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## SURVIVAL OF PATIENTS WITH THYROID PAPILLARY AND FOLLICULAR CARCINOMA: SIMILARITY AND DIFFERENCE OF PROGNOSTIC FACTORS (cohort retrospective study)

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При аналізі причин, які мають бути важливими для прогнозування захворювання та впливу на виживання пацієнта зі злоякісними пухлинами щитоподібної залози, дослідники вивчають багато факторів. **Метою дослідження** було визначити показники кумулятивного виживання пацієнтів з диференційованими карциномами щитоподібної залози різного гістологічного типу залежно від біологічних характеристик пухлин і деяких клінічних чинників.

**Матеріали і методи:** Ретроспективне дослідження когорти хворих, які з приводу злоякісної пухлини перенесли операцію на щитоподібній залозі. Проаналізована інформація щодо пацієнтів (вік і стать, гістологічний тип, розмір і категорії карцином (TNM), їх інвазійні властивості, наявність мультифокальності), а також щодо клінічних характеристик захворювання (стадія, обсяг оперативного втручання та радіоїодного лікування, групи ризику виникнення рецидиву, кількість балів за системою MACIS).

**Результати:** Для хворих з папілярними чи фолікулярними карциномами чинники, які проаналізовані є важливими щодо подальшого прогнозу. Найсуттєвішим є розмір пухлини, з яким пов'язані інші – метастазування, мультифокальний ріст, інтра- та екстратиреоїдна інвазія, виникнення рецидиву. У пацієнтів до 45 років з карциномою без екстратиреоїдного її розповсюдження і метастазування, яким проведена тиреоїдектомія, сприятливий прогноз хвороби не залежить від типу пухлини. За інших умов вплив гістологічного типу карциноми (фолікулярна порівняно з папілярною) є важливішим, а у деяких випадках – для чоловіків, осіб у віці понад 60 років, за пухлини понад 40 мм, мультифокальних, з інтра- і, особливо, з екстратиреоїдною інвазією, за віддаленого метастазування, при проведенні тиреоїдектомії з дисекцією лімфовузлів, наявністю рецидивів – суттєво важливим.

**Висновки.** Результати досліджень підтверджують висновок, що найважливішим предикторами персистенції/рецидиву захворювання чи смертності пацієнтів є гістологічний підтип диференційованих карцином щитоподібної залози, розмір пухлини, вік та стать

**Ключові слова:** папілярна і фолікулярна карциноми, прогностичні чинники, MACIS

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### 1. Introduction

The current strategy of thyroid neoplasm management is based on principles including avoidance of excessive surgical intervention, decreased radioisotopes use, and less intensive follow-up in cases of patient from low and middle risk groups. More aggressive treatment tactics should be applied to patients with more aggressive tumors. It is emphasized that we need now new perspective data, in particular, data about prognostic factors giving a possibility to realize this task.

While studying the role of prognostic factors in patient survival, the majority of authors consider these factors in total for a group of differentiated thyroid carcinoma [1, 2]. Simultaneously, there is information on the existence of differences concerning clinical-pathological properties between different thyroid carcinoma – papillary (PTC) and follicular ones (FTC) including also prognostic factors [3, 4]. Moreover, the FTC diagnosis by itself is thought to be an independent negative prognostic factor [5]. That is why there is an opinion that different prognostic factors have to be evaluated, compared, and confirmed separately for this carcinoma [6]. However, such investigations are rare.

### 2. The aim of the study

Retrospective determination of the survival rate of patients with thyroid differentiated carcinomas of different histological type, depending on the biological characteristics of the tumors and some clinical factors.

### 3. Materials and methods

A retrospective study has been carried out on the cohort of patients, which were operated because of differentiated thyroid cancers in 1994-2014. The studies were conducted in the clinic of the Institute of Endocrinology, in addition, data from the National Cancer Registry was used. The cohort includes 5,346 patients; among them there are 4,346 women and 1,000 men, their age being from 10 to 84 years (average age 40.9±9.1 years); the PTC diagnosis was made for 4,818 patients, 528 persons were with the FTC diagnosis. The tumor classification was realized according to the 7<sup>th</sup> version of the TNM Classification.

The information of patients (age and sex, histological type, size and categories of carcinomas, their invasive properties, the presence of multifocal growth), as well as the clinical characteristics of the disease (stage, volume of surgical intervention and radioiodine treatment, risk of

relapse group, number of points in the system MACIS) was analysed.

The statistical evaluation of obtained data was made using Pearson's criterion of distribution concordance  $\chi^2(P_\chi)$ . The survival curve was plotted according to the Kaplan-Meier approach, a non-parametric log-rank test ( $P_L$ ) was used to compare the index value of cumulative survival in groups. The critical significance level taken here is 0.05.

**4. Results**

The survival of cohort patients with FTC is lower comparing to the PTC patients survival (Fig. 1). For example, the FTC patients survival during 2, 5, 10, and 20 years reaches 98 %, 97 %, 94.8 %, and 94.3 %, respectively, the survival of PTC ones being 99.3 %, 99.0 %, 98.5 %, and 98.4 %, respectively ( $P_\chi=0.0001$ ). The less favorable prognosis of FTC patients may be due to several factors. The analysis results of total patients groups with PTC and FTC show the prevalence of FTC patients with neoplasm above 20 mm as well as of patients with II, III, and IVa disease stages is higher comparing with the percent of PTC patients with the same parameters. The mortality among FTC patients is also higher. At the same time, the percent of the cohort patients with invasive PTC as well as the percent of multifocal tumors are also higher comparing to the FTC patients one (Table 1).

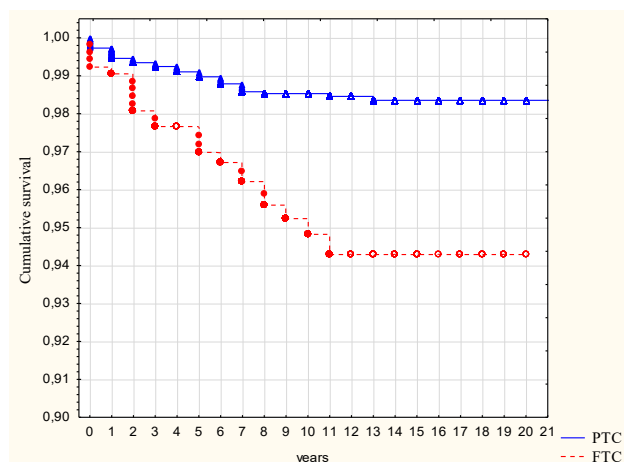


Fig. 1. Cumulative curves of patients' survival with papillary and follicular thyroid carcinoma

The prognosis for patients with thyroid cancer depends on sex of patients. The level of men survival is lower comparing to the level of women survival, especially for FTC patients (Table 2). Among male patients the percent of PTC and FTC above 20 mm, of tumors belonging to T3-T4 categories with intra-nodal metastases as well as the percent of PTC patients with the IV stage of disease are higher comparing to female patients (Table 3). The mortality level of males with the FTC exceeds this value for PTC by 5.5 times, the mortality of females with FTC being thrice higher comparing to PTC patients. Simultaneously, both among men and women higher FTC frequency with size above 20 mm is kept, the percent of patients with invasive and multifocal FTC being lower.

Table 1

Cohort of thyroid carcinoma patients: frequency of patients with different type carcinoma, frequency of patients with different disease stages, and mortality among patients with papillary and follicular carcinoma, n (%)

Index	Carcinoma		$P_\chi$ -value
	papillary (n=4818)	follicular (n=528)	
Tumors above 20 mm	1537 (31.9 %)	243 (46.0 %)	<b>0.0000</b>
Tumors of the T3-T4b category	1294 (26.9 %)	145 (27.4 %)	0.7662
Tumors of the N1a-N1ab category	1703 (35.3 %)	85 (16.1 %)	<b>0.0000</b>
Tumors of M1 category	128 (2.7 %)	11 (2.1 %)	0.4318
Intra-thyroid invasion	2848 (59.1 %)	220 (41.7 %)	<b>0.0000</b>
Extra-thyroid invasion	1064 (22.1 %)	71 (13.4 %)	<b>0.0000</b>
Multifocal growth	874 (18.1 %)	67 (12.7 %)	<b>0.0017</b>
Disease stage: I	3801 (78.9 %)	374 (70.8 %)	<b>0.0000</b>
II	339 (7.0 %)	53 (10.0 %)	<b>0.0120</b>
III	339 (7.0 %)	60 (11.4 %)	<b>0.0003</b>
IVa	314 (6.5 %)	33 (6.3 %)	0.8129
IVb	12 (0.2 %)	1 (0.2 %)	0.7915
IVc	13 (0.3 %)	7 (1.3 %)	<b>0.0001</b>
Mortality	58 (1.2 %)	24 (4.5 %)	<b>0.0000</b>

Table 2

Cumulative survival of different sex and age patients with thyroid carcinomas, %

Groups	Papillary carcinoma				$P_L$ -value	Follicular carcinoma				$P_L$ -value
	survival term, years					survival terms, years				
	2	5	10	20		2	5	10	20	
<b>sex</b>										
women	99.5	99.1	98.7	98.5	<b>0.037</b>	98.7	98.0	96.5	95.9	<b>0.001</b>
men	98.8	98.4	98.0	97.6		95.0	92.2	86.2	86.2	
<b>age, years</b>										
below 18	100	100	100	100	<b>0.000</b>	100	100	100	100	<b>0.000</b>
19-40	99.9	99.7	99.7	99.7		99.2	99.2	99.2	99.2	
41-60	99.6	99.0	98.7	98.7		99.3	97.6	95.0	95.0	
above 60	96.0	94.2	90.1	87.1		92.0	90.8	85.9	-	

Table 3

Cohort of thyroid carcinoma patients: frequency of different sex patients with carcinoma of different properties, frequency of disease stages, and mortality among patients with papillary and follicular carcinoma, n (%)

Index	Carcinoma		P <sub>χ</sub> -value
	papillary n=3896	follicular n=450	
<b>Women</b>			
Tumors above 20 mm	1198 (30.7 %)	199 (44.2 %)	<b>0.0000</b>
Category: T3-T4	995 (25.5 %)	117 (26.0 %)	0.8319
N1a-N1ab	1271 (32.7 %)	65 (14.4 %)	<b>0.0000</b>
M1	92 (2.4 %)	6 (1.3 %)	0.1642
Intra-thyroid invasion	2269 (58.2 %)	192 (42.7 %)	<b>0.0000</b>
Extra-thyroid invasion	819 (21.0 %)	63 (14.0 %)	<b>0.0004</b>
Multifocal growth	718 (18.4 %)	58 (12.9 %)	<b>0.0036</b>
Disease stage: I	3092 (79.4 %)	321 (71.3 %)	<b>0.0000</b>
II	274 (7.0 %)	46 (10.2 %)	<b>0.0141</b>
III	280 (7.2 %)	52 (11.6 %)	<b>0.0009</b>
IV	250 (6.4 %)	31 (6.9 %)	0.7901
Mortality	39 (1.0 %)	14 (3.1 %)	<b>0.0001</b>
<b>Men</b>	<b>n=922</b>	<b>n=78</b>	
Tumors above 20 mm	339 (36.8 %)*	44 (56.4 %)*	<b>0.0006</b>
Category:T3-T4	299 (32.4 %)*	34 (43.6 %)*	<b>0.0446</b>
N1a-N1ab	432 (46.9 %)*	20 (25.6 %)*	<b>0.0003</b>
M1	36 (3.9 %)*	5 (6.4 %)*	0.2838
Intra-thyroid invasion	579 (62.8 %)*	38 (48.7 %)	<b>0.0000</b>
Extra-thyroid invasion	245 (26.6 %)*	14 (17.9 %)	<b>0.0000</b>
Multifocal growth	156 (16.6 %)	9 (11.5 %)	<b>0.0009</b>
Disease stage: I	709 (76.9 %)	53 (67.9 %)	0.0747
II	65 (7.0 %)	7 (9.0 %)	0.5277
III	59 (6.4 %)	8 (10.3 %)	0.1907
IV	89 (9.7 %)*	10 (12.8 %)	0.3684
Mortality	19 (2.1 %)	10 (12.8 %)	<b>0.0000</b>

Note: \* – <0.01 vs. the women

The survival level for PTC and FTC patients below 18 years reaches 100 %; it is the same for patients younger than 40, being somewhat lower for FTC patients of 41–60 years comparing to PTC ones (beginning from the 5 year term) and lower for persons above 60 (beginning from 2-year term) (Table 2). Simultaneously, the carcinoma analysis depending on the patients age suggests the higher percent of PTC cases with tumor size above 20 mm in persons below 18 comparing with elder patients; it concerns tumors of T3-T4 categories, metastazing tumors, patients with intra- or extra-thyroid invasion. In cases of FTC similar tendency is found only for frequencies of tumors above 20 mm and tumors of T3-T4 categories. At the same time, among FTC cases the percent of patients with intra- or extra-thyroid invasion, distant metastases, and multifocality is lower (Table 4).

Table 4

Cohort of thyroid carcinoma patients: frequency of patients with carcinoma of different properties, frequency of disease stages, and mortality among patients with papillary and follicular carcinoma, n (%)

Index	Carcinoma		P <sub>χ</sub> -value
	papillary n=500	follicular n=44	
<b>Patients below 18</b>			
Tumors above 20 mm	236 (47.2 %)	34 (77.3 %)	<b>0.0001</b>
Category: T3-T4	242 (48.4 %)	16 (36.4 %)	0.1253
N1a-N1ab	299 (59.8 %)	3 (6.8 %)	<b>0.0000</b>
M1	68 (13.6 %)	1 (2.3 %)	<b>0.0304</b>
Intra-thyroid invasion	397 (79.4 %)	15 (34.1 %)	<b>0.0000</b>
Extra-thyroid invasion	216 (43.2 %)	0 (0.0 %)	<b>0.0000</b>
Multifocal growth	93 (18.6 %)	1 (2.3 %)	<b>0.0060</b>
Disease stage: I	432 (86.4 %)	43 (97.7 %)	<b>0.0304</b>
II	68 (13.6 %)	1 (2.3 %)	<b>0.0304</b>
<b>Patients of 19–40 years</b>	<b>n=1991</b>	<b>n=121</b>	
Tumors above 20 mm	659 (33.1 %)*	80 (66.1 %)	<b>0.0000</b>
Category: T3-T4	560 (28.1 %)*	39 (32.2 %)	0.3307
N1a-N1ab	826 (41.5 %)*	17 (14.0 %)	<b>0.0000</b>
M1	43 (2.2 %)*	0 (0.0 %)	0.1024
Intra-thyroid invasion	1339 (67.3 %)*	57 (47.1 %)	<b>0.0000</b>
Extra-thyroid invasion	443 (22.3 %)*	9 (7.4 %)	<b>0.0001</b>
Multifocal growth	346 (17.4 %)	10 (8.3 %)	<b>0.0093</b>
Disease stage: I	1938 (97.3 %)*	120 (99.2 %)	0.0560
II	53 (2.7 %)*	1 (0.8 %)	0.2142
Mortality	5 (0.3 %)	1 (0.8 %)	0.5276
<b>Patients of 41–60 years</b>	<b>n=1846</b>	<b>n=273</b>	
Tumors above 20 mm	480 (26.0 %)*	90 (33.0 %)*	<b>0.0154</b>
Category: T3-T4	365 (19.8 %)*	61 (22.3 %)*	0.3223
N1a-N1ab	451 (24.4 %)*	40 (14.7 %)	<b>0.0003</b>
M1	8 (0.4 %)*	8 (2.9 %)	<b>0.0000</b>
Intra-thyroid invasion	885 (47.9 %)*	110 (40.3 %)	<b>0.0181</b>
Extra-thyroid invasion	294 (15.9 %)*	42 (15.4 %)*	0.8190
Multifocal growth	318 (17.2 %)	40 (14.7 %)	0.2893
Disease stage: I	1190 (64.4 %)*	165 (60.4 %)*	0.1961
II	166 (9.0 %)*	41 (15.0 %)*	<b>0.0017</b>
III	262 (14.2 %)*	40 (14.7 %)*	0.8394
IV	228 (12.4 %)	27 (9.9 %)	0.2434
Mortality	17 (0.9 %)*	10 (3.7 %)	<b>0.0001</b>
<b>Patients above 60</b>	<b>n=481</b>	<b>n=90</b>	
Tumors above 20 mm	162 (33.7 %)*	36 (40.0 %)	0.2475
Category: T3-T4	127 (26.4 %)*	29 (32.2 %)	0.2555
N1a-N1ab	126 (26.2 %)	15 (16.7 %)	0.0543
M1	9 (1.9 %)*	2 (2.2 %)	0.8351
Intra-thyroid invasion	227 (47.2 %)	38 (42.2 %)	0.3854
Extra-thyroid invasion	111 (23.1 %)*	20 (22.2 %)	0.8595
Disease stage: I	241 (50.1 %)*	47 (52.2 %)*	0.7122
II	58 (12.1 %)*	10 (11. %)	0.7990
III	73 (15.2 %)	20 (22.2 %)	0.0966
IV	109 (22.7 %)*	13 (14.4 %)	0.0809
Mortality	36 (7.5 %)*	12 (13,3 %)*	<b>0.0304</b>

Note: \* – <0.01 vs. the previous age group

As the body ages (19–60 years), the frequency of large tumors as well as tumors of T3-T4 categories be-

comes lower; however, this index remains higher in FTC patients (Table 4). Simultaneously, among these patients the percent of multifocal tumors gradually increases, although this index and the frequency of tumors with intra- and extra-thyroid invasion is lower than in PTC cases. Besides, distant metastases were found more often in FTC patients of 41–60 years comparing to PTC ones. Therefore, among the absolute majority of patients of 19–40 years, the I disease stage is detected; in patients of 41–60 years this percent is significantly lower, but it is not different for these carcinoma types. The patients mortality (especially among FTC ones) is higher among elder persons. That is why the indices of patients survival among PTC as well as among FTC patients is decreased (Table 2).

The lowest survival level is detected among patients above 60. Should be noted the wide-spreading of large tumors, tumors of T3-T4 categories, multifocal neoplasms as well as those of extra-thyroid invasion and distant metastases concerns only PTC patients; it is less seen in FTC cases. The disease stages I or II have been found in 60 % of thyroid carcinoma cases. No significant difference pertaining the wide-spreading of PTC and FTC with different properties has been registered among

patients above 60, the mortality of FTC patients above 60 being, however, the highest (Table 4).

The worse prognosis for FTC patients may be also due to different biological characteristics of tumors. For instance, the analysis of cumulative patients survival depending on the tumor size demonstrates in cases of microcarcinoma the survival dynamics during the observation term is the same for both PTC and FTC patients; however, if the tumor size increases, the dynamics becomes worse for PTC patients and still more unfavorable for FTC ones (Table 5).

The analysis of possible causes leading to decreased survival of patients depending on the tumor size suggests the percent of patients with metastatic carcinoma becomes higher (especially for PTC belonging to the N1ab category and FTC of N1a and N1b categories) according to the increased tumor sizes (Table 6). The percent of PTC patients with multifocal tumor growth and intra- or extra-thyroid invasion becomes also higher. Such dynamics rate is lower pertaining the percent of FTC patients, the mortality level of patients becoming, however, increased namely among FTC ones when the tumor size becomes larger.

Table 5

Cumulative patients survival with papillary and follicular thyroid carcinomas of different biological characters, %

Groups	Papillary carcinoma					Follicular carcinoma				
	survival term, years				P <sub>L</sub> -value	survival term, years				P <sub>L</sub> -value
	2	5	10	20		2	5	10	20	
<i>tumor size</i>										
<10 mm	100	100	100	100	<b>0.000</b>	100	100	100	100	<b>0.000</b>
11–20 mm	99.8	99.6	99.6	99.6		98.8	98.8	97.9	97.9	
21–40 mm	99.2	98.8	98.1	97.8		98.8	96.6	94.4	92.8	
>40 mm	94.6	92.6	90.2	89.5		92.9	90.0	82.9	82.9	
<i>multifocal growth property</i>										
absent	99.6	99.2	99.1	99.1	<b>0.000</b>	98.9	97.6	95.9	95.2	<b>0.002</b>
present	98.3	97.6	96.0	95.2		92.5	92.5	88.4	–	
<i>intra-thyroid invasion</i>										
absent	100	99.7	99.5	99.5	<b>0.000</b>	99.0	98.6	97.5	97.5	<b>0.003</b>
present	98.9	98.5	97.8	97.6		97.0	95.0	91.8	90.5	
<i>extra-thyroid invasion</i>										
absent	99.9	99.8	99.6	99.6	<b>0.000</b>	99.0	98.8	97.2	97.2	<b>0.000</b>
present	97.2	96.0	94.8	94.1		93.5	87.8	82.0	78.1	
<i>Category</i>										
T1	100	100.0	100	100.0	<b>0.000</b>	99.5	99.5	99.5	99.5	<b>0.000</b>
T2	100	100.0	100	100.0		100	100	98.0	98.0	
T3	99.0	99.0	98.0	98.0		93.5	91.0	86.0	84.0	
T4a	94.0	91.0	90.0	90.0		95.5	86.0	79.0	79.0	
T4b	46.0	29.0	0	0	–	–	–	–		
N0	99.9	99.7	99.4	99.4	<b>0.000</b>	99.0	98.4	96.8	96.0	<b>0.000</b>
N1a	99.9	99.8	99.8	99.1		93.8	90.0	90.0	90.0	
N1b	98.6	98.2	96.6	95.4		100	100	100	–	
Nab	96.9	95.8	94.7	94.7		90.0	83.4	69.8	69.8	
M0	99.4	99.1	98.8	98.6	<b>0.000</b>	98.5	97.0	96.0	95.5	<b>0.000</b>
M1	97.7	94.9	92.9	91.6		75.0	75.0	40.0	–	

Table 6

Cohort of thyroid carcinoma patients: frequency of patients with carcinoma of different properties, frequency of disease stages, and mortality among patients with papillary and follicular carcinoma of different sizes, n (%)

Index	Carcinoma		P <sub>χ</sub> <sup>2</sup> value
	papillary	follicular	
<b>Tumor size below 10 mm</b>	<b>n=1487</b>	<b>n=122</b>	
Category: N1a	175 (11.8 %)	3 (2.5 %)	<b>0.0016</b>
N1b	82 (5.5 %)	2 (1.6 %)	0.0643
N1ab	80 (5.4 %)	0 (0.0 %)	<b>0.0085</b>
M1	8 (0.5 %)	1 (0.8 %)	0.6883
Multifocal growth	198 (13.3 %)	6 (4.9 %)	<b>0.0073</b>
Intra-thyroid invasion	684 (46.0 %)	6 (29.5 %)	<b>0.0004</b>
Extra-thyroid invasion	137 (9.2 %)	9 (7.4 %)	0.4972
<b>Tumor size: 11–20 mm</b>	<b>n=1794</b>	<b>n=163</b>	
Category: N1a	277 (15.4 %)*	11 (6.7 %)	<b>0.0057</b>
N1b	137 (7.6 %)*	4 (2.5 %)	<b>0.0141</b>
N1ab	232 (12.9 %)*	8 (4.9 %)*	<b>0.0087</b>
M1	29 (1.6 %)*	2 (1.2 %)	0.7029
Multifocal growth	331 (18.5 %)*	27 (16.6 %)*	0.5509
Intra-thyroid invasion	1127 (62.8 %)*	81 (49.7 %)*	<b>0.0009</b>
Extra-thyroid invasion	362 (20.2 %)*	23 (14.1 %)	0.0620
Mortality	4 (0.2 %)	3 (1.8 %)	<b>0.0012</b>
<b>Tumor size 21–40mm</b>	<b>n=1161</b>	<b>n=157</b>	
Category: N1a	151 (13.0 %)	11 (7.0 %)	<b>0.0316</b>
N1b	103 (8.9 %)	8 (5.1 %)	0.1712
N1ab	268 (23.1 %)*	11 (7.0 %)	<b>0.0000</b>
M1	60 (5.2 %)*	6 (3.8 %)	0.4678
Multifocal growth	248 (21.4 %)*	24 (15.3 %)	<b>0.0000</b>
Intra-thyroid invasion	780 (67.2 %)*	68 (43.3 %)	<b>0.0000</b>
Extra-thyroid invasion	390 (33.6 %)*	26 (16.6 %)	<b>0.0000</b>
Mortality	18 (1.6 %)	8 (5.1 %)	<b>0.0027</b>
<b>Tumor size: above 40 mm</b>	<b>n=376</b>	<b>n=86</b>	
Category: N1a	44 (11.7 %)	8 (9.3 %)	0.5252
N1b	33 (8.8 %)	6 (7.0 %)	0.5880
N1ab	121 (32.2 %)*	6 (7.0 %)	<b>0.0000</b>
M1	31 (8.2 %)*	2 (2.3 %)	0.0545
Multifocal growth	97 (25.8 %)	9 (10.5 %)	<b>0.0022</b>
Intra-thyroid invasion	257 (68.4 %)*	35 (40.7 %)	<b>0.0000</b>
Extra-thyroid invasion	175 (46.5 %)*	13 (15.1 %)	<b>0.0000</b>
Mortality	32 (8.5 %)	13 (15.1 %)	0.0679

Note: \* – <0.01 vs. the previous group

In cases of FTC patients, the presence of N1ab category tumor is more negative, the patients survival reaching 100 % in cases of carcinoma belonging to the N1b category (Table 5). PTC intranodal metastases are of lesser impact on the patients' survival comparing to distant ones; in cases of FTC patients with distant metastases the survival level is drastically lower comparing to PTC patients with distant metastases (Table 5).

Multifocal tumor growth is a negative prognostic factor for all patients of our cohort, being however, more important for FTC patients (Table 5), although the percent of such carcinoma is lower comparing with PTC ones (Table 1). The impact of extra-thyroid invasion on prognosis for the cohort patients, especially for FTC ones; in cases of intra-thyroid invasion the prognosis is better, the difference between indices for PTC and FTC patients being, however, kept (Table 5).

Since the neoplasm size and its invasive characters are prognostic factors determining the patient's survival with thyroid carcinoma, it is clear the T category is also prognosis-associated. The survival of PTC patients of T1 and T2 categories reaching 100 %, this trend is less strongly marked, the level of patients survival being, however, high (Table 5). The increase of T category (T3, T4a) makes the survival difference between PTC and FTC patients more perceptible. The worst is prognosis for PTC patients of the T4b category.

The list of important prognostic factors includes also the disease stage. For the cohort patients with the 1<sup>st</sup> disease stage, the survival level reaches 100 % independently on any histological type of carcinoma (Table 7). At the same time, the increase of the disease stage lead to significant drop of patients survival both in PTC and FTC cases, the most unfavorable prognosis coincides with the stage IVc.

The surgical intervention volume and radio-iodine therapy are also thought to belong to important clinical prognostic factors. The increased aggressiveness of intervention (from total thyroidectomy up to thyroidectomy together with lymph nodes dissection) in accompanied by moderate decrease of PTC patients survival (Table 7). The survival of patients following thyroid resection is intermediate comparing with persons with hemithyroidectomy; this index is lower than in persons following total thyroidectomy. The radio-iodine therapy promotes the survival of PTC patients, this index being, however, is not dependent on the quantity of courses realized. In cases of FTC, any positive radio-iodine therapy effect is absent (Table 7). The relapse presence decreases the survival levels for PTC and FTC patients; the drop of this index becomes especially impetuous in later post-operation terms, this tendency being more manifested in FTC patients comparing to PTC ones (Table 7).

Taking into consideration all the prognostic factors that are able to impact on the survival level of patients with thyroid carcinoma (it is realized, for example, in the MACIS system), it is possible to obtain an integrated index describing the level of patients survival level. According to this index, the survival levels of PTC and FTC patients of the I disease stage having the score quantity below 6, differ insignificantly (Table 7). However, the increase of factors quantity taken for calculation and being unfavorable for prognosis (increase of scores quantity), decreases significantly the patients survival. It is especially clear from the survival level of FTC patients with the score quantity above 8 (III–IV disease stages) whose survival percent during 10 years is as low as 20 % despite the fact that this level for PTC patients is 66 %.

Table 7

Cumulative patients survival with papillary and follicular thyroid carcinoma with different clinical properties, %

Groups	Papillary					Follicular				
	survival term, years				P <sub>L</sub> -value	survival term, years				P <sub>L</sub> -value
	2	5	10	20		2	5	10	20	
<b>disease stage</b>										
I	100	100	100	100	<b>0.000</b>	100	100	100	100	<b>0.000</b>
II	100	100	98.0	98.0		98.0	98.0	95.0	95.0	
III	100	100	97.0	97.0		91.0	89.0	84.0	77.0	
IVa	96.0	94.0	91.0	88.0		94.0	85.0	79.0	79.0	
IVb	42.0	22.0	–	–		–	–	–	–	
IVc	61.0	48.0	16.0	0		71.0	71.0	0	0	
<b>operation volume</b>										
TE	99.7	99.5	99.2	99.2	<b>0.000</b>	99.1	98.8	96.0	95.2	<b>0.000</b>
hemiTE	99.1	98.3	97.7	97.7		98.9	97.6	96.2	96.2	
TE+ dissection	98.3	97.6	96.9	96.4		89.4	83.0	83.0	83.0	
<b>radio-iodine therapy</b>										
not done	98.4	97.5	97.5	97.5	<b>0.006</b>	97.7	96.4	95.1	95.1	0.769
done	99.4	99.1	98.6	98.4		98.2	97.2	94.8	94.1	
1–3 courses	99.4	99.1	98.6	98.4	0.907	98.1	97.1	94.6	93.9	0.422
4–6 courses	100	98.7	98.7	98.7		100	100	100	100	
> 7 courses	100	100	100	100		–	–	–	–	
<b>relapse</b>										
absent	99.5	99.2	98.8	98.7	<b>0.000</b>	98.0	97.8	96.0	95.5	<b>0.000</b>
present	98.2	96.0	91.3	91.3		79.0	79.0	65.0	65.0	
<b>MACIS system</b>										
< 5.99 scores	100	100	99.8	99.8	<b>0.000</b>	100	99.8	98.5	98.5	<b>0.000</b>
6–6.99 scores	99.0	97.2	95.8	95.8		91.5	86.0	86.0	–	
7–7.99 scores	96.2	94.4	93.0	90.4		93.5	93.5	71.5	–	
> 8 scores	81.0	74.4	66.2	64.6		73.0	58.5	20.0	–	

Note: TE – thyroidectomy

### 6. Discussion

The obtained results concerning the worse prognosis for FTC patients coincide with the data obtained by other authors, which do conform to the opinion that histological type of thyroid carcinoma is a significant prognostic factor [4, 5]. The causes stipulating for this phenomenon are not still completely understood. Of interest, the opinion on the negative prognosis associated with the FTC diagnosis was refuted in earlier studies [7].

While analyzing the causes supposed to be important for disease prognosis and to impact on the patient’s survival of malignant thyroid tumors, the researches examine a lot of factors – patients’ age and sex, tumors size and characteristics, volume of operative intervention, and quality of post-operative management. As to the importance of sex as a prognostic factor for PTC patients, this problem is still discussed [1, 2]; the male sex is mostly thought to be unfavorable for prognosis [8–11]. The lower survival level found by us for both sexes of FTC patients comparing to PTC ones is associated with higher frequency of patients with larger in size

FTC, although for both types of carcinoma, male sex is a negative prognostic factor.

The analysis of data for 124 FTC patients permitted to conclude that the age belongs to the most important prognostic factors for this type of carcinoma [12]; currently, it is also correct for PTC [8, 10]. According to our data, PTC of large size, metastasis and invasive, are mostly observed in patients below 18 (comparing to elder ones); it meets completely the current ideas on “pediatric” PTC [13]. Simultaneously, aggressive FTC wide-spreading in patients below 18 is significantly lower. It is namely this is a circumstance levels the role of thyroid carcinoma histological type in the survival of patients below 18. The increase of patient’s age (up to 60) is accompanied by decreased frequency of PTC sizes above 20 mm as well as tumors with metastases and intra- or extra-thyroid invasion, but not of multifocal ones. It reflects more significantly the levels of both mortality increase and drop of FTC patient’s survival. In cases of both PTC and FTC patients, the most unfavorable survival prognostic factor is patient’s age

above 60 that coincides with other authors opinion [2, 9, 14] underlining that unsatisfactory therapy results in elderly patients are due to their worsened general condition state as well as to their decreased treatment tolerance. According to our data, among patients above 60 (comparing to patients of 41–60) the frequencies of large PTC as well as of tumors with multifocal growth character begin to increase. As to FTC, there is higher wide-spreading of carcinoma with extra-thyroid invasion, the significance of such changes being, however, not confirmed.

The increase of differentiated thyroid carcinoma sizes is shown to be associated with increased patient's mortality; it is considerable higher in cases of tumor sizes exceeding 40 mm [2]. However, in the available literature there are also data concerning microPTC with aggressive properties, the lesser tumor size being no guarantee of positive prognostic results [15]; simultaneously, it is seen more oft tumors above 10 cm to be more aggressive [16]. Multivariate analysis shows that important factors associated with greater tumor size include tumor histological type, multifocality, extra-thyroid invasion, and distant metastases [17]. The decreased survival levels among PTC patients may be due to increased frequency of more aggressive tumors accompanied by their size increase. In FTC cases the conclusion is not so unambiguous; the cause of more significant drop of these patients survival comparing to PTC ones may be associated with a complex of factors including both increased frequency of aggressive tumors and twice higher relative quantity of elderly (above 60) FTC patients in the cohort (19.7 % of FTC patients and 10 % of PTC ones).

The distribution of patients in groups containing different sizes tumors meets the requirements of the current trend, however recently the authors carry out such distribution using some more lesser steps (10 mm), grouping separately also tumors whose sizes are 41–50 and above 50 mm. It has given a chance to understand the patients 8-years-old survival to be significantly lower namely in cases of tumors above 50 mm [17]. A “barrier” tumor size has been determined (8.5 mm) above which the frequencies of metastases, multifocality or extra-thyroid invasion become higher [18].

We have found that increase of tumor size is accompanied by higher percent of patients with metastatic PTC, this dynamics being less marked in FTC cases. Different conclusions of authors concerning the impact of regional PTC metastasis upon the survival indices “oscillate” from the complete refuse up to recognition. An accurate evaluation of metastasis impact to the survival of patients is thought to be impossible without standardized criteria for lymph node damage stratification [19]. An especially negative circumstance is the presence of extra-nodal invasion decreasing the 10-years survival term of patients from 99 % (without such invasion) to 73 % (in its presence). Such a decrease is found to be more significant in patients of elder age groups [20]. The extra-nodal invasion is associated with more aggressive tumors, distant metastases, and higher mortality of patients [21]. The current approaches aiming to understand the prognostic role of intra-nodal PTC metastases foresee

not only the registration of metastases presence and their localization, but also the registration of metastatic nodes quantity and the size of the larger among them [22]. Currently the intra-nodal metastases are not thought to be an independent survival prognostic factor. The presence of microscopic damage is associated with a high risk of local relapse, but the role of microscopic metastases is still disputable [19]. It should be emphasized that studies pertaining the prognostic importance of FTC metastasis to lymph nodes are almost absent because of lesser quantity of carcinoma belonging to this histological type and lower frequency of their metastasis to these structures.

The data available on the distant metastasis contribution into the patients survival are significantly different, the 10-year survival term is of wide diapason – from 25 up to 70 % [23, 24]. Such a fact may be due to the presence in the groups analyzed of both PTC and FTC patients (according to our data, the 10-years survival term among FTC patients is twice lower comparing to this index for PTC ones). Besides, a better prognosis is reported for patients whose distant metastases have been found during the disease diagnostic comparing to ones whose distant metastases have been developed on the later stage [23]. The metastases localization is also important for survival prognosis, the metastases of extra-pulmonary localization being “the most negative” [25].

Our results confirm the conclusion attributing the extra-thyroid tumor invasion to negative prognostic markers. This factor has a higher impact on the FTC patient's survival. The survivals of patients with minimally invasive and widely invasive FTC differ almost by two times (97 % and 46 %) [12]. The 100 % survival level is found only for patients below 45 with minimally invasive FTC without vascular invasion. According to other data, the 10-years survival term in cases of widely invasive FTC is by 16 % lower comparing to non-invading ones [5]. Now the problem is discussed on the vascular invasion contribution as the patients survival prognostic factor, while there is already no doubt that in FTC cases the vascular invasion to be an important predictor of distant metastases and necessity of radio-iodine therapy use [26]. Different invasive properties of FTC and PTC may be due to biological characteristics of these carcinoma. The contribution of tumor sizes and extra-thyroid metastases localization for the further disease prognosis is also discussed [27].

The role of multifocal gland damage by tumor is now considered. Thus, multifocal PTC is associated with higher relapse frequency than unifocal one, the survival differences being, however, not significant [28]. Later studies demonstrate the poor prognosis to be mostly associated with tumor size rather than with quantity of tumor foci [29]. According to our data it is exactly this prognostic factor is important.

Discussing the clinical factors, it is necessary to pay attention on a fact that survival of patients following the gland resection is lower comparing to this index for patients after total thyroidectomy. It may be due to higher quantity of later relapses having developed in the residual gland tissue. As the relapse development may be associated with several factors being prognostic ones, but

possessing different effect pertaining PTC and FTC, it is a complex problem to analyze the causes of decreased patients survival in cases of thyroid carcinoma belonging to these histological types. The use of radio-iodine therapy increases the survival of PTC patients, but this process, however, is not dependent on the quantity of courses having been carried out. In FTC cases, any positive effect associated with radio-iodine therapy is less pronounced.

Therefore, there are a lot of factors being important both for PTC and FTC prognosis. It is thought every histological type possesses “its own set of independent prognostic factors”, only patient sex and volume of surgical intervention being general ones [30]. Our data confirm that all the prognostic factors having been analyzed in our study for both types of thyroid carcinoma are really significant for prognosis. In our opinion, the most important prognosis factor is the neoplasm size, being associated with other ones – metastases development, multifocal growth, intra- and extra-thyroid invasion, relapse development. The patient age and sex are also of great importance.

Together with a lot of generally known prognostic factors (neoplasm size, patient sex, extra-thyroid invasion, distant metastases), other, additional factors should be taken into account to calculate the risks of relapses or

death [19]. These factors may be more specific, in particular, in cases of thyroid carcinoma belonging to different histological types.

This study has the following limitations. Not all patients were observed the same amount of time after surgery; some patients had primary surgery at other clinics.

## 7. Conclusions

1. In patients below 40 with microcarcinoma, without extra-thyroid neoplasm invasion and metastases (T1N0M0 category, I disease stage), the prognosis following thyroidectomy does not depend on the carcinoma type. Under other conditions, the impact of neoplasm histological type (FTC vs PTC) is more important. In some cases (for men, patients above 60, with tumors above 40 mm, with multifocal growth character, with intra- and, especially, extra-thyroid invasion, with distant metastases, in cases of thyroidectomy and lymph node dissection, relapse presence) the neoplasm type becomes significantly more important.

2. The obtained results confirm the conclusion that histological subtype of differentiated thyroid carcinoma is the most important predictor of diseases persistence/disease relapse or patients mortality.

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