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Original Article

Clinical Significance of Tumor Size in Papillary Thyroid Microcarcinoma: a Meta-Analysis

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ABSTRACT

Purpose: To determine whether the tumor size associtates with aggressive clinicopathologic features and tumor recurrence in patients with papillary thyroid microcarcinoma (PTMC) who had undergone thyroidectomy. Clinical significance of tumor size in patients with PTMC is still controversial.
Methods: A search of PubMed, MEDLINE, and EMBASE identified the clinical studies that examined the association of subgroups classified by tumor size (5 mm) in surgical specimens with aggressive clinicopathologic features, and clinical outcomes between 1976 and 2017. Seven hundred twenty relevant studies were searched, and the authors selected 34 studies, including 12,134 PTMC cases. Random effects meta-analyses were performed using odds ratios (ORs) or relative risks (RRs) with 95% confidence intervals (CIs).
Results: In 34 studies, compared with the patients with small PTMC, the patients with large PTMC had a higher risk of multifocality (OR, 1.97; 95% CI, 1.61–2.40; I^2, 40.7%), extrathyroidal extension (OR, 3.42; 95% CI, 2.46–4.75; I^2, 64.9%), and lymph node metastasis (OR, 2.45; 95% CI, 1.79–3.37; I^2, 80.5%). In 10 studies, patient with large PTMC had 1.65-fold increased risk of locoregional recurrence (95% CI, 1.20–2.27; I^2, 0.0%).
Conclusion: This meta-analysis showed that tumor size in PTMC is associated with high-risk clinicopathologic characteristics and tumor recurrence. These findings may be helpful to decide treatment plans for patients with PTMC larger than 5 mm.

Keywords: Papillary thyroid microcarcinoma; Meta-analysis

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is defined as papillary thyroid carcinoma measured ≤1 cm in its greatest diameter according to the World Health Organization classification system for thyroid tumor (1). Recently, the establishment of the technique of ultrasound-guided fine-needle aspiration biopsy has facilitated the detection and diagnosis of papillary thyroid carcinomas, even in the tumor sized 1 cm or less in maximal diameter (2). Recently, the proportion of PTMC accounts for up to 40% of all papillary thyroid carcinomas (3).

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Kyu Eun Lee, Sue K. Park; Data curation: Kyungsik Kim; Formal analysis: Kyungsik Kim, Young peck Song, Ho Kyung Sung; Investigation: Young peck Song; Supervision: Kyu Eun Lee, Sue K. Park; Visualization: Su-jin Kim; Writing - original draft: Su-jin Kim, Kyungsik Kim; Writing - review & editing: Sue K. Park.

Despite the notable increasing incidence of PTMC, the diagnosis and treatment for these patients remain controversial. Less aggressive treatment is recommended in patients with PTMC relative to those with papillary thyroid cancers (PTCs) sized >1 cm because it has been thought that PTMC has characteristics of low malignant potential and rare distant metastases. However, some studies reported that a group of PTMCs could have a potential of worse prognosis since they had relationship with extrathyroidal extension, central lymph node (LN) metastasis, and multifocal and bilateral tumors (4). Although clinical significance of tumor size (≤5 vs. >5 mm) has been determined by several studies (5-7), the association between tumor size and high-risk clinicopathologic factors, and clinical outcome remains unclear.

Therefore, the present meta-analysis was performed to clarify the association of the size of tumor with high-risk clinicopathologic factors, and clinical outcome in PTMC patients who had undergone thyroidectomy. In addition, we performed subgroup analyses to evaluate the effects of the factors that might modify this association.

METHODS

1. Literature search strategy and study selection

We developed a literature search of PubMed, MEDLINE, and EMBASE published from 1976 through 2017 to identify relevant studies using the keyword papillary thyroid microcarcinoma or papillary microcarcinoma with English language publications. Duplicated articles or overlapping data were excluded by examining the author's names, study period, and affiliations. To be eligible, studies had to meet the following inclusion criteria: 1) studies that recruited PTMC cases; 2) the exposure of interest was tumor size (cut-off value: 5 mm) of PTMC; 3) the outcome of interest was multifocality, bilaterality, extrathyroid extension, LN metastasis at diagnosis, known to be prognostic factors in PTC, and tumor recurrence; and 4) providing sufficient data to allow for the calculation of the odds ratio (OR) or relative risk (RR) with 95% confidence intervals (CIs). We also manually searched the all the references of previous meta-analysis (4,8), and identified articles. The following data were extracted from each article; first author's name, year of publication, total number of study population, number of 2 groups (≤5 vs. >5 mm), gender, age, period of study, multifocality, bilaterality extrathyroidal extension, LN metastasis, tumor recurrence, and the ORs/RRs with their 95% CIs. We obtained age-standardized incidence rate (per 100,000 person) for thyroid cancer using the GLOBOCAN 2008 database.

2. Assessment of study quality

Two authors performed quality assessment independently using Risk of Bias Assessment tool for Non-randomized Study (RoBANS) scale (Appendix 1) (9). It contains 6 domains including the selection of participants, confounding variables, measurement of intervention (exposure), blinding of outcome assessment, incomplete outcome data and selective outcome reporting. Each domain was rated as low risk of bias, uncertain risk of bias and high-risk of bias designated following as 3, 2, and 1 score, respectively. Score could range from 6 to 18, with higher scores indicating studies with higher quality. For each article, the sum of the scores of all 6 domains was added Quality score of the 34 studies ranged from 11 to 17, and all studies were considered adequate for the meta-analysis (**Table 1**).

3. Statistical analysis

All statistical analyses were performed with the Stata software, version 14 (Stata Corporation, College Station, TX, USA). The Odds ratios (OR) with 95% confidence intervals (CI) were

https://doi.org/10.16956/jes.2018.18.2.142

JES Journal of Endocrine Surgery

Table 1. Characteristics of the 34 studies included in the meta-analysis

Study	No. of patients*	Gender (M/F)	Age, mean	Period of study	Multifocal tumors*	Bilateral tumors*	Extrathyroidal extension*	LN metastasis*	Recurrence*	Country	Incidence (ASR)†	Study quality
Yoon et al., 1998 (13)	72 (32/40)	10/62	45.0	1985–1995	-	-		7/16	-	Korea	35.4	11
Chow et al., 2003 (14)	203 (70/133)	27/176	46.8	1960–1999	18/45	-	3/39	18/32	4/8 (LR), 0/3 (DM)	Hong Kong	1.4	13
Wada et al., 2003 (15)	259 (61/198)	29/230	48.0	1988–1998	-	-		34/146	-	Japan	3.1	13
Cho et al., 2006 (16)	134 (39/95)	11/123	-	2003–2006	3/24	-	7/29	11/38	-	Korea	35.4	13
Han et al., 2006 (17)	350 (147/203)	54/296	46.5	1990–2004	-	-	-	-	4/22	Korea	35.4	13
Lee et al., 2006 (18)	300 (62/238)	27/273	46.1	2004	-	-	7/77	16/73	-	Korea	35.4	13
Pelizzo et al., 2006 (7)	403 (169/234)	66/337	-	1990–2004	-	-	-	-	6/18	Italy	9.1	12
Roti et al., 2006 (19)	243 (86/157)	46/197	51.5	1993–2002	-	-	-	2/30	0/4	Italy	9.1	13
Park et al., 2007 (20)	218 (71/147)	-	-	2001–2007	18/58	5/31	10/60	4/36	-	Korea	35.4	12
Pakdaman et al., 2008 (21)	429 (274/155)	-	-	2002–2007	140/110	74/77 (140/110)‖	25/39	-	-	Canada	9.4	12
Kim et al., 2008 (22)	254 (72/182)	41/213	48.1	1985–2002	4/8	-	2/12	9/21	1/9	Korea	35.4	13
Kim et al., 2008 (23)	307 (49/258)	32/275	-	1996–2002	9/89	-	-	-	-	Korea	35.4	13
Lee et al., 2008 (24)	52 (26/26)	7/45	47.6	2000–2005	-	-	-	1/15‡	-	Korea	35.4	14
Tae et al., 2008 (25)	142 (62/80)	31/111	48.3	2000–2006	10/17	-	7/22	8/16	-	Korea	35.4	13
Yoo et al., 2009 (26)	165 (62/103)	13/152	46.4	2002–2006	4/17	1/6	-	8/22	0/4	Korea	35.4	12
Kim et al., 2009 (27)	161 (52/109)	24/137	48.3	2003–2007	11/34	10/27	18/58	19/56‡; 3/12§	-	Korea	35.4	14
Friguglietti et al., 2011 (28)	448 (173/275)	52/396	-	2002–2008	26/45	-	23/41	10/45	-	Brazil	2.9	13
Kim et al., 2010 (29)	179 (78/101)	16/163	47.4	1996–2006	8/27 (29/71)‖	4/14 (29/71)‖	3/43	-	-	Korea	35.4	12
Lee et al., 2010 (30)	335 (125/220)	41/294	48.0	2006–2008	-	-	-	16/72	-	Korea	35.4	14
Lombardi et al., 2010 (31)	933 (459/474)	197/736	-	2002–2007	-	-	16/73	12/50	2/7 (100/187)‖	Italy	9.1	13
Lee et al., 2011 (32)	275 (106/169)	13/262	-	2007–2009	29/61	16/40 (79/149)‖	18/44	29/71‡	-	Korea	35.4	13
Buffet et al., 2012 (33)	707 (138/569)	289/418	47.2	1960–2007	-	-	-	56/233	-	France	0.7	15
Vasileiadis et al., 2012 (34)	276 (202/74)	54/222	-	2002–2008	60/42	29/35	3/17	7/16	-	Greece	1.8	13
Zhou et al., 2012 (35)	211 (67/144)	32/179	49.0	2010–2011	-	10/44	-	8/52‡ (23/99)‖	-	China	1.4	14
Ardito et al., 2013 (36)	149 (92/57)	30/119	47.6	2000–2005	-	-	-	-	18/10	Italy	9.1	14
Kim et al., 2013 (37)	483 (213/270)	68/415	45.2	2008	-	-	-	40/99‡	-	Korea	35.4	13
Zhao et al., 2013 (8)	212 (69/143)	36/176	45.1	2003–2011	-	-	-	17/62	-	China	1.4	14
Zheng et al., 2013 (38)	977 (632/345)	223/754	46.0	2001–2010	164/159	86/133	-	61/168	-	China	1.4	16
Karatzas et al., 2013 (39)	319 (249/70)	58/261	50.3	2001–2008	-	44/33	-	-	-	Greece	1.8	14
Kim et al., 2014 (40)	205 (83/122)	36/169	47.2	2005	19/33	13/25	18/52 (81/122)‖	14/26 (39/70)‖	2/7	Korea	35.4	17
Lee et al., 2014 (41)	2,018 (857/1,161)	297/1,721	45.3	1994–2010	-	-	-	-	13/28	Korea	35.4	17
Zeng et al., 2014 (42)	141 (12/129)	37/104	44.0	2004–2011	-	-	-	2/41§	-	China	1.4	16
Al-Qahtani et al., 2015 (43)	326 (161/65)	55/271	42.9	2000–2012	36/89	-	16/46	15/27	6/17, 4/9 (LR), 2/8 (DM)	Saudi Arabia	4.4	15
Usluogullari et al., 2015 (44)	248 (127/121)	47/201	47.8	2007–2012	28/40	17/28	7/21	2/16	4/6	Turkey	10.8	15

LN = lymph node; ASR = age-standardized rate; LR = locoregional recurrence; DM = distant metastasis; CLN = central lymph node; LLN = lateral lymph node.
*The number of patients with tumor size less than 5 mm/over 5 mm was expressed in each cell; †ASR per 100, 000 of thyroid cancer from GLOBACAN 2008; ‡CLN metastasis; §LLN metastasis; ‖Evaluated number of patients (less than 5 mm/over 5 mm).

used to assess the strength of association between the size of tumor and high-risk factors. The relative risks (RR) with 95% CIs were calculated in order to evaluate recurrence. When the ORs and RRs were not present but enough data were available in eligible articles, Cochran Mantel-Haenszel crude estimates of the ORs, RRs and corresponding 95% CI were calculated using Sas software version 9.4 for Windows. (10) Random-effect model was used to obtain the summarized OR, RR and 95% CI.

Statistical heterogeneity among studies was evaluated with the Cochran Q and I^2 statistics (11). Publication bias was evaluated with the use of the Egger regression asymmetry test in which P-value less than 0.1 was considered as representative of statistically significant publication bias (12). To analyze the source of heterogeneity between studies, subgroup

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JES Journal of Endocrine Surgery

analyses were performed according to the following characteristics: 1) incidence rate of thyroid cancer; 2) the quality of the study; and 3) published year. The incidence rate of thyroid cancer was categorized with an age-standardized incidence rate (per 100,000 person) of ≥3.1 and <3.1 using GLOBACAN 2008 database as high and low, respectively. The quality of the study was assessed using the RoBANS scale (9), which were categorized as ≥14 and <14. Published year of the articles was categorized as since 2011 and before 2011.

RESULTS

1. Characteristics of studies

Fig. 1 showed the process of article selection for the meta-analysis. According to our search strategy, a total of 720 potentially relevant articles were identified. Of these articles, duplicated 184 articles were removed. After review of titles and abstracts of 536 articles, we excluded 462 articles. And then 74 articles were thought to be relevant for the meta-analysis, and full-text of these articles were reviewed in detail. After search of the references of initially selected articles, 9 additional articles **were** included. After this review, a total of 34 eligible articles were included in the meta-analysis involving 12,134 PTMC cases. Among them, there are 5,177 cases (42.7%) of the small PTMC (≤5 mm), and 6,867 cases (56.6%) of large PTMC. The characteristics of studies in this meta-analysis are summarized in **Table 1**. Multifocality (14,16,20-23,25-29,32,34,38,40,43,44), bilaterality (20,21,26,27,29,32,34,35,38-40,44), extrathyroidal extension (14,16,18,20-22,25,27-29,31,32,34,40,43,44) and LN metastasis (8,13-16,18-20,22,24-28,30-35,37,38,40,42-44) were reported in 17, 12, 16, and 26 articles, respectively. The data for locoregional (7,14,17,19,22,26,31,36,40,41) and distant metastasis (DM) recurrence (14,43) were available in 10, and 2 articles. There are 17 studies from Korea, 4 studies from Italy, 4 studies from China, 2 studies from Greece, and 1 study from Brazil, Canada, France, Hong Kong, Japan, Turkey, and Saudi Arabia, respectively. There was no study with poor quality. The characteristics of studies in this meta-analysis are summarized in **Table 1**.

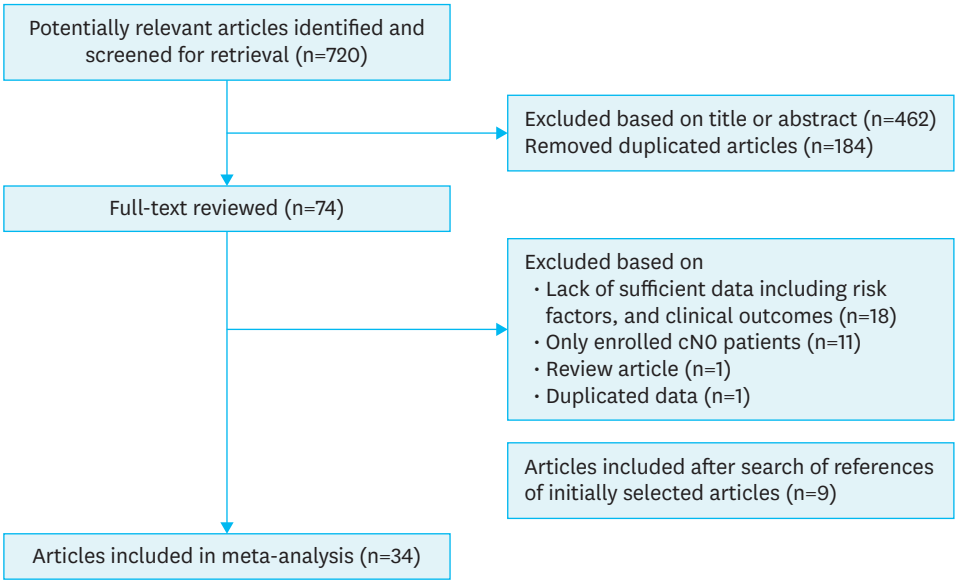

Fig. 1. Flow chart for article selection for the meta-analysis.

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JES Journal of Endocrine Surgery

2. Meta-analysis of the tumor size effects on prognostic factors

Overall, we found that there was increased summary ORs of high-risk factors in patients with larger PTMC **compared** with patient with small PTMC. For multifocality, the summary ORs from 17 studies was 1.97 (95% CI, 1.61–2.40). The heterogeneity of the data was significant (P=0.04), and the I^2 estimate of the variance of the studies was 40.7%. For bilaterality, the summary OR from 12 studies was 2.34 (95% CI, 1.81–3.03). The heterogeneity of the data (P value) was 0.06, and the I^2 estimate of the variance of the studies was 43.7. For extrathyroidal extension, the summary OR from 16 studies was 3.42 (95% CI, 2.46–4.75). The heterogeneity of the data was significant (P<0.01), and the I^2 estimate of the variance of the studies was 64.9%. For LN metastasis, the summary OR from 26 studies was 2.45 (95% CI, 1.79–3.37). The heterogeneity of the data was significant (P<0.01), and the I^2 estimate of the variance of the studies was 80.5%. For central, and lateral node metastasis, the summary OR from 10, and 3 studies was 2.54 (95% CI, 1.79–3.59), and 1.43 (95% CI, 0.78–2.65), respectively. The heterogeneity of these data (P value) were 0.02, and 0.61, and the I^2 estimate of the variance of the studies was 55.9%, and 0.0%, respectively (**Fig. 2** and **Table 2**).

3. Meta-analysis of the tumor size effect on tumor recurrence

For locoregional and DM recurrence, 10, and 2 studies were included in meta-analysis, respectively. In locoregional recurrence (LR), we found increased risk of recurrence in patients with larger PTMC comparing with the patient with small PTMC (RR, 1.65; 95% CI, 1.20–2.27). The heterogeneity of the data was not significant (P=0.57), and the I^2 estimate of the variance of the studies was 0.0%. In DM recurrence, we found increased risk of recurrence in patients with larger PTMC comparing with the patient with small PTMC (RR, 1.37; 95% CI, 0.18–10.49). The heterogeneity of the data (P value) was 0.06, and the I^2 estimate of the variance of the studies was 72.0% in subgroup analysis (**Fig. 3** and **Table 2**).

4. Subgroup analyses of the tumor size effects on the high-risk factors, and tumor recurrence

Except lateral lymph node (LLN) metastasis, and LR, I^2 estimates of the variance of the studies were >20%. To evaluate the potential source of heterogeneity that might modify effects of the tumor on high-risk factors, and tumor recurrence, we performed subgroup analyses according to incidence rate of thyroid cancer, the quality of the study, published year, and their combination (**Table 2**). The effects estimate of subgroup analysis were broadly consistent with initial outcome of meta-analysis. Considering the high incidence, high quality, published year, and combination, low I^2 estimates of the effects on the high-risk factors, and tumor recurrence are in the appendix (Appendix 2).

DISCUSSION

In the present study, we revealed that size of tumor in PTMC was associated with the high-risk factors of PTC, and tumor recurrence. To assess the strength of the association of the size of tumor with adverse clinicopathologic characteristics, and tumor recurrence, we performed a meta-analysis of 34 studies that evaluated 12,134 patients. Our study showed that large PTMC has a 1.20 to 2.27-fold increase in the risk of recurrence in addition to multifocality, bilaterality, extrathyroidal extension, and LN metastasis.

Although PTMC patients showed low LR (231/9,379 patients, 2.4%) and low mortality (32/9,379 patients, 0.34%), previous meta-analysis revealed that some PTMCs (e.g., multifocal PTMCs

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JES Journal of Endocrine Surgery

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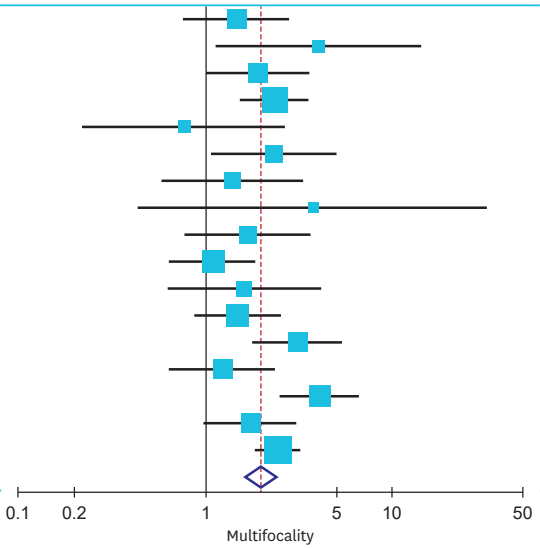

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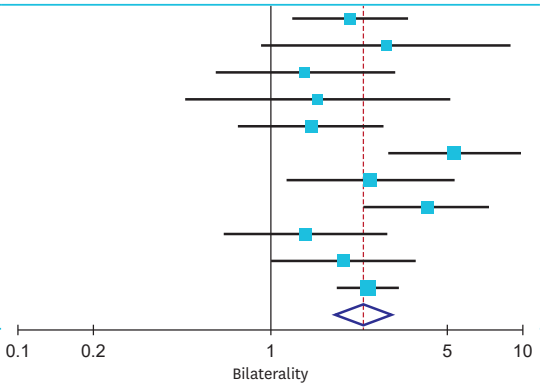

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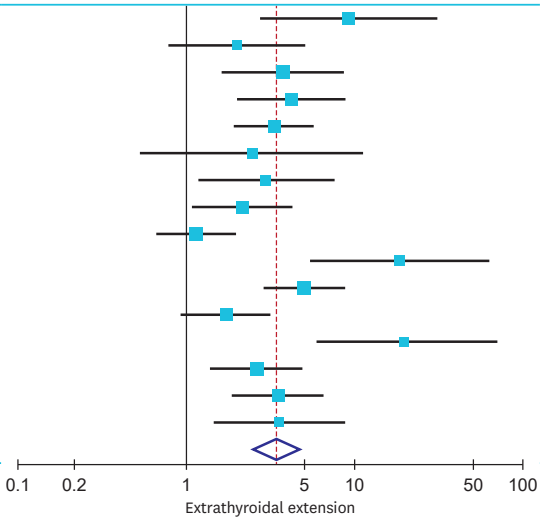

Fig. 2. Summarized statistics and corresponding forest plot on the association of large PTMC (size >5 mm) with the high-risk factors: (A) multifocality, (B) bilaterality, (C) extrathyroidal extension, (D) LN metastasis, (E) CLN metastasis, and (F) LLN metastasis.
PTMC = papillary thyroid microcarcinoma; LN = lymph node; CLN = central lymph node; LLN = lateral lymph node; OR = odds ratio; CI = confidence interval.

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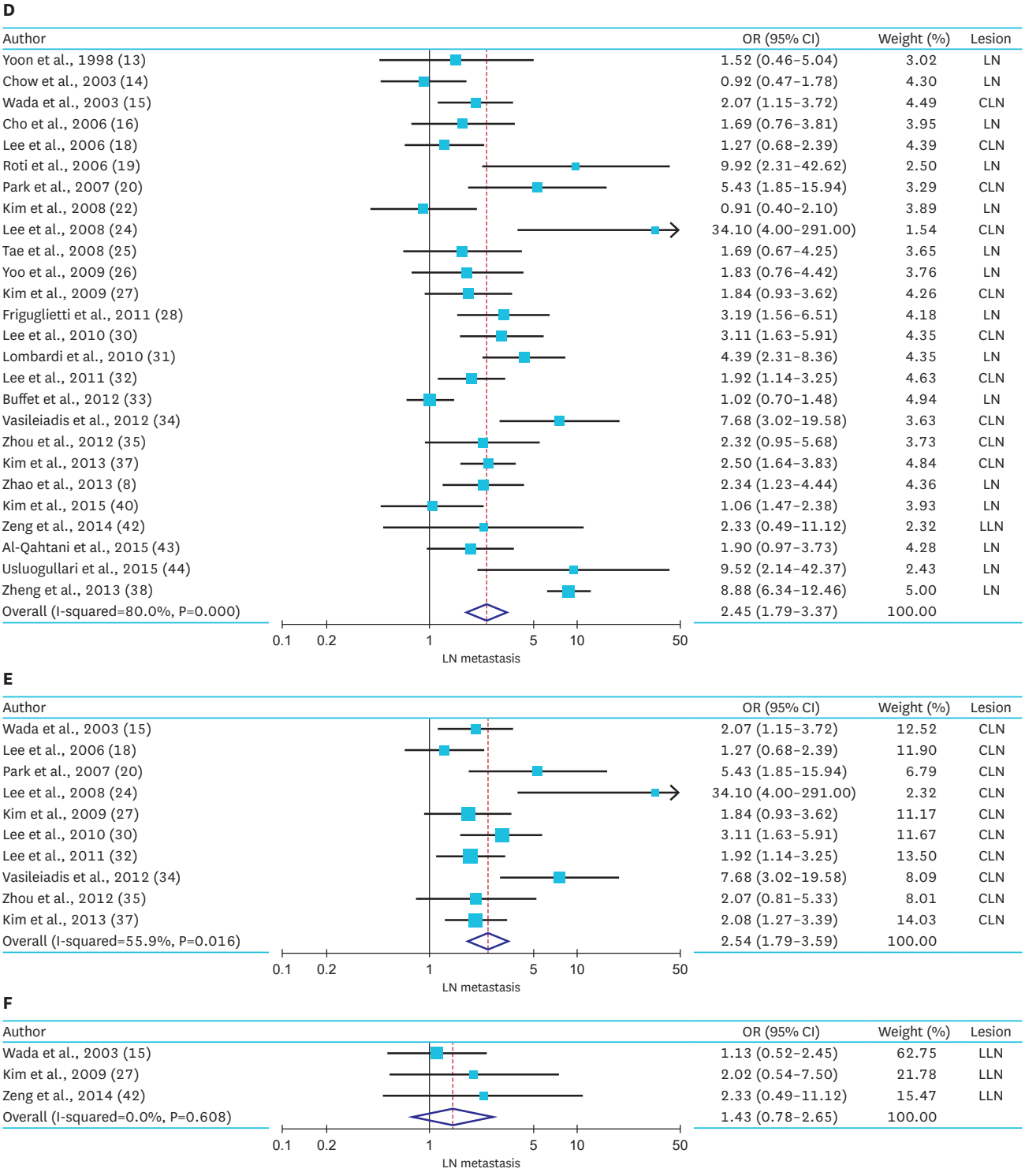

Fig. 2. (Continued) Summarized statistics and corresponding forest plot on the association of large PTMC (size >5 mm) with the high-risk factors: (A) multifocality, (B) bilaterality, (C) extrathyroidal extension, (D) LN metastasis, (E) CLN metastasis, and (F) LLN metastasis.
PTMC = papillary thyroid microcarcinoma; LN = lymph node; CLN = central lymph node; LLN = lateral lymph node; OR = odds ratio; CI = confidence interval.

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Table 2. Subgroup analyses categorized by incidence rate of thyroid cancer, study quality, and published year of the articles; risk with high-risk factors, and tumor recurrence in large PTMC compared with small PTMC

Outcome	Studies (No.)	Summary	I^2 (%)	P		
				Heterogeneity	Begg	Egger
Multifocality						
All studies	17	1.97 (1.61–2.40)	40.7	0.04	0.59	0.27
Study QS						
≥14	4	2.45 (1.71–3.51)	53.6	0.09	0.73	0.77
<14	13	1.78 (1.43–2.21)	20.8	0.23	0.86	0.93
Incidence rate						
High	13	1.98 (1.56–2.50)	29.9	0.15	0.86	0.46
Low	4	1.93 (1.25–2.98)	69.4	0.02	0.73	0.51
Published year						
≥2011	6	2.23 (1.61–3.09)	62.8	0.02	0.26	0.53
<2011	11	1.76 (1.42–2.18)	0.0	0.47	1.00	0.96
Combination						
High incidence and QS ≥14	3	2.38 (1.29–4.41)	68.7	0.04	1.00	0.46
Low incidence and QS ≥14	1	2.44 (1.85–3.22)				
High incidence and ≥2011	4	1.95 (1.13–3.37)	74.2	0.01	0.31	0.18
Low incidence and ≥2011	2	2.56 (2.00–3.28)	0.0	0.44	1.00	
High incidence, ≥2011 and QS ≥14	2	2.71 (1.18–6.18)	79.8	0.03	1.00	
Low incidence, ≥2011 and QS ≥14	1	2.44 (1.85–3.22)				
Bilaterality						
All studies	12	2.39 (1.87–3.06)	40.0	0.07	0.84	0.68
Study QS						
≥14	6	2.29 (1.70–3.09)	35.9	0.17	0.26	0.51
<14	6	2.56 (1.61–4.05)	51.7	0.07	1.00	0.93
Incidence rate						
High	8	1.84 (1.40–2.40)	0.0	0.77	0.71	0.63
Low	4	3.31 (2.22–4.96)	57.8	0.06	0.73	0.33
Published year						
≥2011	7	2.52 (1.79–3.54)	59.4	0.02	1.00	0.88
<2011	5	2.07 (1.44–2.98)	0.0	0.63	1.00	0.80
Combination						
High incidence and QS ≥14	3	1.59 (1.04–2.43)	0.0	0.74	1.00	0.31
Low incidence and QS ≥14	3	2.80 (2.02–3.86)	27.2	0.25	1.00	0.62
High incidence and ≥2011	3	1.59 (1.07–2.36)	0.0	0.75	1.00	0.68
Low incidence and ≥2011	4	3.31 (2.22–4.96)	57.8	0.06	0.73	0.33
High incidence, ≥2011 and QS ≥14	2	1.68 (1.02–2.75)	0.0	0.51	1.00	
Low incidence, ≥2011 and QS ≥14	3	2.80 (2.02–3.86)	27.2	0.25	1.00	0.62
Extrathyroidal extension						
All studies	16	3.42 (2.46–4.75)	64.9	<0.01	0.14	0.05
Study QS						
≥14	4	2.85 (2.02–4.02)	0.0	0.70	0.73	0.78
<14	12	3.78 (2.40–5.93)	73.3	<0.01	0.24	0.08
Incidence rate						
High	13	3.25 (2.51–4.20)	33.6	0.11	1.00	0.52
Low	3	5.58 (0.81–38.26)	91.3	<0.01	0.29	0.11
Published year						
≥2011	5	3.52 (1.93–6.42)	68.8	0.01	0.22	0.07
<2011	11	3.41 (2.25–5.17)	66.6	<0.01	0.53	0.23
Combination						
High incidence and QS ≥14						
Low incidence and QS ≥14	4	2.85 (2.02–4.02)	0.0	0.70	0.73	0.78
High incidence and ≥2011	0					
Low incidence and ≥2011	4	2.63 (1.87–3.70)	4.1	0.37	0.73	0.56
High incidence, ≥2011 and QS ≥14	1	19.78 (6.00–69.90)	-	-	-	-
Low incidence, ≥2011 and QS ≥14	3	3.13 (2.11–4.86)	0.0	0.76	0.75	0.79
LN metastasis						
All studies	26	2.45 (1.79–3.37)	80.5	<0.01	0.11	0.97

(continued to the next page)

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Table 2. (Continued) Subgroup analyses categorized by incidence rate of thyroid cancer, study quality, and published year of the articles; risk with high-risk factors, and tumor recurrence in large PTMC compared with small PTMC

Outcome	Studies (No.)	Summary	I^2 (%)	P		
				Heterogeneity	Begg	Egger
Study QS						
≥14	10	3.14 (1.63–6.06)	89.2	<0.01	0.37	0.96
<14	16	2.13 (1.58–2.87)	60.3	<0.01	0.62	0.57
Incidence rate						
High	18	2.24 (1.72–2.91)	51.5	0.01	0.54	0.15
Low	8	2.66 (1.23–5.78)	92.1	<0.01	0.54	0.73
Published year						
≥2011	11	2.68 (1.54–4.67)	88.8	<0.01	0.35	0.83
<2011	15	2.23 (1.59–3.11)	59.9	<0.01	0.37	0.12
Combination						
High incidence and QS ≥14	5	3.30 (1.69–6.41)	62.1	0.03	0.46	0.04
Low incidence and QS ≥14	5	2.61 (0.89–7.70)	94.5	<0.01	0.81	0.75
High incidence and ≥2011	5	2.09 (1.39–3.15)	46.8	0.11	1.00	0.74
Low incidence and ≥2011	6	3.11 (1.19–8.12)	93.4	<0.01	0.71	0.89
High incidence, ≥2011 and QS ≥14	2	3.68 (0.78–17.43)	73.1	0.05	1.00	
Low incidence, ≥2011and QS ≥14	5	2.61 (0.89–7.70)	94.5	<0.01	0.81	0.75
CLN metastasis						
All studies	10	2.54 (1.79–3.59)	55.9	0.02	0.05	0.01
Study QS						
≥14	4	2.91 (1.45–5.84)	57.5	0.07	0.73	0.23
<14	6	2.42 (1.58–3.73)	61.1	0.03	0.45	0.08
Incidence rate						
High	8	2.28 (1.62–3.19)	48.5	0.06	0.17	0.02
Low	2	3.99 (1.10–14.43)	73.3	0.05	1.00	-
Published year						
<2011	6	2.59 (1.53–4.39)	62.4	0.02	0.13	0.04
≥2011	4	2.58 (1.53–4.34)	57.4	0.07	0.73	0.34
Combination						
High incidence and QS ≥14	3	3.58 (1.34–9.57)	70.5	0.03	1.00	0.31
Low incidence and QS ≥14	2	1.27 (0.67–2.40)	46.6	0.17	1.00	-
High incidence and ≥2011	2	2.00 (1.40–2.87)	0.0	0.83	1.00	0.89
Low incidence and ≥2011	2	3.99 (1.10–14.43)	73.3	0.05	1.00	-
High incidence, ≥2011 and QS ≥14	3	3.58 (1.34–9.57)	70.5	0.03	1.00	0.31
Low incidence, ≥2011 and QS ≥14	2	1.27 (0.67–2.40)	46.6	0.17	1.00	-
LLN metastasis						
All studies	3	1.43 (0.78–2.65)	0.0	0.61	0.30	0.06
LR*						
All studies	10	1.65 (1.20–2.27)	0.0	0.57	0.59	0.20
Study QS						
≥14	5	1.41 (0.95–2.11)	0.0	0.59	0.81	0.30
<14	5	2.22 (1.30–3.77)	0.0	0.55	1.00	0.96
Incidence rate						
High	9	1.71 (1.23–2.39)	0.0	0.54	0.60	0.14
Low	1	1.05 (0.33–3.36)				
Published year						
≥2011	5	1.41 (0.93–2.09)	0.0	0.59	0.81	0.30
<2011	5	2.21 (1.30–3.76)	0.0	0.55	1.00	0.96
Combination						
High incidence and QS ≥14	5	1.41 (0.93–2.09)	0.0	0.59	0.81	0.30
Low incidence and QS ≥14	0					
High incidence and ≥2011	5	1.41 (0.93–2.09)	0.0	0.59	0.81	0.30
Low incidence and ≥2011	0					
High incidence, ≥2011 and QS ≥14	5	1.41 (0.93–2.09)	0.0	0.59	0.81	0.30
Low incidence, ≥2011 and QS ≥14	0					
DM recurrence*						
All studies	2	1.37 (0.18–10.49)	72.0	0.06	1.00	

PTMC = papillary thyroid microcarcinoma; QS = quality score; DM = distant metastasis; LN = lymph node; CLN = central lymph node; LLN = lateral lymph node; LR = locoregional recurrence; RR = relative risk; CI = confidence interval.
*Summary data shown are RR (95% CI).

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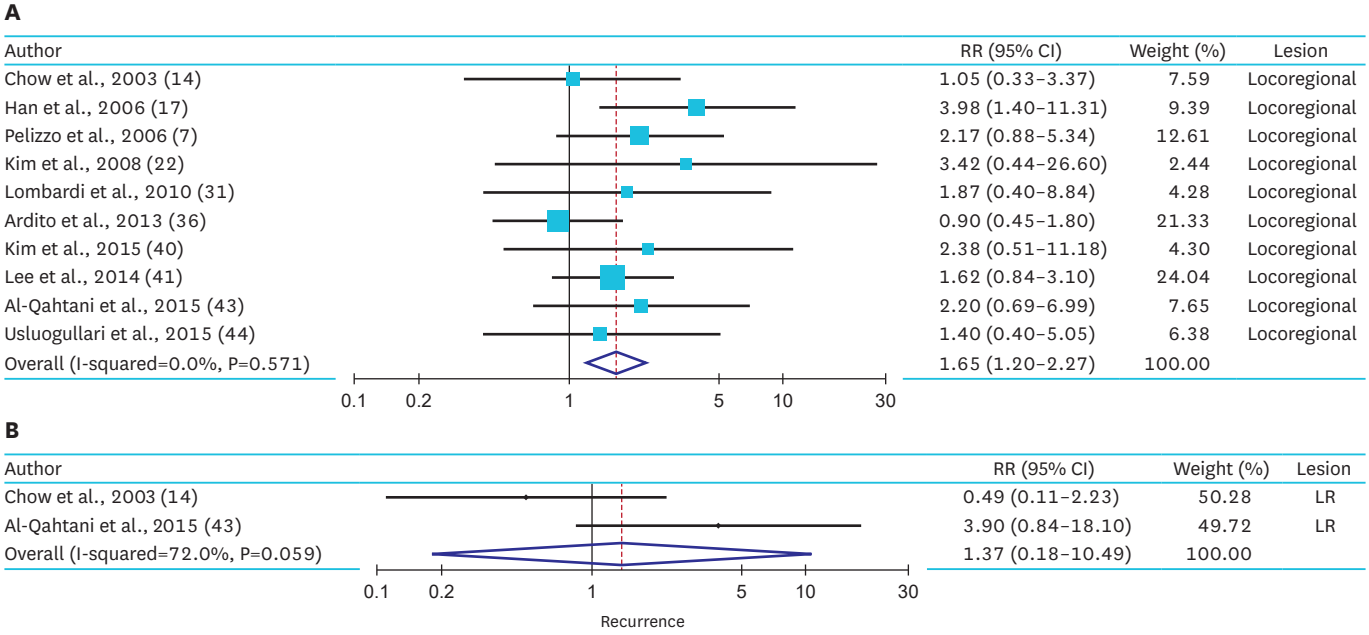

Fig. 3. Summarized statistics and corresponding forest plot on the association of large PTMC (size >5 mm) with the risk of tumor recurrence: (A) LR and (B) DM recurrence.
PTMC = papillary thyroid microcarcinoma; LR = locoregional recurrence; DM = distant metastasis; RR = relative risk; CI = confidence interval.

and those having LNs involvement at diagnosis) have a higher potential for tumor recurrence (4). However, the cancer size was not associated with tumor recurrence (4). However, some studies reported that large sized PTMC were at higher risk for tumor recurrence with various cut-off size of tumor (16,32,40). The present study is the first meta-analysis examining the clinical implication of tumor size (≤0.5 vs. >0.5 cm) on tumor recurrence, including LR, and DM recurrence.

In this meta-analysis, large PTMCs had aggressive characteristics such as multifocality, bilaterality, extrathyroidal extension, and cervical LN metastasis that are well-known prognostic factors in PTC (13,31). Although the result directly does not imply that patients with larger PTMCs are at higher hazard on thyroid cancer specific death, tumor size was associated with aggressive features, which is important to decide the extent of operation, and postoperative treatment including levothyroxine treatment, and radioactive iodine therapy.

Although we found significant association between tumor size and aggressive characteristics, heterogeneity was evident in the results. Therefore, we performed subgroup analysis to identify possible reasons for heterogeneity. In the subgroup analysis by study design type, the heterogeneity of prospective cohort studies was significantly reduced, which indicated that retrospective cohort studies may introduce heterogeneity. By performing a subgroup analysis based on study quality, incidence rate, and published year, there was no significant differences between subgroups except incidence rate, and published year in bilaterality, study quality in extrathyroidal extension.

For LLN metastasis, and LR, there was no significant heterogeneity. In 3 studies included for analysis of LLN metastasis, we found that there was no significant increased risk of LLN metastasis in large PTMC group. In 10 studies included for analysis of LR, we found the higher risk of recurrence in large PTMC group.

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Journal of Endocrine Surgery

Our meta-analysis has several limitations. Most relevant studies are retrospective studies. Retrospective studies, even when well controlled, are susceptible to various biases (e.g., selection or information bias). Individual studies may have failed to adjust for potential confounders in the data analysis which could influence the relationship between size of PTMC and aggressive prognostic factors. Only eights articles provided adjusting risk estimates, so the others were calculated crudely.

Strengths of this study include a comprehensive, systematic review of the literature by a multidisciplinary team including specialists in thyroid cancer and epidemiology, with each article reviewed by 2 team members. The subgroup analysis was conducted precisely according to incidence rate of thyroid cancer, the quality of the study, and published year.

In conclusion, this meta-analysis revealed that larger PTMC has a higher potential of tumor recurrence. The results obtained in the present study may provide useful information to identify patients requiring aggressive diagnostic evaluation, treatment, and intensive surveillance at follow-up.

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