Diagnostic Value of Preoperative Serum Levels of TSH, Tg, TgAb and TPOAb in Thyroid Diseases

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Abstract

Objective: To investigate the relationship between Thyroid Stimulating Hormone (TSH), Thyroglobulin (Tg), Thyroglobulin Antibody (TgAb), Thyroid Peroxidase Antibody (TPOAb) and the benign and malignant thyroid nodules before operation.

Methods: A retrospective analysis of serum TSH, Tg, TgAb and TPOAb levels, sex, age, tumor diameter, lymph node metastasis in 1434 patients with thyroid nodules who were admitted to the Otolaryngology Head and Neck Surgery Department of Shanghai First People's Hospital from June 2011 to May 2016 was carried out, and to explore the relationship between TSH, Tg, TgAb and TPOAb and differentiated thyroid carcinoma.

Result: Postoperative pathological diagnosis of benign thyroid nodules in 915 cases, 519 cases of differentiated thyroid carcinoma. There were 426 male patients, including 152 DTC patients and 274 BTN patients; 1008 female patients, including 367 DTC patients and 641 BTN patients. There was no significant difference in the incidence of thyroid cancer between the two groups. The average age of DTC patients (46.925 ± 13.98 years) was less than that of BTN patients (53.936 ± 11.956 years), and the difference was statistically significant (P<0.05). The mean serum TSH level of DTC patients before operation (2.4885 ± 1.5772) uIU/ml was not significantly different from that of BTN patients (2.4586 ± 2.6947) uIU/ml (P=0.79), but the proportion of thyroid cancer increased with the increase of TSH level (even within the reference value range) (P<0.05). Tg level and positive rate of Tg in DTC patients were lower than those in BTN patients (all P<0.05), positive rate of TgAb and positive rate of Tg combined with TgAb were higher than those in BTN patients (all P<0.05), but positive rate of TPOAb was not different between the two groups (P=0.12). Logistic regression analysis showed that the occurrence of DTC was negatively correlated with age (OR=0.96, P<0.0001) and Tg level (OR=0.302, P<0.05), positively correlated with TgAb positive (OR=2.224, P=0.0002), no correlation with sex (OR=1.036, P=0.7817), elevated TSH (OR=1.110, P=0.05549) and positive TPOAb (OR=1.115, P=0.6459).

Conclusion: Elevated serum TSH, decreased Tg, positive TgAb, younger age, and female may be indicators of predicting the risk of differentiated thyroid cancer, but further large-sample prospective trials are needed to confirm this.

Keywords: Thyroid stimulating hormone; Thyroglobulin; Thyroglobulin antibody; Thyroid peroxidase antibody; Differentiated thyroid carcinoma

Introduction

Thyroid nodules are common and frequently occurring diseases. At present, the diagnosis of benign and malignant thyroid nodules mainly depends on B ultrasound, radionuclide scanning, MRI, CT, Fine Needle Aspiration Biopsy (FNAB), medical records of patients and medical experience of doctors. However, because of their own limitations, these methods have their own shortcomings, and cannot alone, accurately and effectively judge the benign and malignant thyroid nodules. Although FNAB has a high accuracy in the diagnosis of benign and malignant thyroid nodules, it is invasive, difficult to be accepted by patients and their families, and has a certain false

negative. Surgical resection of thyroid nodules is still the preferred treatment. However, a large number of literature studies have shown that the incidence of thyroid cancer after thyroid nodule surgery is very low. Avoiding unnecessary surgery is a problem that every clinician must face. At the same time, it is very important for the treatment and prognosis of thyroid cancer patients to make early diagnosis and timely operation. Therefore, it is of great significance to seek a simple, effective and non-invasive method to determine the nature of thyroid nodules. It is well known that the abnormal increase of Thyroid Peroxidase Antibody (TPOAb) and serum Thyroglobulin Antibody (TgAb) is higher than that of Autoimmune Thyroid Disease (AITDS). It can also be seen in differentiated thyroid cancer and other diseases. It is a predictor of thyroid cancer [1-2]. Elevated serum TSH can be used as an important early warning signal for thyroid cancer screening and an independent risk factor for DTC [3-5]. So, from June 2011 to May 2016, 1434 patients with concurrent thyroid surgery in the Department of Otolaryngology, Head and Neck Surgery, Shanghai First People's Hospital Affiliated to Shanghai Jiaotong University were analyzed retrospectively, to analyze the distribution and difference of TSH, Tg, TgAb and TPOAb levels in differentiated thyroid carcinoma and benign nodular thyroid disease, and to explore their potential predictive value for benign and malignant thyroid nodules.

Materials and Methods

Inclusion criteria and exclusion criteria

Entry criteria: (1) Free triiodothyronine (FT3) and serum free thyroid hormone (FT4) were in the normal range; (2) Every case had complete data; (3) First thyroid surgery was performed in our hospital. All these conditions are satisfied.

Exclusive criteria: (1) Postoperative pathology was myeloid carcinoma, poorly differentiated carcinoma, and squamous cell carcinoma; (2) History of previous thyroid diseases (such as hyperthyroidism or hypothyroidism, subacute thyroiditis or Hashimoto's thyroiditis), history of thyroid surgery or oral administration of thyroid hormones or antithyroid drugs within 6 months before surgery (3) there are other cervical cancer operations or radiotherapy history. Any of the above should not be included in the study.

Patients and study design

From June 2011 to May 2016, 1434 patients (426 males, 1008 females, and aged 10-89 years) with concurrent thyroidectomy were enrolled in the Department of Otolaryngology, Head and Neck Surgery, Shanghai First People's Hospital Affiliated to Shanghai Jiaotong University. 519 patients (512 papillary carcinoma, 7 follicular carcinoma) were diagnosed as differentiated thyroid carcinoma. 877 cases with simple nodular goiter, 26 cases with simple thyroid adenoma and 12 cases with nodular goiter and adenoma. There were 20 cases under 20 years old, 92 cases between 20 and 29 years old, 158 cases between 30 and 39 years old, 286 cases between 40 and 49 years old, 484 Cases between 50 and 59 years old, 308 cases between 60 and 69 years old and 86 cases over 70 years old.

Survey data: (1) General condition of patients: gender, age, family history, head and neck irradiation history; (2) Preoperative laboratory examination: Triiodothyronine (TT3), Thyroid Hormone (TT4), Free Triiodothyronine (FT3), Free Thyroxine (FT4), TSH, Tg, TgAb and PTOAb levels. All of the above indicators are the results of nuclear medicine in our hospital. (3) Postoperative histopathological
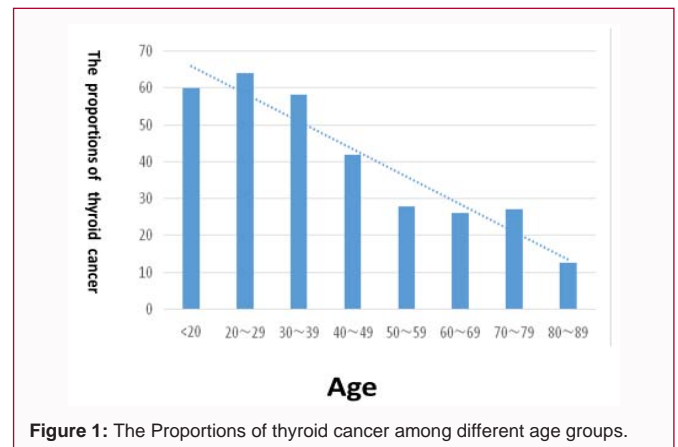

Figure 1: The Proportions of thyroid cancer among different age groups.
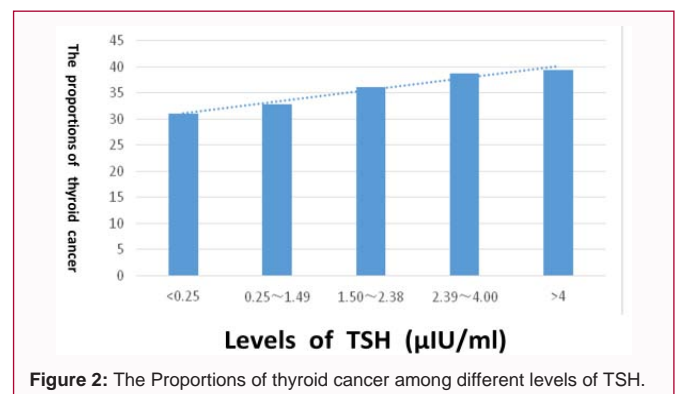

Figure 2: The Proportions of thyroid cancer among different levels of TSH.

report: pathological classification. (4) The TSH reference range is (0.25-4) uIU/ml; the Tg reference range is (0-77) ng/ml; the TPOAb reference range is (5-34) uU/ml; and the TgAb reference range is (10-115) IU/ml. Patients were divided into four groups according to thyroid antibody titer: TgAb positive, that is, TgAb titer >115IU/ml; TPOAb positive, that is, TPOAb titer >34 U/ml; Tg positive, that is, Tg titer >77 ng/ml.

Statistical analysis

According to the above conditions, the patients were divided into two groups: differentiated thyroid carcinoma group and benign thyroid nodule group. The collected data were analyzed by Microsoft Excel worksheet and SAS 9.13 software package. Counting data were compared by Maple χ^2 test and Chi-square test of Cochran-Armitage trend; normal distribution was expressed by $(\chi \pm S)$ and inter-group comparison was performed by t test; multivariate logistic regression was used to analyze the relationship between preoperative gender, age, TSH, Tg, TgAb and TPOAb levels and DTC, P<0.05 thought the difference was statistically significant.

Results

Comparison of basic data between differentiated thyroid cancer (DTC) and benign nodules (BTN)

There were 426 male patients, including 152 DTC patients and 274 BTN patients; 1008 female patients, including 367 DTC patients, 641 BTN patients, the proportion of male DTC patients (35.68%) and female patients (36.41%) were not significantly different (χ^2=0.0687, P>0.05). The mean age of DTC patients was (46.925 ± 13.98) years, while that of BTN patients was (53.936 ± 11.956) years. The mean age of DTC patients was less than that of BTN patients. The difference was statistically significant (t= -9.6, P<0.05), as shown in Table 1.

Table 1: Comparison of general conditions between the two groups.

		DTC	BTN	Statistic	P value
Sex	Male	152	274	0.0687	0.79
	Female	367	641		
Age (year)		46.925 ± 13.98	53.936 ± 11.956	-9.6	<0.05

Table 2: Comparison of incidence of thyroid cancer in different age groups.

variable Age/year	n	BTN	DTC	Z	P
<20	20	8	12 (60.00%)		
20~29	92	33	59 (64.13%)		
30~39	158	66	92 (58.23%)		
40~49	286	166	120 (41.96%)	9.6264	<0.0001
50~59	484	349	135 (27.89%)		
60~69	308	228	80 (25.97%)		
≥ 70	86	65	21 (24.42%)		

Table 3: Comparison of general conditions between the two groups.

Group	n	TSH (uIU/ml)	t	P
DTC	519	2.49 ± 1.58	0.27	0.79
BTN	915	2.46 ± 2.70		

Detection rate of thyroid cancer in different age groups

The detection rate of thyroid cancer in different age groups was statistically significant ($\chi2=106.87$, P<0.05), as shown in Table 2 and Figure 1.

Relationship between serum TSH level and occurrence of thyroid carcinoma

The mean serum TSH level in patients with DTC before operation was (2.4885 ± 1.5772) uIU/ml, and that in patients with BTN (2.4586 ± 2.6947) uIU/ml, there was no significant difference (P>0.05, Table 3). Patients with different levels of TSH expression were divided into two groups according to the lower limit (0.25 uIU/ml) and upper limit (4 uIU/ml). Patients with TSH in the normal range were divided into three groups according to approximately the same number of patients. Five groups were obtained: group <0.25 uIU/mL (29 cases), group 0.25-1.49 uIU/mL (411 cases), group 1.50-2.48 uIU/mL (410 cases), 2.39 to 4.00 uIU/mL group (411 cases), and >4 uIU/mL group (173 cases). Cochran-Armitage trend test showed that the proportion of thyroid cancer increased with the increase of TSH expression level, and the difference was statistically significant, including TSH in the reference range, also showed this phenomenon (P<0.05), Table 4 and Figure 2.

The relationship between serum Tg, TgAb and TPOAb and the occurrence of thyroid cancer

Postoperative pathology confirmed 912 cases of BTN patients, 517 cases of DTC patients (because of incomplete data, excluded 3 cases of BTN patients, 2 cases of DTC patients). The average level of

Table 5: Comparison of preoperative serum Tg levels in patients with benign and malignant thyroid nodules.

Group	n	Tg (ng/ml)	t	P
DTC	517	14.96 ± 10.31	-2.59	0.0097
BTN	912	21.24 ± 71.85		

Tg in DTC group was 14.96 ± 10.31 (ng/ml), 21.24 ± 71.85 (ng/ml) in BTN group, and lower in DTC group than in BTN group (t= -2.59, P<0.05) Table 5. In DTC group, 43 cases were positive for TPOAb, 474 cases were negative, and the positive rate was 8.32%. In BTN group, 54 cases positive for TPOAb, 858 cases were negative, and the positive rate was 5.92%. There was no difference in the positive rate of TPOAb between the two groups $\chi^2=2.4$, P=0.12. In DTC group, 66 cases were positive for TgAb, 451 cases were negative, and the positive rate was 12.77%. In BTN group, 51 cases were positive for TgAb, 861 cases were negative, and the positive rate was 5.59%. The positive rate of TgAb in DTC patients was significantly higher than that in BTN patients ($\chi^2=22.59$, P<0.0001). In DTC group, Tg was positive in 4 cases, negative in 513 cases, the positive rate was 0.77%. In BTN group, Tg was positive in 25 cases, negative in 887 cases, the positive rate was 2.74%. The positive rate of Tg in DTC patients was lower than that in BTN patients ($\chi^2=6.42$, P<0.05). In DTC group, 69 cases were positive for Tg combined with TgAb, 448 cases were negative, the positive rate was 13.35%. In BTN group, 74 cases were positive for Tg, 838 cases were negative, the positive rate was 8.11%. The positive rate of Tg combined with TgAb in DTC patients was higher than that in BTN patients ($\chi^2=10.03$, P<0.05).Tg and TgAb increased simultaneously in 2 benign thyroid nodules and 1 differentiated thyroid carcinoma, respectively Table 6.

Multivariate logistic regression analysis of risk factors for DTC

Regarding gender, age, TPOAb, TgAb, TSH and Tg levels as independent variables and whether DTC occurs as dependent variables, the results of multivariate logistic regression analysis showed that the occurrence of DTC was negatively correlated with age (OR=0.96, P<0.0001), Tg level (OR=0.302, P<0.05), and positively correlated with TgAb positive (OR=2.224, P=0.0002), while positively correlated with gender (OR=1.036, P=0.7817), and TSH increased. (OR=1.110, P=0.05549) and TPOAb positive (OR=1.115, P=0.6459) were not correlated, as shown in Table 7.

Discussion

The prognosis of benign thyroid nodules is good, and only regular follow-up and medical treatments are needed. If most thyroid cancers can be detected early and resected in time, the prognosis is good, and the long-term survival can be achieved. The mortality rate is lower than that of other malignant tumors. At present, fine needle aspiration biopsy and ultrasonography have played an important role in evaluating the nature of thyroid nodules. The detection rate of thyroid nodules under ultrasonography has been increasing, but the

Table 4: The proportion of DTC and BTN in different TSH levels [n(%)].

TSH (uIU/ml)	Number of cases	BTN	DTC	Z	P
<0.25	29	20 (68.97%)	9 (31.03%)		
0.25~1.49	411	276 (67.15%)	135 (32.85%)		
1.50~2.38	410	262 (63.90%)	148 (36.10%)	-1.98	<0.05
2.39~4.00	411	252 (61.31%)	159 (38.69%)		
>4	173	105 (60.69%)	68 (39.31%)		

Table 6: Positive distribution of serum TPOAb, Tg and TgAb in patients with benign and malignant thyroid nodules.

Group	n	TPOAb		Tg		TgAb		Tg combined with TgAb	
		(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
DTC	517	43	474	4	513	66	451	69	448
BTN	912	54	858	25	887	51	861	74	838
χ2		2.4		6.42		22.59		10.03	
P		0.12		0.0113		<0.0001		0.0015	

Note: TPOAb: Thyroid Peroxidase Antibody; Tg: Thyroglobulin; TgAb: Anti-Thyroglobulin Antibody
Tg combined with TgAb positive group is Tg positive and/or TgAb positive, negative group is Tg and TgAb negative.

Table 7: Multivariate logistic regression analysis.

influence factor	β value	Standard error	Wald/χ2	OR value	95% confidence interval	P value
sex	0.0350	0.1262	0.0768	1.036	0.809~1.326	0.7817
age	-0.0408	0.0045	80.7747	0.960	0.952~0.969	<0.0001
TSH rise	0.1039	0.1760	0.3485	1.110	0.786~1.567	0.5549
Tg	-1.1981	0.5676	4.4550	0.302	0.099~0.918	0.0348
TgAb positive	0.7994	0.2167	13.6067	2.224	1.454~3.401	0.0002
TPOAb positive	0.1091	0.2374	0.2111	1.115	0.700~1.776	0.6459

ultrasonographic features of benign and malignant thyroid nodules often overlap [6]. Ultrasound manifestations of thyroid nodules are often lack of characteristics and easy to be misdiagnosed. Fine needle aspiration biopsy will be affected by the level of the operator and the level of the operator. The size and location of nodules have some limitations. Preoperative thyroid serum examinations for patients with thyroid cancer makes up for this defect, and can provide certain reference for clinicians and guide clinical work. Tg is a glycoprotein synthesized and secreted by thyroid follicular epithelial cells. It is a precursor of thyroxine synthesis [7]. Its half-life is 5 days. There is only a small amount of Tg in normal human serum. It circulates only in thyroid follicular cells and thyroid follicular lumen, but Tg increases significantly in thyroid adenocarcinoma, papillary cancer and a small number of patients with acute or subacute thyroiditis, probably because of this. DTC has a complete function of thyroid follicular epithelial cells, which can synthesize Tg, or lysosome can hydrolyze thyroxine on the surface of Tg, then Tg is released into blood. At the same time, some scholars have proposed that Tg can be used as a marker of thyroid cancer, and it has certain significance in monitoring the recurrence and metastasis of thyroid cancer [8,9]. McLeod et al. [10] showed that 85% of differentiated thyroid cancer patients had higher serum Tg levels than the control group. Because serum TgAb can interfere with serum Tg concentration, Tg will lose its predictive value in patients with thyroid cancer and other diseases, so when TgAb exists and increases abnormally, it may lead to negative serum Tg test results. In this study, we excluded the patients with chronic inflammatory and immunogenic thyroiditis in the sample selection, which made the results of this study more credible. Statistical analysis showed that the Tg level of DTC patients was lower than that of BTN patients (P<0.05). Multivariate logistic regression analysis showed that the occurrence of DTC was related to the occurrence of lymph node metastasis. The level of Tg was negatively correlated (OR=0.302, P<0.05). In view of the effect of TgAb on Tg level, which may be due to the abnormal increase of TgAb, the difference of Tg level between DTC patients and BTN patients cannot be determined in this study.

TgAb is an inhibitory autoantibody produced by thyroglobulin in thyroid follicles after it enters the blood, mainly IgG. It has high immune specificity. Most of it is secreted by B lymphocyte in thyroid. TgAb itself has no killing effect on thyroid cells. However, when combined with Tg, it can activate NK cells, attack target cells and destroy thyroid cells. When TgAb accumulates to a certain concentration in thyroid gland, not only Tg decomposition increases, but also other proteins unrelated to Tg are hydrolyzed, which may cause systemic protein decomposition and tissue damage [11-14]. TgAb mostly exists in patients with thyroid autoimmune diseases and is one of the signs of immune dysfunction. Kim et al. [13] reported for the first time in 2010 that serum TgAb positive was an independent predictor of malignant risk of thyroid nodules regardless of the presence or absence of autoimmune thyroiditis. Azizizi et al. [15] Retrospective cohort analysis also found that high concentrations of TgAb were associated with thyroid cancer. Some scholars found that TgAb positive was an independent risk factor for papillary thyroid cancer and a predictor of thyroid cancer, [1,2,13]. Serum TgAb could be used as a monitoring indicator of DTC [16]. However, some scholars believe that TgAb positive is not a risk factor for thyroid cancer [17]. This study found that the positive rate of TgAb in DTC patients was significantly higher than that in BTN patients (χ2=22.59, P<0.0001). Logistic regression analysis showed that the occurrence of DTC was positively correlated with TgAb positive (OR=2.224, P=0.0002). (OR=2.224, P=0.0002), suggesting that a high level of TgAb was a risk factor for thyroid cancer. It is consistent with the above literature reports.

In 2006, Boelaert et al. [18] found that the increase of TSH level would increase the risk of thyroid cancer. In 2008, Haymart studied the serum TSH level of 843 patients with thyroid disease from low to high. It was found that with the increase of serum TSH level, the proportion of thyroid cancer increased gradually. It was suggested that TSH was an independent risk factor for DTC. Subsequently, some scholars found similar regularity. The level was positively correlated with the malignancy of thyroid cancer [4-5]. Many types of thyroid cancer cells have TSH receptors on their surface. TSH can regulate and affect the growth of thyroid epithelial cells and follicular cells [19]. Serum TSH can enhance the activity of iodine pump, enhance peroxidase activity, promote the metabolism of thyroid epithelial cells and protein synthesis [20], and induce the differentiation, proliferation and variation of thyroid follicular cells [21]. However,

some studies do not support TSH as an independent risk factor for thyroid cancer [22]. This study found that there was no significant difference in the mean level of serum TSH between DTC patients and BTN patients before operation (P>0.05). Logistic regression analysis showed that the occurrence of DTC had no correlation with TSH level. However, further analysis showed that patients with different levels of TSH expression were divided into two parts according to the lower limit (0.25 uIU/ml) and upper limit (4 uIU/ml) of normal TSH reference value. The patients with TSH in the normal range were divided into three groups according to roughly the same number of patients. Cochran-Armitage trend test showed that with the increase of TSH expression level, the proportion of thyroid cancer also increased. The difference was statistically significant. Even if TSH was within the reference range, it also showed this phenomenon (P<0.05), which was consistent with the literature reports. In conclusion, although TSH level cannot be used as a basis for judging thyroid cancer, it can provide some reference for clinical practice.

TPO is an important enzyme synthesized by thyroid follicular cells. Its main function is to catalyze the production of thyroid hormones. When TPO is inactivated, the body is stimulated to produce TPOAb. Anti-thyroid peroxidase antibodies are mainly distributed in the top margin of thyroid cells and endoplasmic reticulum. TPOAb is a membrane-bound glycoprotein molecule with heme as its auxiliary group. TPOAb can directly damage thyroid cells. It can also cause direct damage to thyroid cells through complement-dependent cytotoxicity, resulting in autoimmune thyroids. Adenopathy [13,23]. The results of the study on the relationship between TPOAb and thyroid papillary carcinoma are consistent. No independent correlation between TPOAb positive and PTC has been found in many studies [1,2,17]. This study found that there was no difference in the positive rate of TPOAb between the two groups (^{2}=2.4, P=0.12). Multivariate logistic regression analysis also found that there was no correlation between the occurrence of DTC and TPOAB, which was consistent with the above reports.

Females are 2-5 times more likely to suffer from cancer than males. Pregnancy, early menopause and gynecological diseases are all associated with an increased risk of cancer [24], suggesting that sex hormones play an important role in the development of DTC. The expression of estrogen receptor and progesterone receptor is higher in female thyroid cancer patients, and DTC may be a female hormone-dependent tumor [25]. Some scholars believe that estrogen itself is a carcinogen. Estrogen can promote the expansion, adhesion, infiltration and metastasis of DTC cells by regulating the expression of many related proteins and target genes through gene pathway or (and) non-gene pathway after binding with its receptor. The overall incidence of thyroid nodules in women was significantly higher than that in men, and the number of malignant nodules in women was also higher than that in men, but the malignant transformation rate of thyroid nodules in men was higher [26]. In this study, 426 male patients, including 152 DTC and 274 BTN, and 1008 female patients, including 367 DTC and 641 BTNs, had no significant difference in the incidence of thyroid cancer between male and female patients (P>0.79). Multivariate logistic regression analysis showed that the incidence of DTC was not related to gender (OR=1.036, P=0.7817). But at the same time, we can also find that the number of female patients is much higher than that of male patients (about 2.4:1), suggesting that estrogen may participate in the occurrence of thyroid tumors, which is consistent with the literature [25-27].

Sundram et al. [26] found that the younger the patients were, the higher the malignant rate was. Age was an independent predictor of malignant thyroid nodules. The younger the patients were, the higher the risk of malignant thyroid nodules was. Gharib H et al. [29] reported that the incidence of thyroid malignant nodules was higher in people younger than 20 years old or over 70 years old. This study found that the average age of DTC patients was (46.925 (+13.98) years old, BTN patients was (53.936 (+11.956) years old, and DTC patients were younger than BTN patients (P<0.05). Further analysis of thyroid cancer detection rate in different age groups showed that with the increase of age, the detection rate of thyroid cancer decreased, and patients younger than 30 years old had the highest proportion of thyroid cancer. Multivariate logistic regression analysis showed that age was an independent risk factor for thyroid malignant nodules, and the occurrence of DTC was negatively correlated with age (OR=0.96, P<0.0001), which was consistent with the literature reported above. In this study, the incidence of malignant thyroid nodules is the lowest among those over 60 years old, which is inconsistent with Gharib H's report, and may be related to regional differences. This study may also be a retrospective analysis, because some patients are too old to accept surgical treatment when malignant nodules are found, and conservative treatment has been adopted, which is not included in this study. Selective bias is related.

Conclusion

In conclusion, serum TSH elevation, Tg decrease, TgAb positive, younger age and female may be indicators for predicting the risk of differentiated thyroid cancer. This study is a retrospective study after all, and the number of cases is limited. There may be some bias in sample selection. Therefore, whether serum levels of TG, TGAB, TPOAB and TSH can be used as predictors of DTC screening needs further study and confirmation by large sample prospective test.

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