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ORIGINAL ARTICLE

The influence of papillary thyroid microcarcinomas size on the occurrence of lymph node metastases

Merima Goran[1,2], Ivan Markovic[1,2], Marko Buta[1,2], Dusica Gavrilovic[3], Ana Cvetkovic[4], Nada Santrac[1], Marija Rakovic[1], Natasa Medic Milijic[5], Radan Dzodic[1,2]

[1]Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [2]School of Medicine, University of Belgrade, Belgrade, Serbia; [3]Data Center, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [4]Department of Anesthesiology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [5]Department of Pathology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia.

Summary

Purpose: *Lymph node metastases (LNM) in papillary thyroid microcarcinomas (PTMC) are common. PTMC greater than 5 mm are considered to be more aggressive. Tumor greater than 5 mm is predictive factor for occurrence of LNM in PTMC, although there are insufficient data regarding this fact. The purpose of this study was to explore the relation between LNM and patients with small (≤5mm) and large (>5mm) PTMC. The second target was to determine the frequency of multifocality, bilaterality and capsular invasion in small and large PTMC, and their relation with LNM occurrence.*

Methods: *This study included 257 patients with PTMC. In all patients total thyroidectomy was performed, and lymph node checking of central and lateral neck region using sentinel lymph node (SLN) biopsy in clinically N0 patients, or modified radical neck dissection in clinically N1b patients or in case with positive SLN.*

Results: *LNM were detected in 33% of the patients, 27% in the central neck region and 20% in the lateral neck region with 6.23% of skip metastases. LNM were significantly frequent in large PTMC compared with small (46 vs 24%), in the central region (38 vs 19%) and the lateral region (28 vs 14%), with skip metastases 7.62% and 5.26%, respectively. Bilaterality and capsular invasion were frequent in large PTMC. Multifocality and male gander were predictive factors for LNM in small PTMC, while capsular invasion was the only predictive factor in large PTMC.*

Conclusions: *Although LNM are frequent in large PTMC, the percentage of LNM is not negligible in small PTMC, especially if they are multifocal.*

Key words: *bilateral tumors, lymph node metastases, multifocality, papillary thyroid microcarcinomas, skip metastases, tumor size*

Introduction

Papillary thyroid microcarcinomas (PTMC) are, by definition, papillary thyroid carcinomas ≤ 1cm [1]. The incidence of PTMCs is increased and accounts for over than 30% of all papillary carcinomas [2], and in some recent studies up to 50% [3]. Large percentages of these tumors (up to 35%) are found in autopsy studies, indicating that most of these tumors have an indolent course and good prognosis [2,4]. The question is whether the increased the incidence of these tumors is real or it reflects better diagnosis. The increasingly use of ultrasound and fine needle aspiration biopsy (FNAB), increased the number of operative procedures for benign thyroid diseases, and better pathological analyses of thyroid specimens (thinner sections) are possible reasons for the increased incidence [5]. Mortality in PTMC is low, less than 1% [6]. However, some PTMCs may be locally aggressive or

Corresponding author: Merima Goran, MD. School of Medicine, University of Belgrade, Belgrade, Serbia, Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Pasterova 14, Belgrade 11000, Serbia.
Tel: +381 638279575, Fax: +381 112685300, Email: merimaoruci@hotmail.com
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may give, although rarely, distant metastases [7,8]. Tumor size is defined in some papers as aggressiveness factor, therefore PTMC greater than 5 or 7 mm are considered to be more aggressive. Lymph node metastases (LNM) in the neck are very common, but the prognosis of these tumors is good [9].

In 1987, Kasai and Sakamoto divided PTMC into "tiny"- from 6 to 10mm in size, and "minute" - 5 mm and smaller. "Minute" carcinomas gave a lower percentage of LNM and extrathyroid invasion [10]. Tumors smaller than 5 mm are more difficult to diagnose preoperatively by ultrasound, and usually are incidental findings. If they are identified on ultrasound, the management is controversial. According to American Thyroid Association (ATA) guidelines, ultrasonically suspected nodules greater than 5 mm should be biopsied (FNAB), while for those less than 5 mm there are no clear recommendations [11].

The aim of this study was to compare the occurrence of LNM, total and by region, central and lateral, in PTMC ≤ 5 mm (small) and > 5 mm (large). The second target was to determine the frequency of multifocality, bilaterality and capsular invasion in PTMC ≤ 5 mm > 5 mm, and their relation with the occurrence of LNM.

Table 1. Characteristics of patients, tumors and lymph node metastases by tumor size categories

Characteristics	*Total n (%)*	*≤5 mm n (%)*	*>5 mm n (%)*	*p value (Pearson x^2 test)*
Patient characteristics				
Gender				ns
Female	218 (84.82)	132 (86.84)	86 (81.9)	
Male	39 (15.18)	20 (13.16)	19 (18.1)	
Age (years)				ns*
Mean (SD)	47.64 (12.48)	49.03 (12.05)	45.62 (12.87)	
Median (range)	49 (23-75)	49.5 (23-73)	45 (23-75)	
*Tumor characteristics**				
Tumor size (in mm)				-
Mean (SD)	5.13 (2.97)	2.98 (1.48)	8.15 (1.57)	
Median (range)	5 (0.5-10)	3 (0.5-5)	8 (6-10)	
Number of foci				ns
Solitary	150 (58.37)	93 (61.18)	57 (54.29)	
Multiple	107 (41.63)	59 (38.82)	48 (45.71)	
Unilateral	38 (14.79)	31 (20.39)	7 (6.67)	p<0.01
Bilateral	69 (26.85)	28 (18.42)	41 (39.05)	
Size of the smallest focus (in mm)				-
Mean (SD)	1.8 (1.47)	1.4 (1.02)	2.22 (1.75)	
Median (range)	1.5 (0.4-8)	1 (0.4-5)	2 (0.5-8)	
Capsular invasion				<0.01
No	203 (78.99)	134 (88.16)	69 (65.71)	
Yes	53 (20.62)	18 (11.84)	35 (33.33)	
Without data	1 (0.39)	-	1 (0.95)	
*Localization of LNMs**				
Lateral				<0.01
Without metastases	206 (80.16)	131 (86.18)	75 (71.43)	
With metastases	51 (19.84)	21 (13.82)	30 (28.57)	
Central				<0.01
Without metastases	188 (73.15)	123 (80.92)	65 (61.90)	
With metastases	69 (26.85)	29 (19.08)	40 (38.10)	
Lateral and/or Central				<0.01
Without metastases	172 (66.93)	115 (75.66)	57 (54.29)	
With metastases	85 (33.07)	37 (24.34)	48 (45.71)	
Total patients	257 (100)	152 (59.14)	105 (40.86)	

*Wilcoxon rank sum test with continuity correction; ns: not statisticaly significant; LNM: lyph node metastases

Methods

This retrospective study was conducted at the Institute for Oncology and Radiology of Serbia (IORS). From 2004 to 2016, 257 patients with PTMC were included. All patients were subjected to total thyroidectomy, as well as lymph node checking of central neck region (sampling or dissection), and lateral neck region using sentinel lymph node (SLN) biopsy in clinically N0 (cN0) patients or modified radical neck dissection (MRND) in clinically N1b (cN1b) patients or in case with positive SLN. Patients in whom loboisthmectomy was performed and patients without lymph nodes checking, were not included into the study.

Central neck dissection was performed in more than 80% of the patients, while in the others sampling of lymph nodes was done. MRND were performed in about 19% of the patients with cN1b or positive SLN, of which in 2% of the patients on both sides.

In cN0 patients SLN biopsy was performed using 0.2 to 0.5 ml of 1% methylene blue dye which was injected prior to the lobe mobilization, just beneath the thyroid gland capsule, with coagulation of the capsule to avoid leakage of the vital blue dye. If frozen section analysis of SLN identified metastases, selective lateral neck dissection was carried out immediately, and if metastases were diagnosed on the definitive pathological examination dissection was subsequently performed.

After operation patients who had multifocal tumors and/or LNM received radioactive iodine therapy, as recommended.

Statistics

For normal distribution data testing, the Kolgomorov-Smirnov and Shapiro-Wilk tests were used. Descriptive methods (frequencies, percentages, mean, standard deviation (SD), median and range) were used to summarize the data. The statistical significance level was set at $p<0.05$. For comparison of characteristics among different risk subgroups, Wilcoxon rank sum, Pearson chi-square and Fisher exact tests were used. The statistical analyses were done with the program R (version 3.3.2 (2016-10-31) -- "Sincere Pumpkin Patch"; Copyright (C) 2016 The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit).

Results

Patient characteristics and LNM in all PTMC

The mean age of patients was 48 years, with females' predominance. Characteristics of the patients and tumors are shown in Table 1. The mean tumor size was 5.13 mm, while the mean tumor size of the smallest focus in multifocal tumors was 1.8 mm. Multifocality was detected in 42%, and bilaterality in 27% of whole thyroid specimens. Capsular invasion was present in 21% of the cases, while only one patient was detected with vascular invasion (Table 1).

The LNM were detected in 33% of the patients with PTMC, in 27% of the patients in the central neck region, and in about 20% of the patients in the lateral neck region (Table 1), with skip metastases which were detected in 6.23%.

LNM in small and large PTMC

Of the total 257 patients with PTMC, 152 (59%) had small tumors (PTMC ≤ 5) mm and 105 (41%)

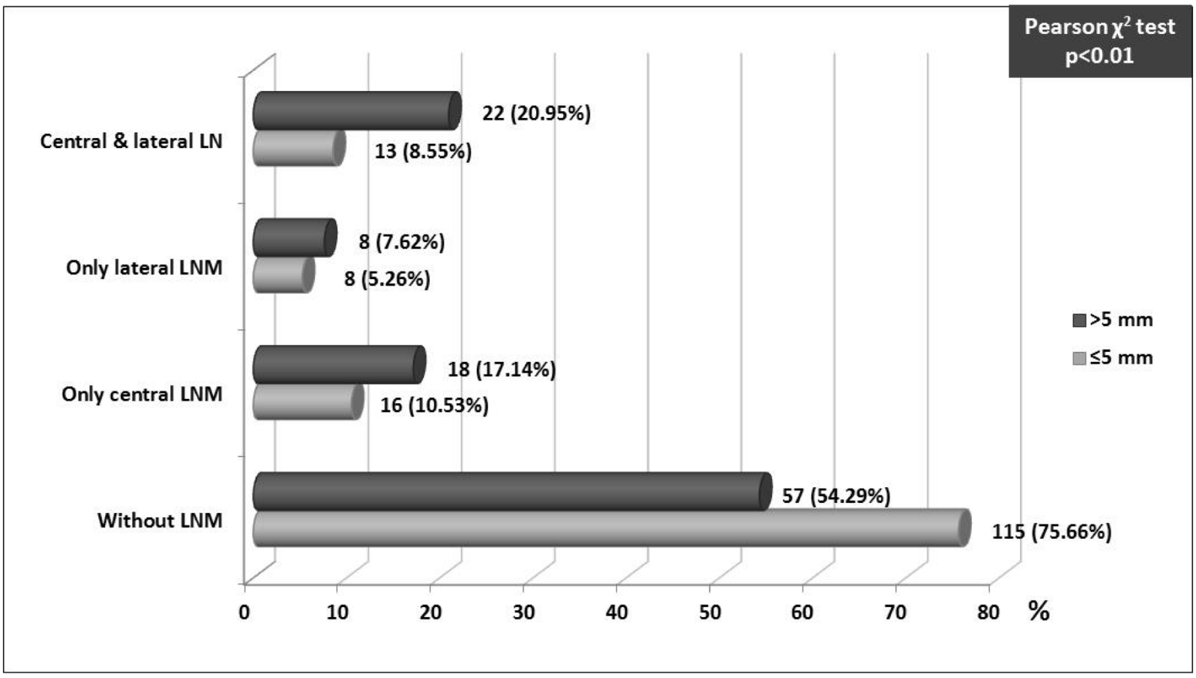

Figure 1. Lymph node metastases and tumor size categories.

Table 2. Relation between gender, multifocality, bilaterality, capsular invasion and LNM by regions in tumors ≤ 5 mm

Characteristics	*LNMs in subgroup with tumors ≤5 mm*					
	Lateral and/or Central		*Lateral*		*Central*	
	+	-	+	-	+	-
	n (%)		*n (%)*		*n (%)*	
Gender						
Female	26 (70.27)	106 (92.17)	12 (57.14)	120 (91.60)	20 (68.97)	112 (91.06)
Male	11 (29.73)	9 (7.83)	9 (42.86)	11 (8.40)	9 (31.03)	11 (8.94)
Pearson x^2 test	$p<0.01$		$p<0.01$		$p<0.01$	
Multifocality						
Solitary	16 (43.24)	77 (66.96)	8 (38.10)	85 (64.89)	13 (44.83)	80 (65.04)
Multiple	21 (56.76)	38 (33.04)	13 (61.90)	46 (35.11)	16 (55.17)	43 (34.96)
Pearson x^2 test	$p<0.05$		$p<0.05$		$p<0.05$	
Bilaterality						
Unilateral	9 (24.32)	22 (19.13)	4 (19.05)	27 (20.61)	7 (24.14)	24 (19.51)
Bilateral	12 (32.43)	16 (13.91)	9 (42.86)	19 (14.50)	9 (31.03)	19 (15.45)
Pearson x^2 test	ns		ns*		ns	
Capsular invasion						
No	30 (81.08)	104 (90.43)	17 (80.95)	117 (89.31)	24 (82.76)	110 (89.43)
Yes	7 (18.92)	11 (9.57)	4 (19.05)	14 (10.69)	5 (17.24)	13 (10.57)
Pearson x^2 test	ns		ns*		ns	

*Fisher exact test, ns: not statistically significant, +: with LNM, -: without LNM

Table 3. Relation between gender, multifocallity, bilateralism, capsular invasion and LNM by regions in tumors >5 mm

Characteristics	*LNMs in subgroup with tumors >5 mm*					
	Lateral and/or Central		*Lateral*		*Central*	
	+	-	+	-	+	-
	n (%)		*n (%)*		*n (%)*	
Gender						
Female	38 (79.17)	48 (84.21)	23 (76.67)	63 (84.00)	32 (80.00)	54 (83.08)
Male	10 (20.83)	9 (15.79)	7 (23.33)	12 (16.00)	8 (20.00)	11 (16.92)
Pearson x^2 test	ns		ns		ns	
Multifocality						
Solitary	24 (50.00)	33 (57.89)	15 (50.00)	42 (56.00)	17 (42.50)	40 (61.54)
Multiple	24 (50.00)	24 (42.11)	15 (50.00)	33 (44.00)	23 (57.50)	25 (38.46)
Pearson x^2 test	ns		ns		ns	
Bilaterality						
Unilateral	5 (10.42)	2 (3.51)	4 (13.33)	3 (4.00)	5 (12.50)	2 (3.08)
Bilateral	19 (39.58)	22 (38.60)	11 (36.67)	30 (40.00)	18 (45.00)	23 (35.38)
Pearson x^2 test	ns		ns		ns	
Capsular invasion						
No	25 (52.08)	44 (77.19)	13 (43.33)	56 (74.67)	20 (50.00)	49 (75.38)
Yes	22 (45.83)	13 (22.81)	16 (53.33)	19 (25.33)	19 (47.50)	16 (24.62)
Pearson x^2 test	$p<0.01$		$p<0.01$		$p<0.05$	

ns:not statistically significant, +: with NLM, -: without NLM had large tumors (PTMC > 5 mm). Multifocal tumors were detected more frequent in large PTMC but without statistical significance, while bilaterality was detected significantly more frequent in large tumors. Capsular invasion was more often present in large PTMC (Table 1).

The LNM were significantly more frequent in large PTMC (45.71% in PTMC > 5 mm and 24.34% in PTMC ≤ 5 mm). LNM were represented more in the central and lateral neck region, separately, in large PTMC compared to the small ones, with statistical significance (Table 1, Figure 1). Skip metastases were detected in 5.26% in PTMC ≤ 5 mm, and 7.62% in PTMC > 5 mm (Figure 1). Analysis of lymph node metastases and tumor size categories showed statistically significant difference between small and large PTMC (Figure 1).

Predictors for LNM in small and large PTCM

In the group of patients with small tumors, LNM were statistically more frequent in males, as well as in multifocal tumors (Table 2), while in the group with large tumors there was no statistical difference (Table 3). In the group of patients with large tumors, predictor for LNM was only capsular invasion (Table 3).

Outcomes

About 36% of the patients postoperatively received radioactive iodine therapy. In only two patients (0.78%) the disease relapsed in the neck and was surgically treated with additionally ablative radioactive iodine therapy. Both patients were presented initially with conglomerate of lymph nodes in the lateral neck region (cN1b). Both of them had multifocal, bilateral and tumors with capsular invasion. In both, total thyroidectomy, central neck dissection, and MRND were performed (from 2 to 5 lateral neck region), in one of them on both side. Relapse occurred in both case in the lateral neck region, in one case after 9 months, and in another case after 7 years. Therefore, re-dissection was done when the recurrence was diagnosed.

In this study, two patients (0.78%) had recurrent laryngeal nerve injury. In one case recurrent laryngeal nerve was accidentally cut and immediately repaired by direct anastomosis. In the second case, recurrent laryngeal nerve paresis occurred, with complete recover after 6 months. No patient had permanent hypoparathyroidism.

Discussion

Lymph node metastases in the neck are very common in PTMC, unlike to distant metastases. Several authors published different percentage of metastases, up to 64% in lymph nodes of the central neck region, and up to 44% in lymph nodes of the lateral neck region [9]. We also recorded high percentage of LNM in PTMC - 33% (27% in the central neck region, and 20% in the lateral neck region).

Tumors greater than 5 mm, multifocal tumors, tumors with capsular invasion or extrathyroid extension and lymphatic and vascular invasion, based on meta-analyses and other large studies, are predictive factors for occurrence of lymph node metastases [12-15].

Starting with Kasai and Sakamoto [10], and then through other studies, tumors larger than 5 mm were considered as more aggressive [12-15]. Aggressiveness is first reflected in the occurrence of LNM and recurrent disease. We recorded more frequent occurrence of LNM in large PTMC compared with small ones (45.71% vs. 24.34%). Also, in study by Wada et al. tumor size had impacted the occurrence of LNM. LNM were present in 55.7% in PTMC ≤ 5 mm, and 73.7% in PTMC > 5 mm, with statistical difference recorded among these groups in the occurrence of LNM in the central and lateral neck region, separately [9]. There were also studies without statistical difference in the occurrence of LNM in PTMC ≤ 5 mm and > 5 mm [16].

Excepting that the percentage of LNM was higher in large tumors, in central as well as in lateral neck region, in our study tumors greater than 5 mm were statistically more frequent bilateral and with capsular invasion. Capsular invasion was more often recorded in larger tumors in study of Lee HS et al. [17]. Our analysis also showed that capsular invasion was the only predictive factor for LNM in PTMC > 5 mm.

Although multifocality was more frequent in large than in small tumors, in our study there was no statistically significant difference among them. Multifocality is significant risk factor for the occurrence of LNM, as well as for recurrent disease, especially in cases where total thyroidectomy was not performed [18]. In one study, the incidence of LNM in multifocal PTMC ≤ 5 mm was 42.3%, and it was only predictive factor for the occurrence of LNM in PTMC ≤ 5 mm [17]. In our study, multifocality was also predictive factor for LNM in small tumors.

Except for multifocal PTMC ≤ 5 mm, we detected that LNM were more often in males with small PTMC. In one study the percentages of LNM were high in male patients with PTMC ≤ 5 mm, but with no statistical significance [17].

Kim et al compared PTMC ≤ 5 mm and > 5 mm in diameter and found statistical significance in relation to gender and extrathyroid extension. Females predominated in PTMC ≤ 5 mm, while extrathyroid extension was significantly higher in PTMC > 5 mm [16]. Unlike Kim et al, we did not reveal significant difference among genders compared to tumor size categories.

In some patients with PTMC, as in the case of larger papillary thyroid carcinoma, metastases may occur in the lateral region without involvement of central lymph nodes (skip metastases). The percentage of skip metastases in papillary thyroid carcinoma is 0.6% to 37.5% and is much more common in microcarcinomas [19,20]. In our study, the percentage of skip metastases was 6.23%, (5.26% and 7.62% in tumors ≤ 5 mm and > 5 mm, respectively). Similar results were recorded by Wada et al among groups (4.9% and 5.6%, respectively) [9]. Using SLN biopsy of the lateral neck region we can detect occult LNM in cN0 patients, with clinically nonpalpable and ultrasonically nondetectable LNM. Accuracy of this method is high, over than 97%, and this method is more precise than physical examination and ultrasonography in the detection of lateral LNM in cN0 patients [21].

Although the extent of surgical resection of the thyroid gland and regional lymph nodes in PTMC is a subject of debate among surgeons [3,7,22], we think that total thyroidectomy is completely justified, considering to high percentage of multifocal and bilateral tumors, which are one of the most common reason for disease recurrence [23,24]. Especially, total thyroidectomy should be done in large PTMC, as well in small multifocal PTMC. Total thyroidectomy is recommended not only for eradicating the potential focus in the contralateral lobe, but also for more accurate postoperative monitoring by measuring thyroglobulin levels, and to conduct postoperative whole body scintigraphy or radioactive iodine therapy, if necessary. If lymphadenopathy exists, therapeutic central or lateral neck dissection is an integral part of the operation. Opinions are contradictory in terms of prophylactic central neck dissection. In the hands of experienced surgeons, it is justifiable considering the high percentage of LNM and the fact that LNM are, with multifocality, the most common reasons for locally recurrent disease, keeping in mind that reoperation carries a greater risk of complications [21]. Finally, SLN biopsy in lateral neck region is suggested in all PTMK as method with high accuracy for detection of occult lateral LNM. Using SLN biopsy, we can detect patients with LNM who would be candidates for radioactive iodine therapy, thus avoiding sub-staging of the disease.

Acknowledgements

The study was reviewed by the Medical Ethics Committee of the School of Medicine in Belgrade, Republic of Serbia and performed in accordance with the ethical standards laid down in the appropriate version of the 1964 Declaration of Helsinki. Our study was approved by the Institutional Review Board of the Institute of Oncology and Radiology of Serbia and conducted with the understanding and consent of all subjects involved. Study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript and in the decision to submit the manuscript for publication.

Conflict of interests

The authors declare no conflict of interests.

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