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REVIEW and SCHOLARLY DIALOG

Serum Thyroglobulin Measurement Following Surgery Without Radioactive Iodine for Differentiated Thyroid Cancer: A Systematic Review

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Background: The utility of serum thyroglobulin (Tg) measurement following partial thyroidectomy or total/near-total thyroidectomy without radioactive iodine (RAI) for differentiated thyroid cancer is unclear. This systematic review examines the diagnostic accuracy of serum Tg measurement for persistent, recurrent, and/or metastatic cancer in these situations.

Methods: Ovid MEDLINE, Embase, and Cochrane Central were searched in October 2021 for studies on Tg measurement following partial thyroidectomy or total/near-total thyroidectomy without or before RAI. Quality assessment was performed, and evidence was synthesized qualitatively.

Results: Thirty-seven studies met inclusion criteria. Four studies ($N = 561$) evaluated serum Tg measurement following partial thyroidectomy, five studies ($N = 751$) evaluated Tg measurement following total/near-total thyroidectomy without RAI, and 28 studies ($N = 7618$) evaluated Tg measurement following total or near-total thyroidectomy before RAI administration. Following partial thyroidectomy, Tg measurement was not accurate for diagnosing recurrence or metastasis, or estimates were imprecise. Following total/near-total thyroidectomy without RAI, evidence was limited due to few studies with very low rates of recurrence or metastasis, but indicated that Tg levels were usually stable and low.

For Tg measurements before RAI administration, diagnostic accuracy for metastatic disease or persistence varied, although sensitivity appeared high (but specificity low) at a cutoff of >1 to 2.5 ng/mL. However, applicability to patients who do not undergo RAI is uncertain because patients selected for RAI are likely to represent a higher risk group. The evidence was very low quality for all scenarios. All studies had methodological limitations, and there was variability in the Tg thresholds evaluated, patient populations, outcomes assessed, and other factors.

Conclusions: Very limited evidence suggests low utility of Tg measurement for identifying recurrent or metastatic disease following partial thyroidectomy. Following total/near-total thyroidectomy, Tg levels using a cutoff of 1–2.5 ng/mL might identify patients at low risk for persistent or metastatic disease. Additional research is needed to clarify the role of Tg measurement in these settings, determine optimal Tg thresholds, and determine appropriate measurement intervals.

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Introduction

THYROGLOBULIN (TG) IS a protein produced by the thyroid follicular cells roughly in proportion to the amount of thyroid gland tissue present (1,2). In patients with differentiated thyroid cancer (DTC) who undergo total or near-total thyroidectomy and receive radioactive iodine (RAI) for remnant ablation or therapy, postoperative serum Tg levels are monitored to identify patients with persistent or recurrent disease, disease progression, and to provide prognostic information (3). However, the role of postoperative Tg measurement in patients who undergo partial thyroidectomy, in whom noncancerous thyroid tissue is not removed, is uncertain. Similarly, the role of Tg measurement in patients who have undergone total or near-total thyroidectomy but have not received RAI is a challenge, as Tg-producing noncancerous residual thyroid tissue will be present.

A 2015 American Thyroid Association guideline recommends that periodic serum Tg measurement on thyroid hormone therapy be considered during follow-up of patients with DTC who have undergone less than total thyroidectomy and in patients who have had a total thyroidectomy but who have not received postoperative RAI (3). Although the guideline states that optimal Tg cutoff levels to distinguish normal residual thyroid tissue from persistent thyroid cancer are unknown, it notes that rising Tg values over time may indicate recurrence. To inform an updated guideline, the American Thyroid Association commissioned a systematic review examining Tg testing of patients following partial thyroidectomy or total/near-total thyroidectomy without RAI. The purpose of this systematic review is to address the utility of Tg testing in persons with DTC following (a) partial thyroidectomy or (b) total or near-total thyroidectomy who have not received postoperative RAI.

Methods

In conjunction with the American Thyroid Association's Guidelines Task Force for the management of adult patients with DTC, we determined the Key Question for this review: In adult patients with DTC, what is the accuracy of serum Tg measurement for diagnosing or predicting persistent, recurrent, or metastatic disease following (a) partial thyroidectomy or (b) total or near-total thyroidectomy without or before RAI remnant ablation? This review is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) 2020 statement (4).

Search strategies

We searched the Cochrane Central Register of Controlled Trials, Elsevier Embase®, and Ovid MEDLINE® (through October 2021) for relevant studies. Search strategies utilized keywords and terms for DTC and Tg measurement (detailed search strategies are shown in Supplementary Appendix SA). Searches were supplemented by reference list review of relevant articles.

Study selection

Abstracts and full-text articles were evaluated using pre-specified eligibility criteria. The population was adults with DTC who underwent Tg measurement following partial thyroidectomy or following total or near-total thyroidectomy without RAI. We also included studies of patients who underwent total or near-total thyroidectomy and had Tg tested before RAI administration, as few studies evaluated patients who did not receive RAI, and Tg measurement before RAI ablation may provide some information about the usefulness of Tg monitoring. We included randomized controlled trials, nonrandomized clinical trials, and cohort studies (retrospective or prospective) that reported diagnostic accuracy of Tg measurement for detection of residual disease, DTC recurrence, and/or metastatic disease, as these outcomes were defined in the studies. Inclusion was restricted to English language studies, and studies published only as conference abstracts were excluded. We did not restrict inclusion based on the reference standard used.

Data abstraction

We extracted the following data from studies: author, year, country, study dates, data collection method (retrospective or prospective), sample size, age, percent female, DTC type and stage, surgery type, RAI use, thyroid stimulation status at time of Tg measurement, timing of Tg measurement, Tg antibody status, duration of follow-up, reference standard, proportion experiencing outcomes, and results (sensitivity, specificity, positive predictive value, and negative value). Data were extracted by one investigator and verified by a second.

Assessing methodological quality of individual studies

The quality (risk of bias) of each study was rated as "good," "fair," or "poor" using predefined criteria for studies on diagnostic accuracy adapted from the U.S. Preventive Services Task Force criteria (Supplementary Appendix SB). Studies rated "good quality" are generally considered valid, with unbiased patient selection methods; low attrition or missing data; prespecified Tg cutoffs; no data discrepancies; and use of an appropriate reference standard in all patients, interpreted without knowledge of the Tg result. Studies rated "poor quality" have a significant flaw or combination of flaws that may invalidate the results. These include biased selection methods; high attrition or missing data; no prespecified Tg cutoff; significant data discrepancies; inadequate reference standard; inconsistent application of the reference standard; or nonblinded interpretation of the reference standard to Tg results.

Studies rated "fair quality" have some methodological limitations but not enough to warrant a "poor" rating. We broadly defined an appropriate reference standard as one that utilized some combination of pathological findings, imaging, iodine scan, and/or clinical follow-up; a reference standard based solely on ultrasonography or iodine scan or based solely or primarily on Tg measurement was considered inadequate.

Synthesizing the evidence

The evidence was synthesized qualitatively; we planned to conduct meta-analysis if there were sufficient poolable data, but this was not done because few studies were identified for the key populations (partial thyroidectomy and total or near-total thyroidectomy without RAI ablation), with methodological limitations in the studies and differences in populations studied, Tg monitoring strategies, and thresholds used to define an elevated Tg level. The overall quality of evidence (indicating the confidence in findings) was graded "high," "moderate," "low," or "very low" using GRADE methods, based on methodological limitations, consistency, directness, precision, and reporting bias (5,6).

Results

Literature searches

Database searches resulted in 843 potentially relevant articles (Fig. 1). After dual review of abstracts and titles, 96 articles were selected for full-text review. Of these, 37 met inclusion criteria (7–43). Among the 59 excluded articles, the most common reasons for exclusion following full-text review were ineligible population (e.g., underwent total or near-total thyroidectomy and received RAI, or mixed population of patients who did and did not receive RAI; 27 studies), diagnostic accuracy not reported (15 studies), ineligible

outcome (e.g., prediction of ablation success; 7 studies), or Tg not obtained before RAI or timing of Tg testing unclear (7 studies) (see Supplementary Appendix SC for full list of excluded studies with reasons for exclusions).

Tg measurement following partial thyroidectomy

Four retrospective studies of unstimulated Tg measurement following partial thyroidectomy met inclusion criteria (Tables 1 and 2) (7,30,33,39). Tg measurement was performed every 3–6 months in 2 studies and at least 3 months after surgery and then annually in 1 study; one study (7) did not report timing of Tg measurement. Sample sizes ranged from 70 to 223 ($N = 561$). The procedure was lobectomy in two studies (30,33), lobectomy with or without isthmusectomy in one study (39), and a variety of partial thyroidectomy procedures (most commonly, unilateral lobectomy [36%], hemithyroidectomy [35%], and subtotal thyroidectomy [13.9%]), in one study (7). Mean or median age ranged from 35 to 53 years, and the proportion that was female ranged from 77% to 94%. In three studies, 96–100% of DTCs were papillary, and in one study (39), 80% were papillary. The majority of cancers were classified as T1 or Union for International Cancer Control/American Joint Committee Cancer (AJCC) stage I or II.

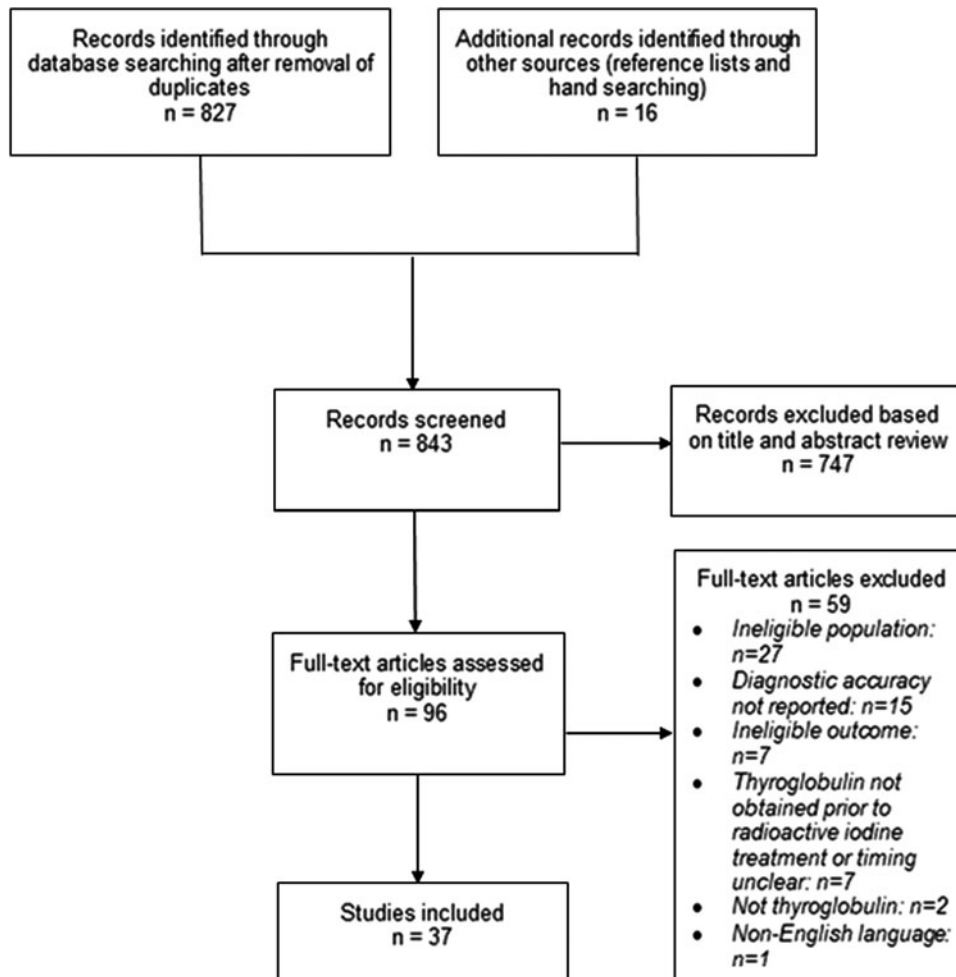All studies excluded patients with Tg antibodies or reported a low proportion (11%) of patients with Tg antibody.

FIG. 1. Literature flow diagram.

TABLE 1. STUDIES OF THYROGLOBULIN TESTING—POPULATION CHARACTERISTICS

Study, year	Country	Study dates	Data collection	Sample size	Age	Female	DTC type	Stage at time of testing
Tg testing following partial thyroidectomy								
Alzahrani, 2002 (7)	Saudi Arabia	1989–1999	Retrospective	101	Median 35 years	85%	PTC: 96% FTC: 4.0%	Perithyroidal tumor extension: 26% Invasion of surrounding muscles: 8.9% Metastatic: 8.9%
Park, 2018 (30)	South Korea	2008–2009	Retrospective	223	Mean 47 years	77%	PTC: 100%	N1: 26% I or II: 65% III 35%
Ritter, 2020 (33)	Israel	2002–2017	Retrospective	167	Median 53 years	87%	PTC: 100%	I, age <55 years: 54% I, age ≥55 years: 46%
Vaisman, 2013 (39)	Brazil	Not reported	Retrospective	70	Median 35.5 years	94%	PTC: 80% FTC: 20%	T1a: 23% T1b: 37% T2: 23% T3: 17% N0: 20% N1a: 7.1% Nx: 63%
Tg testing following total or near-total thyroidectomy without RAI therapy								
Durante, 2012 (9)	Italy	Not reported	Retrospective	290	Median 47 years	87%[a]	Not reported	T1a: 99% T1b: 0.7% T2: 0.3%
Janovsky, 2016 (14)	Brazil	Not reported	Prospective	57	Mean 48 years	89%	PTC: 98% FTC: 1.8%	Not reported (all <4 cm and restricted to thyroid gland)
Matrone, 2020 (24)	Italy	2005–2014	Retrospective	271	Median 50 years	72%	PTC, classical variant: 72% PTC, follicular variant: 25% PTC, aggressive variant: 2.5% FTC: 0.4%	T1a: 98% T1b: 1.8%
Nascimento, 2013 (27)	France	2006–2010	Retrospective	86	Mean 50 years	87%	PTC: 78% FTC: 4.7% Tumor of uncertain malignant potential: 10% PTC + tumor of uncertain malignant potential: 7.0% (6/86)	T1: 97% T2: 1.3% T3: 1.3% N1: 7.8% Nx: 40%
van Wyngaarden, 1997 (40)	the Netherlands	Not reported	Retrospective	47	Mean 39 years	68%	Not reported	Not reported

(continued)

616

TABLE 1. (CONTINUED)

Study, year	Country	Study dates	Data collection	Sample size	Age	Female	DTC type	Stage at time of testing
Postoperative Tg testing before RAI therapy								
Caballero-Calabuig, 2008 (8)	Spain	1998–2005	Retrospective	128	Not reported (range 16–71 years)	77%	PTC: 72% FTC: 28%	Not reported
Giovanella, 2008 (10)	Italy	Not reported	Retrospective	126	Mean 44 years	71%	PTC: 77% FTC: 23%	T1: 34% T2: 53% T3: 10% T4: 3% Nx: 41% N0: 20% N1a: 30% N1b: 9%
Grunwald, 1996 (11)	Germany	Before 1989	Retrospective	111	Not reported	Not reported	PTC: 66% FTC: 34%	Not reported
Hasbek, 2014 (12)	Turkey	Not reported	Retrospective	221	Mean 46 years	86%	PTC: 76% FTC: 14% Thyroid tumors of uncertain malignant potential: 6.3% Poorly differentiated: 1.8% Aggressive histology (tall cell and insular variant): 0.9% Anaplastic: 0.5%	Not reported (mean 18 mm)
Heemstra, 2007 (13)	the Netherlands	1986–2003	Retrospective	222	Mean 48 years	75%	PTC: 55% FTC: 20% Follicular variant: 19% Hurthle cell: 6.3%	T1: 6.0% T2: 51% T3: 15% T4: 26% Tx: 1.1% N1: 29% M1: 14%
Kim, 2013 (15)	South Korea	2006–2008	Retrospective	185	Median 46 years	81%	PTC: 100%	AJCC TNM stage I: 51% II: 2.7% III: 37.3% IV: 8.6%
Kim, 2005 (16)	South Korea	1996–1998	Retrospective	394	Mean 44 years	85%	PTC: 95% FTC: 5%	AJCC TNM stage I: 55% II: 14% III: 31% IV: 0%

(*continued*)

TABLE 1. (CONTINUED)

Study, year	Country	Study dates	Data collection	Sample size	Age	Female	DTC type	Stage at time of testing
Krajewska, 2016 (17)	Poland	1994–1997	Retrospective	1033	Mean 42 years	80%	PTC: 71% FTC: 29%	T1: 12% T2: 35% T3: 8.4% T4: 9.4% Tx: 36% N1: 25% M1: 0%
Latrofa, 2016 (18)	Italy	Not reported	Retrospective	177	Median 47 years	76%	Not reported	T1: 45% T2: 18% T3: 36% T4: 1.1% N1: 14% M1: 1.7%
Ledwon, 2021 (19)	Poland	2008–2011	Retrospective	650	Median 53 years	82%	PTC: 91% DTC: 8% Poorly differentiated: 0.9%	T0: 0.5% T1: 56% T2: 13% T4: 22% T4: 1.1% N1: 21% M1: 0%
Lima, 2002 (20)	Brazil	Not reported	Prospective	42	Median 42 years	76%	PTC: 83% DTC: 17%	T1: 0% T2: 81% T3: 0% T4: 19% N1: 38% M1: 14%
Lin, 2011 (21)	China	2007–2010	Retrospective	244	Mean 43 years	68%	PTC: 95% FTC: 5%	Not reported
Makarewicz, 2006 (22)	Poland	Not reported	Retrospective	178	Range 14–79	90%	PTC: 74% FTC: 26%	<1 cm: 22% >1 to <4cm: 60% >4 cm: 18%
Makarewicz, 2006 (23)	Poland	Not reported	Retrospective	247	Range 14–79	90%	PTC: 72% FTC: 20% Oxyphilic variant of follicular carcinoma: 8.5%	Not reported

TABLE 1. (CONTINUED)

Study, year	Country	Study dates	Data collection	Sample size	Age	Female	DTC type	Stage at time of testing
Matrone, 2017 (25)	Italy	2010–2011	Retrospective	505	Mean 47 years	72%	PTC, classical variant: 40% PTC, follicular variant: 32% PTC, aggressive variant: 20% FTC: 6.9%	T1a: 15% T1b: 20% T2: 20% T3: 35% N1: 13% I: 67% II: 10% III: 20% IV: 2.6%
Matthews, 2016 (26)	Australia	1989–2010	Retrospective	100	Mean 48 years	68%	PTC: 70% FTC: 29% Tall cell: 1%	T1: 45% T2: 34% T3: 13% T4: 8% N1: 31% M1: 0%
Ng, 2000 (28)	Singapore	Not reported	Retrospective	360	Mean 47 years	71%	PTC: 80% FTC: 20%	Not reported
Oyen, 2000 (29)	The Netherlands	1987–1997	Retrospective	254	Mean 45 years	74%	PTC or mixed papillary–follicular: 62% FTC: 31% Hurthle: 7%	Not reported
Polachek, 2011 (31)	Israel	Not reported	Retrospective	420	Mean 49 years	75%	PTC: 95% FTC: 3% Hurthle: 1%	I: 55% II: 13% III: 20% IV: 11% T1: 49% T2: 22% T3: 26% T4: 3.2% N1: 31% M0: 93%
Prabhu, 2018 (43)	India	2015–2016	Retrospective	100	Mean 40 years	71%	PTC: 82% FTC: 18%	T1: 14% T2: 26% T3: 56% T4: 4.9% N0: 26% N1: 54% N2: 1.2% Nx: 17% M0: 93% M1: 4.9% Mx: 2.2%

(continued)

TABLE 1. (CONTINUED)

Study, year	Country	Study dates	Data collection	Sample size	Age	Female	DTC type	Stage at time of testing
Ren, 2021 (32)	China	2016–2019	Retrospective	235	Mean 46 years	64%	PTC: 97% FTC: 3.0%	Not reported
Ronga, 1999 (34)	Italy	1982–1994	Retrospective	370	Mean 42 years	76%	PTC: 75% FTC: 25%	Not reported
Rosario, 2011 (35)	Brazil	Not reported	Retrospective	237	Median 43 years	82%	PTC: 87% FTC: 13%	T1: 26% T2: 38% T3: 36%
Szujo, 2021 (36)	Hungary	2005–2018	Retrospective	222	Median 48 years	71%	PTC: 77% FTC: 23%	T1: 35% T2: 23% T3: 30% T4: 10% N1: 32% M1: 7%
Torlantano, 2006 (37)	Italy	1999–2004	Retrospective	80	Mean 49 years	86%	PTC: 100%	T1: 100% N0: 14% Nx: 86%
Toubeau, 2004 (38)	France	1990–2000	Retrospective	212	Mean 47 years	72%	PTC: 87% FTC: 13% (3.3% Hurthle cell)	≤4 cm: 89% >4 cm: 11% N0: 30% N1: 26% Nx: 44%
Zerva, 2006 (41)	Greece	1997–2002	Retrospective	248	Mean 50 years	79%	PTC: 76% FTC: 24%	T1: 33% T2: 53% T3: 8.5% T4: 4.8% N1: 0% M1: 0%
Zhao, 2017 (42)	China	2012–2014	Retrospective	317	Mean 42 years	67%	PTC: 98% FTC: 2.2%	T1: 37% T2: 5.4% T3: 16% T4: 42% N0: 18% N1a: 33% N1b: 49% M1: 23% I: 48% II: 12% III: 11% IV: 29%

TABLE 2. STUDIES OF THYROGLOBULIN TESTING—INTERVENTION AND TEST CHARACTERISTICS

Study, year	Surgery type	RAI	TSH level	Tg testing timing (from surgery)	TgAb status	Duration of follow-up	Reference standard
Tg testing following partial thyroidectomy							
Alzahrani, 2002 (7)	Lumpectomy: 7.9% Unilateral lobectomy: 36% Hemithyroidectomy: 35% Bilateral partial thyroidectomy: 7.9% Subtotal thyroidectomy: 13.9% Unilateral modified neck dissection: 3.0% Cervical lymph node sampling: 8.9%	None	Not described; median TSH 3.25 mU/L	Unclear	Not routinely performed; negative in 30 patients with at least 1 Tg level >20 ng/mL	Median 3.2 months (time to completion surgery)	Pathological (completion surgery, with modified neck dissection in 89%)
Park, 2018 (30)	Lobectomy: 100%	None	Not described; mean TSH not reported	3–6 Months after lobectomy, then every 6–12 months	Excluded if TgAb positive	Median 6.9 years	Neck US, histology
Ritter, 2020 (33)	Lobectomy: 100%	None	Not described; mean TSH not reported	At least 3 months after surgery, then annually	11% had TgAb (mean 438 IU/mL)	Mean 78 months	Not described
Vaisman, 2013 (39)	Lobectomy with or without isthmusectomy	None	TSH <0.5 mIU/L	Every 6 months during the first year, then at 6–12-month intervals	Excluded if TgAb positive	6–13 Months	Cytology/histology, neck US
Tg testing following total or near-total thyroidectomy without RAI therapy							
Durante, 2012 (9)	Total or near-total thyroidectomy Central neck dissection: 12%	None	24% had TSH >1 mU/L	Not reported (varied)	Negative: 100%	Median 5 years (range 2.5–22 years)	Clinical, ultrasonography, and Tg findings
Janovsky, 2016 (14)	Total thyroidectomy	None	(a) TSH <0.05 mIU/L (b) Stimulated Tg (TSH level not reported) (c) TSH 0.5–2.0 mIU/L (d) TSH 0.5–2.0 mIU/L	3 Months	No patients developed anti-TgAb	(a) 3 Months (b) 6 Months (c) 18 Months (d) 24 Months	[123]I total body scan and neck US

621

TABLE 2. (CONTINUED)

Study, year	Surgery type	RAI	TSH level	Tg testing timing (from surgery)	TgAb status	Duration of follow-up	Reference standard
Matrone, 2020 (24)	Total thyroidectomy	None	On thyroid replacement	Median 5 months, then every 12–18 months	Excluded for TgAb >8 IU/mL	Median 73 months	Neck US and other imaging (CT, MRI, and/or PET) as indicated
Nascimento, 2013 (27)	Total thyroidectomy Central neck dissection: 3% Central and ipsilateral neck dissection: 50% Central and bilateral neck dissection: 3%	None	Not reported	Mean 9 months, then at discretion of physician (timing of repeat Tg not reported)	12% with detectable postoperative TgAb	Median 2.5 years	Neck US and other imaging (CT, MRI, and/or PET) as indicated
van Wyngaarden, 1997 (40)	Subtotal or near-total thyroidectomy: 83% Lobectomy with or without isthmusectomy: 17%	None	On thyroid replacement	Not described	Not described	Mean 60 months	Not described
Postoperative Tg testing before RAI therapy							
Caballero-Calabuig, 2008 (8)	Total lymph node dissection not reported	Tg obtained before RAI	TSH >30 mU/mL	4–6 Weeks	Excluded for positive Tg antibodies and negative Tg	4–6 Weeks	^{131}I total body scan
Giovanella, 2008 (10)	Total central neck dissection: 41%	Tg obtained before RAI	No (on T4)	4–6 Weeks	Excluded for TgAb levels >60 U/mL and/or recovery <80% or >120%	4–6 Weeks	^{131}I total body scan
Grunwald, 1996 (11)	Thyroidectomy, not otherwise described	Tg obtained before RAI	TSH >30 mU/mL	4–5 Weeks	Excluded for positive Tg antibodies or recovery <80% or >120%	4–5 Weeks	^{131}I upper thorax scintigraphy
Hasbek, 2014 (12)	Thyroidectomy, not otherwise described	Tg obtained before RAI	Thyroid hormone withdrawal for 4 weeks (TSH not reported)	Not reported	Excluded if anti-TgAb positive	8 or 9 Days	^{131}I total body scan
Heemstra, 2007 (13)	Thyroidectomy, not otherwise described	Tg obtained before RAI	Thyroid hormone withdrawal (duration and TSH not reported)	Not reported	Excluded if anti-TgAb positive	Within 1 year	Pathological or radiological evidence of tumor presence
Kim, 2013 (15)	Total thyroidectomy	Tg obtained before RAI	TSH >30 mU/mL	Not reported	44% had increasing TgAb levels	Median 54 months	Cytology/pathology

(continued)

TABLE 2. (CONTINUED)

Study, year	Surgery type	RAI	TSH level	Tg testing timing (from surgery)	TgAb status	Duration of follow-up	Reference standard
Kim, 2005 (16)	Total thyroidectomy	Tg obtained before RAI	TSH >30 mU/mL	5–6 Weeks	25% had elevated TgAb levels	7–13 Months (6–12 months following remnant ablation)	Cytology/pathology, ^{131}I total body scan
Krajewska, 2016 (17)	Total thyroidectomy	Tg obtained before RAI	TSH ≥25 uIU/mL	Not reported	Not reported	Not reported (median freedom from progression 155 months)	^{131}I total body scan, neck US, and stimulated Tg level
Latrofa, 2016 (18)	Total thyroidectomy	Tg obtained before RAI	Thyroid hormone withdrawal (mean 54.0 mIU/L)	3 Months	12–24% had positive TgAb, depending on assay used	3 Months	^{131}I total body scan and CT
Ledwon, 2021 (19)	Total or near-total thyroidectomy	Tg obtained before RAI	Nonstimulated	Median 2.7 months	14% had elevated TgAb levels	Median 6 years	Neck US with confirmatory biopsy, CT, MRI, or [^{18}F]FDG PET/CT for metastatic disease
Lima, 2002 (20)	Total thyroidectomy	Tg obtained before RAI	Appears to be nonsuppressed	3 Weeks	Excluded if TgAb positive	3 Weeks	Not reported
Lin, 2011 (21)	Total thyroidectomy	Tg obtained before RAI	No thyroid replacement or withdrawal	3–8 Weeks	Excluded if TgAb positive	3–8 Weeks	^{131}I total body scan and CT
Makarewicz, 2006 (22)	Thyroidectomy, not otherwise described	Tg obtained before RAI	Thyroid hormone withdrawal (median 48.2 mIU/L)	17–98 Days	Excluded if TgAb >60 U/mL	6 Months	Imaging, ^{131}I total body scan
Makarewicz, 2006 (23)	Thyroidectomy, not otherwise described	Tg obtained before RAI	Not reported	Unclear	Excluded if TgAb >60 U/mL	At least 18 months	Imaging, ^{131}I total body scan
Matrone, 2017 (25)	Total thyroidectomy	Tg obtained before RAI	On thyroid replacement	3–4 Months	Excluded if TgAb ≥20 ng/mL	3–4 Months	^{131}I total body scan, neck US, cytology
Matthews, 2016 (26)	Total thyroidectomy	Tg obtained before RAI	Not reported	Not reported	Excluded if TgAb positive	Not reported (at least 12 months after RAI therapy)	Not reported
Ng, 2000 (28)	Total or near-total thyroidectomy	Tg obtained before RAI	Thyroid replacement withdrawal for at least 5 weeks	Not reported	25% had TgAb levels >0.3 U/mL	1 Week before RAI therapy	(a) ^{131}I whole body scan (b) 99mTc-sestamibi whole body scan
Oyen, 2000 (29)	Total thyroidectomy	Tg obtained before RAI	No thyroid replacement	Not reported	Not reported	4–6 Weeks	Histology or 131I total body scan and Tg level; with clinical follow-up, CT, and/or ultrasonography in some cases

(continued)

TABLE 2. (CONTINUED)

Study, year	Surgery type	RAI	TSH level	Tg testing timing (from surgery)	TgAb status	Duration of follow-up	Reference standard
Polachek, 2011 (31)	Total or near-total thyroidectomy	Tg obtained before RAI	Suppressed (on thyroid hormone treatment, TSH <0.1 mU/L) and stimulated (TSH >30 ng/mL after thyroid hormone withdrawal)	Not reported	Excluded if TgAb positive	2 Years	Imaging, cytology, and/or RAI uptake, and suppressed Tg
Prabhu, 2018 (43)	Total thyroidectomy	Tg obtained before RAI	Mean 106 ng/mL (stimulated)	Not reported	Excluded if TgAb positive (defined as >100 IU/mL)	2–6 Weeks	^{131}I whole body scan
Ren, 2021 (32)	Total thyroidectomy	Tg obtained before RAI	Thyroid replacement withdrawal for at least 4 weeks with TSH >30 ng/mL	Not reported	Excluded if TgAb positive (defined as >115 IU/mL)	5–7 Days	^{131}I whole body scan, other imaging, with pathology confirmation
Ronga, 1999 (34)	Total thyroidectomy	Tg obtained before RAI	Tg obtained before starting therapy	∼40 Days	Not reported	Within 18 months	^{131}I whole body scan, other imaging and clinical evaluation if ^{131}I scan negative and Tg high
Rosario, 2011 (35)	Total thyroidectomy	Tg obtained before RAI	Thyroid hormone withdrawal before Tg testing (TSH target not reported)	3–6 Months	Excluded if TgAb positive	3–6 Months	Imaging and ^{131}I whole body scan
Szujo, 2021 (36)	Total or near-total thyroidectomy	Tg obtained before RAI	Nonstimulated	Not reported	Excluded if TgAb positive	Median 4.5 years	Not reported
Torlantano, 2006 (37)	Near-total thyroidectomy	Tg obtained before RAI	rhTSH stimulated	6–12 Months	Excluded if TgAb positive	6–12 Months	Ultrasonography
Toubeau, 2004 (38)	Total or near-total thyroidectomy	Tg obtained before RAI	Thyroid hormone withdrawal before Tg testing (TSH target not reported)	Mean 2.7 months	Excluded if TgAb positive or not measured	6–12 Months	Imaging modalities or surgery
Zerva, 2006 (41)	Total or near-total thyroidectomy	Tg obtained before RAI	TSH >30 IU/mL	Not reported	Excluded if TgAb positive	15 Months following RAI therapy	^{123}I whole body scan
Zhao, 2017 (42)	Total or near-total thyroidectomy	Tg before RAI	Thyroid hormone withdrawal (TSH >30 mIU/mL)	Not reported; serial Tg at median interval 8 days	Excluded if TgAb >46 IU/mL	Not reported (at time of RAI therapy)	^{131}I whole body scan with SPECT in patients with negative WBS

CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine; rhTSH, recombinant human thyrotropin; SPECT, single-photon emission computerized tomography; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TSH, thyrotropin; US, ultrasound; WBS, whole body scan.

The thyrotropin (TSH) level at the time of Tg measurement was <0.5 mIU/L in one study; one study reported median TSH level of 3.25 mIU/L; and two studies did not report the TSH level. One study focused on patients who underwent Tg measurement following partial thyroidectomy and before completion thyroid surgery (mean 3.2 months following initial surgery); outcomes were persistent disease and persistent or recurrent cervical lymph node metastatic disease based on pathological findings from completion surgery (7). In this study, completion thyroidectomy was performed to remove residual thyroid tissue as a definitive cancer therapy, not due to pathological findings on partial thyroidectomy. The other studies evaluated Tg measurement in unselected patients who underwent partial thyroidectomy (did not necessarily undergo completion surgery) and evaluated risk of persistence or recurrence, based on imaging and cytology/histology [two studies (30,39)] or an unreported reference standard [one study (33)].

Follow-up ranged from 6 months to 6.9 years. Two studies (7,39) were rated fair quality and two studies poor quality (Table 3) (30,33). Methodological shortcomings included potential selection bias, assessment of clinical outcomes not blinded to Tg results, unclear or high attrition or missing data, and lack of prespecified Tg thresholds to define a positive result.

One fair-quality study (n = 101) of patients who underwent completion surgery (89% with modified neck dissection) following partial thyroidectomy found 39% had residual thyroid cancer, and 40% had cervical lymph node metastasis (Table 4) (7). Tg >20 ng/mL before completion surgery was associated with a sensitivity of 0.44–0.47 for diagnosing residual thyroid cancer or lymph node metastasis and a specificity of 0.79–0.80. The positive predictive value was 0.57–0.60, and negative predictive value was 0.69.

In the three other studies, the proportion of patients who experienced DTC recurrence ranged from 7.1% at 6–13 months to 8.5% at 6.9 years (30,33,39). Evidence on Tg accuracy for identifying patients with recurrence was limited. One study found a ''rising'' (undefined) Tg associated with sensitivity of 0.80 and specificity of 0.80 (positive predictive value 0.24 and negative predictive value 0.98), but there were only 5 cases of recurrence (39). Another study found that Tg levels were not associated with high sensitivity and specificity for recurrence at various thresholds (≥20% Tg increase associated with sensitivity of 0.74 and specificity of 0.08; ≥100% increase associated with sensitivity of 0.26 and specificity of 0.75) (30). Positive predictive values ranged from 0.07 to 0.09, and negative predictive values ranged from 0.76 to 0.92. The third study did not report diagnostic accuracy at 1 year, but found that Tg levels at that time did not differ between recurrence and nonrecurrence groups (22.5 ng/mL vs. 11.3 ng/mL, $p = 0.16$); at 2 years, 3 of 6 patients with recurrence had rising Tg levels (33).

Tg measurement following total or near-total thyroidectomy without or before RAI

Tg following total or near-total thyroidectomy, without RAI. Five studies evaluated Tg measurement in patients who underwent total or near-total thyroidectomy without RAI (Tables 1 and 2) (9,14,24,27,40). All studies were retrospective, except for one (14). Sample sizes ranged from 47 to 290 (N = 751). Mean or median age ranged from 39 to 50 years. The proportion female ranged from 68% to 89%. Three studies reported that all or nearly all cancers were T1; one study (14) restricted inclusion to T1 and T2 tumors, but did not report the proportion of tumors by stage, and one study (40) did not report tumor stage. In 3 studies, 78–98% of cancers were papillary; 2 studies (9,40) did not report DTC type. Timing of initial Tg measurement ranged from 3 to 9 months after surgery in 3 studies [timing not reported in 2 studies (9,40)]. Thyroid stimulation before Tg measurement was not reported in any study, except for one (14), which reported no stimulation at 3 months after total thyroidectomy, recombinant TSH stimulation at 6 months, and Tg measurement with TSH 0.5–2.0 mIU/L at 18 and 24 months.

Four studies excluded patients with Tg antibodies or reported a low proportion of patients with Tg antibodies; one study (40) did not report Tg antibody status. The duration of follow-up ranged from 2 to 6 years. Outcomes were persistent or recurrent disease, based on whole-body iodine scan and other imaging. Two studies (9,14) were rated fair quality and three studies (24,27,40) poor quality (Table 3). No study reported assessment of outcomes blinded to results of Tg measurement, and no study reported the proportion of patients with missing data. Other methodological limitations included unclear application of the same reference standard to all patients and no prespecification of the threshold used to define a positive Tg level. The reference standard was neck ultrasound (US) (with other imaging as indicated) in two studies (24,27); ^{123}I scan and US in one study (14): a combination of clinical, ultrasonography, and Tg findings in one study (9); and not reported in one study (40) (Table 2).

Evidence on the accuracy of Tg measurement in patients who underwent total or near-total thyroidectomy without RAI was limited due to very low prevalence or incidence of recurrence or persistence across studies (Table 4). No cases of persistence or recurrence occurred in two studies [n = 57 and n = 271 (14,24)], and two studies (9,27) reported one case each (n = 86 and n = 290); the fifth study (40) did not report the number of persons with recurrence. One study (14) found Tg >1 ng/mL associated with specificity of 0.95, and 1 study (27) found that the Tg level was 11 ng/mL in a single patient with recurrent disease at 7 months. Otherwise, information on diagnostic accuracy was not reported, and findings were largely descriptive. The studies generally found Tg levels were stable and low (usually defined as <1 ng/mL) or undetectable following thyroidectomy.

One study (9) found that 97.9% of patients had a final (median 5 years) Tg ≤1 ng/mL, and 1 study (14) reported a mean Tg level at 18 months of 0.28 ng/mL. One study (24) found postoperative Tg levels were stable in most patients, although there was some variability according to first postoperative Tg level (78% in those with first postoperative Tg <0.2 ng/mL and 51% in those with first postoperative Tg >1 ng/mL). One study with mean follow-up of 60 months found that Tg was consistently undetectable in 62% of patients, and that 85% had a level <5 ng/mL (40).

Tg following total or near-total thyroidectomy, before RAI. Twenty-eight studies of patients who underwent total or near-total thyroidectomy and underwent RAI evaluated the accuracy of Tg measurement obtained before receiving

TABLE 3. QUALITY ASSESSMENT

Study, year	Consecutive or random sample	Blinding of outcomes assessment to Tg test	Low attrition or missing data	Appropriate reference standard	Same reference standard in all patients	Prespecified Tg threshold	Timing of Tg testing and assessment of outcomes reported	Quality	Other limitations
Tg testing following partial thyroidectomy									
Alzahrani, 2002 (7)	Unclear	No	Unclear	Yes	Yes	Yes	No (Tg testing)	Fair	
Park, 2018 (30)	Unclear	No	No	Yes	Yes	No	Yes	Poor	
Ritter, 2020 (33)	Unclear	No	Unclear	Unclear	Unclear	Unclear	Yes	Poor	
Vaisman, 2013 (39)	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Fair	Minor data discrepancy[a]
Tg testing following total or near-total thyroidectomy without RAI therapy									
Durante, 2012 (9)	Yes	No	Unclear	Yes	Unclear	Yes	Unclear (Tg testing and follow-up duration)	Fair	
Janovsky, 2016 (14)	Yes	No	Unclear	Yes	Yes	Yes	Yes	Fair	
Matrone, 2020 (24)	Yes	No	Unclear	Yes	Unclear	Unclear	Unclear (Tg testing and follow-up duration)	Poor	
Nascimento, 2013 (27)	Yes	No	Unclear	Yes	Unclear	Unclear	Yes	Poor	
van Wyngaarden, 1997 (40)	Unclear	No	Unclear	Unclear	Unclear	Not applicable	Unclear (Tg testing)	Poor	
Postoperative thyroglobulin testing before RAI therapy									
Caballero-Calabuig, 2008 (8)	Yes	No	Yes	No	Yes	No	Yes	Fair	
Giovanella, 2008 (10)	Yes	No	Unclear	No	Yes	No	Yes	Fair	
Grunwald, 1996 (11)	Unclear	No	Unclear	No	Yes	No	Yes	Poor	
Hasbek, 2014 (12)	Yes	No	Unclear	No	Yes	No	No (Tg testing)	Poor	
Heemstra, 2007 (13)	Yes	No	Unclear	Unclear	Unclear	No	No (Tg testing)	Poor	82 patients with anti-TgAb excluded
Kim, 2013 (15)	Yes	No	Unclear	Yes	Unclear	No	No (Tg testing)	Poor	
Kim, 2005 (16)	Yes	No	Unclear	Yes	Yes	No	Yes	Fair	
Krajewska, 2016 (17)	Yes	No	Unclear	Yes	Yes	Yes	No (Tg testing)	Fair	
Latrofa, 2016 (18)	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Fair	
Ledwon, 2021 (19)	Unclear	No	Unclear	Yes	No	No	Yes	Poor	
Lima, 2002 (20)	Unclear	No	Unclear	Unclear	Yes	No	Yes	Poor	Data discrepancy present[b]
Lin, 2011 (21)	Unclear	No	Unclear	Yes	Yes	Unclear	Yes	Poor	
Makarewicz, 2006 (22)	Unclear	No	Unclear	Yes	Yes	Not applicable	Yes	Poor	Data discrepancy present[b]

TABLE 3. (CONTINUED)

Study, year	Consecutive or random sample	Blinding of outcomes assessment to Tg test	Low attrition or missing data	Appropriate reference standard	Same reference standard in all patients	Prespecified Tg threshold	Timing of Tg testing and assessment of outcomes reported	Quality	Other limitations
Makarewicz, 2006 (23)	Unclear	No	Unclear	Yes	Yes	No	No (Tg testing and follow-up duration)	Poor	
Matrone, 2017 (25)	Yes	No	Unclear	Yes	Yes	No	Yes	Fair	
Matthews, 2016 (26)	Yes	No	No	Unclear	Unclear	No	No (Tg testing and follow-up duration)	Poor	
Ng, 2000 (28)	Unclear	No	Unclear	No	No	Yes	No (Tg testing)	Poor	
Oyen, 2000 (29)	Unclear	No	Yes	Unclear	No	Yes	No	Poor	
Polachek, 2011 (31)	Yes	No	Unclear	Yes	No	No	No (Tg testing)	Poor	
Prabhu, 2018 (43)	Unclear	Unclear	Unclear	No	Yes	No	Yes	Poor	
Ren, 2021 (32)	Unclear	No	Unclear	Yes	No	No	No (Tg testing)	Poor	
Ronga, 1999 (34)	Yes	No	Unclear	Yes	Yes	No	No (follow-up duration)	Poor	
Rosario, 2011 (35)	Yes	No	Unclear	Yes	Yes	No	Yes	Fair	
Szujo, 2021 (36)	Unclear	No	No	Unclear	Unclear	No	No (Tg testing)	Poor	Data discrepancy present[b]
Torlantano, 2006 (37)	Yes	No	Unclear	Unclear	Yes	Unclear	Yes	Poor	
Toubeau, 2004 (38)	Yes	No	No	Yes	Unclear	Unclear	Yes	Poor	
Zerva, 2006 (41)	Unclear	No	Unclear	No	Yes	No	No (Tg testing)	Poor	
Zhao, 2017 (42)	Yes	No	Unclear	Yes	Yes	No	No (Tg testing and follow-up duration)	Poor	Cutoffs for change in Tg and change in Tg/change in TSH unclear

[a]Study reports 14 false-positive patients, which would result in specificity of 0.78 (51/65) rather than 0.80 as reported in study.
[b]Discrepancy between reported diagnostic accuracy and data reported in study; diagnostic accuracy calculated from data in study.

TABLE 4. STUDIES OF THYROGLOBULIN TESTING—RESULTS

Study, year	Outcome	Outcome prevalence	Tg threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
Tg testing following partial thyroidectomy								
Alzahrani, 2002 (7)	(a) Residual thyroid cancer	(a) 39% (39/100)	>20 ng/mL	(a) 0.44 (17/39)	(a) 0.79 (48/61)	(a) 0.57 (17/30)	(a) 0.69 (48/70)	None
	(b) Cervical lymph node metastasis	(b) 40% (36/90)		(b) 0.47 (17/36)	(b) 0.80 (43/54)	(b) 0.61 (17/28)	(b) 0.69 (43/62)	
Park, 2018 (30)	Recurrent/ persistent disease	8.5% (19/223)	(a) ≥20% increase	(a) 0.74 (14/19)	(a) 0.08 (16/204)	(a) 0.07 (14/202)	(a) 0.76 (16/21)	None
			(b) ≥50% increase	(b) 0.47 (9/19)	(b) 0.38 (79/204)	(b) 0.07 (9/134)	(b) 0.89 (79/89)	
			(c) ≥100% increase	(c) 0.26 (5/19)	(c) 0.75 (153/204)	(c) 0.09 (5/56)	(c) 0.92 (153/167)	
Ritter, 2020 (33)	Recurrence	7.2% (12/167)	Not reported	Not reported	Not reported	Not reported	Not reported	Mean Tg 1 level after lobectomy 22.5 ng/mL in 11 of 12 patients with recurrence; 1-year Tg levels did not differ between recurrence and nonrecurrence groups (22.5 vs. 11.3, *p*=0.16); at 2 years 3 of 6 patients with recurrence had rising Tg levels
Vaisman, 2013 (39)	Recurrence	7.1% (5/70)	"Rising" Tg, not defined	0.80 (4/5)	0.80 (52/65)	0.24 (4/17)	0.98 (52/53)	Minor data discrepancy present (study reports 14 false-positive patients which would result in specificity of 0.78 (51/65) rather than 0.80 as reported in study)

(*continued*)

628

TABLE 4. (CONTINUED)

Tg testing following total or near-total thyroidectomy without RAI therapy

Study, year	Outcome	Outcome prevalence	Tg threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
Durante, 2012 (9)	Recurrent/ persistent tumor	0.3% (1/290)	>1.0 ng/mL on final TSH	Not reported (only 1 case)	Not reported (only 1 case)	Not reported	Not reported	97.9% (274/280) had final Tg ≤1 ng/mL
Janovsky, 2016 (14)	Positive ^{123}I total body scan or neck US	0% (0/57)	>1 ng/mL	Not reported (no cases)	0.95 (54/57)	Not reported	Not reported	Mean Tg level at 18 months 0.28 ng/mL. No cases of tumor recurrence observed; Tg levels stable or decreasing throughout follow-up
Matrone, 2020 (24)	Recurrence	0% (0/271)	Not specified	Not reported (no cases)	Not reported (no cases)	Not reported	Not reported	Tg levels were stable in 78%, 60%, and 51% of patients with first postoperative Tg <0.2 ng/mL, 0.2–1 ng/mL, and >1 ng/mL, respectively
Nascimento, 2013 (27)	Recurrence	1.2% (1/86)	Not specified	Not reported (1 case)	Not reported (1 case)	Not reported	Not reported	1 patient with recurrent disease at 7 months had Tg level of 11 ng/mL
van Wyngaarden, 1997 (40)	Not reported	Not reported	Not applicable	Not reported	Not reported	Not reported	Not reported	Subtotal or near-total thyroidectomy: Tg consistently undetectable in 62% and <5 ng/mL in 85% Lobectomy: Tg undetectable in 12% and <5 ng/mL in 25% In patients with higher Tg values, levels remained constant within narrow range provided TSH was not high

(continued)

TABLE 4. (CONTINUED)

Study, year	Outcome	Outcome prevalence	Tg threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
Postoperative thyroglobulin testing before RAI therapy								
Caballero-Calabuig, 2008 (8)	Thyroid remnant, positive lymph nodes, or metastatic disease	100% (128/128)	>3 ng/mL (1998–2000); >1.5 ng/mL (2001–2003); >0.5 ng/mL (2004–2005)	0.90 (115/128)	No noncases	Not calculable	Not calculable	None
Giovanella, 2008 (10)	Positive ^{131}I total body scan	Not reported	>1.10 ng/mL	0.83 (n/N not reported)	0.66 (n/N not reported)	Not calculable	Not calculable	None
Grunwald, 1996 (11)	(a) Lymph node metastases	(a) 12% (11/92)	>6 ng/mL	(a) 0.27 (3/11)	(a) 1.0 (81/81)	(a) 1.0 (3/3)	(a) 0.91 (81/89)	Threshold not prespecified
	(b) Distant metastases	(b) 12% (11/92)		(b) 0.73 (8/11)	(b) 1.0 (81/81)	(b) 1.0 (8/8)	(b) 0.96 (81/84)	
	(c) Recurrence	(c) 9.0% (8/89)		(c) 0.38 (3/8)	(c) 1.0 (81/81)	(c) 1.0 (3/3)	(c) 0.94 (81/86)	
Hasbek, 2014 (12)	(a) Positive ^{131}I total body scan	(a) 5.9% (13/221)	(a) >10 ng/mL	(a1) 0.69 (9/13) (b1) 0.92 (11/13)	(a1) 0.66 (138/208)	(a1) 0.11 (9/79)	(a1) 0.97 (138/142)	3.6% of patients had aggressive tumor subtypes
	(b) Distant or lymph node metastases on ^{131}I total body scan	(b) 5.0% (11/221)	(b) >2 ng/mL	(a2): 0.82 (9/11) (b2): 0.91 (10/11)	(b1) 0.35 (73/2080)	(b1) 0.08 (11/146)	(b1) 0.97 (73/75)	
Heemstra, 2007 (13)	(a) Tumor presence	(a) 14.9% (33/222)	>27.5 ng/mL	(a) 0.88 (29/33)	(a) 0.90 (171/189)	(a) 0.62 (29/47)	(a) 0.38 (18/48)	None
	(b) Distant metastases	(b) 9.5% (21/222)		(b) 0.86 (18/21)	(b) 0.85 (171/201)	(b) 0.98 (171/175)	(b) 0.98 (171/174)	
Kim, 2013 (15)	Recurrence	3.2% (among those with biochemical remission)	>5.3 ng/mL	Not reported	Not reported	Not reported	Not reported	AUROC 0.87 (CI not reported); adjusted OR 36.14 [CI 7.48–174.60] Change in stimulated Tg around time of ablation did not predict recurrence

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630

TABLE 4. (CONTINUED)

Study, year	Outcome	Outcome prevalence	Tg threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
Kim, 2005 (16)	Recurrence	13.0% (35/268)	(a) >10 ng/mL (b) >2 ng/mL	(a) 0.77 (27/35) (b) 0.94 (33/35)	(a) 0.84 (196/233) (b) 0.53 (123/233)	(a) 0.42 (27/64) (b) 0.23 (33/143)	(a) 0.96 (196/204) (b) 0.98 (123/125)	None
Krajewska, 2016 (17)	Relapse or progression	9.4% (48/510)	>30 ng/mL	0.50 (24/48)	0.92 (37/462)	0.05 (24/449)	0.61 (37/61)	Discrepancy between reported diagnostic accuracy and data reported in study; diagnostic accuracy calculated from data in study
Latrofa, 2016 (18)	Metastatic disease (distant or lymph node)	5.6% (10/177); 1.7% (3/177) distant and 4.0% (7/177) lymph node	Detectable	0.80 (8/10)	Not reported	Not reported	Not reported	Both patients with undetectable Tg and metastatic disease had positive TgAb
Ledwon, 2021 (19)	Recurrence	6.6% (43/650)	>0.7 ng/mL	0.54 (23/43)	0.76 (461/607)	0.14 (23/169)	0.96 (461/481)	Stimulated pre-RAI Tg was not predictive of recurrence (diagnostic accuracy not reported)
Lima, 2002 (20)	Metastatic disease (distant or lymph node)	52.4% (22/42); 14.3% (6/42) distant and 38.1% (16/42) lymph node	>2.3 ng/mL	0.73 (16/22)	0.95 (19/20)	0.94 (16/17)	0.76 (19/25)	Discrepancy between reported diagnostic accuracy and data reported in study; diagnostic accuracy calculated from data in study
Lin, 2011 (21)	Distant metastatic disease	19.3% (47/244)	Not reported	Not reported	Tg: 0.913 [CI 0.85–0.97] Tg/TSH ratio: 0.92 [CI 0.86–0.97]	Not reported	Not reported	None

(continued)

631

Table 4. (Continued)

Study, year	Outcome	Outcome prevalence	Tg threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
Makarewicz, 2006 (22)	Metastatic disease or recurrence	18.0% (32/178); 10.1% (18/178) distant and 11.2% (20/178) lymph node	Not reported	Not reported	Not reported	Not reported	Not reported	AUROC: 0.77 (0.66–0.89)
Makarewicz, 2006 (23)	Metastatic disease (distant or lymph node) or recurrence	14.2% (35/247); 7.3% (18/247) lymph node (no. of patients with distant metastases unclear)	>38.1 ng/mL	0.57 (20/35)	0.96 (204/212)	0.09 (20/232)	0.93 (204/219)	None
Matrone, 2017 (25)	Metastatic disease (distant or lymph node)	5.3% (27/505); 0.8% (4/505) distant and 4.6% (23/505) lymph node	>2 ng/mL	0.41 (11/27)	0.88 (421/478)	0.16 (11/68)	0.96 (421/437)	None
Matthews, 2016 (26)	Recurrence	11.0% (11/100)	>3 ng/mL	1.0 (11/11)	0.55 (49/89)	0.22 (11/51)	1.00 (49/49)	Positive predictive value for Tg >27.5 μg/L 0.31 [CI 0.11–0.59]; OR 4.50 [CI 1.35–15.04]
Ng, 2000 (28)	Thyroid remnant, positive lymph nodes, or metastatic disease	(a) 58.3% (210/360) (b) 45.3% (163/360)	≥30 ng/mL	(a) 0.46 (97/210) (b) 0.50 (81/163)	(a) 0.97 (146/150) (b) 0.90 (177/197)	(a) 0.96 (97/101) (b) 0.80 (81/101)	(a) 0.56 (146/259) (b) 0.68 (177/259)	(a) Reference standard ^{131}I whole body scan (b) Reference standard ^{99m}Tc-sestamibi scan
Oyen, 2000 (29)	Distant metastatic disease	9.8% (25/254)	≥0.78 ng/mL (≥10 pmol/L)	1.00 (25/25)	0.42 (96/229)	0.16 (25/158)	1.0 (96/96)	None

(continued)

TABLE 4. (CONTINUED)

Study, year	Outcome	Outcome prevalence	Tg threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
Polachek, 2011 (31)	Persistent disease (active disease [structural disease on imaging or detectable suppressed Tg] within 1 year of treatment)	25.0% (105/420)	(a) >10 ng/mL (b) >2.5 ng/mL	(a) 0.73 (77/105) (b) 0.90 (94/105)	(a) 0.73 (230/315) (b) 0.42 (132/315)	(a) 0.48 (77/162) (b) 0.66 (94/277)	(a) 0.89 (230/258) (b) 0.92 (132/143)	Model with sex, lymph nodes, distant metastasis, tumor invasion, tumor size, and baseline Tg <10 ng/mL associated with sensitivity of 0.80 and specificity of 0.68
Prabhu, 2018 (43)	Metastatic disease (distant or lymph node)	12.0% (12/100); 10.0% (10/100) lymph node and 4.0% (4/100) distant	(a) ≥1 ng/mL (b) ≥2 ng/mL (c) >5 ng/mL	(a) 1.00 (12/12) (b) 0.92 (11/12) (c) 0.83 (10/12)	(a) 0.24 (22/90) (b) 0.37 (33/90) (c) 0.57 (51/90)	(a) 0.15 (12/80) (b) 0.19 (11/58) (c) 0.20 (10/49)	(a) 1.00 (22/22) (b) 0.97 (33/34) (c) 0.96 (51/53)	None
Ren, 2021 (32)	Metastatic disease (distant or lymph node)	85.5% (201/235); 19.6% (46/235) distant and 66.0% (155/235) lymph node	(a) >61.87 ng/mL (distant metastasis) (b) >32.13 ng/mL (lymph node metastasis)	(a) 0.98 (45/46) (b) 0.19 (29/155)	(a) 0.88 (30/34) (b) 0.71 (24/34)	(a) 0.92 (45/49) (b) 0.74 (29/39)	(a) 0.97 (30/31) (b) 0.16 (24/150)	(a) AUROC 0.96 [CI 0.93–0.99] (b) AUROC 0.57 [CI 0.45–0.69]
Ronga, 1999 (34)	Metastatic disease (distant or lymph node)	23.7% (79/334); 9.6% (32/334) distant and 14.1% (47/334) lymph node	(a) >30.25 ng/mL (b) >11.05 ng/mL (c) >2.25 ng/mL	(a) 0.84 (66/79) (b) 0.94 (75/79) (c) 0.99 (78/79)	(a) 0.86 (219/255) (b) 0.54 (138/255) (c) 0.10 (26/229)	(a) 0.65 (66/102) (b) 0.39 (75/192) (c) 0.25 (78/307)	(a) 0.94 (219/232) (b) 0.97 (138/142) (c) 0.96 (26/27)	None
Rosario, 2011 (35)	Persistent disease	3.4% (8/237)	(a) >1 ng/mL (b) >10 ng/mL	(a) 1.0 (8/8) (b) 0.50 (4/8)	(a) 0.58 (132/229) (b) 0.93 (213/229)	(a) 0.06 (8/140) (b) 0.02 (4/217)	(a) 1.0 (97/97) (b) 0.80 (16/20)	None
Sjuzo, 2021 (36)	Recurrent or persistent disease	16% (36/222)	>34.6 ng/mL	0.83 (29/35)	0.86 (160/187)	0.52 (29/56)	0.96 (160/166)	AUROC 0.82 (SD not reported)
Torlontano, 2006 (37)	Persistent nodal disease	3.8% (3/80)	>1 ng/mL	0.67 (2/3)	0.57 (43/77)	0.06 (2/36)	0.98 (43/44)	Basal (unstimulated) Tg <1 ng/mL in all patients with nodal disease

(continued)

633

TABLE 4. (CONTINUED)

Study, year	Outcome	Outcome prevalence	Tg threshold	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
Toubeau, 2004 (38)	Progression (clinical reappearance after complete ablation)	9.6% (20/208)	>30 ng/mL	0.65 (13/20)	0.91 (171/188)	0.43 (13/30)	0.96 (171/178)	Tg >30 ng/mL: Adjusted OR 10.1 [CI 4.0–25.7] for progression (not included in multivariable model that included post iodine therapy variables)
Zerva, 2006 (41)	Metastatic disease following RAI therapy (distant or lymph node)	9.3% (23/248); 7.7% (19/248) distant and 2.8% (7/248) lymph node	(a) Tg >8 ng/mL (b) Tg/^{131}I uptake >7 ng/mL/%	(a) 0.91 (21/23) (b) 0.96 (22/23)	(a) 0.86 (194/225) (b) 0.96 (215/225)	(a) 0.40 (21/52) (b) 0.69 (22/32)	(a) 0.99 (194/196) (b) 0.995 (215/216)	None
Zhao, 2017 (42)	Distant metastatic disease	22.7% (72/317)	(a) Initial Tg >12.35 ng/mL (b) Second Tg >22.10 ng/mL (c) Change in Tg 3.90–6.55 ng/mL (d) Change in Tg/change in TSH −0.40 to −0.41 ng/mIU	(a) 0.90 (65/72) (b) 0.90 (65/72) (c) 0.89 (64/72) (d) 0.83 (60/72)	(a) 0.83 (204/245) (b) 0.86 (210/245) (c) 0.79 (194/245) (d) 0.90 (221/245)	(a) 0.61 (65/106) (b) 0.65 (65/100) (c) 0.56 (64/115) (d) 0.71 (60/84)	(a) 0.97 (204/211) (b) 0.97 (210/217) (c) 0.96 (194/202) (d) 0.95 (221/233)	AUROC (SE) (a) 0.92 (0.02) (b) 0.95 (0.02) (c) For >0, 0.91 (0.02) and for <0, 0.86 (0.08) (d) For >0, 0.91 (0.02) and for <0, 0.90 (0.07) Cutoffs for change in Tg and change in Tg/change in TSH unclear

Ab, antibody; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; SD, standard deviation; SE, standard error.

RAI and may also provide some information on utility of Tg measurement in patients who do not undergo RAI (Tables 1 and 2) (8,10–13,15–23,25,26,28,29,31,32,34–38,41–43). All studies were retrospective, except for one (20). Sample sizes ranged from 42 to 1033 ($N = 7618$). Mean or median age ranged from 40 to 53 years, and the proportion of female ranged from 64% to 90% in studies that reported sex. The proportion of tumors that were papillary ranged from 55% to 97%; in studies that reported stage, the proportion with T1 or T2 tumors ranged from 40% to 100%, and the proportion with stage I or II tumors ranged from 54% to 69%. Stimulation of TSH with thyroid hormone withdrawal before Tg testing appears to have occurred in all studies, except for six (10,19–21,25,36). When reported, the timing of Tg measurement ranged from 4 to 5 weeks to 3 months following surgery, and the duration of follow-up ranged from 4 to 6 weeks to 54 months following surgery

Outcomes assessed were progression, persistent local disease, local recurrence, and metastatic disease (distant, lymph node, or both) (Table 4). Seven studies (8,10,16–18,25,35) were rated fair quality, and the rest were rated poor quality (Table 3). No study reported assessment of outcomes blinded to results of Tg measurement, and no study reported the proportion of patients with missing data. Other methodological limitations included failure to apply the same reference standard to all patients and no prespecification of the threshold used to define a positive Tg level. The reference standards used in the studies varied (Table 2). Eight studies used reference standards considered inadequate: one study (37) used ultrasonography alone, and six studies (8,10–12,28,41,43) used whole-body scan alone. In the other studies, the reference standard was cytological or pathological findings or some combination of pathology, imaging, or ^{131}I scan.

Fifteen studies assessed the accuracy of postoperative Tg measurement for diagnosing metastatic or persistent disease before administration of RAI (8,10–12,18,20,21,25,28,29, 32,35,37,42,43). Ten studies evaluated accuracy for lymph node or distant metastatic disease (Table 4) (11,12,18,20,21, 25,29,32,42,43). The proportion of patients with lymph node metastases ranged from 0.8% to 66.0% (6 studies), and the proportion with distant metastases ranged from 1.7% to 22.7% (9 studies); in 1 study the proportion of patients with lymph node or distant metastasis was 5.0% (12). Sensitivity of Tg for any metastatic disease (lymph node or distant) ranged from 0.41 to 1.00 [8 studies (11,12,18,20,25,29, 42,43)], and specificity ranged from 0.24 to 1.0 [7 studies (11,20,21,25,29,42,43)]. Tg thresholds ranged from ''detectable'' [sensitivity 0.80, specificity not reported (18)] or ≥0.89 ng/mL [sensitivity 1.00, specificity 0.42 (29)] to >12.35 ng/mL [sensitivity 0.90, specificity 0.83 (42)].

One additional study reported higher accuracy of pre-RAI Tg for distant metastasis (sensitivity 0.98, specificity 0.88, Tg threshold >61.87 ng/mL) than for lymph node metastasis (sensitivity 0.19, specificity 0.71, Tg threshold >32.13 ng/mL) (32). In studies that did not report TSH stimulation before Tg measurement, sensitivity was 0.41 and 0.73 [2 studies (20,25)], and specificity ranged from 0.88 to 0.95 [3 studies (20,21,25)]. Seven studies assessed accuracy for persistent disease or the composite outcome of persistence or metastatic disease before administration of RAI (8,10–12,28,35,37). One study (8) restricted inclusion to patients with persistent or metastatic disease; in the other studies, the proportion with

persistence or the composite outcome ranged from 5.4% to 58%. Sensitivity of Tg ranged from 0.38 to 1.0 [7 studies (8,10–12,28,35,37)], and specificity ranged from 0.33 to 1.0 [6 studies (8,11,12,28,35,37)]. Tg thresholds ranged from >1 or 1.10 ng/mL (sensitivity 0.67–1.0 and specificity 0.57–0.66) (10,35,37) to >10 ng/mL (sensitivity 0.50 and 1.0 and specificity 0.68 and 0.93) (12,35).

In four studies that evaluated diagnostic accuracy for persistence or the composite outcome at different Tg threshold levels, sensitivity decreased, and specificity increased at higher thresholds (12,16,31,35). However, no Tg testing threshold was associated with both high sensitivity and high specificity. In these studies, at a Tg threshold of >1 to >2.5 ng/mL, sensitivity ranged from 0.90 to 1.0 (median 0.93) and specificity ranged from 0.35 to 0.58 (median 0.48); at a Tg threshold of >10 ng/mL, sensitivity ranged from 0.69 to 0.77 (median 0.71), and specificity ranged from 0.66 to 0.93 (0.77). One study reported a sensitivity of 1.00 and specificity of 0.24 for metastatic disease at a Tg threshold ≥1 and sensitivity of 0.83 and specificity of 0.57 at a Tg threshold of >5 ng/mL (43). In one study, in which Tg was obtained without prior TSH stimulation, the sensitivity was 0.90 (specificity not reported) (8).

Thirteen studies assessed the accuracy of postoperative, pre-RAI Tg measurement for predicting outcomes that occurred following RAI (mean or duration of follow-up, 6–72 months) (Table 4) (13,15–17,19,22,23,26,31,34,36,38,41). However, results are more difficult to interpret than for outcomes assessed at the time of RAI administration, because they could be impacted by response to RAI or other intervening factors. For predicting metastatic disease, sensitivity ranged from 0.57 to 0.94 and specificity from 0.54 to 0.96 in 4 studies (13,22,34,41), based on pre-RAI Tg thresholds of >8 to >38.1 ng/mL. In one study that evaluated different Tg testing thresholds, sensitivity was high (≥0.94) but specificity was low (0.10 or 0.54) at thresholds of >2.25 to >11.05 ng/mL; however, a testing threshold of >30.25 ng/mL was associated with high sensitivity and specificity [0.84 and 0.86, respectively (34)].

For predicting recurrence, sensitivity ranged from 0.50 to 1.0, and specificity ranged from 0.55 to 0.92 in 8 studies (13,16,17,19,26,31,36,38), based on pre-RAI Tg thresholds of >0.7 to >34.6 ng/mL. Two studies (15,36) found postoperative, preablation Tg associated with an area under the receiver operating characteristic curve (AUROC) of 0.82 and 0.87 for recurrence following RAI treatment, and one study (22) found Tg associated with an AUROC of 0.77 (confidence interval 0.66–0.89) for metastatic disease following RAI treatment.

Discussion

Evidence for the utility of serum Tg measurement in persons with DTC following partial thyroidectomy or following total or near-total thyroidectomy without administration of RAI after surgery is limited. Due to imprecision, methodological limitations, and inconsistency, the evidence on diagnostic accuracy was graded as very low for all outcomes (Table 5). One study of patients who underwent partial thyroidectomy and subsequent completion surgery found Tg >20 ng/mL associated with sensitivity of <0.50 and specificity of ~0.80 for detection of cervical lymph node

Table 5. Overall Quality of Evidence, Diagnostic Accuracy of Thyroglobulin Measurement

Clinical scenario	No. of studies	Methodological limitations	Imprecision	Inconsistency	Indirectness	Overall quality[a]
Partial thyroidectomy	4 (N=561)	Very serious	Serious	Serious	Not serious	Very low
Total/near-total thyroidectomy, no RAI	5 (N=751)	Very serious	Serious	Serious	Not serious	Very low
Total/near-total thyroidectomy, Tg measurement obtained before RAI	28 (N=7618)	Very serious	Not serious	Serious	Serious[b]	Very low

Formal assessment for small sample effects and potential publication bias was not performed, due to the small number of studies (partial thyroidectomy and total/near-total thyroidectomy without RAI), very serious methodological limitations, and heterogeneity in populations, Tg thresholds, Tg methods, and outcomes.

[a]The overall quality of evidence on diagnostic accuracy for all clinical outcomes (metastasis, recurrence, persistence, or a composite) was graded very low.

[b]Downgraded for indirectness because of reduced generalizability to patients who undergo total/near-total thyroidectomy and do not receive RAI.

metastasis or residual thyroid cancer based on pathological findings at completion surgery (7), for a positive likelihood ratio of 2.4 and negative likelihood ratio of 0.66. Based on these estimates, in a hypothetical cohort of patients who underwent partial thyroidectomy with a 10% pretest probability of cervical lymph node metastasis or residual thyroid cancer, the post-test probability in those with a Tg level >20 ng/mL would be 21% and with a Tg level ≤20 ng/mL would be 7%, indicating modest utility, given the relatively small changes in diagnostic probabilities.

Similarly, in a hypothetical cohort with a 40% pretest probability, the post-test probability following a Tg level >20 ng/mL would be 61% and the post-test probability following a Tg level ≤20 ng/mL would be 31%. However, these estimates are based on a single study of patients who underwent completion surgery, with uncertain applicability to other partial thyroidectomy populations. Three other studies of Tg testing after partial thyroidectomy that did not restrict enrollment to persons who underwent completion surgery and used an imaging or histological reference standard did not identify patients with recurrence or were limited by small sample size, and it was not possible to estimate diagnostic accuracy or likelihood ratios (30,33,39). In these studies, decreases in Tg levels were observed in some patients who experienced recurrence following partial thyroidectomy, potentially related to natural fluctuations in Tg or TSH levels.

For patients who underwent total or near-total thyroidectomy and did not receive RAI, there was very low-quality evidence from five studies to determine diagnostic accuracy of Tg measurement for recurrence, persistence, or metastatic disease due to very low rates of these outcomes. In these cohorts, Tg levels were low (usually <1 ng/mL) and stable in most patients during follow-up. Evidence for postoperative Tg measurement before RAI therapy suggests high specificity but variable (moderate to high) sensitivity for diagnosing metastatic disease or recurrence. Some variability was due to the Tg threshold used, with higher Tg thresholds associated with lower sensitivity and higher specificity. Although no Tg threshold was associated with both high sensitivity and high specificity, the utility of Tg testing depends on the Tg threshold used and the purpose of Tg testing. For example, four studies that compared different Tg thresholds found that at a Tg threshold of >1 to 2.5 ng/mL, median sensitivity for

persistence or a composite outcome (persistence or metastatic disease) was 0.93 and median specificity was 0.48, resulting in a modest positive likelihood ratio (1.8) but strong negative likelihood ratio (0.15).

In a hypothetical cohort with a pretest probability of 10%, the post-test probability for the outcomes following a Tg level <1 to 2.5 ng/mL would decline fivefold, to 2%, suggesting potential usefulness for ruling out these outcomes. However, a Tg level >1 to 2.5 ng/mL would only have a modest impact on increasing the post-test probability (17%). At a Tg threshold of >10 ng/mL, the median sensitivity was 0.71 and median specificity was 0.78, for a positive likelihood ratio of 3.2 and negative likelihood ratio of 0.37. A Tg value >10 ng/mL would result in a greater increase in the post-test probability (26%) than using the lower threshold, while a Tg value <10 ng/mL would decrease the post-test probability to 4%. The clinical utility of using a Tg threshold >10 ng/mL would depend on whether a post-test probability for these outcomes of 4% is low enough to rule out the need for additional evaluation or otherwise alter the clinical approach. Other studies reported variable accuracy of postoperative, pre-RAI Tg for predicting outcomes following RAI and are difficult to interpret due to potential effects of RAI and other intervening factors on subsequent outcomes.

Our review had limitations. First, we restricted inclusion to English language articles, which could result in language bias. However, only one study (44) was excluded due to non-English language; it evaluated pre-RAI Tg and was unlikely to impact conclusions. Second, we did not assess for potential publication bias, due to the small number of studies and variability in Tg thresholds used and other factors, which complicate interpretation of graphical and statistical tests for small sample effects (45). Third, the protocol was not registered before initiating the review. However, the scope and methods were developed before conducting the review, and no protocol changes occurred. Fourth, we did not address other potential uses of Tg measurement, such as assessing the adequacy of thyroid hormone dose or predicting response to RAI.

Despite these limitations, our review is the first to synthesize the evidence around Tg testing in patients who have undergone partial thyroidectomy or total/near-total thyroidectomy who have not received RAI. A prior systematic

review evaluated Tg measurement following thyroidectomy but did not address patients who had undergone partial thyroidectomy, did not report findings from studies of patients who underwent total or near-total thyroidectomy separately, included fewer studies, and did not evaluate studies of patients who underwent Tg measurement before RAI administration separately (46). A major limitation of the evidence in this review is the presence of methodological shortcomings in all studies. Almost all studies were retrospective, no study was rated good quality, and over half were rated poor quality. No study reported assessment of outcomes blinded to Tg results, and few reported attrition or missing data. Other common methodological shortcomings included failure to report enrollment of a consecutive or random sample, no prespecification of the Tg threshold to define a positive test, lack of clarity regarding TSH levels at the time of Tg testing, and unclear timing of Tg measurement or follow-up in relation to surgery.

Interpretation of the evidence is also challenging due to low event rates (particularly for patients who underwent total/near-total thyroidectomy without RAI) and differences in patient populations, outcomes assessed, duration of follow-up, variability in serum Tg concentrations depending on the measurement method used and study year (studies indicate less variability in more recent studies) (47), reference standards for outcomes, use of TSH-stimulated Tg in some studies and non-TSH-stimulated Tg levels in other studies, and other factors. Some studies did not define outcomes well and for the outcome of metastatic disease, studies did not distinguish between persistent disease, recurrent disease, or incident development in the contralateral lobe. In addition, due to study methodological limitations and heterogeneity, we did not perform meta-analysis, to avoid misleading pooled results. In patients who have undergone total or near-total thyroidectomy, the applicability of studies in which patients had Tg measurement before RAI to patients who do not receive RAI is uncertain, because the former is likely to represent a higher risk category.

Future research is needed to clarify the accuracy of Tg measurement in these situations, how the utility of Tg measurement varies according to patient or tumor factors, and optimal approaches to Tg monitoring (including timing, intervals, interpretation of single values vs. change, optimal Tg thresholds). Additionally, because the impact of Tg measurement depends on the actions that are taken as a result of Tg test results and the downstream effects of these actions, studies that assess the effects of Tg measurement on clinical decision making (e.g., additional testing, RAI administration, or surgery) and patient outcomes are needed. If Tg levels are obtained, anti-Tg antibodies should also be measured for appropriate interpretation.

In conclusion, very limited evidence suggests low utility of Tg measurement for identifying recurrent or metastatic disease following partial thyroidectomy. In persons who have undergone total or near-total thyroidectomy, incidence of recurrence is low, and Tg levels appear to be stable and low in most patients who do not receive RAI. Tg levels using a low cutoff (e.g., 1–2.5 ng/mL) might be useful to identify patients at low risk of persistent disease or metastasis. Therefore, in patients who have undergone total or near-total thyroidectomy without RAI, measuring Tg levels in conjunction with other monitoring may be helpful for identifying patients not

requiring additional evaluation. Additional research is needed to clarify the role of Tg measurement in these settings, determine optimal Tg thresholds, and determine appropriate testing intervals.

Authors' Contributions

All authors conceived the study. R.C. designed the study and R.C. and T.D. carried out the review. R.C. prepared the first draft of the article. All authors were involved in the revision of the draft article and have agreed to the final content.

Author Disclosure Statement

Funding Information

Supplementary Material

Supplementary Appendix SA
Supplementary Appendix SB
Supplementary Appendix SC

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