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**Original Article / Оригинални рад**

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# Lymphocytic infiltration as a prognostic factor in papillary thyroid carcinoma

Лимфоцитна инфилтрација као прогностички фактор папиларног карцинома штитасте жлезде

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**SUMMARY**

**Introduction/Objective** The aims of this manuscript was to establish whether the presence of lymphocytic infiltration in the classical type of papillary thyroid carcinoma is a favourable prognostic factor for survival.

**Methods** This is a retrospective study of patients treated for papillary thyroid carcinoma over a period of 7 years (2010–2017). A total of 105 patients aged 12–84 were included in the study, of which 74% showed concomitant histological evidence of lymphocytic infiltration. The patients were divided into two groups, one with lymphocytic infiltration and the other without lymphocytic infiltration. Anti-CD3 and anti-CD20 antibodies were used to identify T- and B-lymphocytes. The Prognostic outcome was assessed using the Kaplan-Meier survival plots.

**Results** The cohort with lymphocytic infiltration revealed a lower frequency of extrathyroidal invasion ($p$<0.0001), nodal metastases ($p$<0.0001) and the absence of distant metastases, respectively, compared with those without lymphocytic infiltration. Chronic lymphocytic thyroiditis is a favourable prognostic factor for survival in our examined group ($p$<0.0001).

**Conclusion** The present study has shown that immune reaction involving lymphocytic infiltration plays a role in extrathyroidal tumour growth and development of nodal and distant metastases in patients with papillary thyroid cancer. The presence of lymphocytic infiltration is a favourable factor for survival in the classical form of papillary thyroid carcinoma.

**Keywords:** Papillary thyroid carcinoma; lymphocytic infiltration; prognostic factors

**САЖЕТАК**

**Увод/Циљ** Циљ рада је био да утврдити да ли присуство лимфоцитне инфилтрације представља повољан прогностички фактор за преживљавање код класичне форме папиларног карцинома штитасте жлезде.

**Методе** У ретроспективну студију укључено је 105 болесника лечених због папиларног карцинома штитасте жлезде у периоду од седам година (2010–2017). Болесници старости 12–84 година су подељени у две групе: са (74% болесника) и без лимфоцитне инфилтрације. За идентификацију Т и Б лимфоцита коришћена су анти-ЦД3 и анти-ЦД20 антитела. Каплан-Мејерова крива је коришћена за поређење временски зависних варијабли.

**Резултати** Одсуство лимфоцитних инфилтрата је лош прогностички фактор за преживљавање код болесника са инвазивним екстратироидним туморима ($p$<0,0001) и на појаву лимфогених и хематогених метастаза ($p$<0,0001). Хронични лимфоцитарни тироидитис представља повољан прогностички фактор за преживљавање у нашој испитиваној групи ($p$<0,0001).

**Закључак** Лимфоцити у ткиву као део имуног одговора имају позитиван утицај на екстратироидни раст тумора и мању учесталост лимфогених и хематогених метастаза. Присуство лимфоцитне инфилтрације представља повољан прогностички фактор за преживљавање код класичне форме папиларног карцинома штитасте жлезде.

**Кључне речи**: карцином тиреоидеје, папиларни; лимфоцитна инфилтрација, прогностички фактори

## INTRODUCTION

Lymphocytic infiltrates (LI) may be found in the context of or surrounding a variety of malignancies and are commonly believed to represent the host's immune response to the tumor [1]. A more favourable clinical evolution has been reported in various malignancies when associated with lymphocytic infiltrates [2]. Heterogeneous immune infiltrates have been shown in diverse tissue types and may portend an improved prognosis [3,4]. Different typeof tumour-associated lymphocytes have been identified in thyroid cancer [5]. These consist of cells of the immune system, macrophages, mast cells, and neutrophils, as well as associated with an adaptive immune response (T and B cells) [6]. Several studies have shown that patients whose tumours are not infiltrated by lymphocytes present a high recurrence rate, suggesting that the presence of lymphocytes in the thyroid tumour microenvironment indicate a favourable prognosis [7]. The results from a meta-analysis investigating



 

the correlation between papillary thyroid carcinoma and Hashimoto's thyroiditis revealed that thyroiditis was more frequently observed in papillary thyroid cancer than in benign thyroid diseases, and cancer patients with thyroiditis had a longer duration of recurrence-free survival [8]. According to the current classifications of the World Health Organization, papillary carcinoma is the most frequent type of differentiated thyroid carcinoma. Differentiated thyroid cancer is a suitable model to study tumour-associated macrophages, as they are associated with signs of immune reaction, including lymphocytic infiltrates. Surgery represents primary and basic treatment for papillary thyroid cancer. The occurence of LI in patients with papillary carcinoma has been reported to predict fewer recurrences and an improved survival [9].

The aim of our study is to determine the statistical relationship between groups with and without lymphocytic infiltration, from a retrospective review of our series of 105 patients with the classical type of papillary thyroid carcinoma, treated at the Clinical Centre of Montenegro from 2010-2017, and to establish whether the presence of lymphocytic infiltration in the classical type of papillary thyroid carcinoma is a favourable prognostic factor for survival.

## METHODS

This study was done in the Surgery Clinic of the Clinical Centre of Montenegro, and all data are from the history of diseases. This is a retrospective cohort study of patients treated for papillary thyroid carcinoma at the Clinical Centre of Montenegro over a period of 7 years (2010-2017). A total of 105 patients aged 12 to 84 were included in the study. Including factors are all patients with the classical type of papillary thyroid carcinoma. Excluding factors are all subtypes of papillary carcinomas; follicular, medullar and anaplastic carcinomas. Based on insight into the medical documentation and medical history, the official pathohistological logbook of the Clinic of Pathology of the Clinical Centre of Montenegro, and the electronic database of the patients, we have collected all data regarding the following: gender, age, sex, tumour size, presence of the lymph or distant metastases, histopathologic characteristics of the tumour, surgical treatment, tumour invasion, multicentric tumours, and clinical features (Tumour Nodes Metastasis) classification of tumours. This study was carried out in archival, paraffin-embedded tissues from 105 patients with the classical form of papillary carcinoma. All patients have undergone a total thyroidectomy and central lymph node dissection, adjuvant radioactive iodine 131 therapy, and postoperative L-Thyroxine TSH-suppressive therapy. After surgery distant metastases were diagnosed, where, in addition to high serum thyroglobulin levels, the metastatic tissue was localized by total body scanning and other imaging tests (X-rays, computed tomography scan). A diagnosis of regional lymph node recurrence was made when ultrasound evidence of suspicious lymph nodes was confirmed by either radioiodine uptake or a cytological finding of neoplastic epithelial cells in the lymph node.

Patients were classified on the extent of disease at presentation as class I - patients with intrathyroid disease, class II - patients with positive cervical lymph nodes, class III - patients with



 

extrathyroid tumour invasion, and class IV - patients with distant metastases. The patients were divided into two groups, those with or without lymphocytic infiltration. Both groups were mutually compared for their prognostic factors.

The group of patients with the presence of lymphocytic infiltration was divided into four groups of various extent of lymphocytic infiltration. The follow-up period was between 6 and 84 months.

The diagnosis of differentiated thyroid carcinoma was made according to the WHO criteria [10]. At the Institute of Pathology of the Clinical Centre of Montenegro, the samples obtained by surgical resection were fixed in a 10% buffered formalin, then moulded into paraffin blocks from which semi-serial cuts 3 micrometres thick were obtained. On the basis of hematoxylin and eosin processing of the sample, one moulded extract from each processed case was obtained of the bordering area of non-necrotic tumour tissue and thyroid gland tissue.

The occurrence of peritumoural lymphocytic infiltrate or Hashimoto's thyroiditis was recorded. The group of patients with the presence of lymphocytic infiltration was divided into four groups in various extent of lymphocytic infiltration. The degree of lymphocytic infiltration varied from a small number of lymphocytes (grade I), islands of lymphocytic infiltration in or around the tumour (grade II), thyroid tissue surrounding groups of a large number of lymphocytes (grade III), to Hashimoto's thyroiditis (grade IV) (Figure 1), characterized by the presence of Hürthle cells and a varying degree of acini atrophy. Identification of lymphocytes was done on hematoxylin eosin colored slides and confirmed using anti-CD3 and anti-CD20 antibodies for identification of T- and B- lymphocytes. All antibodies were obtained from Dako (Copenhagen, Denmark).

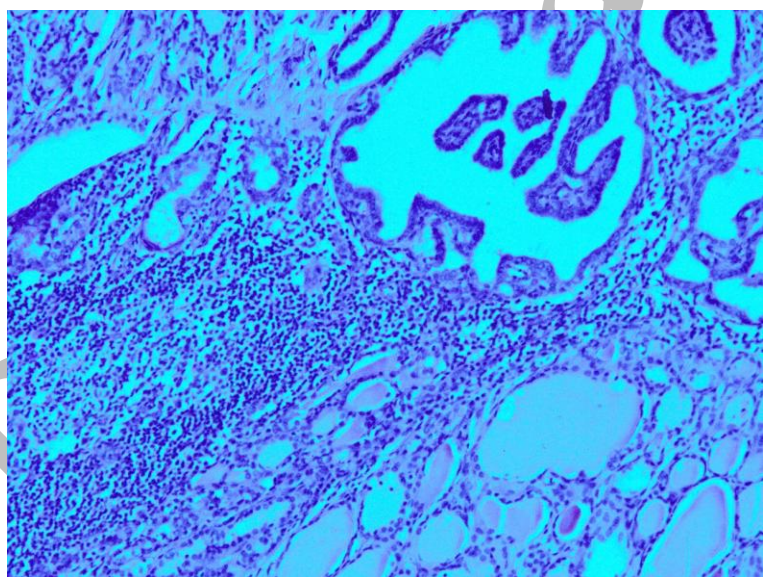

**Figure 1. Lymphocytic infiltration - gradus IV (HE, x10).**

The student's t-test was used for comparison of clinical and pathological parameters among groups. The survival curve (Kaplan-Meier) is used for comparison of time dependent variables (survival, death). A prognostic outcome was assessed using the Kaplan-Meier survival plots. The quantitative variables were expressed as mean ± standard deviation, while the categorical ones were presented as percentages. A univariate Cox regression analysis was performed in order to determine which variables were significantly associated with survival. Statistical analyses were performed using SPSS 15.0 software.



 

## RESULTS

Histological evidence of lymphocytic infiltration was found in 74% of the patients evaluated. The mean or median age at diagnosis did not differ between the cohorts. Our series showed that lymphocytic infiltration could be identified in the thyroid tissue of patients of all ages, with the highest prevalence noted in the fifth decade of life.

Factors with a significant impact on survival rate include: age, sex, size of tumour, invasiveness, lymphogenic and hematogenic metastases, which are shown in Table 1. The median tumour size was 20mm in the group with lymphocytic infiltration with a range of 3–60mm. In the group without lymphocytic infiltration, median tumour size was 35mm, with a range of 4–140mm.

**Table 1. Clinical characteristics and clinical stages of disease of patients with papillary thyroid carcinoma associated with or without lymphocytic infiltration .**

| | LI present 78 (74%) | LI absent 27 (26%) | P value |
|---|---|---|---|
| Age | 12–84 y (48±36) | 25–72 y (49±23 ) | n.s. |
| Sex M : F | 1:7 | 1:4 | <0,0001 |
| Tumor size | 3–60 mm (20 mm) | 4–140 mm (35mm) | <0,0001 |
| Lymph metastases | 21 (27%) | 5 (18 %) | n.s. |
| Distant metastases | 0 | 4 (15%) | <0,0001 |
| Multicentric | 11(14 %) | 4 (15%) | n.s. |
| Tumor invasion | 8 (10%) | 9 (33%) | <0,0001 |
| Stage I | 37 (48%) | 10 ( 37%) | n.s. |
| Stage II | 25 (32%) | 4 (15%) | n.s. |
| Stage III | 7 ( 9%) | 6 (22%) | <0,0001 |
| Stage IV | 9 (11%) | 7 (26%) | <0,0001 |

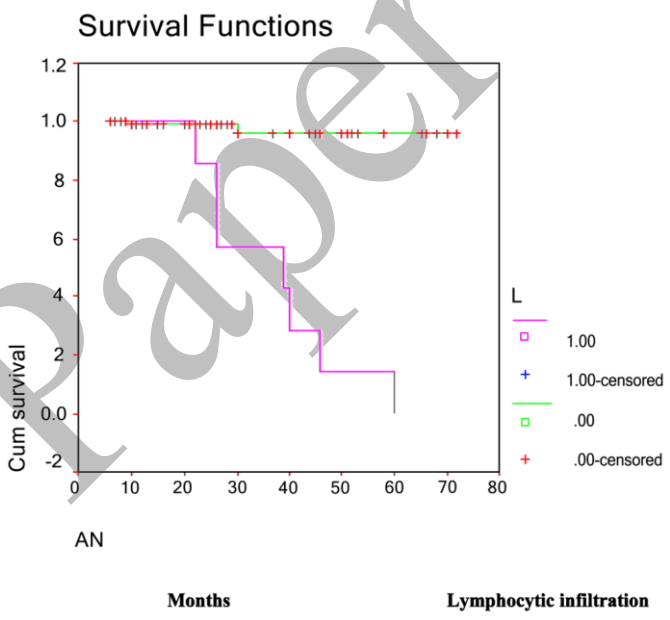


**Figure 2. Data on disease-free survival and cancer-specific survival for the respective cohorts, with and without lymphocytic infiltration.**

By means of univariate analysis, we found that factors with a significant impact on survival rate and shorter survival rate include: age ($p<0.0001$), tumour size ($p<0.018$), regional tumour infiltration ($P<0.0001$), and hematogenic metastases ($p<0.049$).

In our study of age >45, male, tumours up to 30mm in size are a worse significant prognostic factor for survival ($p<0.0001$).

A greater female preponderance was noted in the group with lymphocytic infiltration. At diagnosis, patients with lymphocytic infiltration tend to have more limited disease, with a significantly lower frequency of extrathyroidal invasion (10% vs. 33%), distant metastases (0% vs. 15%), and better survival compared to those without lymphocytic infiltration (Figure 2). The average overall survival was 97.3 %. The average cancer-specific survival in the group with lymphocytic infiltration was 95%. The average cancer-specific survival in the group without lymphocytic infiltration was 72%.



 

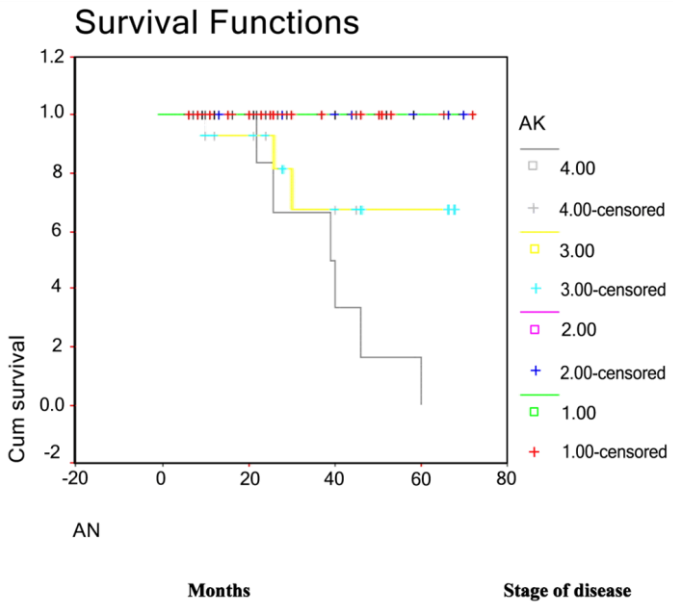


**Figure 3. Comparation of disease-free survival of patients in different stages of disease, showing a significant difference in the fourth stage of the disease.**

There is no distant metastases occurrence in the group with lymphocytic infiltration.

The cohort without lymphocytic infiltration had a higher proportion of patients in the fourth stage of the disease (P<0.0001), compared to those with lymphocytic infiltration (Figure 3).

## DISCUSSION

The etiological ratio between thyroid carcinoma and lymphocytic infiltration remains a cause of concern. The presence of lymphocytic infiltration was noted in four-fifths of our series of patients with papillary carcinoma.

The prognosis of thyroid cancer with Hashimoto's thyroiditis is better than that of patients with thyroid cancer alone [11]. About 75% of the patients with papillary thyroid cancer had lymphocytic infiltration of the thyroid gland, and that group with infiltration had a high frequency of positive anti-thyroid antigen antibody, mild extent of the tumour at diagnosis, and better prognosis of non-recurrence of the tumour [ 12]. A character of infiltrated lymphocytes is cytotoxic T-cells with natural killer or lymphokine-associated killer activity acting as carcinoma cell killers and secreting cytokines, such as interleukin-1, that inhibit thyroid carcinoma cell growth .

In the ten year follow-up of patients with differentiated thyroid carcinoma, Matsubayashi and authors find a significantly smaller incidence of recurrence in the group of patients with lymphocytic infiltration, compared to the group of patients without lymphocytic infiltration.

However, the presence of lymphocytic infiltration as part of the immune response has a significant impact on tumour variables, such as size of tumour, local invasiveness, incidence of lymphogenic and hematogenic metastases [13]. The absence of lymphocytic infiltration is a poor prognostic factor in patients with invasive tumours. Also, the absence of lymphocytic infiltration is a poor prognostic factor for the incidence of lymphogenic and hematogenic metastases, as well as for a histologic type of tumour.

Most patients are older than 45 years and represent two-thirds of examined patients. Older age as a poor prognostic factor was described earlier. Using univariate analysis of 234 patients, Bellantone et al. have reported that survival is significantly affected by age (P=0.0001), tumour size (P=0.018), extrathyroid expansion (P=0.000001), lymphogenic metastases (P = 0, 03), and distant metastases (P



 

= 0.0149) . A study by Mazzaferri and Kloss confirmed that the main factor affecting the disease prognosis is the age [14], which is confirmed by our study as well.

A male sex is a poor prognostic factor. In our study, papillary carcinoma occurs in females in 83.8% of cases. Cancer was most commonly reported in women in the fifth decade of life. In men it occurs more frequently in the sixth decade of life. In groups with present or absent lymphocytic infiltration, the results of age and sex show that females are dominant in both groups, except that in the group with lymphocytic infiltrates a female gender is more prevalent.

A male sex aged over 60 years, tumours over 4cm in size, a poorly differentiated histological type of tumour and the presence of hematogenic metastases in multivariate analysis are important factors of poor prognosis for mortality in differentiated thyroid carcinoma [15]. Similar results were obtained in our study. A male sex, according to a study by Cunningham, has a worse prognosis in differentiated thyroid carcinoma (P = 0.003), but does not affect the recurrence [16].

In our study, cervical lymphogenic metastases were verified in 25.7% of patients, and hematogenic metastases in 8% of patients, which correlates with the results of other authors. The incidence of relapse in the form of lymphogenic metastases (level III) was recorded in 16% of patients, which also corresponds to the results of similar studies. Similar results are found in large studies of Gilliland, where, with the association of lymphogenic metastases with relapse, they report greater tumour-specific mortality [17]. The study of Mazzaferri and Kloss in 2001 found that bilateral jugular metastases and mediastinal metastases are poor prognostic factors. In our study, the presence of lymphogenic metastases does not affect survival, while the presence of hematogenic metastases significantly increases mortality in the studied group of patients.

Our study showed that invasive tumours which show infiltrative growth compared to healthy thyroid tissue as well as in relation to the gland capsule and prethyroid muscles, lymph and blood vessels or trachea represent a poor prognostic factor. In our series, 28 patients had infiltrative tumours. In the highest number, 14 patients, infiltration of the gland capsule appeared; infiltration of prethyroid muscles was confirmed in 13 patients, and in one patient, infiltration of all layers in front of the gland and even on the skin appeared.

In the group without hematogenic metastases, cancer-specific mortality was significantly dependent on an age of over 40 years, a tumour size of more than 1.5cm with invasive tumours, and lymphogenic metastases present. In our study, mortality was significantly higher in patients with invasive extrathyroid tumours, which corresponds to the results of other authors [18].

Rare forms of papillary carcinoma were recorded in 12% of patients - as a follicular variant of papillary carcinoma. Shaha in 2007 published the last TNM classification of cancers of the thyroid gland and confirms that the clinical stages of the disease to assess risk factors are more useful than histopathological grouping of patients, because histological stages overestimate the biological characteristics of many N1b tumours [19].



 

Given that all patients underwent total thyroidectomy, multifocality as a poor prognosis factor is reduced to a minimum. In our study, multifocality of the tumour did not affect survival.

In our study, tumours T1 and T2 represent a good prognostic factor, while larger tumours with extrathyroid expansion are a poor prognostic factor. Most studies that examine the importance of the size of the primary thyroid cancer suggest that T1 tumours up to 10mm in size are a favorable prognostic factor [20], which proved right in our study.

Clinical staging of the disease was more useful than TNM pathological staging of the disease as a predictor of prognosis in Ito and authors' study of 5,768 patients with papillary thyroid carcinoma. Cancer-specific survival was significantly lower in groups T4a and T4b with tumours with extrathyroid invasion [21]. The largest number of thyroid cancers is in the first and second stage of the disease [22], and it is expected that the number of high-risk patients is reduced, which fits with the results obtained in our study.

In our study, the absence of lymphocytic infiltrate is a poor prognostic factor for the occurrence of hematogenic metastases, as well as recurrence.

Chronic lymphocytic thyroiditis represents a favorable prognostic factor in our study group ($P < 0.0001$), while local invasiveness and extrathyroid expansion were significantly lower in the group of patients with lymphocytic thyroiditis present ($P < 0.0001$). In our group we also have significantly lower survival in patients who have no lymphocytic infiltrate.

The etiological relationship between thyroid cancer and lymphocytic infiltration remains a stumbling block, because it is not clear whether the lymphocytic thyroiditis is induced by neoplasm or the presence of a lymphocytic thyroiditis induces the neoplastic process. A second series of patients showed that patients with chronic thyroiditis have a lower level of TNM at diagnosis. It was demonstrated that cytotoxic T lymphocytes are most frequent, and can secrete interleukin-1 which inhibits tumour growth [23]. During 11 years of follow-up, Kimura et al. report a lower incidence of recurrence and cancer-specific mortality in patients with present lymphocytic thyroiditis [24]. In a study of 1,533 patients, Kashima et al. report a 5% cancer-specific mortality and an 85% ten-year period without relapse in the group of patients without lymphocytic thyroiditis [25].

In our study of a group of patients without lymphocytic infiltrates, there was a significantly higher incidence of recurrent disease in the form of hematogenic metastases. In the group with the presence of lymphocytic infiltrates, relapses were exclusively lymphogenic metastases. Since lymphogenic metastases do not affect survival, and hematogenic significantly reduce survival, we can say that the absence of lymphocytic infiltrate is a poor prognostic factor for cancer-specific survival. Other studies suggest that cervical metastases are found in 50-80% of cases of papillary carcinoma, most commonly in the central section of the neck (level VI), followed by middle jugular (level III), supraclavicular (level IV), and subdigastric node (level I) [26]. The study by Mazzaferri found that bilateral jugular metastases and mediastinal metastases are a poor prognostic factor and influence recurrence and survival [27].



 

## CONCLUSION

Lymphocytic infiltration surrounding or inside the tumour might be useful in predicting a good prognosis.

This research has shown that lymphocytes in tissue as part of the immune response have a good effect on factors related to the tumour characteristics such as size, invasiveness, extrathyroid tumour growth and incidence of hematogenic metastases.

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