RESEARCH COMMUNICATION

A Retrospective Analysis of Thyroid Cancer in China

Yumei Yang, Qiang Li*, Lin Guo, Mingming Cui, Tana Bao, Zhiying Zhang, Chi Wang, Yanan Ni, Jinchao Zhang

Abstract

Background: Thyroid nodules are a common clinical problem that require close attention to determine the risk of malignancy. This study was designed to investigate the diagnostic values of pathological characteristics, ultrasonographically-detected calcification, and serum TSH levels in thyroid cancer in Han Chinese. Methods: A retrospective analysis was carried out using 1,685 patients with thyroid cancer or benign nodules, who had undergone thyroidectomy between 2008 and 2009 in our hospital. Results: Among the 1,685 cases, 222 had thyroid carcinomas and, of those, 113 (50.9%) developed different benign thyroid diseases. The frequency of thyroid cancer showed a progressive decrease from the younger to the older patients. The frequency of malignancy was closely related to the level of calcification, with the lowest frequency occurring in patients with no calcification and the highest in those with micro-calcification. The frequency of malignancy was also closely related to serum TSH levels, with the lowest occurring in patients with TSH levels <0.40 uIU/mL, and the highest with >1.34 uIU/mL; in addition, <4.00 uIU/mL TSH showed a progressive increase from the lower to the upper of normal range. Conclusions: Thyroid malignancies often coexist with benign thyroid disease. Age, TSH levels, and calcification of the nodules are predictors of malignancy.

Key words: Thyroid cancer - retrospective analysis - TSH - calcification - Han Chinese

Asian Pacific J Cancer Prev, **12**, 2245-2249

Introduction

The incidence of goiters is 5–7% in the world's population (Gaitan et al., 1991; Muller et al., 2001). Epidemiological studies have shown that, in some areas rich in iodine, 6–7% of the adult population have a thyroid nodule that can be detected by clinical examination, and 5% of the clinically identified nodules are malignant (Hegedus, 2004). There are four main types of thyroid cancers (based on pathology observed under a microscope): papillary, follicular, medullary, and anaplastic lesions. Differentiated thyroid cancer (DTC, including papillary and follicular) accounts for 90% of all the thyroid malignancies diagnosed, with papillary thyroid cancer (PTC) accounting for 80% of all thyroid cancers. Since thyroid nodules are highly prevalent, it is a common clinical task to predict the risk of malignancy of a given nodule.

Up to now, other than fine needle aspiration (FNA), there are no effective noninvasive preoperative methods for the differential diagnosis of thyroid nodules. Furthermore, some nodules are too small to perform FNA; thus, new and improved noninvasive methods are urgently needed. Ultrasonography is widely used as a preferred, noninvasive approach for diagnosis and prognosis of many different types of diseases. A high-resolution ultrasound has been reported as capable of detecting thyroid nodules in about 20-24% of randomly selected women and elderly individuals (Hegedus, 2004). Many studies have shown that calcification detected by ultrosnography is correlated with thyroid malignancy (Hegedus, 2004). However, the concrete odds ratio of the different types of calcification remains unknown. It has also been reported that, in patients with nodular thyroid diseases, the risk of thyroid malignancy increases in parallel with serum TSH levels (Boelaertet al., 2006; Haymart et al., 2008; Polyzos et al., 2008). However, this hypothesis still needs to be validated in large studies using individuals from different ethnicities or geographic areas; in addition, the cut-off point of the TSH levels that can predict the risk of thyroid cancer still needs to be determined.

Herein, we retrospectively analyzed the pathological characteristics of thyroid nodules, and determined the significance of thyroid nodule calcifications detected by ultrasonography and of serum TSH levels in the diagnosis of thyroid malignancy. Our results suggested that calcification, especially micro-calcification, and

*Department of Endocrinology and Metabolism, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China *For correspondence: liqiang2000@live.com*

high TSH levels can accurately predict thyroid cancer, and that the majority of thyroid cancers coexist with benign nodules.

Materials and Methods

Patients' characteristics and tissue collection

We retrospectively analyzed data from 1685 consecutive Han Chinese patients who underwent thyroidectomy for nodular thyroid disease between January 2008 and December 2009 in the Second Affiliated Hospital of Harbin Medical University, located in Northern China. The inclusion and exclusion criteria were as follows: 1) patients had undergone a diagnostic FNA examination (patients with non-diagnostic or indeterminate cytology were excluded); 2) patients had TSH, free thyroid hormones, and serum anti-thyroid antibodies measured simultaneously with FNA; 3) patients with Grave's disease or Hashimoto's thyroiditis were excluded. The final subject population was composed of 265 males and 1420 females (male:female ratio of 1:5.53), with mean age of 48.41±11.53 years (range: 8–81 years). All the 1685 patients had definitive pathological diagnosis after surgery. Of those, 1366 (205 males and 1161 females) had ultrasonographical examination before surgery; the 319 patients without an ultrasonogram or with incomplete ultrasonographical information were excluded. Serum TSH was quantified using a routine chemiluminescence test (Chiron Diagnostics, Wiesentheid, Germany). The normal range for serum TSH was set at 0.40–4.00 mIU/L. Patients with a benign lesion accompanying cancer were assigned to the malignant group. In this study, when logistic regression models were performed, the malignant group (n=212) included papillary cancer and follicular cancer, but excluded six cases of medullary cancer, one of anaplastic cancer and three of malignant lymphoma. In a second analysis, the malignant group included all the cancers (n=222). Radioactive iodine (131I) thyroid ablation was carried out in the patients with DTC postoperatively, after measuring 131I uptake in the thyroid bed.Thyroid hormone therapy was routinely initiated to all patients postoperatively with DTC in a dose adequate to suppress TSH to undetectable levels, according to the TSH assay sensitivity.

All patients gave written informed consent for inclusion in the study.

Statistical analysis

The data were analyzed according to age, gender, preoperative examination findings, and pathology. Continuous data are expressed as means ± standard deviation (SD), and categorical data are expressed as percentages. The nonparametric tests Chi-square or Mann-Whitney were used for comparisons of the categorical data. Binary logistic regression models were used to adjust for potential confounders (for example, age and gender). A two-sided p-value <0.05 was considered to indicate statistical significance. The data analyses were carried out by using the SPSS 13.0 software for Windows.

Results

Patients' demographic data

The data on patients' gender, age of disease onset, and pathology of thyroid nodules are shown in Table 1. Most of the patients' lesions were benign (1463/1685; 86.82%), while 13.18% (222/1685) were malignant. The 222 patients diagnosed with thyroid cancer were composed of 29 males and 193 females (male:female ratio of 1:6.66). The 1463 patients with benign lesions were composed of 236 males and 1227 females (male:female ratio of 1:5.20). Among the patients with thyroid cancer, 60.81% (135/222) were 31–50 years of age, of which 120 were females and 15 were males (male:female ratio of 1:8.00). The initial complaint of these patients was most often a mass anterior to the cervicum. A total of 110 of the 1685 patients presented with hoarseness as the first symptom, of which 21 were eventually diagnosed with thyroid cancer.

The frequency of thyroid cancer was closely related to age. The lowest frequency occurred in patients aged 20 years or younger, and the highest occurred in patients between the ages of 20-29 years old. There was a trend of progressive decrease in frequency from the younger to the older patients after 29 years old (Table 4). Here, the age (in years) data were changed from a consecutive form to a categorical form for analysis by binary logistic regression models.

Pathology findings

Among the 222 patients with thyroid cancers, 199 (89.64%) were characterized as papillary cancers, 13 as follicular cancers, one as papillary adenoma, six as medullary cancer, one as undifferentiated cancer, and three as malignant lymphomas. Forty (18.02%) tumors that were smaller than 1 cm in diameter were defined as microcarcinomas. Among the 222 cancer patients, 113 (50.90%) had thyroid cancers combined with one or more benign lesions (Table 2). Most of the malignancies were papillary (104/113; 92.04%) or in combination with nodular goiters (83/113; 73.45%). The pathological results indicated that nodular goiters were found in 1342 patients, adenoma in 28, and nodular goiter with Hashimoto's thyroiditis in 93. Other pathological subtypes existed, but were only rarely represented (data not shown). Many patients showed two or more pathological subtypes, as reflected by the difference in patient numbers listed above (>1685). Therefore, with the exception of three patients who had thyroid malignant lymphoma, the incidence of benign lesions occurring concurrently with cancer was determined to be 6.56% (88/1342) in nodular goiters, 27.78% (15/54) in Hashimoto's thyroiditis, 4.44%

Table 1. Ages at the Onset of Disease and Pathological and Gender Data for 1685 Patients with Thyroid Nodules

Age (years)	Thyroid cancer n(%)	Papillary cancer	Gender M	Gender F	Male/ female ratio
≤20	2 (7.69)	2	7	19	1/2.71
21–30	29 (29.0)	27	15	85	1/5.67
31-40	60 (23.5)	52	30	225	1/7.50
41-50	75 (14.5)	72	75	443	1/5.91
51-60	38 (6.73)	32	94	471	1/5.01
61-70	14 (7.69)	11	40	142	1/3.55
≥71	4 (10.3)	3	4	35	1/8.75

Table 2. Distribution of Benign Thyroid Lesions Accompanied by Cancer

Benign lesion	Malignancy			Total
	Papillary	Follicular	TML	
Nodular goiter	83	5	3	91
Hashimoto's thyroiditis	14	1		15
Diffuse goiter	2			2
Subacute thyroiditis	1			1
Adenoma	1			1
Nodular goiter with Hashimoto's thyroiditis	3			3
Total	104	6	3	113

Table 3. Distribution of Calcification in Thyroid Nodules*

	No calcification	Coarse calcification	Micro-calcification	Total
Malignant	94	39	61	194
Benign	877	164	131	1172
Total	971	203	192	1366

*$\chi 2=69.107$, $p<0.05$

Table 4. Odds Ratio (OR) and 95% Confidence Interval (CI) of Malignancy, According to Age, TSH Levels, and Calcification

	Regression coefficient	OR	95% CI	p-value
Age	0.427	0.652	0.562-0.758	0
Calcification				0
none	-	1	-	-
micro-	1.377	3.964	2.589-6.068	0
coarse	0.861	2.365	1.473-3.797	0
TSH, uIU/mL				0.005
<0.40	-	1	-	-
0.40-1.34	0.745	2.106	1.063-4.176	0.033
1.34-4.00	1.144	3.14	1.603-6.151	0.001
>4.00	1.096	2.993	1.265-7.081	0.013

(2/45) in diffuse goiter, 3.57% (1/28) in adenomas, and 3.23% (3/93) in nodular goiter with Hashimoto's thyroiditis.

Ultrasonography findings

In the 1366 patients who underwent ultrasonography detection prior to surgery, 290 patients had single nodules and 1076 patients had multiple nodules. Overall, malignancies were found in 194 (14.20%) of the 1366 patients examined by ultrasonography, and the male:female ratio was 1:7.08. The incidences of thyroid cancer in the patients with single nodules and those with multiple nodules were not significantly different ($\chi 2=0.699$, $p=0.403$). Of the 1366 patients, 1172 had benign lesions, and the male:female ratio was 1:5.48. Among those 194 malignant patients, calcification occurred in 89 of the 174 patients with papillary carcinoma (51.15%), seven of 12 patients with follicular cancer, three of five patients with medullary cancer, and the one patient with anaplasia. The distribution pattern of calcification is shown in Table 3. The differences in calcification observed among the different types of malignancies was statistically significant ($\chi 2=69.107$, $p=<0.05$). The frequency of malignancy in the micro-calcification group (61/131, 46.56%) was the highest observed, followed by the coarse calcification group (39/164, 23.78%) and the no calcification group (94/877, 10.71%). The frequency of malignancy in relation to calcification levels, including the odds ratio and 95% confidence intervals (CI), are reported in Table 4.

Serum TSH levels

The serum TSH levels in patients with malignancy (median: 1.47 uIU/mL, 25-75p 0.79-2.33 uIU/mL) were significantly higher than that those in patients with benign lesions (median: 1.12 uIU/mL, 25-75p 0.48-2.01 uIU/mL) (Mann-Whitney test $p<0.05$). The frequency of malignancy in relation to serum TSH levels, including the odds ratio and 95% CI, are reported in Table 4. Of 1456 patients, 290 (19.92%) had serum TSH levels below the lower limit of normal range (<0.40 uIU/mL), and 113 (7.76%) had serum TSH levels above the upper limit of normal range (>4.00 uIU/mL). In addition, 1053 (72.32%) had serum TSH levels within the normal range (>0.40 uIU/mL and <4.00 uIU/mL; median: 1.34 uIU/mL), and these patients were subdivided into two groups according to TSH levels. The frequency of malignancy was found to be closely related to serum TSH levels, with the lowest frequency occurring in patients with TSH levels <0.40 uIU/mL and the highest occurring in patients with serum TSH levels between 1.34 uIU/mL. The patients with 4.00 uIU/mL TSH also showed an increased incidence of malignant cancer from the lower to the upper values of the TSH normal range (Table 4).

Discussion

Our results showed that the patients who suffered from thyroid nodules were mainly females aged 21–70 years, and the gender difference was statistically significant for all age groups. Most of the thyroid cancers were papillary cancers (94.14%), and occurred more frequently in women aged 21–40 years, which was different from previous reports that found the highest frequency in patients of 31-50 years old .

Our results also showed a higher incidence of thyroid cancers in thyroid nodules (13.18%) than those reported by previous studies (5–10%) (Hegedus, 2004). One study found that the frequency of differentiated thyroid cancer was significantly lower in patients with multiple nodules than in patients with single nodules (Christensen et al., 1984), and that male patients were more at risk than female patients (Rago et al., 2010). However, in our studies, no statistically significant difference was found to exist between gender and type of nodules.

Our results showed that advanced age correlated with elevated incidence of thyroid cancer. In our study, 50.45% of patients with thyroid cancer also experienced benign lesions. In addition, the concurrent presence of nodular goiters or Hashimoto's thyroiditis with thyroid cancers was observed at rates of 6.78% (91/1342) or 13.27% (15/113), respectively. Therefore, patients with benign thyroid nodules, especially nodular goiters and Hashimoto's thyroiditis, should be cautiously examined and monitored for any evidence of developing malignancy, such as hardening of the nodule, loss of boundaries or calcification during long-term follow-up. When a malignancy is suspected, surgical intervention is recommended.

Recently, many studies in the literature have discussed the potential significance of detecting thyroid calcifications because of the suspected correlation to thyroid malignancy. Development of calcifying foci is a fairly common finding in the human thyroid in pathological states. Psammoma bodies and very fine calcifications are particularly well-known characteristics of papillary cancer, and have diagnostic value (Carcangiu et al., 1985; Johannessen and Sobrinho-Simoes, 1980). Micro-calcification has been shown to increase the risk for malignancy of the thyroid nodule (Li et al., 2010). Micro-calcification is also considered the most important indicator of PTC, with a reported sensitivity of 29-59% and specificity of 96.77%; however, PTC appears in only 0.74% of goiters (Iannuccilli et al., 2004). Our studies have confirmed these findings. Micro-calcification was also reported as detected in up to nearly 60% of the primary thyroid cancers, with the majority in PTC (Papini, et al. 2002). It has also been visualized in follicular thyroid carcinomas (Taki et al., 2004). Furthermore, micro-calcification may appear not only in the primary thyroid cancer but also in metastatic thyroid cancer (Ahuja et al., 1995). Therefore, the appearance of micro-calcification in the thyroid nodule could be considered as an indicator of high risk for malignancy. Coarse calcification, presenting as irregular hyperechoic foci with acoustic shadowing, can be seen in benign nodules of the thyroid. The diagnosis of a malignant thyroid nodule is highly suggested when there is a single solid nodule with internal abundant blood supply and high resistance index in a young patient (Khoo et al., 2002).

TSH is the fundamental regulator of thyroid function and is related to the secretion of thyroid hormones, maintenance of thyroid-specific gene expression (differentiation), and thyroid cell proliferation. TSH is used clinically as a confirmative growth factor for thyroid nodules, and the administration of L-thyroxine (L-T4) is a routine medical treatment for nodular goiter. Suppression of TSH levels by administering exogenous thyroid hormone may interfere with the growth of established nodules, as well as with the formation of new thyroid nodules (Papini et al., 1998). It has been reported that, in patients with nodular thyroid diseases, the risk of thyroid malignancy increases with their TSH levels, and that, even within normal ranges, the higher TSH concentration is associated with higher frequency and more advanced stage of thyroid cancer (Boelaert et al., 2006; Haymart et al., 2008; Polyzos et al., 2008). In a previous study, it was shown that development of thyroid autonomy in patients with nodular goiter is associated with a lower risk of PTC, suggesting that thyroid autonomy may postpone cancer progression by reducing TSH levels (Fiore et al., 2009). Experimental animal models have shown an increased incidence of thyroid cancer in mice and golden hamsters fed on a low iodine diet, and it was demonstrated that thyroid over-stimulation by TSH leads to hyperplasia and eventually to the development of cancer (Fortner et al., 1960; Schaller and Stevenson, 1966). No difference was observed in TSH levels between patients with papillary thyroid micro-cancer and those with medullary thyroid cancer or c-cell hyperplasia (Gerschpacher et al., 2010).

In our study presented herein, we analyzed the risk of thyroid cancer in patients with nodular thyroid diseases. We performed a retrospective study to evaluate the frequency of thyroid cancer in a series of patients with nodular goiter at the time of their first clinical observation in our department. As expected, the TSH levels in patients with thyroid cancer were significantly higher than those in patients with benign thyroid nodules. The serum TSH levels were found to have a close relationship with the frequency of thyroid cancer, showing a progressive increase from the lower to the upper concentrations, even within the normal range. Our results were generally in agreement with those of previous studies; however, our finding of the highest incidence of malignant cancer correlating to the TSH range of 1.3352 and 4.000 uIU/mL (normal), was different from a previous report (Fiore et al., 2010).

In conclusion, age, TSH levels, and calcification are associated with thyroid cancer and may be useful predictors of malignancy risk of thyroid nodules. Thyroid malignancy often coexists with benign thyroid disease. We suggest that when a thyroid nodule is first discovered upon clinical examination, further evaluation be carried out by using a combination of ultrasound and serum TSH measurements, along with other well-established diagnostic techniques like the fine needle aspiration, to detect thyroid malignancy at the earliest possible stage.

References

Ahuja AT, Chow L, Chick W, et al (1995) Metastatic cervical nodes in papillary carcinoma of the thyroid: ultrasound and histological correlation. *Clin Radiol*, **50**, 229-31.

Boelaert K, Horacek J, Holder RL, et al (2006) Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *J Clin Endocrinol Metab*, **91**, 4295-301.

Carcangiu ML, Zampi G, Pupi A, et al (1985) Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer*, **55,** 805-28.

Christensen SB, Ljungberg O, Tibblin S (1984) Thyroid carcinoma in Malmo, 1960-1977. Epidemiologic, clinical, and prognostic findings in a defined urban population. *Cancer* , **53**, 1625-33.

Fiore E, Rago T, Provenzale MA, et al (2009) Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. *Endocr Relat Cancer*, **16,** 1251-60.

Fiore E, Rago T, Provenzale MA, et al (2010) L-thyroxine-treated patients with nodular goiter have lower serum TSH and lower frequency of papillary thyroid cancer: results of a cross-sectional study on 27 914 patients. *Endocr Relat Cancer*, **17**, 231-39.

Fortner JG, George PA, Sternberg SS (1960) Induced and spontaneous thyroid cancer in the Syrian (golden) hamster. *Endocrinology*, **6**, 364-76.

Gaitan E, Nelson NC, Poole GV (1991) Endemic goiter and endemic thyroid disorders. *World J Surg,* **15**, 205-15.

Gerschpacher M, Gobl C, Anderwald C, et al (2010) Thyrotropin serum concentrations in patients with papillary thyroid microcancers. *Thyroid*, **20**, 389-92.

Haymart MR, Repplinger DJ, Leverson GE, et al (2008) Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab*, **93**, 809-14.

Hegedus L (2004) Clinical practice. The thyroid nodule. *N Engl J Med*, **351**, 1764-71.

Iannuccilli JD, Cronan JJ, Monchik JM (2004) Risk for malignancy of thyroid nodules as assessed by sonographic criteria: the need for biopsy. *J Ultrasound Med*, **23**, 1455-64.

Johannessen JV, Sobrinho-Simoes M (1980) The origin and significance of thyroid psammoma bodies. *Lab Invest* , **43**, 287-96.

Khoo ML, Asa SL, Witterick IJ, et al (2002) Thyroid calcification and its association with thyroid carcinoma. *Head Neck*, **24**, 651-5.

Li QS, Chen SH, Xiong HH, et al (2010) Papillary thyroid carcinoma on sonography. *Clin Imaging*, **34**, 121-6.

Muller PE, Jakoby R, Heinert G, et al (2001) Surgery for recurrent goitre: its complications and their risk factors. *Eur J Surg*, **167**, 816-21.

Papini E, Guglielmi R, Bianchini A, et al (2002) Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. *J Clin Endocrinol Metab*, **87**, 1941-6.

Papini E, Petrucci L, Guglielmi R, et al (1998) Long-term changes in nodular goiter: a 5-year prospective randomized trial of levothyroxine suppressive therapy for benign cold thyroid nodules. *J Clin Endocrinol Metab*, **83**, 780-3.

Polyzos SA, Kita M, Efstathiadou Z, et al (2008) Serum thyrotropin concentration as a biochemical predictor of thyroid malignancy in patients presenting with thyroid nodules. *J Cancer Res Clin Oncol*, **134**, 953-60.

Qian BY, He M, Dong SF (2005) Incidence and mortality of thyroid cancers in Tianjin from 1981 to 2001. *J Chin Endocrinol Metab*, **21**, 432-4.

Rago T, Fiore E, Scutari M, et al (2010) Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. *Eur J Endocrinol*, **162**, 763-70.

Schaller RT, Jr. ,Stevenson JK (1966) Development of carcinoma of the thyroid in iodine-deficient mice. *Cancer,* **19**, 1063-80.

Taki S, Terahata S, Yamashita R, et al (2004) Thyroid calcifications: sonographic patterns and incidence of cancer. *Clin Imaging*, **28**, 368-71.