PROGNOSTIC VALUES OF THYROID TUMOURS

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Abstract

Thyroid cancer accounts for approximately 1% of total cancer cases in developed countries. The aim of this study has been to analyze the histopathological variants of thyroid tumours with regard to gender and age. Despite their relative rarity in our material, they exhibit a wide range of morphological patterns and biological behaviour.

During the period from 2001-2007, 138 biopsy cases of thyroid tumours, which were fixed in buffered neutral formalin and embedded in paraffin, have been reviewed. Tissue sections (4μm thick) were cut and stained with hematoxylin and eosin (H&E).

Follicular adenomas have been found in 39, 1% of cases, thyroid carcinomas in 60, 12%, whereas thyroid secondary carcinomas have been found in 0, 72% of cases. As far as histological variants of thyroid carcinomas are concerned, most frequently found were papillary carcinomas in 39,85% of cases; followed by follicular carcinomas in 9,42% of cases; follicular variants of papillary carcinomas in 5,79% of cases; medullary carcinomas in 3,62% of cases, while anaplastic and Hurthle cell carcinomas have been found in 0,72% of cases each. All histological variants of thyroid tumours occurred more frequently in women than in men. Papillary carcinoma has been found in 80% of female cases. Thyroid tumours in our material mainly occurred in the third, the fourth and the fifth decade of life.

Our data indicate that apart from the fact that papillary carcinomas, well differentiated, and characterised by relatively good prognosis, were most frequent variants, certain morphological variants of it were associated with poor prognosis.

KEY WORDS: thyroid, thyroid tumours, histopathology, prognostic values.

Introduction

Human thyroid neoplasia represents a variety of lesions ranging from well-differentiated benign tumours to anaplastic malignant tumours (1). Thyroid tumours can be divided into two groups, nonmedullary and medullary thyroid cancer of hereditary or nonhereditary origin. Nonmedullary includes papillary carcinoma, follicular carcinoma; Hurthle variant of follicular cancer, insular cancer and anaplastic cancer (2). Thyroid cancer represents 1% of all cancers. Women are affected 3 times more than men. Peak incidence is 30-40s. It arises from the two cell types in the gland. Follicular cells cause papillary, follicular, and anaplastic tumours. C-cells produce medullary tumours. A higher proportion of follicular and anaplastic cancers is found in populations with low dietary iodine. 5% female, 75% sporadically and 25% familial preponderance is reported. Familial cases are typically all over the gland, while sporadic frequently are not multifocal. 1, 0%-1, 5% of all new cancer cases are reported in the United States. 3% of patients who die of other causes have occult thyroid cancer and 10% have microscopic cancers. 35% of thyroid gland at autopsy in some studies have papillary carcinomas (<1,0 cm) (Overall, fewer than 5% of nodules are malignant (3, 4, 5).

Well-Differentiated Thyroid Carcinomas (WDTC)-Papillary, Follicular, and Hurthle cell

Pathogenesis of these tumours is unknown. Papillary carcinoma (PTC) has been associated with the RET proto-oncogene; however no definitive link has been proven. Certain clinical factors increase the likelihood of developing thyroid cancer. Histological subtypes are: Follicular variant, tall cell, columnar cell, diffuse sclerosing and Encapsulated. Prognosis is 80% survival at 10 years. Females predominate. Mean age of 35 years (6, 7). Cytological features alone cannot predict patient outcome in PTC. This study indicates for the first time that loss of cellular polarity and the tumour growth pattern are useful parameters for identifying the so called low risk group in common type PTC and in predicting patient outcome in terms of tumour recurrence and cancer related death (8). Microscopic vascular invasion is well recognized in thyroid cancer particularly in the follicular and poorly differentiated histological types. However massive invasion of tumour into the great veins or external compression of the superior vena cava is rare. Lymph node involvement is common. Major route of metastasis is lymphatic. 46%-90% of patients have lymph node involvement. Clinically undetectable lymph node involvement does not worsen the prognosis. Papillary/follicular carcinoma must be considered a variant of papillary thyroid carcinoma (mixed form), and Hürthle cell carcinoma should be considered a variant of Follicular thyroid carcinoma (FTC). In the US about 10-15% of all thyroid cancers are follicular. Thyroid cancers are quite rare, accounting for only 1,5% of all cancers in adults and 3% in children. During the last few years, the frequency of FTC has appeared to increase; however, this increase is related to improvement in diagnostic techniques and a successful campaign of information about this carcinoma. Of all thyroid cancers, 17-20% is follicular. According to world epidemiologic data, follicular carcinoma is the second most common thyroid neoplasm; in some geographic areas, however, FTC is the most common thyroid tumour. Relative incidence of follicular carcinoma is higher in areas of endemic goitre. In papillary carcinoma, it should be noted that histological vascular invasion may be considered as a sign of an increased tendency toward hematogenic invasion and consequent increase in the relative percentage of metastases; ultimately, this means a poorer prognosis. In the presence of risk factors indicating a possible increase in biologic aggressiveness adequate postoperative treatment and close follow up become essential (9). Among 986 patients with differentiated thyroid cancer, 23 presented symptoms and signs of hyperthyroidism. Graves' disease was diagnosed in 11 cases, multinodular goitre in eight, whereas toxic adenoma was found in four cases. Differentiated thyroid cancer found incidentally at surgery for hyperthyroidism has a good prognosis (10). The relative importance of prognostic factors in papillary and follicular thyroid cancer has been studied in 113 patients using Cox's proportional hazards model. Prognostic factors studied were: histology, tumour grade, extra thyroidal growth, nodal involvement, distant metastases at diagnosis, nuclear DNA content, age at diagnosis, and sex. The present study demonstrates that nuclear DNA content is a prognostic factor in those patients with papillary and follicular thyroid cancer without distant metastases at diagnosis (11). The second most important factor was the histological (sub) type (well differentiated papillary carcinoma vs. moderately differentiated papillary carcinoma and follicular carcinoma) (12).

Medullary thyroid Carcinoma (MTC)

It represents 10% of all thyroid malignancies and arises from the parafollicular cell or C-cells of the thyroid

gland, derivatives of neural crest cells of the branchial arches. It secretes calcitonin which plays a role in calcium metabolism. It develops in 4 clinical settings:

- Sporadic MTC (SMTC)
- Familial MTC (FMTC)
- Multiple endocrine neoplasia IIa (MEN IIa)
- Multiple endocrine neoplasia IIb (MEN IIb)

Anaplastic thyroid carcinoma (ATC)
It is a highly lethal form of thyroid cancer. Median survival is 8 months. It represents 1%-10% of all thyroid cancers and affects the elderly (30% of thyroid cancers in patients >70 years), mean age being 60 years. 53% have had previous benign thyroid disease history. Pathology: classified as large cell or small cell. Large cell is more common and has a worse prognosis. Histology: sheets of very poorly differentiated cells, little cytoplasm, numerous mitosis, necrosis, extra thyroidal invasion, 47% have previous history of WDTC (13, 14). The aim of this research has been to analyze the histopathological variants of thyroid tumours with regard to their incidence and prognosis according to the histological type and subtype, gender and age. Despite their relative rarity in our material, they exhibit a wide range of morphological patterns and biological behaviour.

Material and Methods

During the period from 2001-2007, 138 biopsy cases of thyroid tumours, which were classified according to the WHO histological classification as well as pTNM system, have been reviewed. (19) Thyroid tumour tissues were fixed in 10% buffered neutral formalin from Bio-Optica (Italy) and embedded in paraffin (Sigma-Aldrich, Germany). Tissue sections (4μm thick) were cut and stained with hematoxylin-eosion (Merck, Darmstadt, Germany).

Anamnesis:
Anamnestic clinical data were collected from the University Clinical Centre of Kosovo (UCCK) register, as well as follow-up clinic visits of patients referred to the UCC of Kosovo. Specimens from 138 biopsy cases diagnosed at the Institute of Pathology, UCCK, during the period from 2001 to 2007 were reviewed retrospectively. Information regarding gross feature were collected from the protocols.

Analysis in detail:
The data on patients' gender and age; blood tests, thyroid scan, ultrasound and fine needle aspiration cytology results as well as extent of disease, pathomorphological characteristics, therapy, locoregional control, disease-free survival and disease-specific survival, were collected.

Diagnosis:
The 138 cases included in our study had tumours larger than 1cm in diameter.

Histopathological examination, determining the histologic type of the tumour, grading, and staging, as well as other characteristics, such as the vascular extension, infiltration into the adjacent parenchyma or in the thyroid capsule, was performed. The major attributes of the staging system pTNM system (19) were included: age as the most important prognostic factor, below and above the age of 45; T1 tumours were considered to be those below 2 cm; T3 tumours included minor extrathyroidal extension invading the strap muscles; T4 tumours included T4a and T4b, T4a being operable tumours; all anaplastic cancers were T4, although operable anaplastic thyroid cancers were considered to be T4a.

Therapy:
Therapeutic choices were: 1. total thyroidectomy in the treatment of the apparently benign pathology when spread bilaterally (the final histological examination of a cancer should lead to considering the operation adequate); 2. lobo-isthmectomy in the treatment of unilateral benign pathology or suspected FNAB for follicular neoplasm (the histological examination of a cancer led to consider this operation adequate only in presence of favourable prognostic parameters. However, in presence of even one unfavourable variable, we considered the totalisation necessary); 3. total thyroidectomy in presence of a strongly suspected preoperative diagnosis of cancer. The first management stage for those with tumour diameters >1 cm included total thyroidectomy with central node dissection and postoperative 131I ablation (Sigma-Aldrich, Germany. Most patients have undergone fine-needle aspiration cytology for diagnosis and for planning of treatment. Clinical, imaging and biological postoperative monitoring as well as suppress and substitution hormone therapy were mandatory.

Statistical analysis:
Statistically significant differences were analyzed using the χ^2 test. Statistical correlation between possible prognostic factors and the duration of disease-free interval was analyzed by univariate and Cox's multivariate survival analysis.

Results

During our study, out of 138 cases with thyroid tumours, benign tumours (follicular adenomas) have been found in 39,1% of cases, whereas thyroid carcinomas in 60,86% of cases. (Table1. & Figure 1.)

	Nº	%
Benign tumours	54	39,10
Malignant tumours	84	60,86
Total	**138**	**100**

TABLE 1. Thyroid tumours

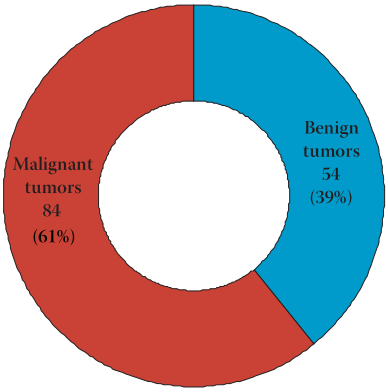

FIGURE 1. Thyroid tumours

From the overall number of cases with thyroid tumours (138), papillary carcinomas have been most frequently found (Table 1a).

Histopathological variants	*Nº*	*%*
Follicular adenoma	54	39,1
Papillary carcinoma	55	39,9
Papillary carcinoma, follicular variant	8	5,79
Follicular carcinoma	13	9,42
Medullary carcinoma	5	3,62
Anaplastic carcinoma	1	0,72
Hurthle cell carcinoma	1	0,72
Secondary thyroid carcinoma	1	0,72
Total	**138**	100,00

TABLE 1a. Histopathological variants of Thyroid tumours

Great statistical significance between histopathological variants of thyroid tumours (χ^2-test = 88, 0, p<0,001) has been found. The tumours with highest frequency of occurrence were papillary carcinoma – pure variant (39, 9%) followed by follicular adenoma (39, 1%).

The graphic shows thyroid tumour incidence according to histological variants. The highest blue and red columns represent the percentage of follicular adenoma and papillary carcinoma (Figure 1a).

	Nº	*%*
Papillary carcinoma	55	65,47
Papillary carcinoma, follicular variant	8	9,52
Follicular carcinoma	13	15,47
Medullary carcinoma	5	5,92
Anaplastic carcinoma	1	1,19
Hürthle cell carcinoma	1	1,19
Secondary thyroid carcinoma	1	1,19
Total	**84**	100

TABLE 1b. Histopathological variants of thyroid cancer

Out of 84 cases of thyroid carcinomas (Table 1b.), 74, 94% papillary carcinomas in total have been found (65,47% pure papillary carcinoma + 9,52% follicular variant of papillary carcinomas), being the most frequent histological variant, while follicular carcinomas were found to be increasing 15,47%. Our results have shown approximately similar percentage in correlation with the published data.

Figure 1b illustrates the percentage of histological variants of thyroid cancer, representing the highest incidence of papillary carcinoma - blue column.

Thyroid tumours in general were more frequent in women than in men (Table 2), 83, 3% vs. 16,7% (≈17%).

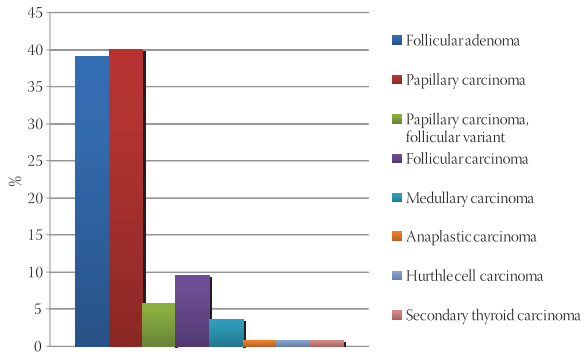

FIGURE 1a. Histopathological variants of thyroid tumour

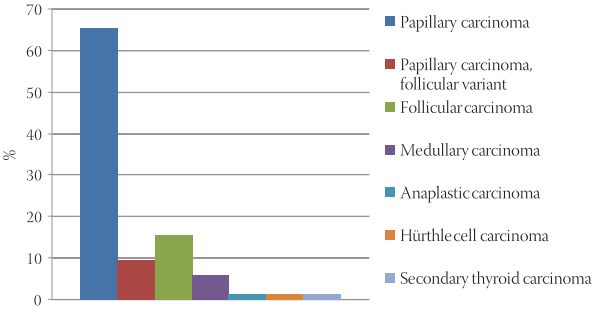

FIGURE 1b. Histopathological variants of thyroid cancer

Histopathological variants	*F*		*M*		*Total*		χ^2-*test* *p-value*
	Nº	%	Nº	%	Nº	%	
Papillary carcinoma	44	80	11	20	55	100	p<0,0001
Follicular variant of Papillary carcinoma	7	87,5	1	12,5	8	100	p<0,0001
Follicular carcinoma	10	76,9	3	23,1	13	100	p<0,0001
Medullary carcinoma	4	80	1	20	5	100	p<0,0001
Anaplastic carcinoma	1	100	0	0	1	100	p<0,0001
Hürthle cell carcinoma	1	100	0	0	1	100	p<0,0001
Follicular adenoma	47	87	7	13	54	100	p<0,0001
Secondary carcinoma	1	100	0	0	1	100	p<0,0001
Total	**115**	**83,3**	**23**	**16,7**	**138**	**100**	p<0,0001

TABLE 2. Thyroid tumours with regard to gender within the period 2001-2007

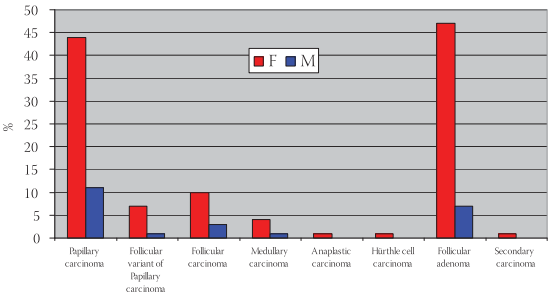

FIGURE 2. Thyroid tumours with regard to gender within the period 2001-2007

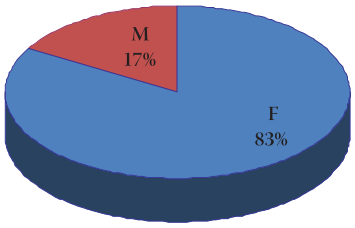

FIGURE 2a. Thyroid tumours with regard to gender within the period 2001-2007

The difference was of great statistical significance (χ^2-test = 61, 3, p<0, 0001). However, histological variants of thyroid tumours were analyzed regarding the gender predominance and it was found that they were all more frequent in women than in men. The most important statistical significance was detected in cases of papillary carcinoma (χ^2-test = 19, 8, p<0, 0001), as well as in follicular adenoma (χ^2-test = 29, 6; p<0, 0001). The highest red columns represent female patients affected by papillary carcinoma and follicular adenoma (Figure 2.). Figure 2a. reflects the gender perspective of thyroid tumours involvement within the period of seven years. Thyroid tumours in our material mainly occurred in the third, the fourth and the fifth decade of life. Age groups under 45 years of age are more affected by papillary carcinoma, whereas those above 45 years of age are affected by other carcinomas (Table 3). The mean age at presentation of thyroid tumours was 39, (SD ± 14,1). As far as follicular adenoma is concerned, the mean age 35, 6 (SD ± 13, 3 age) was presented, while the mean age of papillary carcinoma was 36, 1 (SD ±11, 9 age). Important significance between follicular adenoma and papillary carcinoma regarding the mean age was not found (T-test=0,206, p> 0, 05). The mean age of all malignant variants was 41, 3 (SD ±14, 5). Great statistical significance between benign and malignant cases was found (T-test =2, 32, p<0, 05). The five year survival rates present the percentage of patients who survive 5 years having been diagnosed with thyroid cancer. These rates do not include patients who died from unrelated causes. Papillary and follicular cancer, in our study, have affected age group of 45 years and

Age group (year)	Follicular adenoma		Papillary carcinoma		Follicular variant of Papillary carcinoma		Follicular carcinoma		Anaplastic carcinoma		Medullary carcinoma		Hürthle cell Ca		Secondary carcinoma		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
11 – 20	-	-	5	9,1	1	12,5	-	-	-	-	-	-	-	-	-	-	6	4.3
21 – 30	16	29,6	19	34,5	2	25,0	-	-	-	-	-	-	-	-	-	-	37	26,8
31 – 40	13	24,1	11	20,0	-	-	-	-	-	-	-	-	-	-	-	-	24	17,4
41 – 50	16	29,6	8	14,5	3	37,5	4	30,8	-	-	2	40,0	1	100,0	-	-	34	24,6
51 – 60	4	7,4	6	10,9	-	-	3	23,1	-	-	-	-	-	-	-	-	13	9,4
61 – 70	3	5,6	5	9,1	1	12,5	4	30,8	-	-	3	60,0	-	-	-	-	16	11,6
71 – 80	2	3,7	1	1,8	1	12,5	1	7,7	1	100,0	-	-	-	-	1	100,0	7	5,1
Total	54	100,0	55	100,0	8	100,0	13	100,0	1	100,0	5	100,0	1	100,0	1	100,0	138	100,0
Mean ± SD	35,6 ± 13,3		36,1 ± 11,9		44,0 ± 13,4		52,7 ± 9,9		76		53,0 ± 9,8		43		74		39,1 ± 14,1	

TABLE 3. Thyroid tumours with regard to decades

below stage I, any T, No, Mo; stage II, any T, No, Mo; while follicular cancer has affected age group of 45 years and above stage III, T3, No,Mo. Medullary thyroid cancer was presented with stage IVA, T4a, No, Mo. Anaplastic thyroid cancer was present in one case, stage IV (Table 4).

Stage	Papillary	Follicular	Medullary	Anaplastic
I	70%	65%	0	0
II	30%	25%	0	0
III	0	10%	0	0
IV	0	0	100%	100%

TABLE 4. The five year survival rates of thyroid cancer according to histopathological variants

Five year age-standardised survival rates for thyroid cancer by sex in Kosovo have shown increased incidence and survival rates during the years especially in females (Figure3).

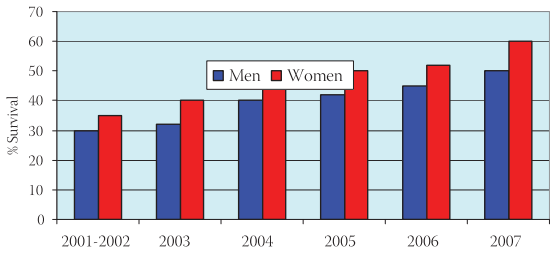

FIGURE 3. Five year age-standardised survival for thyroid cancer by sex for patients diagnosed in Kosovo during 2001-2007

It is important to note that our study has shown that age represents the major factor when determining prognosis for differentiated thyroid cancer. Young people rarely died of this disease regardless of whether the surrounding lymph nodes were affected, tumour was left behind, or the tumour extended into the veins or outside the tissue that encapsulated it. Nevertheless, in older patients all of these factors played a significant role in long term disease-free survival (Figure 4).

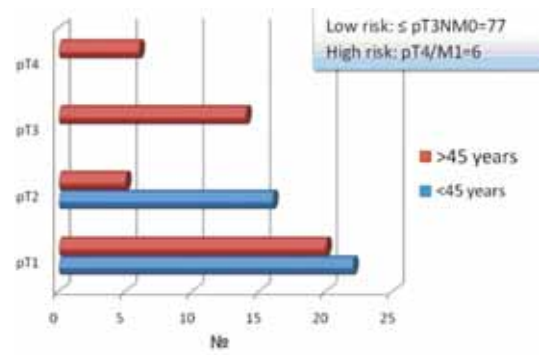

FIGURE 4. Evaluation of thyroid cancer staging by age at diagnosis in Kosovo during the period 2001-2007

Discussion

PTC and FTC are well differentiated slow growing, and have unique characteristics. Factors associated with a less favourable outcome are male sex, family history of papillary cancer, age >40 years, tumour diameter >4 cm, invasive or poorly differentiated tumour and lymph node or distant metastases. PTC is the most frequent endocrine cancer which amount up to 85-95% (15, 16, 17, 18). Our data refers to a percentage 70-80% of PTCs. There are numerous classification systems to determine predictive factors such as: AGES (age, grade, extent, size) classification using Cox model; AMES (age, metastasis and extent, size). All of these classifications showed to be helpful for predicting low and high risk tumours during our study. The age of patient and the size of the tumour can be determined preoperatively, while cytology and biopsy will determine the grade and extent after surgery. (19) It was suggested that the extent of surgery should be based on prognostic parameters, such as gender and lateral neck node metastasis, in patients with PTC. (20) Some investigators have reported that histopathologic characteristics such as the vascular extension, infiltration into the adjacent parenchyma or in the thyroid capsule are all indicative of a poor prognosis. (21) Others have found that longer disease-free interval was found in the patients with a tumour diameter < or =6 mm and without lymph-node metastases. (22) Previous studies have documented that PTC is usually indolent and the prognosis is favourable, with a 10 year survival generally reported to exceed 90%. (23) According to literature, follicular variant of PTC is more aggressive than pure PTC. Other authors support another opinion assuming that the number of patients who are diagnosed as pure PTC may be higher when associated with Hashimoto's thyroiditis. (24) Our study supports the first opinion. It is certainly understandable why in WDTC patients, in addition to traditional risk factors, prognostic factors, such as vascular invasion and capsular invasion, need to be evaluated; not only for achieving an adequate therapeutic approach, but also for avoiding over treatment of low-risk patients. In another study, it was reported that PTCs are associated with metastases and decreased survival in a small group of patients. (25) The incidence of FTC is increasing in Kosovo (15, 47%). In the US the increase of the incidence of the FTC has also been observed recently. Of all

thyroid cancers, 17-20% was follicular. FTCs account for about 20% of all thyroid cancers (1). During our research we have found thyroid cancers of different histological types and subtypes, from well differentiated to low differentiated (Table 1). The biology of thyroid cancer represents a spectrum of behaviour ranging from well-differentiated lesions with an excellent prognosis to ATC, which is almost uniformly fatal. ATC in our material represents less than 1% of cases. ATC (undifferentiated cancer) accounts 1% or even 3% to 5% (26, 27). FTC in Japan is generally a nonaggressive disease with a good prognosis. However, since poorly differentiated or widely invasive carcinomas showed a worse prognosis, postoperative pathological examination is important in predicting patient prognosis. (28)

Gender is an important prognostic factor (29, 30, 31, 32, 33.). According to some authors gender does not play a significant role both in recurrence and survival. (34) Age at presentation is a well-established strong prognostic factor for WDTC. (35, 36,37,38,39). In the paediatric population, PTC is a more aggressive disease. Because paediatric cancers have a better prognosis than their adult counterparts, this does not influence patient outcome. Age can then be considered the most important factor in determining prognosis. (40) Patient age at first treatment and the extent of disease are significant and independent prognostic factors. (41) According to our data, age at presentation is an important risk factor for PTC because it affects younger patients, while FTC patients present with a higher age as well as with more frequent distant and less frequent lymph node metastases. Generally, there are studies which indicate a correlation between cervical lymph node involvement and poor prognosis in WDTCs (42). Our data document that the five year survival rates of thyroid cancer in Kosovo were 70% stage I and 30% stage II for PTC; 65% stage I, 25% stage II and 10% stage III for FTC; while 100% of cases for MTC and ATC. Distant metastases at presentation were an independent prognostic factor only for FTC, but not for PTC (43). This was the case in our study, too. Tumour extension beyond the thyroid capsule (pT4) is one of the strongest prognostic factors (44,45). The increased primary tumour size is a prevalent and accepted factor for poorer prognosis (46, 47, 48, 49, 50, 51.). The 138 cases included in our study had tumours larger than 1cm in diameter. The overall survival rate has been investigated within a five-year period, and it has been found to be 63%, whereas the metastasis-free survival rate was 57%. An older age at the time of diagnosis and a larger tumour size were associated with an increased risk of distant metastases and of cancer-related death.(52) In Kosovo five year-age standardised survival rates increased during the years. High risk patients with thyroid cancer stage pT4/M1 and pT3 were over 45 years of age. Patients < or =40 years of age presenting with pulmonary metastasis from well-differentiated thyroid cancer had an excellent prognosis. Older patients have a poor survival outcome. Postoperative I-131 therapy is recommended in all patients. (53) Prognosis for PTC is not worse in younger patients. Patients with confined intra thyroid lesion (<or=T2, No, Mo) may be regarded "low risk" PTC patients. (54) Low risk patients with thyroid cancer stage pT1 and pT2 in Kosovo were under 45 years of age. Tumour size > 4 cm, distant metastasis, and non-radical tumour resection are the independent predictors of patients survival. Early diagnosis and early therapy can improve significantly the prognosis of MTC. (55, 56) Our patients with MTC have been stage IV. Although the early diagnosis and the extensive surgical treatment of these patients might have influenced the outcome of the MTC, this is not always an indicator of the definitive cure of the disease, due to the capsular infiltration which is a bad prognostic factor.

Conclusion

Our data indicate that besides the fact that PTC were most frequent variants, well differentiated, and characterized by relatively good prognosis, certain morphological variants of this disease were associated with poor prognosis. PTC was presented more frequently in younger patients alongside with lymph node involvement in some cases. Furthermore we have found that the incidence of follicular carcinoma is increasing, which could be related to improvement in diagnostic techniques. They were presented with higher age and more frequent distant metastasis. Laboratory and clinical techniques could help predict whether a particular tumour will behave in an aggressive or benign manner. Combined therapy seems to results in fewer recurrences and better survival than less aggressive initial therapy.

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