Features and Trends of Thyroid Cancer in Patients with Thyroidectomies in Beijing, China between 1994 and 2015

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Features and Trends of Thyroid Cancer in Patients with Thyroidectomies in Beijing, China between 1994 and 2015

Running Title: Evolution of thyroid cancer in China

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Keyword: Thyroid cancer; Papillary thyroid carcinoma; microPTC

Abstract

Objectives: This study aims to summarize the features and trends of thyroid carcinoma in the past two decades in China.

Design, Setting and Participants: Clinical data obtained from 10,798 patients treated by thyroidectomy from 1994 to 2015 at the Department of General Surgery of the People's Liberation Army General Hospital, Beijing, China were retrospectively analyzed.

Outcome measures: Incidence and histopathological features of thyroid cancer were compared and the risk factors for local lymph node metastasis analyzed.

Results: Our data indicated a significant increase in the detection of thyroid cancer (from 16.8% to 69.8%, P<0.01). Among the 5,235 thyroid cancer cases, papillary thyroid carcinoma (PTC) was the most common histotype, accounting for 95.1% of all malignancies over the 22-year period. Among the 4,979 PTCs, microPTCs (mPTC) with the largest diameter ≤ 10 mm has gradually become the dominant form, and the percentage of it in PTCs has increased from 13.3% in the biennial period of 1994-1995 to 51.2% in 2010-2011. Furthermore, the size of the tumor has decreased significantly from 2.3±1.1 cm in 1994 to 1.2±0.9 cm in the largest diameter (P<0.01), while the average age at diagnosis and female dominance remained unchanged during the period. Logistic regression showed that tumor nodules > 1 cm and male gender are the main risk factors for local lymph node metastasis (LNM) whereas patients over 45 years had lower risk.

Conclusions: During the 22-year period, an increased detection of thyroid cancer, particularly mPTC, was found while occurrence of LNM decreased. Our results suggest that the current preoperative diagnosis and risk stratification are adequate, supporting the published guidelines for the diagnosis of thyroid cancer.

Strengths and limitations of this study

- The retrospective study analyzed the clinicopathological data of thyroid cancer over a period of 22 years
- The study identified major risk factors for the lymph node metastasis of thyroid cancer
- The retrospective nature of this study led to limited survival data which should have been included to evaluate the improvement of clinical outcome during the 22-year period.

Introduction

Thyroid nodules occur in about 4-7% of the population and 8-16% of them contain malignant elements [1]. Thyroid cancer is the most common endocrine cancer [1], and approximately 90% of them are differentiated, including predominantly papillary thyroid carcinoma (PTC) and, to a less extent, follicular thyroid carcinoma [2]. These subtypes are generally associated with a more favorable prognosis and higher cure rate [3], compared with less common but more aggressive forms of thyroid cancer, such as medullary thyroid cancer, anaplastic thyroid cancer, and thyroid sarcoma or lymphoma [4].

The past few decades have witnessed an increase in the incidence of thyroid cancer while the associated mortality remains unchanged [5-9] . Also increased is the number of cases of newly diagnosed thyroid cancer with smaller tumors. Between 2008 and 2009, 39% of thyroid cancer patients were diagnosed with tumors smaller than 1 cm, compared to 25% between 1988 and 1989 [10]. This is due to the proactive screening of thyroid cancer, particularly by the application of sensitive surveillance modality in recent years [11-15]. Advanced imaging techniques, such as ultrasonography, computational tomography, magnetic resonance imaging, and positron emission tomography, along with fine-needle aspiration biopsy, have dramatically improved the detection of small thyroid nodules and facilitated the early diagnosis of thyroid cancer [16-18].

However, the increased incidence of thyroid cancer isalso believed to be associated with over-diagnosis [18-22]and environmental factors [6 23]. The screening of highly prevalent thyroid nodules for those with malignant potential remains to be challenging although a number of guidelines have recently been proposed for the diagnosis and management of thyroid nodules [24]. Identifying nodules with high risk of malignancy during thyroidectomy represents a cost-effective approach [25 26]. Therefore in this study the features and trends of thyroid cancer in patients with thyroidectomies in China were retrospectively analysed to examine whether the decrease in the diagnosable size of thyroid nodules is associated with misdiagnosis, and provide further insight into its diagnosis and management.

Materials and methods

This study was approved by the Chinese People's Liberation Army (PLA) General Hospital Ethics Committee and written informed consents obtained from all patients for retrospective studies.

Data collection

Clinical database for patients undergoing thyroidectomies from 1994 to 2015 at the Department of General Surgery of PLA General Hospital (Beijing, China) was revisited, and the reported thyroid pathology screened and reviewed to analyse the correlation of the size of thyroid nodules with other pathological features.

Clinical parameters used in the analysis included front neck discomfort or pain, dysphagia, dysphonia or hoarseness, dyspnea, sign of thyroid nodule and thyroid gland enlargement, as well as ultrasound features. Data were individually checked and cases with inconsistent data were excluded before statistical analysis. As a result, 10,798 eligible cases with thyroidectomies from 1994 to 2015 were recruited.

Data analysis and statistics

Benign or malignant thyroid nodules were diagnosed based on pathological features, and malignant nodules were reported as papillary (PTC), follicular (FTC), medullary (MTC), or anaplastic thyroid carcinoma (ATC). Papillary thyroid carcinomas were further sub-classified into clinically relevant PTCs (crPTCs) > 10 mm in diameter and micro-PTCs (mPTCs) ≤ 10 mm in diameter (the largest diameter of a nodule). These sub-groups were compared, when appropriate, in the analysis.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Version 17.0, IBM, Armonk, NY). Data are shown as mean±standard deviation or mean±standard error, when appropriate. Chi-square test was used to compare different categories and generate the trend lines, *t*-test employed to compare between groups, and logistic regression performed to calculate the risk factors for lymph node metastasis (LNM). Data analysis was adjusted for confounders such as age, gender, nodule size, and the presence of Hashimoto thyroiditis, and two-tailed $P < 0.05$ was considered statistically significant.

Patient and public involvement

This is a retrospective study, with no involvement of patients or publics in the development of research initiative and outcome measures and the design and implementation of the study. It covers a period of 22 years between 1994 and 2015; therefore, there is no possibility or plan to disseminate the results among the participants.

Results

Malignancy rate increased from 1994 to 2015.

The numbers of benign and malignant cases of thyroid cancer detected during thyroidectomy from 1994 to 2015 are summarized in table 1. With an increase in the number of thyroidectomy surgeries, as a result of improved diagnosis of thyroid cancer, the numbers of benign and malignant cases increased gradually. Noticeably, the malignancy rate of thyroid nodules increased dramatically from 16.8% during the biennial period of 1994-1995 to 69.8% during 2014-2015 (P<0.05), whereas the benign rate decreased from 83.2% to 30.2% (P<0.05).

Diagnosis rate of PTC increased from 1994 to 2015.

Among the 10,798 cases recruited, 5,235 cases were found to be malignant (Table 2). A majority of patients (63.6%) were found with multiple cancers. Moreover, 48.1% of the patients had unilateral cancer and the remaining 51.9% had bilateral cancer (Table 2). In addition, most of the malignant cases were recorded as PTCs, which exhibited a significant increase from 65.3% during period of 1994-1995 to 98.2% during 2014-2015 (P<0.05, Figure 1), while the diagnosis rates of other histotypes decreased concurrently (Table 2 and Figure 1).

Detection size of thyroid nodules decreased from1994 to 2015.

Reviewing the clinicopathological information of malignant cases suggested that most of the patients were free of clinically relevant symptoms and physical signs (Figure 2A, 2B), with only 9% showing different degrees of discomfort, such as pain and dysphagia. Enlargement of thyroid glands were often noticed, unnecessarily by health professionals, during routine physical examination; however, 34% of tumors were impalpable likely due to the depth of intra-thyroidal microcarcinoma. By ultrasonography, 37% of patients were detected with single thyroid tumors, while the others had multiple lesions (Figure 2C).

From 1994 to 2015, the size of thyroid nodules reported decreased significantly, with the mean diameter reduced from 2.6±1.4 cm to 1.2±0.9 cm (Figure 2D). This trend roughly correlated with an increase in the rate of preoperative fine needle aspiration (FNA), from 15% in 2004 to 74% in 2013, although this rate regressed to 57% between 2014 and 2015 (Figure 2E). Also of relevance, during the same period, the total thyroidectomy rate remained unchanged from 1994 to 2007, but gradually increased from 2008 to 2013, and decreased sharply to 3% from 2014 to 2015 (Figure 2F).

Size of thyroid cancer at diagnosis and metastasis rate decreased from1994 to 2015

Considering the high prevalence of PTCs, 4,980 cases compared to 255 cases of other subtypes all-together, further data analysis was restricted to this type of thyroid cancer. As shown in Table 3, the mean age of patients at diagnosis was 43.7±11.3 years old, with no significant variation from 1994 to 2015. Incidence of PTC in women was considerably higher than in men, with approximately two thirds of these patients were female. Of note, the average diameter of PTCs at diagnosis decreased from 2.3±1.1 cm in 1994 to 1.2±0.9 cm in 2015 (P<0.05, Table 3). Correlating with this trend was the increase in the percentage of mPTCs from 13.3% between 1994 - 1995 to 51.2% during 2010 – 2011 (P<0.05, Table 3). Interestingly, the detection rate of mPTCs decreased to 26.5 between 2014 and 2015.

Analysis of the incidence of LNM of thyroid cancer in parallel among 4,980 cases of PTCs demonstrated a significant reduction in the occurrence of LNM with a decrease of tumor size (P<0.05, Table 3). This is associated with the increased diagnosis rate of mPTCs, which shows an apparently lower LNM potential in comparison with crPTCs (Table 4). Before 2007, the difference between the LNM rates of mPTC and crPTC were appreciable but most of time not statistically significant due to the limited cohort sizes. With the increase of PTC diagnosis after 2008, a significantly lower LNM occurrence was found for mPTCs, compared to crPTCs (Table 4).

Determinant factors of local lymph node metastasis in PTC, mPTC and crPTC

To identify the risk factors for local LNM in PTC, mPTC, and crPTC, logistic regression was performed. The results support a correlation of LNM with nodules >1 cm [odd ratio (OR): 2.480, confidence interval (CI): 0.428 – 0.613, P<0.001] and male gender (OR: 1.627, CI: 1.376 – 1.923, P<0.001) as well as an inverse correlation with ≥45 years (OR: 0.512, CI: 2.040 – 2.902, P<0.001) after adjustment for other covariates in all PTCs (Figure 3A, Table 2). Hashimoto's thyroiditis presented no risk for LNM (Figure 3A). Consistent data were also obtained in patients with mPTC and crPTC (Figure 3B & 3C, Table 3 and Table 4).

Discussion

Thyroid cancer is diagnosed in nearly 65000 people annually all over the world [25 27-29]. Although these malignancies are mostly differentiated and generally associated with good prognosis, involvement of local lymph nodes is frequently observed. Proactive screening for malignancies from a substantial population of thyroid nodes and accurate histopathological stratification are crucial for the clinical decision and improvement of patient outcome. This study reviewed 10,798 cases of thyroidectomy undertaken in a major hospital in one of the most populated city in the world over a period of 22 years, summarized the clinical features of 5,235 cases of thyroid cancer, and analysed the trend of PTCs and risk factors predicting LNM.

Our analysis unveiled a gradual but significant increase of thyroid malignancy detection rate over the period from 1994 to 2015, from 16.8% to 69.8%. These percentages are generally within the wide-range of detection rate (6.7-56%) of thyroid cancer worldwide [25 28 29], although data between 2014 and 2015 was relatively higher than earlier periods. Variations in the detection rates across different centers are likely caused by the different guidelines and algorithms followed by physicians and surgeons. The increase of detection rate from 1994 to 2015 reflects an improvement in the diagnosis, through the advances in imaging technologies and the increasing use of FNA. In addition, appropriate preoperative risk stratification of thyroid nodules, as a result of improved clinical evaluation, thyroid function test, ultrasonography, and molecular diagnosis, in recent years diverts a lot of patients from thyroidectomy, contributing to the increased diagnosis of thyroid cancer. These data support the published guideline [30 31] and highlight the importance of combining imaging, FNA, cytology, and molecular diagnosis. However, we can't rule out the contribution of social and environmental stresses, which is beyond the scope of this retrospective study. It is noteworthy that this study covered a period during which China was undergoing the largest scale of industrialisation in modern history that inevitably led to dramatic social and environmental changes.

Papillary carcinoma accounts for 95.1% of malignancies in the whole cohort, and as high as 98.2% among patients diagnosed between 2014 and 2015. These rates are comparable to the findings of another study performed in Nanjing, China [25], but higher than other reports [32], likely due to the increase of PTCs, as previously suggested[33] . The high detection rate for PTC is attributable to the increasing use of head and neck imaging, which detects sub-palpable (yet potentially malignant) thyroid nodules, and ultrasound-guided FNA, which improves the preoperative detection of malignancy. With the use of head and neck ultrasonography and other diagnostic approaches, the average size of PTC at diagnosis has significantly reduced from 2.3±1.1 cm in 1994 to 1.2±0.9 cm in 2015, similar to the trends reported in previous studies [10 25]. This progress allows early detection of thyroid cancer which leads to an increasing trend of hemithyroidectomy, compared to total thyroidectomy, and intensified follow-up of thyroid cancer patients in recent years in our practice following the American Thyroid Association (ATA) guidelines [30 31 33].. However, the overdiagnosis and overtreatment of indolent diseases have been increasingly recognized. The most recent ATA guidelines suggest a more parsimonious evaluation of thyroid nodules and a more judicious use of thyroid cancer treatment to minimize risks and maximize benefits to patients [33] .

Our data suggests that >1 cm nodules and the male gender predict a high risk of LNM while age ≥45 years is associated with low LNM potentials, consistent with previous finding [25]. Therefore, more attention is needed for these patients in future practice. In this single-center study, however, factors taken into account for logistic regression analysis were limited due to the retrospective nature of this study. Future studies are needed to characterise the association of other clinical and biochemical parameters with thyroid cancer metastasis and patient outcome. Characterising the contribution of social and environmental stresses to the occurrence of thyroid cancer will also be of significant social economical value.

In this study, we retrospectively analysed the clinical data of 10,798 patients treated by thyroidectomy to study the features and trends of thyroid cancer in the past 22 years. Our data suggest significant increase in the detection rate of thyroid cancer, in particular mPTC, which has become the dominant form of thyroid cancer. As a result, the occurrence of LNM has been decreasing with time. Our results suggest the adequacy of current preoperative diagnosis and risk stratification, although overdiagnosis and overtreatment require future attention of physicians and surgeons in view of the rapid increase in the number of thyroidectomies.

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Authors' contributions

ZL designed the study, collected and analysed data, and wrote the manuscript. PP contributed to manuscript writing. ZL, LYK, WFL, YGQ, DJ, and WXL assisted with data presentation and manuscript writing. LZH, DJT and MYM contributed into study design, data analysis, and manuscript writing. All authors read and approved the final manuscript.

Competing interests

The authors have no conflicts of interest to disclose.

Data sharing statement: Data will be available upon request to the corresponding author

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Table 1. Detection rate of malignancy among patients undergoing thyroidectomy from1994 to 2015

Period	94.1-95.12	96.1-97.12	98.1-99.12	00.1-01.12	02.1-03.12	04.1-05.12	06.1-07.12	08.1-09.12	10.1-11.12	12.1-13.12	14.1-15.12	Total	*P*
Benign, *n*	114	136	169	268	286	495	535	738	901	1033	890	5563	<0.001
(%)	(83.2)	(86.1)[a,b]	(88.0)[a,b]	(83.0)[a]	(80.1)[a,b]	(79.2)[b]	(71.4)[a,b]	(64.6)[a,b]	(52.4)[a,b]	(42.2)[a,b]	(30.2)[a,b]	(51.5)	
Cancer, *n*	23	22	23	55	71	130	214	405	817	1413	2060	5235	
(%)	(16.8)	(13.9)[a,b]	(12.0)[a,b]	(17.0)[a]	(19.9)[a,b]	(20.8)[b]	(28.6)[a,b]	(35.4)[a,b]	(47.6)[a,b]	(57.8)[a,b]	(69.8)[a,b]	(48.5)	
Total	137	158	192	323	357	625	749	1143	1718	2446	2950	10798	

[a] Percentages significantly different from the previous year; [b] Percentages significantly different from period 94.1-95.12.

Table 2. Pathological classification of all thyroid malignancies from 1994 to 2015

Period	94.1-95.12	96.01-97.12	98.1-99.12	00.1-01.12	02.1-03.12	04.1-05.12	06.1-07.12	08.1-09.12	10.1-11.12	12.1-13.12	14.1-15.12	*P* for difference	*P* for trend
PTC, *n* (%)	15 (65.3)	17 (77.3)	17 (73.9)	39 (70.9)	50 (70.4)	107 (82.3)	185 (86.4)	383 (94.6)	768 (94.0)	1376 (97.4)	2023 (98.2)	<0.001	<0.001
FTC, *n* (%)	3 (13.0)	1 (4.5)	4 (17.3)	10 (18.1)	9 (12.7)	17 (13.1)	18 (8.4)	9 (2.2)	25 (3.0)	17 (1.2)	20 (0.9)	<0.001	<0.001
MTC, *n* (%)	1 (4.3)	2 (9.1)	1 (4.3)	4 (7.3)	2 (2.8)	1 (0.8)	2 (0.9)	5 (1.2)	14 (1.7)	12 (0.8)	12 (0.6)	<0.001	<0.001
ATC, *n* (%)	0 (0)	0 (0)	1 (4.3)	1 (1.8)	3 (4.2)	1 (0.8)	1 (0.5)	2 (0.5)	1 (0.1)	1 (0.1)	2 (0.1)	<0.001	<0.001
Other, *n* (%)	4 (17.4)	2 (9.1)	0 (0)	1 (1.8)	7 (9.9)	4 (3.1)	7 (3.3)	6 (1.5)	9 (1.1)	7 (0.5)	3 (0.1)	<0.001	<0.001
Unilateral	14 (60.9)	14 (63.6)	13 (56.5)	31 (56.4)	38 (53.5)	72 (55.4)	122 (57.0)	213 (52.6)	389 (47.6)	616 (43.6)	991 (48.1)	0.071	<0.001
Bilateral	9 (39.1)	8 (36.4)	10 (43.5)	24 (43.6)	33 (46.5)	58 (44.6)	92 (43.0)	192 (47.4)	428 (52.4)	797 (56.4)	1069 (51.9)		
Solitary	7 (30.4)	13 (59.1)	11 (47.8)	27 (49.1)	28 (39.4)	59 (45.4)	105 (49.0)	172 (42.5)	292 (35.7)	456 (32.3)	749 (36.4)	<0.001	<0.001
Multiple	16 (69.6)	9 (40.9)	12 (52.2)	28 (50.9)	43 (60.6)	71 (54.6)	109 (51.0)	233 (57.5)	525 (64.3)	957 (67.7)	1311 (63.6)		
All cancer, *n*	23	22	23	55	71	130	214	405	817	1413	2060		

PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma; other histotypes of carcinoma collectively refer to cancer other than PTC, FTC, MTC, and ATC, including poorly differentiated thyroid cancer, squamous cell carcinomas, B cell lymphomas of thyroid, spindle cell carcinoma, adenoid cystic carcinoma, renal clear cell metastasis and Langerhans cell histocytosis of the thyroid gland.

Table 3. Clinicopathological feature of PTCs from1994 to 2015

Period	94.1-95.12	96.1-97.12	98.1-99.12	00.1-01.12	02.1-03.12	04.1-05.12	06.1-07.12	08.1-09.12	10.1-11.12	12.1-13.12	14.1-15.12	Total	*P* for difference	*P* for trend
Age, year	46.9±14.3	43.1±10.7	41.1±12.9	44.9±14.8	44.6±14.5	43.8±12.4	44.6±12.4	42.7±12.4	43.9±11.2	43.9±11.1	43.6±10.9	43.7±11.3	0.643	
Male, *n*	5	3	6	11	18	34	60	115	227	366	616	1461	0.434	0.664
(%)	(33.3)	(17.6)	(35.3)	(28.2)	(36)	(31.8)	(32.4)	(30.0)	(29.6)	(26.6)	(30.4)	(29.3)		
Female, *n*	10	14	11	28	32	73	125	268	541	1010	1407	3519		
(%)	(66.7)	(82.4)[ab]	(64.7.0)[a,]	(71.8)[a]	(64)[a,b]	(68.2)[b]	(67.6)[a,b]	(70.0)[a,b]	(70.4)[a,b]	(73.4)[a,]	(69.6)[a,]	(70.7)		
Size[c], cm	2.3±1.1	2.6±1.9	2.1±1.3	2.2±1.6	2.2±1.4	2.2±1.6	1.7±1.1[ab]	1.5±1.0b	1.3±0.9[ab]	1.2±0.8[ab]	1.2±0.9[b]	1.4±1.0	<0.001	
CrPTC, *n*	13	15	12	32	41	87	118	238	375	696	1486	3113	<0.001	0.213
(%)	(86.7)	(88.2)	(70.6)	(82.1)	(82.0)	(81.3)	(63.8)[a]	(62.1)[b]	(48.8)[ab]	(50.6)b	(73.5)[a]	(62.5)		
mPTC, *n*	2	2	5	7	9	20	67	145	393	680	537	1866		
(%)	(13.3)	(11.8)	(29.4)	(17.9)	(18.0)	(18.7)	(36.2)	(37.9)	(51.2)	(49.4)	(26.5)	(37.5)		
LNM, *n*	5	5	7	22	17	27	55	96	192	372	414	1212	<0.001	<0.001
(%)	(33.3)	(29.4)	(41.2)	(56.4)	(34)	(25.2)	(29.7)	(25.1)	(25.0)	(27.0)	(20.5)[a]	(24.3)		
No-LNM, *n*	10	12	10	17	33	80	130	287	576	1004	1609	3768		
(%)	(66.7)	(70.6)	(58.8)	(43.6)	(66)	(74.8)	(70.3)	(74.9)	(75.0)	(73.0)	(79.5)	(75.7)		
Total	15	17	17	39	50	107	185	383	768	1376	2023		<0.001	<0.001

[a] Percentages significantly different from the previous year; [b] Percentages significantly different from period 08.1-09.12; [c] Mean diameter; crPTC, clinical relevant papillary thyroid carcinoma; mPTC, micro papillary thyroid carcinoma; LNM, lymph node metastasis; LN, lymph node.

Table 4. Rate of local lymph node metastasis in patients with crPTC and mPTC from 2008 to 2013

	94.1 -95.12	96.1 -97.12	98.1 -99.12	00.1 -01.12	02.1 -03.12	04.1 -05.12	06.1 -07.12	08.1 -09.12	10.1 -11.12	12.1 -13.12	14.1 -15.12	Total	*P* for difference	*P* for trend
crPTC, *n* (%)	3 (23.1)	5 (33.3)	6 (50.0)	19 (59.4)	17 (41.5)	24 (27.6)	35 (29.7)	73 (30.7)	130 (34.7)	243 (34.9)	330 (22.2)	885 (28.4)	<0.001	<0.001
mPTC, *n* (%)	2 (100)	0 (0)	1 (20.0)	3 (42.9)	0 (0)	3 (15.0)	20 (29.9)	23 (16.0)	62 (15.8)	129 (19.0)	84 (15.6)	327 (17.5)	0.005	0.087
P-value	0.032	0.331	0.252	0.425	0.017	0.243	0.978	0.001	0.000	0.000	0.001			

crPTC, clinical relevant papillary thyroid carcinoma; mPTC, micro papillary thyroid carcinoma.

Figure legends

Figure 1. Trends in the diagnosis of various subtype thyroid malignancies from 1994 to 2015.

Figure 2. Clinical, surgical and ultrasound features during the evolvement of thyroidectomy and the diagnosis of thyroid cancer from 1994 to 2015. Data on the symptoms (**A**), physical signs (**B**), nodule multiplicity (**C**), ultrasonographic sizes of nodules (**D**), FNA ratio (**E**), and thyroidectomy types (**F**) were summarized.

Figure 3. Determinant factors of lymph node metastasis of PTC (**A**), mPTC (**B**) and crPTC (**C**). Logistic regression was performed to define factors associated with local lymph node metastasis.

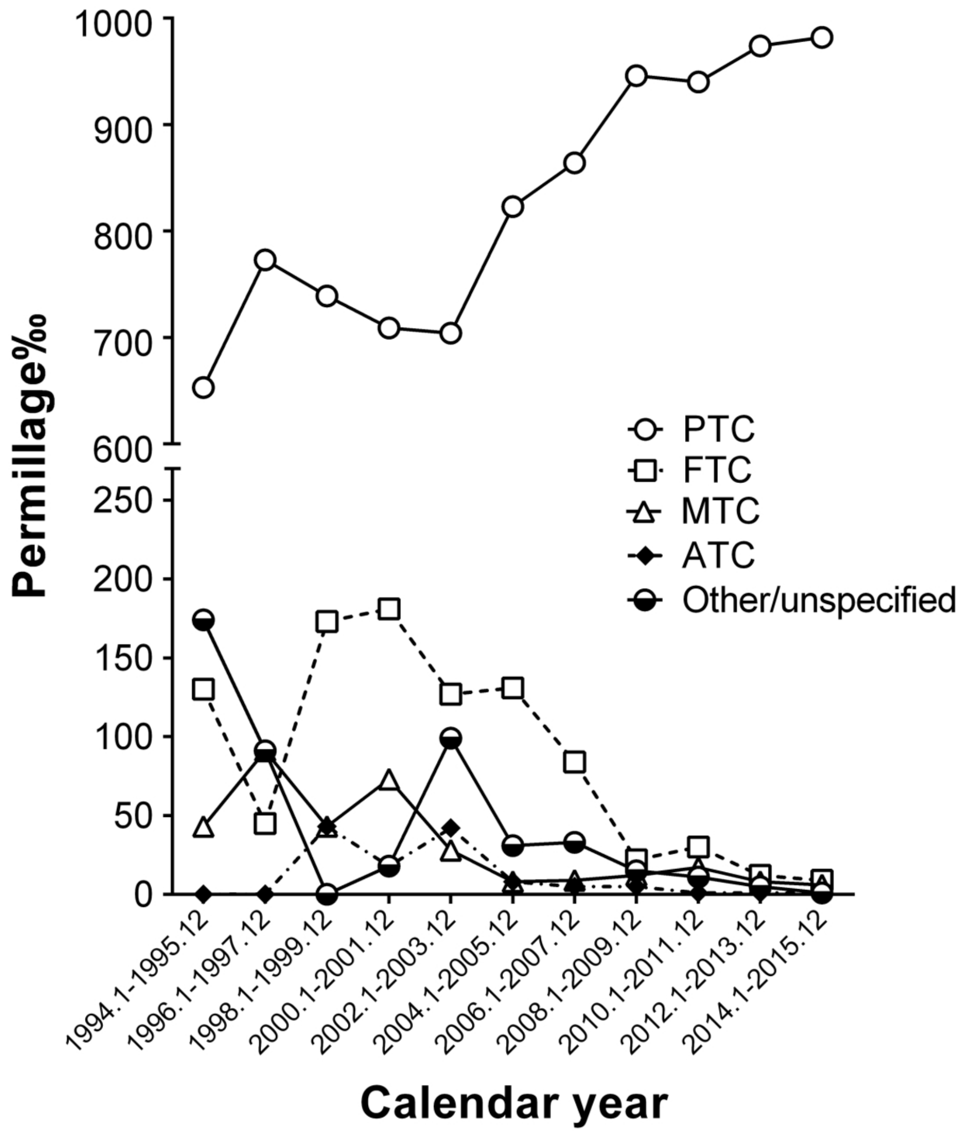

Figure 1

94x111mm (600 x 600 DPI)

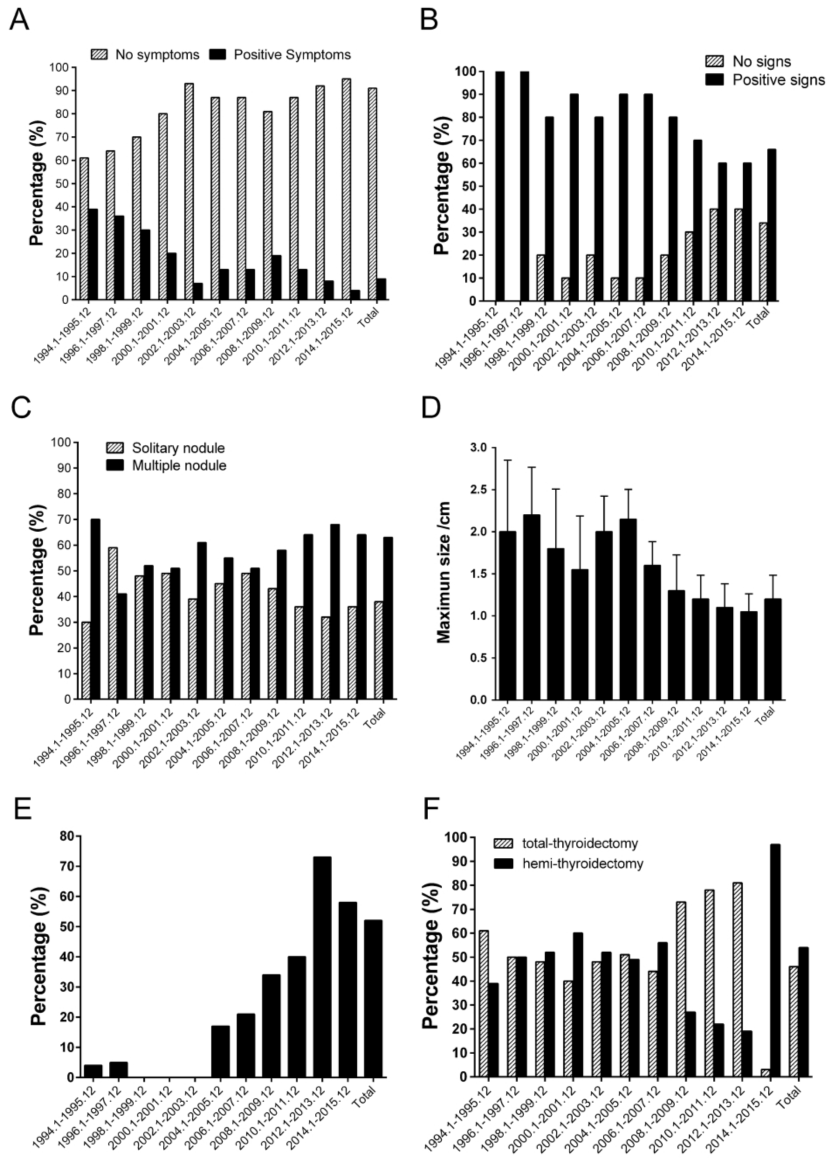

Figure 2

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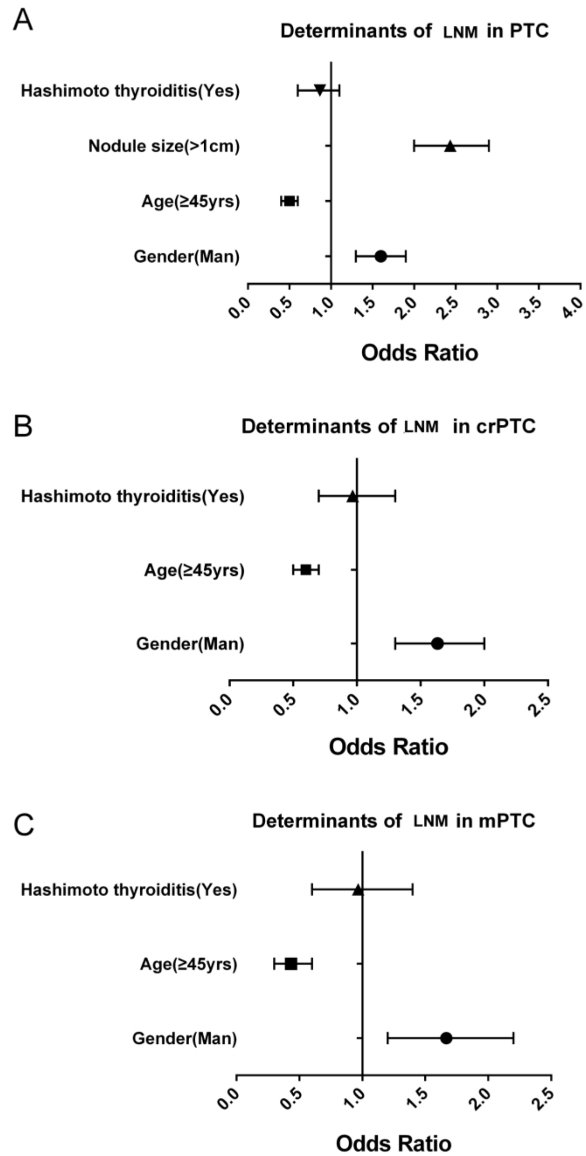

Figure 3

170x313mm (300 x 300 DPI)

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Features and Trends of Thyroid Cancer in Patients with Thyroidectomies in Beijing, China between 1994 and 2015

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Features and Trends of Thyroid Cancer in Patients with Thyroidectomies in Beijing, China between 1994 and 2015

Running Title: Evolution of thyroid cancer in China

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Keyword: Thyroid cancer; Papillary thyroid carcinoma; microPT4C

Abstract

Objectives: This study aims to summarize the features and trends of thyroid carcinoma in the past two decades in China.

Design, Setting and Participants: Clinical data obtained from 10,798 patients treated by thyroidectomy from 1994 to 2015 at the Department of General Surgery of the People's Liberation Army General Hospital, Beijing, China were retrospectively analyzed.

Outcome measures: Incidence and histopathological features of thyroid cancer were compared and the risk factors for local lymph node metastasis analyzed.

Results: Our data indicated a significant increase in the detection of thyroid cancer (from 16.8% to 69.8%, $P<0.01$). Among the 5,235 thyroid cancer cases, papillary thyroid carcinoma (PTC) was the most common histotype, accounting for 95.1% of all malignancies over the 22-year period. Among the 4,979 PTCs, microPTCs (mPTC) with the largest diameter ≤ 10 mm has gradually become the dominant form, and its percentage in PTCs has increased from 13.3% in the biennial period of 1994-1995 to 51.2% in 2010-2011. Furthermore, the size of the tumor has decreased significantly from 2.3±1.1 cm in 1994 to 1.2±0.9 cm in the largest diameter ($P<0.01$), while the average age at diagnosis and female dominance remained unchanged during the period. Logistic regression showed that tumor nodules > 1 cm and male gender were the main risk factors for local lymph node metastasis (LNM) whereas patients over 45 years old had lower risk.

Conclusions: During the 22-year period, an increased detection of thyroid cancer, particularly mPTC, was found while the occurrence of LNM decreased. Our results suggest that the current preoperative diagnosis and risk stratification are adequate, supporting the published guidelines for the diagnosis of thyroid cancer.

Strengths and limitations of this study

- The strength of this study lies in that more than 10,000 cases of thyroid cancer over a period of 22 years were retrospectively studied to summarize the features and trends of thyroid cancer in patients with thyroidectomies in Beijing, China.
- The clinical practice was reviewed over this long period of time to evaluate the performance of the preoperative diagnosis and risk stratification in a major hospital in Beijing.
- The retrospective nature of this study led to limited survival data, which should have been included to evaluate the improvement of clinical outcome during the 22-year period.

Introduction

Thyroid nodules occur in about 4-7% of the population, and 8-16% of these contain malignant elements [1]. Thyroid cancer is the most common endocrine cancer [1], and approximately 90% of these are differentiated, including predominantly papillary thyroid carcinoma (PTC) and, to a less extent, follicular thyroid carcinoma [2]. These subtypes are generally associated with a more favorable prognosis and higher cure rate [3], when compared with less common but more aggressive forms of thyroid cancer, such as medullary thyroid cancer, anaplastic thyroid cancer, and thyroid sarcoma or lymphoma [4].

The past few decades have witnessed an increase in the incidence of thyroid cancer, while the associated mortality remains unchanged [5-9] . In addition, the number of newly diagnosed thyroid cancer cases with smaller tumors increased. Between 2008 and 2009, 39% of thyroid cancer patients were diagnosed with tumors smaller than 1 cm, when compared to 25% of patients diagnosed between 1988 and 1989 [10]. This was due to the proactive screening of thyroid cancer, particularly through the application of sensitive surveillance modalities in recent years [11-15]. Advanced imaging techniques, such as ultrasonography, computational tomography, magnetic resonance imaging and positron emission tomography, along with fine-needle aspiration biopsy have dramatically improved the detection of small thyroid nodules, and facilitated the early diagnosis of thyroid cancer [16-18].

However, the increased incidence of thyroid cancer has also been considered to be associated with over-diagnosis [18-22] and environmental factors [6 23]. The screening of highly prevalent thyroid nodules for those with malignant potential remains challenging, although a number of guidelines have recently been proposed for the diagnosis and management of thyroid nodules [24]. Identifying nodules with high risk of malignancy during thyroidectomy represents a cost-effective approach [25 26]. Therefore, in this study, the features and trends of thyroid cancer in patients with thyroidectomies in China were retrospectively analyzed to examine whether the decrease in diagnosable size of thyroid nodules is associated with misdiagnosis, providing further insight into its diagnosis and management.

Materials and Methods

This study was approved by the Chinese People's Liberation Army (PLA) General Hospital Ethics Committee, and written informed consents obtained from all patients for retrospective studies.

Data collection

The clinical database for patients undergoing thyroidectomies from 1994 to 2015 at the Department of General Surgery of PLA General Hospital (Beijing, China) was revisited, and the thyroid pathology reports were screened and reviewed to analyze the correlation of the size of thyroid nodules with other pathological features.

The clinical parameters used in the analysis included front neck discomfort or pain, dysphagia, dysphonia or hoarseness, dyspnea, sign of thyroid nodule and thyroid gland enlargement, as well as ultrasound features. These data were individually checked, and cases with inconsistent data were excluded before the statistical analysis. As a result, 10,798 eligible cases with thyroidectomies from 1994 to 2015 were recruited.

Data analysis and statistics

Benign or malignant thyroid nodules were diagnosed based on pathological features, and malignant nodules were reported as papillary (PTC), follicular (FTC), medullary (MTC), or anaplastic thyroid carcinoma (ATC). Papillary thyroid carcinomas were further sub-classified into clinically relevant PTCs (crPTCs) >10 mm in diameter and micro-PTCs (mPTCs) ≤10 mm in diameter (the largest diameter of a nodule). These sub-groups were compared, when appropriate, in the analysis.

Patients were treated by surgery, often with lymph node dissection, depending on the clinical features and the number, location and size of the involved lymph node, which was assessed by pre-operative imaging analysis and intraoperative frozen section pathological analysis. Tumors within 10 mm in size and had no involvement of lymph nodes were resected without the removal of lymph nodes. When the pre-operative imaging revealed no abnormalities in the lymph nodes, but malignancy was confirmed by intraoperative frozen section analysis, ipsilateral central neck node dissection was performed. If the preoperative sonography or intraoperative examination revealed abnormal lymph nodes, and frozen section analysis confirmed the malignancy, improved lateral neck lymph node dissection was performed.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Version 17.0; IBM, Armonk, NY). Data were presented as mean ± standard deviation or mean ± standard error, when appropriate. Chi-square test was used to compare different categories and generate the trend lines. Furthermore, *t*-test was used for comparisons between groups, and logistic regression was performed to calculate the risk factors for lymph node metastasis (LNM). The data analysis was adjusted for confounders, such as age, gender, nodule size and the presence of Hashimoto thyroiditis. A two-tailed $P<0.05$ was considered statistically significant.

Patient and public involvement

This retrospective study did not involve patients or the public in the development of research initiatives and outcome measures, as well as the design and implementation of the study. The study covered a period of 22 years, which ranged between 1994 and 2015. Therefore, there was no possibility or plan to disseminate the results among the participants.

Results

Malignancy rate increased from 1994 to 2015

The numbers of benign and malignant cases of thyroid cancer detected during thyroidectomy from 1994 to 2015 are summarized in Table 1. As the number of thyroidectomy surgeries increased due to the improved diagnosis of thyroid cancer, the number of benign and malignant cases gradually increased. Noticeably, the malignancy rate of thyroid nodules dramatically increased from 16.8% during the biennial period of 1994-1995 to 69.8% during the period of 2014-2015 (P<0.05), while the benign rate decreased from 83.2% to 30.2% (P<0.05).

The diagnosis rate of PTC increased from 1994 to 2015

Among the 10,798 cases recruited, 5,235 cases were found to be malignant (Table 2). Furthermore, a majority of patients (63.6%) were found with multiple cancers. Moreover, 48.1% of patients had unilateral cancer, and the remaining 51.9% of patients had bilateral cancer (Table 2). In addition, most of the malignant cases were recorded as PTCs, which exhibited a significant increase from 65.3% during the period of 1994-1995 to 98.2% during the period of 2014-2015 (P<0.05, Figure 1), while the diagnosis rates of other histotypes concurrently decreased (Table 2 and Figure 1).

Detection size of thyroid nodules decreased from1994 to 2015

The review of the clinicopathological information of malignant cases suggested that most of these patients were free of clinically relevant symptoms and physical signs (Figures 2A and 2B), and only 9% of patients exhibited different degrees of discomfort, such as pain and dysphagia. The enlargement of thyroid glands were often noticed, but not necessarily by health professionals, during routine physical examination. However, 34% of tumors were impalpable, which was likely due to the depth of the intra-thyroidal microcarcinoma. By ultrasonography, 37% of patients were detected with single thyroid tumors, while the remaining patients had multiple lesions (Figure 2C).

From 1994 to 2015, the size of thyroid nodules has been reported to significantly decrease, with the mean diameter reduced from 2.6 ± 1.4 cm to 1.2 ± 0.9 cm (Figure 2D). This trend roughly correlates with the increase in the rate of preoperative fine needle aspiration (FNA), which ranged from 15% in 2004 to 74% in 2013, although this rate regressed to 57% between 2014 and 2015 (Figure 2E). In addition, during the same period, the total thyroidectomy rate remained unchanged from 1994 to 2007, but gradually increased from 2008 to 2013, and decreased sharply to 3% from 2014 to 2015 (Figure 2F).

The size of the thyroid cancer at diagnosis and metastasis rate decreased from1994 to 2015

Considering the high prevalence of PTCs, 4,980 cases were compared to 255 cases of other subtypes all-together, and further data analysis was restricted to this type of thyroid cancer. As shown in Table 3, the mean age of patients at diagnosis was 43.7 ± 11.3 years old, with no significant variation from 1994 to 2015. Furthermore, the incidence of PTC was considerably higher in women than in men, in which approximately two thirds of these patients were female. It is noteworthy that the average diameter of PTCs at diagnosis decreased from 2.3 ± 1.1 cm in 1994 to 1.2 ± 0.9 cm in 2015 (P<0.05, Table 3). Correlating with this trend was the increase in the percentage of mPTCs from 13.3% between 1994 and 1995 to 51.2% between 2010 and 2011 (P<0.05, Table 3). This likely resulted from a more meticulous pathological examination. Interestingly, the detection rate of mPTCs decreased to 26.5 between 2014 and 2015.

Among the PTC cases studied, 1,212 patients were found with LNM, but its occurrence significantly decreased with the reduction in tumor size (P<0.05, Table 3). This was associated with the increased diagnosis rate of mPTCs, which shows an apparently lower LNM potential in comparison with crPTCs (Table 4). Before 2007, the difference between the LNM rates of mPTC and crPTC were appreciable, but this not statistically significant most of time due to the limited size of the cohort. With the increase in PTC diagnosis after 2008, a significantly lower LNM occurrence was found for mPTCs, when compared to crPTCs (Table 4).

Determinant factors of local lymph node metastasis in PTC, mPTC and crPTC

To identify the risk factors for local LNM in PTC, mPTC and crPTC, a logistic regression analysis was performed. The results support the correlation of LNM with nodules >1 cm (odd ratio [OR]: 2.480, confidence interval [CI]: 0.428 – 0.613; P<0.001) and male gender (OR: 1.627, CI: 1.376-1.923; P<0.001), and its inverse correlation with the age of ≥45 years old (OR: 0.512, CI: 2.040-2.902; P<0.001) after adjustment for other covariates in all PTCs (Figure 3A, Table 2). Hashimoto's thyroiditis presented no risk for LNM (Figure 3A). Consistent data were also obtained from patients with mPTC and crPTC (Figures 3B and 3C; Tables 3 and 4).

Discussion

Thyroid cancer is diagnosed in nearly 300,000 people annually all over the world [27]. Although these malignancies are mostly differentiated and generally associated with a good prognosis, the involvement of local lymph nodes is frequently observed. Proactive screening for malignancies from a substantial population of thyroid nodes and accurate histopathological stratification are crucial for the clinical decision and improvement of patient outcome. The present study reviewed 10,798 cases of thyroidectomy undertaken in a major hospital located in one of the most populated city in the world for a period of over 22 years, summarized the clinical features of 5,235 cases of thyroid cancer, and analyzed the trend of PTCs and risk factors for predicting LNM.

The present analysis unveiled a gradual but significant increase in thyroid malignancy detection rate between the period of 1994 and 2015, which ranged from 16.8% to 69.8%. These percentages are generally within the wide-range detection rate (6.7-56%) of thyroid cancer worldwide [25 28 29], although data between 2014 and 2015 was relatively higher than earlier periods. Furthermore, the detection rates varied across different centers, which were likely caused by the different guidelines and algorithms followed by physicians and surgeons. The increase in detection rate from 1994 to 2015 reflects the improvement in diagnosis through the advances in imaging technology, and the increasing use of FNA. In addition, the appropriate preoperative risk stratification of thyroid nodules, which was a result of improved clinical evaluation, thyroid function test, ultrasonography and molecular diagnosis in recent years, has diverted a lot of patients from thyroidectomy, contributing to the increased diagnosis of thyroid cancer. These data support published guidelines [30 31] and highlights the importance of combining imaging, FNA, cytology and molecular diagnosis. However, the contribution of social and environmental stresses could not be rule out, which is beyond the scope of the present retrospective study. It is noteworthy that the present study covered a period during which China was undergoing the largest scale of industrialization in modern history. This inevitably led to dramatic social and environmental changes.

Papillary carcinoma accounts for 95.1% of malignancies in the whole cohort, and reached as high as 98.2% among patients diagnosed between 2014 and 2015. These rates were comparable to the findings of another study performed in Nanjing, China [25], but were higher than those in other reports [32], which was likely due to the increase in PTCs, as previously suggested [33] . The high detection rate for PTC was attributable to the increasing use of head and neck imaging, which detects sub-palpable (yet potentially malignant) thyroid nodules, and ultrasound-guided FNA, which improves the preoperative detection of malignancy. With the use of neck ultrasonography and other diagnostic approaches, the average size of PTCs at diagnosis has significantly reduced from 2.3 ± 1.1 cm in 1994 to 1.2 ± 0.9 cm in 2015, and this was similar to the trends reported in previous studies [10 25]. This progress allows for the early detection of thyroid cancer, which leads to the increasing trend of hemithyroidectomy, when compared to total thyroidectomy, and the intensified follow-up of thyroid cancer patients in recent years in our practice following the American Thyroid Association (ATA) guidelines [30 31 33]. However, the overdiagnosis and overtreatment of indolent diseases have been increasingly recognized. The most recent ATA guidelines suggest a more parsimonious evaluation of thyroid nodules and a more judicious use of thyroid cancer treatment, in order to minimize risk and maximize benefits to patients [33].

The present data suggests that nodules >1 cm and the male gender predict a high risk of LNM, while the age of ≥45 years old is associated with low LNM potentials, and this is consistent with a previous finding [25]. Therefore, more attention is needed for these patients in future practice. However, in this single-center study, factors taken into account for the logistic regression analysis were limited due to the retrospective nature of the study. Future studies are needed to characterize the association of other clinical and biochemical parameters with thyroid cancer metastasis and patient outcome. Characterizing the contribution of social and environmental stresses to the occurrence of thyroid cancer would also be of significant social economical value.

In the present study, the clinical data of 10,798 patients treated by thyroidectomy was retrospectively analyzed to determine the features and trends of thyroid cancer in the past 22 years. The present data suggested a significant increase in the detection rate of thyroid cancer, particularly mPTC, which has become the dominant form of thyroid cancer. As a result, the occurrence of LNM has been decreasing with time. The present results suggest the adequacy of present preoperative diagnosis and risk stratification, although overdiagnosis and overtreatment require future attention of physicians and surgeons in view of the rapid increase in the number of thyroidectomies.

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Authors' contributions

ZL designed the study, collected and analyzed data, and wrote the manuscript. PP contributed in writing the manuscript. ZL, LYK, WFL, YGQ, DJ and WXL assisted with the data presentation and manuscript writing. LZH, DJT and MYM contributed in the study design, data analysis and manuscript writing. All authors read and approved the final manuscript.

Competing interests

The authors have no conflicts of interest to disclose.

Data sharing statement

Data will be available upon request to the corresponding author

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Table 1. Detection rate of malignancy among patients undergoing thyroidectomy from1994 to 2015

Period	94.1-95.12	96.1-97.12	98.1-99.12	00.1-01.12	02.1-03.12	04.1-05.12	06.1-07.12	08.1-09.12	10.1-11.12	12.1-13.12	14.1-15.12	Total	*P*
Benign, *n*	114	136	169	268	286	495	535	738	901	1033	890	5563	<0.001
(%)	(83.2)	(86.1)[a,b]	(88.0)[a,b]	(83.0)[a]	(80.1)[a,b]	(79.2)[b]	(71.4)[a,b]	(64.6)[a,b]	(52.4)[a,b]	(42.2)[a,b]	(30.2)[a,b]	(51.5)	
Cancer, *n*	23	22	23	55	71	130	214	405	817	1413	2060	5235	
(%)	(16.8)	(13.9)[a,b]	(12.0)[a,b]	(17.0)[a]	(19.9)[a,b]	(20.8)[b]	(28.6)[a,b]	(35.4)[a,b]	(47.6)[a,b]	(57.8)[a,b]	(69.8)[a,b]	(48.5)	
Total	137	158	192	323	357	625	749	1143	1718	2446	2950	10798	

[a] Percentages significantly different from the previous year; [b] Percentages significantly different within the period of 94.1-95.12.

Table 2. Pathological classification of all thyroid malignancies from 1994 to 2015

Period	94.1-95.12	96.01-97.12	98.1-99.12	00.1-01.12	02.1-03.12	04.1-05.12	06.1-07.12	08.1-09.12	10.1-11.12	12.1-13.12	14.1-15.12	*P* for difference	*P* for trend
PTC, *n* (%)	15 (65.3)	17 (77.3)	17 (73.9)	39 (70.9)	50 (70.4)	107 (82.3)	185 (86.4)	383 (94.6)	768 (94.0)	1376 (97.4)	2023 (98.2)	<0.001	<0.001
FTC, *n* (%)	3 (13.0)	1 (4.5)	4 (17.3)	10 (18.1)	9 (12.7)	17 (13.1)	18 (8.4)	9 (2.2)	25 (3.0)	17 (1.2)	20 (0.9)	<0.001	<0.001
MTC, *n* (%)	1 (4.3)	2 (9.1)	1 (4.3)	4 (7.3)	2 (2.8)	1 (0.8)	2 (0.9)	5 (1.2)	14 (1.7)	12 (0.8)	12 (0.6)	<0.001	<0.001
ATC, *n* (%)	0 (0)	0 (0)	1 (4.3)	1 (1.8)	3 (4.2)	1 (0.8)	1 (0.5)	2 (0.5)	1 (0.1)	1 (0.1)	2 (0.1)	<0.001	<0.001
Other, *n* (%)	4 (17.4)	2 (9.1)	0 (0)	1 (1.8)	7 (9.9)	4 (3.1)	7 (3.3)	6 (1.5)	9 (1.1)	7 (0.5)	3 (0.1)	<0.001	<0.001
Unilateral	14 (60.9)	14 (63.6)	13 (56.5)	31 (56.4)	38 (53.5)	72 (55.4)	122 (57.0)	213 (52.6)	389 (47.6)	616 (43.6)	991 (48.1)	0.071	<0.001
Bilateral	9 (39.1)	8 (36.4)	10 (43.5)	24 (43.6)	33 (46.5)	58 (44.6)	92 (43.0)	192 (47.4)	428 (52.4)	797 (56.4)	1069 (51.9)		
Solitary	7 (30.4)	13 (59.1)	11 (47.8)	27 (49.1)	28 (39.4)	59 (45.4)	105 (49.0)	172 (42.5)	292 (35.7)	456 (32.3)	749 (36.4)	<0.001	<0.001
Multiple	16 (69.6)	9 (40.9)	12 (52.2)	28 (50.9)	43 (60.6)	71 (54.6)	109 (51.0)	233 (57.5)	525 (64.3)	957 (67.7)	1311 (63.6)		
All cancer, *n*	23	22	23	55	71	130	214	405	817	1413	2060		

PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma; other histotypes of carcinoma collectively refer to cancer other than PTC, FTC, MTC and ATC, including poorly differentiated thyroid cancer, squamous cell carcinomas, B cell lymphomas of thyroid, spindle cell carcinoma, adenoid cystic carcinoma, renal clear cell metastasis and Langerhans cell histocytosis of the thyroid gland.

Table 3. Clinicopathological features of PTCs from1994 to 2015

Period	94.1-95.12	96.1-97.12	98.1-99.12	00.1-01.12	02.1-03.12	04.1-05.12	06.1-07.12	08.1-09.12	10.1-11.12	12.1-13.12	14.1-15.12	Total	*P* for difference	*P* for trend
Age, year	46.9±14.3	43.1±10.7	41.1±12.9	44.9±14.8	44.6±14.5	43.8±12.4	44.6±12.4	42.7±12.4	43.9±11.2	43.9±11.1	43.6±10.9	43.7±11.3	0.643	
Male, *n*	5	3	6	11	18	34	60	115	227	366	616	1461	0.434	0.664
(%)	(33.3)	(17.6)	(35.3)	(28.2)	(36)	(31.8)	(32.4)	(30.0)	(29.6)	(26.6)	(30.4)	(29.3)		
Female, *n*	10	14	11	28	32	73	125	268	541	1010	1407	3519		
(%)	(66.7)	(82.4)[ab]	(64.7.0)[a,]	(71.8)[a]	(64)[a,b]	(68.2)[b]	(67.6)[a,b]	(70.0)[a,b]	(70.4)[a,b]	(73.4)[a,]	(69.6)[a,]	(70.7)		
Size[c], cm	2.3±1.1	2.6±1.9	2.1±1.3	2.2±1.6	2.2±1.4	2.2±1.6	1.7±1.1[ab]	1.5±1.0b	1.3±0.9[ab]	1.2±0.8[ab]	1.2±0.9[b]	1.4±1.0	<0.001	
CrPTC, *n*	13	15	12	32	41	87	118	238	375	696	1486	3113	<0.001	0.213
(%)	(86.7)	(88.2)	(70.6)	(82.1)	(82.0)	(81.3)	(63.8)[a]	(62.1)[b]	(48.8)[ab]	(50.6)b	(73.5)[a]	(62.5)		
mPTC, *n*	2	2	5	7	9	20	67	145	393	680	537	1866		
(%)	(13.3)	(11.8)	(29.4)	(17.9)	(18.0)	(18.7)	(36.2)	(37.9)	(51.2)	(49.4)	(26.5)	(37.5)		
LNM, *n*	5	5	7	22	17	27	55	96	192	372	414	1212	<0.001	<0.001
(%)	(33.3)	(29.4)	(41.2)	(56.4)	(34)	(25.2)	(29.7)	(25.1)	(25.0)	(27.0)	(20.5)[a]	(24.3)		
No-LNM, *n*	10	12	10	17	33	80	130	287	576	1004	1609	3768		
(%)	(66.7)	(70.6)	(58.8)	(43.6)	(66)	(74.8)	(70.3)	(74.9)	(75.0)	(73.0)	(79.5)	(75.7)		
Total	15	17	17	39	50	107	185	383	768	1376	2023		<0.001	<0.001

[a] Percentages significantly different from the previous year; [b] Percentages significantly different within the period of 08.1-09.12; [c] Mean diameter; crPTC, clinical relevant papillary thyroid carcinoma; mPTC, micro papillary thyroid carcinoma; LNM, lymph node metastasis; LN, lymph node.

Table 4. Rate of local lymph node metastasis in patients with crPTC and mPTC from 2008 to 2013

	94.1 -95.12	96.1 -97.12	98.1 -99.12	00.1 -01.12	02.1 -03.12	04.1 -05.12	06.1 -07.12	08.1 -09.12	10.1 -11.12	12.1 -13.12	14.1 -15.12	Total	*P* for difference	*P* for trend
crPTC, *n* (%)	3 (23.1)	5 (33.3)	6 (50.0)	19 (59.4)	17 (41.5)	24 (27.6)	35 (29.7)	73 (30.7)	130 (34.7)	243 (34.9)	330 (22.2)	885 (28.4)	<0.001	<0.001
mPTC, *n* (%)	2 (100)	0 (0)	1 (20.0)	3 (42.9)	0 (0)	3 (15.0)	20 (29.9)	23 (16.0)	62 (15.8)	129 (19.0)	84 (15.6)	327 (17.5)	0.005	0.087
P-value	0.032	0.331	0.252	0.425	0.017	0.243	0.978	0.001	0.000	0.000	0.001			

crPTC, clinical relevant papillary thyroid carcinoma; mPTC, micro papillary thyroid carcinoma.

Figure legends

Figure 1 Trends in the diagnosis of various subtype thyroid malignancies, presented as permillage (rate per thousand) of thyroid cancer, from 1994 to 2015.

Figure 2 Clinical, surgical and ultrasound features during the evolvement of thyroidectomy and the diagnosis of thyroid cancer from 1994 to 2015. Data on the symptoms (**A**), physical signs (**B**), nodule multiplicity (**C**), ultrasonographic sizes of nodules (**D**), FNA ratio (**E**), and thyroidectomy types (**F**) were summarized.

Figure 3 Determinant factors of the lymph node metastasis of PTC (**A**), mPTC (**B**) and crPTC (**C**). Logistic regression was performed to define factors associated with local lymph node metastasis.

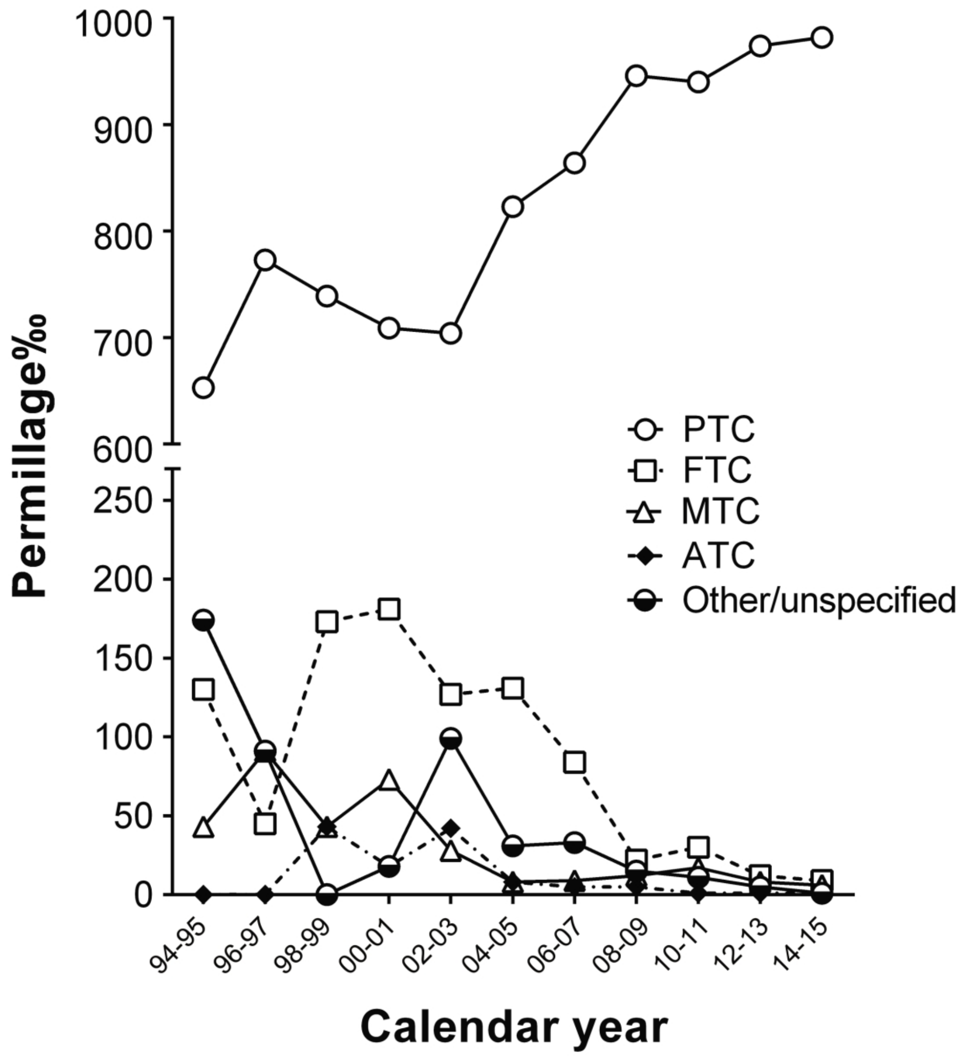

Figure 1

98x108mm (600 x 600 DPI)

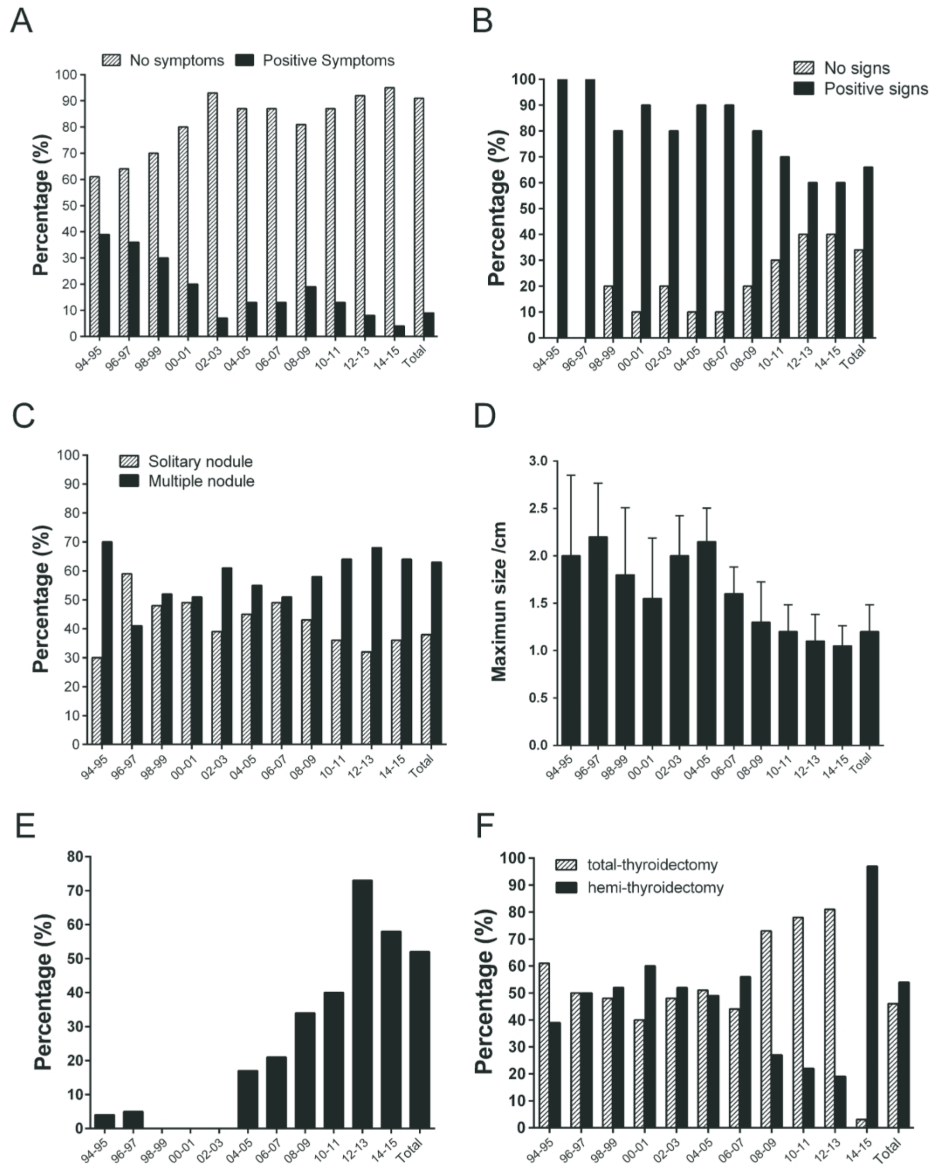

Figure 2 (Revised)

211x262mm (300 x 300 DPI)

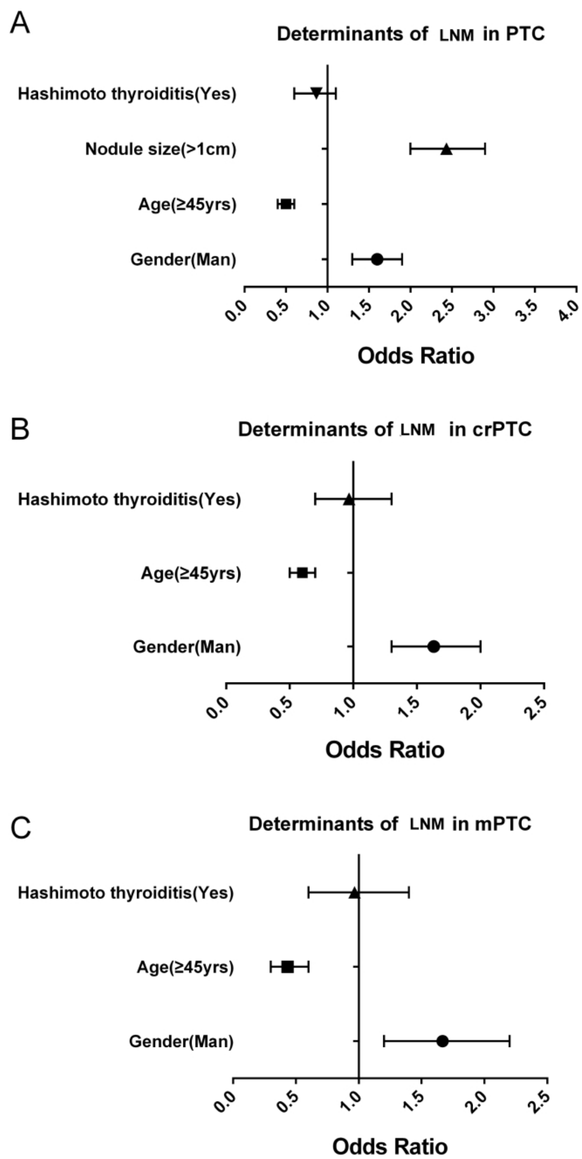

Figure 3

170x313mm (300 x 300 DPI)

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1&2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5&6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5&6

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5&6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5&6
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5&6
		(*b*) Describe any methods used to examine subgroups and interactions	5&6
		(*c*) Explain how missing data were addressed	5&6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	NA
		Case-control study—If applicable, explain how matching of cases and controls was addressed	NA
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key Results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Features and Trends of Thyroid Cancer in Patients with Thyroidectomies in Beijing, China between 1994 and 2015 – a Retrospective Study

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Secondary Subject Heading:	Ear, nose and throat/otolaryngology
Keywords:	Thyroid cancer, Papillary thyroid carcinoma, microPTC

Features and Trends of Thyroid Cancer in Patients with Thyroidectomies in Beijing, China between 1994 and 2015 – a Retrospective Study

Running Title: Evolution of thyroid cancer in China

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Keyword: Thyroid cancer; Papillary thyroid carcinoma; microPT4C

Abstract

Objectives: This study aims to summarize the features and trends of thyroid carcinoma in the past two decades in China.

Design, Setting and Participants: Clinical data obtained from 10,798 patients treated by thyroidectomy from 1994 to 2015 at the Department of General Surgery of the People's Liberation Army General Hospital, Beijing, China were retrospectively analyzed.

Outcome measures: Incidence and histopathological features of thyroid cancer were compared and the risk factors for local lymph node metastasis analyzed.

Results: Our data indicated a significant increase in the detection of thyroid cancer (from 16.8% to 69.8%, $P<0.01$). Among the 5,235 thyroid cancer cases, papillary thyroid carcinoma (PTC) was the most common histotype, accounting for 95.1% of all malignancies over the 22-year period. Among the 4,979 PTCs, microPTCs (mPTC) with the largest diameter ≤ 10 mm has gradually become the dominant form, and its percentage in PTCs has increased from 13.3% in the biennial period of 1994-1995 to 51.2% in 2010-2011. Furthermore, the size of the tumor has decreased significantly from 2.3±1.1 cm in 1994 to 1.2±0.9 cm in the largest diameter ($P<0.01$), while the average age at diagnosis and female dominance remained unchanged during the period. Logistic regression showed that tumor nodules > 1 cm and male gender were the main risk factors for local lymph node metastasis (LNM) whereas patients over 45 years old had lower risk.

Conclusions: During the 22-year period, an increased detection of thyroid cancer, particularly mPTC, was found while the occurrence of LNM decreased. Our results suggest that the current preoperative diagnosis and risk stratification are adequate, supporting the published guidelines for the diagnosis of thyroid cancer.

Strengths and limitations of this study

- The strength of this study lies in that more than 10,000 cases of thyroid cancer over a period of 22 years were retrospectively studied to summarize the features and trends of thyroid cancer in patients with thyroidectomies in Beijing, China.
- The clinical practice was reviewed over this long period of time to evaluate the performance of the preoperative diagnosis and risk stratification in a major hospital in Beijing.
- The retrospective nature of this study led to limited survival data, which should have been included to evaluate the improvement of clinical outcome during the 22-year period.

Introduction

Thyroid nodules occur in about 4-7% of the population, and 8-16% of these contain malignant elements [1]. Thyroid cancer is the most common endocrine cancer [1], and approximately 90% of these are differentiated, including predominantly papillary thyroid carcinoma (PTC) and, to a less extent, follicular thyroid carcinoma [2]. These subtypes are generally associated with a more favorable prognosis and higher cure rate [3], when compared with less common but more aggressive forms of thyroid cancer, such as medullary thyroid cancer, anaplastic thyroid cancer, and thyroid sarcoma or lymphoma [4].

The past few decades have witnessed an increase in the incidence of thyroid cancer, while the associated mortality remains unchanged [5-9] . In addition, the number of newly diagnosed thyroid cancer cases with smaller tumors increased. Between 2008 and 2009, 39% of thyroid cancer patients were diagnosed with tumors smaller than 1 cm, when compared to 25% of patients diagnosed between 1988 and 1989 [10]. This was due to the proactive screening of thyroid cancer, particularly through the application of sensitive surveillance modalities in recent years [11-15]. Advanced imaging techniques, such as ultrasonography, computational tomography, magnetic resonance imaging and positron emission tomography, along with fine-needle aspiration biopsy have dramatically improved the detection of small thyroid nodules, and facilitated the early diagnosis of thyroid cancer [16-18].

However, the increased incidence of thyroid cancer has also been considered to be associated with over-diagnosis [18-22] and environmental factors [6 23]. The screening of highly prevalent thyroid nodules for those with malignant potential remains challenging, although a number of guidelines have recently been proposed for the diagnosis and management of thyroid nodules [24]. Identifying nodules with high risk of malignancy during thyroidectomy represents a cost-effective approach [25 26]. Therefore, in this study, the features and trends of thyroid cancer in patients with thyroidectomies in China were retrospectively analyzed to examine whether the decrease in diagnosable size of thyroid nodules is associated with misdiagnosis, providing further insight into its diagnosis and management.

Materials and Methods

This study was approved by the Chinese People's Liberation Army (PLA) General Hospital Ethics Committee, and written informed consents obtained from all patients for retrospective studies.

Data collection

The clinical database for patients undergoing thyroidectomies from 1994 to 2015 at the Department of General Surgery of PLA General Hospital (Beijing, China) was revisited, and the thyroid pathology reports were screened and reviewed to analyze the correlation of the size of thyroid nodules with other pathological features.

The clinical parameters used in the analysis included front neck discomfort or pain, dysphagia, dysphonia or hoarseness, dyspnea, sign of thyroid nodule and thyroid gland enlargement, as well as ultrasound features. These data were individually checked, and cases with inconsistent data were excluded before the statistical analysis. As a result, 10,798 eligible cases with thyroidectomies from 1994 to 2015 were recruited.

Data analysis and statistics

Benign or malignant thyroid nodules were diagnosed based on pathological features, and malignant nodules were reported as papillary (PTC), follicular (FTC), medullary (MTC), or anaplastic thyroid carcinoma (ATC). Papillary thyroid carcinomas were further sub-classified into clinically relevant PTCs (crPTCs) >10 mm in diameter and micro-PTCs (mPTCs) ≤10 mm in diameter (the largest diameter of a nodule). These sub-groups were compared, when appropriate, in the analysis.

Patients were treated by surgery, often with lymph node dissection, depending on the clinical features and the number, location and size of the involved lymph node, which was assessed by pre-operative imaging analysis and intraoperative frozen section pathological analysis. Tumors within 10 mm in size and had no involvement of lymph nodes were resected without the removal of lymph nodes. When the pre-operative imaging revealed no abnormalities in the lymph nodes, but malignancy was confirmed by intraoperative frozen section analysis, ipsilateral central neck node dissection was performed. If the preoperative sonography or intraoperative examination revealed abnormal lymph nodes, and frozen section analysis confirmed the malignancy, improved lateral neck lymph node dissection was performed.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Version 17.0; IBM, Armonk, NY). Data were presented as mean ± standard deviation or mean ± standard error, when appropriate. Chi-square test was used to compare different categories and generate the trend lines. Furthermore, *t*-test was used for comparisons between groups, and logistic regression was performed to calculate the risk factors for lymph node metastasis (LNM). The data analysis was adjusted for confounders, such as age, gender, nodule size and the presence of Hashimoto thyroiditis. A two-tailed $P<0.05$ was considered statistically significant.

Patient and public involvement

This retrospective study did not involve patients or the public in the development of research initiatives and outcome measures, as well as the design and implementation of the study. The study covered a period of 22 years, which ranged between 1994 and 2015. Therefore, there was no possibility or plan to disseminate the results among the participants.

Results

Malignancy rate increased from 1994 to 2015

The numbers of benign and malignant cases of thyroid cancer detected during thyroidectomy from 1994 to 2015 are summarized in Table 1. As the number of thyroidectomy surgeries increased due to the improved diagnosis of thyroid cancer, the number of benign and malignant cases gradually increased. Noticeably, the malignancy rate of thyroid nodules dramatically increased from 16.8% during the biennial period of 1994-1995 to 69.8% during the period of 2014-2015 ($P<0.05$), while the benign rate decreased from 83.2% to 30.2% ($P<0.05$).

The diagnosis rate of PTC increased from 1994 to 2015

Among the 10,798 cases recruited, 5,235 cases were found to be malignant (Table 2). Furthermore, a majority of patients (63.6%) were found with multiple cancers. Moreover, 48.1% of patients had unilateral cancer, and the remaining 51.9% of patients had bilateral cancer (Table 2). In addition, most of the malignant cases were recorded as PTCs, which exhibited a significant increase from 65.3% during the period of 1994-1995 to 98.2% during the period of

2014-2015 (P<0.05, Figure 1), while the diagnosis rates of other histotypes concurrently decreased (Table 2 and Figure 1).

Detection size of thyroid nodules decreased from1994 to 2015

The review of the clinicopathological information of malignant cases suggested that most of these patients were free of clinically relevant symptoms and physical signs (Figures 2A and 2B), and only 9% of patients exhibited different degrees of discomfort, such as pain and dysphagia. The enlargement of thyroid glands were often noticed, but not necessarily by health professionals, during routine physical examination. However, 34% of tumors were impalpable, which was likely due to the depth of the intra-thyroidal microcarcinoma. By ultrasonography, 37% of patients were detected with single thyroid tumors, while the remaining patients had multiple lesions (Figure 2C).

From 1994 to 2015, the size of thyroid nodules has been reported to significantly decrease, with the mean diameter reduced from 2.6 ± 1.4 cm to 1.2 ± 0.9 cm (Figure 2D). This trend roughly correlates with the increase in the rate of preoperative fine needle aspiration (FNA), which ranged from 15% in 2004 to 74% in 2013, although this rate regressed to 57% between 2014 and 2015 (Figure 2E). In addition, during the same period, the total thyroidectomy rate remained unchanged from 1994 to 2007, but gradually increased from 2008 to 2013, and decreased sharply to 3% from 2014 to 2015 (Figure 2F).

The size of the thyroid cancer at diagnosis and metastasis rate decreased from1994 to 2015

Considering the high prevalence of PTCs, 4,980 cases were compared to 255 cases of other subtypes all-together, and further data analysis was restricted to this type of thyroid cancer. As shown in Table 3, the mean age of patients at diagnosis was 43.7 ± 11.3 years old, with no significant variation from 1994 to 2015. Furthermore, the incidence of PTC was considerably higher in women than in men, in which approximately two thirds of these patients were female. It is noteworthy that the average diameter of PTCs at diagnosis decreased from 2.3 ± 1.1 cm in 1994 to 1.2 ± 0.9 cm in 2015 (P<0.05, Table 3). Correlating with this trend was the increase in the percentage of mPTCs from 13.3% between 1994 and 1995 to 51.2% between 2010 and 2011 (P<0.05, Table 3). This likely resulted from a more meticulous pathological examination. Interestingly, the detection rate of mPTCs decreased to 26.5 between 2014 and 2015.

Among the PTC cases studied, 1,212 patients were found with LNM, but its occurrence significantly decreased with the reduction in tumor size (P<0.05, Table 3). This was associated with the increased diagnosis rate of mPTCs, which shows an apparently lower LNM potential in comparison with crPTCs (Table 4). Before 2007, the difference between the LNM rates of mPTC and crPTC were appreciable, but this not statistically significant most of time due to the limited size of the cohort. With the increase in PTC diagnosis after 2008, a significantly lower LNM occurrence was found for mPTCs, when compared to crPTCs (Table 4).

Determinant factors of local lymph node metastasis in PTC, mPTC and crPTC

To identify the risk factors for local LNM in PTC, mPTC and crPTC, a logistic regression analysis was performed. The results support the correlation of LNM with nodules >1 cm (odd ratio [OR]: 2.480, confidence interval [CI]: 0.428 – 0.613; P<0.001) and male gender (OR: 1.627, CI: 1.376-1.923; P<0.001), and its inverse correlation with the age of ≥45 years old (OR: 0.512, CI: 2.040-2.902; P<0.001) after adjustment for other covariates in all PTCs (Figure 3A, Table 2). Hashimoto's thyroiditis presented no risk for LNM (Figure 3A). Consistent data were also obtained from patients with mPTC and crPTC (Figures 3B and 3C; Tables 3 and 4).

Discussion

Thyroid cancer is diagnosed in nearly 300,000 people annually all over the world [27]. Although these malignancies are mostly differentiated and generally associated with a good prognosis, the involvement of local lymph nodes is frequently observed. Proactive screening for malignancies from a substantial population of thyroid nodes and accurate histopathological stratification are crucial for the clinical decision and improvement of patient outcome. The present study reviewed 10,798 cases of thyroidectomy undertaken in a major hospital located in one of the most populated city in the world for a period of over 22 years, summarized the clinical features of 5,235 cases of thyroid cancer, and analyzed the trend of PTCs and risk factors for predicting LNM. Among these patients, about 20% were from Beijing, while the rest 80% were from other regions in China where the disease could not be diagnosed definitely in local hospitals. Therefore, our patient cohort generally represented all China even though bias towards the difficult cases might exist.

The present analysis unveiled a gradual but significant increase in thyroid malignancy detection rate between the period of 1994 and 2015, which ranged from 16.8% to 69.8%. These percentages are generally within the wide-range detection rate (6.7-56%) of thyroid cancer worldwide [25 28 29], although data between 2014 and 2015 was relatively higher than earlier periods. Furthermore, the detection rates varied across different centers, which were likely caused by the different guidelines and algorithms followed by physicians and surgeons. The increase in detection rate from 1994 to 2015 reflects the improvement in diagnosis, through the advances in imaging technology and the increasing use of FNA, together with the shift of routine node dissection towards therapeutic dissection in the treatment. In addition, the appropriate preoperative risk stratification of thyroid nodules, which was a result of improved clinical evaluation, thyroid function test, ultrasonography and molecular diagnosis in recent years, has diverted a lot of patients from thyroidectomy, contributing to the increased diagnosis of thyroid cancer. These data support published guidelines [30 31] and highlights the importance of combining imaging, FNA, cytology and molecular diagnosis. However, the contribution of social and environmental stresses could not be rule out, which is beyond the scope of the present retrospective study. It is noteworthy that the present study covered a period during which China was undergoing the largest scale of industrialization in modern history. This inevitably led to dramatic social and environmental changes.

Papillary carcinoma accounts for 95.1% of malignancies in the whole cohort, and reached as high as 98.2% among patients diagnosed between 2014 and 2015. These rates were comparable to the findings of another study performed in Nanjing, China [25], but were higher than those in other reports [32], which was likely due to the increase in PTCs, as previously suggested [33] . The high detection rate for PTC was attributable to the increasing use of head and neck imaging, which detects sub-palpable (yet potentially malignant) thyroid nodules, and ultrasound-guided FNA, which improves the preoperative detection of malignancy. With the use of neck ultrasonography and other diagnostic approaches, the average size of PTCs at diagnosis has significantly reduced from 2.3 ± 1.1 cm in 1994 to 1.2 ± 0.9 cm in 2015, and this was similar to the trends reported in previous studies [10 25]. This progress allows for the early detection of thyroid cancer, which leads to the increasing trend of hemithyroidectomy, when compared to total thyroidectomy, and the intensified follow-up of thyroid cancer patients in recent years in our practice following the American Thyroid Association (ATA) guidelines [30 31 33]. However, the overdiagnosis and overtreatment of indolent diseases have been increasingly recognized. The most recent ATA guidelines suggest a more parsimonious evaluation of thyroid nodules and a more judicious use of thyroid cancer treatment, in order to minimize risk and maximize benefits to patients [33] .

The present data suggests that nodules >1 cm and the male gender predict a high risk of LNM, while the age of ≥45 years old is associated with low LNM potentials, and this is consistent with a previous finding [25]. Therefore, more attention is needed for these patients in future practice. However, in this single-center study, factors taken into account for the logistic regression analysis were limited due to the retrospective nature of the study. Future studies are needed to characterize the association of other clinical and biochemical parameters with thyroid cancer metastasis and patient outcome. Characterizing the contribution of social and environmental stresses to the occurrence of thyroid cancer would also be of significant social economical value.

In the present study, the clinical data of 10,798 patients treated by thyroidectomy was retrospectively analyzed to determine the features and trends of thyroid cancer in the past 22 years. The present data suggested a significant increase in the detection rate of thyroid cancer, particularly mPTC, which has become the dominant form of thyroid cancer. As a result, the occurrence of LNM has been decreasing with time. The present results suggest the adequacy of present preoperative diagnosis and risk stratification, although overdiagnosis and overtreatment require future attention of physicians and surgeons in view of the rapid increase in the number of thyroidectomies.

Acknowledgements

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Authors' contributions

ZL designed the study, collected and analyzed data, and wrote the manuscript. PP contributed in writing the manuscript. ZL, LYK, WFL, YGQ, DJ and WXL assisted with the data presentation and manuscript writing. LZH, DJT and MYM contributed in the study design, data analysis and manuscript writing. All authors read and approved the final manuscript.

Competing interests

The authors have no conflicts of interest to disclose.

Data sharing statement

Data will be available upon request to the corresponding author

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Table 1. Detection rate of malignancy among patients undergoing thyroidectomy from1994 to 2015

Period	94-95[a]	96-97	98-99	00-01	02-03	04-05	06-07	08-09	10-11	12-13	14-15	Total	*P*
Benign, *n*	114	136	169	268	286	495	535	738	901	1033	890	5563	<0.001
(%)	(83.2)	(86.1)[b,c]	(88.0)[b,c]	(83.0)[b]	(80.1)[b,c]	(79.2)[c]	(71.4)[b,c]	(64.6)[b,c]	(52.4)[b,c]	(42.2)[b,c]	(30.2)[b,c]	(51.5)	
Cancer, *n*	23	22	23	55	71	130	214	405	817	1413	2060	5235	
(%)	(16.8)	(13.9)[a,b]	(12.0)[a,b]	(17.0)[a]	(19.9)[a,b]	(20.8)[b]	(28.6)[a,b]	(35.4)[a,b]	(47.6)[a,b]	(57.8)[a,b]	(69.8)[a,b]	(48.5)	
Total	137	158	192	323	357	625	749	1143	1718	2446	2950	10798	

[a] The last 2 digits of the years are displayed (hereafter); [b] Percentages significantly different from the previous year; [c] Percentages significantly different within the period of 94-95.

Table 2. Pathological classification of all thyroid malignancies from 1994 to 2015

Period	94-95	96-97	98-99	00-01	02-03	04-05	06-07	08-09	10-11	12-13	14-15	*P* for difference	*P* for trend
PTC, *n* (%)	15 (65.3)	17 (77.3)	17 (73.9)	39 (70.9)	50 (70.4)	107 (82.3)	185 (86.4)	383 (94.6)	768 (94.0)	1376 (97.4)	2023 (98.2)	<0.001	<0.001
FTC, *n* (%)	3 (13.0)	1 (4.5)	4 (17.3)	10 (18.1)	9 (12.7)	17 (13.1)	18 (8.4)	9 (2.2)	25 (3.0)	17 (1.2)	20 (0.9)	<0.001	<0.001
MTC, *n* (%)	1 (4.3)	2 (9.1)	1 (4.3)	4 (7.3)	2 (2.8)	1 (0.8)	2 (0.9)	5 (1.2)	14 (1.7)	12 (0.8)	12 (0.6)	<0.001	<0.001
ATC, *n* (%)	0 (0)	0 (0)	1 (4.3)	1 (1.8)	3 (4.2)	1 (0.8)	1 (0.5)	2 (0.5)	1 (0.1)	1 (0.1)	2 (0.1)	<0.001	<0.001
Other, *n* (%)	4 (17.4)	2 (9.1)	0 (0)	1 (1.8)	7 (9.9)	4 (3.1)	7 (3.3)	6 (1.5)	9 (1.1)	7 (0.5)	3 (0.1)	<0.001	<0.001
Unilateral	14 (60.9)	14 (63.6)	13 (56.5)	31 (56.4)	38 (53.5)	72 (55.4)	122 (57.0)	213 (52.6)	389 (47.6)	616 (43.6)	991 (48.1)	0.071	<0.001
Bilateral	9 (39.1)	8 (36.4)	10 (43.5)	24 (43.6)	33 (46.5)	58 (44.6)	92 (43.0)	192 (47.4)	428 (52.4)	797 (56.4)	1069 (51.9)		
Solitary	7 (30.4)	13 (59.1)	11 (47.8)	27 (49.1)	28 (39.4)	59 (45.4)	105 (49.0)	172 (42.5)	292 (35.7)	456 (32.3)	749 (36.4)	<0.001	<0.001
Multiple	16 (69.6)	9 (40.9)	12 (52.2)	28 (50.9)	43 (60.6)	71 (54.6)	109 (51.0)	233 (57.5)	525 (64.3)	957 (67.7)	1311 (63.6)		

All cancer, *n*	23	22	23	55	71	130	214	405	817	1413	2060

PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma; other histotypes of carcinoma collectively refer to cancer other than PTC, FTC, MTC and ATC, including poorly differentiated thyroid cancer, squamous cell carcinomas, B cell lymphomas of thyroid, spindle cell carcinoma, adenoid cystic carcinoma, renal clear cell metastasis and Langerhans cell histocytosis of the thyroid gland.

Table 3. Clinicopathological features of PTCs from1994 to 2015

Period	94-95	96-97	98-99	00-01	02-03	04-05	06-07	08-09	10-11	12-13	14-15	Total	*P* for difference	*P* for trend
Age, year	46.9±14.3	43.1±10.7	41.1±12.9	44.9±14.8	44.6±14.5	43.8±12.4	44.6±12.4	42.7±12.4	43.9±11.2	43.9±11.1	43.6±10.9	43.7±11.3	0.643	
Male, *n*	5	3	6	11	18	34	60	115	227	366	616	1461	0.434	0.664
(%)	(33.3)	(17.6)	(35.3)	(28.2)	(36)	(31.8)	(32.4)	(30.0)	(29.6)	(26.6)	(30.4)	(29.3)		
Female, *n*	10	14	11	28	32	73	125	268	541	1010	1407	3519		
(%)	(66.7)	(82.4)[ab]	(64.7.0)[a,]	(71.8)[a]	(64)[a,b]	(68.2)[b]	(67.6)[a,b]	(70.0)[a,b]	(70.4)[a,b]	(73.4)[a,]	(69.6)[a,]	(70.7)		
Size[c], cm	2.3±1.1	2.6±1.9	2.1±1.3	2.2±1.6	2.2±1.4	2.2±1.6	1.7±1.1[ab]	1.5±1.0b	1.3±0.9[ab]	1.2±0.8[ab]	1.2±0.9[b]	1.4±1.0	<0.001	
CrPTC, *n*	13	15	12	32	41	87	118	238	375	696	1486	3113	<0.001	0.213
(%)	(86.7)	(88.2)	(70.6)	(82.1)	(82.0)	(81.3)	(63.8)[a]	(62.1)[b]	(48.8)[ab]	(50.6)b	(73.5)[a]	(62.5)		
mPTC, *n*	2	2	5	7	9	20	67	145	393	680	537	1866		
(%)	(13.3)	(11.8)	(29.4)	(17.9)	(18.0)	(18.7)	(36.2)	(37.9)	(51.2)	(49.4)	(26.5)	(37.5)		

LNM, *n*	5	5	7	22	17	27	55	96	192	372	414	1212	<0.001	<0.001
(%)	(33.3)	(29.4)	(41.2)	(56.4)	(34)	(25.2)	(29.7)	(25.1)	(25.0)	(27.0)	(20.5)[a]	(24.3)		
No-LNM, *n*	10	12	10	17	33	80	130	287	576	1004	1609	3768		
(%)	(66.7)	(70.6)	(58.8)	(43.6)	(66)	(74.8)	(70.3)	(74.9)	(75.0)	(73.0)	(79.5)	(75.7)		
Total	15	17	17	39	50	107	185	383	768	1376	2023		<0.001	<0.001

[a] Percentages significantly different from the previous year; [b] Percentages significantly different within the period of 08-09; [c] Mean diameter; crPTC, clinical relevant papillary thyroid carcinoma; mPTC, micro papillary thyroid carcinoma; LNM, lymph node metastasis; LN, lymph node.

Table 4. Rate of local lymph node metastasis in patients with crPTC and mPTC from 2008 to 2013

	94-95	96-97	98-99	00-01	02-03	04-05	06-07	08-09	10-11	12-13	14-15	Total	*P* for difference	*P* for trend
crPTC, *n* (%)	3(23.1)	5(33.3)	6(50.0)	19(59.4)	17(41.5)	24(27.6)	35(29.7)	73(30.7)	130(34.7)	243(34.9)	330(22.2)	885(28.4)	<0.001	<0.001
mPTC, *n* (%)	2(100)	0(0)	1(20.0)	3(42.9)	0(0)	3(15.0)	20(29.9)	23(16.0)	62(15.8)	129(19.0)	84(15.6)	327(17.5)	0.005	0.087
P-value	0.032	0.331	0.252	0.425	0.017	0.243	0.978	0.001	0.000	0.000	0.001			

crPTC, clinical relevant papillary thyroid carcinoma; mPTC, micro papillary thyroid carcinoma.

Figure legends

Figure 1 Trends in the diagnosis of various subtype thyroid malignancies, presented as permillage (rate per thousand) of thyroid cancer, from 1994 to 2015.

Figure 2 Clinical, surgical and ultrasound features during the evolvement of thyroidectomy and the diagnosis of thyroid cancer from 1994 to 2015. Data on the symptoms (**A**), physical signs (**B**), nodule multiplicity (**C**), ultrasonographic sizes of nodules (**D**), FNA ratio (**E**), and thyroidectomy types (**F**) were summarized.

Figure 3 Determinant factors of the lymph node metastasis of PTC (**A**), mPTC (**B**) and crPTC (**C**). Logistic regression was performed to define factors associated with local lymph node metastasis.

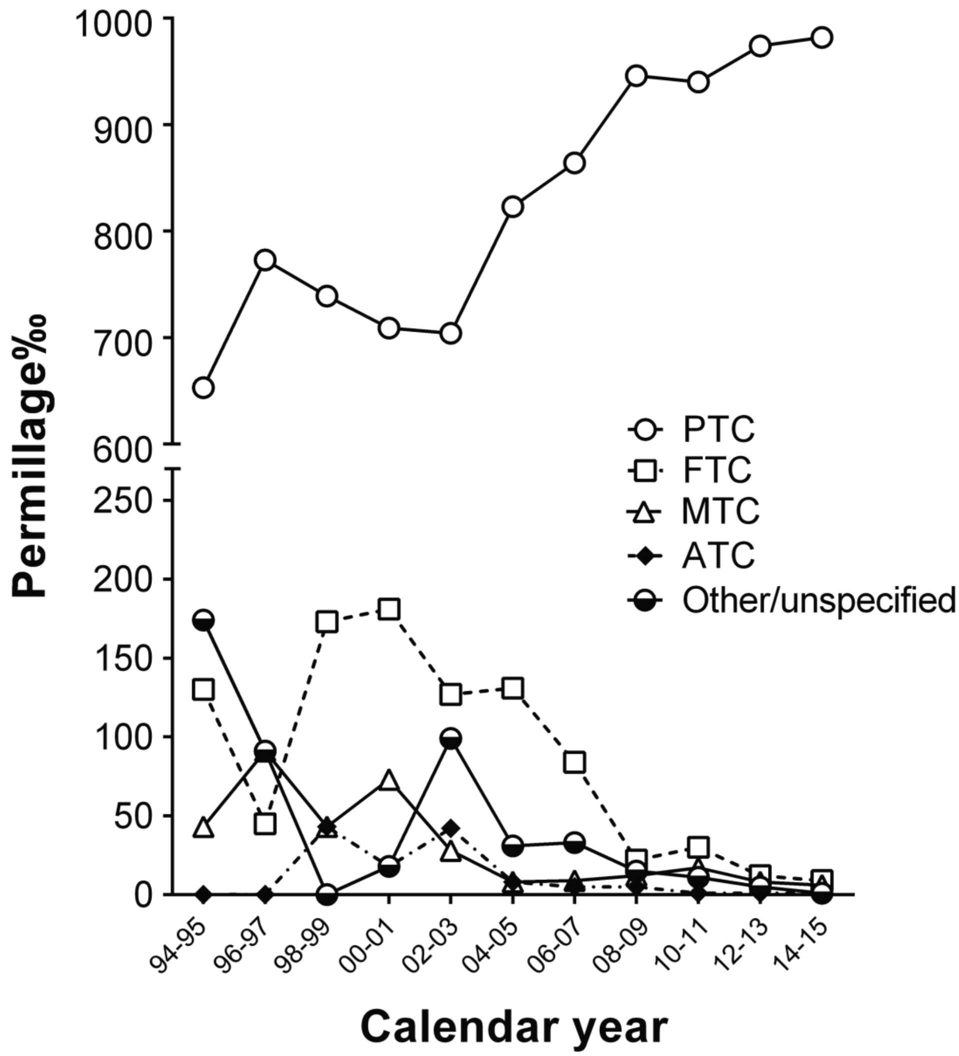

Figure 1

98x108mm (600 x 600 DPI)

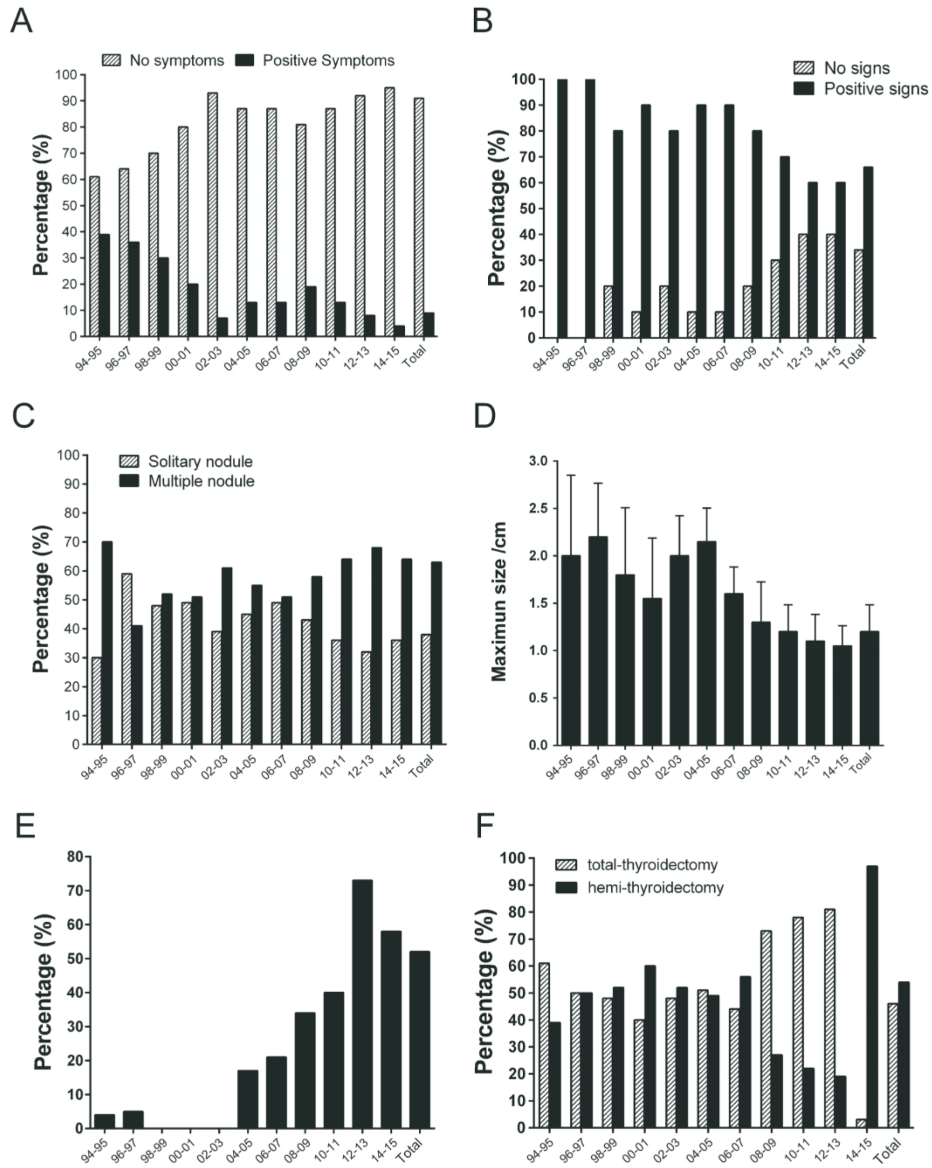

Figure 2 (Revised)

211x262mm (300 x 300 DPI)

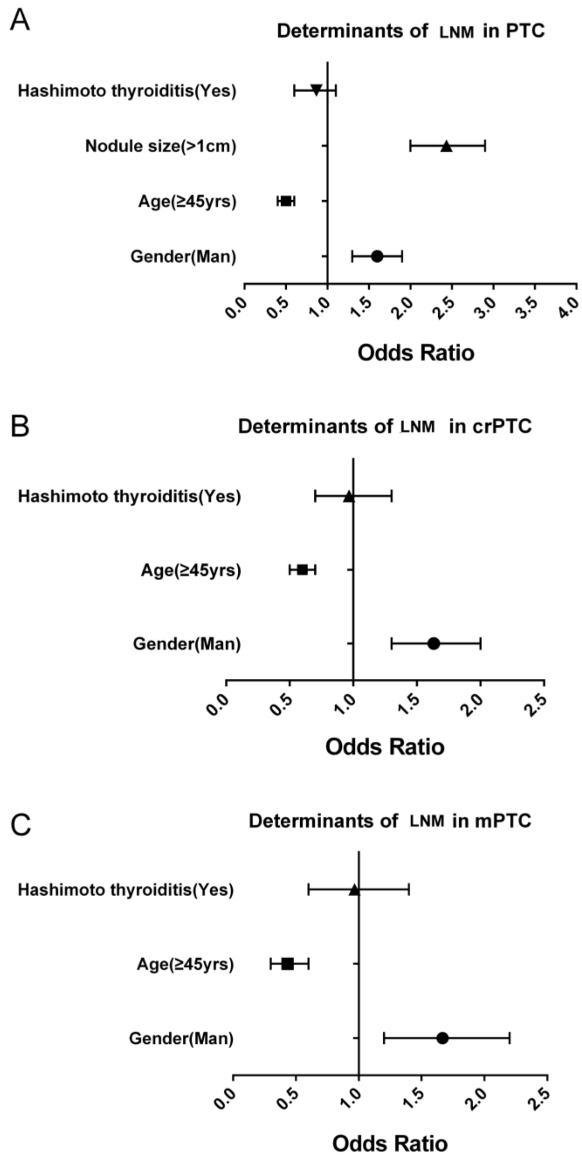

Figure 3

170x313mm (300 x 300 DPI)

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1&2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5&6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5&6

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5&6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5&6
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5&6
		(*b*) Describe any methods used to examine subgroups and interactions	5&6
		(*c*) Explain how missing data were addressed	5&6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	NA
		Case-control study—If applicable, explain how matching of cases and controls was addressed	NA
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key Results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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