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Research Article

Associations between Prognostic Factors Determining the Survival of Thyroid Papillary Carcinoma Patients

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Abstract:
Several systems enabling the evaluation of prognosis for patients with differentiated thyroid cancers include, together with some other clinical variables, such ones as patient's tumor size and age. Associations between these prognostic factors are not yet completely understood; that is why the aim of this investigation was to study the frequency of thyroid papillary carcinoma spreading with different tumor aggressive characteristics depending on patient sex and age as well as on primary neoplasm size. All these three factors are significant for the disease prognosis, their impact being, however, not the same. The results suggest the tumor size as well as patient age and sex to be also essential and to impact on the spreading of tumor characters determining their aggressiveness. The effect of the tumor size differs in patients of different sex and age.

Keywords: Thyroid papillary carcinoma, Prognostic factors, Tumor size, Sex, Age.

Introduction

Currently, there are several systems enabling the evaluation of prognosis for patients with differentiated thyroid cancer regarding their life span or/and relapse risk. Algorithms of almost all these systems include, together with some other clinical variables, such ones as patient's tumor size and age: AGES (age, grade, extent, size), MACIS (metastases, age, completeness of resection, invasion, size), AMES (age, metastases, size), DAMES (DNA, age, metastases, size), GAMES (grade, age, metastases, extent, size); there is only a single prognosis system (SAG) taking into consideration the patients age and sex (sex, age, grade) [2].

However, associations between these prognostic factors are not yet completely understood; that is why the aim of this investigation was to study the frequency of thyroid papillary carcinoma spreading with different tumor biological characters (invasive and metastasizing potencies, multifocality) depending on patient sex and age as well as on primary neoplasm size.

Research Methods

Our retrospective study was carried out with a patient cohort having undergone thyroid surgical interventions at the Department of Surgery of the state enterprise "V.P. Komisarenko Institute of Endocrinology and Metabolism, National Academy of Medical Sciences" in 1996-2014. Our cohort includes 4,818 patients, 3,896 females and 922 males among them. Patients' age diapason is between 10 up to 84 years old.

The patients were divided into several groups taking into account their sex, age (up to 18 years; 19-40 years; 41-60 years, and above 60), and neoplasm size (up to 10 mm; 11-20 mm; 21-40 mm; and above 40 mm). We have calculated the spreading frequency of tumors belonging to N1a, N1b, N1ab, M1 categories, with capsular, intra-thyroid, extra-thyroid invasion and also with the presence of multifocal tumor growth.

Research Ethics

The research protocol was approved by the Health Research Ethics Committee of the "V. P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences".

Data Analysis

The statistical evaluation of data obtained was made using Pearson's criterion (P_χ) of distribution concordance (χ^2). The cumulative survival curve was plotted according to the Kaplan-Meyer approach, a non-parametric Log-rank test (P_L) having been used to compare the index value of cumulative survival in groups. The statistical calculations are realized using the statistical program package «Statistica 12" by StatSoft, Inc. The critical significance level taken here is 0.05.

Results

The survival of papillary carcinoma patients is lower for male sex persons (Fig. 1; P = 0.0374), patients above 60 (Fig. 2; P = 0.0000), and persons with carcinoma whose size is above 20 mm and especially above 40 mm (Fig. 3; P = 0.0000). It is evident all these three factors are significant for the disease prognosis, their impact being, however, not the same.

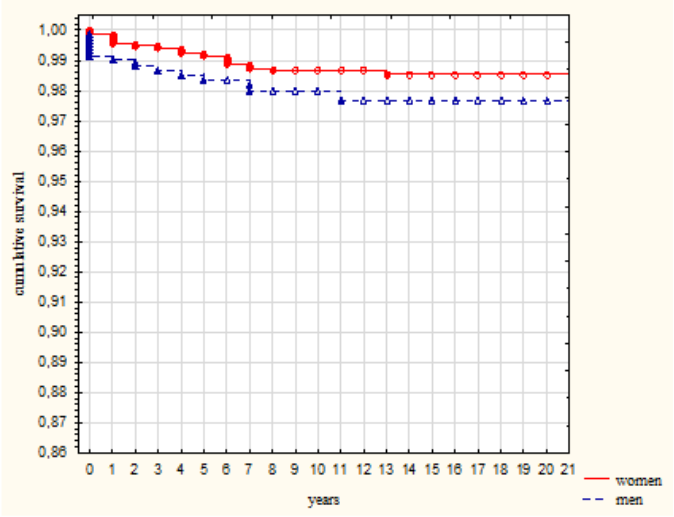

Fig. 1. Survival cumulative curves for patients of different sex with papillary carcinoma.

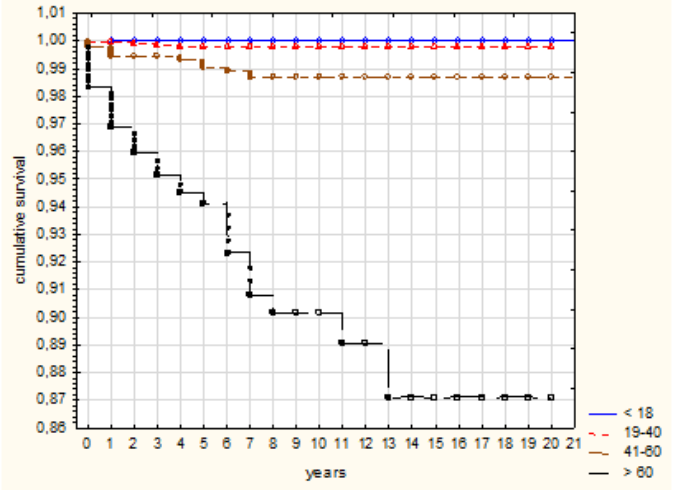

Fig. 2. Survival cumulative curves for patients of different age with papillary carcinoma.

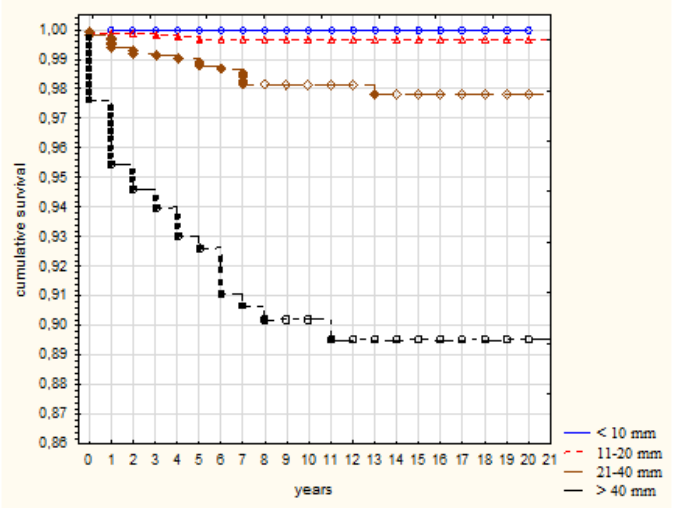

Fig. 3. Cumulative survival curves for patients with thyroid papillary carcinoma of different size.

Simultaneously, our results suggest the tumor size as well as patient age and sex to be also essential and to impact on the spreading of tumor characters determining their aggressiveness. For instance, the separate analysis of factors mentioned here shows the increase of papillary carcinoma size to be accompanied by spreading of metastasizing tumors (it is especially clear for carcinoma belonging to N1ab and M1 categories) and for invasive neoplasms (especially for ones with extra-thyroid invasion) being less significant for multifocal tumors (Table 1).

Table 1. Percent of thyroid papillary carcinoma patients with tumors of different sizes and different characters (n, %)

Indices	Quantity of patients with tumor sizes:			
	up to 10 mm (n = 1,487)	11-20 mm (n = 1,794)	21-40 mm (n = 1,161)	above 40 mm (n = 376)
Category: N1a	175 (11.8 %)	277 (15.4 %)*	151 (13.0 %)	44 (11.7 %)
N1b	82 (5.5 %)	137 (7.6 %) *	103 (8.9 %)	33 (8.8 %)
N1ab	80 (5.4 %)	232 (12.9 %)*	268 (23.1 %)*	121 (32.2 %)*
M1	8 (0.5 %)	29 (1.6 %) *	60 (5.2 %) *	31 (8.2 %) *
Multifocal growth	198 (13.3 %)	331 (18.5 %)*	248 (21.4 %)*	97 (25.8 %)
Intra-thyroid invasion	684 (46.0 %)	1127 (62.8 %)*	780 (67.2 %)*	257 (68.4 %)
Extra-thyroid invasion	137 (9.2 %)	362 (20.2 %)*	390 (33.6 %)*	175 (46.5 %)*

* – difference from previous data (on respective characters) for the group is significant (P<0.05).

In turn, in children and adolescent patients where aggressive tumors percent (both invasive and metastasizing ones) is higher, lower frequency of micro-carcinoma and higher frequency of great tumors (above 21-40 mm) has been registered (Table 2). At the same time, in patients above 60 (comparing to the previous group), the frequency of great tumors as well as of neoplasms belonging to N1ab and M1 categories, tumors with multifocal growth and extra-thyroid invasion becomes increased. Among male patients, the percent of aggressive tumors (of the M1 category and invasive ones) is higher, the percent of papillary carcinoma above 40 mm being also higher (Table. 3).

Table 2. Percent of thyroid papillary carcinoma patients of different age with tumors of different characters (n, %)

Indices	Quantity of patients with tumor sizes:			
	up to 18 years (n = 500)	19-40 years (n = 1,991)	41-60 years (n = 1,846)	above 60 (n =481)
Size: up to 10 mm	75 (15.0 %)	605 (30.4 %)*	646 (35.0 %)*	161 (33.5 %)
11-20 mm	189 (37.8 %)	727 (36.5 %)	720 (39.0 %)	158 (32.8 %)*
21-40 mm	193 (38,6 %)	485 (24.4 %)*	373 (20,2 %)*	110 (22.9 %)
> 40 mm	43 (8.6 %)	174 (8.7 %)	107 (5.8 %)*	52 (10.8 %)*
Category: N1a	67 (13.4 %)	338 (17.0 %)*	200 (10.8 %)*	42 (8.7 %)
N1b	36 (7.2 %)	160 (8.0 %)	121 (2.5 %)	37 (7.7 %)
N1ab	196 (39.2 %)	328 (16.5 %)*	130 (7.0 %)*	47 (9.8 %)*
M1	68 (13.6 %)	43 (2.2 %)*	8 (0.4 %)*	9 (1.9 %)*
Multifocal growth	93 (18.6 %)	346 (17.4 %)	318 (17.2 %)	115 (23.9 %)*
Intra-thyroid invasion	397 (79.4 %)	1339 (67.3 %)*	885 (47.9 %)*	227 (47.2 %)
Extra-thyroid invasion	216 (43.2 %)	443 (22.3 %)*	294 (15.9 %)*	111 (23.1 %)*

* – difference from previous data (on respective characters) for the age group is significant (P<0.05).

Analyzing our cohort data when taking simultaneously into consideration three factors (age, sex, and tumor size) we have found the spreading of papillary carcinoma belonging to the N1a category among patients below 18 to fluctuate from 13 up to 19% depending on the tumor size: from 14 up to 18% in patients of 19-40 years, from 8 up to 13% in patients of 41-60 years, and from 5 up to 14 % in patients above 60 No "general rule" regarding such tumor spreading

Table 3. Percent of thyroid papillary carcinoma patients of different sex with tumors of different characters (n, %)

Indices	Quantity of	
	women (n = 3,896)	men (n = 922)
Size: up to 10 mm	1215 (31.2 %)	272 (29.5 %)
11-20 mm	1483 (38.1 %)	311 (33.7 %) *
21-40 mm	935(24.0 %)	226 (24.5 %)
> 40 mm	263 (6.8 %)	113 (12.3 %) *
Category: N1a	509 (13.1 %)	490 (53.1 %) *
N1b	268 (6.9 %)	138 (15.0 %)
Nab	494 (12.7 %)	87 (9.4 %) *
M1	92 (2.4 %)	207 (22.5 %) *
Multifocal growth	718 (18.4 %)	36 (3.9 %) *
Intra-thyroid invasion	2269 (58.2 %)	579 (62.8 %) *
Extra-thyroid invasion	819(21.0 %)	245 (26.6 %) *

* – difference for data in women group (on respective characters) is significant ($P < 0.05$).

dependent on capillary carcinoma size has been found. Such a statement concerns also carcinoma belonging to the N1b category being very similarly common, from 6 to 9 %, among different age patients, their frequency becoming as high as 17.8 % in female patients above 60.

Simultaneously, the spreading frequency of papillary carcinoma belonging to the N1ab category among girl patients as well as among females (19-40 years old) becomes progressively higher in parallel to the increase of tumor size. Such a general rule is less marked for male patients (Figs. 4, A, B). In elderly patient groups, the inter-dependence of tumor spreading frequency and wide metastasizing looses its significance (Figs. 4, C, D). It should be underlined the frequency of N1ab category carcinoma above 40 mm to be higher in males of all groups comparing to women.

In all the groups having been analyzed the frequency of papillary carcinoma with capsular invasion is high, reaching: 75-96 % for women and 75-100 % for men; however, there is no dependence of this character frequency on the tumor size. No association between papillary carcinoma size and the development of intra-thyroid invasion has been registered among both females and males below 40 (Figs 4, A, B). Such an association becomes, however, gradually seen

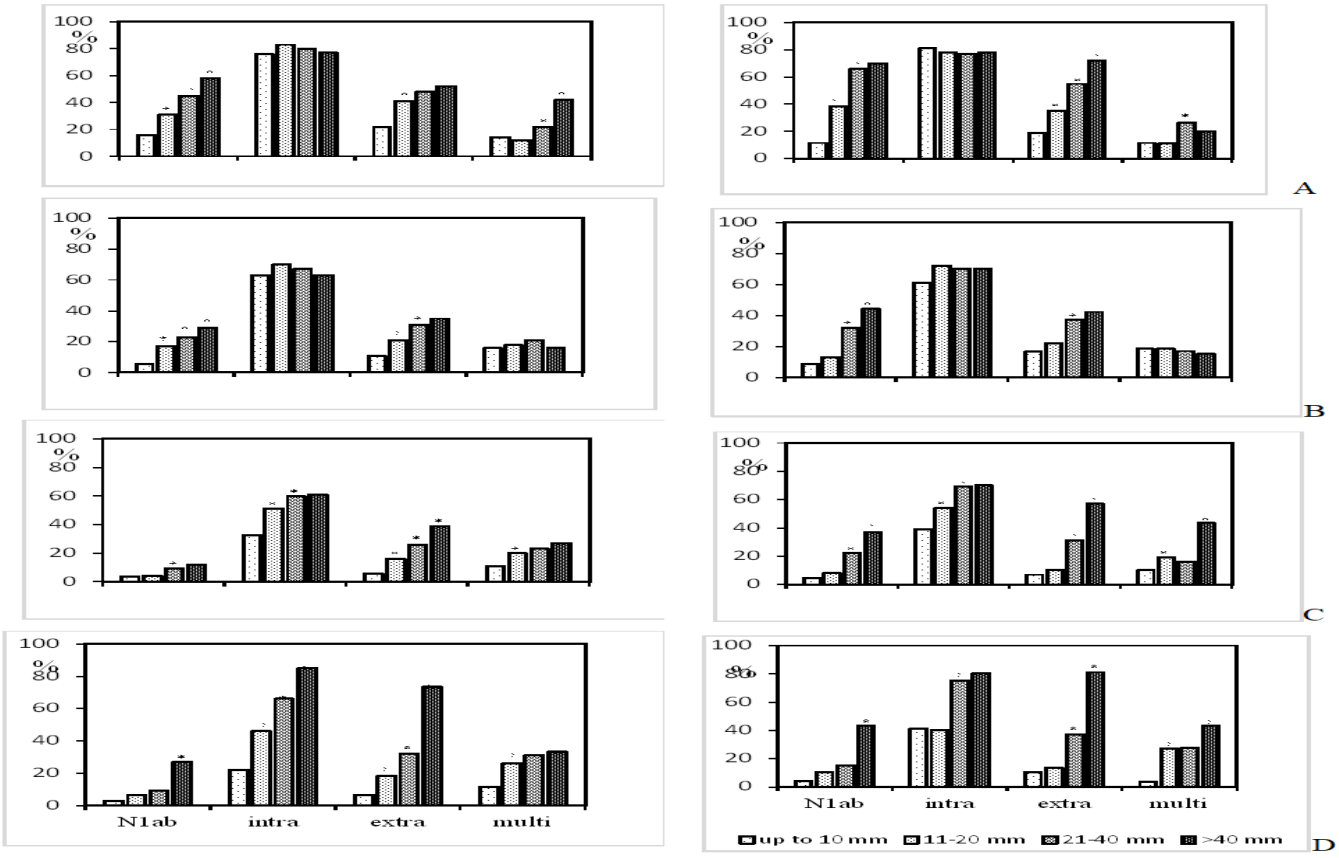

Fig. 4. Spreading of thyroid papillary carcinoma with different characters depending on neoplasm size and patient. age and sex. I – women; II – men; A – below 18; B – 19-40 years; C – 41-60 years; D – above 60. * - difference from previous data (on respective characters) for the age group is significant ($P<0.05$).

with patient age increase (Fig. 4, C, D) being the most markedly expressed in females above 60 (see Fig 1, D). It is

namely among these patients as well as among females of 41-60 years a clear association is seen between the tumor size and the spreading of extra-thyroid invasion (see Figs 4, C, D); among men patients this association is the clearest for children and adolescents (Fig. 4, A); in elder male patients, it is registered only in cases of carcinoma with sizes 21-40 and above 40 mm (see Figs. 2, B, C, D).

The association between capillary carcinoma size and the development of its multifocal growth in patients of different sexes is absent; we have seen its frequency to be higher among patients with great tumors, both girls and men above 40 (Fig. 4, A, C, D).

Discussion

It is well known the incidence of differentiated thyroid cancer to be significantly higher among females comparing to males [1]. At the same time, in our patient cohort papillary carcinoma of higher size (21-40 mm and above 40 mm), metastasizing (N1b, Nab, M1) neoplasms and invasive tumors are found more oft in men. Consequently, more aggressive carcinoma are detected more oft in male patients comparing to female ones. Such a fact may be a cause determining the male survival in papillary carcinoma cases to be somewhat lower comparing to female one. The available literature data present contradictory information leading to doubts concerning the prognostic significance of sex factor [4, 8, 12]. According to some information, the sex factor has been found to be a significant prognostic one; however, the use of multivariate analysis abolishes this opinion [11]. Our results, however, support conclusions suggesting the male sex to be an unfavorable prognostic factor for patients with papillary carcinoma [7, 10, 13].

Analysis of age-dependent cumulative patients survival has been carried out for 4 patient groups, as it is currently recommended, taking into consideration a recent discussion regarding the necessity of age limit correction (before and after 45 years), this limit being taken into account when the disease stage is to be determined [3, 5, 7, 9, 10, 13]. Among our cohort patients, the worst results have been found for persons above 60 років. All the clinical surveys suggest currently the mortality of patients with differentiated thyroid cancer to grow with age [6, 7, 13]. While explaining the causes of poorer prognosis, the following facts are to be taken into account. The age group of patients above 60 contains higher percent of patients with great carcinoma (i.e. higher percent of men with namely such tumors), as well as with metastasizing, multifocal tumors and ones with extra-thyroid invasion.

The increase of tumor size is accompanied by their metastasizing frequency, by frequency of their intra- and extra-thyroid invasion, and by multifocal growth. Such facts are present among causes determining the gradual survival prognosis worsening which accompanies the increase of tumor size. Such a fact is also detected by other researchers [7].

Consequently, each factor taken separately – papillary carcinoma size as well as patient's age and sex – is a prognostic one. Aiming to determine the role of their association for patient survival, we have found the papillary carcinoma size to be the most significant among factors mentioned. In young patients, this factor has an effect on tumor metastasizing to neck lymph nodes, in elder persons it is associated with carcinoma invasive characters. These processes are somewhat modulated with such a factor as patient's sex, these general rules being less clear in men. We think these data are certainly to be taken into account for evaluation of disease prognosis in patients with thyroid papillary carcinoma.

Conclusions

The survival level of patients with thyroid papillary carcinoma depends on the neoplasm size determining their aggressiveness. Simultaneously, the effect of this prognostic factor differs in patients of different sex and age.

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