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ORIGINAL ARTICLE

Multifocality as independent prognostic factor in papillary thyroid cancer – A multivariate analysis

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Summary

Purpose: *The incidence of multifocality of papillary thyroid carcinoma (PTC) ranges from 18 to 87.5% The mechanisms of multifocal spreading, correlation with tumor size, histology variants of PTC, lymph node metastases, and prognostic impact remains unclear. The purpose of this study was to clarify the prognostic significance of multifocality on relapse and survival rates of patients with PTC by analyzing the correlation of multifocality with patient age, gender, tumor size, histological variants of PTC, presence of lymph node metastases and extent of surgery.*

Methods: *153 patients with PTC were included in this study. Patients with pT4 tumors or initially distant metastases were excluded from study. Total thyroidectomy was done in all 153 patients. Central and level III and IV lateral neck lymph node dissection was done in 76.5% of the patients, followed by modified radical neck dissection if positive.*

Results: *Multifocality was found in 43 (28%) whole thyroid gland specimens, and was significantly more frequent in patients older than 45 years and in tumors greater than 4 cm in diameter ($p<0.01$). Presence of multifocality didn't significantly correlate with gender, histology variants of PTC or lymph node metastases. In a median follow up of 84 months locoregional relapse occurred in 8.4% and 1.3% of the patients, while 7.2% patients died due to PTC. The incidence of relapse was significantly higher ($p<0.01$), and relapse free interval and survival were significantly shorter ($p=0.0095$, $p=0.0004$, respectively) in patients with multifocal PTC. Cox multivariate regression analysis showed that multifocality was independent prognostic factor for both disease-free interval (DFI) and cancer-specific survival (CSS) of patients with PTC.*

Conclusion: *Due to high incidence of multifocality and potential prognostic impact, total thyroidectomy should be advocated in all patients with PTC, aiming to reduce relapse rate and improve DFI and CSS.*

Key words: *multifocality, papillary thyroid carcinoma, relapse, survival*

Introduction

Multifocality is common characteristic of PTC and indicates the existence of more than one tumor focus, regardless of localization in the thyroid gland. The incidence of multifocality in PTC ranges from 18 to 87.5% [1-7]. Some authors stated that multifocality is a result of metastasing through intra-thyroid lymphatic vessels [4,5]. Others believe that multicentric transformation is in the nature of PTC. Sugg and coworkers reported that in most of the cases, multifocal tumors have different structural rearrangement of RET/PTC proto-oncogenes, so tumor foci have independent development in regard to dominant tumor [8]. Studies of clones have shown that multicentric transformation starts very early in tumorigenesis of primary unifocal PTC [9,10].

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Most of the authors agree that surgery is the therapy of choice for patients with PTC. Still, there are controversies regarding the extent of primary surgery of thyroid gland and management of regional lymph nodes. Numerous retrospective studies have shown that different prognostic factors have influence on disease free interval and overall survival of patients with PTC [11-17]. Mazzaferri [18] showed that the presence of more than 3 foci of PTC is a bad tumor-related prognostic factor. The results of this study suggested a more extensive surgical approach to the management of differentiated thyroid carcinoma, namely near total or total thyroidectomy is likely to render about 90% of patients permanently free of disease. A similar study of prognostic factors patients with PTC from Mayo Clinic has resulted in suggesting a MACIS prognostic scoring system, where the completeness of surgery (at least near total thyroidectomy) was recognized as an independent prognostic factor [9].

The purpose of this study was to clarify the prognostic significance of multifocality on relapse and survival rates by analyzing the correlation of multifocality with patient age, gender, tumor size, histological variant of PTC, presence of lymph node metastases, extent of surgery, and its potential correlation with relapse and survival rates of patients with PTC.

Methods

The study included 153 patients with PTC surgically treated in a tertiary cancer comprehensive institution. Patients with locally invasive tumors (pT4) and initial distant metastases (M1) were excluded from the study.

Total thyroidectomy (TT) was performed in all 153 patients. Central neck dissection (CND) was performed in 117 patients (76.5%), while surgical biopsy (sampling) of lymph nodes in the ipsilateral compartment (level III and IV) for frozen-section histology was done in 102 patients (66.7%). Modified radical neck dissection (MRND) was performed in all cases of lymph node metastases (LNM) in the lateral neck compartment.

Thyro-suppresive therapy was applied in all patients. Radioiodine ablation was administered to 19 patients (12.4%). Nine patients (5.9%) had external beam radiotherapy for gross lymph node metastases or histological findings of perinodal infiltration.

Relapse was defined as occurrence of new tumor in thyroid bed, enlargement of lymph nodes in the neck, development of distant metastases, or rising levels of serum thyroglobulin more than 6 months after primary treatment.

Statistics

Univariate analysis was used to identify factors associated with DFI and CSS. DFI and CSS were compared by log-rank test. All comparisons were two sided, and a p value of <0.05 was considered statistically significant. Survival curves were generated according to the Kaplan–Meier method. Cox multivariate regression model was used to identify independent prognostic factors of DFI and CSS. For statistical analysis, the statistical package PASW 18 (SPSS Inc., Chicago, IL, USA) was used.

Results

Mean age at diagnosis was 43.07±14.14 years (range 7-76). Around 60% of patients were younger than 45 years at diagnosis. PTC was 4-fold higher in females (ratio 3.9:1).

Patient characteristics and extent of surgery are shown in Table 1. One-hundred fifty-three

Table 1. Patient and tumor characteristics

Prognostic factors / Categories	*n (%)*
Patients	
Age at diagnosis (years)	
≤ 45	93 (60.8)
> 45	60 (39.2)
Gender	
≤ 45	122 (79.7)
> 45	31 (21.3)
Tumor	
Size (cm)	
≤ 1	54 (34.3)
> 1 - ≤ 4	90 (58.8)
> 4	9 (5.9)
Multifocality	
No	110 (71.9)
Yes	43 (28.1)
PTC variants	
Classic (NOS)	87 (56.8)
Microcarcinoma	54 (34.3)
Follicular	8 (5.2)
Poorly differentiated	4 (2.6)
Lymh node metastases*	
No	23 (19.6)
Yes	94 (80.4)
Treatment	
Surgery	
Total thyroidectomy(TT)	36 (23.5)
TT + CND±MRND**	117 (76.5)
Adjuvant therapy	
RAI***	19 (12.4)
RT****	9 (5.9)
RAI+RT	1 (0.7)

*Patients that underwent lymph node dissection (n=117); **Central neck dissection (CND); Modified radical neck dissection (MRND); ***Radioiodine ablation of thyroid remnant or radioiodine therapy (RAI); ****External beam radiotherapy (RT).

whole thyroid gland specimens were histologically examined. Median tumor diameter was 1.5 cm. More than one third were papillary microcarcinomas and the majority of tumors (59%) were between 1 cm and 4 cm in diameter. Multifocal tumors were found in 28% of the whole thyroid gland specimens. The smallest focus was 2 mm in diameter. LNM were found in 94 out of 117 (80%) patients who underwent neck dissections. Similar incidence of LNM was observed in both central and lateral neck compartments (78 vs. 73%).

At the time of surgery, the incidence of multifocality was significantly higher in patients older than 45 years than in youngers (p=0.024), and in patients with tumors greater than 4 cm in diameter (p = 0.0001; Table 2).

The incidence of multifocality did not significantly correlate with gender, histology variants of PTC or presence of LNM. The incidence of LNM in patients with multifocal PTC was 29% vs. 44% in patients with solitary tumors, but the difference was not statistically significant.

Median follow up was 84 months (range 2-229). Relapse occurred in 15 (9.8%) patients. Of these, relapse occurred in not dissected lymph nodes in 13 patients, while distant metastases occurred in 2 patients. During follow-up 11 (7.2%) patients died, 8 of which (5.2%) died due to PTC. Median time to relapse was 32 months (range 8-148). CSS in our series was 94% (Figure 1).

Time to relapse in male patients was significantly shorter than in female patients, as well as in patients with multifocal PTC (Table 3). Time to relapse did not differ significantly with regard to age, tumor size, histological variants of PTC, LNM and extent of surgery (p>0.05).

Relapse was significantly more frequent in patients with multifocal than in solitary PTC (p<0.01).

DFI and CSS were significantly shorter in patients with multifocal in comparison to those

Table 2. Incidence of multifocality according to age at diagnosis and tumor size

*Incidence of multifocality according to age at diagnosis**			
Multifocality	*Age at diagnosis (years)*		*Total n (%)*
	≤ 45 n (%)	*> 45 n (%)*	
No	73 (47.71)	37 (24.18)	110 (71.9)
Yes	20 (13.07)	23 (15.03)	43 (28.1)
Total	93 (60.78)	60 (39.22)	153 (100)
*Incidence of multifocality according to tumor size***			
Tumor size (cm)	*Multifocality*		*Total n (%)*
	No n (%)	*Yes n (%)*	
≤ 1	47 (30.72)	7 (4.58)	54 (35.29)
> 1 - ≤ 4	61 (39.87)	29 (18.95)	90 (58.82)
> 4	2 (1.31)	7 (4.58)	9 (5.88)
Total	110 (71.9)	43 (28.1)	153 (100)

*x^2_1= 5.111, p= 0.024; **x^2_2= 17.873, p= 0.0001

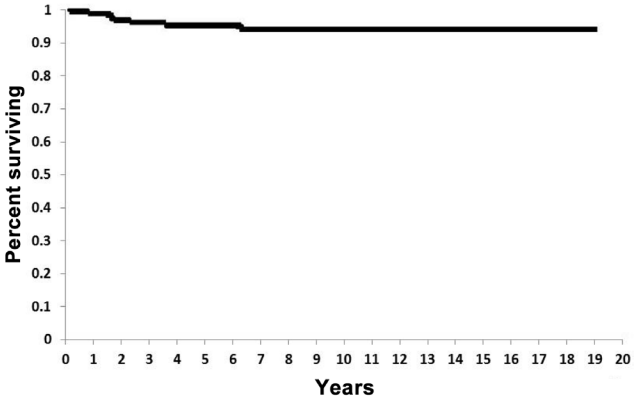

Figure 1. Cancer-specific survival in patients with papillary thyroid carcinoma.

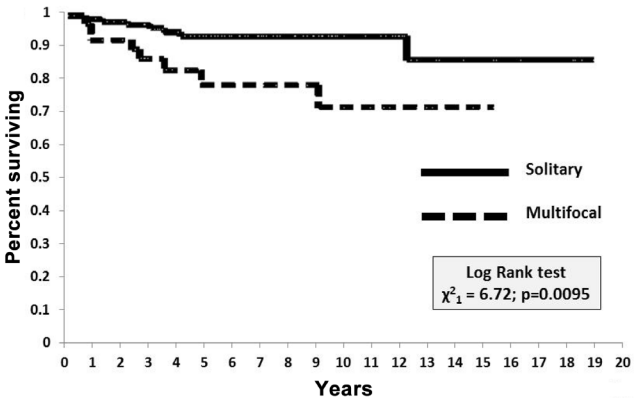

Figure 2. Disease-free interval in patients with papillary thyroid carcinoma with respect to multifocality.

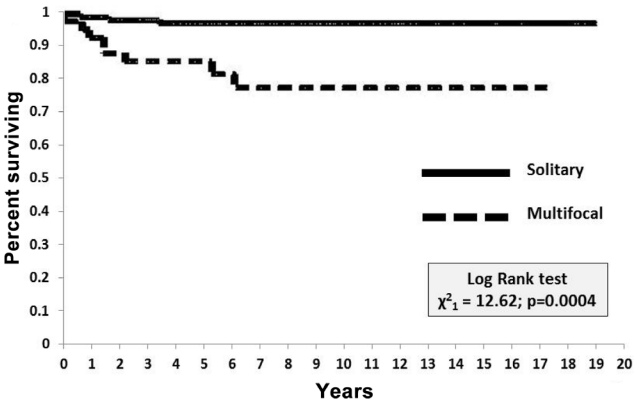

Figure 3. Cancer-specific survival in patients with papillary thyroid carinoma with respect to multifocality.

Table 3. Disease free interval (Cox proportional hazard model - forward stepwise)

Characteristics	*HR (95%CI) for DFI*	*Wald test*
Age at diagnosis	-	ns
Gender	0.31 (0.11 - 0.85)	0.0232
Multifocality	3.30 (1.19 - 9.15)	0.0217
Tumor size	-	ns
Variants of PTC	-	ns
Extent of surgery	-	ns

DFI: disease-free interval, HR: hazard ratio, ns: not statistically significant

Table 4. Cancer specific survival (Cox proportional hazard model - forward stepwise)

Characteristics	HR (95%CI) for CSS	Wald test
Age at diagnosis	13.77 (1.73 - 109.34)	0.0131
Gender	-	ns
Multifocality	5.11 (1.34 - 19.43)	0.0169
Tumor size	-	ns
Variants of PTC	-	ns
Extent of surgery	-	ns

CSS: cancer-specific survival, HR: hazard ratio, PTC: papillary thyroid carcinoma, ns: not statistically significant

with solitary PTCs (Figures 2 and 3). DFI was significantly shorter in males compared to female patients (log rank test; p=0.01), but did not differ significantly with regard to age, tumor size, histological variants of PTC, LNM and extent of surgery (p>0.05).

CSS was significantly worse in males (log rank test; p=0.042) and in patients with tumors bigger than 4 cm (log rank test; p=0.003), as well as in those with poorly differentiated PTC in comparison to other observed variants of PTC (log rank test; p=0.0001).

Multivariate Cox proportional hazard model analysis showed that multifocality and gender were independent prognostic factors for DFI. Furthermore, DFI in male patients was significantly shorter compared with females, as well as in patients with multifocal PTC (Table 3). Multifocality and age at diagnosis were independent prognostic factors for CSS of patients with PTC. Patients older than 45 years and those with multifocal PTC had a significantly worse CSS (Table 4).

Discussion

According to several reports the incidence of multifocal tumors in PTC ranges from 18 to 87.5% [1-5]. Most probably this wide difference in the incidence of multifocality is related to the adequacy of the thyroid sampling, cross-section thickness and the pathologist's interpretation.

The aim of our study was to analyze the correlation of multifocality with prognostic factors related to tumor characteristics, patient characteristics and treatment. Our results showed an increase in the frequency of multifocality that accompanies an increase in the tumor size. Multifocality was found in tumors smaller than 1 cm, from 1 to 4 cm and larger than 4 cm in 13, 32 and 78%, respectively (p<0.01). Furthermore, multifocality was more frequent in patients older than 45 years at diagnosis in comparison to younger ones (p<0.05). Similarly, Lo Gerfo et al. have analyzed the correlation of multifocality and tumor size in PTC and found that patients with dominant tumor's size between 2 and 3 cm had the highest rate of additional tumor foci (59%). Tumors smaller than 2 cm had 33% and tumors larger than 3 cm had only 11% of multifocal lesions [3]. Likewise, De Groot states that a primary PTC larger than 1 cm in diameter, gives multifocality in more than 40% [19].

Katoh and coauthors have shown 78% multifocality in patients with PTC, of whom 59% were detected in the vicinity of the primary tumor, while 61% were found in the other lobe. The average number of foci were 19.2 (from 2 to 125), with diameters from 0.1 to 35 mm. In over 95% of the cases, foci were less than 4 mm in diameter. Similarly to our findings they found out that older patients were more likely to have multifocal PTC. But in their series the frequency of multifocality was not significantly different with regard to the size of the dominant tumor. Furthermore, they did not find significant differences in the frequency of multifocal tumors in patients with and without LNM, but the number of foci was significantly higher in the presence of LNM. They concluded that the risk of local relapse in residual foci after subtotal and hemithyroidectomy ranged from 30 to 50%. Therefore, total thyroidectomy should be considered as logical operation in the prevention of disease relapse [4].

Ricci and coauthors observed 34% of multifocal tumors in patients with papillary thyroid microcarcinomas and about 52% in tumors larger than 1 cm in diameter [20]. On the other hand, Kuo and colleagues analyzed the prognostic significance of multifocal tumors in a series of 2,418 patients with PTC who had undergone TT and found that multifocal tumors were present in 20% of the patients, with a higher incidence in microcarcinomas. They have shown that patients with multifocal PTC had a significantly higher incidence of postoperative disease progression compared to pa-

tients with solitary tumors, but no significant difference was noticed with regard to cancer specific or overall survival [21].

Kim et al. have analyzed the prognostic significance of multifocality in a series of 2,095 patients who underwent TT for PTC. Multifocal tumors were allocated into two groups - unilateral and bilateral. They showed that extra thyroidal extension, LNM and advanced stage of disease were significantly more common in multifocal tumors in comparison to solitary tumors. In the multivariate analysis multifocality was an independent prognostic factor for disease recurrence, but bilaterality was not. In their more recent study, Cox regression analyses indicated that multifocality was an independent risk factor for disease persistence and recurrence in patients who had PTC with a tumor exceeding 1 cm, but not in patients with microcarcinoma [22].

Riss et al. showed no correlation of multifocality with gender, age, tumor size, extra thyroidal extension, LNM in the central compartment of the neck and the risk of relapse [23]. Similarly, the results of our study did not show significant correlation between the incidence of multifocality and gender, histological variants of PTC or the presence of lymph node metastases in the neck. We have noticed a higher but statistically nonsignificant incidence of LNM in multifocal than in solitary PTCs (44 vs. 29%). A similar trend, which was not statistically significant, was already reported by Katoh et al. [4].

Another aim of this study was to analyze the correlation of multifocality and other prognostic factors on relapse and survival of patients with PTC. We found that the incidence of relapse was significantly higher in patients with multifocal PTC in comparison to those with a solitary tumor. Also, Kuo et al. [21] have shown that patients with multifocal PTC had a significantly higher incidence of postoperative progression of disease compared to patients with a solitary tumor. In our patients also the DFI and CSS were significantly shorter in patients with multifocal tumors. A multivariate analysis has shown that multifocality and male gender were independent prognostic factor for DFI, while multifocality and older age were independent prognostic factor for CSS in patients with PTC.

From a surgeon's point of view, it is important to obtain tumor related parameters during the primary surgery so that to perform an adequate operation. Unfortunately, those data are available only after standard histopathology examination and it is not available on frozen-section examination.

The question of debate among surgeons is whether to perform completion thyroidectomy as second operation in cases of primary lobectomy for PTC. Different prognostic scoring index were proposed (EORTC, Institute Gustave-Roussy system, AGES, MACIS, AMES, DAMES, Ohio State University) aiming at justifying the optimal therapy at the first-option surgical procedure based on prognostic factors [11-17].

A number of authors, mostly from Japan, perform ipsilateral lobectomy in seemingly solitary PTC. Finding multifocal tumors on the definitive histopathological examination or tumor growth in residual tissue is an indication of completion thyroidectomy in the second step. Nowadays, the majority of authors accept the 2015 American Thyroid Association guidelines for decision about reoperation [24]. Most guidelines and authors recommend TT in patients with PTC, especially in tumors larger than 1 cm in diameter.

The results of our multivariate Cox analysis have shown that multifocality and gender were independent prognostic factors for disease-free interval. Furthermore, multifocality and age at diagnosis were independent prognostic factors for CSS of patients with PTC. Due to high incidence of multifocality, higher relapse rate and worse survival, TT should be considered as optimal treatment in patients with PTC, with an aim to remove all tumor foci, reduce relapse rate and improve disease free and overall survival.

Acknowledgements

This study was reviewed by the Medical Ethics Committee of the School of Medicine in Belgrade, 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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