

## RESEARCH ARTICLE

# Clinical Features and Prognosis of Patients with Benign Thyroid Disease Accompanied by an Incidental Papillary Carcinoma

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### Abstract

**Purpose:** To investigate the clinical features and prognosis of papillary thyroid carcinoma (PTC) with a background of benign disease. **Method:** A total of 709 patients with papillary thyroid carcinoma undergoing surgical resection were analyzed retrospectively. In 147 patients who underwent surgery for benign thyroid disease, incidental PTC (IPC group) were identified by intraoperative or postoperative pathological examination of surgical specimens but were not detected by preoperative imaging studies. In the other group, according to the pathological examination with or without co-existing benign thyroid disease, 253 cases were clarified as concomitant PTC and 309 cases were clarified as dominant PTC. **Results:** Incidental PTC was more common in women, about 85.7%, the mean age was 47.6±11.3 years old. Average tumor diameter was 4.4±2.2 mm, multiple lesions accounted for 12.9% (19/147), and the cervical lymph node metastasis rate was 6.1% (9/147). After radical resection 8 cases recurred, the median time of recurrence was about 12 months (0.5 to 162), there was no tumor-related death. The tumor-free survival rates were 97.3%, 95.9%, 91.5%, and 79.3% in 1, 5, 10 and 14 year respectively. **Conclusion:** Incidental PTC with a background of benign lesions is common, and the generally good prognosis can be attributed to tumor early detection and early treatment. On the intraoperative finding of incidental PTC, lobectomy (unilateral) or total thyroidectomy (bilateral) should be the first choice, but with a postoperative pathologic finding of incidental PTC, further treatment, such as completion thyroidectomy or immediate lymph dissection is not necessary. Central lymph node dissection is also not needed unless lymphadenectomy is present.

**Keywords:** Papillary thyroid carcinoma - occult carcinoma - thyroid resection - prognosis

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### Introduction

There has the fastest-growing incidence for thyroid carcinoma in recent years (Qian et al., 2005; Davies and Gilbert, 2008; Alevizaki et al., 2009), according to the United States 1989-2008 annual statistical data, its incidence have increased by 6.2% per year, new cases of papillary thyroid carcinoma (PTC) accounting for 85 -90%, especially the tiny carcinoma less than 1 cm in diameter. The conclusions suggest that increasing incidence reflects increase detection of subclinical disease, not an increase in the true occurrence of thyroid cancer (Davies and Gilbert, 2008). A survey in Tianjin China also drew similar conclusions (Qian et al., 2005).

Thyroid nodules come to clinical attention when noted by the patients, or as an incidental finding during routine physical examination, or image procedure, which are present in 4% to 7% of the population (the incidence increases with increasing age) and 30% to 50% by ultrasonography (US) (Hagag et al., 1998; Lin et al., 2005; Pang and Chen, 2007). The clinical importance

of the thyroid nodule evaluation is primarily related the need to exclude thyroid cancer, which is present in 4.0 to 6.5 percent of thyroid nodules. Nonpalpable nodules have the same risk of malignancy as palpable nodules (Hagag et al., 1998; Lin et al., 2005; Pang and Chen, 2007). The incidence of thyroid carcinoma, which is diagnosed via the surgery for benign thyroid disease or postoperative pathology, also have showed a clear upward trend in recent years (Pang and Chen, 2007; Alevizaki et al., 2009; Pisanu et al., 2009; Lombardi et al., 2010). It is reported that the ratio of multiple nodular goiter with malignant tumors about 4% -17% (Koh and Chang, 1992). Wilhelm reported 41 cases of other malignancies with incidental thyroid nodules, therein 20 cases received surgical resections, and thyroid carcinoma accounted for 16 cases (Wilhelm et al., 2007). Stoffer et al. (1960) reported that 13% of the glands resected in the thyroid operations for any reason contained carcinoma in 1960, however, 21.2% nodular goitres contained malignant foci from 2002 to 2004 (Pang and Chen, 2007). Arora et al. (2009) believed there exist some differences between the occasional thyroid

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microcarcinoma and tiny carcinoma from clinical findings, the invasiveness of the latter is higher. Incidental thyroid carcinoma should receive a clinical close follow-up or positive surgical (total thyroidectomy + neck lymph node dissection) or other treatments, there has not been determined (Ito et al., 2007; Sakorafas et al., 2007; Dralle et al., 2009; Pisanu et al., 2009; Lombardi et al., 2010; Papini et al., 2011). Sokal (1957) suggest that the incidence of carcinoma in non-toxic thyroid nodules is low and patients can be followed up safely for up to 15 years. In Japan, 162 patients with small papillary cancer were diagnosed by ultrasound-guided needle biopsy (Ito et al., 2003). The average nodule size was 6.9 mm. During follow-up (half the patients were followed three to four years, 35 percent later opted for surgery), 70 percent were stable or were reduced in size, 1.2 percent developed lymph node metastases, and no one developed distant metastases. Ito et al. (2007) concluded that total thyroidectomy for benign disease due to the possible presence of incidental papillary carcinoma is not required, because the incidence of recurrent in the remnant thyroid being rare in their series (5 of 317 patients). But Carlini et al. (2009) recommended total thyroidectomy. In addition, the clinical features and prognosis of patients with benign thyroid diseases accompanied by an incidental papillary carcinoma still is not completely understood. So 709 PTC, of 5859 patients with thyroid diseases were underwent surgery, were analyzed retrospectively from January 1997 to December 2006, and we have planed to reveal the clinical features and outcomes of papillary thyroid carcinoma (PTC) started with benign disease for guiding the clinical treatment.

## Materials and Methods

### General Information

From January 1997 to December 2006, there were 5859 cases with thyroidectomies, included 940 cases of thyroid malignancies. In the same period in initial treatment of papillary thyroid carcinoma with complete datas there were 709 cases. In the group of 709 cases, we had 142 male and 567 female, the mean age about 43 years old (8 to 80 years old). Their surgeries began with benign focus, preoperative imaging studies did not found tumor lesions, intraoperative or postoperative pathology displayed tumor lesions (incidental carcinoma group), and 147 cases conformed to the diagnosis of carcinoma. If the tumor lesions were the preoperative findings, they were divided into concomitant benign disease group (253 cases) and dominant carcinoma group (309 cases) according to whether they accompanied by benign thyroid diseases in postoperative pathology. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the combining traditional Chinese and western medicine hospital and the First affiliated hospital of Zhejiang University, Written informed consent was obtained from all participants.

### Surgery

The surgery scheme as follows: 38 cases (ipsilateral

partial or subtotal resection), 63 cases (the affected side lobe resection±isthmus resection), 90 cases (ipsilateral lobe +isthmus+contralateral part or sub-total resection), 88 cases (the bilateral subtotal or partial resection), 430 cases (thyroid total resection); 311 cases (initial surgery without neck dissection); 217 cases (the central lymph node dissection, in 23 cases dissection number of lymph nodes were 0, the success rate was 89%), 181 cases (modified neck dissection, 15 cases were bilateral); 10 cases (4 cases with the lungs, bones and other distant metastases, 6 cases with locally trachea or/and esophagus, vascular invasion) in initial diagnosis (palliative resection).

### Statistical analysis

Data processing were completed by SPSS 15.0 for windows, Comparisons between groups were performed by Pearson's chi-square method and F-test. Tumor recurrence or patient death was regarded as tumor-free survival or overall survival statistical indicators. Survival curves were evaluated using the Kalain-Meier method and compared by using the Long-rang test, a two-tailed  $\alpha=0.05$  could be considered as the significant difference indicators.

## Results

### Pathological findings

All 709 cases were papillary carcinoma, 312 cases accompanied by nodular goiter, 58 cases were Hashimoto's disease, 16 cases were diagnosed as hyperthyroidism, 12 cases with follicular adenoma, in which there were 53 cases accompanied by two or more benign lesions (including 3 cases with three benign lesions). Two IPC patients were found in the surgery for thyroid hemangioma and parathyroid adenoma.

### Follow-up

The follow-up ended in July 2011, all patients were followed up for more than 4 years and 6 months. During this period after radical resection 71 cases recurred, 66 cases received the second surgical resection, 5 patients with distant metastases. 13 patients died after radical resection, one patient with IPC died in 102 month for cerebrovascular accident, one suicide after 5 months in the concomitant group, the other cases were due to the tumor-related death.

### Clinical and pathologic feature

The IPC was more common in women than concomitant PTC and dominant PTC (85.7%, 126/147 vs 82.6%, 209/253, 75.1%, 232/309), and older age (average age 47.6±11.3 years old vs 42.8±12.1, 41.6±12.9). There had significant difference ( $X^2=8.740, 12.070; P=0.013, 0.000$ ). The initial symptoms of three groups were neck mass, their ratios were 74.8% (110/147), 69.6% (176/253) and 69.9% (216/309) respectively. 684 routine preoperative B-ultrasound implied the ratios of deradenoncus were 20.3% (29/143), 36.6% (86/235) and 39.2% (120/306), and the statistical difference was significant ( $X^2=17.048, P=0.000$ ). The tumors of 260 cases were located in the left side, 292 cases were the right side, 28 cases were the

**Table 1. Comparison of Incidental PTC Lymph Node Metastasis and TNM Stage**

	Incidental carcinomas (N=147)	Concomitant carcinomas (N=253)	Dominant Carcinomas (N=309)	X <sup>2</sup> /F	P
Age≥45years old	86 (58.5%)	99 (39.1%)	117 (37.9%)	19.285	0
Female	126 (85.7%)	209 (82.6%)	232 (75.1%)	8.74	0.013
Cervical lymph node metastasis	9 (6.1%)	104 (41.3%)	159 (51.5%)	85.006	0
Central district metastasis	9 (6.1%)	100 (39.5%)	154 (49.8%)	82.577	0
Lateral metastasis	2 (1.4%)	48 (19.0%)	83 (26.8%)	42.515	0
Dmax (mm)	4.4±2.2	18.0±11.5	20.4±13.0	109.11	0
Thyroid external infiltration	1 (0.7%)	29 (11.5%)	51 (16.5%)	24.651	0
TNM stage					
I	143	201	227		
II	0	10	12		
III	4	26	28		
IVa	0	15	37		
IVb	0	0	3		
IVc	0	1	2	45.284	0

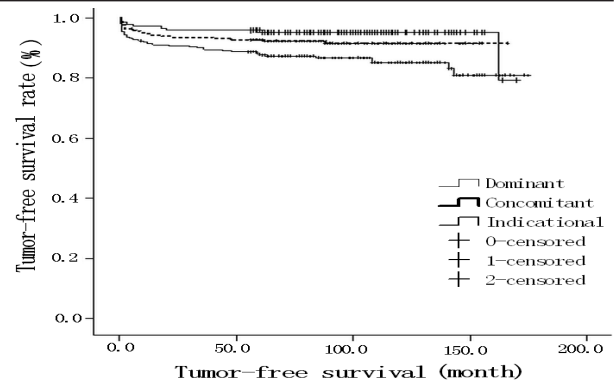
isthmus, 126 cases were bilateral, and there had 3 ectopic cases; except the ectopic cases, the morbidity of bilateral lesion in IPC (6.8%, 10/147) was significant lower than that in concomitant (17.8%, 45/253) and dominant group (23.0%, 71/306) ( $X^2=16.643$ ,  $P=0.000$ ). 182 cases had more than two tumor lesions, the proportions of three groups with the multiple lesions were 12.9% (19/147), 26.5% (67/253) and 31.1% (96/309). ( $X^2=17.320$ ,  $P=0.000$ ).

The central lymph node dissection with 0 lymph node was attributed to the group without neck dissection, during the follow-up, 17 patients had lymph node recurrence. 1 of them received central lymph node dissection, 16 cases were supplied with modified neck dissections. The 5 cases after the central lymph node dissection were found the lateral metastasis, and received lateral dissections. By the end of in July 2011, 317 cases did not undergo neck dissection, 202 cases underwent modified neck dissection, the rest 190 cases underwent central lymph node dissection. The cervical lymph node status and TNM stage of three groups could be seen in Table 1. The central lymph node metastasis rate was 37.1% (263/709), lateral lymph node metastasis rate was 18.9% (133/709); in which the central lymph node metastasis, lateral lymph node metastasis rate was 47.1% (124/263), if the central LN was negative, the lateral transfer rate was only 2% (9/446) ( $X^2=221.106$ ,  $P=0.000$ ).

In preoperative US examination of 684 cases, 235 cases were judged as lymphadenectasis, cervical lymph node metastasis rates were 20.7% (6/29), 55.8% (48/86), 71.6% (86/120) ( $X^2=25.998$ ,  $P=0.000$ ); central metastasis rates were 20.7% (6/29), 53.5% (46/86), and 69.2% (83/120); the lateral metastasis rates were 6.9% (2/29), 36.5% (31/86), 47.5% (57/120) ( $X^2=16.586$ ,  $P=0.000$ ). The cervical lymph node metastasis rates of the rest 449 cases were 2.6% (3/114), 32.9% (51/155), 37.7% (68/180) ( $X^2=47.498$ ,  $P=0.000$ ), in which central metastasis rates were 2.6% (3/114), 31.6% (49/155), 36.7% (66/180) ( $X^2=45.206$ ,  $P=0.000$ ) and lateral metastasis rates were 0% (0/114), 9.7% (15/155), 12.2% (22/180) ( $X^2=14.435$ ,  $P=0.000$ ).

#### Recurrent and prognosis

After radical resection 71 cases recurred, included 8 cases with IPC (residual glands: 5 cases, 1 of 5 case



**Figure 1. The Tumor-free Survival Rate of Clinical Papillary Carcinomas and Incidental Papillary Carcinomas**

combined cervical lymph node; neck lymph nodes: 3 cases); 20 cases with concomitant carcinomas (residual glands :11 cases; 6 of 11 cases combined cervical lymph node; cervical lymph node: 9 cases); 43 cases with dominant carcinomas (residual glands: 21 cases; 15 of 21 cases combined cervical lymph node recurrence; cervical lymph node: 17 cases; distant metastasis: 5 cases). The median time of recurrence in three groups was 12 months (0.5 to 162), 6.5 months (0.5 to 88) and 6 months (0.5 to 143). 1-, 5-, 10-, 14- year tumor-free survival rates were 97.3%, 95.9%, 91.5% and 79.3%; 94.8%, 92.8%, 91.5% and 91.5%; 91.4%, 87.7%, 85.2% and 81.0% ( $X^2=9.472$ ,  $P=0.009$ ) (Figure 1). The overall survival in our series at 1-, 5-, 10-, 14- years were 100%, 100%, 98.6% and 98.6%; 99.6%, 99.2%, 99.2% and 99.2%; 99.3%, 98.7%, 96.2% and 91.8% respectively ( $X^2=4.930$ ,  $P=0.085$ ).

#### Discussion

Incidental PTC started with benign lesions increased in recent years. Lombardi et al. (2010) reported 2220 cases of PTC from goiter endemic areas, incidental small papillary carcinoma accounted for 933 cases (42%). In this study it was 21% (147/709). Pisanu et al. (2009) reported 149 cases of tiny PTC, in which there were 73 cases of incidental groups, non-episodic 76 cases, average tumor diameters of two groups were 4.2mm and 7.5mm. To date, detailed studies of the biologic behaviors of IPC have not been performed. Arora et al. (2009) believed there exist some differences between incidental thyroid

microcarcinoma and the tiny carcinoma from clinical findings, the invasiveness of the latter is higher. Barbaro et al. (2005) showed that the incidence of extracapsular extension, lymph node metastasis, and most histologic aggressive features could not be observed in IPC. Comparing with clinical PTC in this series, the incidental demonstrated that (1) more common in women, older age (mean age was 47 years old), smaller tumor size (average diameter was 4mm); (2) multiple lesions accounted for 12.2%, the bilateral thyroid involving rate was low (6.8% vs 17.8%, 21.8%), lymph nodes metastasis rate was 6.1%. (3) 8 patients (5.4%) have had recurrences, the median time of recurrence was 12 months, and recurrent lesions were residual thyroid and cervical lymph nodes, and no tumor-related deaths. 5, 10-year DFS was 95.9%, 91.5%. We also compared microcarcinoma (maximum tumor diameter  $\leq 1$  cm) cases in three groups, the maximum tumor diameters were 4.4 mm, 8.4 mm and 8.0mm; neck lymph node metastasis rates were 6.1%, 26.5% and 34.5%, respectively. Ugolini et al. (2007) detected the expression of BRAFV600E in early PTC, suggested that the expression can be detected when tumor only 0.5-4 mm, in incidental carcinoma, preoperative tiny carcinoma and non-small carcinoma the expression rates of BRAF V600E were 17.6%, 38.3% and 45%, respectively. The authors believe that early detection and early treatment of benign lesions as the first symptom for incidental PTC can provide a good prognosis, and for incidental carcinoma accompanied by BRAFV600E mutations needs to paid more attention in clinical treatment. So IPC is common, and its excellent prognosis should be attributed to the tumor early detection and early treatment.

Recently the tumor studies have focused on the biological behavior of tumor itself, while often overlooked the background or soil surrounding it, that means few study for the organ background of tumor. In clinic it is common that in the context of a thyroid there have a variety of diseases simultaneously, such as thyroid carcinoma, goiter, secondary hyperthyroidism, focal lymphocytic thyroiditis, etc. This is clinical difficult for the diagnosis of thyroid disease. From the aspect of tumor pathology, the pathological type of thyroid malignancy started with benign lesions is PTC mainly, follicular adenocarcinoma (FC) and medullary carcinoma (MC) were rare. Our group had 4922 cases with benign thyroid lesions surgical resection in 10 years, except the incidental thyroid PTC in thyroid hemangioma and parathyroid tumor surgery, the incidences of incidental PTC, FC, MC were 2.95% (145/4922), 0.04% (2/4922) and 0.02% (1/4922). In incidental carcinoma, PTC was most common, the group accounted for 98% (147/150), while FC and MC only took 1.3% (2/150) and 0.6% (1/150). Pang et al. (2007) reported nodular goiter accompanied by PTC in incidental carcinoma was 77% (44/57), FC and MC take 9%, the other is lymphoma. In our group at the same period PTC, FC, MC accounted for 88.8% (835/940), 6.9% (65/940), and 1.4% (13/940) of malignancies. The reason lies in the different incidences of different tumors or different benign carcinogenic susceptibilities is still needed to be revealed.

Mishra et al. (2001) reported the findings of occult thyroid carcinoma in the total thyroidectomy for thyroid benign diseases achieve 6.3% (8/127). The concomitant rate of PTC in benign thyroid disease as follows: nodular goiter (8.2%, 312/3788), Hashimoto's disease (HT) (80.5%, 58/72), hyperthyroidism (5.6%) and thyroid adenoma

(1%, 12/1150). Nodular goiter accompanied by PTC was generally 4 to 17% Koh and Chang, 1992), Pang et al. (2007) reported this ratio is 21.2% (57/268). Ito et al. (2007) reported 317 cases of incidental carcinoma accompanied by nodular goiter (50%), hyperthyroidism (34%), HT (2%) and adenoma (14%). That in our group was 86%, 4%, 4%, 4%, respectively. The risk factors of nodular goiter, adenoma and hyperthyroidism surrounding carcinoma were not yet clear, although most prognosis were good, but there were indeed a small part of tumors showed a higher malignant degree. In Ito's report (2007) one patient has bone metastases. during the follow-up in IPC. The ratio of Hashimoto's disease accompanied with PTC varies from 0.6% to 45.7% (Ito et al., 2007; Gul et al., 2010; Yoon et al., 2012). Gul et al. (2010) report 613 total thyroidectomy cases, included the 92 HT cases, and suggested concomitant rate of PTC in HT was 45.7%, without HT about 29%. Correspondingly, concomitant rate of HT in PTC was 21.8%. Yoon et al. (2012) investigated 195 cases of PTC, HT accounted for 28.7%, and multiple factor analysis showed the patients with concomitant HT are often young, female, the tumor with smaller diameter and low envelope infringe, and the central lymph node metastasis rate (12.5 %) was significant lower than non-HT group in PTC. It suggested that concomitant HT in PTC has a better prognosis, in our group concomitant rate of PTC in HT surgical resection reached to 80.5%, in addition to an indeed higher rate of carcinoma for Hashimoto's disease, the selection of patients was the main reason. Our selection criterias were based on the suspect malignant nodules or oppression symptoms of thyroid. The questions about the similar BRAF, RAS gene mutations and RET rearrangement in HT nodules and PTC were still controversial (Sadow et al., 2010). Royer et al. (2010) showed that a commonalities hOGG1 allelic loss (LOH) in HT and PTC (key DNA damage repair enzyme), their ratio about 73%, 94%, and only 8% were nodular goiter. They believed carcinomatous HT is attributed to a long-term accumulation of thyroid follicular epithelium genetic mismatch.

The central metastasis rate of incidental carcinoma is 6.1%, only 1.4% for the lateral. If the enlargement of lymph nodes implied by preoperative B- ultrasonic, the lymph node metastasis rate increase to 21% and 6.9% respectively, however without lymph node exploration and enlargement by B- ultrasonic, the rate were 2.6% and 0%. Moreno et al. (2011) found that preoperative B-ultrasound can predict PTC's tumor-free interval at lateral neck and the tumor-free survival. Shen et al. (2010) reported the central lymph node dissection after initial or recurrent tumor, except for a higher temporary hypocalcemia of initial dissection, both of their post-operative complications are similar. Roh et al. (2011) suggested in 184 cases total thyroidectomy+preventive central lymph node dissection the central lymph node metastasis rate is 42.9%. And multivariate analysis showed that tumor diameter > 1cm and extrathyroidal extension are independent factors for the central lymph node metastasis. Therefore, the central lymph node intraoperative exploration is enough for incidental PTC, the central lymph node dissection is only needed for lymphadenectomy.

Sakorafas et al. (2007) recommended the total or near-total thyroidectomy of incidental PTC under a microscope, which can avoids the risk of reoperation and have the possibility of better monitoring of treated patients by

scintigraphic scan and thyroglobulin measurements to detect residual or recurrent disease and the increase of the yield of postoperative radioactive iodine therapy. Ito et al. (2007) believed that the prognosis of incidental PTC is good, the incidence of recurrence is low and none of the patients died of cancer., so an immediate further surgical treatment (total thyroidectomy/neck dissection) is not needed after pathologic diagnosis. We collected 240 patients of pathological examination of residual glands, that include 185 in intraoperation and 55 in postoperation from partial/subtotal to lobectomy or total thyroidectomy Tumor detected in residual thyroid were 21.6% (8/37, contralateral 8.1%, 3/37), 31.2% (34/109, the contralateral 21.1%, 23/109) and 43.6% (41/94, the contralateral 22.3%, 21/94) respectively. If changing surgical approach in intraoperation (partial/subtotal to lobectomy or total thyroidectomy), thyroid carcinoma recurrence rates were significant lower to 3.4% (5/147), 4.4% (11/249) and 6.9% (21/303). Therefore, in our view, lobectomy (unilateral carcinoma) or total thyroidectomy (bilateral carcinoma) is the most preferred for the intraoperative PTC findings, and for postoperative PTC findings, firstly, clinical observation should be kept, if there were no metastases during one year, the risk of recurrence of residual glands would reduced significantly.

In conclusion, IPC is common, and its excellent prognosis should be attributed to the tumor early detection and early treatment. On the intraoperative finding of IPC, lobectomy (unilateral) or total thyroidectomy (bilateral) should be the first choice, but to the postoperative pathologic finding of IPC, further treatment, such as completion thyroidectomy or lymph dissection immediately is not necessary. The central lymph node dissection is also not need unless lymphadenectomy.

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