REVIEW

Prevalence, Risk Factors And Location Of Skip Metastasis In Papillary Thyroid Carcinoma: A Systematic Review And Meta-Analysis

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Background: Skip metastasis is a special type in cervical lymph node metastasis (LNM) of patients diagnosed with papillary thyroid carcinoma (PTC) which induced poor prognosis. There are few studies about skip metastasis and conclusions remained uncertain. Therefore, this study aims to explore the frequency and to investigate risk factors of skip metastasis in PTC.
Methods: Through searching the keyword by PubMed and Embase databases which articles published up to 1st August 2018 about skip metastasis in papillary thyroid carcinoma, we extract data in order to assure whether those materials meet the criteria.
Results: The prevalence of skip metastasis is 12.02% in light of our meta-analysis of 18 studies with 2165 patients. The upper pole location (RR = 3.35, 95% CI =1.65–6.79, P = 0.0008) and tumors size ≤1 cm (RR = 2.65, 95% CI =1.50–4.70, P = 0.0008) are significantly associated with skip metastasis, whereas lymphovascular invasion (RR = 0.33, 95% CI =0.15–0.75, P = 0.0083) exists lower rate of skip metastasis. Multifocality, gender, age, bilaterality, thyroiditis and Extrathyroidal extension (ETE) are insignificantly associated with skip metastasis. Level II and level III are the most frequently affected areas.
Conclusion: The lateral compartment should be carefully examined especially for those PTC patients who present primary tumors in the upper lobe with a primary tumor size ≤10 mm which could be detected with skip metastasis.
Keywords: papillary thyroid carcinoma, skip metastasis, lateral neck dissection, meta-analysis

Introduction

Over the past three decades, the incidence of papillary thyroid cancer (PTC) has increased threefold, where the PTC accounts for approximately 90% of thyroid cancer.[1–3] Nevertheless, prognosis of PTC is relatively good and the mortality is stable at the rate of approximately 0.5 deaths per 100,000.[2] Thus, up to 95% of patients with PTC can be cured by surgery and accessory therapies.[3] PTC tends to metastasize to cervical lymph nodes the first time. Cervical lymph nodes are divided into two main areas. Central lymph nodes (CLN) are called as level VI, including precricoid (Delphian), pretracheal, paratracheal, and perithyroidal nodes.[4] Lateral lymph nodes (LLN) include levels II, III, IV, and V, of which Level II extends from skull-based to the level of inferior border of hyoid bone for which medial boundary is the stylohyoid muscle and lateral boundary is posterior border of sternocleidomastoid (SCM) muscle. The nodes of Level III extend from the

inferior border of the hyoid bone to the inferior border of the cricoid cartilage, level IV nodes extend from the inferior border of the cricoid cartilage to the clavicle. Medial and lateral boundaries of these two levels are the same as Level II. Level V is also called the posterior triangle group, including the superior boundary which is the apex formed by convergence of the SCM and trapezius muscle, the inferior boundary which is clavicle, the medial boundary which is the posterior border of the SCM muscle, and the lateral boundary which is the anterior border of the trapezius muscle.[5] Generally, ipsilateral CLN is the first step of lymph nodes metastasis, and then it metastasizes to contralateral CLN and finally to LLN. According to different studies on postoperative histology of metastatic lymph nodes, the rate of CLNM is 14.6–52%, and the rate of both CLNM and LLNM are 42–65%.[6,7] The rate of only LLNM with negative CLNM defined as skip metastasis is about 3–19.7%.[8–11]

To treat lymph node metastasis, prophylactic CLN dissection (CLND) is accepted as a standard treatment in the world, while whether LLN dissection (LLND) can be prevented is still under discussion.[4] Various thyroid centers reached a consensus that it was an overtreatment of clearing LLN without histologic basis. Meanwhile, larger operative extent would prolong the surgery and give rise to additional complications including intractable chyle leakage and injuries of vagus nerve, accessory nerve, hypoglossal nerve, or facial nerve.[12] However, in case of locoregional recurrence, cleaning tumor foci is of crucial importance during the first operation. Otherwise, patients will be confronted with reoperation and greater risks.[13] At present, according to the 2015 ATA guidelines, most thyroid surgeons make therapeutic dissection of LLN under the evidence of histologic metastatic tumor thus clearing tumor foci and reducing complications.[14] Therefore, to identify the involved lateral lymph nodes accurately before the surgery is urgent.

Metastatic lymph nodes are commonly under ultrasound examination, followed by CT and MRI. Sonographic features of metastatic lymph nodes include enlargement, calcifications, loss of the fatty hilum, hyperechogenicity, a rounded rather than oval shape, cystic change, and peripheral vascularity.[14] Sometimes, abnormal lymph nodes may not be found when it was microcalcification or overlaid by thyroid tissue.[15] On the basis of present reports, the preoperative sonographic sensitivity in initial patients is about 30–55% for central compartment, and 62–94% for lateral compartment.[16,17] CT or MRI can be used for patients' suspected clinically apparent multiple or bulky lymph node involvement, and preoperative 18FDG-PET scanning is not recommended to be used frequently. According to various studies, the false-positive and false-negative rate of ultrasound to palpable LLN both range from 20% to 30%.[18] In addition, in previous studies, ultrasonic examination cannot identify abnormal lymph node for which the diameter is less than 5 mm.[19]

Hence, determining the risk factors of skip metastasis can guide performers strengthen the awareness when CLN is negative and lead them to choose appropriate extent of procedure. Features of normal LLNM were discussed by So et al, but the conclusions of skip metastasis were still controversial.[20] There are few studies focusing on predictive factors of skip metastasis. Therefore, the aim of this meta-analysis is to explore the frequency and investigate risk factors of skip metastasis in PTC.

Methods
Our meta-analysis was registered to PROSPERO (https://www.crd.york.ac.uk/PROSPERO) and ID was CRD42018087681.

Search Strategy
We searched PubMed and Embase databases up to 1st August 2018. The search terms were the following: 1) papillary thyroid cancer OR papillary thyroid carcinoma OR papillary thyroid neoplasm OR PTC; 2) skip metastasis OR skip metastases OR lateral lymph node OR lateral compartment. Two independent investigators do the study selection by screening the titles and abstracts; meanwhile, relevant reviews and reference lists were also checked. Discrepancies were resolved by discussion.

Selection Criteria
We included studies which met the following criteria:

1. Prospective or retrospective cohort studies;
2. PTC and LNM were confirmed by histopathology;
3. Definition of skip metastasis corresponded to our article;
4. Patients were under thyroidectomy and CLND or LLND;
5. Any one of the prevalence or risk factors or location of skip metastasis were available;
6. English studies.

We excluded studies by the following criteria:

1. Reviews, case reports, letters to the editor, conference abstracts, and so on;
2. Studies enrolled patients with follicular thyroid carcinoma, medullary thyroid carcinoma, or anaplastic carcinoma;
3. Sample size less than 10.

Data Extraction And Quality Assessment

Each eligible study was extracted by two independent reviewers. Study characteristics were needed including first author, publication years, countries of study, study design, study population (PTC or PTMC), number of patients, surgical extent, indication of LLND (prophylactic or therapeutic). Outcomes including prevalence, risk factors, and location of skip metastasis were extracted. The risk factors included multifocality, sex, tumor location, age, tumor size, lymphovascular invasion, tumor bilaterality, thyroiditis, extrathyroidal extension (ETE), and capsule invasion.

We assessed the quality of each eligible study using Newcastle-Ottawa Scale (NOS),[21] which offers capacity in evaluating cohort studies by a total of eight items of three major parts, including the study population selection (selection), comparability (comparability), and result (outcome). NOS uses the semi-quantitative principles of star system to do quality assessment and full score is 9 stars. All quality assessments were performed by two independent reviewers.

Statistical Analysis

Statistical analysis was performed using the R version 3.5.1 (Vienna, Austria; https://www.r-project.org) plus RStudio version 1.1.456 (250 Northern Ave, Boston, MA 02210) with "meta" package (version 4.9–2). For prevalence and location of skip metastasis, ratios were calculated using Freeman-Tukey double arcsine transformation.[22] For each risk factor, the relative risk ratio (RR) was calculated with a 95% confidence interval (CI). A P-value <0.05 was considered statistically different. Heterogeneity was examined by using Q-test and I2 statistic. Random effects model was used when studies were heterogeneous (P <0.1 or I^2 >50%); otherwise, fixed-effects model was applied.[23] There are still some biases about Egger's linear regression test and Begg's rank correlation test or funnel plot.

Results

After searching the databases, 646 studies from PubMed and 967 studies from Embase were initially found and 1047 articles were non-overlapping articles. A total of 169 articles were excluded because they were not written in English and 394 studies were also excluded due to the fact that they are reviews, letters, case reports, and conference abstracts. After scanning the titles and abstracts of the remaining 484 studies, 31 articles were subjected to a full-text evaluation. After the full-text review, 20 studies met our selection criteria. However, four of those twenty studies were excluded because the study population is overlapping. Finally, a total of 18 studies were included in our meta-analysis. All the patients included in those studies were with LLNM who may not be with CLNM and were pN1b patients. Patients in those studies were first diagnosed or highly suspicious of LNM by ultrasound, and then they under went fine-needle aspiration (FNA) biopsy to check LNM. Finally, a thyroidectomy with CLND which has a modified or selective LLND (therapeutic) was performed. If FNA biopsy could not determine the nature of lymph nodes, intra-operational frozen biopsy was applied. Thus, all patients with skip metastasis were confirmed by histopathology. Flow chart with details was displayed in Figure 1 and for study characteristics, see Table1.

Prevalence Of Skip Metastasis

All 18 studies reported the prevalence of skip metastasis in each LLNM population.[8–11,24–37] Overall, 260 patients (12.02%) had to skip metastasis in the sample of 2165 patients who had LLNM. The ratio of skip metastasis ranged from 5% to 25% (median 13.16%, inter-quartile range 8.22–19.56%). A random-effects model was used because of the relatively stable heterogenicity (P< 0.0001, I^2 = 65.3%). The prevalence of skip metastasis was 12.02% (95% CI = 9.45%-14.82%). No significant publication bias was found in Begg's rank correlation test (P = 0.3065) and Egger's linear regression test (P = 0.1730; Figure 2).

Risk Factors For Skip Metastasis

All risk factors for skip metastasis are shown in Table 2.

Multifocality Of Tumor

Data of 7 included studies were analyzed using fixed effects model (P = 0.0849, I^2 = 46.0%).[8–11,24–26] Tumor multifocality was not significantly associated with skip metastasis (RR = 0.95, 95% CI =0.65–1.40, P = 0.8047).

Gender (Male)

A fixed effects model was applied owing to little heterogenicity in 6 enrolled articles (P = 0.4578, I^2 = 0.0%).[9–11,24–26]
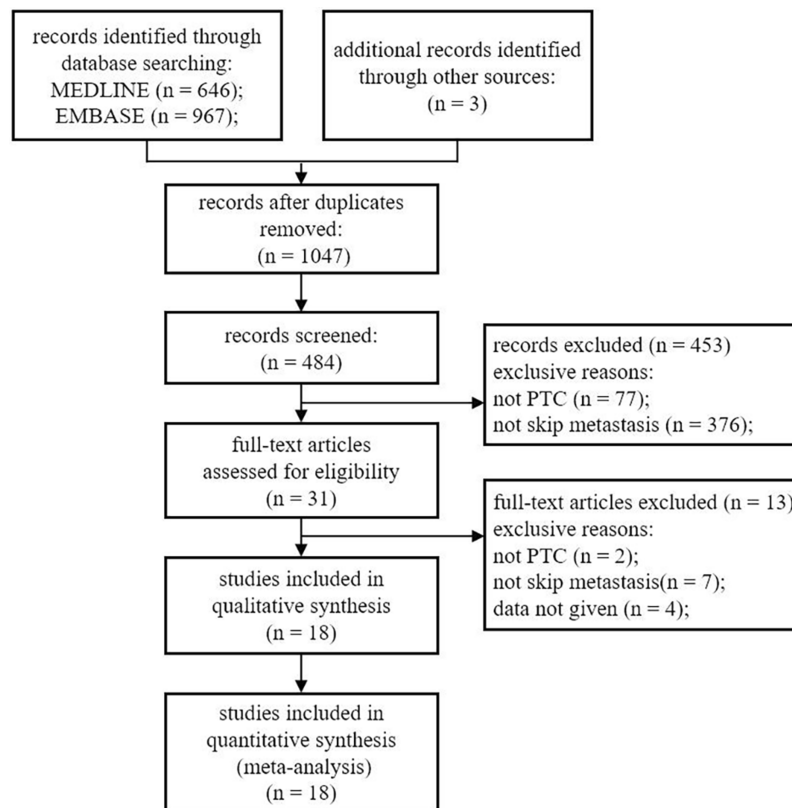
Figure 1 PRISMA flow chart of the included studies.

Gender was not statistically related to skip metastasis (RR = 0.94, 95% CI =0.68–1.30, P = 0.4578).

Tumor Location

Six studies reported the association between tumor location (upper pole) and skip metastasis.[9–11,24–26] Data were analyzed by random effects model (P = 0.0019, I^2 = 73.7%). Tumors located in the upper pole had a significantly higher ratio for skip metastasis than those located in the mid-lower pole (RR = 3.35, 95% CI =1.65–6.79, P = 0.0008; Figure 3).

Age (<45 Years)

A fixed effects model was used (P = 0.3293, I^2 = 13.3%) to analyze data from 5 studies.[9,11,24–26] Age (<45 years) was not significantly connected with skip metastasis (RR = 0.84, 95% CI =0.63–1.14, P = 0.2685).

Tumor Size (≤1 Cm)

A medium to high heterogenicity was detected (P = 0.0027, I^2 = 72.5%) in 6 articles and a random effects model was applied.[9–11,24–26] Tumors (≤1 cm) existed a significantly higher odd for skip metastasis than those >1 cm (RR = 2.65, 95% CI =1.50–4.70, P = 0.0008; Figure 4).

Lymphovascular Invasion

Only two articles reported outcomes of lymphovascular invasion and a fixed effects model was applied (P = 0.9872, I^2 = 0.0%).[9,10] Lymphovascular invasion has a statistically lower rate of skip metastasis (RR = 0.33, 95% CI =0.15–0.75, P = 0.0083; Figure 5).

Tumor Bilaterality

No obvious heterogenicity was found in 5 enrolled studies (P = 0.7504, I^2 = 0.0%). Data were analyzed by fixed effects model.[8,10,11,24,26] Tumor bilaterality was not significantly associated with skip metastasis (RR = 1.08, 95% CI =0.74–1.56, P = 0.6989).

Thyroiditis

A fixed effects model was used in 2 studies (P = 0.2048, I^2 = 37.8%).[24,26] No significant difference was found in PTC patients with or without thyroiditis (RR = 1.36, 95% CI =0.88–2.10, P = 0.1646).

Extrathyroidal Extension (ETE)

Six studies had outcomes of ETE and a fixed effects model was applied (P = 0.2488, I^2 = 24.7%).[8–10,24–26] ETE was

Table 1 Characteristics Of The 18 Included Studies

Author	Year	Country	Study Period	Study Design	Study Population	Case	Age	Male	Female	Surgical Extent	LND Extent	NOS-Gen
Jin WX[24]	2018	P.R.China	2014/1–2016/12	Retrospective	PTC	355	48.8±12.51§(15–85)*	112	243	TT+ CND + LND	Selective	8
Lei JY[26]	2017	P.R.China	na	Retrospective	PTC	450	40.5±13.7§	120	330	TT + CND + LND	Selective	7
Likhterov L[27]	2017	U.S.	2006/6–2015/10	Retrospective	PTC	80	45.8 (16–98)*	24	56	TT + CND + LND	Selective	8
Nie XL[25]	2017	P.R.China	2008/1–2011/12	Retrospective	PTC	271	44.8 (12–85)*	64	207	TT + CND + LND	Modified radical	9
Lee YS[9]	2013	South Korea	2004/1–2009/6	Retrospective	PTC	131	50.4 (12–76)*	26	105	TT + CND + LND	Selective	8
Shi L[28]	2013	P.R.China	2003/6–2007/6	Retrospective	PTC	165	39.7 (14–76)*	36	129	TT + CND ± LND	Selective	8
Park JH[11]	2012	South Korea	2006/1–2009/12	Retrospective	PTC	147	41.9±11.6§	21	126	TT + CND + LND	Selective	8
Kim YS[30]	2012	South Korea	2007/5–2010/9	Retrospective	PTMC	490	45.95±10.56§	62	428	TT + CND ± LND	Selective	8
Kliseska E[29]	2012	Croatia	2007–2011	Retrospective	PTC	42	na	na	na	TT + CND + LND	Na	6
Lim YC[10]	2011	South Korea	2004/3–2010/5	Retrospective	PTC	90	47±13.9§	20	70	TT + CND + LND	Modified radical	9
Xiao GZ[32]	2010	P.R.China	2001/12–2007/9	Retrospective	PTC	121	43.5 (6–73)*	25	96	TT + CND + LND	Selective	8
Koo BS[31]	2010	South Korea	2003/3–2009/5	Retrospective	PTC	70	47 (22–78)*	15	55	TT + CND + LND	Selective	8
Chung YS[8]	2009	South Korea	2006/1–2008/1	Retrospective	PTMC	245	48.2 (23–76)*	34	211	TT + CND ± LND	Selective	8
Roh JL[34]	2008	South Korea	2003–2006	Retrospective	PTC	52	46.9±14.4§	12	40	TT + CND + LND	Selective	7
Lee BJ[36]	2007	South Korea	2000/3–2006/4	Retrospective	PTC	46	37.8 (12–86)*	8	38	TT + CND + LND	Modified radical	7
Roh JL[35]	2007	South Korea	2002–2004	Retrospective	PTC	22	50.6±16.4§(29–76)*	5	17	CND + LND	Modified radical	7
Wada N[33]	2007	Japan	1986–2006	Retrospective	PTC	231	51.3±15.9§(15–85)*	58	173	TT or ST or LT + CND + LND	Modified radical	8
Machens A[37]	2004	Germany	1994/11–2002/11	Retrospective	PTC&MTC	66	na	na	na	TT + CND + LND or CND + LND	Selective	7

Notes: ±, with or without; §, Mean ± SD; *Mean (range).
Abbreviations: na, not reported; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; MTC, medullary thyroid cancer; TT, total thyroidectomy; ST, sub thyroidectomy; LT, lobectomy; CND, central neck dissection; LND, lateral neck dissection.
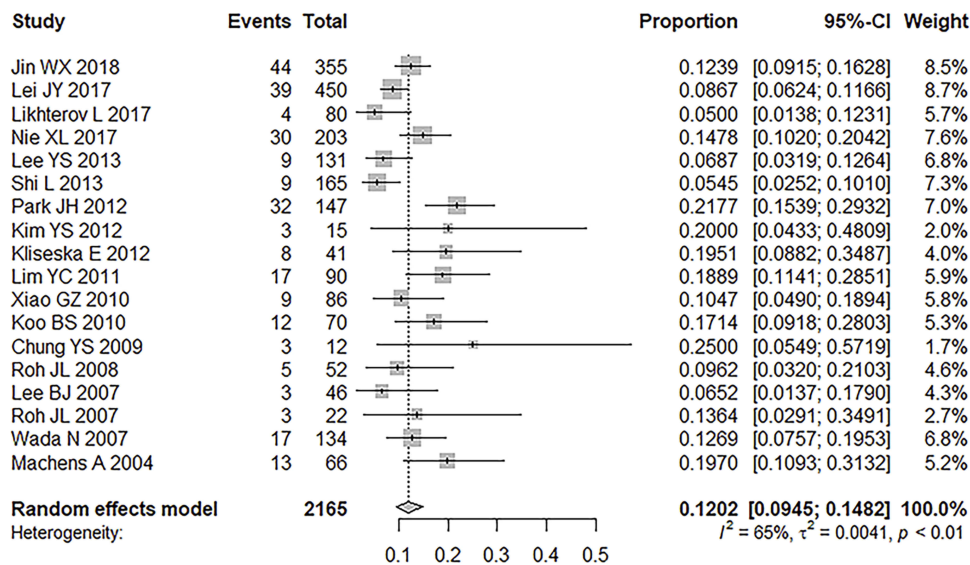
Figure 2 Prevalence of skip metastasis in patients with lateral lymph node metastasis.

Table 2 Risk Factors For Skip Metastasis

	RR	95% CI	P	P value Of Q-test	I^2
Multifocality of tumor	0.95	0.65–1.40	0.8047	0.0849	46.0%
Gender (male)	0.94	0.68–1.30	0.4578	0.4578	0.0%
Tumor location (upper pole)	3.35	1.65–6.79	0.0008	0.0019	73.7%
Age (<45 years)	0.84	0.63–1.14	0.2685	0.3293	13.3%
Tumor size (≤1 cm)	2.65	1.50–4.70	0.0008	0.0027	72.5%
Lymphovascular invasion	0.33	0.15–0.75	0.0083	0.9872	0.0%
Tumor bilaterality	1.08	0.74–1.56	0.6989	0.7504	0.0%
Thyroiditis	1.36	0.88–2.10	0.1646	0.2048	37.8%
Extrathyroidal extension (ETE)	1.20	0.88–1.65	0.2469	0.2488	24.7%
Capsule invasion	1.02	0.32–3.28	0.9734	0.0004	83.5%

Abbreviations: RR, risk ratio; 95% CI, 95% confidence interval.

not significantly associated with skip metastasis (RR = 1.20, 95% CI =0.88–1.65, P = 0.2469).

Capsule Invasion

A high heterogenicity was found in 4 included studies (P = 0.0004, I^2 = 83.5%) and a random effects model was applied.[8,10,24,26] Capsule invasion was not associated with skip metastasis (RR = 1.02, 95% CI =0.32–3.28, P = 0.9734).

Location Of Skip Metastasis

Four studies reported outcomes of the location of skip metastasis and a total of 132 patients had skip metastasis.[10,11,24,26] Seventy-six patients were skip metastasis positive in level II, 86 in level III, 18 in level IV, and 6 in level V. Ratio of skip metastasis was 56.29% (95% CI = 39.77–72.16%) in level II, 68.85% (95% CI = 42.11–90.46%) in level III, 15.95% (95%

CI = 0.66–45.34%) in level IV, and 3.67% (95% CI = 0.72–8.11%) in level V (Table 3).

Subgroup Analysis

Owing to the fact that 2 studies reported outcomes of PTMC, subgroup analysis was conducted in studies of PTC.[8,30]

Prevalence of skip metastasis in PTC was 11.88% (95% CI = 9.33–14.68%) and heterogenicity remained stable (P< 0.0001, I^2 = 67.3%).

Tumor multifocality was not significantly associated with skip metastasis (RR = 0.95, 95% CI = 0.50–1.81, P = 0.8838). However, heterogenicity increased (P = 0.0533, I^2 = 53.7%) and random effects model was applied. Tumor bilaterality was not significantly associated with skip metastasis (RR = 1.09, 95% CI = 0.75–1.59, P = 0.6346)
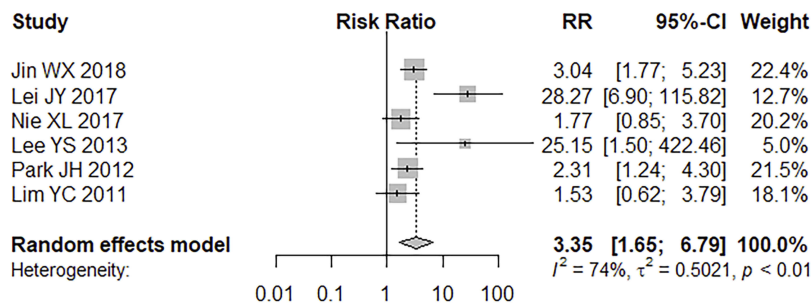
Study | **Risk Ratio** | **RR** | **95%-CI** | **Weight**

Jin WX 2018 — 3.04 [1.77; 5.23] 22.4%
Lei JY 2017 — 28.27 [6.90; 115.82] 12.7%
Nie XL 2017 — 1.77 [0.85; 3.70] 20.2%
Lee YS 2013 — 25.15 [1.50; 422.46] 5.0%
Park JH 2012 — 2.31 [1.24; 4.30] 21.5%
Lim YC 2011 — 1.53 [0.62; 3.79] 18.1%

Random effects model — 3.35 [1.65; 6.79] 100.0%
Heterogeneity: $I^2 = 74\%$, $\tau^2 = 0.5021$, $p < 0.01$

0.01 0.1 1 10 100

Figure 3 Forest plot of tumor location (upper pole).

Study | **Risk Ratio** | **RR** | **95%-CI** | **Weight**

Jin WX 2018 — 2.38 [1.35; 4.21] 19.4%
Lei JY 2017 — 9.51 [4.92; 18.40] 18.2%
Nie XL 2017 — 1.60 [0.81; 3.13] 18.0%
Lee YS 2013 — 2.28 [0.65; 8.01] 11.1%
Park JH 2012 — 2.34 [1.28; 4.27] 19.0%
Lim YC 2011 — 1.52 [0.58; 3.97] 14.3%

Random effects model — 2.65 [1.50; 4.70] 100.0%
Heterogeneity: $I^2 = 73\%$, $\tau^2 = 0.3558$, $p < 0.01$

0.1 0.5 1 2 10
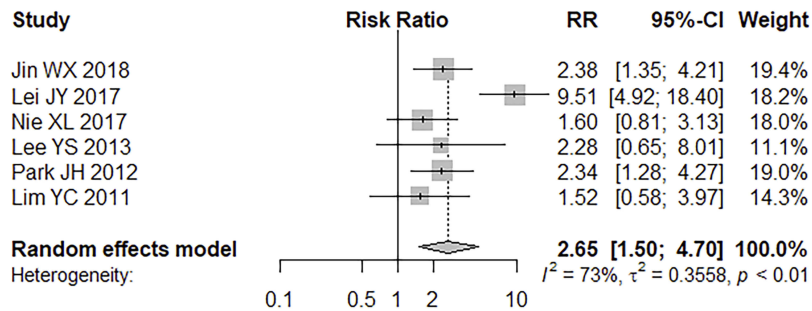
Figure 4 Forest plot of tumor size (≤1 cm).

Study | **Risk Ratio** | **RR** | **95%-CI** | **Weight**

Lee YS 2013 — 0.34 [0.04; 2.60] 27.5%
Lim YC 2011 — 0.33 [0.15; 0.75] 72.5%

Fixed effect model — 0.33 [0.15; 0.75] 100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$
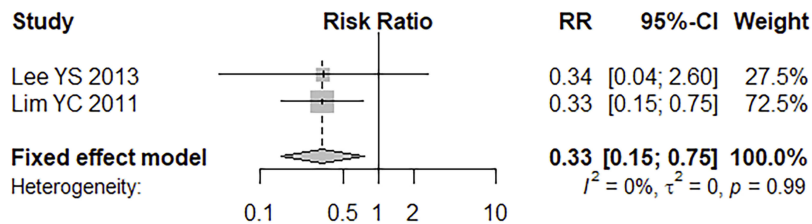
0.1 0.5 1 2 10

Figure 5 Forest plot of lymphovascular invasion.

Table 3 Location Of Skip Metastasis

Level	No. Of Studies	Proportion %	95% CI	P value Of Q-test	I^2
II	4	56.29	39.77–72.16	0.0162	70.9%
III	4	68.85	42.11–90.46	<0.001	89.2%
IV	4	15.95	0.66–42.34	<0.001	90.8%
V	4	3.67	0.72–8.11	0.2348	29.6%

and heterogeneity did not change obviously (P = 0.6362, I^2 = 0.0%). Extrathyroidal extension did not exhibit a significant association with skip metastasis (RR = 1.21, 95% CI = 0.88–1.66, P = 0.2422) but heterogenicity slightly increased (P = 0.1580, I^2 = 39.5%). Capsule invasion was not significantly associated (RR = 1.25, 95% CI = 0.33–4.69, P = 0.7460) and heterogenicity was still high (P = 0.0003, I^2 = 87.9%).

Sensitive Analysis

Sensitive analysis was conducted in factors where heterogenicity existed.

Heterogenicity of prevalence of skip metastasis did not decrease significantly when omitting any article. However, heterogenicity of tumor size significantly decreased (I^2 = 0.0%) and tumors (≤1 cm) existed a surprisingly higher odd for skip metastasis than those >1 cm (RR = 2.08, 95%

CI =1.51–2.86, P < 0.0001), when omitting one study.[26] Capsule invasion was not greatly associated with skip metastasis (RR = 0.64, 95% CI =0.30–1.36, P < 0.2437) after omitting one study (I^2 = 42.4%).[26] About location of skip metastasis, ratio was 65.19% (95% CI = 55.34–74.46%) in level II and 55.03% (95% CI = 44.98–64.89%) in level III and heterogenicity decreased remarkably (I^2 = 0.0%) when omitting this study.[11] Ratio was 5.17% (95% CI = 1.51–10.38%) in level IV and 3.67% (95% CI = 0.72–8.11%) in level V in both levels (I^2 = 0.0%) when omitting this article.[10]

Discussion

Lymph node metastasis has been reported in 30–80% PTC patients including PTMC.[38] It is controversial whether LNM is associated with a relatively poor prognosis. However, there is a consensus that LNM will increase the risk of lymph node recurrence and the reoperation of recurrence will increase operative complications and also increase medical costs to some degree.[39–41]

In our meta-analysis, the prevalence of skip metastasis was 12.02% (95% CI = 9.45–14.82%), and ranged from 5% to 25%, which could be explained by different sample sizes and regions. Most of the studies (11/18) had limited number of patients (<100); as a result, that the incidence of skip metastasis was very low,[20] especially when the rate of normal LNM was 20.9%. Therefore, as a rare event in PTC patients, it might be ignored by clinicians who advocated routine CLND given that the central compartment is the first site of lymph node metastasis. Then, LNM involves ipsilateral lateral compartment and followed by the contralateral lateral compartment and the mediastinal lymph nodes.[42,43] This regularity might also contribute to the ignorance of skip metastasis.

In our meta-analysis, tumors located in upper lode, no larger than 1 cm, and without lymphovascular invasion, were more likely to have skip metastasis, while multifocality, gender, age, bilaterality, thyroiditis, and ETE were not significantly associated with skip metastasis.

Tumors presented in the upper pole of thyroid were significant risk factors of skip metastasis. A tumor located in the upper pole thyroid may migrate along the superior thyroid artery to lateral lymph nodes and bypass central lymph nodes. This anatomical structure could explain higher possibility of metastasis in tumors in upper pole.

Tumors no larger than 1 cm were more frequent in skip metastasis. In addition, Nie et al found that tumors ≤0.5 cm tend to metastasize to the lateral neck instead of central compartment, while surgeries were proceeded in patients with a suspicious thyroid node ≤0.5 cm in the US report according to the ATA guideline.[14,25] It seems that the arguments were against common sense, but this result agreed with what was concluded by Machens et al that skip metastasis was observed to be more recurrent in less aggressive forms of PTC.[37]

This study found that tumors without lymphovascular invasion were more likely to have skip metastasis. We considered only 2 studies were included and one study[10] contributed mostly in fixed effect model (72.5%). Thus, this result may not be that much convictive.

In particular, age <45 years was often referred as a risk factor for CLNM, but So et al found this was not significantly related to LLNM.[20,44] In addition, age <45 years was also not associated with skip metastasis in our meta-analysis. According to 7th AJCC TNM staging system, 45 years old was cut-off age and patients aging <45 could have lower risk factors for LNM.[45] However, in view of the 8th AJCC TNM staging system published in 2018, the cut-off age has been changed to 55 years old. Maybe there is a lower risk of skip metastasis for patients <55, but no research paper found about this aspect till now, so the age of 45 was applied in this analysis. Tumor multifocality is present in more than 80% PTC patients.[46] However, tumor multifocality was unassociated with skip metastasis in our analysis. According to some previous reports, intraglandar spread was not associated with LLNM or skip metastasis.[10,25,30] Tumor multifocality and intraglandar spread were considered as strong association before, but there is current debate about whether tumor multifocality in PTC represented the intraglandular spread of a single tumor or de novo occurrence of distinct tumors. They both were not significant of skip metastasis. Our analysis showed ETE was not significantly in line with skip metastasis. However, ETE has higher incidence of nodal disease in both central and lateral compartment according to the previous studies. A meta-analysis indicated that ETE was significantly connected with CLNM (pooled OR=2.10, 95% CI=1.81–2.43, P < 0.001).[47] According to a meta-analysis in 2018, ETE presented a surprisingly high odds ratio for LLNM with or without CLNM (pooled OR = 3.22, 95% CI=2.21–4.70, P < 0.0001).[48] We thought PTC with ETE was more likely to spread to central lymph nodes due to its spatially shorter distance. Therefore, when LNM happened, the central compartment had already been affected. In summary, skip metastasis was not dominant among patients with ETE in our analysis.

Three hypotheses of skip metastasis were suggested by Lim et al in 2012: 1) Anatomical lymphatic channels existed that enables skip metastasis. 2) Normal anatomical lymphatic channels could be altered by neck surgeries. 3) There is false negative of limited or missed lymph node samples.[10] In our analysis, included studies ruled out patients with neck operation history, so skip metastasis appeared to have developed through normal lymphatic systems bypassing the central lymph node compartment in our opinion. Further preclinical studies could be conducted for micro lymph structures in order to confirm these hypotheses. The significance of association between skip metastasis and PTC remained unclear. Previous studies have found that skip metastasis was more frequent in less aggressive PTC such as low-density LLNM and PTMC.[10,11,37] Our included study found no significant difference of tumor-free survival of 450 PTC patients between 39 patients with skip metastasis and 411 patients without skip metastasis.[26] Considered the similar form of skip metastasis in non-small-cell lung cancer and colorectal cancer, previous studies evaluated and compared the impact of skip metastases on tumor recurrence and survival, and then they obtained negative results. This indicated that skip metastasis may have a positive impact on prognosis.[49,50] However, if this analogy was meaningful in PTC patients, it had to be studied afterward.

There are several limitations of our meta-analysis. Firstly, the number of included studies is limited, which may affect the result of our study, especially in the part of risk factor analysis. Secondly, all included studies were of retrospective design and our analysis was limited by their nature. Thirdly, most included studies were conducted in East-Asia except 3 articles which may cause some ethnic limitations.

Conclusion

In conclusion, the rate of skip metastasis was 12.02% in PTC patients with LNM. Therefore, the lateral compartment should be carefully examined especially for PTC patients who present primary tumors in the upper lobe, which have a primary tumor size ≤10 mm, even though they have no obvious evidence of CNM. Whether skip metastasis is related to less aggressive PTC needs further preclinical and clinical studies.

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Disclosure

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