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Analysis of Survival and of Time Until Recurrence of Disease of Patients With Papillary Thyroid Carcinoma–Multivariant Analysis

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ABSTRACT

Background: We examined survival and time until recurrence of disease by multivariant analysis in patients treated for papillary thyroid carcinoma (PTC). **Patients and Methods:** In the period from January 2003 to January 2018, we analyzed 102 patients with PTC in Public Health Institution–Hospital "Sveti Vracevi" in Bijeljina. Survival and time until recurrence of the disease were analyzed using patients' general data and factors based on preoperative, intraoperative and postoperative examinations. Many prognostic factors were analyzed together; the AGES prognostic score, consisting of age, grade, extent and size, and the AMES prognostic score, consisting of age, metastases, extent and size. **Results:** We analyzed 102 patients with PTC. Out of these 87 patients had AGES p.s ≤ 3.99 and 15 patients had AGES p.s> 4. The survival of patients was affected by the presence of distant metastases at the time of diagnosis p = 0.00109 and age p = 0.0436. Recurrence of the disease was recorded in 14 patients. Most patients had recurrence of the disease in the first 5 years after initial surgery. Analyzing the time until recurrence, we concluded that, statistically speaking, AGES p.s> 4 affect recurrence of the disease p = 0.0355 in a significant way, while distant metastases affect it in a very significant way (p = 0.008). **Conclusions:** Prognostic factors of papillary thyroid carcinoma can be divided into 4 categories, patients' general data and factors based on preoperative, intraoperative and postoperative examinations.

Keywords: Papillary thyroid carcinoma, survival, time until recurrence of the disease.

1. INTRODUCTION

Prognostic factors of the papillary thyroid carcinoma can be divided into 4 categories: patients' general data, factors based on preoperative, intraoperative and postoperative examinations (1). Patients' general data include: patients' age, gender and family medical history. Preoperative examination is mainly performed by ultrasound examination of the thyroid primary tumor and enlarged lymph nodes in the neck. Metastases in mediastinal and retrofaringeal lymph nodes can be found by CT scanning, nuclear magnetic resonance imaging (MRI) and positron emission tomography (PET-CT). Ultrasound can detect both the quantity and quality of the nodes in the thyroid gland. An ultrasound scan can detect malignant and benign nodes in the thyroid gland. During this examination a monitored biopsy with a thin needle (FNAB) can also be done, as well as the determination of the size, location, and the number of primary tumors.

Metastases in the lymph nodes in the neck can be diagnosed on the basis of ultrasound criteria. Among the significant criteria proposed by Antinelli et al. are maximal diameter of >1 cm, clear hypoechoic pattern, and rounded (shorter/longer diameter ratio >0.7) or bulging shape with increased anteroposterior diameter. Ultrasonography-guided FNAB and thyroglobulin measurements on wash-out needles used for FNAB could be a great help to diagnose whether the node is metastatic or reactive. It is particularly useful to determine whether there are metastases in lymph nodes on the side of the neck (level II-IV) in order to plan a therapeutic dissection of the neck (2).

Intraoperative examination is based on findings during surgery, including extratiroide tumor expansion as well as extranodal tumor extension to adjacent organs. Degree of expansion, i.e. where and how the tumor spreads, significantly affects the prognosis of patients.

Postoperative examination includes findings based on pathohistological and molecular examinations. Pathohistological tests refer to the determination of morphological variants of PTC and the presence of metastases in the lymph nodes. There are several morphological variants of PTC: a pure PTC, a follicular variant, an encapsulated and diffuse sclerotic variant of PTC. Molecular examinations include e.g. BRAF mutation analysis (3).

Recurrence of the disease signifies a real risk of mortality, as it was pointed out by many authors. They reported that 5.7% of local recurrences were in contralateral thyroid residues, and 7 patients or 41% died due to underlying disease. However, they stressed out that there are 5.7% of local recurrences as compared to 38% of microscopic multicentric focuses that could later lead to a recurrence of disease (4). Defining of local recurrences can cause confusion. An inaccurate definition of the concept of local recurrence probably contributes to the lack of prognostic influence and the recurrence due to lymphogenic metastases. This term should be reserved for recurrent diseases originated in the thyroid bed or thyroid residue. Attention must be paid in any local recurrence analysis to exclude those patients in whom the initial operation was palliative and in whom the tumor remained after surgery. In studies of survival and time analysis until recurrence of the disease, comparable patient groups are needed which would allow a significant comparison of different therapeutic options. Retrospective studies using multivariate analysis have been reported and they have often provided for the detection of disease estimation and its treatment (5, 6, 7).

2. PATIENTS AND METHODS

From January 2003 to January 2018, 102 patients with PTC were treated in the Public Health Institution–Hospital "Sveti Vracevi" in Bijeljina. All patients underwent surgery of thyroid and/or neck lymph nodes tumor. We analyzed the survival and time until recurrence comparing prognostic factors. We determined the prognosis score of AGES and AMES as well. We determined AGES p.s. in the following way: 0.05 x age of the older patients (if the age is 40 years or more); + 1 if the tumor is of grade 2 or +3 if the tumor is of grade 3 or 4, +1 if the extracapsular extension is present, + 3 if there are distant metastasis, and + 0.2 x tumor size (maximum diameter in cm). Low-risk groups of AGES ps. ≤ 3.99 and high-risk groups with AGES p.s> 4 were identified. AMES p.s. Low risk: Younger patients (men ≤40, women ≤50) with no metastases. Older patients (intra thyroid papillary, minor capsular invasion for follicular lesions). Primary cancers 40, women >50). High risk: All patients with distant metastases Extrathyroid papillary, major capsular invasion follicular. Primary cancers ≥5 cm in older patients (men >40, women >50) Total thyroidectomy (TT) was performed in 20 patients and near-total thyroidectomy leaving <1 g of thyroid tissue with recurrent laryngeal nerve in 7 patients. TT and dissection of the lymph nodes were performed in 71 patients. Palliative surgery was performed due to locally advanced disease or enormous tumor size in 3 patients. In our clinical study we analyzed survival and time to recurrence in relation to prognostic factors based on patients' general data and factors based on preoperative, intraoperative and postoperative examinations. By regular postoperative check-ups as well as subsequent referral to check-ups the assessment of the general condition and local condition of the patients were determined. During the check-ups, clinical, laboratory and X-ray treatments were used. Patients with recurrence of the disease were hospitalized again and a diagnostic standard in the extended form was used to prove the recurrence of the disease.

The results of our research were determined by using statistical analysis. The hazard and survival likelihood, Cox's function as well as the Cox model, using the "step-by-step backwards" method, were used. This model rejected the least-contributing factors (first, the factor that has the highest likelihood of zero hypothesis, i.e. the likelihood of risk or error, is rejected, since likelihood of the working hypothesis, i.e. likelihood of certainty, is the smallest).

3. RESULTS

Prognostic factors based on patients' general data

Age of patients: The average age of patients with PTC was X +/- SD = 43.71 +/- 15.03 years with interval variation of individual age between 7-80. The youngest patient at the time of diagnosing PTC with bilateral metastases of lymph nodes in the neck and lungs was a 7-year old girl, while the youngest boy at the time of diagnosis of PTC was 13 years old. The highest frequency of PTC was in female patients in the 4th decade of life and in male patients in the 5th decade, while, collectively looking, men and women were most commonly ill in the 5th decade of life.

Gender: The majority of patients were of a female gender–84 of them, while 28 were male patients. The ratio M: F = 1: 3.

Family medical history: In our study, we had 3 patients who had a positive family medical history of PTC recurrence.

Prognostic factors based on preoperative examination of patients

Clinically enlarged lymph nodes in the neck: initially, there were 14 patients who did not clinically have enlarged lnn N0 (clinical illness cN0), but in 5 patients the presence of metastases confirmed by pathohistological analysis was discovered. In 45 patients there were clinically enlarged lnn in the neck. Metastases were confirmed by pathohystological analyzes in 89% of patients. Patients with cN0 had a risk of recurrence by 2% compared to patients who had clinically enlarged lnn cN1 by 22%.

Distant metastases in the preoperative evaluation of patients: 10 patients or 9.80%. had them.

Prognostic factors based on intraoperative examination of patients

Tumor size: tumor size <40 mm was present in 76 patients (74.4%), histological tumor size ≥40 mm was in 19 patients (18.6%). *Extrathyroid expansion of the disease and involvement of adjacent organs:* 7 patients (6,86%)

Factors	Gradtion factors	B	SE	Wald	Df	pHo	R	Exp (B)
Age of petients	< 45 years	0,673	0,512	3,680	1	0,782	-1,274	0,971
	≥ 45 years.	-0.840	0,416	4,070	1	0,044	-0,103	0,432
Gender of patients	Male	0,299	0,267	1,254	1	0,263	0,000	1,348
	Female	0,381	0,143	1,421	1	0,257	0,078	1,0
AGES p.s.	≤ 3,99	0,237	0,353	2,278	1	0,250	0,071	1,512
	> 4	-0,360	0,456	0,624	1	0,430	0,000	0,697
Tumor size	≤ 40 mm	-0,198	0,292	0,460	1	0,498	0,000	0,821
	> 40 mm	0,3858	0,330	1.434	1	0,317	0,073	1,621
Metastases in lnn	No	0,347	0,286	2,414	1	0,158	0,041	1,789
	Yes	-0,428	1,332	0,103	1	0,748	0,000	0,625
Distant metastases	No	0,459	0,231	0,412	1	0,569	0,982	1,276
	Yes	0,948	0,373	6,749	1	0,0011	-0,151	0,387
Total surgery	TT	/	/	0,544	2	0,762	0,000	/
	TT+MRND	0,240	1,779	0,018	1	0,893	0,000	1,271

Table 1. Analysis of patient survival estimated by Cox model. -2 log Likelihood= 135,603; Chi Square= 149,176; Df =10; Ph=0,000; p<0,01, Legend: AGES- Age, Grade, Extent, Size, TT- Total thyroidectomy, MRND- Modified radical neck dissection, Lnn – lymph node

Factors	Gradation factors	B	SE	Wald	df	pH0	R	Exp (B)
AGES p.s.	≤ 3,99	0,1798	0,4364	1,7193	1	0,9214	0,225	0,7810
	> 4	-0,7970	0,3036	6,7193	1	0,0095	-0,1549	0,4552
Age of patients	< 45	0,5635	0,5320	3,278	1	0,4393	0,4204	0,2816
	≥ 45	0,8802	0,4000	4,811	1	0,0278	-0,1202	0,4147
Distant metastases	No	0,5215	0,5891	2,8367	1	0,3689	0,7215	0,4009
	Yes	-1,0629	0,3309	10.3215	1	0,0013	-0,2056	0,3454

Table 2. Analysis of patient survival estimated by Cox model with "step-by-step backwards". -2 log Likelihood = 139,292; Chi Squere = 143,904; Df = 3; pH0=0,000; P<0,01, Legend: AGES–Age, Grade, Extent, Size

had extracapsular enlargement. Multicentric or bilateral tumors were present in 24 patients or 23.5%.

Prognostic factors based on postoperative examination of patients

Presence of metastases in the lymph nodes of the neck: histologically verified metastases in the lymph nodes of the neck were present in 71 patients or 69.6%. In total, 102 patients with PTC underwent surgery. Total thyroidectomy (TT) was performed in 20 patients or 19.6%. TT + dissection of central and lower jugular lymph nodes with ex tempore Hp verification was performed in 71 patients (69.6%). Metastases in the lower jugular lymph nodes were verified in 50 patients (70.42%), out of these 71 patients (71.81%). Modified radical neck dissection (MRND) was done as well. A reduction in tumor mass and biopsy were made in 4 patients (3.9%), due to the enormous tumor size and disease progression. In addition, the risk of recurrence of the disease in pN1 depended on the number of metastases affected lnn. <5 metastases affected lnn had a risk of 4% of recurrence in relation to >5 metastases affected lnn, who had a risk of recurrence of 19%. *Histological variants of PTC*: in our clinical material, 82 patients or 80.4% had pure PTC, while the other 20 patients (19.6%) had other variants of PTC.

Analysis of patient survival

Patients who had distant metastases at the time of diagnosis had, statistically speaking, significantly less chance to survive compared to patients who did not have distant metastases at the time of diagnosis p = 0.0011. Patients who were over 40 years of age had, statistically speaking, significantly lower survival rate compared to patients who were under 40 years of age p = 0.044 (Table 1).

Estimating by Cox model using "step-by-step backwards" procedure, we concluded that, statistically speaking, AGES p.s p=0.0095 and distant metastases at the time of diagnosis p=0.0013 affect survival of patients with PTC in a very significant way, while patient's age p=0.0278 affect survival in a significant way. The estimated significance is of a negative type (Table 2).

Analysis of the time until the recurrence of the disease in patients with PTC

In our clinical study, the time until recurrence in reference to prognostic factors based on patients' general data, factors based on preoperative, intraoperative and postoperative examinations, was analyzed. Patients who initially did not have clinically enlarged lnn N0 (clinical illness cN0) had a risk of 2% of recurrence in reference to patients who had clinically enlarged lnn cN1 of 22%.

Time until recurrence of the disease estimated by Cox model

Statistically speaking, AGES p.s affect recurrence of the disease in a significant way (p=0.035), while distant metastases at the time of diagnosis affect it in a highly significant way (p=0.008). These significant or highly significant statistical correlations are of a negative type (Table 3).

Factors	Gradation factors	B	SE	Wald	df	pHo	R	Exp (B)
Age of patients	< 45 god.	0,358	0,341	1,103	2	0,294	0,000	1,431
	≥ 45 god.	0,588	0,4370	1.547	1	0,215	0,064	1,800
Gender of patients	Male	0,407	0,283	2,070	1	0,150	0,021	1,502
	Female	0,678	0,342	1,997	1	0,345	0,019	1.789
AGES p.s.	≤ 3,99	0,456	0,431	1,786	1	0,295	0,280	1,649
	> 4	-1,177	0,560	4,420	1	0,035	-0,122	0,308
Tumor size	≤ 40 mm	0,265	0,465	0,325	1	0,568	0,000	1,304
	> 40 mm	-1,205	0,344	5,763	1	0,069	-0,201	0,300
Metastases in lnn	No	-0,669	1,058	0,399	1	0,528	0,000	0,512
	Yes	-0,371	0,468	3,429	1	0,078	-0,221	0,418
Distant metastases	No	0,167	0,226	0,525	1	0,462	0,000	1,489
	Yes	-1,207	0,455	7,042	1	0,008	-0,176	0,299
Total surgery	TT	/	/	4,711	2	0,095	0,066	/
	TT+MRND	-0,611	1,418	0,186	1	0,666	0,000	0,543

Table 3. Time until recurrence of the disease estimated by Cox model. -2 log Likelihood = 130,470; Chi Squere =79,722; Df =10; pH0=0,000; P<0,01, Legend: AGES- Age, Grade, Extent, Size, TT- Total thyroidectomy, MRND- Modified radical neck dissection, Lnn – lymph node

Factors	Gradation factors	B	SE	Wald	Df	pH0	R	Exp (B)
AGES p.s.	≤ 3,99	0,8336	0,8241	1,9226	1	0,1406	0,0159	0,1740
	> 4	-0,9836	0,4804	4,1926	1	0,0283	-0,1159	0,3740
Total surgery	TT	/	/	5,3128	2	0,7025	0,0897	/
	TT+MRND	-1,403	0,7574	3,7690	1	0,5227	-0,1041	0,2298
Distant metastases	No	0,1836	0,0467	2,9126	1	0,4106	-0,5119	0,4037
	Yes	-1,2569	0,4754	6,9893	1	0,0067	-0,1748	0,2845

Table 4. Time until recurrence of the disease estimated by Cox model with "step-by-step backwards", -2 log Likelihood = 134,080; Chi Squere = 74,431; df = 6; pH0=0,000; P<0,01, Legend: AGES- Age, Grade, Extent, Size, TT- Total thyroidectomy, MRND- Modified radical neck dissection

Time until recurrence was estimated by the Cox model "step-by-step backwards" method.

By using Cox model with "step-by-step backwards" method, it was found that AGES p.s. p=0.018 affect recurrence significantly, while distant metastases at the time of diagnosis of the disease affect it, statistically speaking, in a highly significant way p=0.0067. Significant or highly statistically significant correlations are of a negative type (Table 4).

4. DISCUSSION

Papillary thyroid carcinomas (PTC) typically have a good prognosis with a 20-year survival after tumor resection of over 90%. However, some patients with PTC experience poor outcomes, which are dependent on the following factors: patients' general data, factors based on preoperative, intraoperative and postoperative examinations (9). In the group operated on in the Public Health Institution–Hospital "Sveti Vračevi" in Bijeljina, most of 102 patients were 40-60 years of age, which is in accord with the findings of most demographic studies on PTC (10). Women suffer from PTC more often and make 76.19%. Ratio M:F = 1:3.

Histological analysis found that 82 patients (80.4%) had pure PTC, while the other 20 patients (17.01%) had other variants of PTC. Multicentric or bilateral tumors were found in 24 patients (23.5%). PTC expansion of metastases into lymph nodes of the neck is generally the most common way of expansion. In our clinical material, histologically verified metastases in the lymph nodes of the neck were verified in 71 patients (69.6%). Our results comply with the results of other authors who reported the incidence of lymph nodes of the neck in 20-85% of patients with PTC (11).

One of the earliest studies on prognostic factors is the analysis of European Organization for Research and Treatment of Cancer EORTC-Thyroid Cancer Cooperative Group. Fifteen-year survival is up to 80%. In our study, we recorded a fifteen-year survival of 84.15%. The Italian Association of Oncological Surgeons (SICO) reported that the four-year survival of patients with PTC was 97%. In the original EORTC-TCCG reports, presented results show that survival is significantly worse in elderly patients. SICO studies confirmed this trend by reporting a four-year survival of patients under the age of 60. Out of total amount 84.6% of patients were over 60 years of age (12).

Analyzing the survival of patients with PTC using our clinical material by Cox's model estimation, we found that distant metastases at the time of diagnosis have a statistically significant effect on survival p=0.011. Statistically speaking, the age of older patients (≥ 45 years) significantly affect survival p=0.044. These statistically significant or highly statistically significant correlations are of a negative type (13).

Distant metastases are an important prognostic factor in patients with PTC. Kim and Park (13, 14) reported the results related to distant metastases showing 10-year survival with distant metastases; 53% of patients with metastases in the lungs and only 15% of patients with

metastases in the bones. Applying the Cox model using "step-by-step backwards" method, it was found that the age significantly affect survival p=0.0278, while AGES p.s. p = 0.0095 and distant metastases p=0.0013 affect it highly significantly, statistically speaking. Significant and highly statistically significant correlations are of a negative type. The Cox model, applied by "step-by-step backwards" method, disregards factors that have the greatest likelihood of zero hypothesis, i.e. the likelihood of risk or error, because the likelihood of certainty presents itself as logical for the model. Recurrence of the disease was recorded in 14 patients or 13.7%, according to the reference data (14). The risk of recurrence is the highest in the first 5 years after the initial operation. In spite of this tendency, recurrences continue to occur throughout the monitoring period. This study is limited to the analysis of time until recurrence of the disease takes place, with reference to prognostic factors. The time until recurrence of the disease was analyzed in relation to the following factors: sex, age of the patients, histological tumor type, AGES p.s., AMES p.s., tumor size, presence of metastases in the lymph nodes of the neck, presence of distant metastases at the time of diagnosis and overall surgery. Statistically speaking, AGES p.s. p=0.035 affect significantly, while distant metastases at the time of diagnosis (p = 0.008) affect highly significantly the time until the recurrence of the disease occurs. Statistically speaking, these significant or highly significant correlations are of a negative type.

Analyzing the time of recurrence of the disease estimated by Cox's "step-by-step backwards" model, we concluded that, statistically speaking, AGES p.s. p=0.0283 affect the recurrence of the disease significantly, while distant metastases at the time of diagnosis (p=0.0067) affect it highly significantly. These estimated significant or highly statistically significant correlations are of a negative type.

The selection of the surgery and its significance in recurrence of the decease is a debatable prognostic factor. On the basis of their studies, other authors have suggested that TT and even radical lymph node dissections do not prevent recurrence of the disease, being of the opinion that recurrence in the lymph nodes of the neck or thyroid bed is not an indicator of the fatal PTC (15). Others take the opposite stand and emphasize the improvement in survival and reduction in the number of patients with recurrence of the disease when they compare TT with more conservative surgery (16). In the elimination of multicentric PTC sites, ranging from 20-88%, other reasons in favor of TT include the prevention of possible PTC transformations to anaplastic thyroid cancer and the possibilities of facilitating the use of RaJ 131 in metastatic ablation (17).

5. CONCLUSIONS

Prognostic factors of the papillary thyroid carcinoma can be divided into 4 categories, patients' general data, factors based on preoperative, intraoperative and postoperative examinations. Analyzing the survival of patients with PTC on our clinical material doing estimations using the Cox model, we found that distant metastases at the time of diagnosis have a statistically significant effect on survival. Statistically speaking the age of older patients (≥45 years) significantly affect survival. Applying the Cox model using the "step-by-step backwards" method, it was found that the age, AGES p.s p = 0.0095 and distant metastases affect the survival significantly. Statistically speaking, AGES p.s. and distant metastases at the time of diagnosis affect significantly the time until recurrence of the disease occurs. Introduction of perioperative diagnostics of the presence of metastases in the lymph nodes significantly reduces the risk of recurrence of the disease.

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