

ORIGINAL ARTICLE

Analysis of malignancy predictors for oxyphile thyroid tumors

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Summary

Purpose: In contrast to other thyroid carcinomas it is difficult to establish a correct preoperative diagnosis for oxyphile carcinoma of the thyroid. In this study we looked for predictive malignancy factors in order to enable surgeons to choose operative treatment and to perform an adequate operation for each patient with an oxyphile neoplasm of the thyroid.

Methods: In this retrospective study we have analyzed the medical files of all patients with oxyphile tumors of the thyroid operated between 1999 and 2008 in our institution. A total of 256 patients were included and divided into oxyphile adenomas (142) and carcinomas (114) on the basis of their definite histopathological diagnosis. The most important demographic and clinical characteristics were analyzed by univariate and multivariate logistic regression analysis.

Results: Univariate analysis showed that male gender, thyroglobulin concentrations ≥ 300 ng/ml and tumor diam-

eter >30 mm were significantly more frequent in patients with oxyphile carcinoma compared to patients with oxyphile adenoma, while coexisting Hashimoto thyroiditis and positive AntiTPO antibodies appeared significantly less frequent in the carcinoma group. All variables with a p value <0.1 in the univariate test were subjected to multivariate regression analysis in which elevated preoperative thyroglobulin concentrations (≥ 300 ng/ml) was shown as the only independent predictive factor for oxyphile thyroid carcinomas (OR=5.88, 95%CI 2.78-12.05, $p=0.001$).

Conclusions: Preoperative thyroglobulin concentration is an independent predictor of malignancy for oxyphile thyroid carcinomas.

Key words: Hurthle cell, oxyphile, risk factors, thyroglobulin, thyroid carcinoma, thyroidectomy

Introduction

Thyroid malignancies represent an inhomogeneous group of tumors considering their origin, histopathological characteristics, clinical course and prognosis. Differentiated thyroid carcinoma (papillary and follicular) originate from follicular cells and make up 90% of all thyroid carcinomas [1]. A subtype of papillary and follicular carcinoma, the clinical relevance of which is being differently assessed, is the oxyphile variant, also called Hürth-

le cell carcinoma. These tumors appear more often in follicular than in papillary carcinoma [2,3] and are classified as a variant of follicular carcinoma by the World Health Organization [4]. On the other hand, contemporary data from various authors suggest that Hürthle cell carcinoma should be considered as a distinct thyroid malignancy due to its more aggressive clinical behavior, worse survival and clear genomic differences [5,6].

Oxyphile tumors of the thyroid gland are encapsulated neoplasms composed of 50-75% of Hürthle cells [7,8], whereby non-encapsulated Hürthle cells don't show these characteristics since such cells can be found in other histopathological entities of the thyroid (chronic autoimmune thyroiditis, Graves disease etc) [7].

In contrast to papillary carcinoma, which can be preoperatively diagnosed by ultrasonographic examination or fine-needle aspiration biopsy (FNAB), it is difficult to establish a correct preoperative diagnosis for follicular and oxyphile tumors considering the fact that their benign and malignant counterparts have a very similar cytological morphology and that capsular and vascular invasion cannot be verified by cytological examination [9]. According to the Bethesda system for reporting thyroid cytopathology, such lesions are classified as oxyphile neoplasms [10], whereby these patients need further surgical clarification in order to designate a definite histopathological diagnosis which can be oxyphile carcinoma in 13-70% of the cases [7,11].

Intraoperative frozen-section examination is a useful complement in the operative treatment of papillary, follicular and anaplastic carcinoma, while its role in the treatment of follicular and oxyphile neoplasms remains controversial [12].

Investigations for predictive factors of malignancy in patients with oxyphile tumors of the thyroid gland are justified in consideration to all existing preoperative and intraoperative uncertainties. In order to enable the surgeon to establish an adequate indication for operative treatment and to adapt the extent of thyroidectomy to each patient, such data could provide helpful information. Since oxyphile carcinoma has a more aggressive clinical behavior than papillary and follicular carcinoma a total or completion total thyroidectomy should always be carried out [13].

Methods

In this retrospective study we have analyzed the medical files of all patients with oxyphile tumors of the thyroid operated between 1999 and 2008 in a highly specialized Center for endocrine surgery in Belgrade, Serbia. A total of 256 patients were included in this study which were, on the basis of their definite histopathological diagnosis, divided into oxyphile adenomas (142 patients) and oxyphile carcinomas (114 patients). After studying the complete medical history of these patients the most important demographic and clinical characteristics were analyzed including gender (male, female), age (≤ 30 , 31-40, 41-50, 51-60, 61-70,

≥ 71 years), antiTPO antibodies (negative < 100 , positive ≥ 100 U/ml), serum thyroglobulin (< 300 ≥ 300 ng/ml), sonographic echostructure (unifocal, multifocal), tumor diameter (≤ 30 > 30 mm), coexisting benign thyroid diseases (yes, no), coexisting Hashimoto thyroiditis (yes, no), coexisting Graves disease (yes, no) and coexisting multinodular goiter (yes, no).

Statistics

All the variables were tested by univariate logistic regression analysis and those with $p < 0.1$ in the univariate analysis were included in the multivariate logistic regression analysis to test for independence in the prediction of malignancy with a 95% CI for the ORs. A p value < 0.05 was considered as statistically significant. The software package SPSS 12.0 for windows was used for all statistical analyses.

Results

Results were descriptively evaluated and are presented in Table 1. with demographic and clinical characteristics of all patients operated for Hürthle cell tumors of the thyroid gland in the aforementioned period. Oxyphile carcinoma was found in 114 patients (32 males and 82 females, age range: 26-89 years, mean age: 52.1 years) and oxyphile adenoma in 142 patients (16 males and 126 females, age range: 15-77, mean age: 52.9 years). The mean tumor diameter in the carcinoma group was 42.6 mm (range 8-160) and 28.2 mm (range 3-80) in the adenoma group. The mean preoperative serum thyroglobulin levels in patients with and without carcinoma were 293.9 and 151 ng/ml, respectively.

Patients in the carcinoma group were significantly more often males ($p=0.001$), had a tumor diameter over 30 mm ($p < 0.001$) and serum thyroglobulin levels ≥ 300 ng/ml ($p=0.001$) compared to the adenoma group. Coexisting Hashimoto thyroiditis ($p=0.064$) and positive antiTPO antibodies ($p=0.007$) appeared significantly and more frequently in the adenoma group. Between these two groups no significant difference was found regarding age, sonographic echostructure, coexisting benign thyroid diseases, coexisting Graves disease and coexisting multinodular goiter.

All variables in which the univariate analysis showed a p value < 0.1 (gender, antiTPO antibodies, serum thyroglobulin, tumor diameter, coexisting benign thyroid diseases and coexisting Hashimoto thyroiditis) were subjected to multivariate logistic regression analysis, whereby only serum thyroglobulin levels ≥ 300 ng/ml showed independent prediction of malignancy for pa-

Table 1. Demographic and clinical characteristics of all patients

Characteristics	Carcinoma		Adenoma		p value*
	N	%	N	%	
Gender					
Male	32	28.07	16	11.27	
Female	82	71.93	126	88.73	0.001
Age (years)					
≤30	5	4.38	9	6.33	
31-40	18	15.79	12	8.45	
41-50	29	25.44	32	22.54	
51-60	34	29.82	51	35.92	
61-70	16	14.04	27	19.01	
≥71	12	10.53	11	7.75	0.31
AntiTPOAt (U/ml)					
Positive	14	12.28	37	26.06	
Negative	100	87.72	105	73.94	0.007
Thyroglobulin (ng/ml)					
<300	60	52.63	128	90.14	
≥300	54	47.37	14	9.86	0.001
Echostructure					
Unifocal lesions	41	35.96	57	40.14	
Multifocal lesions	73	64.04	85	59.86	0.276
Tumor diameter (mm)					
≤ 30	43	37.72	93	65.49	
> 30	71	62.28	49	34.51	0.001
Coexisting benign thyroid diseases					
Yes	72	63.16	105	73.94	
No	42	36.84	37	26.06	0.064
Coexisting Hashimoto thyroiditis					
Yes	8	7.02	29	20.42	
No	106	92.98	113	79.58	0.004
Coexisting Graves disease					
Yes	0	0	5	3.52	
No	114	100	137	96.48	0.199
Coexisting multinodular goiter					
Yes	61	53.51	64	45.07	
No	53	46.49	78	54.93	0.180

* p values by univariate analysis

tients with an oxyphile tumor of the thyroid gland (OR=5.88, 95%CI 2.78-12.05, p=0.001). In patients with serum thyroglobulin levels ≥300 ng/ml, the malignancy rate was 79.4%, while in those with a lower thyroglobulin level, it was 31.9%.

Discussion

According to the current literature the inci-

dence of malignancy in patients with oxyphile tumors of the thyroid gland lies between 13 and 70% [7,11,14-16]. The results of our survey fit in this range with 44.5%. The correct assessment of malignancy in patients with oxyphile tumors is of great importance since it is impossible to establish an appropriate preoperative diagnosis and considering the fact that total thyroidectomy (with or without central lymph node dissection) is the first

and mostly the only therapeutic option for patients with oxyphile carcinoma [13]. Several facts stand in favor of total thyroidectomy including:

1. Increase of the sensitivity of serum thyroglobulin as the most important postoperative tumor marker in patients with differentiated thyroid carcinoma [17];
2. Offering of the possibility to render about 90% of patients with differentiated thyroid carcinoma permanently free of disease, considering the high percentage of multifocality of these tumors which lies between 19.2 % (our survey) and 28% [16,17];
3. Overcoming the ineffectiveness of radioiodine therapy in 90% of patients with oxyphile carcinoma [14,15];
4. Reduce the incidence of local recurrence [18].

Hemithyroidectomy as the initial surgical approach for the management of solitary Hürthle cell non-suspicious neoplasms is also justified [19].

Many authors described potentially predictive factors of malignancy in patients with oxyphile tumors of the thyroid gland in the current literature. In the most of these studies gender was not of great importance as a predictive factor [16,20,21]. In contrast to these reports, our opinion is, as well as the opinion of Raparia and his colleagues [22], that male gender could be a predictive factor of malignancy although it was not significant in the multivariate logistic regression analysis. Age had no predictive value in our survey with an almost identical average age in both groups (carcinoma group 52.1 years, adenoma group 52.9 years) which coincides with results from the majority of studies in this domain [16,20-25].

Although serum thyroglobulin is not a screening test and is primarily used as a postoperative tumor marker in patients with differentiated thyroid carcinoma, elevated thyroglobulin levels could indicate differentiated thyroid carcinoma, especially in patients with undetermined cytology [26]. Strazisar et al. showed that in 43% of the patients with oxyphile tumors and serum thyroglobulin levels ≥ 1000 ng/ml, carcinoma was present [24]. A number of authors from the same center also stated a few years later, that serum thyroglobulin level ≥ 80 ng/ml is an independent predictive factor of malignancy for small oxyphile carcinoma (≤ 2 cm) [25]. Likewise, our survey revealed that elevated thyroglobulin levels (≥ 300 ng/ml) are an independent predictive factor of malignancy for patients with oxyphile tumors

with a malignancy rate of 79.4%, while in those with a lower thyroglobulin level, it was 31.9%. The mean serum thyroglobulin concentrations of our carcinoma patients were almost twice as high compared with the concentrations in the adenoma group (293.9 vs 151 ng/ml). On the other hand, Suh and his group published controversial results and claimed that elevated thyroglobulin level had no predictive value in oxyphile tumors [27].

The diameter of oxyphile tumors as a predictive factor for carcinoma has been mentioned in literature many times [16,19,21,22,24,28]. Pisanu and coauthors stated that a tumor diameter ≥ 3 cm is an independent predictive factor of malignancy for oxyphile tumors whereby the authors didn't find oxyphile adenomas with a diameter over 4 cm [16]. Similar results reported Sippel et al. with no oxyphile carcinomas smaller than 2 cm and no adenomas bigger than 6 cm [21]. In the present study, univariate regression analysis showed that the carcinoma group had a significantly larger tumor diameter than 3 cm. Other authors claimed that tumor size is no significant predictive factor neither for oxyphile carcinoma nor for thyroid carcinoma generally [20,29-31] whereby in these surveys the cytological findings of FNAB served as a starting point instead of definite histopathological analysis.

Coexisting Hashimoto thyroiditis showed as a protective factor for oxyphile adenomas in the univariate analysis, which coincides with a significantly higher percentage of patients with positive antiTPO antibody in the adenoma group than in the carcinoma group. In such patients, as in patients with coexisting multinodular goiter, predictive factors of malignancy have limited influence on the extent of thyroid resection since we performed mostly total thyroidectomies in these cases.

Conclusions

According to our results, preoperative thyroglobulin levels ≥ 300 ng/ml were an independent predictive factor for oxyphile carcinomas of the thyroid gland. In order to gain further conclusions considering the predictive factors for malignancy in patients with oxyphile tumors of the thyroid it would be necessary to analyze a higher number of such patients which could only be possible through large multicentric studies.

Conflict of interests

The authors declare no conflict of interests.

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