 cm at greatest diameter, have been diagnosed with increasing frequency and associated with an increase in thyroid cancer incidence over the past few decades.[1] The proportion of PTMCs increased from 25% of new thyroid cancer diagnoses in 1999 to 39% of new thyroid cancer diagnoses in 2009. Despite the increase in incidence, specific mortality from all stages of papillary thyroid cancer remains rare, with a 5-year relative survival rate of 99.71%.[2] A better understanding of the natural history of PTMCs has led to changes in treatment recommendations.[3-7] Whereas total thyroidectomy (TT) has historically been the primary treatment for PTMC, more recent guidelines recommend hemithyroidectomy (HT) and surveillance for low-risk differentiated cancers with specific sonographic features.[8-12] Although the use of HT has increased from 3.7% to 21.9% for treatment of papillary thyroid carcinoma less than 4 cm following the release of the 2014-2015 American Thyroid Association guidelines, TT remains the most common surgical approach for all T-stage categories, used for 52% to 78% of PTMC.[13-15] Among patients treated by endocrine surgeons, 75.8% of PTMC are treated using TT.[13]

Studies have shown no survival advantage for TT compared with HT for small papillary thyroid carcinomas, and locoregional recurrence in HT is rare with proper patient selection (1%-4%).[16-18] Moreover, appropriately treated recurrences are not associated with survival outcomes.[16-18] Although TT may reduce recurrence, it is associated with a higher surgical complication risk profile, greater cost, and longer hospital length of stay compared with HT.[19,20] Total thyroidectomy also necessitates lifelong postoperative thyroid hormone replacement, whereas this risk is estimated to affect 22% of patients undergoing HT.[21]

The choice between TT and HT for PTMC requires surgeons and patients to weigh surgical complication risk with the risk of recurrence. Systematic reviews have compared recurrence and survival outcomes between TT and HT for PTMC[22,23]; however, none has examined and quantified the differential risks of specific complications including hypocalcemia, hypoparathyroidism, vocal fold paralysis (VFP), and hematoma. Treating clinicians must be aware of complication risks so they can appropriately counsel patients. To assess TT and HT in the context of surgical risk and to assess strength of evidence in published literature, we conducted a systematic review and meta-analysis to compare surgical complication rates between TT and HT for the treatment of PTMC.

Key Points

Question What are the rates of common surgical complications in hemithyroidectomy (HT) compared with total thyroidectomy (TT) in the treatment of papillary thyroid microcarcinoma?

Findings In this systematic review and meta-analysis of 17 studies including 1416 patients undergoing HT and 2411 patients undergoing TT, patients undergoing HT were found to have a lower risk of temporary or permanent vocal fold paralysis compared with patients undergoing TT. Patients undergoing HT had a lower risk of temporary or permanent hypoparathyroidism compared with patients undergoing TT, and a higher risk of contralateral lobe malignant neoplasm recurrence compared with patients undergoing TT.

Meaning The findings of this study suggest that complications in the surgical management of micropapillary thyroid carcinoma increase with the extent of surgery performed, although complications and recurrence were low for both operations.

Methods

Search Strategy

This study followed the applicable portions of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline for assessing data quality and validity[24] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[25] We searched SCOPUS, Medline via the PubMed interface, and the Cochrane Central Register of Controlled Trials (CENTRAL) with no starting publication date restriction by using relevant vocabulary and key terms related to papillary thyroid carcinoma and microcarcinoma and its treatment, through January 1, 2021 (eMethods in the Supplement). Reference lists for all included articles and recent reviews related to papillary thyroid carcinoma, its treatment, and its complications were searched to identify any additional relevant articles.

Study Selection

Inclusion and exclusion criteria were developed in consultation with a panel of clinicians and researchers who treat and study thyroid cancer, a reference librarian, and systematic review experts. Original investigations of adult patients (aged ≥18 years; minimum sample size n = 20) that reported outcomes of primary surgical treatment of PTMC and at least 1 complication of interest were included. Articles that evaluated only secondary operations, non-open surgical approaches (eg, endoscopic or robotic) without an open surgical comparison, or that did not separate results for TT and HT were excluded. Complications were abstracted from randomized clinical trials and prospective or retrospective cohort studies. Two investigators (V.H. and A.A.A. or T.J.L. and M.T.) independently screened each abstract for inclusion in full-text review. Full-text records were then reviewed against inclusion criteria by 2 independent investigators (V.H. and A.A.A. or T.J.L. and M.T.).

Data Extraction

Two investigators (V.H. and A.A.A. or T.J.L. and M.T.) extracted data regarding study design, description of the study population, interventions and comparison groups, and outcomes using standardized forms. Primary outcomes of interest were cancer recurrence and site, mortality (all-cause and disease-specific), temporary and permanent VFP, temporary and permanent hypoparathyroidism, and hemorrhage or hematoma. All complications were defined by the investigators in each individual study. Hypoparathyroidism includes both hypocalcemia and hypoparathyroidism, as

Table. Pooled Unweighted Summary Data for Total Thyroidectomy and Hemithyroidectomy[a,b]

Variable	Hemithyroidectomy (n = 1416)		Total thyroidectomy (n = 2411)	
	No. in pooled mean (No. in pooled SD)[c]	No. or mean (% or SD)	No. in pooled mean (No. in pooled SD)[c]	No. or mean (% or SD)
Age, mean (SD), y	1347 (640)	47.0 (10.0)	2160 (943)	48.8 (10.0)
Female sex	1347	1139 (84.6)	2160	1671 (77.4)
Size, mean (SD), mm	1175 (399)	6.2 (2.2)	2160 (1386)	6.3 (2.3)
Multifocality	903	202 (22.4)	2380	669 (28.1)
Extrathyroidal extension	1093	362 (33.1)	2024	816 (40.3)
Concurrent				
CLND	1349	875 (64.9)	2380	2185 (91.8)
Lateral LND	98	0	288	116 (40.3)
VFP	1416	48 (3.4)	2411	124 (5.4)
Temporary	1416	47 (3.3)	2411	109 (4.5)
Permanent	617	1 (0.2)	1620	15 (0.9)
Hypoparathyroidism	1293	28 (2.2)	2411	556 (23.1)
Temporary	1293	28 (2.2)	2411	513 (21.3)
Permanent	1245	0	2380	43 (1.8)
Hemorrhage/hematoma	783	7 (0.9)	1593	11 (0.7)
Chyle leak	0	0 (U/NE)	1010	8 (0.8)
Thyroid hormone replacement	771	74 (9.6)	1392	1350 (97.0)
RAI[d]	215	14 (6.5)	1320	820 (62.1)
Reoperation	430	19 (4.4)	1281	8 (0.6)
Recurrence	1293	49 (3.8)	2150	22 (1.0)
Thyroid bed	1293	4 (0.3)	2150	4 (0.2)
Contralateral lobe	1293	30 (2.3)	2150	0
Neck	1293	15 (1.2)	2150	18 (0.8)
Distant metastasis	1293	0 (U/NE)	2150	0
Follow-up, mean (SD), mo	665 (209)	61.3 (22.3)	549 (200)	79.8 (21.0)
All-cause mortality	292	7 (2.4)	295	9 (3.1)
Disease-specific mortality	1001	0	1275	0

Abbreviations: CLND, central lymph node dissection; LND, lymph node dissection; RAI, radioactive iodine therapy; U/NE, undefined/not estimable; VFP, vocal fold paralysis.

[a] Continuous variables are expressed as mean (SD); dichotomous variables are expressed as frequency (percentage).

[b] Unweighted summary data of included studies. Table includes only data from articles that specified sample size for each operation.

[c] Total columns represent the number of participants at risk, based on whether collected study reported the outcome or not.

[d] RAI therapy was given to patients initially treated with hemithyroidectomy only in the case they ultimately underwent completion thyroidectomy because RAI is not recommended in patients with remaining thyroid parenchyma present.

reported definitions of each were inconsistent and overlapping. Additional end points abstracted included mean tumor size, multifocality, extrathyroidal extension, lymph node dissection, chyle leak, thyroid hormone replacement, radioactive iodine, reoperation, and mean follow-up time. Discrepancies between reviewers were resolved by consensus, then by a senior investigator (D.O.F.) if consensus could not be reached.

Study Quality Assessment

Two investigators (V.H. and A.A.A. or T.J.L. and M.T.) independently conducted quality assessment of each study using standardized forms with input from content experts. Discrepancies between reviewers were resolved by consensus with resolution by a senior investigator (D.O.F.) if consensus was not reached. Because this review primarily focuses on harms, risk of bias was assessed using a 4-question subset of the McMaster Quality Assessment Scale of Harms deemed most relevant, determined prior to the start of the analysis.[26] For this study we propose the following system to reach an overall risk of bias judgment: a study was considered to be at low risk of bias if it received positive ratings on all 4 questions, moderate risk if it received 3 positive ratings, and high risk if it had between 0 and 2 positive ratings.

Statistical Analysis

Frequencies were calculated for all dichotomous variables, and pooled means and SDs for continuous variables. A combined effect estimate was calculated for all primary outcomes using a random-effects inverse-variance weighting method. A funnel plot was used to visualize recurrence in each site; all other weighted estimates were presented as forest plots. *P* values were 2-tailed and statistical significance was defined as $P < .05$. Data analysis was conducted using the Python programming language, version 3.8.10 (Python Software Foundation) and Review Manager (RevMan, version 5.4.1) (The Cochrane Collaboration).[27,28]

Results

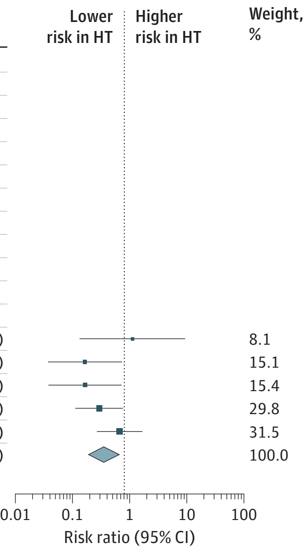
Of the 1824 studies retrieved, 938 full-text articles were reviewed, and 17 met inclusion criteria[29-45] for inclusion for systematic review and meta-analysis (eFigure in the Supplement). Studies originated from Korea (n = 9), China (n = 5), Italy (n = 1), France (n = 1), and Serbia (n = 1), and all took place in academic settings except 2 that were conducted at military centers.[31,36] A summary of study setting, design and participants, and ratings of evidence quality is pre-

Figure 1. Summary of VFP Complications From Meta-analysis Results

A Temporary VFP

Study or subgroup	Hemithyroidectomy No. of events	Hemithyroidectomy Total No.	Total thyroidectomy No. of events	Total thyroidectomy Total No.	Risk ratio (95% CI)	Weight, %
Chun et al,[34] 2015	19	63	0	0	Not estimable	
Chung et al,[42] 2019	0	0	5	106	Not estimable	
Goran et al,[39] 2017	0	0	0	111	Not estimable	
He et al,[34] 2011	0	0	1	105	Not estimable	
He et al,[36] 2016	0	0	0	50	Not estimable	
Hong et al,[32] 2011	2	60	0	0	Not estimable	
Kim et al,[45] 2020	1	164	0	0	Not estimable	
Li et al,[44] 2019	6	143	0	0	Not estimable	
Ren et al,[41] 2017	4	35	0	0	Not estimable	
Roh et al,[29] 2008	0	0	1	72	Not estimable	
So et al,[30] 2010	0	0	28	551	Not estimable	
So et al,[33] 2012	0	0	8	232	Not estimable	
Dobrinja et al,[38] 2017	1	19	4	86	1.13 (0.13-9.56)	8.1
Kwon et al,[40] 2017	2	688	12	688	0.17 (0.04-0.74)	15.1
Jeon et al,[43] 2019	2	127	12	128	0.17 (0.04-0.74)	15.4
Ding et al,[37] 2017	5	48	11	31	0.29 (0.11-0.76)	29.8
Donatini et al,[35] 2016	5	69	27	251	0.67 (0.27-1.68)	31.5
Total events (95% CI)	47	1416	109	2411	0.36 (0.19-0.68)	100.0

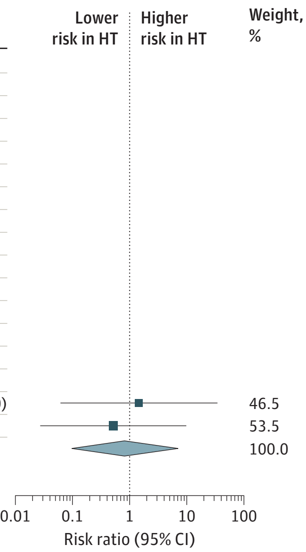
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 5.12$, $df = 4$ ($P = .28$); $I^2 = 22\%$
Test for overall effect: $z = 3.16$ ($P = .002$)



B Permanent VFP

Study or subgroup	Hemithyroidectomy No. of events	Hemithyroidectomy Total No.	Total thyroidectomy No. of events	Total thyroidectomy Total No.	Risk ratio (95% CI)	Weight, %
Chun et al,[34] 2015	0	63	0	0	Not estimable	
Chung et al,[42] 2019	0	0	0	106	Not estimable	
Ding et al,[37] 2017	0	48	0	31	Not estimable	
Goran et al,[39] 2017	0	0	1	111	Not estimable	
He et al,[31] 2011	0	0	0	105	Not estimable	
He et al,[36] 2016	0	0	0	50	Not estimable	
Hong et al,[32] 2011	0	60	0	0	Not estimable	
Kim et al,[45] 2020	0	164	0	0	Not estimable	
Kwon et al,[40] 2017	0	688	0	688	Not estimable	
Li et al,[44] 2019	1	143	0	0	Not estimable	
Ren et al,[41] 2017	0	35	0	0	Not estimable	
Roh et al,[29] 2008	0	0	0	72	Not estimable	
So et al,[30] 2010	0	0	7	551	Not estimable	
So et al,[33] 2012	0	0	3	232	Not estimable	
Jeon et al,[43] 2019	0	127	0	128	Not estimable	
Dobrinja et al,[38] 2017	0	19	1	86	1.45 (0.06-34.30)	46.5
Donatini et al,[35] 2016	0	69	3	251	0.51 (0.03-9.84)	53.5
Total events (95% CI)	1	617	15	1620	0.83 (0.10-7.21)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.22$, $df = 1$ ($P = .64$); $I^2 = 0\%$
Test for overall effect: $z = 0.17$ ($P = .87$)



Forest plots summarizing the effect size of HT vs total thyroidectomy and risk of temporary VFP (A) and permanent VFP (B). Studies are shown in ascending order of their weight in the meta-analysis according to the inverse-variance weighting technique. The 95% confidence interval is shown for each individual study, and represented by the width of the diamond in the pooled estimate. HT indicates hemithyroidectomy; VFP, vocal fold paralysis.

sented in eTable 1 in the Supplement. eTable 2 in the Supplement summarizes the methods of all included studies.

Five studies directly compared outcomes between HT and TT,[35,37,38,40,43] 5 reported solely on HT outcomes,[32,34,41,44,45] and 7 reported solely on TT outcomes.[29-31,33,36,39,42] Study designs included randomized clinical trials (n = 3; none of which compared HT to TT),[31,34,45] prospective cohort studies (n = 3),[30,36,41] and retrospective cohort studies (n = 11).[29,32,33,35,37-40,42-44]

Ten studies explicitly defined hypocalcemia or hypoparathyroidism.[31-33,35,38,40-44] Of these, 7 defined temporary vs permanent hypocalcemia or hypoparathyroidism: 4 used a time cutoff point of 6 months,[32-34,41] 2 used 12 months,[40,43] and 1 defined permanent hypocalcemia as requiring lifelong substitutive treatment.[38] Ten studies gave definitions for VFP.[29,32-34,36,37,41-44] Five defined permanent VFP as loss of function at 6 months after operation (n = 3) or at end of follow-up (n = 2), which was a mean of 36 months (n = 1)[29] or not reported (n = 1).[33]

Meta-analysis

A total of 1416 patients undergoing HT and 2411 patients undergoing TT were included (HT: pooled mean [SD] age, 47.0 [10.0] years; 1139 [84.6%] were female; and TT: pooled mean [SD] age, 48.8 [10.0] years; 1671 [77.4%] were female).

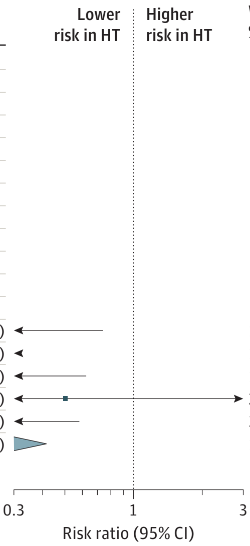
Figure 2. Summary of Hypoparathyroidism Complications From Meta-analysis Results

A Temporary hypoparathyroidism

Study or subgroup	Hemithyroidectomy No. of events	Hemithyroidectomy Total No.	Total thyroidectomy No. of events	Total thyroidectomy Total No.	Risk ratio (95% CI)	Weight, %
He et al,[31] 2011	0	0	19	105	Not estimable	
He et al,[36] 2016	0	0	17	50	Not estimable	
Hong et al,[32] 2011	0	60	0	0	Not estimable	
Kim et al,[45] 2020	0	164	0	0	Not estimable	
Li et al,[44] 2019	10	143	0	0	Not estimable	
Ren et al,[41] 2017	9	35	0	0	Not estimable	
Roh et al,[29] 2008	0	0	17	72	Not estimable	
So et al,[30] 2010	0	0	19	551	Not estimable	
So et al,[33] 2012	0	0	87	232	Not estimable	
Chun et al,[34] 2015	0	63	0	0	Not estimable	
Chung et al,[42] 2019	0	0	33	106	Not estimable	
Goran et al,[39] 2017	0	0	1	111	Not estimable	
Jeon et al,[43] 2019	0	127	11	128	0.04 (0.00-0.74)	15.5
Kwon et al,[40] 2017	0	688	103	688	0.00 (0.00-0.08)	15.8
Donatini et al,[35] 2016	0	69	46	251	0.04 (0.00-0.62)	15.8
Dobrinja et al,[38] 2017	1	19	9	86	0.50 (0.07-3.74)	21.2
Ding et al,[37] 2017	8	48	18	31	0.29 (0.14-0.58)	31.7
Total events (95% CI)	28	1293	380	2411	0.09 (0.02-0.42)	100.0

Heterogeneity: $\tau^2 = 1.74$; $\chi^2 = 11.19$, $df = 4$ ($P = .02$); $I^2 = 64\%$

Test for overall effect: $z = 3.10$ ($P = .002$)

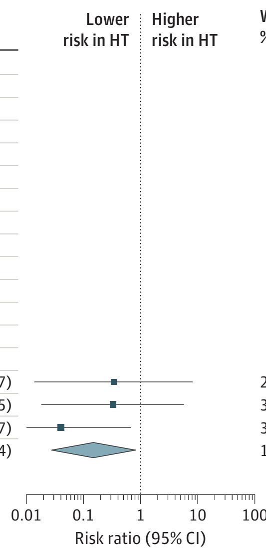


B Permanent hypoparathyroidism

Study or subgroup	Hemithyroidectomy No. of events	Hemithyroidectomy Total No.	Total thyroidectomy No. of events	Total thyroidectomy Total No.	Risk ratio (95% CI)	Weight, %
Chun et al,[34] 2015	0	63	0	0	Not estimable	
Chung et al,[42] 2019	0	0	0	106	Not estimable	
Ding et al,[37] 2017	0	48	0	31	Not estimable	
Dobrinja et al,[38] 2017	0	19	0	86	Not estimable	
Goran et al,[39] 2017	0	0	0	111	Not estimable	
He et al,[31] 2011	0	0	0	105	Not estimable	
He et al,[36] 2016	0	0	0	50	Not estimable	
Hong et al,[32] 2011	0	60	0	0	Not estimable	
Kim et al,[45] 2020	0	164	0	0	Not estimable	
Li et al,[44] 2019	0	143	0	0	Not estimable	
Ren et al,[41] 2017	0	35	0	0	Not estimable	
Roh et al,[29] 2008	0	0	1	72	Not estimable	
So et al,[30] 2010	0	0	6	551	Not estimable	
So et al,[33] 2012	0	0	9	232	Not estimable	
Jeon et al,[43] 2019	0	127	1	128	0.34 (0.01-8.17)	28.6
Donatini et al,[35] 2016	0	69	5	251	0.33 (0.02-5.85)	35.0
Kwon et al,[40] 2017	0	688	12	688	0.04 (0.00-0.67)	36.4
Total events (95% CI)	0	1245	34	2380	0.15 (0.03-0.84)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.37$, $df = 2$ ($P = .50$); $I^2 = 0\%$

Test for overall effect: $z = 2.16$ ($P = .03$)



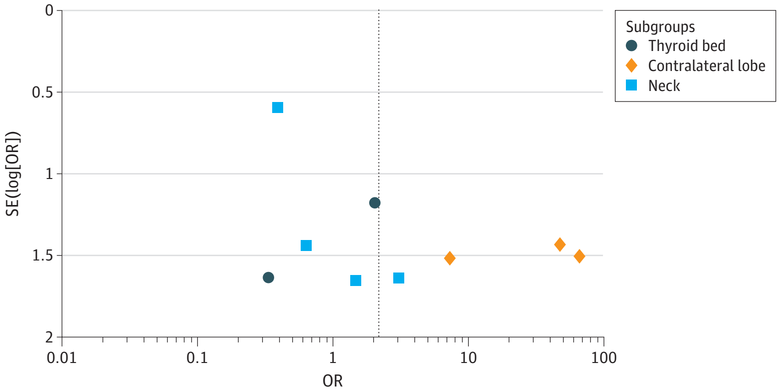
Forest plots summarizing the effect size of HT vs total thyroidectomy and risk of hypoparathyroidism (A) or permanent hypoparathyroidism (B). Studies are shown in ascending order of their weight in the meta-analysis according to the inverse-variance weighting technique. The 95% confidence interval is shown for each individual study, and represented by the width of the diamond in the pooled estimate. HT indicates hemithyroidectomy.

The **Table** presents an unweighted summary of the end points collected for meta-analysis, and results for the inverse-variance weighted meta-analysis can be found in **Figure 1**,[29-45] **Figure 2**,[29-45] and **Figure 3**.[29-45] Hemithyroidectomy was associated with a lower risk of temporary VFP than TT (3.3% vs 4.5%) (weighted RR, 0.4; 95% CI, 0.2-0.7), temporary hypoparathyroidism (2.2% vs 21.3%) (weighted RR, 0.1; 95% CI, 0.0-0.4), and permanent hypoparathyroidism (0% vs 1.8%) (weighted RR, 0.2; 95% CI, 0.0-0.8) (Figure 1 and Figure 2). No statistically significant difference was detected in the rates of permanent VFP (0.2% vs 0.9%) (weighted RR, 0.8; 95% CI, 0.1-7.2).

Overall recurrence rates were higher for HT than TT (3.8% vs 1.0%) (weighted RR, 2.6; 95% CI, 1.3-5.4) (weighted absolute risk difference, −5%); contralateral lobe recurrence was associated with overall higher recurrence rates for HT than TT (2.3% vs 0% in the TT group by definition) (weighted absolute risk difference, −16%). However, no recurrence rate difference was detected in the thyroid bed (0.3% vs 0.2%) (weighted RR, 0.8; 95% CI, 0.2-4.1) or neck (1.2% vs 0.8%) (weighted RR, 0.6; 95% CI, 0.2-1.5) (Figure 3). There were no cases of distant metastasis or mortality due to thyroid cancer in this population. An unweighted summary of mean tumor size, multifocality,

Figure 3. Summary of Recurrence From Meta-analysis Results

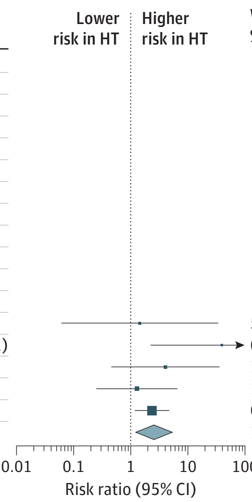
A Funnel plot analysis of relative risk of recurrence in HT compared with TT



B Effect size of HT vs TT on risk of recurrence

Study or subgroup	Hemithyroidectomy No. of events	Hemithyroidectomy Total No.	Total thyroidectomy No. of events	Total thyroidectomy Total No.	Risk ratio (95% CI)	Weight, %
So et al,[30] 2010	0	0	1	551	Not estimable	
So et al,[33] 2012	0	0	6	232	Not estimable	
Chun et al,[34] 2015	0	63	0	0	Not estimable	
Chung et al,[42] 2019	0	0	0	106	Not estimable	
Goran et al,[39] 2017	0	0	0	111	Not estimable	
He et al,[31] 2011	0	0	0	105	Not estimable	
He et al,[36] 2016	0	0	0	50	Not estimable	
Hong et al,[32] 2011	0	60	0	0	Not estimable	
Kim et al,[45] 2020	4	164	0	0	Not estimable	
Li et al,[44] 2019	6	143	0	0	Not estimable	
Ren et al,[41] 2017	0	35	0	0	Not estimable	
Roh et al,[29] 2008	0	0	0	72	Not estimable	
Dobrinja et al,[38] 2017	0	19	1	86	1.45 (0.06-34.30)	5.0
Donatini et al,[35] 2016	5	69	0	251	39.60 (2.22-707.51)	6.0
Jeon et al,[43] 2019	4	127	1	128	4.03 (0.46-35.58)	10.2
Ding et al,[37] 2017	4	48	2	31	1.29 (0.25-6.63)	17.2
Kwon et al,[40] 2017	26	688	11	688	2.36 (1.18-4.75)	61.5
Total events (95% CI)	49	1416	22	2411	2.60 (1.26-5.36)	100.0

Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 4.48$, $df = 4$ ($P = .35$); $I^2 = 11\%$
Test for overall effect: $z = 2.59$ ($P = .010$)



Summary of risk and site of recurrence in HT vs TT. A, Funnel plot showing relative risk of recurrence in HT compared with TT reported by each study included in the weighted meta-analysis; points marked by different symbols for each site of recurrence. Each point is a single study. Points to the right of the vertical dotted line represent higher recurrence risk in HT. Points higher on the plot represent studies with lower variance in reported recurrence rates. B, Forest plot summarizing the effect size of HT vs TT on risk of recurrence at any site. Studies shown in ascending order of their weight in the meta-analysis according to the inverse-variance weighting technique. The 95% CI is shown for each study and is represented by the width of the diamond in the pooled estimate. HT indicates hemithyroidectomy; OR, odds ratio; SE(log[OR]), standard error of the log odds ratio; TT, total thyroidectomy.

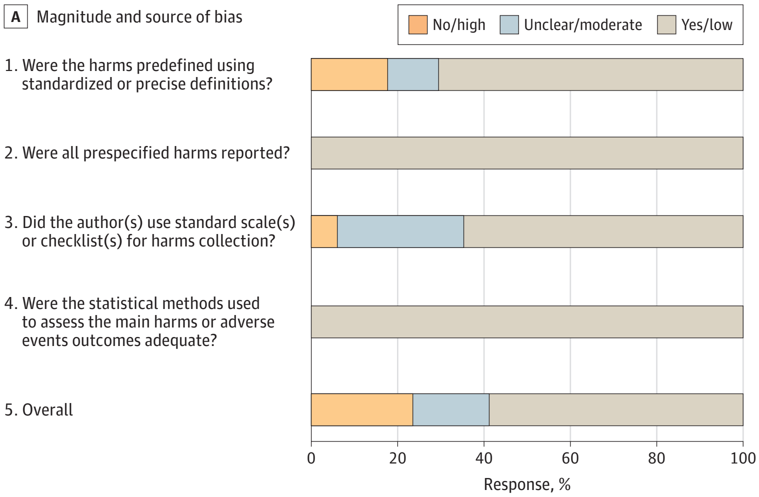
extrathyroidal extension, lymph node dissection, chyle leak, thyroid hormone replacement, radioactive iodine, reoperation, and mean follow-up time (9.6%) is also presented in the Table.

The risk of bias assessment is presented in **Figure 4**. Ten studies were judged to have an overall low risk of bias, 3 a moderate risk of bias, and 4 a high risk of bias. The most common source of bias was a failure to predefine complications or adverse events using standardized or precise definitions, and failure to use standard scales or checklists for harms collection. A sensitivity analysis performed after excluding high-risk of bias studies from the weighted meta-analysis found that HT was associated with lower risk of temporary VFP (3.3% vs 4.2%) (weighted RR, 0.2; 95% CI, 0.1-0.5), temporary hypoparathyroidism (1.7% vs 14.7%%) (weighted RR, 0.05; 95% CI, 0.0-0.9), permanent hypoparathyroidism (0% vs 1.6%) (weighted RR, 0.1; 95% CI, 0.01-0.9), and a higher cancer recurrence risk (3.4% vs 1.1%) (weighted RR, 2.4; 95% CI, 1.3-4.7).

Discussion

To our knowledge, the present study represents the most comprehensive review comparing and quantifying common complications of HT vs TT for treatment of PTMC. We found that PTMC treatment with HT was associated with a reduced risk of postoperative complications and higher overall recurrence rates than treatment with TT, a finding similar to another review that focused on mortality and recurrence rate in HT vs TT.[46] Specifically, patients undergoing HT had a 31% relative risk (weighted absolute risk difference, −5%) of developing temporary or permanent VFP and a 9% relative risk (weighted absolute risk difference, −16%) of postoperative temporary or permanent hypoparathyroidism. As most studies were published in the last decade, these data are primarily from an era in which intraoperative nerve monitoring was commonplace, which may have played a role in reducing complication rates. The 260%

Figure 4. Risk of Bias



B Risk of bias assessment (Yes / Unclear / No)

Study	Risk of bias 1	2	3	4	Overall
Roh et al,[29] 2008	+	+	+	+	Low
So et al,[30] 2010	+	+	+	+	Low
He et al,[31] 2011	–	+	–	+	High
Hong et al,[32] 2011	+	+	+	+	Low
So et al,[33] 2012	+	+	+	+	Low
Chun et al,[34] 2015	+	+	+	+	Low
Donatini et al,[35] 2016	–	+	–	+	High
He et al,[36] 2016	+	+	–	+	Moderate
Ding et al,[37] 2017	×	+	–	+	High
Dobrinja et al,[38] 2017	+	+	–	+	Moderate
Goran et al,[39] 2017	×	+	×	+	High
Kwon et al,[40] 2017	+	+	+	+	Low
Ren et al,[41] 2017	+	+	+	+	Low
Chung et al,[42] 2019	+	+	+	+	Low
Jeon et al,[43] 2019	+	+	+	+	Low
Li et al,[44] 2019	+	+	+	+	Low
Kim et al,[45] 2020	×	+	+	+	Moderate

Risk of bias analyses for all included studies. A, Bar chart of magnitude and sources of bias for each of 4 questions selected from the McMaster Quality Assessment Scale of Harms (McHarm); B, Risk of bias assessment for each study, in order of publication date.

relative risk of recurrence (weighted absolute risk difference, 2%) among those treated with HT was associated with contralateral lobe recurrences, which may instead represent discrete and independent cancer in the remaining lobe.[47] Our study did find a lower lifelong postoperative thyroid hormone replacement rate in HT patients (9.6%) compared with that reported by Verloop et al[21] (22%), which may be associated with limiting the present study to microcarcinomas, which may have a lower rate of completion thyroidectomy rate and consequently decrease the need for hormone replacement therapy.

Additional considerations are important in preoperative counseling. First, TT necessitates lifelong thyroid hormone replacement therapy, which, in turn, increases health care use, reduces quality of life, and adds to the cost of health care.[48-50] Second, surgical complications can be temporary or permanent. Although clinicians tend to focus on complications causing permanent disability, temporary complications should not be minimized. Temporary complications, including hypocalcemia and VFP, can last from weeks to months and have substantial quality of life costs. For example, patients with VFP may experience an inability to communicate, social isolation, dysphagia, and shortness of breath.[51] Thus, the risk of temporary or permanent complications must be balanced against risks of cancer recurrence resulting in further treatment.

Randomized clinical trials comparing TT with HT are rare because of high costs, practicality, and ethics questions surrounding randomization. Most studies included in our analysis were cohort studies, and only 5 studies had the primary objective of comparing TT and HT. In all, 11 studies defined complications or adverse events prior to data collection and analysis. Studies for which outcomes could be pooled and compared were all conducted between 2016 and 2019.[35,38,40,43,52] Consensus regarding procedure-specific reporting for complications and a uniform set of definitions of those complications may help decrease heterogeneity in the findings of studies evaluating surgical extent and outcomes.

Limitations

This study has limitations. First, a lack of uniformity of definitions and heterogeneity in reported outcomes limited our ability to conduct weighted pooled analysis of all outcomes. Although national collaborations, such as the American College of Surgeons National Surgical Quality Improvement Program and the American Association of Endocrine Surgeons Collaborative Endocrine Surgery Quality Improvement Program,[53,54] have helped to simplify and standardize the major complications in thyroid surgery, collaboration remains a somewhat underused process. Second, the TT group had more tumors with multifocality and extrathyroidal extension. This difference may be partially due to ascertainment bias, as extrathyroidal extension and multifocality may more likely be detected if the entire thyroid undergoes pathologic examination and may be associated with increased detection of recurrences. However, selection bias may also play a role: TT is indicated in small cancers less than 1 cm if there is preoperative evidence of extrathyroidal extension, multifocality, cervical nodal metastasis, familial thyroid carcinoma, prior head and neck radiotherapy or indications to remove the contralateral lobe. Total thyroidectomy is also more often performed with concomitant central and lateral lymph node dissection. Increased dissection may increase complication rates and may further inflate reported TT complication estimates.

Conclusions

In this systematic review and meta-analysis, complications in the surgical management of micropapillary thyroid carcinoma were found to increase with the extent of surgery performed, although complications and recurrence were low for both operations. Selection bias is likely present because patients undergoing TT were more likely to receive central and lateral lymph node dissection and have higher rates of multifocality. These results characterize and quantify current knowledge of the risk-benefit ratio of HT compared with TT for the treatment of PTMC and provide data that may have utility in patient counseling surrounding treatment decisions.

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