

Impact of Gross Strap Muscle Invasion on Outcome of Differentiated Thyroid Cancer: Systematic Review and Meta-Analysis

Running Title: Impact of gSMI in DTC

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Abstract:

Background: Gross strap muscle invasion (gSMI) in patients with differentiated thyroid cancer (DTC) was defined as high-risk recurrent group in the 2015 American Thyroid Association guidelines. However, controversy persists because several studies suggested gSMI had little effect on disease outcome. Herein, a systematic review and meta-analysis was conducted to investigate impact of gSMI on outcome of DTC.

Methods: A systematic search of electronic databases (PubMed, EMBASE, Cochrane Library, and MEDLINE) for studies published until February 2020 was performed. Case-control studies and randomized controlled trials that studied the impact of gSMI on outcome of DTC were included.

Results: Six studies (all retrospective studies) involving 13639 patients met final inclusion criteria. Compared with no extrathyroidal extension (ETE), patients with gSMI were associated with increased risk of recurrence ($P=0.0004$, OR, 1.46; 95% CI: 1.18 to 1.80) and lymph node metastasis (LNM) ($P<0.00001$, OR 4.19; 95% CI: 2.53 to 6.96). For mortality ($P=0.34$, OR 1.47; 95% CI: 0.67 to 3.25), ten-year disease-specific survival ($P=0.80$, OR 0.91; 95% CI: 0.44 to 1.88) and distant metastasis (DM) ($P=0.21$, OR 2.94; 95% CI: 0.54 to 15.93), there was no significant difference between gSMI and no ETE group. In contrast with maximal ETE, patients with gSMI were associated with decreased risk of recurrence ($P<0.0001$, OR, 0.58; 95% CI: 0.44 to 0.76), mortality ($P=0.0003$, OR 0.20; 95% CI: 0.08 to 0.48), LNM ($P=0.0003$, OR 0.64; 95% CI: 0.50 to 0.81) and DM ($P=0.0009$, OR 0.28; 95% CI: 0.13 to 0.59).

Conclusions: DTC patients with gSMI had a higher risk of recurrence and LNM than those without ETE. However, in contrast with maximal ETE, a much better prognosis was observed in DTC patients with only gSMI. The findings of our meta-analysis provide supportive evidence for the validity of the T category changes in the 8th edition American Joint Committee on Cancer system. The actual impact of gSMI should be re-evaluated and revised in the recurrent risk stratification system in the future.

1 Introduction

Extrathyroidal extension (ETE), which is defined as tumor spread outside of the thyroid gland and into the surrounding tissues, occurs in up to 30% of patients with differentiated thyroid cancer (DTC)[1, 2]. Minimal ETE (mETE), detectable only on histological examination, was not regarded as a negative predictor for either survival or disease recurrence[3-5]. Accordingly, mETE was removed from the T3 definition in the 8th edition of the American Joint Committee on Cancer (AJCC) classification, as it would not affect either T category or overall stage[6]. In contrast, gross ETE is believed to be an important risk factor for recurrence and mortality[7, 8]. Thus, DTC patients with gross ETE are classified as T3b or T4 in the AJCC system[9]. Moreover, the 2015 American Thyroid Association (ATA) guidelines grouped tumors with gross ETE in the high risk of recurrence category, with a nearly 20% risk of structural recurrence[10]. Therefore, gross ETE was an absolute indication for total thyroidectomy and the administration of postoperative radioactive iodine.

In addition to the degree of gross ETE, the site of gross tumor invasion also plays important roles in disease-specific survival (DSS) and disease-free survival (DFS). Recently, several studies reported that gross strap muscle invasion (gSMI) had little effect on DSS and DFS, which was different from the findings of previous studies[8, 11]. Increasing evidence suggests that DTC patients with only gSMI have the same DFS as those with microscopic ETE[11]. In our previous study, we also found that only 4 of 30 (13.3%) Braf-mutated thyroid papillary microcarcinoma patients with gSMI were diagnosed with recurrence[12]. Accordingly, Shaha AR suggested that a detailed distinction of gross ETE should be performed[13]. Patients with anterior ETE involving the strap muscle had a relatively good prognosis compared with those with posterior gross ETE to the recurrent laryngeal nerve, trachea or esophagus[8]. A possible reason is that gSMI can be easily resected with negative margins[13].

In light of the conflicting data on the recurrence risk and mortality conferred by gSMI, we performed a systematic review and meta-analysis to assess the impact of gSMI on the outcomes of DTC patients.

2 Materials and Methods

This meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions guidelines[14]. There was no funding received for this study.

2.1 Search strategy

We searched the EMBASE, PubMed, MEDLINE, and Cochrane databases from inception to February 26, 2020, without any language limitations. The following terms were used in the search: “thyrohyoid muscle”, “sternothyroid muscle”, “sternohyoid muscle”, “strap muscle”, “gross extrathyroidal extension”, “invasion”, “extension”, “thyroid cancer*”, “thyroid carcinoma*”, and “thyroid neoplasm*”.

2.2 Inclusion and exclusion criteria

The studies returned from the search were checked according to the following inclusion criteria: ① patients were more than 18 years old; ② pathologically proven DTC patients who underwent surgery; ③ complete clinical data and follow-up information; and ④ DTC patients with SMI.

The exclusion criteria were as follows: ① patients with less than 12 months of follow-up; ② those with incomplete medical records; ③ those with medullary thyroid carcinoma and undifferentiated carcinoma; and ④ publication styles were letters to the editor, abstracts and meeting posters.

2.3 Data Extraction and Risk of Bias Assessment

L Zhang and J Liu assessed the search results according to the relevance in providing information for the review. Two reviewers (L Zhang and S Xue) independently assessed the titles and abstracts of the remaining records for relevance according to the protocol criteria. Then, they browsed the full text of the studies in detail. Any disagreements were resolved by consulting a third reviewer (J Li). L Zhang assessed the risk of bias of each included study using the relevant, validated tool for each study

design. J Liu performed the risk of bias assessment. The risk of bias of the included trials was assessed using the Newcastle-Ottawa Scale[15].

2.4 Statistical analysis

Review Manager (RevMan) 5.3 software was used for the analysis. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data. We assessed the heterogeneity across studies using the Q test and the I^2 statistic. $P < 0.1$ and $I^2 > 50\%$ indicated statistical significance[16]. If there was obvious heterogeneity, we used a random-effects model; otherwise, we used a fixed-effects model. We conducted sensitivity analysis by excluding each single study at a time to test its influence on the pooled effects. The source of heterogeneity was also explored by subgroup analyses of operation type and histopathological subtype based on available information. When the p-value was less than 0.05, it was considered statistically significant.

3. Results

3.1 Literature Search

We initially identified a total of 219 studies. Fifty-two duplicate studies and another 118 studies were excluded after reviewing the titles and abstracts. After scrutiny of the full texts of the remaining 49 articles, six studies were finally included in this meta-analysis, all of which were retrospective studies[8, 11, 17-20]. Fig 1 shows the study selection process.

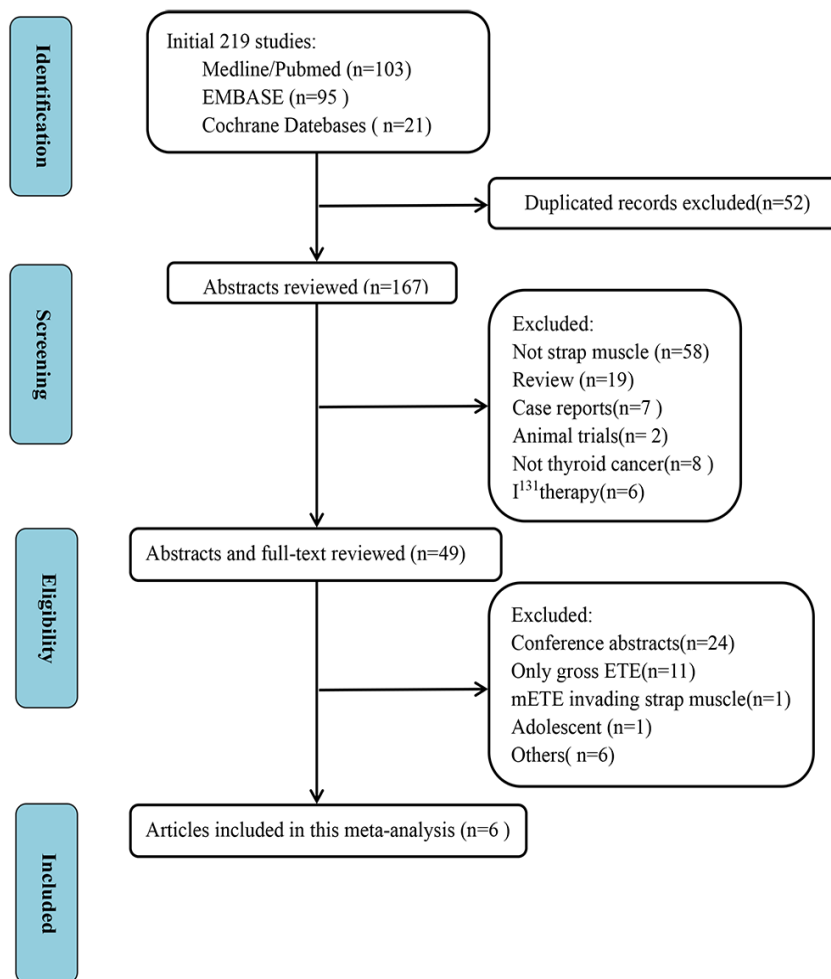


Fig 1: Selection process of studies in meta-analysis

3.2 Study Characteristics and Quality

In this meta-analysis, a total of 13639 patients were included, and the characteristics of the included studies are presented in Table 1. The maximal ETE means extension of the primary tumor to the trachea, esophagus, recurrent laryngeal nerve, larynx, subcutaneous soft tissue, skin, internal jugular vein, or carotid artery. No ETE means no extrathyroidal extension. The quality assessment of the included studies by the Newcastle-Ottawa Scale is presented in Table 2. All studies used hospital controls, who were accessed by the same method as gross ETE into the strap muscle (gETE st+ group). Multivariate analysis was conducted by all the studies. The scores of all the studies were over 5; thus, the quality of the selected studies was generally high.

Table1:Baseline Characteristics of included studies

Study	Patients No.	Groups	Patient No.	Female, n, %	Age (y)	Tumor Size (mm)		Multifocality (n,%)	N Stage	Follow-Up
					Mean (SD) /Median (rang)	Mean (SD) /Median (rang)	RAI(n, %)			Mean (SD) /Median (rang)
Amit,2018	2084	no ETE (group 1)	1291	966 (75)	47(18-87)		555 (44)	479(37)	Nx N0 N1a N1b	66(12-192)
		ETE into perithyroidal soft tissue (group 2)	732	527 (72)	47(18-97)	N/A	527 (74)	397(54)		51(12-189)
		gETE into strap muscle (group 3)	61	52 (85)	48(19-83)		48 (78)	29(48)		64(17-155)
Li,2018	4045	no ETE	2300	1679(73.0)	42.6(10.5)	11.17(8.11)	928 (40.3)	625(27.1)	N/A	30(12-63)
		ETE into perithyroidal tissue	1004	726(72.3)	43.2(12.1)	13.64(9.61)	634 (63.2)	274(27.3)		34(12-63)
		T3b (gETE into the strap muscles)	371	286(77.1)	44.1(10.4)	18.42(10.61)	325 (87.6)	124(33.4)		32(13-58)
		ETE beyond the strap muscles	370	262 (70.8)	46.3(11.1)	21.15(9.88)	361 (97.6)	134(36.2)		30(12-59)
Park,2018	3174	no ETE	1362	1170(85.9)	45.5(11.6)	12.5(11.0)	1024 (75.2)	N/A	N0 N1	148.8(133.2-174)
		microscopic ETE	1377	1199 (87.1)	46.2(12.2)	15.3(11.9)	1299 (94.3)			
		gETE invading only strap muscles	261	227 (87.0)	49.0(13.1)	19.1(13.5)	246 (94.3)			
		gETE invading perithyroidal structures	174	150 (86.2)	52.4(15.0)	24.2(18.7)	153 (87.9)			
Song,2018	3104	T1	1997							
		T2	496							
		Y3a	96							
		T3b(≤4 cm and gETE to strap muscle)	376	2712(87.4)	45.9(37.8-54.2)	13(8-22)	2363(76.1)	N/A	N0 N1	120(97.2-144)
		T3b(>4 cm and gETE to strap muscle)	38							
Song,2019	636	T4a	101							
		without gETE	586	457(78.0)	45.0(11.4)	12(10-15)		53 (9.0)	N0 N1a	91.2(61.2-130.8)
		those with gETE to strap muscle	50	45 (90.0)	49.9(8.9)	12(11-15)	N/A	7 (14.0)		84(60-102)
	596	low-risk PTC without ETE (low w/o ETE)	251	231 (92)	50.8(12)	14.9(16.4)	102(40.6)	107 (43)	N0 N1a	48(12-322)

Danilovic,2019	intermediate-risk PTC without ETE (intermediate w/o ETE)	89	76(85.4)	44.9(15.8)	24.1(18.9)	81 (91)	57(64.8)	43.2(12-217)
	minimal(mETE)	191	166(86.9)	50.0(13.7)	17.3(13.4)	186(97.4)	121(63.4)	39.6(12-142)
	gETE into the strap muscles(gETE)	65	54(83.1)	51.6(14.5)	28.0(16.0)	64 (98.5)	35(54.7)	43.2(12-260)

Abbreviations: N/A: Not applicable; SD: Standard Deviation; ETE: extrathyroidal extension; gETE: gross extrathyroidal extension; RAI: radioactive iodine; LN: lymph node; RLN: recurrent laryngeal nerve.

Table 2. Quality assessment of the included studies by the Newcastle-Ottawa Scale

Items	Amit 2018	Li 2018	Park 2018	Song 2018	Song 2019	Danilovic 2019
Selection						
Is the case definition adequate?	1	1	1	1	1	1
Representativeness of the cases	1	1	1	1	1	1
Selection of Controls	0	0	0	0	0	0
Definition of Controls	1	1	1	1	1	1
Comparability of cases and controls on the basis of the design or analysis	2	2	2	2	2	2
Outcome						
Ascertainment of exposure	1	1	1	1	1	1
Same method of ascertainment for cases and controls	1	1	1	1	1	1
Non-Response rate	0	0	1	0	0	0
Total score	7	7	8	7	7	7

3.3 Outcomes

3.3.1 Locoregional recurrence (LRR)

Five studies evaluated the impact of gSMI on recurrence in 6687 patients with DTC (no ETE in 5879 subjects, gETE st+ in 808 subjects). gSMI in patients was associated with an increased risk of recurrence ($P=0.0004$; OR, 1.46; 95% CI: 1.18 to 1.80) without heterogeneity ($I^2=0\%$) (Fig. 2A). Two studies compared the impact of gSMI on recurrence with maximal ETE. Compared with maximal ETE, gSMI was associated with a decreased risk of recurrence ($P<0.0001$; OR, 0.58; 95% CI: 0.44 to 0.76) without heterogeneity ($I^2=0\%$) (Fig. 2B). At the same time, two studies compared the impact of gSMI on recurrence with perithyroidal soft tissue invasion. The locoregional recurrence between patients with gSMI and those with perithyroidal soft tissue invasion was not significantly different ($P=0.07$; OR, 1.28; 95% CI: 0.98 to 1.68) without heterogeneity ($I^2=0\%$) (Fig. 2C).

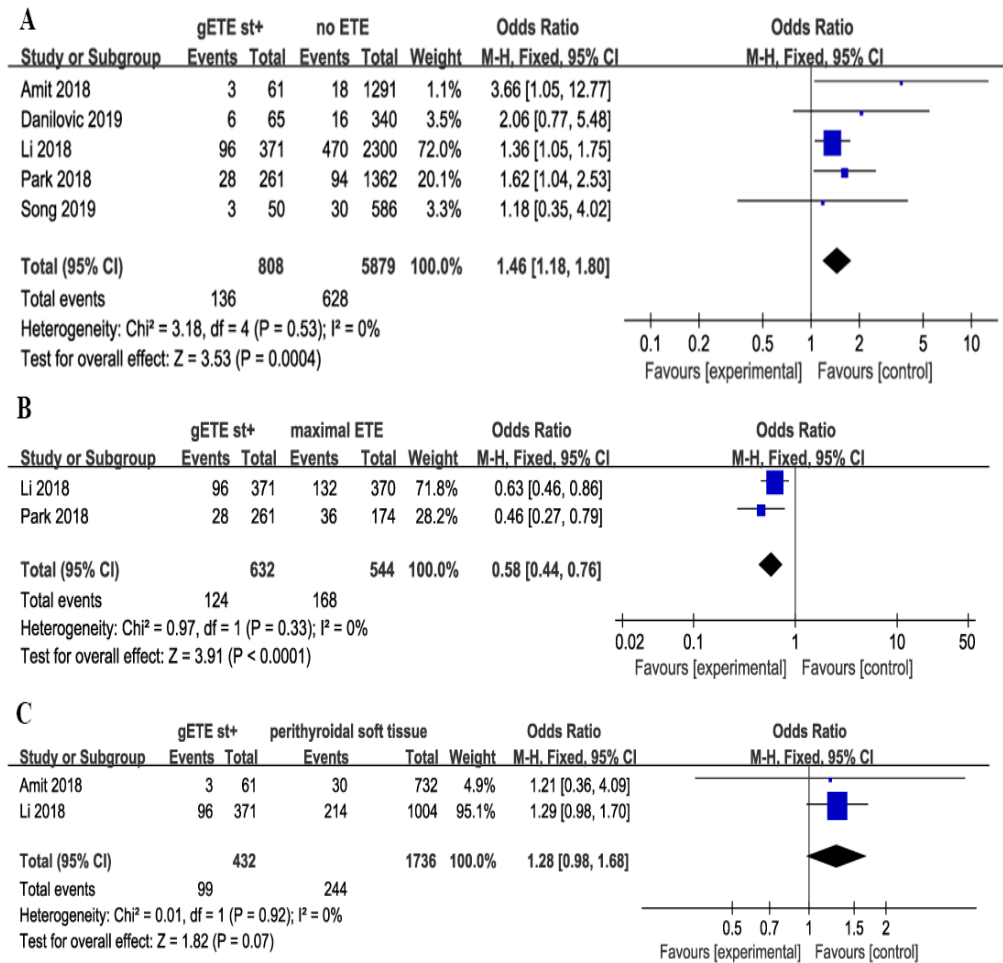


Fig 2: Forest plot for LRR comparison between gETE st+ with (A) no ETE (B) maximal ETE (C) perithyroidal soft tissue

3.3.2 Overall mortality

Three studies compared the impact of gSMI on cancer-related mortality with no ETE group among 4699 patients with DTC (no ETE in 4002 subjects, gETE st+ in 697 subjects). Two studies compared the impact of gSMI on cancer-related mortality with the maximal ETE group. The mortality of patients with gSMI was not increased compared with that of no ETE patients ($P=0.34$; OR, 1.47; 95% CI: 0.67 to 3.25) (Fig. 3A). Compared with maximal ETE, gSMI was associated with decreased mortality ($P=0.0003$; OR, 0.20; 95% CI: 0.08 to 0.48) (Fig. 3B).

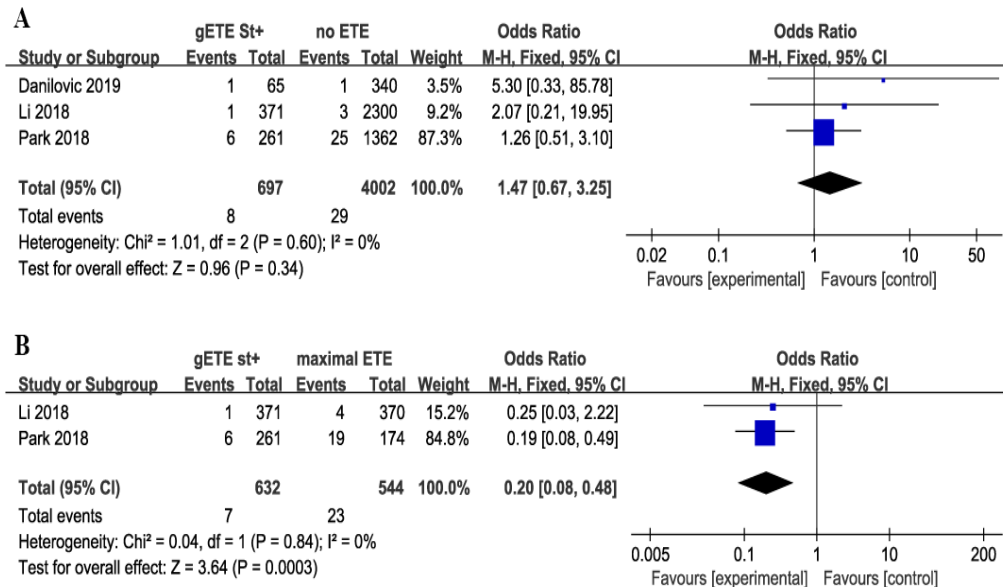


Fig 3: Forest plot for overall mortality comparison between gETE st+ with (A) no ETE (B) maximal ETE

3.3.3 Ten-year Disease-specific Survival

Three studies analyzed the impact of gSMI and no ETE on ten-year DSS among 3981 patients with DTC. There was no significant difference between the no ETE and gSMI groups ($P=0.80$; OR, 0.91; 95% CI: 0.44 to 1.88) with no heterogeneity ($I^2=0\%$) (Fig. 4).

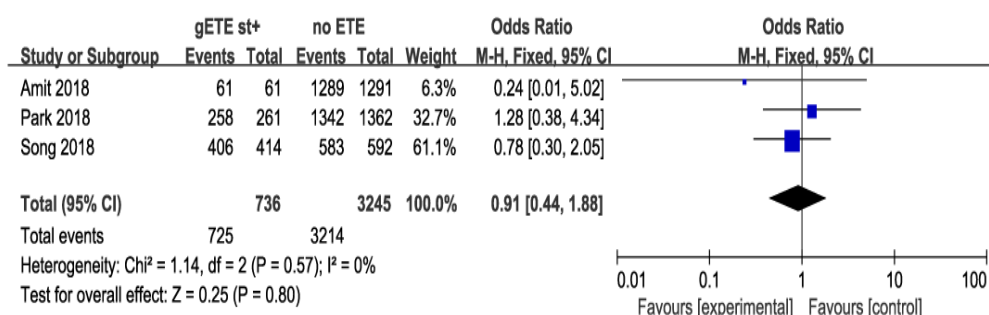


Fig 4: Forest plot for ten-year DSS comparison between gETE st+ with no ETE

3.3.4 Lymph Node Metastases

Four studies compared the impact of gSMI and no ETE on baseline lymph node metastases (LNM) among 6051 patients. gSMI was associated with an elevated LNM ratio ($P<0.00001$; OR, 4.19; 95% CI: 2.53 to 6.96) with significant heterogeneity

($I^2=86\%$) (Fig. 5A). Moreover, only two studies investigated the impact of gSMI and maximal ETE on LNM among 1176 patients. Compared with maximal ETE, gSMI in patients was associated with decreased LNM ($P=0.0003$; OR, 0.64; 95% CI. 0.50 to 0.81) (Fig. 5B).

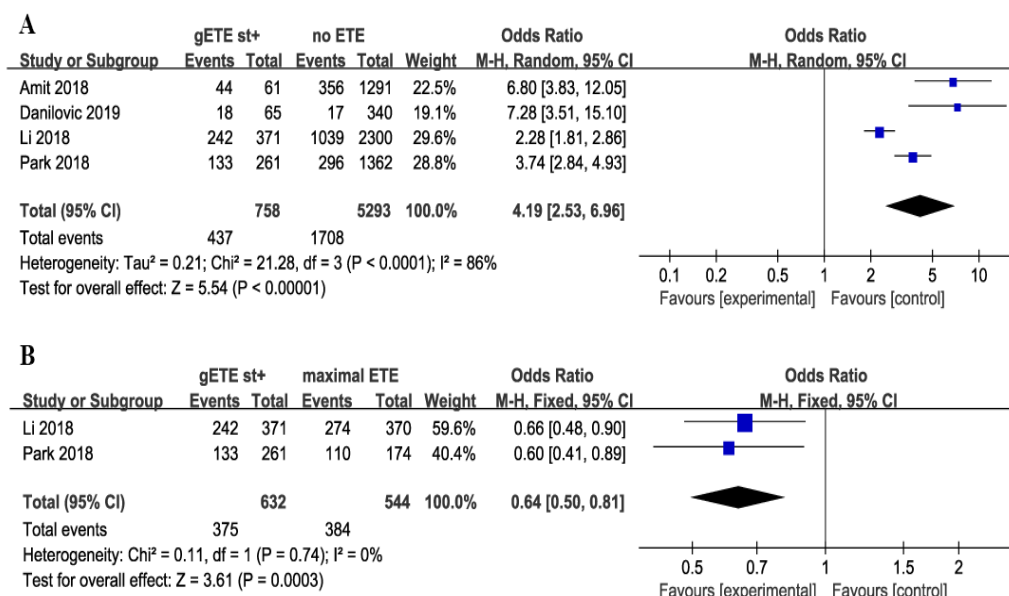


Fig 5: Forest plot for LNM between gETE st+ with (A) no ETE (B) maximal ETE

3.3.5 Distant Metastases

Four studies assessed the impact of gSMI and no ETE on distant metastases (DM). There was no significant difference in the DM ratio between the gSMI and no ETE groups ($P=0.21$), with significant heterogeneity ($I^2=87\%$) (Fig. 6A). Moreover, only two studies investigated the impact of gSMI and maximal ETE on DM. gSMI in patients was associated with decreased DM ($P=0.0009$; OR, 0.28; 95% CI. 0.13 to 0.59) with no heterogeneity ($I^2=19\%$) (Fig. 6B).

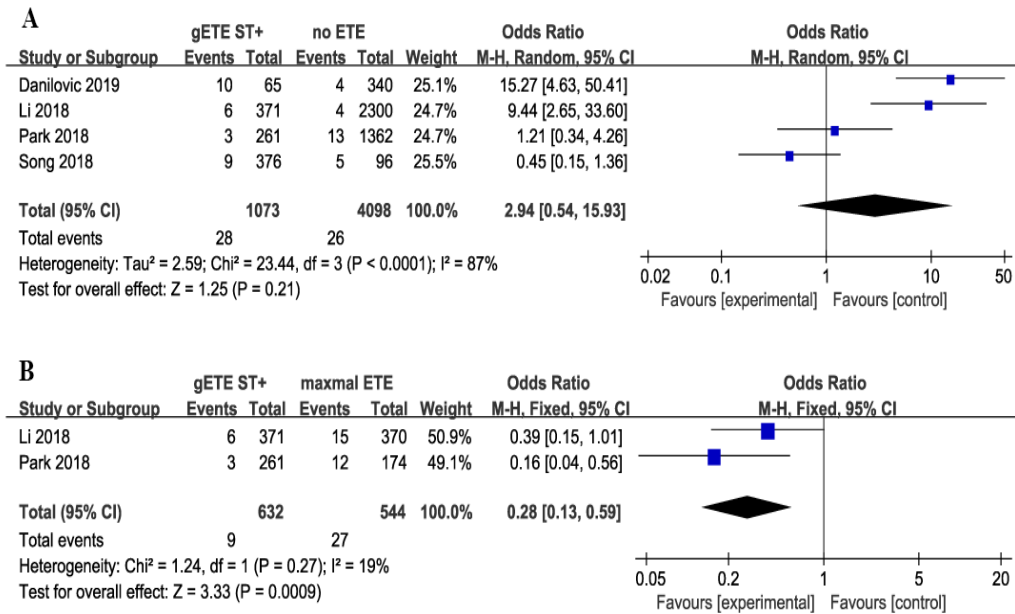


Fig 6: Forest plot for DM comparison between gETE st+ with (A) no ETE (B) maximal ETE

3.4 Sensitivity analysis and subgroup analysis

For the comparisons with significant heterogeneity, we conducted sensitivity analysis. The leave-one-out meta-analysis revealed that LNM (compared with no ETE) and DM (compared with no ETE) did not identify a single study that may have caused the substantial heterogeneity. (Data not shown)

Furthermore, the degree of LNM is highly dependent on the type of lymph node dissection (LND). Prophylactic LND will identify many microscopic LNM, while therapeutic LND is only performed for patients with clinical metastatic lymph nodes. All and some patients underwent prophylactic LND in the Li and Park studies, respectively. Therapeutic LND was performed in the studies by Danilovic and Amit. In the therapeutic LND subgroup, patients with gSMI had increased LNM compared with patients without ETE. ($P < 0.00001$; OR, 6.94; 95% CI. 4.40 to 10.95; $I^2 = 0\%$) (Fig. 7).

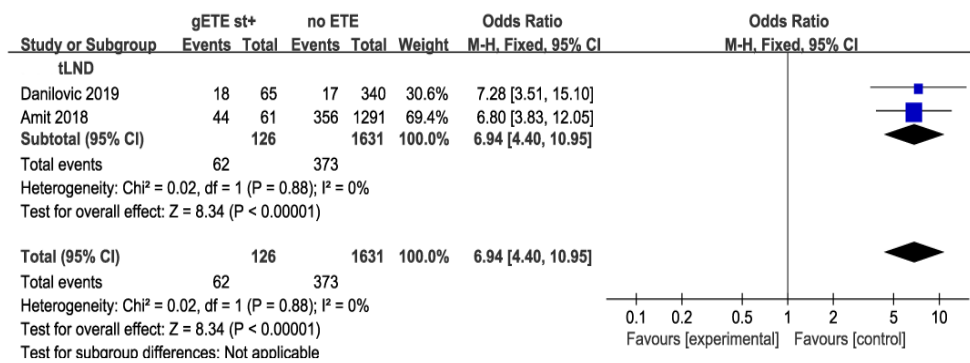


Fig 7: Subgroup analysis for LNM comparison between gETE st+ with no ETE

Patients with follicular thyroid carcinoma are more likely to present with DM than those with papillary thyroid carcinoma (PTC). We believe the significant heterogeneity of the DM analysis is mainly attributed to histopathological types. In the DTC subgroup, there was still no significant difference in DM between the gSMI and no ETE groups ($P=0.45$) without heterogeneity ($I^2=25\%$) (Fig. 8A). However, in the PTC subgroup, we found that gSMI increased DM significantly compared with no ETE ($P<0.0001$; OR, 12.35; 95% CI. 5.20 to 29.29; $I^2=0\%$) (Fig. 8B).

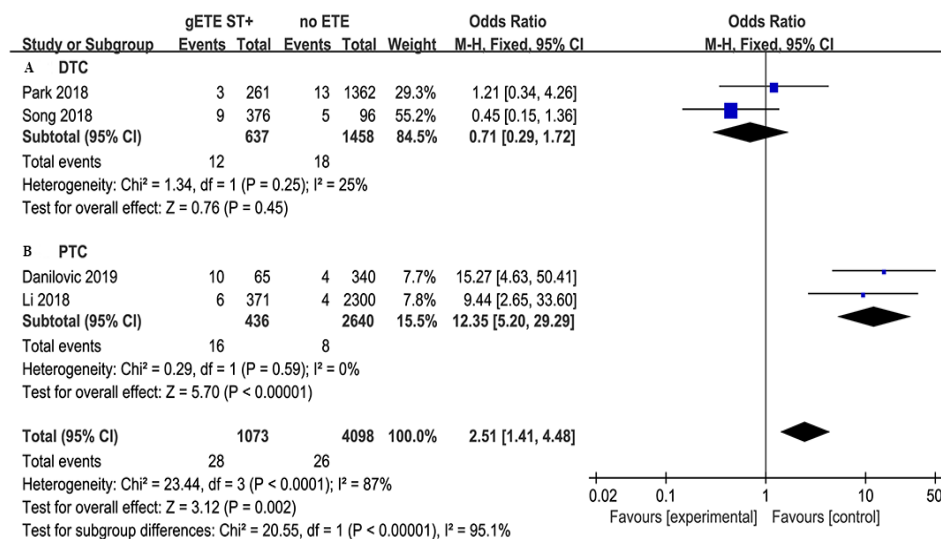


Fig 8: Subgroup analysis for DM comparison between gETE st+ with no ETE

4 Discussion

Increasing evidence has shown that the site of gross tumor invasion also plays important roles in the recurrence and mortality of DTC patients[21, 22]. Some

researchers believed that gSMI had a relatively good prognosis compared with gross ETE to the recurrent laryngeal nerve, trachea or esophagus, which was different from the findings of previous studies[11, 20, 23]. It is still controversial whether DTC with only gSMI should be downgraded to a lower tumor stage and recurrent risk category. To the best of our knowledge, this is the first meta-analysis to assess the impact of gSMI on outcomes in DTC patients. Compared with patients with no ETE, patients with gSMI had an increased risk of recurrence and LNM. For mortality, ten-year DSS and DM, there were no significant differences between the gSMI and no ETE groups. In contrast with those with maximal ETE, patients with gSMI had a decreased risk of recurrence, mortality, LNM and DM.

According to ATA guidelines, tumors with gross ETE are categorized into the high-risk group because of the more than 20% structural recurrence rate[10]. In our study, the LRR rate of the gSMI group ranged from 5% to 25.9%. These relatively lower LRR rates were mainly attributed to the exclusion of some high-risk recurrent patients in these studies[11, 19, 20]. In the Danilovic and Li studies, which included all kinds of DTC cases, the LRR rates of gSMI were 24.6% and 25.9%[17, 18]. These data were consistent with the ATA guidelines. Based on the site of tumor invasion, gross ETE can be further divided into 3 subgroups: invasion only to perithyroidal soft tissue, invasion only to strap muscle and invasion beyond the strap muscles (recurrent laryngeal nerve, trachea, esophagus, skin or subcutaneous tissues). We found that DTC patients with gETE beyond the strap muscle suffered a much higher LRR than the other two groups. A possible reason is that gSMI can be easily resected with negative margins[13]. In the future, it may be reasonable that gETE beyond the strap muscle is categorized into an extremely high-risk group in the new recurrence risk stratification system, although further high-quality evidence is needed.

The eighth edition of the AJCC/TNM cancer staging system for DTC was published in 2016[6]. It made a substantial change with regard to the T3 category definition. Because mETE, which is identified only on histological examination, carried much less prognostic importance, the new AJCC/TNM system removed mETE in determining the T category[24]. Moreover, T3b was defined as a tumor of

any size with gSMI. The 8th edition made clear distinctions of disease with no ETE (T1, T2, T3a), gETE only to the strap muscle (T3b) and gETE beyond the strap muscle (T4)[25]. In our study, we also found that patients with gSMI presented with a higher recurrence rate than patients with no ETE. At the same time, the presence of gETE beyond the strap muscle was associated with a far worse prognosis than that of gSMI. These findings of our meta-analysis provide supportive evidence for the validity of the T category changes in the 8th edition AJCC/TNM system.

Usually, the T stage of tumors is associated with LNM and DM. The invasiveness of tumors represents its severity and differentiation[26]. Patients with aggressive tumors are always accompanied by more LNM and early DM[27]. Compared with patients with no ETE, patients with gSMI present with more LNM. Maximal ETE was considered an independent risk factor for LNM and DM in contrast with gSMI. This finding in our study suggests that the degree of ETE carries much more prognostic significance for DTC[7].

High heterogeneity with an $I^2 > 50\%$ was found in the analysis of LNM (compared with no ETE) and DM (compared with no ETE). Additionally, after the removal of each study from the analysis, similar results were confirmed, and the heterogeneity was not changed significantly. Furthermore, subgroup analysis was performed to explore the source of heterogeneity. In the therapeutic LND subgroup, gSMI increased LNM in comparison with ETE. This finding suggested that clinical LNM was more frequent in patients with gSMI. In the PTC subgroup, we found that gSMI increased DM significantly compared with no ETE. Histopathological types may be correlated with the high heterogeneity in the analysis of DM.

5 Strengths and weaknesses

By performing a meta-analysis with populations from different studies, this is the first study to assess the impact of gSMI on outcomes in DTC patients in a larger study sample and to adjust the results for the presence of some confounding factors. High heterogeneity was found in the analysis of LNM (compared with no ETE) and DM

(compared with no ETE) and was compensated by subgroup analysis. The results of LNM (compared with no ETE) and DM (compared with no ETE) should be interpreted with caution because of the limited number of enrolled articles, and further study is needed to confirm the corresponding results.

This meta-analysis has some potential limitations. First, the treatment strategies for DTC patients were different among the enrolled studies. These treatment disparities, such as thyroidectomy, lymph node dissection, radioiodine ablation or follow-up, might contribute to different patient outcomes. Second, the limited number of studies hindered the implementation of meta-regression analysis and publication bias assessment. The results of the subgroup analysis should be interpreted with caution because of the small number of studies, although heterogeneity was eliminated by subgroup analysis. Third, the retrospective and non-randomized nature of all studies included in the analysis might be considered a source of bias. This provided associative, not causal, evidence and mandates caution when interpreting these results. In future studies, randomized controlled trials with a higher methodological quality are needed to improve the quality of evidence.

6 Conclusion

Patients with gSMI had a higher risk of recurrence and LNM than those without ETE. However, in contrast with maximal ETE, a much better prognosis was observed in DTC patients with only gSMI. The findings of our meta-analysis provide supportive evidence for the validity of the T category changes in the 8th edition AJCC system. The actual impact of gSMI should be re-evaluated and revised in the recurrent risk stratification system in the future.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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