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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Incidence and morphological features of thyroid papillary microcarcinoma in Graves' disease

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SUMMARY

Introduction/Objective Association of Graves' disease (GD) and thyroid cancer is reported in a wide range from 0% to 33.7%. Papillary thyroid carcinoma (PTC) is the most commonly diagnosed malignancy in GD, namely its variant – papillary thyroid microcarcinoma (PTMC). The increasingly frequent PTMC disclose favorable biological behavior with low mortality and recurrence rates.
The aim of this work is to report our experience on the frequency and morphological features of PTMC in surgically treated patients with GD.

Methods Over a period of three years, total or near-total thyroidectomy was performed in 129 patients with GD.

Results Incidental PTMC was diagnosed in 24 (18.7%) patients with GD. The mean tumor diameter was 3.03 ± 2.17 mm. The average age of patients in the GD with PTMC group was 48.50 ± 13.07 years, while in the GD without PTMC group it was 41 ± 13.12 years, and it proved to be statistically significant (p = 0.045). Most of the PTMC were unifocal (83%), and the most common morphological features of PTMC were intraparenchymal localization (62.5%), follicular morphology (66.7%), and infiltrative growth pattern (62.5%). Extrathyroidal extension, lymphatic invasion and multifocality of PTMC were more commonly related with subcapsular localized PTMC. The presence of at least one nodule in the GD with PTMC group was 58.3%, while in the GD without PTMC group it was 26.7%, and it was statistically significant (p = 0.003).

Conclusion Our results showed a high incidence of PTMC (18.7%) in patients with GD. Clinically, the most important morphological characteristics of PTMC were related with its subcapsular localization.

Keywords: Grave's disease; thyroid papillary microcarcinoma; morphology

INTRODUCTION

Graves' disease (GD) is an organ-specific autoimmune disease of the thyroid gland that occurs in the presence of autoantibodies to TSH receptors, leading to gland hyperfunction, hyperproduction of hormones (thyroxine, triiodothyronine), and the development of a specific clinical presentation [1]. Macroscopically, the thyroid gland is usually diffusely enlarged, and the histological picture is characterized by follicular hyperplasia with intraluminal/follicular infolding, occasionally in the form of papillary proliferation. Thyroid gland lobularity and vascularisation are increased and it is possible to detect a patchy lymphoid infiltration (LI) in the stroma. In long-standing medically treated Grave's disease, a nodular transformation of the adenomatous type can be detected, as well as development of different degrees of fibrosis, cellular atypia and oncocytic cell transformation [2, 3]. Association of GD and thyroid carcinoma is well documented with frequencies ranging from 0% to 33.7% [4–8]. The most common malignancy in reported studies of GD is papillary carcinoma (PTC), namely its variant papillary microcarcinoma (PTMC) – defined as incidentally discovered PTC with size less than or equal to 10 mm [9]. The increasingly frequent PTMC disclose favorable biological behavior with low mortality and recurrence rates [10, 11, 12].

The malignant potential of well-differentiated thyroid carcinomas of follicular origin in GD is still contradictory. Some studies suggest that immunological basis of GD, which is characterized by permanent autoantibody stimulation of gland epithelial and tumor cells, as well as the presence of antiapoptotic Il-4 and Il-10, could affect the growth, survival, and biological behavior of thyroid carcinomas [6, 13, 14, 15].

The aim of this work is to report our experience on the frequency and morphological features of PTMC in surgically treated patients with GD.

METHODS

From January 2013 to December 2015 in the Clinic for Endocrine and General Surgery at the Military Medical Academy in Belgrade,

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Serbia, total or near-total thyroidectomy was performed in 129 patients. General epidemic and clinical data (gender, age, type of surgery) were obtained from the medical history of patients. Indication for surgery in 125 patients was medically uncontrolled thyroid hyperfunction, compressive symptoms, nodular presence or esthetic reason. In four patients, indication for thyroidectomy was clinical suspicion for PTC, after fine-needle aspiration biopsy was performed. Macroscopic processing of surgical specimens was done according to guidelines for handling surgical specimens from Rosai and Ackerman's Surgical Pathology [2]. The scar lesion – fibrous and/or calcified foci – was fully processed. The diagnosis of PTMC was reached according to the classification of the World Health Organisation [9]. The following morphological features of PTMC were analyzed: size, multifocality, localization, histomorphology (classical, follicular, tall cell), growth pattern (infiltrative vs. circumscribed), extrathyroidal extension, lymphovascular invasion and lymph node metastasis. According to the localization, PTMC were divided into those localized in the peripheral or subcapsular/superficial zone according to the criteria applied by Niemeier et al. [16], and those localized deep in the thyroid parenchyma. The study of remaining non-neoplastic thyroid tissue included the search for nodular transformation and abundance and frequency of LI. We defined nodular transformation as the presence of at least one nodule in the gland (adenomatoid, colloid, oncocytic). The abundance and frequency of LI are graded by the 0–4 scale according to Williams and Doniach [17]. In cases where we incidentally discovered lymph nodes in peri isthmic or peri thyroid tissue, they were fully processed and examined for the presence of metastasis.

Review of all cases was done by two pathologists (SC, BK). Cases where there was a different opinion in the diagnosis of PTMC and four cases of PTC with preoperative suspicion for malignancy were excluded from the series.

The data are presented as mean ± standard deviation or count (percentage), depending on the data type. Significant differences between groups were assessed using the t-test, Mann–Whitney U-test, and χ^2 test, depending on the data type and distribution. Data were analyzed using SPSS 20.0 (IBM corp.) statistical software. All p-values less than 0.05 were considered significant.

RESULTS

In the analyzed period, a total of 125 patients with GD without previous suspicion of malignancy were surgically treated. After histopathological examination the diagnosis of PTMC was made in 24 (19.2%) patients, with the mean tumor size of 3.03 ± 2.17 mm (0.45–7 mm). The mean weight of the gland in the GD with PTMC group was 37 ± 40.90 g, and in the GD without PTMC group it was 54.94 ± 43.64 g. Statistical significance was not determined according to the weight of the gland (Z = -0.940, p = 0.347). One hundred and one (80.8%) patients were female, while 24 (19.2%) patients were male. Eighteen of the patients who had PTMC were female, whereas six were male, to which no statistically significant difference can be attributed (χ^2 = 0.644, p = 0.564). The average age of patients in the GD with PTMC group at the time of surgery was 48.50 ± 13.07 years, while in the GD without PTMC group it was 41 ± 13.12 years, and it proved to be statistically significant (t = 2.023, p = 0.045). Clinical and pathological characteristics of the patients are shown in Table 1.

Table 1. Clinical and pathological characteristics of patients

Variable	TOTAL	GD without PTMC	GD with PTMC	p-value
Number of patients	125	101	24	/
SEX				
Female	101 (80.8%)	83 (82.2%)	18 (17.8%)	0.564[a]
Male	24 (19.2%)	18 (75%)	6 (25%)	/
Age (years)	44.27 ± 13.28	43.09 ± 13.12	49.13 ± 13.07	0.045[b]
Thyroid weight (g)	53.95 ± 43.02	54.94 ± 43.64	49.80 ± 40.90	0.347[c]
NODULAR PRESENCE				
Without nodular transformation	84 (67.2%)	74 (73.3%)	10 (41.7%)	/
With nodular transformation	41 (32.8%)	27 (26.7%)	14 (58.3%)	0.003[a]
LYMPHOID INFILTRATION				
Grade 0	35 (28%)	30 (29.7%)	5 (20.8%)	/
Grade I	80 (64%)	65 (64.36%)	15 (62.5%)	/
Grade II	10 (8%)	6 (5.94%)	4 (16.7%)	0.129[d]
Grade III	0 (0%)	0 (0%)	0 (0%)	/
Grade IV	0 (0%)	0 (0%)	0 (0%)	/

[a]χ^2 test;
[b]t-test;
[c]Mann–Whitney U-test;
[d]χ^2 test for trend

PTMC characteristics

Most of the PTMC were unifocal (n = 20; 83%), and multifocality was detected in only four cases (16.2%). The most common localization of PTMC was intraparenchymal (n = 15; 62.5%), two were located in the isthmic region, while the subcapsular localization was detected in nine cases (37.5%). Follicular morphology of the tumor was the most common (n = 16; 66.7%), followed the classical (n = 5; 20%) and tall-cell morphology (n = 3; 12.5%). Infiltrative growth pattern was found in 15 cases (62.5%), compared to nine circumscribed cases (37.5%). Lymphatic invasion was present in four cases (n = 4; 16.7%), and vascular invasion was not found in any of the cases. Extrathyroidal microscopic extension was detected in three of 24 cases (12.5%), and it was related to subcapsular localization of PTMC. Subcapsular PTMC were also more commonly related with morphological features such as multifocality and lymphatic invasion. Three of four cases with lymphatic invasion and all cases with multifocal distribution were subcapsular PTMC. In 12 cases of the GD with PTMC group, between one and five lymph nodes were found. In none of these cases lymph node metastases were found. The pathomorphological characteristics of PTMC of all patients are shown in Table 2. Figures 1A–D show several histomorphological findings.

Table 2. Pathomorphological characteristics of PTMC for all patients

Case No.	Age (years)	Sex	Size (mm)	TNM	Localization	Morphology	GP	Multifocality	LV
1	35	M	0.9	T1aNx	IP	Fol.	Circ.	No	L0V0
2	73	M	0.9	T1aNx	SC	Fol.	Inf.	No	L0V0
3	46	F	4	T1aN0 (0/2)	IP	Fol.	Inf.	No	L0V0
4	56	F	4	T1aNx	IP	Fol.	Inf.	No	L0V0
5	48	F	3.9	T1aN0 (0/4)	IP	Fol.	Inf.	No	L1V0
6	58	M	1.8	T1aNx	IP	Fol.	Circ.	No	L0V0
7	63	F	1.35	T1aNx	IP	Clas.	Inf.	No	L0V0
8	63	F	2.4	T1aNx	IP	Fol.	Inf.	No	L0V0
9	33	F	2.4	T1aN0 (0/4)	IP	Clas.	Inf.	No	L0V0
10	47	F	7	T3Nx	SC	Tall	Inf.	No	L1V0
11	49	F	5	T1aN0 (0/2)	IP	Fol.	Circ.	No	L0V0
12	46	M	3.3	T1aN0 (0/3)	SC	Fol.	Circ.	Yes	L0V0
13	25	F	7	T3Nx	SC	Clas.	Inf.	No	L1V0
14	60	F	1.95	T1aNx	IP	Clas.	Inf.	No	L0V0
15	53	F	6	T1aNx	IP	Clas.	Circ.	No	L0V0
16	36	F	2	T1aNx	SC	Fol.	Inf.	No	L0V0
17	58	F	6	T1aNx	IP	Fol.	Inf.	No	L0V0
18	64	M	1.2	T1aN0 (0/1)	SC	Fol.	Circ.	No	L0V0
19	47	F	1.5	T1aN0 (0/2)	SC	Tall	Inf.	Yes	L0V0
20	41	M	0.9	T1aN0 (0/2)	IP (Ist.)	Fol.	Circ.	No	L0V0
21	24	F	1.35	T1aN0 (0/3)	IP	Fol.	Circ.	No	L0V0
22	65	F	2	T1aNx	SC	Fol.	Inf.	Yes	L0V0
23	35	F	0.45	T1aN0 (0/1)	IP (Ist.)	Fol.	Circ.	No	L0V0
24	54	F	7	T3N0 (0/5)	SC	Tall	Inf.	Yes	L1V0

GP – growth pattern; LV – lymphovascular invasion; IP – intraparenchymal; SC – subcapsular; Ist.– isthmic; Fol. – follicular morphology; Clas. – classical morphology; Tall – tall cell morphology; Inf. – infiltrativ growth; Circ. – circumscribed

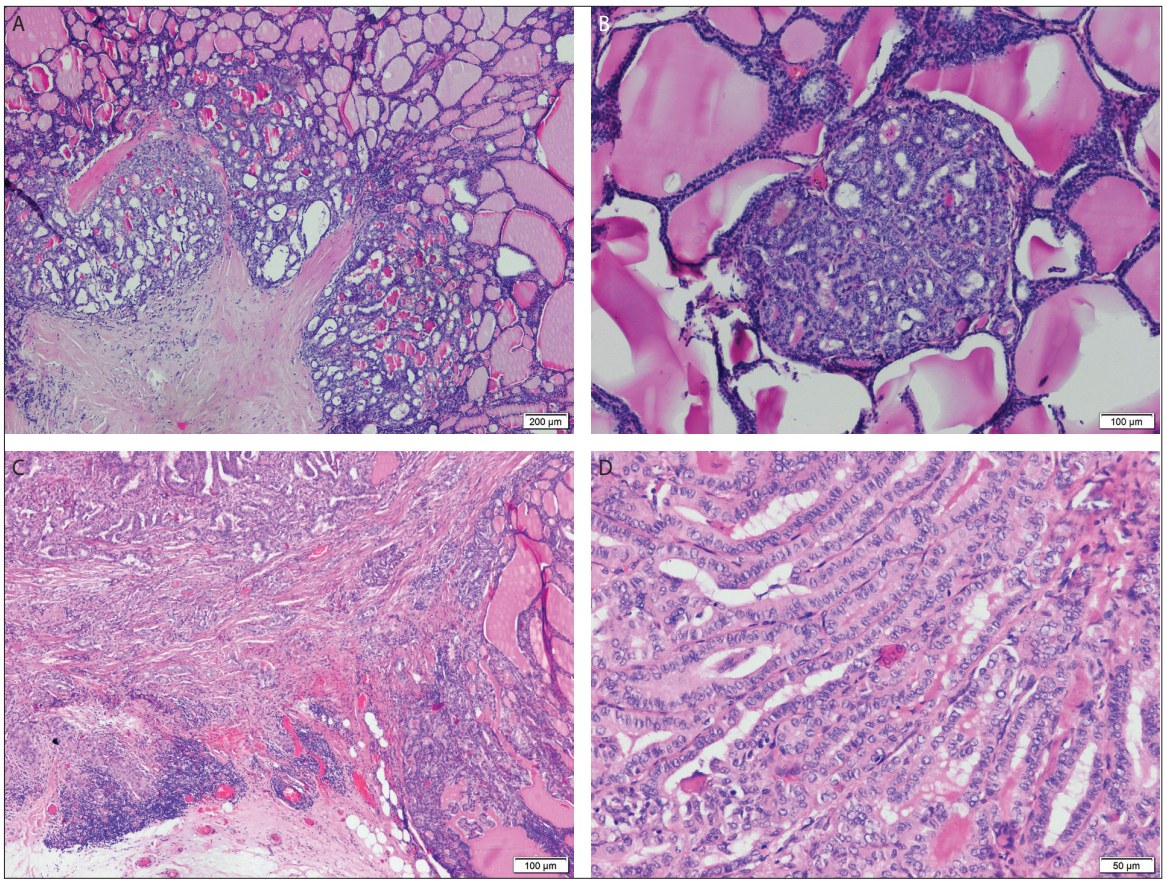

Figure 1. A – follicular PTMC with infiltrative growth pattern (H&E, ×40); B – submillimeter size circumscribed PTMC (H&E, ×100); C – subcapsular PTMC with extrathyroidal extension (H&E, ×40); D – tall cell PTMC (H&E, ×200)

Additional findings in GD in relation to PTMC

Nodular presence

The nodular presence was detected in 41 of 125 (32.8%) cases. In five cases (12%) the nodules were solitary, with diameter ranging from 7 mm to 25 mm. Three of them were of the adenomatous type and one was of colloid type. In 36 cases (82%) the nodules were multiple with the diameter ranging from 2 mm to 30 mm. The morphology of these nodules was a mix of hyperplastic/adenomatous type and/or colloidal type. Oncocytic nodules were detected in three cases. The presence of nodules in the GD with diagnosed PTMC group was found in 14 of 24 cases, or in 58.3%, while in the GD without PTMC group the presence of nodules was found in 27 of 101, or in 26.7%, and it proved to be statistically significant ($\chi^2 = 8.786$; $p = 0.003$).

Presence of lymphoid infiltration

In the group of analyzed patients the most prevalent presence of lymphoid infiltration was within grade I. Grade I of LI was detected in 84 out of 125 cases, or in 64%, followed by grade 0 and grade II with 28% and 8% of the cases, respectively. In the GD with PTMC group, the results were very similar: grade 0 of LI was present in five out of 24 cases, or in 20.8%, grade I of LI was present in 15 out of 24 cases, or in 62.5%, followed by grade II in four of 24 cases or 16.7%. Grades III and IV of LI, which would correspond to lymphocytic and Hashimoto's thyroiditis, respectively, according to the applied criteria, were not detected in any of the cases. PTMC was most commonly detected within Grade I, but we did not prove it to be statistically significant ($p = 0.129$).

DISCUSSION

Reported presence of malignancy in GD is very different, but in two recent studies its frequency is very high, with the rate of 32% and 33.7%, respectively [8, 18]. The increase of cancer incidence in GD is well-presented in the study reported by Phitayakorn et al. [19]. This study involves a time interval of 25 years divided into three periods. In the first period (1985–1993), the frequency of carcinoma was 0%, while in the third period (2003–2010), the frequency of carcinoma was 16.4%. In the cohort study reported by Chen et al. [20], patients with GD, particularly in older age, are at a greater risk of developing thyroid carcinoma compared to general population.

The most common malignancy in GD is PTC, with the participation of 23–88% of its variant PTMC [5, 6, 18, 21, 22]. Our results show a high incidence of malignancy in surgically treated patients with GD (28/129; 21.7%) with high participation of PTMC (24/28; 85.7%). The incidence of PTMC in patients with GD is 18.7% (24/129). The frequency of PTMC in GD was statistically significantly higher ($p = 0.045$) in older patients of our series, similar by to the results of other studies [19, 21, 22]. These results are in accordance with the general trend of worldwide increasing incidence of PTMC, most often as early clinical detection or as incidental pathohistological findings in patients undergoing thyroid surgery for benign thyroid lesions [10–12].

Thyroid nodules in GD are a common finding and its prevalence is different depending on the detection method: thyroid palpation, ultrasonography, or pathohistological examination. Thyroid nodules are found in 28.5–53% of patients with GD using thyroid ultrasonography as the most sensitive method [18, 23, 24]. Relation of thyroid nodules and carcinoma in GD is already established in a number of studies and increases the risk of developing thyroid carcinoma [5, 18, 21–24]. Carcinoma can be localized within nodules or into thyroid parenchyma outside nodules, most often as an incidental PTMC. In our work, the presence of thyroid nodules was detected in 32.8%, which is similar to 33.6% reported by Tam et al. [22] and 39% reported by Ergin et al. [21]. The frequency of PTMC was statistically significantly higher in thyroid glands with present nodules as opposed to the gland without present nodules, which is consistent with results of previous studies [5, 18, 21–24]. This result is also opposed to the study by Wei et al. [18], who reported a higher incidence of PTMC in GD without nodules. Localization of PTMC in our work was outside of detected nodules except in two cases. This could be a result of a larger number of analyzed slides in case of nodular presence, usually in order to assess its invasive growth.

The presence of lymphoid infiltrate in the thyroid glands of GD is usually small, most often in the form of patchy and small groups of lymphocytes, usually in the interfollicular stroma, and sometimes with germinal center formation. Foci of LI were accompanied by secondary changes in thyrocyte, usually in the form of its degeneration and rarely oncocytic transformation [1, 2, 3, 25]. According to the medical records in our work, the clinical significance of a moderate amount of LI was associated with medically uncontrolled thyroid hyperfunction. This could be an expected finding, because intrathyroid lymphocytes are one of the main sources of autoantibodies [1]. Also, the presence of LI can lead to the follicular destruction and increased hormone release. The abundance and frequency of LI in our work were not statistically significantly associated with the presence of PTMC. The interpretation of secondary changes related to the presence of LI, development of fibrosis, and cellular atypia is problematic since it could be associated with therapy-induced changes, especially in the long-standing and medically treated disease, which was not a subject of this analysis [2, 3].

In addition to the differences in the reporting cancer frequency in GD, opinions and results about its malignant potential are also disparate. A study by Pellegriti et al. [13] shows that well-differentiated thyroid cancers in GD have a more aggressive biological behavior, which is, according to Ozaki et al. [26], also applicable to tumors with diameter under 10 mm. Other studies, however, show that there are no differences in the biological behavior of cancer in GD according to other pathological conditions, and the prognosis of PTMC is excellent [6, 13, 27, 28].

Usually, clinical behavior of PTMC is favorable, with excellent outcome. In rare cases, PTMC can show aggressive behavior presented by local lymph node metastases, extrathyroid invasion, or local recurrence, while a distant metastasis and fatal outcome are extremely rare [29]. A potentially different biological behavior of PTMC can be related to patient's age, specifically in children and younger adolescents up to 19 years old. Clinical presentations and behavior of PTMC are mostly related to its morphological features such as tumor size, its multifocality, infiltrative growth, lymphovascular invasion, histological type, and its localization [10, 30]. According to Niemeier et al. [16], the most specific and sensitive assessment of aggressiveness of PTMC is obtained by applying the combined molecular-pathological score.

Clinical impact of morphological characteristics of PTMC in our work was related to their peripheral/subcapsular localization. Only PTMC within this localization is able to infiltrate thyroid capsule and can show extrathyroidal extension which was in our work present in 12.5% of cases. Other features (multifocality, lymphatic invasion), related to potentially more aggressive biological behavior of PTMC, were also more commonly associated with subcapsular PTMC. Another important morphological characteristic of PTMC in our results was the high frequency of PTMC with tall cell morphology, detected in 12.5% of cases. Tall cell variant is a clinically more aggressive form of PTC with reported incidence of 4–12% [30]. In recent studies, Boutzios et al. [8] presented higher incidence of tall cell variant of PTC (18%) in patients with GD, and Wei et al. [18] reported incidence of PTC with tall cell morphology in 16% (7% were tall cell variant, and 9% of PTC showed tall cell features). These results indicate that tall cell morphology as a pure PTC variant or as a part of PTC with tall cell features could be a more common finding in patients with GD than in euthyroid patients. It is also interesting that all cases of PTMC with tall cell morphology in our work were of subcapsular localization.

More precise results could be expected in larger series, which is the main flaw and limitation of our present work.

Pathohistological diagnosis of PTMC is rarely problematic, but from a practical standpoint, it is important to emphasize that differentially diagnostic lesions can be mostly seen in GD. Foci of papillary proliferations can be problematic, especially the ones localized in the vicinity of the fibrotic area with the picture of pseudoinvasion. Small hypercellular and often pseudo-encapsulated nodule with nucleomegaly and some degree of hypochromasia could be a diagnostic challenge. The most significant differential diagnostic issue represents stellate fibrotic foci as solitary or multifocal findings. In these cases, the definite diagnosis usually requires a serial section examination in order to assess invasive growth, and/or the detection of more typical PTC nuclear features or psammoma body.

CONCLUSION

Thyroid carcinomas in GD are not rare, and in our results, most of them represent an incidental PTMC. Clinical impact of PTMC is mostly related to its morphological features and tumor localization. Reporting of these features and long-term follow-up could help a better understanding of true biological nature of PTMC in GD.

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Учесталост и морфолошке карактеристике папиларног микрокарцинома штитасте жлезде у Грејвсовој болести

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САЖЕТАК

Увод/Циљ Удруженост Грејвсове болести (ГБ) и карцинома штитасте жлезде пријављује се у широком распону од 0% до 33,7%. Папиларни карцином (ПК) штитасте жлезде је најчешћи малигнитет у ГБ, односно његова варијанта – папиларни микрокарцином (ПМК). Упркос сталном порасту учесталости ПМК, његова стопа рецидива и смртности је константна и ниска.

Циљ рада је да се одреде учесталост и морфолошке карактеристике ПМК код болесника са ГБ и тиреоидектомијама.

Методе У периоду од јануара 2013. године до децембра 2015. године анализирани су општи клинички и морфолошки параметри код 129 болесника са ГБ и учињеном тоталном или скоро тоталном тиреоидектомијом.

Резултати Код 24 (18,7%) болесника са ГБ дијагностикован је ПМК. Пречник тумора износио је 3,03 ± 2,17 *mm* (0,45–7 *mm*). Старост болесника у групи са ГБ и ПМК износила је 48,50 ± 13,07 година, а у групи без ПМК 41 ± 13,12 година и била је статистички значајна ($p = 0,045$). Микроскопски, најзаступљенији параметри били су: само један фокус ПМК (83,3%), фоликуларни подтип ПМК (66,7%), ифилтративна форма раста (62,5%), интрапаренхимска локализација (54,2%). Присуство најмање једног чвора у штитастој жлезди детектовано је код 26,7% болесника са ГБ без ПМК, док их је у групи са ПМК било више (58,3%), статистички високо значајних ($p = 0,003$).

Закључак Учесталост карцинома штитасте жлезде код болесника са ГБ је висока и износи 18,7%. Његове клинички најзначајније морфолошке карактеристике везане су за супкапсуларну локацију тумора.

Кључне речи Грејвсова болест; штитаста жлезда; папиларни микрокарцином; морфологија