



Microscopically positive surgical margins and local recurrence in thyroid cancer. A meta-analysis

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ABSTRACT

Background: Microscopically positive surgical margins are a prognostic factor of recurrence in advanced thyroid carcinoma. However, information on early and completely resected thyroid tumors is scarce. Some studies do not identify any association between positive margin and local recurrence. The objective of this study was to perform a meta-analysis to measure the association of microscopically positive surgical margins and local recurrence in patients who underwent total thyroidectomy.

Methods: Clinical trials assessing the association between microscopically positive surgical margin and local recurrence in patients with early-stage, well-differentiated thyroid carcinoma who underwent total thyroidectomy were evaluated. The outcome measured was local recurrence in the thyroid bed. A systematic review and meta-analysis was done using a random-effects model.

Results: Six studies with 7696 patients were identified. Methodological quality was good, and we did not identify statistical heterogeneity or publication bias. The risk difference for microscopically positive surgical margin and local recurrence was 0% (95% CI 0 to 1).

Conclusion: Meta-analysis did not find a statistically significant association between microscopically positive surgical margin and local recurrence in this population. A finding of microscopically positive surgical margin in the absence of other adverse factors is not an indication for adjuvant treatment.

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Introduction

A positive surgical margin (PSM) is the most relevant predictor of local recurrence in malignant tumors [1–3]. Achieving clear margins at resection can decrease the rate of recurrence. However, the effect of margin status on prognosis varies with both histology and organ. Thyroid cancer is the most common endocrine tumor, and several specialties, including surgery, nuclear medicine, endocrinology, radiotherapy, medical oncology and histopathology, participate in its multidisciplinary management and indication of

adjuvant treatment [4,5].

The most important risk factors for local recurrence in thyroid cancer are gross extrathyroidal extension (ETE), evidence of residual gross disease at completion of surgery and a histologically confirmed positive margin on pathology. However, there are differences between macroscopic and microscopic margins, and the importance of microscopically positive surgical margin (MPSM) has not been comprehensively evaluated in well-differentiated thyroid carcinoma (WDTC). As there are various clinical presentations and biological behaviors of thyroid malignancies, the finding of a MPSM may not have the same impact in all cases. Most intrathyroid tumors remain stable for years [6], while others invade adjacent structures early [7]. Finally, the differentiation of the prognostic value of MPSM from that of extrathyroidal extension (ETE) or lymphovascular invasion (LVI) is important in the decision-making process and in the selection of adjuvant treatments.

The objective of the present study was to determine the

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association between MPSM and local recurrence in patients with early-stage WDTC who underwent total thyroidectomy, using a systematic review method.

Materials and methods

This review was registered at the International prospective register of systematic reviews (PROSPERO) with the number CRD42018085377. The review followed the recommendations of the MOOSE guidelines [8]. Clinical trials that evaluated the presence or absence of MPSM in surgical specimens of total thyroidectomy for early WDTC were evaluated. No limitations on the number of patients, source, language of the article or follow-up time were considered. The studies included adult patients with a diagnosis of early WDTC (papillary or follicular) scheduled for total thyroidectomy with or without central neck dissection (CND) and with complete resection during surgery.

The risk factor assessed was the presence or absence of MPSM in conventional microscopic evaluation of surgical specimens. The outcome measured was the frequency of local recurrence during follow-up, defined as structural evidence of residual tumor in the surgical bed, detected clinically and/or by imaging, recorded as yes or no (primary outcome).

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2017), PubMed (1966 to December 2017), EMBASE (1980 to December 2017) and LILACS (1980 to December 2017) databases without a language restriction. Non-English-language papers were translated. The search strategy used a mixture of MESH subject headings and text words (thyroid cancer, thyroid neoplasms, margin, microscopic). A “snow ball” strategy using references of the identified studies was also performed to include pertinent articles. Authors were contacted for clarifications when necessary. Only cohort studies were included in the review, be they prospective or retrospective. Trials were excluded if the inclusion criteria were not fulfilled and reasons were listed. For comparative non-randomized trials, methodological quality was assessed using the Newcastle-Ottawa scale [9]. We classified studies as high- or intermediate-/low-quality according to the number of quality factors found with no response.

Statistics

The statistical package Review Manager[®] (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used. For analysis, the effect of the exposure was expressed as the risk difference (RD) with the 95% confidence interval. RD is the difference between the observed risk of events between experimental and control interventions and was chosen over risk ratio or odds ratio because it can be calculated for any study, even when there are no events in either group, as occurs in cases of events of low frequency. A more-conservative Mantel-Haenszel random-effects model was used expecting a high heterogeneity and to avoid large trials effect. The chi-square test for heterogeneity was used, and the heterogeneity was quantified using the I-squared statistic. Sensitivity analysis by methodological quality was performed. A sensitivity analysis is a repeat of the meta-analysis, substituting alternative ranges of variables in order to explore the impact of different decisions on results. If results remain consistent across the different analyses, the results can be considered robust. Subgroup analysis by the frequency of T1-2 tumors was also performed (<70% vs ≥ 70%). Subgroup analyses involve splitting the data into subgroups to make comparisons as a

means of answer specific questions about particular patient groups. If heterogeneity was found, (chi-squared test $P < 0.10$ or $I^2 > 50\%$), the causes were explained subjectively. A funnel plot was used to assess publication bias. The GRADEpro[®] software was used to classify quality of evidence [10].

Results

In total, 108 references were reviewed, and only seven studies were identified by the primary search (Fig. 1) [11–17]. Later, a study by Tsang et al. [17] was excluded due to inclusion of various histological types and extension of treatments. Inclusion criteria were similar for all studies: patients with WDTC or PTC, with the primary tumor limited to the thyroid gland and who underwent total thyroidectomy with/without central/lateral neck dissection. Only one study [13] included 112 patients with histology different from PTC. Radowsky et al. [12] included 14% partial thyroidectomies. Hong et al. [11], Wang et al. [13], and Suh et al. [14] included less than 70% T1-2-classification tumors, and Radowsky et al. [12] included a high number of pN + patients. Hong et al. [11] included a small number of low-risk patients according to the ATA risk system. Radowsky et al. [12] and Suh et al. [14] used different definitions of positive margin than other studies (<1 mm of normal tissue from the tumor to the inked edge). Other characteristics of the studies are shown in Table 1. Suh et al. [14] provided the specific data of local recurrence by margin group after personal communication.

Methodological quality

The studies included were retrospective cohorts. Only Radowsky et al. [12] reported that data were obtained from a prospective recording. Methodological quality was good for all studies except for Hong et al. [11] and Radowsky et al. [12], who did not perform a multivariable analysis (Table 2). The funnel plot did not show publication bias, but the number of trials was small.

Outcomes

The six studies recruited a total of 7696 patients: 6958 in the microscopically negative surgical margin (MNSM) group and 738 in the MPSM group. Local recurrence occurred in 19 patients in the MNSM (19/6958, 0.3%) and in 7 patients in the MPSM (7/738, 0.9%), with mean follow-up times that ranged from 37 to 130 months. The range of postoperative treatment with RAI in the included studies were from 50 to 100% and in univariate analysis, all studies except Suh et al. [14], and Hong et al. [11], reported a higher frequency of RAI use in the MPSM group, but its effect was null in studies that included multivariate analysis. A similar variability occurred with T classification (38–100% T1/2 tumors). Table 3 shows other characteristics of the included studies.

The RD between groups was 0% (95% CI 0 to 1), without statistical heterogeneity ($I^2 = 0\%$). It means that the risk of local recurrence between MPSM and MNSM groups was similar (Fig. 2). We found no differences in methodological quality (RD 0% (95% CI 0 to 1)) by sensitivity analysis or in T1-2 frequency (RD 0% (95% CI -1 to 2)) by subgroup analysis.

Quality was rated high due to a low rate of local recurrence with large sample sizes and the loss of association after multivariate adjustment in the GRADE evidence profile.

Discussion

A positive margin is an important prognostic factor for local recurrence in locally advanced thyroid cancers [18]. Studies from reference centers have shown an obvious increase in recurrence

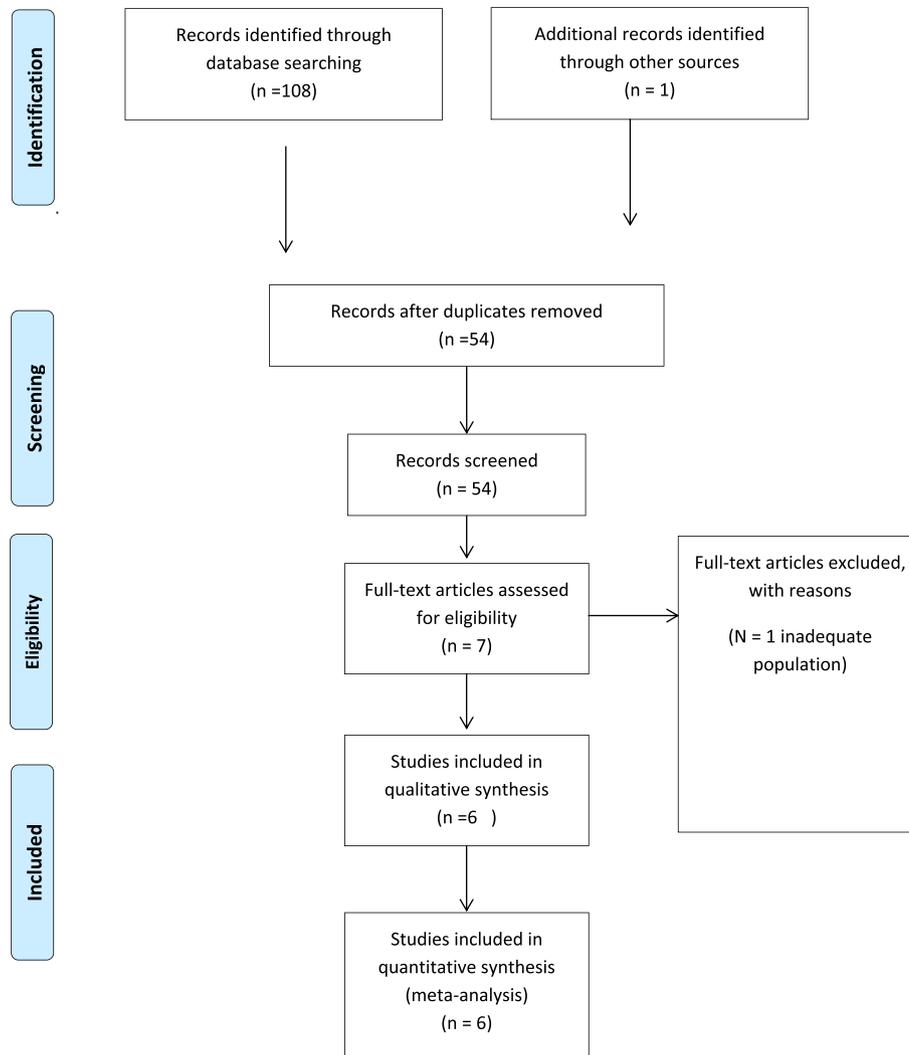


Fig. 1. Flow diagram.

rates and a decrease in overall survival if the definitive margins are reported as positive [19]. Examples of this effect are evident in cases of shaving tumors off the trachea or esophagus [20]. Kim et al. [21] reported that in a series of advanced thyroid tumors, a microscopic positive margin increased the risk of locoregional recurrence more than three times, and Wang et al. [22] found R2 resection as the most important predictor factor for locoregional recurrence in pT4 disease. However, most thyroid tumors are located inside or at the surface of the gland, and invasion to surrounding structures, such as strap muscles, trachea, esophagus or nerves, is not demonstrated intraoperatively. In these cases, the surgery progresses without difficulty, and MPSM is described only in the pathological report. This establishes a discrepancy between operative and pathological findings. The surgeon has a clear distinction between a tumor firmly adhering to adjacent structures, which requires an extension of the resection, and an intrathyroidal tumor, which does not compromise adjacent planes and is therefore easily separated from the surrounding structures; the same is not the case for pathologists, for whom all the margins are classified similarly (negative, close and positive) according to the ink test. The current lack of robust information regarding this discordant finding prompts some teams to disregard the result whereas others may consider such a result an indication for treatment intensification. Therefore, this systematic review intended to review the

evidence about the prognostic effect of MPSM on early tumors.

A wide search in public databases yielded 108 articles, from which only six were relevant to the question [11–16]. The majority of excluded studies dealt with advanced thyroid tumors, where the prognostic effect of a positive margin was clear.

In what follows, the studies that were included in the current meta-analysis, are commented in more detail. Wang et al. [13] analyzed 2616 patients. Patients with MPSM had larger tumors ≥ 2 cm (40.3% vs 28.9%), a higher rate of ETE (79.1% vs 28.55), more advanced disease (T3/4, 81.1% vs 33.6%) and more N+ tumors (61.2% vs 30.4%) than patients without MPSM. Their recurrence rate was 0.45%. They found a 5-year local recurrence free survival of 98.9% for patients with MPSM compared to 99.5% in those with negative margins in univariate analysis. Although statistically significant ($p = 0.018$), the results are unlikely to be perceived as clinically relevant (absolute difference 0.6%). A multivariate analysis adjusting for T classification and ETE presence did not find a statistically significant association between MPSM and recurrence. An analysis stratified by the American Thyroid Association (ATA) risk group did not report any recurrence in the low-risk group, in which 29 patients had MPSM; in the intermediate-risk group, none of the five recurrences occurred in the positive-margin group of 144 patients. Lang et al. [15] studied 638 patients. Patients with MPSM had a higher proportion of tumors larger than 2 cm (36% vs 19.9%),

Table 1
Characteristics of included studies assessing microscopically positive surgical margins in completely resected well differentiated thyroid cancer.

Study	Year of recruiting	Country	Methods	Participants	Exposure	Outcomes
Hong et al. [11]	2002–2003	Korea	Retrospective trial of consecutive recruited patients. Total thyroidectomy without gross residual remnant. Surgical specimen reviewed by pathologist with 15 years of experience. Tumor staging was performed according to the AJCC 2010. Stratification by the ATA guidelines was used. Patients were given 3.7–7.4 GBq of I-131.	197 patients with WDTC who underwent total thyroidectomy with or without neck dissection. Excluded: patients with distant metastases, with an insufficient follow-up, who did not have a diagnostic radioactive iodine whole-body scan and without serum thyroglobulin measurements.	Margin positive or negative in surgical specimen.	Cancerous lesions detected within 12 months were defined as early recurrence and lesions detected after 12 months were defined as late recurrence. Examinations for recurrences were performed every year for 5 years.
Radowsky et al. [12]	1955–2004	USA	Retrospective trial of a prospective database of consecutive recruited patients.	218 patients with PTC who underwent total thyroidectomy with or without neck dissection. Exclusion not reported.	Margin-negative resection was defined as having >1 mm of normal tissue at the surgical resection margin. Close-margin categorization required the presence of carcinoma within 1 mm of the specimen border.	Persistent disease was classified as structural if found on cross-sectional imaging, biopsy, and/or post-radioactive iodine remnant ablation scan; or biochemical, defined as a stimulated Tg value > 2 ng/mL in the absence of structural evidence of disease. Disease recurrence was defined as anatomic or biochemical evidence of disease following an interval period during which the patient had been NED.
Wang et al. [13]	1986–2010	USA	Retrospective trial of consecutive recruited patients treated surgically. Remnant.	2616 patients with WDTC Excluded: patients with less than total thyroidectomy, distant metastases, unresectable disease or gross residual disease, patients in whom histological margin status was unknown.	Microscopically positive margin status was defined as a tumor at the inked surgical margin edge on histopathological analysis. Margin status was categorized as negative if no tumor was present at the inked edge.	Local recurrence was determined by clinical examination supplemented with imaging and FNAB. Confirmation of disease by cytology and/or histopathology was required. Outcome data were calculated at five years.
Suh et al. [14]	2004–2012	Korea	Retrospective trial of consecutive recruited patients who underwent total thyroidectomy and CND with or without LND. Tumors were staged according to the 7th edition of the AJCC.	3381 patients with conventional PTC. Excluded patients who had distant metastasis before surgery and patients without remission after surgery.	Margin-negative resection was defined as having >1 mm of normal tissue at the surgical resection margin.	Disease recurrence was defined as structural evidence of disease following a remission period of 2 years. Local recurrence was defined as recurrence in the thyroid operative bed. Regional recurrence was defined as recurrence in the regional lymph nodes.
Lang et al. [15]	1990–2011	China	Retrospective trial of consecutive recruited patients. Any excised specimen with close or involved margin was retrospectively reviewed by pathologist. Tumor risks were coded according to the ATA risk stratification system.	638 patients with PTC who underwent surgery. Exclusion: less than total thyroidectomy, distant metastasis, gross or macroscopic positive margins, or resection margins not assessed or reported	A margin was deemed involved if tumor cells were found at the inked border.	Disease recurrence made by a combination of basal Tg trend, USG, CT/MRI, or FDG-PET scan and confirmed by FNAB or histology.
Kluijfhout et al. [16]	2000–2010	USA	Retrospective trial of consecutive recruited patients.	684 patients with WDTC who underwent total thyroidectomy and T1-2 stage. Exclusion: complete thyroidectomy >6 months, tumors >4 cm; extrathyroidal extension; or distant metastases.	A positive margin was defined as tumor presence at the inked margin.	Recurrent disease was defined as positive pathologic analysis of a suspicious tumor/lymph node, or by gross systemic disease identified on cross-sectional imaging.

with a higher frequency of ETE (55% vs 22.3%), higher rates of LVI (23% vs 13.9%), more advanced (T3/4) classification of primary disease (55% vs 40.8%), more N+ tumors (46% vs 32.2%) and higher ATA classification (intermediate/high, 76% vs 34.6%) than patients without MPSM. The authors divided patients into two groups: anterior margins (57%) and posterior margins (43%). After

multivariate analysis, MPSM on the posterior surface had a statistically significant association with nodal recurrence but not local relapse. Kluijfhout et al. [16] studied 684 patients. The MPSM group had a higher frequency of N+ tumors (44% vs 25%). In the multivariate analysis, MPSM did not show a statistically significant association with recurrence, even after adjustment for RAI use and

Table 2
Methodological quality of included trials assessing microscopically positive surgical margins in completely resected well differentiated thyroid cancer.

Quality assessment criteria	Hong et al. [11]	Radowsky et al. [12]	Wang et al. [13]	Suh et al. [14]	Lang et al. [15]	Kluijfhout et al. [16]
Representativeness of exposed cohort?	+	+	+	+	+	+
Selection of the non-exposed cohort?	+	+	+	+	+	+
Ascertainment of exposure?	+	+	+	+	+	+
Demonstration that outcome of interest was not present at start of study?	+	+	+	+	+	+
Comparability of cohorts on the basis of the design or analysis	–	–	+	+	+	+
Assessment of outcome?	+	+	+	+	+	+
Was follow-up long enough for outcome to occur?	+	+	+	+	+	+
Adequacy of follow-up of cohorts?	+	+	+	+	+	+

Table 3
Characteristics of studies assessing microscopically positive surgical margins and recurrence in completely resected well differentiated thyroid cancer.

	Hong et al. [11]	Radowsky et al. [12]	Wang et al. [13]	Suh et al. [14]	Lang et al. [15]	Kluijfhout et al. [16]
Year	2012	2013	2015	2015	2016	2016
Number of patients	197	218	2616	3381	638	684
Mean time of follow-up (range) (months)	86 (12–101)	37 to 82	50 (1–330)	67 (25–121)	130	46
% Female sex	93	73	74	84	75	81
% of PTC	100	100	96	100	100	91
% T1/2 stage	38	92	62	44	72	100
% pN + stage	46	69	34	35	34	27
% ETE	56	NR	33	55	27	NR
% TT	100	86	100	100	100	100
% Low risk ATA group	19	NR	42	NR	59	NR
% CND	52	NR	NR	100	NR	30
% MRND	15	NR	NR	3	NR	13
% MPSM	6	7	10	NR	16	11
% RAI (RAI in MPSM vs RAI in MNSM)	100 (100 vs 100)	84 (89 vs 81)	52 (76 vs 56)	62 (NR)	50 (78 vs 45)	56 (60 vs 51)
% Local recurrence	0	7 ^a	0.5	0.1	0	0.1
% Nodal recurrence	19.7		NR		3.4	7.4
Association of MPSM with recurrence	Not for loco-regional recurrence in univariate analysis	Not for loco-regional recurrence in univariate analysis	Not for local recurrence in multivariate analysis	Not for loco-regional recurrence in multivariate analysis	Not for local recurrence in multivariate analysis	Not for loco-regional recurrence in multivariate analysis

PTC: papillary thyroid carcinoma; pN+: pathological positive lymph nodes; TT: total thyroidectomy; ETE: extrathyroid extension; CND: central neck dissection; MRND: lateral modified radical neck dissection; MPSM: microscopic positive surgical margins; RAI: radioactive iodine; NR: not reported.

^a There was no discrimination of local or nodal recurrence.

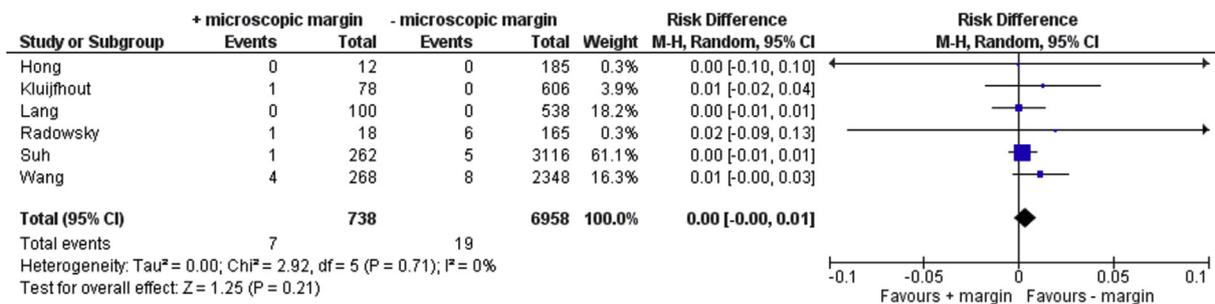


Fig. 2. Forest plot for association between microscopic positive surgical margin and local recurrence in well differentiated thyroid carcinoma.

lymphovascular invasion. Hong et al. [11] studied 197 patients. Patients with MPSM showed a higher frequency of ETE (100% vs 54%), more advanced (T3/4) classification of primary disease (100% vs 57%), more N+ tumors (66.6% vs 44.3%) and a higher ATA classification (100% vs 80%). The frequency of early nodal recurrence (<1 year of follow-up) was higher for the MPSM group (25% vs 5.9%); however, no difference was observed in late recurrence frequency (8.3% vs 13%). The authors demonstrated a lower recurrence free survival for the MPSM group (66.7% vs 81.1%) but did not conduct a multivariate analysis that adjusted for other pathologic factors. Suh et al. [14] studied 3381 patients with PTC. After a

multivariate analysis, MPSM was not significantly associated with recurrence when adjusted for size and ETE. Radowsky et al. [12] studied 218 patients. Patients with MPSM had a higher frequency of tumors >4 cm (16% vs 5%) and more N+ tumors (32% vs 26%); however, no differences were observed in terms of recurrence (6% vs 4%).

There was a high variability in use of RAI treatment (50–100%) and it could be suggested that the eventual negative effect of MPSM on local recurrence may have been affected by the RAI treatment. Although the MPSM groups received more RAI, this was not correlated with a lower frequency of local recurrence in studies that

included multivariate analysis [13–16] and, in those without this analysis [11,12] the differences in RAI use were not statistically significant as shown in Table 3.

In general, the MPSM group had a higher frequency of other adverse factors including ETE and LVI, which may also explain the higher use of RAI. However, multivariate analysis adjusting with these factors, didn't show a statistically significant effect of MPSM on local recurrence.

The overall frequency of MPSM was 9.6%, while the overall frequency of local recurrence was 0.3%, i.e., 32 times less frequent. A meta-analysis of these studies with more than 7600 patients found a risk difference in local recurrence of 0%, with a confidence interval that crosses the line-of-no-effect (not statistically significant). The methodological quality of the included studies was good, and no publication bias was detected. Even after sensitivity analysis by quality, subgroup analysis by T classification and multivariate statistical adjustment by adverse factors as ETE and LVI the results were consistent.

These results are important due to the high frequency of pathological reports describing MPSM after a complete resection and in the absence of lymphovascular or extrathyroid extension. Some clinicians interpret this finding as an adverse prognostic factor and consequently advise adjuvant treatment. The most recent guidelines [23–26] do not address this question, so the present information offers data to avoid potential overtreatment.

Some clarifications are necessary to interpret these results. As the rate of local recurrence was low, it is possible that lack of power was still present, even with the large number of patients analyzed. However, to get a larger population seems difficult and would only narrow the limits of the confidence interval. With a risk difference of 0% in the rate of local recurrence and without histological adverse factors, the effect of MPSM after a complete thyroidectomy is imperceptible and clinically insignificant.

The impact of these results in clinical practice should be taken in account. As the expected difference of local recurrence in absolute numbers was close to 0%, the use of RAI in such cases based on this finding alone should be questioned. In addition, when primary surgical therapy is thyroid lobectomy and an isolated MPSM is identified, the need for completion thyroidectomy to facilitate RAI should also be challenged.

The most important weakness of this study is the observational design of the primary studies included in the systematic review. Observational studies are prone to selection and verification bias [27]. If studies are combined, it is possible to amplify the effect of these biases. We tried to decrease the risk of bias with a strict selection of studies, a methodological quality assessment (the Newcastle-Ottawa score), adherence to published guidelines (MOOSE) and a conservative analysis (random effects model). On the other hand, to solve this research question, it is impractical to design an RCT; thus, observational studies are the only potential data source. Moreover, we used the GRADE methodology as a more objective tool of evaluation of evidence because it considers methodological quality, inconsistency, imprecision and indirectness.

In conclusion, in six observational studies of good methodological quality, we found no statistically significant prognostic effect of MPSM on local recurrence in patients with early WDTC who underwent total thyroidectomy. Our results suggest that when a low risk thyroid cancer is excised and the surgeon is happy regarding the completeness of excision, the finding of MPSM in absence of adverse factors as ETE and LVI on histopathological examination should not be considered an indication for adjuvant therapy.

Conflict of interest

Authors don't have conflict of interest.

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