Systematic Review of Recurrence Rate after Hemithyroidectomy for Low-Risk Well-Differentiated Thyroid Cancer

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Keywords

Thyroid cancer · Hemithyroidectomy · Cancer recurrence · Disease-free survival

Abstract

Background: Surgical extent in the management of well-differentiated thyroid cancer (DTC) remains a recurrent subject of debate. This is especially relevant in low-risk DTC of 1–4 cm, which represent the majority of new thyroid cancer diagnoses. With trends towards treatment de-escalation and recent guidelines from the American Thyroid Association and British Thyroid Association endorsing hemithyroidectomy (HT) alone for low-risk DTC of 1–4 cm, we sought to systematically appraise the literature to examine recurrence rate outcomes after HT in this low-risk group. **Summary:** Searching PubMed, Cochrane Library, and Ovid MEDLINE, we conducted a systematic review to assess the survival and recurrence rate data presented in all published studies that had a cohort of patients treated with HT for the treatment of DTC. Pooled 10-year survival and recurrence rates, odds ratios, and 95% confidence intervals were calculated for meta-

analysis. We identified 31 studies (with a total of 228,746 patients (HT: 36,129, total thyroidectomy, TT: 192,617), which had published recurrence and/or survival data for patients having had HT for DTC. We discovered a pooled recurrence rate of 9.0% for HT, which is significantly higher than in previously published reports. Further, this rate is maintained when examining patients within low-risk cohorts established with recognised risk classifications. We also discovered that of those patients who develop recurrent disease, 48% recur outside the central neck. **Key Messages:** Our study provides a comprehensive systematic review of evidence aimed primarily at defining the recurrence rate in DTC after HT, and more specifically within the low-risk subgroup. We describe pooled recurrence and 10-year survival rates from a larger, broader, and more contemporary patient population than has been previously reported. Our findings indicate that there is a small but significantly higher recurrence rate after HT than TT, but the evidence base is heterogeneous and subject to confounding factors and would ultimately benefit from prospective randomised trials to overcome these deficiencies.

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Introduction

The incidence of well-differentiated thyroid cancer (DTC) is increasing faster than any other malignancies and estimated to increase by 30% by 2022 [1]. Most new cases are less than 4-cm tumours (T1–2), often diagnosed early due to increased use of imaging. Adequate surgery remains the most important prognostic determinant in the management of DTC [2]. The standard of care until recently has been total thyroidectomy (TT) and adjuvant radio-active iodine (RAI) for all such patients, which achieves excellent prognosis: 10-year overall survival of 98–99% and recurrence rates of 1–3% in low-risk DTC [3]. However, recognising their general indolent nature and excellent survival outcome, there have been calls for treatment de-escalation, aiming to provide patients with the optimum balance of effective long-term survival rates with reduced side-effects from treatment [4, 5]. In a landmark study by Adam et al. [6] of 61,775 patients with DTCs of 1–4 cm from the US National Cancer Data Base, overall survival was not materially higher when comparing TT with hemithyroidectomy (HT). This has been supported by other retrospective studies but with a slightly higher recurrence rate after HT [7–12]. Proponents of HT propose that it may benefit patients by reducing the potential sequelae of surgery compared to the more extensive TT. A large multicentre study in Italy described an overall definitive complication rate of 7.1% with higher rates of permanent hypocalcaemia, recurrent laryngeal nerve (RLN) palsy, and haemorrhage in TT cases compared to HT [13]. In recognition of these reports, the American Thyroid Association (ATA) and British Thyroid Association (BTA) suggest that HT may be adequate treatment for carefully selected low-risk DTC patients with tumour size ≤ 4 cm [3]. However, they acknowledge the lack of any randomised controlled trials. Indeed, recent studies provide evidence against HT. In 2017, Hwangbo et al. [14] reported a large (3,282 patients) multicentre study in DTCs < 2 cm and identified HT as an independent prognostic factor for recurrent disease. Their HT cohort had 10-year recurrence rates of 18.3% compared to 7.5% in the TT cohort (hazard ratio, HR 1.71, $p = 0.003$). Subsequently, Rajjoub et al. [15] re-analysed the same data examined by Adam et al. [6] and reported that TT was associated with better overall survival (HR 1.53, CI 1.06–2.19, $p = 0.023$) in patients with papillary thyroid cancers (PTC) > 2 cm when histological data were taken into consideration.

A major issue with the current evidence base for HT is that there are only observational studies. Nearly all are

retrospective reviews of patient records and often from single centres with established expertise in thyroid surgery. In the absence of any randomised trial comparing HT with TT, differential interpretation and implementation of international guidelines by local clinical teams have resulted in variable practices [16, 17]. Practice variability and uncertainty could further exacerbate the existing incongruity in the perceptions of thyroid cancer between clinicians and patients, particularly in the controversial “low-risk” category. In 2 papers focusing on patient experiences of diagnosis and treatment of thyroid cancer, Nickel et al. [18, 19] demonstrate the need for clinicians to be empowered by robust evidence base to reassure patients that not all cancer diagnoses are equal and that the shared decision-making process is very much advocated in the management of low-risk DTC.

The literature confirms the widely held view that mortality from small DTCs is low compared to other solid tumours. There have been systematic reviews comparing overall survival outcomes of HT with TT, but few have addressed recurrence rates. To date, none have addressed the specific subgroup of “low-risk differentiated thyroid cancers.” The aim of this systematic review was to examine the evidence base surrounding recurrence after HT, with particular focus on those patients with low-risk DTC.

Methods

Literature Search

Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, we searched PubMed, Cochrane Library, and Ovid MEDLINE up to September 2019 (see online suppl. Appendices 1, 2 for full search strategy and PRISMA checklist; see www.karger.com/doi/10.1159/000504961 for all online suppl. material). The following keywords were used: thyroid neoplasms, thyroid cancer, thyroidectomy, HT, thyroid lobectomy, overall survival, disease-free survival, recurrence, neoplasm recurrence local. Additional studies were identified by hand searching references in original articles and review articles. The language was limited to English. All studies selected for analysis met the following criteria: (1) published case-control or cohort studies, (2) patients with differentiated thyroid cancer confirmed on histopathological examination, (3) studies providing sufficient recurrence and/or survival data for patients undergoing thyroid lobectomy, and (4) publications after 1997.

The major exclusion criteria were: (1) abstracts, (2) population under the age of 18 years, (3) non-English papers, (4) published before 1997, (5) limited or unavailable recurrence or survival data, and (6) limited or unavailable data pertaining to surgical extent.

Data Extraction and Quality Assessment

Two investigators extracted all relevant data independently and followed the selection criteria. Consensus was reached by

Fig. 1. PRISMA flow chart.

both investigators, and in cases of disagreement the lead investigator assessed the articles and informed the final decision. The following data were extracted: publishing author's name, date of publication, country of origin, type of database used, time frame of study, gender, mean age, study design, numbers for each surgical approach, follow-up time, and outcomes assessed. We used the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies to evaluate the internal validity of the cohort studies. These tools are not designed to tally scores to arrive at a summary judgement of quality but were used to aid investigators to isolate areas of potential bias within study design [20].

Statistical Analysis

Meta-analysis was facilitated using Review Manager v5.3 software. Pooled recurrence rates and 95% confidence intervals (95% CI) were calculated. Heterogeneity among studies was estimated by Cochran's Q statistic [21].

Results

Characteristics of Studies Included

The initial search strategy returned 598 potential articles from the 3 main databases, and 6 additional studies were identified via manual searching. Investigator filtering using title and abstract assessment to remove duplicates and obviously irrelevant studies resulted in 71 studies. After full-text reading and assessment of the studies, we identified 31 studies (with a total of 228,746 patients (HT: 36,129, TT: 192,617) that satisfied our inclusion criteria and which included recurrence and/or survival data for patients treated with HT for either PTC or follicular thyroid cancer. Figure 1 shows the flow chart describing the final study inclusion and exclusion process. They

Table 1. Characteristics of the studies included

First author, year of publication	Country	Database used	Years	Female, %	Mean/median age	Study design	Total thyroidectomy, <i>n</i>	Lobectomy, <i>n</i>	Follow-up (mean/median, range), months	Outcomes assessed
Adam [6], 2014	USA	NCDB	1998–2006	79	NA	Cohort	54,926	6,849	60–179	Survival
Adam [35], 2015	USA	NCDB/SEER	1988–2006	84	34±7	Cohort	38,502	4,530	84	Survival
Baek [36], 2010	South Korea	Local	1992–2003	80	44.7	Cohort	178	11	81±44 (48–386)	Recurrence
Bilimoria [2], 2007	USA	NCDB	1985–1998	76	43	Cohort	43,227	8,946	69.7	Survival, recurrence
Choi [37], 2019	South Korea	Local	1978–2011	85	45±12	Cohort	4,292	974	57.3±58.1	Survival, recurrence
Ebina [28], 2014	Japan	Local	1993–2010	76	54±14	Cohort	176	791	99.6 (36–240)	Recurrence, CSD
Farrar [38], 1980	USA	Local	1952–1977	NA	NA	Cohort	29	126	10	Survival, recurrence
Gemsenjäger [39], 1997	Switzerland	Local	1974–1994	77	53	Cohort	100	66	90 (1–240)	Survival, recurrence
Grogan [40], 2013	USA	Local	1968–1988	67	36±16	Cohort	178	83	324	Survival, recurrence
Haigh [41], 2005	USA	SEER	1988–1995	77	NA	Cohort	4,612	820	88.8 (1–144)	Survival
Hay [23], 1998	USA	Local	1940–1991	NA	43	Cohort	1,451	187	192 (1–648)	Survival, recurrence
Huang [8], 2017	China	Local	1999–2008	68	NA	Cohort	NA	123	96 (12–157)	Survival, recurrence
Hwangbo [14], 2017	South Korea	National	2000–2004	88	47	Cohort	2,839	443	69.6 (52–122)	Recurrence
Ito [42], 2010	Japan	Local	1987–2005	94	51±12	Cohort	1,037	1,601	91 (6–240)	Recurrence, DFS
Kim [43], 2012	South Korea	Local	1983–2006	88	44	Cohort	332	84	120.8	Recurrence, DSS
Kim [44], 2017	South Korea	Local	2004–2008	83	44	Cohort	298	147	84	Recurrence, DFS
Kuba [45], 2017	Japan	Local	1994–2008	86	53	Cohort	53	120	112	Survival, recurrence
Lim [46], 2002	Singapore	Local	1990–1997	76	43.9	Cohort	123	44	40.3±26.5	Survival, recurrence
Liu [47], 2019	China	Local	1996–2008	59	42	Matched cohort	341	341	125 (46–192)	Survival, recurrence
Matsuzu [10], 2014	Japan	Local	1986–1995	90	46	Cohort	NA	1,088	211.2	REF, CSS
Mendelsohn [48], 2010	USA	SEER	1988–2001	78	44	Cohort	16,760	5,964	109	Survival, DSS
Nixon [7], 2012	USA	Local	1986–2005	79	46	Cohort	507	382	99 (13–291)	Survival, recurrence
Rajjoub [49], 2018	USA	NCDB	2004–2008	79	45	Cohort	21,589	1,310	78±26	Survival
Robinson [50], 2017	USA	Local	1993–2016	60	55	Cohort	33	29	40	DFS
Sanders [51], 1998	USA	Local	1940–1990	72	44	Cohort	NA	NA	156 (0–564)	Survival, recurrence
Shah [9], 1993	USA	Local	1930–1980	62	57	Matched cohort	73	73	NA	Survival, recurrence
Shaha [22], 1997	USA	Local	1930–1985	74	31	cohort				
Song [52], 2019	South Korea	Local	1998–2007	85	45	Matched cohort	170	276	240	Survival, recurrence
							381	381	117.6	Recurrence, DFS
Sugino [53], 2014	Japan	Local	1989–2010	78	45	Cohort	101	223	90	CSS, DMFS
Tsui [54], 2019	Hong Kong	Local	1993–2016	48	53	Cohort	92	45	54	Survival, recurrence
Vaisman [12], 2011	USA	Local	NA	84	45±13	Cohort	217	72	60 (6–408)	Recurrence

Fig. 2. Forest plots for pooled recurrence rate (**a**) and 10-year survival data (**b**).

Table 2. Studies included in low-risk subgroup analysis with available site of recurrence data

First author, year (<i>n</i>)	Classification	HT with recurrence, % (<i>n</i>)	TT with recurrence, % (<i>n</i>)	<i>p</i> value
Shaha [22], 1997 (446)	AJCC	16 (44)	8 (14)	0.06
Hay [23], 1998 (1,638)	AMES	22.2 (42)	8.3 (120)	–
Sanders [51], 1998 (795)	AMES	5	5	1.0
Vaisman [12], 2011 (289)	ATA	0	1.3 (3)	–
Nixon [7], 2012 (889)	AJCC	2.7 (10)	3.8 (19)	–
Pooled		9.2	5.3	–

First author, year	Local, central, % (<i>n</i>)		Lateral, % (<i>n</i>)		Distant, % (<i>n</i>)	
	TT	HT	TT	HT	TT	HT
Shaha [22], 1997 (446)	1.0 (2)	4.0 (11)	6.0 (10)	9.0 (25)	1 (2)	3 (8)
Hay [23], 1998 (1,638)	2.0 (29)	14.0 (26)	6.00 (87)	19.00 (36)	3.20 (46)	3.60 (7)
Nixon [7], 2012 (889)	0	2.7 (10)	0.80 (4)	0	3 (15)	0
Vaisman [12], 2011 (289)	0	0	1.30 (3)	0	0	0
Average %	0.8	5.2	3.53%	7.0%	1.8%	1.7%

Table 3. Studies that provided recurrence site data versus surgical extent

First author, year (<i>n</i>)	Local/central, % (<i>n</i>)		Regional/lateral, % (<i>n</i>)		Distant, % (<i>n</i>)	
	TT	HT	TT	HT	TT	HT
Choi [37], 2019 (5,266)	0.3 (13)	8.8 (86)	4.3 (185)	0.4 (4)	0.8 (34)	0
Ebina [28], 2014 (967)	6.6 (12)	8.3 (66)	0	0	3 (5)	4 (32)
Hay [23], 1998 (1,638)	2.0 (29)	14.0 (26)	6.00 (87)	19.00 (36)	3.20 (46)	3.60 (7)
Huang [8], 2017 (123)	–	4.9 (6)	–	4.90 (6)	–	0.80 (1)
Kim [44], 2017 (445)	0.3 (1)	5.4 (8)	5.00 (15)	3.40 (5)	0.30 (1)	0
Kuba [45], 2017 (173)	0.0	4.2 (5)	1.90 (1)	3.33 (4)	7.60 (4)	0
Liu [47], 2019 (167)	5.0 (6)	9.1 (4)	5.0 (6)	7.9 (3)	3.8 (5)	3.2 (1)
Matsuzu [10], 2014 (1,088)	–	13.3 (145)	–	0	–	3.20 (35)
Nixon [7], 2012 (889)	0.0	2.7 (10)	0.80 (4)	0	3 (15)	0
Shah [9], 1993 (146)	7.0 (5)	8.4 (6)	8 (6)	11 (8)	19 (14)	13.70 (10)
Shaha [22], 1997 (446)	7.0 (12)	13.0 (36)	6.0 (10)	9.0 (25)	1 (2)	3 (8)
Song [52], 2019 (762)	0.8 (3)	3.4 (13)	3.90 (15)	2.60 (10)	0	0.30 (1)
Vaisman [12], 2011 (289)	0.5 (1)	4.2 (3)	1.80 (4)	0	0	0
Average	2.7	7.7	3.9	4.7	3.8	2.4

comprised 28 cohort and 3 matched-cohort studies, with 7 studies using national or international cooperative databases (from 1952 to 2019). The characteristics of each study are summarised in Table 1.

Study Quality and Heterogeneity

Quality assessment (see online suppl. Table S1) was undertaken using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. The overall quality of the individual studies was found to be good within the remit of observational cohort studies.

The studies included for meta-analysis of pooled recurrence and overall survival rates were moderate to high

in terms of heterogeneity with I^2 values of 70 and 85%, respectively. The 3 largest weighted studies in the full-study cohort were Bilimoria et al. [2] (2007), Choi et al. [37] (2019) and Hwangbo et al. [14] (2017), all of which favour TT in terms of recurrence rate. They also have the biggest effect on total heterogeneity of the study population. A degree of publication bias was observed as demonstrated in the funnel plot diagrams (see online suppl. Fig. S1).

Quantitative Assessment

Of the 31 studies included in this systematic review, only 13 studies defined and stratified their surgical extent

Fig. 3. Pie charts describing recurrence site proportions in TT – risk non-stratified (**a**), HT – risk non-stratified (**b**), TT – stratified low-risk cohorts (**c**), and HT – stratified low-risk cohorts (**d**).

by tumour size in a way amenable to comparison. Within these studies, the majority were T1 cancers (T1: TT 64.4% vs. HT 62.7%; T2: TT 27.8% vs. HT 28.1%). Only 5 studies stated inclusion of T1–2 cancers only. In the remaining 8 studies that defined tumour size, a significant proportion were T3+ cancers (TT 26.9% vs. HT 21.0%) (see online suppl. Table S2).

Recurrence and Survival Rates

From all included studies reporting recurrence data, pooled recurrence rates were 9.0% for HT compared to 7.4% for TT, (odds ratio, OR, 1.45; CI 1.16–1.81, $p = 0.001$). Pooled 10-year overall survival rates were 95.7% for thyroid lobectomy and 95.8% for TT (OR 0.92; CI 0.73–1.18, $p = 0.52$). Figure 2 demonstrates the forest plots for each assessment.

We identified those studies that defined a low-risk cohort of patients using a recognised risk classification (AGES, MACIS, AMES, AJCC). Subgroup analysis of these 5 studies demonstrated a pooled recurrence rate of 9.2% for HT and 5.3% for TT (Table 2).

Subanalysis of Site/Type of Recurrence

Eleven studies reported recurrence rates for different sites (Table 3). Due to the diverse reporting standards, we categorised site of recurrence as being local (contralateral lobe, thyroid bed, level 6) versus regional (lateral neck) and distant disease. Averaged recurrence rates in the local/central compartment were 2.7 and 7.7% in TT and HT, respectively. Averaged recurrence rates from distant metastases were 3.8 and 2.4% in TT and HT, respectively.

Figure 3 depicts recurrence site proportions. After TT, recurrence occurred in similar proportions within central, regional, and distant disease categories (26, 37, and 37%, respectively). The most common site for recurrence after HT was local (52%). However, 48% of recurrences occurred regionally in the lateral neck (32%) or at distant sites (16%).

Given the heterogeneity of the studies, again we examined only those studies that had stratified their study cohort as low-risk patients (using recognised risk assessment criteria). In these low-risk cohorts, the proportion of local versus regional and distant disease after TT was different to the overall cohort above. After HT, just over

half of recurrences (51%) were seen in the lateral compartment with less disease recurring locally (37.4%) or at distant sites (12%).

Discussion

The optimal extent of thyroid resection for low-risk DTC is presently one of the most controversial issues of concern among endocrinologists, surgeons, and patients. Clinicians and patients should weigh up the potential benefits of less extensive surgery against a potentially higher recurrence rate. To assess and better define the recurrence rate after HT and assist treatment decision making, we undertook a systematic review of the literature on outcomes for patients with DTC having undergone HT.

Oncological Outcomes after HT

The pooled 10-year overall survival and recurrence rates after HT for DTC was 95.7 and 9.0%, respectively. In those studies that compared both surgical modalities, the overall survival rates were similar (TT 95.8% vs. HT 95.7%) and consistent with current opinion that overall survival in low-risk DTC is favourable independent of surgical extent. However, we observed a small but significantly higher recurrence rate after HT when compared to TT (HT 9.0% vs. TT 7.4%; $p = 0.001$). These findings must be interpreted on the background of significant study heterogeneity. There is variability in patient inclusion between studies. Many did not define or attempt risk stratification, and even when retrospective or prospective risk stratification was performed, different criteria were employed. Several studies included patients with high-risk features (such as vascular invasion and extrathyroidal extension) and included a significant proportion of T3+ patients, all of which are considered independent risk factors for recurrence. Additionally, in many studies the surgical extent and use of RAI were inconsistent or not clearly defined. Importantly, all studies were not randomised and thus open to bias and confounding variables.

In order to limit the confounding effects of heterogeneous patient populations with varying disease severity, we isolated 5 studies that provided low-risk patient cohorts, identified using established risk stratification scoring systems. Analysis of these studies showed a greater difference in recurrence rate between HT and TT (HT 9.2% vs. TT 5.3%). The comparatively lower recurrence rate after TT observed in these low-risk cohorts is expected because high-risk patients (who would have preferen-

tially populated the TT arms in non-stratified studies) have been excluded. However, the rate of recurrence after HT remains stable compared to the complete study cohort, suggesting a true recurrence rate after HT is approximately 8–9% in low-risk DTC. This is higher than the widely accepted recurrence rate of 1–3% in low-risk DTC [3]. More concerning, however, is the wide variability in reported recurrence rates after HT, with 2 studies by Shaha et al. [22] and Hay et al. [23], both examining outcomes in low-risk stratified cohorts, reporting recurrence rates of 16 and 22%, respectively.

Complications after HT Compared to TT

Large retrospective studies in the past have demonstrated differences in complication rates for HT compared to TT. This includes significantly higher rates of post-operative hypocalcaemia, unilateral vocal cord palsy, bilateral vocal cord palsy, tracheotomy, haemorrhage, and wound infection after TT [13, 24]. Few of the studies included in this systematic review recorded or discussed complication rates, and fewer still divided complication rates into surgical extent to allow meaningful comparison. Lim et al. [46], Kuba et al. [45], and Kim et al. [44], all demonstrated significantly lower complication rates after HT than TT. These trends are mirrored in a recent single-centre cohort study by Nicholson et al. [25] describing a retrospective review of 300 consecutive cases with rates of having any complication at 3 and 7% for HT and TT, respectively. RLN injury is an important potential complication after either HT or TT, as it can have a huge impact on future social interactions for the patient. Rosato et al. [13] showed that RLN injury represents 22.2% of TT complications. After TT, there was a total incidence of RLN lesions in 4.3% of cases (2.4% transient, 1.3% definitive, and 0.6% bilateral), and after HT there was an overall incidence of 2.0% (1.4% transient and 0.6% definitive).

A commonly cited reason for HT over TT is the avoidance of hypothyroidism requiring oral replacement. Verloop et al. [26] performed a meta-analysis that concluded that approximately 1 in 5 patients will develop some form of hypothyroidism after HT, with clinical hypothyroidism in 1 in 25 operated patients, which may be transient.

A further major benefit of HT over TT is to avoid hypocalcaemia. It is expected that hypocalcaemia is almost completely avoided in HT; however, a recent meta-analysis found the median incidence of transient hypocalcaemia after TT was 27% (range 19–38%), and permanent hypocalcaemia was 1% (range 0–3%) [27]. Full compari-

son of all surgical outcomes is outside the remit of this review, but the varied and sometimes conflicting data call for a prospective randomised trial to resolve these deficiencies.

The Effect of Prophylactic Central Neck Dissection and Adjuvant RAI

Direct comparisons of surgical extent are often considered confounded by the addition of adjuvant RAI, usually but not exclusively following TT, and the variable practice of prophylactic neck dissection. Use of RAI and prophylactic neck dissection was inconsistent, and rates were poorly reported within the reviewed studies; therefore, it was difficult to assess their impact. Ebina et al. [28] highlighted that their study cohorts are potentially free from the confounding effects of adjuvant RAI, due to the low rates of RAI used as a result of sociocultural reasons in Japan. However, their study is confounded by the standard practice of prophylactic ipsilateral neck dissection, which is not recommended by the BTA and ATA for low-risk DTC (those patients in whom HT would be potentially suitable), which may have an effect on recurrence rates, particularly within the central compartment.

Hay et al. [23] was the only study to specifically address the issue of adjuvant RAI as a confounding factor. They re-analysed outcomes of HT versus TT after excluding the 371 cases that had received RAI in either group. They showed that HT was still associated with a significantly higher risk at 20 years of local (7 times greater) and regional (4 times greater) recurrence ($p = 0.0001$), and they concluded that the apparent advantage of TT cannot be ascribed to adjuvant RAI use [23].

The true role of RAI awaits the outcomes from prospective controlled trials such as the IoN and Estimab2.

Site of Recurrence after HT

One of the main arguments for the use of HT as a treatment de-escalation option is that, despite comparatively higher rates of recurrence, these patients do not appear to have subsequent higher mortality and are readily salvageable with low-risk surgery. Chinn et al. [29] demonstrated that in “highly experienced hands, comprehensive salvage neck dissection...had 10-year lateral neck control of 88% in 307 patients with recurrent WDTC.” Ease of salvage treatment is dependent on the site of recurrence, with patients presenting with multiple surgeries or distant metastases demonstrating significantly worse overall or disease-specific survival, or disease control [29–32].

In our review, 13 studies reported recurrence rates for different sites (local vs. regional vs. distant) (Table 3). Af-

ter TT, recurrence occurred in similar proportions within central, regional, and distant categories. Perhaps as anticipated due to the remnant contralateral lobe, the most common site for recurrence after HT is local/central (52%). Unfortunately, many studies did not differentiate between recurrence within the contralateral lobe and recurrence in the central compartment. However, of importance is that of those patients that recurred, 48% of recurrences after HT were regional or distant disease that may prove difficult to salvage.

Given the heterogeneity of the studies included within our systematic review and the possibility of higher-risk patients being included in the overall analyses, again we examined only those 4 studies that had performed risk stratification, identifying a low-risk patient cohort. After HT, 51% of the recurrences were seen regionally in the lateral neck compartment, and 12% of recurrences were at distant sites. Therefore, even in *stratified* low-risk cohorts of patients, it appears the majority of disease recurrences (63%) after HT occurs outside the central compartment. These patients would require more extensive treatment (neck dissection vs. simple completion thyroidectomy, systemic RAI treatment, or external beam radiotherapy), which is associated with higher morbidity.

How Our Study Improves on Other Existing Systematic Reviews?

A systematic review by Guo et al. [33] examined risk factors for recurrence in PTC and identified extent of surgery as a predictive factor. However, their review appeared to exclude many key papers and was not aimed at low-risk DTC. More recently, a systematic review by Gartland and Lubitz [34] aimed to compare outcomes in low-risk (T1–2) DTC patients after TT and HT, providing a descriptive review of the 13 studies. They commented briefly that only 3 studies included in their review documented disease recurrence, reporting a higher recurrence rate after HT. They concluded that a meta-analysis to estimate the effect of surgical extent on disease-free survival for patients with PTC of 1–4 cm would, therefore, be useful. Our study provides a comprehensive systematic review of evidence aimed primarily at defining the recurrence rate in DTC after HT and more specifically within the low-risk subgroup. We describe pooled recurrence and 10-year survival rates from a larger, broader, and more contemporary patient population than has been reported previously. In addition, we analysed the site and rate of recurrence after HT.

Study Limitations

Throughout the analysis for this study, the heterogeneity of the study design and reporting of data were major limitations for meaningful cross-sectional analysis. This is a systematic review of published literature and, therefore, reflects the strengths and weaknesses of the individual studies included. There was a moderately high degree of study heterogeneity (pooled recurrence and overall survival rate I^2 values of 70 and 85%, respectively), which is likely to be explained by the variability in study design, cohort sizes, and execution between them. We found studies that included mixed populations of patients (including cohorts of T3+ tumours, prophylactic neck dissections, and RAI after HT) without publishing sufficient data to separate into cleaner comparative groups of HT and TT.

Lack of randomisation, variable inclusion criteria, and different treatments used represent significant risk of bias and effects of confounding variables. Strong conclusions are, therefore, challenging, particularly given the paucity of studies that have employed recognised risk stratification systems to identify true low-risk patients.

The results should, therefore, be interpreted with caution, and the level of evidence is at best level 2B. A prospective randomised trial would overcome these deficiencies in evidence.

Conclusion

There is a lack of level 1 evidence to provide surgeons and patients with the assurance that treating low-risk (1–4 cm) DTC with HT alone will not result in clinically relevant higher recurrence rates compared to TT, which has been the standard of care to date and has been shown

extensively to offer excellent overall and disease-free survival outcomes. On the contrary, our systematic review suggests that there is a significant increase in recurrence rates for patients treated with HT compared to TT. Further, following HT, recurrent disease is more likely to occur outside the central compartment and may subsequently require higher morbidity salvage surgery, contrary to current assumptions. However, the available evidence is fraught with bias and effects from confounding variables producing a wide variation in results. A prospective randomised trial comparing the outcomes after HT and TT in the low risk DTC patients would both overcome these deficiencies in evidence and also provide assessment of the true level of benefits (complication rates, cost-effectiveness, and quality of life) of HT as a treatment de-escalation option and thus ultimately give both patients and clinicians reliable data to enable best decision making.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.K. conceived and designed the study, and S.C. wrote the manuscript. S.C., K.K., and A.K. performed the literature search and data extraction. S.C. and D.K. performed data analysis and interpretation. G.O., J.W., V.P., I.N., and DK provided critical appraisal of the manuscript. All authors read and approved the final manuscript.

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