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ORIGINAL ARTICLE

Predictive factors of lateral lymph node metastasis in solitary papillary thyroid microcarcinoma without gross extrathyroidal extension

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Summary *Background:* Solitary papillary thyroid microcarcinoma (PTMC) without gross extrathyroidal extension (ETE) were the main candidates for active surveillance (AS). Predictive factors of lateral lymph node metastasis (LLNM) in solitary PTMC without gross ETE were essential but still unknown.
Methods: Altogether, 171 patients of solitary PTMC without gross ETE were enrolled in our study and divided into two groups. Group A: 123 patients without lateral lymph node dissection (LLND) were considered to be LLNM negative because there was no lateral recurrence by at least 8-year follow up for all patients. Group B: 48 patients with LLND were considered to be LLNM positive which confirmed by postoperative pathology.
Results: Multivariate logistic regression showed male gender, upper location of tumor and diameter of tumor $\geq$7 mm to be predictive factors (odds ratio = 4.237 [confidence interval (CI) 1.365–13.149, p = 0.012; odds ratio = 2.933 [CI 1.117–7.700, p = 0.029; odds ratio = 4.557 [CI 1383–15.016, p = 0.013) for LLNM in solitary PTMC patients without gross ETE. Multiple level metastasis happened in 29 (60.42%) cases while single level metastasis in 19 (39.58%). Within the lateral cervical lymph node chain, level III nodes were consistently the most frequently involved (38/48, 79%), following by level IV (27/48, 56%), level II (25/48, 52%) and level V (5/48, 10%). Most interesting, there are 12 (12/48, 25%) skip metastatic (positive in lateral neck and negative in central neck) patients among LLNM positive group.

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Conclusions: Male gender, upper location of tumor and diameter of tumor ≥0.7 cm to be predictive factors of LLNM in solitary PTMC without gross ETE.

1. Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as a papillary carcinoma measuring ≤10 mm in its greatest dimension.[1] Annual percent changes about PTMC incidence between 1974 and 2013 in the United States is 9.3%, which leading to the proportion of papillary thyroid carcinoma (PTC) in endocrine malignancy raised year by year.[2] The increased diagnosis of PTMC by high quality ultrasound (US) with fine needle aspiration (FNA) and stable overall mortality highlight the overtreatment of PTMC. However, the treatment strategy of PTMC, especially active surveillance (AS) vs immediate surgery, is still controversial right now.

A 10-year observation in the Kuma Hospital of 1235 PTMC patients without immediate surgery found AS could be considered as the first-line management for low-risk PTMC.[3] Furthermore, Leboulleux et al also demonstrated that AS with curative intent should be considered in low-risk PTMC patients (cN0, no extrathyroid extension (ETE) by US evaluation, distant from the recurrent laryngeal nerve or trachea).[4] Because they believe that surgery can be delayed until the cancer shows signs of progression in order to avoid side-effects of operation.[4] However, many clinicians may not be ready to recommend AS to their patients, as they were worried about the risk of metastases, did not feel that evidence to support this approach was strong enough.[5] Until now, no clinicopathological features or molecular biomarkers can reliably differentiate the relatively small number of aggressive PTMC from the larger population of indolent PTMCs that will not have disease progression during their whole lives.[6]

In Kuma hospital's study of 1235 low-risk PTMC patients, 3.8% of the patients showed novel lymph node metastasis at 10 years of AS.[3] Another study from the same institution demonstrated that 6 of 1179 (0.5%) patients in AS group develop novel lymph node metastasis while only 2 of 974 (0.2%) cases in immediate surgery group.[7] According to 2015 American Thyroid Association (ATA) risk stratification, clinical apparent lymph node will re-stratified PTMC patient from low-risk to intermediate-risk.[8] The possibility of lymph node metastasis during AS is the major concern for clinicians and patients, although there is no strong evidence to affirm whether lymph node metastasis happens at the time of diagnosis or during the AS.

The incidence of lateral lymph node metastasis (LLNM) in solitary PTMC without gross ETE is low, however, solitary PTMC without gross ETE are the main candidates for AS. Predictive factors of LLNM in solitary PTMC without gross ETE is essential but still unknown. Thus, we aimed to carry out a retrospective study to investigate clinical risk factors for LLNM in order to minimize the potential risk of AS for these "high-risk" (high risk of LLNM) PTMC patients.

2. Materials and methods

2.1. Patients

The Ethical Committee of the 1st Hospital of the Jilin University approved this study. A total of 7975 consecutive PTMC patients, between January 2006 and December 2017, who underwent initially surgery for the treatment of PTMC at the First Hospital of Jilin University were retrospectively analyzed. Inclusion criteria for patient selection: 1): patient information found in a hospital database; 2): total thyroidectomy (TT) with unilateral or bilatera central lymph node dissection (CLND) as initial surgery; 3): postoperative pathological diagnosis of solitary PTMC without gross ETE; Exclusion criteria: 1): age < 18 years; 2): incomplete tumor resection/persistent disease; 3): lack of a preoperative FNA examination; 4): history of neck radiotherapy; 5): history of previous thyroid surgery. Finally, 171 solitary PTMC patients without ETE were enrolled in our study. Group A: 123 patients without lateral lymph node dissection (LLND) were considered to be LLNM negative group because there was no lateral neck recurrence by at least 8-year follow up for all patients. Group B: 48 patients with LLND were considered to be LLNM positive group because metastatic lymph nodes were confirmed by postoperative pathology. The flowchart of patient's selection was shown as Fig. 1. Moreover, we gave these 171 patients the written informed consents and informed them that their clinical records would be used in this study.

2.2. Treatment

Initially, clinical diagnosis was made by examination of US and FNA. US cervical mapping was done to evaluate thyroid tumor and neck lymph nodes by experienced, specially trained radiologist and surgeon preoperatively. For group A, we performed total thyroidectomy (TT), and unilateral or bilateral CLND without LLND. For group B, we performed TT, and bilateral CLND with LLND. All LLND was therapeutic because of metastatic LN in lateral neck which confirmed by US guided FNA. All patients enrolled in group A with at least 8-year follow up were diagnosed and treated before 2009. At that time, lack of any guideline or expert consensus contributed to the aggressive treatment for solitary PTMC without gross ETE, which also gave us the opportunity to design this experiment. Another reason for that we performed TT and prophylactic CLND for solitary PTMC without gross ETE was the patient had severe chronic thyroiditis and overtly hypothyroidism. CLND was performed to remove all lymph nodes and fibro-fatty tissue vertically from the hyoid bone to the thoracic inlet and

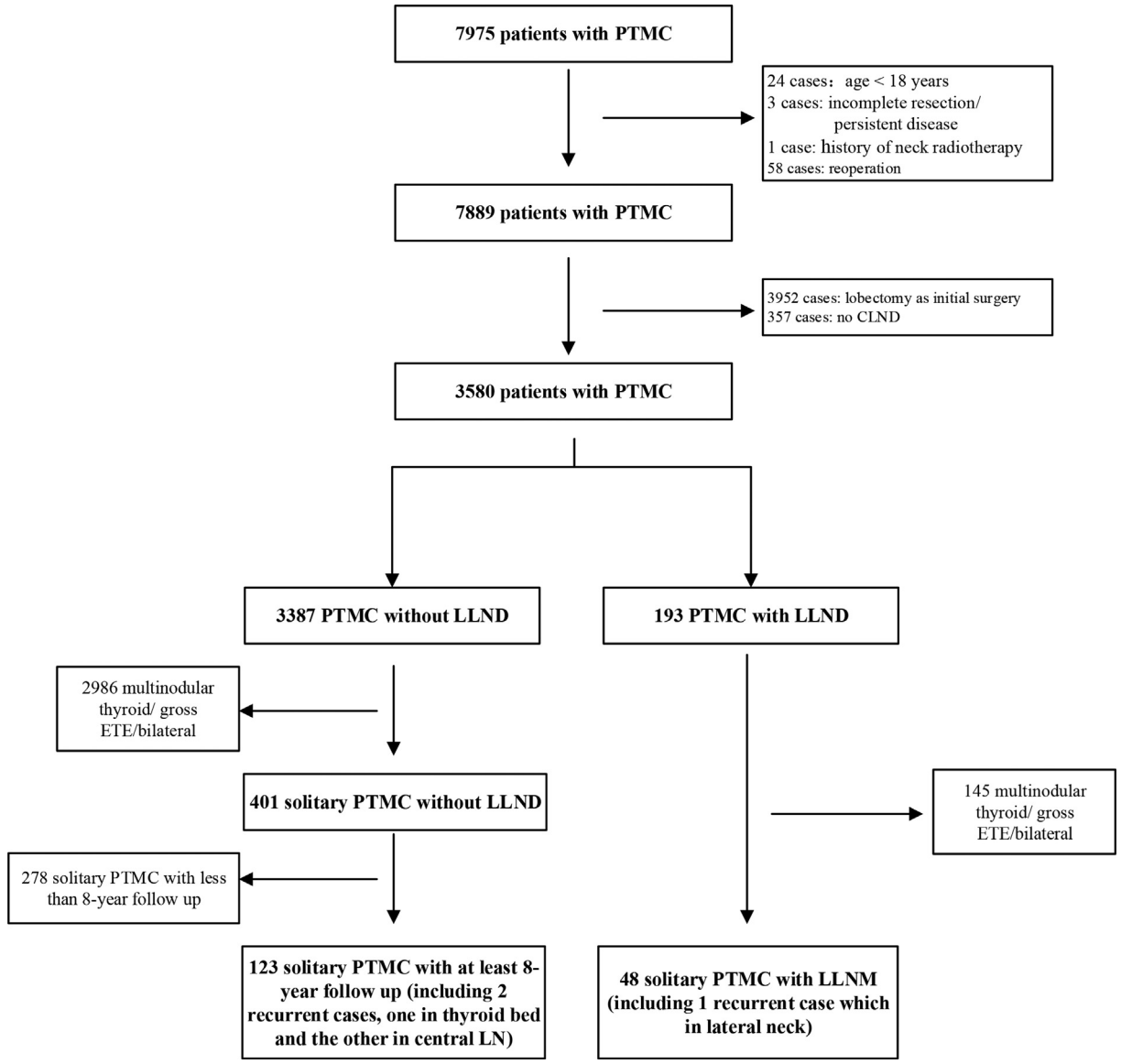

Figure 1 Flowchart of patient's selection in this study. There was no recurrence in lateral neck among 401 solitary PTMC without LLND whatever follow-up times. In LLNM negative group, we also included 2 recurrent cases whose recurrent sites were not lateral neck. In LLNM positive group, we included 1 patient with lateral lymph node recurrence. PTMC: papillary thyroid microcarcinoma; CLND: central lymph node dissection; LLND: lateral lymph node dissection; ETE: extrathyroidal extension; LN: lymph node; LLNM: lateral lymph node metastasis.

laterally from the common carotid artery to the midline of the trachea. Modified LLND including levels II—V was performed for patients with the preservation of the internal jugular vein, spinal accessory nerve and sternocleidomastoid muscle. RAI was not routinely recommended to patients. We explained both the risks and benefits of RAI ablation to patients and decision was made according to patients' preference.

2.3. Clinicopathological features

Demographic information about patient's clinical features like gender and age at diagnosis, family history of thyroid cancer, smoke addiction, alcohol addiction, and thyroid function (TSH level, FT3, FT4, Anti-TgAb, Anti-TPOAb) along with histopathological characteristics diameter of tumor, location of tumor, variants of PTMC, presence of chronic thyroiditis and lymph node metastasis as well as follow-up time were recorded. The upper location of tumor was determined according to the concordance between radiologist and surgeon.

2.4. Statistical analysis

Descriptive statistics were reported as a frequency with a percentages for nominal variables and a mean with a

standard deviation for continuous variables. To identify differences between groups for specific variables, SPSS version 22 software (SPSS Inc, Chicago, IL) was used for statistical analysis. Nominal variables was performed by Pearson's chi-square test or Fisher's test while continuous variables were compared by Mann–Whitney U test. All variables in univariate analysis were enrolled in multivariate logistics regression analysis for exploring predictive factors. A p value < 0.05 was considered statistically significant.

3. Results

Altogether, 171 patients of solitary PTMC without gross ETE were enrolled in our study, in which 123 cases and 48 cases were in group A and B respectively. The clinicopathological features of the enrolled patients (N = 171) were shown in Table 1. Compared between group A and B, male gender, diameter of tumor, location of tumor, total number of metastatic central lymph node (CLN) and central lymph node metastasis (CLNM) ratio as well as RAI ablation were found to be different significantly between two group patients (p = 0.000, 0.000, 0.000, 0.011, 0.000,0.000).

All variables in univariate analysis were enrolled in multivariate logistics regression analysis (Table 2), which showed male gender, upper location of tumor and diameter of tumor to be predictive factors (odds ratio = 4.237 [confidence interval (CI) 1.365–13.149, p = 0.012; odds ratio = 2.933 [confidence interval (CI) 1.117–7.700, p = 0.029; odds ratio = 4.557 [confidence interval (CI) 1383–15.016, p = 0.013) when compared group A and B. Metastatic CLN and CLNM ratio were not predictors of LLNM in solitary PTMC without ETE. No other risk ratios obtained were of interest.

In group B, the distribution of LLNM was shown in Table 3. Multiple level metastasis happened in 29 (60.42%) cases while single level metastasis in 19 (39.58%). Within the lateral cervical lymph node chain, level III nodes were consistently the most frequently involved (38/48, 79%), following by level IV (27/48, 56%), level II (25/48, 52%) and level V (5/48, 10%). Most interesting, there are 12 skip metastatic (positive in LLN and negative in CLN) patients among group B. And the details of patients were shown in Table 4.

4. Discussion

Miyauchi et al from Kuma Hospital, have made great contributions and pioneering extensive works in the field of AS in PTMC. However, a significant challenge of AS lies in the ability to exclude patients who have tumors that are likely to grow, spread to regional lymph nodes, or metastasize to distant sites.[6] Focusing on this concern, Hirokawa M et al demonstrated three characteristics (intraglandular dissemination, psammoma bodies in normal thyroid tissue, and a high Ki-67 labeling index) on pathological examination as indicators of progressive PTMC.[9] The former two features were mostly associated with appearance of node metastasis, while a high Ki-67 labeling index was mostly associated with tumor growth.[9] However, these pathological features can't be identified cytologically or ultrasonographically before surgery.

Metastasis to regional cervical lymph nodes occur early and frequently in patients with differentiated thyroid cancer.[10] Studies suggested that nodal disease was associated with poorer outcomes, particularly in older patients.[11,12] Risk of lymph node recurrence and/or distant metastasis (DM) increased 6.5-fold in patients with neck lymph node metastasis at presentation.[13] Jeon MJ et al summarized 12 PTMC with DM and found all DM patients had tumor tumors >0.5 cm and cervical lymph node metastasis at their initial surgery. Ten patients of 12 PTMC with DM had LLNM.[14] The study may highlight the probability of that distant metastatic cells derived from primary tumor as well as metastatic lymph nodes. It also supports the concept of a metastatic cascade, suggesting that cancers sequentially progress from primary tumors to lymph nodes and then systematically to distant organs with sequential mutations.[15] Another study also demonstrated that indolent cancer cells from the primary tumor developed aggressive features because of certain specific LN microenvironment in metastatic lymph nodes. The aggressive cells in lymph node may be the major source of distant metastasis and promote systemic progression.[16] There was no doubt that no patients showed life-threatening tumor progression during the active surveillance or after the rescue surgery.[3,4,17] However, as the major candidate of AS, solitary PTMC without gross ETE should be risk stratified according to predictive factor for LLNM. On one hand, we can give patients more information to help them to make decision about whether they will attend AS or not. Moreover, evidence is not strong enough to say LLNM happens at the time of diagnosis or during the AS although LLNM could occur even after immediate surgery. On the other hand, we can increase frequency of ultrasound and decrease cutoff of FNA for enlarged lymph node according to their risk stratification for early diagnosis and treatment.

Group A patients are solitary PTMC without gross ETE who don't had LLND. We used these patients who followed up at least 8 years to minimize the possibility of occult LLNM because they were not treated with LLND. Moreover, among 401 solitary PTMC without ETE, no recurrence in lateral neck was seen whatever their follow-up times were (Fig. 1). In our study, we found male gender, upper location of tumor and diameter of tumor ≥0.7 cm to be predictive factors of LLNM in solitary PTMC without gross ETE. Consistent with published articles, Liu et al also found upper portion location was one of the risk factors for LLNM in PTMC.[18] And Min et al demonstrated that PTMC in male patients or upper lobe had the higher risk of LLNM although they included all PTMC not just solitary ones without ETE.[19] However, in Ito's study, they found young age (<40 years) was the only predictor of novel lymph-node appearance of low-risk PTMC under observation using multivariate analysis.[20] However, in our study we don't find significant difference in age no matter as polytomous pattern like Ito's study or continuous variant. The reason would be as following: 1): The cases enrolled in our study is small because of the low incidence of solitary PTMC with LLNM. 2): In Ito's study, they took multiplicity into multivariate analysis but not tumor location. In our study, we just investigated solitary PTMC patients who will be the major

Table 1 Clinicopathological characteristics of solitary PTMC patients.

	Group A (N = 123)	Group B (N = 48)	A vs B
			P Value
Gender			
Female	108 (87.8)	30 (62.5)	
Male	15 (12.2)	18 (37.5)	**0.000**
Age			
Polytomous			
<40 yr	38 (30.9)	22 (45.8)	
40～59	74 (60.2)	23 (47.9)	
≥60 yr	11 (8.9)	3 (2.3)	0.187
Continuous (mean ± SD)	44.21 ± 9.21	41.31 ± 12.66	0.116
Family history of thyroid cancer			
No	118 (95.9)	43 (89.6)	
Yes	5 (4.1)	5 (10.4)	0.219
Smoke addiction			
No	113 (91.9)	43 (89.6)	
Yes	10 (8.1)	5 (10.4)	0.862
Alcohol addiction			
No	115 (93.5)	47 (97.9)	
Yes	8 (6.5)	1 (2.1)	0.434
Preoperative thyroid function (mean ± SD)			
TSH level	3.19 ± 1.09	2.99 ± 2.30	0.565
FT3	4.23 ± 0.18	4.92 ± 0.76	0.598
FT4	16.33 ± 2.87	16.67 ± 2.30	0.318
Preoperative Anti-TgAb			
High	36 (29.3)	11 (22.9)	
Normal	87 (70.7)	37 (77.1)	0.403
Preoperative Anti-TPOAb			
High	30 (24.4)	8 (16.7)	
Normal	93 (75.6)	40 (83.3)	0.275
Diameter of tumor			
Dichotomous			
<7 mm	90 (73.2)	21 (43.8)	
≥7 mm	33 (26.8)	27 (56.2)	**0.000**
Continuous (mean ± SD)	0.51 ± 0.11	0.7 ± 0.24	**0.003**
Location of tumor			
Upper	13 (10.6)	18 (37.5)	
Non-upper	110 (89.4)	30 (62.5)	**0.000**
With chronic thyroiditis			
Absent	82 (66.7)	29 (60.4)	
Present	41 (33.3)	19 (39.6)	0.442
Variants of PTMC			
Classical	123 (100)	47 (97.9)	
Follicular	0 (0)	1 (2.1)	1.000
Total number of removed CLN (mean ± SD)	6.99 ± 3.78	7.27 ± 5.18	0.996
Total number of metastatic CLN (mean ± SD)	1.37 ± 1.44	2.48 ± 2.66	**0.011**
Total number of removed LLN (mean ± SD)	0	18 ± 12.3	NA
Total number of metastatic LLN (mean ± SD)	0	3.94 ± 4.63	NA
CLNM ratio			
<0.5	103 (83.7)	28 (58.3)	
≥0.5	20 (16.3)	20 (41.7)	**0.000**
Follow-up months (mean ± SD)	109 ± 7	103 ± 8	0.562
RAI ablation	3	37	**0.000**
Recurrence	2 (thyroid bed and central LN)	1 (lateral neck)	1.000

PTMC: papillary thyroid microcarcinoma; CLN: central lymph node; LLN: lateral lymph node; CLNM ratio: central lymph node metastasis ratio (Positive lymph node number/sum lymph node number); SD: standard deviation; RAI:radioactive iodine.

Table 2 Multivariate logistic regression analysis of risk factors for LLNM.

Factors analyzed	Comparison between group A vs B	
	Odds ratio (95% CI)	*P* value
Gender	4.237 (1.365—13.149)	**0.012**
Age	3.185 (0.985—5.695)	0.521
Family history of thyroid cancer	1.002 (0.156—7.352)	0.685
Smoke addiction	0.989 (0.115—2.032)	0.451
Alcohol addiction	0.655 (0.238—2.339)	0.568
Preoperative thyroid function		
TSH	8.512 (0.123—10.985)	0.351
FT3	5.168 (0.698—8.354)	0.526
FT4	4.625 (0.788—7.369)	0.598
Preoperative Anti-TgAb	1.982 (0.916—3.658)	0.268
Preoperative Anti-TPOAb	2.214 (0.856—5.325)	0.321
Diameter of tumor	2.933 (1.117—7.700)	**0.029**
Location of tumor	4.557 (1.383—15.016)	**0.013**
With chronic thyroiditis	0.986 (0.624—3.689)	0.421
Variants of PTMC	1.369 (0.654—3.699)	0.712
Removed CLN	0.865 (0.432—2.111)	0.389
Metastatic CLN	0.885 (0.685—1.142)	0.348
CLNM ratio	2.287 (0.645—8.114)	0.200

LLNM: lateral lymph node metastasis; PTMC: papillary thyroid microcarcinoma; CLN: central lymph node; CLNM ratio: central lymph node metastasis ratio (Positive lymph node number/sum lymph node number).

candidates for AS and took tumor location as variant for analysis. 3): In Ito's study, their novel lymph node appearance included both lateral and central neck. In our study, we just explored solitary PTMC with LLNM.

Considering distribution of LLNM in solitary PTMC without gross ETE, multiple level metastasis happened in 29 (60.42%) cases while single level metastasis in 19 (39.58%). In another study which summarized all PTMC patients with LLNM, they found multiple level metastasis exist in 54/62 (87.10%) cases.[18] Selective LLND should not be recommended even when the patient was diagnosed LLNM only in solitary PTMC without gross ETE. Within the lateral cervical lymph node chain, level III nodes were consistently the most frequently involved (38/48, 79%), following by level IV (27/48, 56%), level II (25/48, 52%) and level V (5/48, 10%). Moreover, there are 12 skip metastatic (positive in LLN and negative in CLN) patients among group B. The incidence of skip metastasis is around 20% in PTC.[21] Predictive factors of skip metastasis, which reported mostly are PTMC and tumor located in upper lobe.[21,22] In our study, all patients were PTMC and 18/48 (37.5%) tumors located in upper portion of thyroid lobe. The clinic pathological features of these 18 patients with upper tumor were listed in Table 5. That may explain why the incidence of skip metastasis (12/48, 25%) is a little higher than other studies reported.

There are some limitations in our study. The first limitation is the small number of patients in the study population; Due to the LLNM incidence of solitary PTMC without gross ETE is low, we just summarized 48 patients between January 2006 and December 2017. Another limitation is that we don't divided the location of tumor into upper, middle and lower. There is no exact definition of tumor location in thyroid cancer. We decided it according to concordance between radiologist and surgeon. We found high consistency in upper tumor but disconcordance in middle and low tumor. So we just divided location of tumor into two categories (upper and non-upper). Despite these limitations, our study was the first article to analyze predictors of LLNM in solitary PTMC without gross ETE to our knowledge. Moreover, all the predictors we found like male gender, tumor diameter and location could be identified before surgery using imaging like US and CT scan. We think it has important implications for AS in PTMC management and provides significant information for PTMC guideline formation.

Table 3 Metastatic lateral lymph nodes distribution.

Cervical level (%)	Cases (% of cases)
Single level (39.58%)	
II	4 (8.33%)
III	11 (22.92%)
IV	3 (6.25%)
V	1 (2.08%)
Two levels (27.08%)	
II+III	4 (8.33%)
II+IV	2 (4.17%)
III+IV	6 (12.5%)
III+V	1 (2.08%)
Three levels (29.16%)	
II+III+IV	13 (27.08%)
III+IV+V	1 (2.08%)
Four levels (4.17%)	
II+III+IV+V	2 (4.17%)

Table 4 The characteristics of skip metastasis cases.

Patient	Age/Sex	Max Tumor size (mm)	Family history	Location of tumor	chronic thyroiditis	RCLN	MLLN	RLLN	LLNR	LLN distribution	Follow up (month)	Outcome
1	28/F	0.8	−	+	+	16	1	9	−	II	55	Cure
2	30/F	0.4	−	+	−	12	1	10	−	III	57	Cure
3	31/M	0.6	+	+	−	7	1	17	−	III	101	Cure
4	38/F	0.7	−	−	−	5	3	21	−	II、III、V	78	Cure
5	41/F	1.0	−	−	+	4	1	10	−	III	69	Cure
6	43/F	0.7	−	+	+	12	2	15	−	III	99	Cure
7	43/F	1.0	−	−	+	6	2	30	−	III、V	101	Cure
8	43/M	0.7	−	−	+	9	10	27	−	II、III、IV	83	Cure
9	51/F	0.8	−	+	−	6	1	17	−	III	115	Cure
10	54/M	0.5	−	−	−	5	3	23	−	III、IV	58	Cure
11	61/M	0.4	−	−	−	4	3	26	−	III、IV、V	92	Cure
12	78/M	0.6	−	−	−	4	1	16	−	III	68	Cure

Location of tumor (Upper was defined as positive while non-upper as negative); RCLN: removed central lymph node; MLLN: metastatic lateral lymph node; RLLN: removed lateral lymph node; LLNR: lateral lymph node ratio (MLLN/LLNR); LLN: lateral lymph node.

Table 5 The characteristics of LLNM positive patients with upper located tumor.

Patient	Age/Sex	Max Tumor size (mm)	Family history	chronic thyroiditis	MCLN	RCLN	MLLN	RLLN	LLN distribution	Follow up (month)	Outcome
1	28/F	0.8	−	+	0	16	1	9	II	55	Cure
2	30/F	0.4	−	−	0	12	1	10	III	57	Cure
3	31/M	0.6	+	−	0	7	1	17	III	101	Cure
4	28/F	0.8	−	+	1	5	2	15	II、III	112	Cure
5	38/M	0.7	−	−	2	6	1	12	III	114	Cure
6	43/F	0.7	−	+	0	12	2	15	III	99	Cure
7	67/F	0.6	−	−	2	7	2	11	III	108	Cure
8	45/F	0.7	−	−	3	10	1	9	II	103	Cure
9	51/F	0.8	−	−	0	6	1	17	III	115	Cure
10	35/F	0.5	−	−	2	7	1	19	II	115	Cure
11	38/M	0.4	−	−	3	9	2	22	III、IV	113	Cure
12	42/F	0.8	+	+	4	10	3	26	II、III、IV	125	Cure
13	44/F	0.7	−	+	5	9	4	27	II、III、IV	99	Cure
14	56/F	0.6	−	−	4	11	3	16	II	117	Cure
15	29/M	0.6	−	−	3	9	2	19	III	98	Cure
16	52/F	0.6	+	+	1	8	3	22	II、III	108	Cure
17	59/F	0.8	−	−	2	12	5	24	II、III、IV	99	Cure
18	55/F	0.9	−	−	2	11	4	28	II、III	117	Cure

Location of tumor (Upper was defined as positive while non-upper as negative); RCLN: removed central lymph node; MLLN: metastatic lateral lymph node; RLLN: removed lateral lymph node; LLNR: lateral lymph node ratio (MLLN/LLNR); LLN: lateral lymph node.

5. Conclusion

Taken together, male gender, upper location of tumor and diameter of tumor $\geq$0.7 cm to be predictive factors of LLNM in solitary PTMC without gross ETE. Modified LLND with level II-V was recommended when LLNM was diagnosed in solitary PTMC without gross ETE because of high incidence of multiple level metastasis.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

Guang Chen contributes to study design and critical revise manuscript. Xi Zhang and Li Zhang contribute to collect original data, analyse and interpret data, and write manuscript. Shuai Xue and Peisong Wang contribute to minor revision for the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.07.003.

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