



SKIP METASTASES IN PAPILLARY THYROID CARCINOMA – PREVALENCE, PREDICTIVE AND CLINICOPATHOLOGICAL FACTORS

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SUMMARY – Background: Cervical lymph node metastases are frequently found in papillary thyroid carcinoma (PTC) and occur in a stepwise fashion. Skip metastases that omit the central compartment and spread initially in lateral neck levels are present in a certain share of patients, and their significance is poorly understood. The aim of this prospective study was to identify their possible predictors and clinicopathological factors in a group of patients with PTC with lateral lymph node (LLN) metastases. **Methods:** We enrolled 68 patients with PTC with preoperatively evaluated LLN metastases who underwent total thyroidectomy with lateral lymph node dissection between 2011 and 2018. We analysed the clinicopathological features and pattern of dissemination of continuous and skip metastases. **Results:** The prevalence of skip metastases was 23.5%. Compared with the continuous metastases group, the patients were older, had primary tumors that were more often situated unilaterally, and had smaller primary tumor size. Level II was less often involved, and none of the patients with skip metastases had all LNN positive ($p = 0.05$). **Conclusion:** Skip metastases occur more frequently in older patients and display certain clinicopathological features like smaller size of the primary tumor and dissemination in less lateral neck levels. In the view of the fact that they are found rather frequently, lateral neck regions should be meticulously investigated in patients with PTC without central lymph node (CLL) metastases.

Key words: *skip metastases, clinicopathological features, papillary thyroid carcinoma, lateral neck metastases*

Introduction

Cervical lymph node metastases are relatively common in papillary thyroid cancer (PTC) (1) and occur in 30-80% of patients (2). They have a characteristic way of disseminating initially in the pretracheal, paratracheal, and upper mediastinal lymph nodes (central neck lymph nodes, CLN). Afterwards, tumor cells spread to ipsilateral neck lymph nodes (LLN), levels II to V. Finally, they disseminate in contralateral lymph nodes of the neck (3-7). There is also an unconven-

tional pathway in which tumor cells omit the CLL and metastases first occur in LLN (8,9). This kind of metastases is termed a skip metastasis, and it is hypothesized that they display different clinicopathological features compared with continuous metastases (10) and therefore have a different prognosis (11). There are several studies and meta-analyses in the literature regarding PTC skip metastases, but they were either performed on a smaller number of patients or larger groups from multiple hospitals; some of them with recurring patients and/or treated by different surgeons (12-14). The aim of our study was to determine the general occurrence, predictors, and association of skip metastases with certain clinicopathological features in a group of patients with primary PTC with proven

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LLN metastases. Our results will provide further insight into management options and altering the treatment according to our findings.

Patients and methods

This prospective study was approved by the local Institutional Review Boards. We enrolled all patients with PTC who had LLN metastases. The patients were surgically treated between 2011 and 2018 at the University Hospital Centre, Department of Otolaryngology, Head and Neck Surgery. All surgeries were carried out by the same surgeon. All of the patients had previously untreated PTC with LLN metastases, preoperatively confirmed and evaluated by ultrasonography (US) for tumor size, location, and the presence of lymph node metastases (LNM). LNM were afterwards investigated with fine needle aspiration biopsy (FNAB). Exclusion criteria were prior thyroid surgery or radiotherapy, extensive PTC with distant metastases, or other thyroid malignancy. The patients underwent total thyroidectomy alongside with CLN and LLN dissection. Levels of the neck were categorized according to the American Head and Neck Society (15). Specimens were afterwards subjected to pathological analysis (PA). Skip metastases are defined as lateral lymph node metastasis with no positive nodes in the central compartment. Extracapsular spread refers to spreading beyond the lymph node capsule. All results are presented as mean \pm SD if not stated otherwise.

Ethics

This study was approved by the Zagreb University Hospital Centre Bioethical Board adhering to the Helsinki Declaration of 2013. All patients have read and signed a written consent document.

Statistics

SPSS version 14 (IBM, Chicago, IL, USA) was used to perform statistical analysis. Associations between skip metastases in the LLN and several clinicopathologic factors were assessed with univariate analyses using the Pearson Chi-square test or the Fishers exact test. Continuous variables, such as primary tumor size and number of positive lymph nodes according to the presence or absence of skip metastasis were

evaluated using the t-test. Statistical significance was defined as $P < 0.05$.

Results

Patient demographics

Out of 100 patients, 68 met the requirements for our study. Out of 32 patients that did not meet the requirements, 15 underwent surgery prior to the study, 9 underwent radiotherapy, 7 underwent surgery and radiotherapy, and one had an extensive tumor with distant metastases. Mean age was 36.5 years (range 11-74) and the male to female ratio was 1:4 (17 vs 51). The mean primary tumor size was 2.04 cm (\pm 1.65, range 0.2-7.0 cm); 26.5% percent of tumors were smaller than 1 cm in diameter. Tumors were mostly situated in the right lobe (44.11%) while localization in the left lobe was observed in 26.4% of the patients and bilateral location in 29.4% of the patients. Multicentric growth was found in 73% of the patients.

Mean number of total dissected lateral lymph nodes was 33.73 (\pm 17.66, range 10-107), while the number of positive nodes was 5.07 (\pm 4.03, range 1-19).

Level III was involved most often (79.4%), followed by level IV, level II, and V (Table 1). Skip metas-

Table 1. Demographics and clinical characteristics

Variables	Results
Age	36.5 \pm 16.3 (11-74)
Gender	
Male	25%
Female	75%
Mean primary tumor size	2.04 cm* \pm 1.66 (0.2-7.0)
Microcarcinoma	35.3%
Localization	
Left	26.47%
Right	44.11%
Bilateral	29.41%
Multifocality	73.5%
Extrathyroidal spread	54.4%
Level II	48.5%
Level III	79.4%
Level IV	73.5%
Level V	30.0%

Table 2. Clinicopathological factors of skip compared with continuous LLN metastases

Variables	Skip metastases	Continuous metastases	p value
Total (n=68)	23.5%	76.5%	
Mean age	54.0±16.7	33 ± 15.26	p = 0.02*
> 45	62.5%	30.7%	p = 0.042*
Gender (%men)	31.25% men	23% men	p = 0.06
Localization			
Left	31.25%	25%	p = 0.62
Right	50%	42.3%	p = 0.68
Bilateral	18.75%	32.7%	p = 0.014*
Tumor size	1.49 cm ± 0.78	2.211 cm ± 1.81	p = 0.13
Microcarcinoma	31.25%	25%	p = 0.620
Multicentric	62.5%	76.9%	p = 0.33
Extrathyroidal spread	56.25%	53.84%	p = 0.86
Lateral LN			
Total	516 (mean 32.25 ± 14.14)	1778 (34.20 ± 18.7)	p = 0.7
Metastatic	58 ± (11.24%)	278 ± (16.14%)	p = 0.1
Metastatic nodes			
Level II	18.75%	57.60%	p = 0.006 *
Level III	62.5%	84.60%	p = 0.05 *
Level IV	62.5%	76.92%	p = 0.25
Level V	31.25%	30.70%	p = 0.97
All levels positive	0.0%	17.30%	p 0.05 *
Extracapsular (LN)	54.9%	53.84%	p = 0.86

tases were present in 23.5% of patients. There were 8 patients (11.8%) with false-negative ultrasonography finding of the central neck levels prior to pathological analysis.

Prevalence and distribution of skip metastasis on the lateral neck

We compared the clinicopathological characteristics of patients with skip and continuous metastases (Table 2). Patients with skip metastases were significantly older (median age: 54 vs 33 years). Skip metastases were more common in men than in women (31.25% vs 23.0%).

Regarding tumor localization, we did not find a significant difference in prevalence of localization in either lobe, but the primary tumors with skip metastases showed a trend of being situated bilaterally less often (18.75% vs 32.70%). The mean size of primary tumors was smaller in the skip metastases group (1.49 cm vs 2.21 cm). There was however no significant dif-

ference in microcarcinoma frequency between the two groups. The number of harvested lateral lymph nodes was similar (32.25% vs 34.20%), but the mean number of positive nodes was smaller in the skip group (11.24% skip vs 16.14% continuous). In contrast to the continuous metastases group, LNN in the skip metastases group had a smaller proportion of positive nodes in each level, especially in level II ($p = 0.006$) and somewhat in level III ($p = 0.05$) (Table 2). Moreover, none of the patients in that group had all LLN levels positive, while 17,3% of patients in the continuous metastases group had all LLN levels positive ($p = 0.05$).

Frequencies of tumors with extrathyroidal growth and positive lymph nodes with extracapsular spread of metastases were similar in both groups.

Discussion

The thyroid gland has an extensive and rich lymphatic drainage which makes predicting metastases

dissemination quite challenging. It is generally accepted that tumor cells spread in a stepwise fashion: initially into pretracheal, paratracheal, and upper mediastinal LN, then into ipsilateral neck lymph nodes, and finally to contralateral neck regions (6). Some authors even theorized that lymphatic systems of the lobes are separated (16), but practice reveals that contralateral regional metastases are possible (17). Skip metastases, which initially disseminate in the lateral region, are not so rare, and they occur in 6.5-27.5% of PTC with LLN metastases (8,14,18-20). Our result (23%) falls into the upper end of that range. Ito *et al.* even proposed that continuous spread does not exist and that there is an equal chance for continuous and skipping dissemination. Their explanation was based on the finding that the percentage of solely LLN and CLN metastases was similar (18.1% vs 22.9%). In another study by Ito, it was 29.0% vs 33.3% (21,22).

LLN metastases in PTC are associated with a higher risk of regional recurrence (9,23). Re-operation increases the risk of intra- and postoperative complications as well as overall medical costs (3,4,24,25); surgeons are therefore confronted with the question whether to perform para- and pretracheal dissection in patients with present LLN metastases and absent CLN metastases. The significance of PTC skip metastases is still not fully understood, and their wide range of prevalence between different studies could be a result of studies which were limited by low patient numbers and the inclusion of primary and recurrent patients in their research populations (26).

Our results show that the mean number of harvested positive LLN was smaller in the skip metastases group and that there was a tendency of fewer positive nodes in each level. Another finding of ours is that none of the patients with skip metastases had all LLN positive, while that was not the case in the continuous metastases group. We did not find such data in similar studies on PTC with skip metastases, but this can be explained by characteristics of PTC skip metastases that seem to induce better prognosis (8,14).

According to some theories, PTC skip metastases occur when the primary tumor is situated in the upper poles of the thyroid gland, where the lymphatic drainage follows the pathway of the upper thyroid artery. Another possibility is that it spreads *per continuitatem* in the lateral regions (27,28). In our case, it is evident that mostly middle and lower LLN levels were affect-

ed in the skip group, and especially level II (and to some extent level III) had significantly fewer positive nodes (Table 2). This is different from studies which stated that skip metastases disseminated more frequently in level II (14), possibly as a result from the aforementioned hypothetical lymphatic drainage situated around superior thyroid artery (14,29). In all our patients, we found skip metastases only in level IIa and none in level IIb. From our results, it is clear that continuous metastases – as compared with skip metastases – disseminate more evenly in all LLN levels.

We obtained a similar number of lymph nodes in each patient group, therefore excluding the probability of false-negative data as a result of inadequate lymph node sampling or possible previous surgeries.

Primary tumor size was another clinicopathological feature which showed a trend of being smaller in the skip group. Similar results can be seen in most of the studies in the literature, with the tumor size being inversely associated with the probability of skip metastases (11,14,26).

Over 70% of all our patients had multifocal tumor growth, which is quite a high percentage as compared with other studies (30). Multifocality was, however, less often present in patients with skip metastases, which is to some extent similar to findings by Nie *et al.* (11). Extracapsular LN spread was another factor inversely correlated with skip metastases in a study by Lim and Koo (26), but we did not find significant differences between our groups. These facts have led to several authors concluding that skip metastases could mean better prognosis and could be associated with less aggressive forms of PTC (8,11). This would in fact be in concordance with skip metastases outcomes in other primary tumor localizations such as colorectal or small cell lung cancer, where they positively affect survival rate (31,32).

In the present study, we found a significantly higher chance for skip metastases in older patients (62.5% vs 32.7%, $p = 0.02$) who were above 45 years of age. It is known that higher age is negatively correlated with prognosis in PTC (33,34) and that it does not affect the tumor metastasizing potential significantly (35), which is contradictory to the previously mentioned hypothesis (8,11). On the other hand, studies have also shown that there is a smaller chance for continuous LLN metastases in older patients (36).

Possible limitations of our study include the lack of information on the exact tumor location in the thyroid gland. However, we found a smaller proportion of bilateral tumors in the skip metastases group. Some studies found localization in upper lobe to be associated with skip metastases (13,14), but that was also demonstrated for increased frequency of continuous LNM in other studies (37). Another possible drawback is the fact that lateral neck dissection (levels II-IV) which we performed was therapeutical rather than prophylactic. According to one study, latent LLN metastases which were not found preoperatively clinically nor with US were found after PA in over 50% of patients who underwent prophylactic lateral dissection (22). Therefore, including such patients might have revealed other possible predictive factors.

Conclusion

In summary, our results showed that PTC with skip metastases tend to present different clinicopathological characteristics than PTC with continuous metastases. Primary tumors were often smaller in size, displayed bilateral growth less often, and occurred more frequently in older patients. Moreover, skip metastases seem to less frequently metastasize in certain lateral neck levels, and they almost never affect all lateral neck levels.

All of this implies the need for thorough lateral neck regions investigation in patients with PTC who do not have central neck levels metastases, bearing in mind the aforementioned facts. Further prospective studies with a larger number of patients with PTC with skip metastases should be undertaken to assess the impact on patient outcomes and other possible predictive factors.

Author's note

This study was approved by the University Hospital Centre Zagreb, Zagreb, Bioethical Board adhering to the Helsinki Declaration of 2013. All of the authors have read and approved the manuscript.

Declaration of conflicting interests

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Abbreviations:

- CLL – central lymph nodes
- FNAB – fine-needle aspiration biopsy
- LN – lymph nodes
- LLN – lateral lymph nodes
- LNM – lateral neck metastases
- PTC – papillary thyroid carcinoma
- PA – pathological analysis
- SD – standard deviation
- US – ultrasonography

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Sažetak

PRESKAČUĆE METASTAZE PAPILARNOG KARCINOMA ŠTITNJAČE
– UČESTALOST, PREDIKTIVNI I KLINIČKO-PATOLOŠKI ČIMBENICI*B. Miličić, R. Prstačić i D. Prgomet*

Uvod: Metastaze u limfnim čvorovima vrata čest su nalaz kod papilarnog karcinoma štitnjače i pojavljuju se određenim redoslijedom. Tzv. „skip“ metastaze koje „preskaču“ centralni odjeljak te se šire inicijalno u lateralne regije vrata mogu se naći u određenom broju tih pacijenata, a njihov značaj nije još dobro istražen. Cilj ove prospektivne studije jest identificirati njihove moguće prediktore i kliničko-patološke značajke u skupini pacijenata s lateralnim metastazama papilarnog karcinoma štitnjače. *Metode:* U studiju je bilo uključeno 68 pacijenata s papilarnim karcinomom kojima su prethodno verificirane lateralne metastaze te su bili podvrgnuti totalnoj tiroidektomiji uz lateralnu disekciju vrata, u razdoblju od 2011 do 2018 godine. Analizirane su i uspoređene kliničko-patološke značajke te obrazac metastaziranja kontinuiranih i skip metastaza. *Rezultati:* Učestalost skip metastaza bila je 23,5%. U usporedbi sa skupinom s kontinuiranim metastazama, ti pacijenti bili su stariji, primarni tumori bili su rjeđe bilateralni, te su bili manjih dimenzija. Regija II bila je rjeđe zahvaćena, te nitko od tih pacijenata nije imao sve regije zahvaćene metastazama. *Zaključak:* Skip metastaze pojavljuju se češće u starijih pacijenata te pokazuju određene kliničko-patološke značajke kao što su manja dimenzija primarnih tumora, te diseminacija u manje lateralnih regija vrata. Uzevši u obzir da se takve metastaze relativno često susreću, lateralne regije vrata trebale bi se temeljito istražiti u pacijenata s papilarnim karcinomom štitnjače bez metastaza u centralnim odjeljcima vrata.

Ključne riječi: skip metastaze, papilarni karcinom štitnjače, kliničko-patološke značajke, lateralne metastaze vrata