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ORIGINAL ARTICLE

RISK FACTORS AND SURVIVAL RATE FOR PRIMARY THYROID LYMPHOMA: A CASE-CONTROL STUDY

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Summary

Aim. The aim of the study was to evaluate demographic and clinical characteristics of patients with primary thyroid lymphoma (PTL), to identify risk factors associated with PTL and determine overall survival.

Methods. We performed a retrospective case-control study of patients operated for PTL from 1995 to 2017. There were 41 patients with PTL who formed the cases group. The control group consisted of 82 patients with Hashimoto thyroiditis without concurrent thyroid disease. In statistical analysis we used standard descriptive statistics, logistic regression analysis, Kaplan-Meier survival curves and log rank test.

Results. In the cases group there were 35 patients with non-Hodgkin lymphoma and six patients with Hodgkin lymphoma. The cases group and the control group had a predominantly female population (>90%). In the control group nearly 70% of patients were younger than 55 years, while in the cases group over 60% of patients were older than 55 years. Risk factors for the development of PTL in patients with Hashimoto thyroiditis are older age, long standing Hashimoto thyroiditis, elevated level of TSH and a suspicious FNAB finding. Independent risk factors for PTL are older age (>55 years) and long standing Hashimoto thyroiditis (>10 years). The mean overall survival for patients with PTL is 92.8 months. Patients with longstanding Hashimoto thyroiditis have a shorter survival (84 month).

Conclusion. Patients older than 55 years with longstanding Hashimoto thyroiditis have a higher risk of developing PTL. Additionally, patients with longstanding Hashimoto thyroiditis have worse prognosis compared to other patients with PTL.

Key words: primary thyroid lymphoma, Hashimoto thyroiditis, risk factors, survival

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INTRODUCTION

Lymphoma is the seventh most common malignancy for both sexes together, with extra-nodal involvement in approximately 25–40% of cases.[1] Primary thyroid lymphoma (PTL) represents 2.5% to 7% of all extra-nodal lymphomas and comprises up to 5% of all thyroid malignancies.[2] PTL, although a rare type of thyroid tumour, is the most common nonepithelial thyroid neoplasm together with neoplasms arising from mesenchymal elements.[3] Most PTL are of B-cell origin, predominantly non-Hodgkin lymphoma which accounts for nearly 98% of all cases. Hodgkin lymphoma is much less common and accounts for less than 2% of PTL.[4] Non-Hodgkin lymphomas represent a histologically heterogeneous group of tumours with the most common type being diffuse large B-cell (DLBC) lymphoma followed by mucosal-associated lymphoid tissue (MALT), follicular lymphoma and small lymphocytic lymphoma.[5]

Thyroid DLBC lymphoma, apart from being the most common type, is unfortunately the most aggressive type as well. Disseminated disease is present (stage IVE) in nearly 60% of these patients at the time of diagnosis and the overall five year survival is below 50%.[6] Fortunately, if patients are diagnosed in stage IE of the disease, with a modern multimodal approach, a five-year survival is as high as 90%.[7] The gold standard for treatment of PTL consists of a combined modality therapy that includes chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and external beam radiation.[6] In rare cases, such as patients with intrathyroid MALT lymphoma (stage IE), surgery alone can be curative. More often, the most important role of surgery is confirmation of diagnosis through surgical excision of tissue and definitive pathohistological examination. Furthermore, surgery is useful in the palliation of obstructive symptoms for large thyroid lymphomas.

The best known risk factor for PTL is long standing Hashimoto thyroiditis. It is estimated that it takes 20-30 years for Hashimoto thyroiditis to progress to PTL.[8] The risk of PTL in patients with Hashimoto's thyroiditis is 67-80 times higher than in those without thyroiditis.[6, 8, 9] Other known risk factors are age and gender. PTL most typically occurs in middle-aged to old female individuals.[10, 11]

The aim of the study was to evaluate demographic and clinical characteristics of patients with PTL and identify risk factors associated with it. Establishing risk factors for PTL is important since early recognition of such patients is essential as it is curable if treated in earlier stages of the disease.

MATERIAL AND METHODS

We performed a retrospective case-control study of patients operated for PTL, at a tertiary referral academic hospital, in the period from January 1995 to January 2017. In this period there were 41 patients with PTL that underwent thyroid surgery at our hospital, and these patients formed the cases group. The inclusion criteria for the control group were patients operated for Hashimoto thyroiditis that do not have other concurrent thyroid disease (i.e. thyroid cancer). For each patient with PTL we randomly chose two controls using the following system: one control was the first patient that met the inclusion criteria and underwent surgery before the patient from the cases group; while the other control was the first patient that met the inclusion criteria and had surgery after the patient from the cases group. This way we formed a randomized control group that consisted of 82 patients with Hashimoto thyroiditis without concurrent thyroid disease.

Data of all patients included in the study were retrieved from the electronic database of the surgical department. We collected and analysed the following variables: sex (female/male), age (≤55/>55 years), duration of disease - Hashimoto thyroiditis (≤10/>10 years), preoperative level of TSH (≤10.0/>10.0 mlU/L), preoperative level of T4 (≤104.96/>104.96 nmol/L), cytology findings, type of operation and definitive pathohistological findings. For TSH, instead of using the median value of TSH, that was not statistically significant when analysed, we used a cut-off point of 10mlU/L to identify patients with long-term insufficient levels of hormones. We used this value because it was common practice among endocrinologists at one time not to introduce levothyroxine substitution before TSH levels exceeded 10mlU/L. For T4 we used the mean value (Kolmogorov-Smirnov and Shapiro-Wilk test not significant, $p>0.05$). Cytology findings were first graded using the Bethesda system for reporting thyroid cytopathology.[12] Afterwards we grouped Bethesda I-II as benign and III-VI as potentially malignant to obtain a dichotomous variable. The logic being that Bethesda III-VI will usually be referred for surgery, whereas I-II could have other outcomes other than surgery (repeat FNAB, follow-up). Type of operation included the following procedures: tumour biopsy, tumour reduction, thyroid lobectomy, total thyroidectomy (includes near-total thyroidectomy). Definitive pathohistological findings for the cases group were reported as Hodgkin lymphoma or Non-Hodgkin lymphoma. The reason for such a division was because Non-Hodgkin lymphoma was frequently reported as such, without further information whether it was DLBC lymphoma, MALT lymphoma or lymphoma of another subtype. This was the initial pathohistological finding that was received by the surgical department and which was available from our electronic database. These patients were further referred to the haematology department where the pathohistological findings were further analysed before commencing specific therapy. Unfortunately these data were not available for us and retrieving this information would be timely and dubious. Data regarding patient survival (whether the patient is still alive

Table 1. Descriptive statistics of cases and controls

Variable	Cases		Controls				Chi-square test		
	n[1]	%[2]	n	%	n	%	n	%	p[3]
Sex (female vs. male)	37	90.2	4	9.8	78	95.1	4	4.9	0.439
Age (years) (≤55 vs. >55)	16	39.0	25	61.0	56	69.1	25	30.9	**0.002**
Duration of disease[4] (years) (≤10 vs. >10)	26	66.7	13	33.3	71	93.4	5	6.6	**0.001**
TSH[5] (mlU/L) (≤2.43 vs. >2.43)	17	51.5	16	48.5	33	49.3	34	50.7	1.000
TSH (mlU/L) (≤10.0 vs. >10.0)	27	81.8	6	18.2	65	97.0	2	3.0	**0.015**
T4[6] (nmol/L) (≤104.96 vs. >104.96)	10	41.7	14	58.3	36	57.1	27	42.9	0.146
FNAB[7] (Bethesda) (I-II vs. III-VI)	20	60.6	13	39.4	43	93.5	3	6.5	**0.000**
Extent of operation[8] (less thanTT vs. TT)	24	58.5	17	41.5	5	6.1	77	93.9	**0.000**
FNAB	n		%		n		%		
Bethesda I	2		6.1		0		0		N/A[9]
Bethesda II	18		54.5		43		93.5		
Bethesda III	1		3.0		0		0		
Bethesda IV	0		0		2		4.3		
Bethesda V	8		24.2		1		2.2		
Bethesda VI	4		12.1		0		0		
Type of operation	n		%		n		%		
Tumour biopsy	8		19.5		0		0		N/A
Tumour reduction	13		31.7		0		0		
Lobectomy	3		7.3		5		6.1		
Total thyroidectomy	17		41.5		77		93.9		

1 Number of patients; 2 Percentage of patients; 3 Statistical significance; 4 Duration of Hashimoto disease; 5 Thyroid-stimulating hormone; 6 Thyroxine; 7 Fine needle aspiration biopsy; 8 Less than total thyroidectomy vs. total thyroidectomy (including near-total thyroidectomy) 9 Not applicable

or not and the date when they passed away) were obtained through direct contact with the patients or members of their families using contact details from our database.

Standard descriptive statistics was used to describe the variables included in the study. To determine independent risk factors for PTL we used univariate (ULRA) and multivariate logistic regression analysis (MLRA). All variables that were statistically related to PTL in ULRA at the level of significance of $p<0.05$ were further included in the MLRA model. Variables that had less than 80% of data available were not included in the MLRA. The level of statistical significance of $p<0.05$ was considered statistically significant, while $p<0.001$ was considered highly statistically significant. Kaplan-Meier survival curves were used to determine overall survival, while the log rank test was used to determine specific probability of survival for each of the observed significant variables. IBM SPSS Statistics, version 20.0.0 (SPSS Inc., Chicago, Illinois, USA) was used to perform the statistical analysis.

RESULTS

Descriptive statistics of variables analysed in the study are presented in **Table 1**. In our study of 123 patients (41 cases and 82 controls) there were 93.5% females and 6.5% males with sex ratio 14:1. There were more patients (58.5%) in our younger age group (≤55 years) than in the older group. The youngest patient was 20 years old, while the oldest patient was 82 years old. The mean age was 52.92 years (SD ±13.76 years), with a normal distribution (Kolmogorov-Smirnov test not significant, $p=0.200$). In the cases group there were 90.2% females and 9.8% males, with sex ratio 9:1. The youngest patient was 22 years old, while the oldest patient was 82 years old. The median age was 60 years (IQR25–75 44.5–71.0), with a skewed distribution (Shapiro-Wilk test significant, $n<50$, $p<0.001$). In the control group there were 95.1% females and 4.9% males, with sex ratio of nearly 20:1. The youngest patient was 20 years old, while the oldest patient was 74 years old. The mean age was 51.04 years (SD ±11.43 years), with a normal distribution (Kolmogorov-Smirnov test not significant, $p=0.200$). There was no statistical significance between the cases and control group in relation to sex or age (as a continuous variable) according to Pearson Chi-square (respectively $p=0.439$ and $p=0.142$).

Although there was no statistical difference in relation to age as a continuous variable, a statistically significant difference between cases and controls was noted (OR 3.56, 95% CI 1.60-7.80, $p=0.001$) when age was an-

Table 2. Univariate and multivariate logistic regression analysis

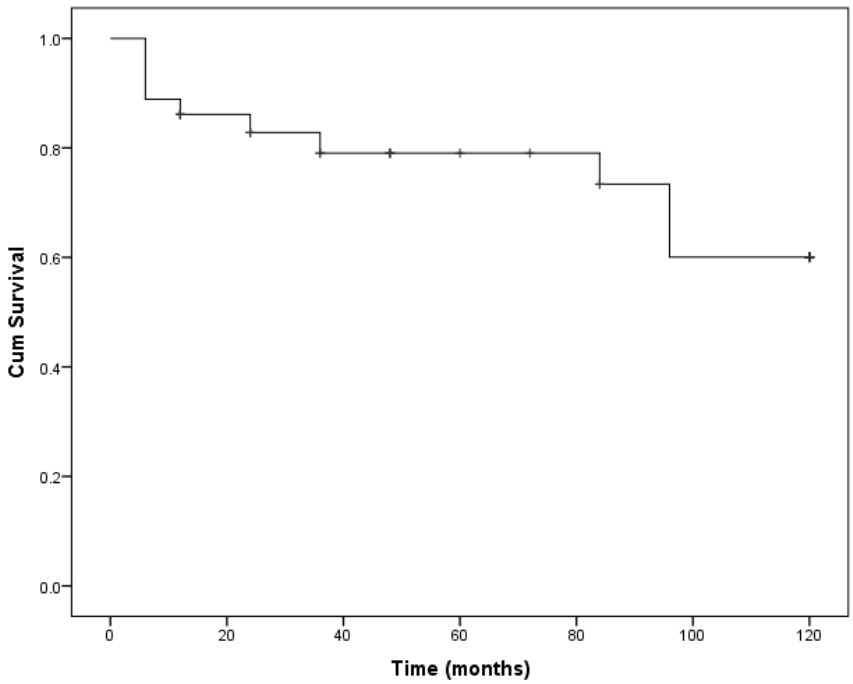
Variable	N[1] (%)	OR[2]	95% CI[3]	p[4]
Univariate logistic regression analysis				
Sex (female vs. male)	100	2.11	0.50-8.90	0.310
Age (years) (≤55 vs. >55)	100	3.50	1.60-7.67	**0.002**
Duration of disease[5] (years) (≤10 vs. >10)	92.7	7.10	2.30-21.87	**0.001**
TSH[6] (mlU/L) (≤10.0 vs. >10.0)	81.3	7.22	1.37-38.06	**0.020**
T4[7] (nmol/L) (≤104.96 vs. >104.96)	70.7	1.87	0.72-4.84	0.199
FNAB[8] (Bethesda) (I-II vs. III-VI)	64.2	9.32	2.38-36.40	**0.001**
Multivariate logistic regression analysis (N>80%, p<0.05)				
Age (years) (≤55 vs. >55)	100	4.44	1.61-12.22	**0.004**
Duration of disease (years) (≤10 vs. >10)	92.7	7.01	1.73-28.35	**0.006**
TSH (mlU/L) (≤10.0 vs. >10.0)	81.3	3.73	0.68-20.52	0.130

1 Percentage of data available for variable 2 Odds ratio; 3 Confidence interval; 4 Statistical significance; 5 Duration of Hashimoto disease; 6 Thyroid-stimulating hormone; 7 Thyroxine; 8 Fine needle aspiration biopsy

alysed as age groups of patients (≤55 years vs. >55 years); meaning there were significantly more patients with PTL in the older age group. A similar pattern was noted for patients with the duration of Hashimoto thyroiditis of more than 10 years (OR 7.38, 95% CI 2.39-22.80, p=0.001) and for patients with TSH level greater than 10 mlU/L (OR 7.22, 95% CI 1.37-38.06, p=0.015). In the control group, the most common finding of FNAB (93.5%) was Bethesda II (Hashimoto thyroiditis), while in the cases group there was a surprisingly high percentage of Bethesda II (54.5%), followed by Bethesda V and VI (24.2% and 12.1% respectively). When FNAB was examined as a dichotomous variable, there were highly significantly more patients in the cases group with a potentially malignant cytological finding (Bethesda III-VI), (OR 9.32, 95% CI 2.38-36.40, p=0.000). In the cases group the most common operation type was total thyroidectomy (41.5%), followed by tumour reduction (31.7%), while in the control group the vast majority of patients had a total thyroidectomy (93.9%). Naturally, examining the extent of operation there was a highly statistically significant difference between the cases and controls group (OR 0.46, 95% CI 0.15-0.138, p=0.000), which was expected.

The results of ULRA and MLRA are presented in Table 2. According to ULRA, risk factors for the development of PTL in patients with Hashimoto thyroiditis are older age (>55 years), OR 3.56, 95% CI 1.63-7.80, p=0.001; long standing Hashimoto thyroiditis (>10 years), OR 7.10, 95% CI 2.30-21.87, p=0.001; elevated level of TSH (>10 mlU/L), OR 7.22, 95% CI 1.37-38.06, p=0.020; and a suspicious FNAB finding (Bethesda III-VI), OR 9.32, 95% CI 2.38-36.40, p=0.001.

Figure 1. Overall survival of patients with primary thyroid lymphoma



According to the results of MLRA, independent risk factors for the development of PTL in patients with Hashimoto thyroiditis are an older age (>55 years), OR 4.54, 95% CI 1.65-12.49, p=0.003 and long standing Hashimoto thyroiditis (>10 years), OR 7.01, 95% CI 1.73-28.35, p=0.006. We did not include the variable FNAB in MLRA, even though it proved to be significant in ULRA, because the data was available for only 64.2% of patients.

Kaplan-Meier survival curve of overall survival for patients with PTL is shown on **Figure 1**. The mean survival time was 92.8±7.5 (95% CI 78.1-107.4) months. Kaplan-Meier survival curves of overall survival for patients with PTL in relation to age group and duration of Hashimoto thyroiditis are shown in **Figure 2** (graph A and graph B). The median survival time for patients with PTL was 96.0±7.6 months (95% CI 81.2-110.8, log rank p=0.029) in relation to the age group (graph A), and 84.0±59.0 months (95% CI 0.0-199.6, log rank p=0.036) in relation to the duration of Hashimoto disease (graph B). The median survival time for patients with PTL in relation to the extent of operation did not prove to be significant (log-rank p>0.05)

DISCUSSION

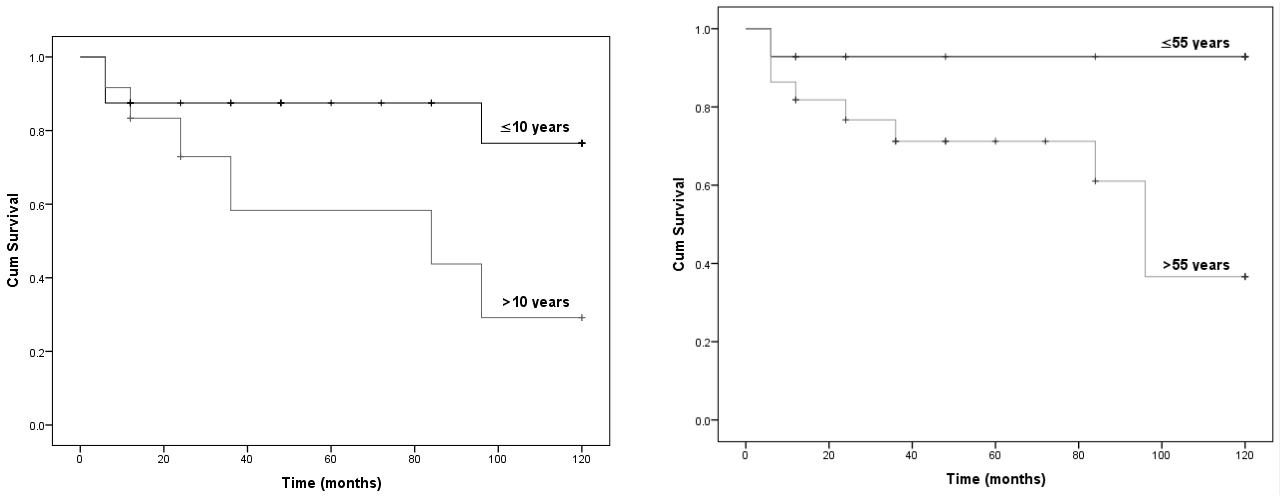
In our study, over 90% of patients with PTL were females. In comparison to other studies, our study had a rather high percentage of females, compared to the rates reported in literature ranging from 49% to 80%.[4, 5, 11, 13-15] Naturally, a high rate of female patients is expected since Hashimoto thyroiditis affects mostly females and is considered an aetiological factor for PTL.[15] Such a high rate of females in our study could further be attributed to the fact that there is a well-established gender-related detection bias in the setting of developing countries, such as Serbia, where women are screened earlier and more thoroughly for diseases than men who are often reluctant to attend medical consultations.[16] In our control group of patients with Hashimoto thyroiditis there was an even higher rate of females (over 95%). Although female gender is a well-known risk factor for PTL it was not statistically proven to be a risk factor in our study, probably because there was such a high ratio of females in both the cases group and the control group.

The youngest patient with PTL in our study was 22 years old. In literature, the youngest reported patient with PTL was 21.[17] The oldest patient in our study was 82 years old. In literature the oldest reported patient was 90.[11] We did not find many studies where age group was evaluated as a risk factor and no studies where a cut-off of 55 years was used as a risk factor. Although there were more patients (58.5%) altogether in our younger age group (≤55 years), there were significantly more patients with PTL in the older age group (61%). The study of Kuribayashi-Hamada et al. used 65 years as a cut-off point and, like us, found more patients with PTL in the older age group (80%).[18] Also, a study by Jin S. et al. showed that the age group of patients was an independent risk factor for PTL, and that the risk was the highest in the oldest age group (>80 years).[19] In our study, we found a much lower cut-off point (age group >55 years) to be an independent risk factor for PTL.

A previous history of Hashimoto thyroiditis is a well-known factor for PTL.[5, 9, 13] Patients with Hashimoto's thyroiditis have 67 to 80 times higher risk of developing PTL.[20, 21] It is estimated that it takes two to three decades for this transformation to happen.[8] In our study this time was much shorter; and a history of Hashimoto thyroiditis of more than ten years was adequate for it to be an independent risk factor for developing PTL.

In our study, to estimate the long-term effect of hypothyroidism we used the cut-off point for TSH (10.0mlU-/L) for reasons previously explained. This proved to be a risk factor for PTL. It is interesting to note that these patients were mainly patients that did not have a concom-

Figure 2. Overall survival of patients with primary thyroid lymphoma in relation to age group (A) and in relation to duration of disease (B)



itant long-term history of Hashimoto thyroiditis. This implies that it is possible that elevated TSH levels have a different mechanism, different from Hashimoto thyroiditis, which can lead to PTL. The evidence that can sustain this theory can be found in patients with PTL and with a recognised resistance to thyroid hormone. Patients with resistance to thyroid hormone can have extremely elevated TSH levels without having Hashimoto thyroiditis. Such is the reported case of a 67-year-old woman with PTL and with point mutation of the thyroid hormone receptor β gene in exon 10.[22] There have not been many studies which considered TSH as a risk factor for PTL. The main reason is probably inability to have adequate data for patients with highly elevated TSH, who naturally went untreated for hypothyroidism for long periods of time, and hence did not have recorded contacts with health services. There are several studies which reported hypothyroidism in patients with PTL. In these studies 36% to 45% of patients with PTL were also hypothyroid. [11, 23, 24]

Fine-needle aspiration cytology has not been a dependable method for diagnosing PTL, and the main diagnostic method had been ultrasound-guided puncture biopsy or surgical biopsy.[25, 26] Nowadays, with the implementation of immunohistochemical staining of the FNA-biopsied specimens the accuracy of FNA biopsy diagnosis has improved, although frequently additional tissue sampling for subtype confirmation through open biopsy is still required.[27] In our study, we did not evaluate FNA as an independent risk factor for the above mentioned reasons and because the data was available for less than 80% of the patients.

In our study, the median survival time for patients with PTL in relation to the extent of operation did not prove to be significant; thus this reinforces the main role of surgery in patients with PTL. The main role of surgery in the treatment of PTL is to acquire an adequate tissue sample and therefore biopsy is favoured above thyroidectomy.[19] For some subtypes of PTL (especially MALT lymphoma) surgery is beneficial.[28]

The mean overall survival for patients with PTL in our study was over 92 months. Patients with PTL and long-term Hashimoto thyroiditis had a much shorter median survival time (86 months) than patients in the older age group (96 months). Therefore it seems that long standing Hashimoto thyroiditis, apart from being an independent risk factor is also an important factor that affects long-term survival.

There are several limitations when conducting a case-control study. The main limitation of a case-control research is the difficulty to generalize the findings from one case-control study to other settings. Risk of bias may also influence the research and this is especially true when choosing the controls for the case-control study. The choice of the control group in our study was based on previous well established facts and was adequate to examine the association of Hashimoto thyroiditis and PTL, but a different control group could potentially lead to identifying other less known risk factors for PTL. The relatively low number of cases in our study is also a limitation, and could be overcome if a multi-centre study was undertaken with a similar methodology. Naturally, this could further strengthen the findings of our study or lead to new conclusions.

CONCLUSION

Patients older than 55 years with longstanding Hashimoto thyroiditis have a higher risk of developing PTL. Additionally, patients with longstanding Hashimoto thyroiditis have a shorter median survival time compared to other patients with PTL. The main role of surgery in the treatment of PTL is to acquire an adequate tissue sample, and therefore the extent of surgery usually does not affect survival.

Ethical approval: The study was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

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FAKTORI RIZIKA I STOPA PREŽIVLJAVANJA ZA PRIMARNI LIMFOM ŠTITASTE ŽLEZDE: STUDIJA SLUČAJEVA I KONTROLA

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Sažetak

Cilj studije. Cilj studije je bio da se analiziraju demografske i kliničke karakteristike pacijenata sa primarnim tiroidnim limfomom (PTL), identifikuju faktori rizika i utvrdi preživljavanje kod pacijenata sa PTL.

Metodologija. Sprovedena je retrospektivna studija slučaj-kontrola kod pacijenata obolelih od PTL u periodu od 1995. do 2017. godine. U grupu slučajeva su uključeni svi pacijenti sa PTL koji su operisani u datom periodu (ukupno 41). U kontrolnu grupu je uključeno 82 pacijenata sa Hašimoto tiroiditisom bez konkomitatnih oboljenja štitaste žlezde. U statističkoj analizi korišćena je standardna deskriptivna statistika, logistička regresiona analiza, Kaplan-Meier kriva preživljavanja i log-rang test.

Rezultati. U grupi slučajeva je bilo 35 pacijenata sa non-Hodžkin limfomom i šest sa Hodžkin limfomom. Grupa slučajeva i kontrolna grupa su imale predominatno žensku populaciju (>90%). U kontrolnoj grupi skoro 70% pacijenata je bilo mlađe od 55 godina, dok je u grupi slučajeva preko 60% pacijenata bilo starije od 55 godina. Faktori rizika za PTL kod pacijenata sa Hašimoto tiroiditisom su: starije životno doba, dugogodišnji Hašimoto tiroiditis, povišen nivo TSH i sumljiv nalaz aspiracione biopsije. Nezavisni faktori rizika za PTL kod pacijenata sa Hašimoto tiroiditisom su: starije životno doba (>55 godina) i dugogodišnji Hašimoto tiroiditis (>10 godina). Srednje vreme ukupnog preživljavanja kod pacijenata sa PTL je 92.8 meseci. Pacijenti sa dugogodišnjim Hašimoto tiroiditisom imaju kraće vreme preživljavanja (84 meseca).

Zaključak. Pacijenti stariji od 55 godina sa dugogodišnjim Hašimoto tiroiditisom su u povećanom riziku za nastanak PTL. Dodatno, pacijenti sa dugogodišnjim Hašimoto tiroiditisom imaju lošiju prognozu u odnosu na druge pacijente sa PTL.

Ključne reči: primarni tiroidni limfom, Hašimoto tiroiditis, faktori rizika, preživljavanje

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