

## Original Article

# Multifocality predicts poor outcome of patients with insular thyroid cancer: a clinicopathological study

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**Abstract:** Insular thyroid carcinoma (ITC) is a rare type of thyroid malignancy whose aggressiveness and propensity to local recurrence differentiate it from other thyroid malignancies. However, data pertaining to its clinical characteristics is still lacking. In this study, we retrospectively analyzed 10 ITC patients treated and followed in Tianjin Medical University Cancer Institute and Hospital during Apr 2007 to Aug 2010, and compared the clinical and pathological characteristics and long-term follow-up with 2220 patients with papillary thyroid carcinoma (PTC). These ten ITC cases comprised 7 women and 3 men, of whom 6 patients are multifocal ITC (mITC) and showed cervical lymph node metastasis to the lateral compartment, while the other 4 solitary ITC (sITC) had regional metastasis confined to level VI or even no cervical metastasis. The ITC group had more frequent retrosternal metastasis (40% vs. 7.5%), recurrent laryngeal nerve invasion (40% vs. 4.4%), esophageal invasion (50% vs. 1.9%), a higher proportion of distant metastasis (50% vs. 3.2%), and vascular invasion (50% vs. 1.0%). While the presence of lymph node metastasis showed no significant difference. Interestingly, although patients with ITC are lacking in number to perform survival analysis, we still noticed that all the four sITC patients (4/4, 100%) have survived much longer (at least 45 months) than those who have multinodularity (mITC, 5/6, 83.3%). Our results indicated that ITC is an aggressive disease and the presence of multifocality might be a risk factor for long time survival of ITC patients.

**Keywords:** Insular thyroid cancer, multifocality, vascular invasion, poorly differentiated thyroid cancer

## Introduction

Thyroid cancer has become the fastest growing malignancy in recent years worldwide, with most of which being differentiated thyroid cancer (DTC), accounting for over 90% of all thyroid cancers [1]. Insular thyroid cancer (ITC) is a rare type of thyroid cancer that represents a distinct entity of all thyroid cancers. Different from that of DTC, the biological and clinical behavior of ITC lies between DTC and undifferentiated thyroid cancer and therefore characterized as a specific type of poorly differentiated thyroid cancer [2].

A typical appearance of ITC consists of well-defined nests or “insulae” of tumor cells with round “dark” and monomorphic nuclei and scant cytoplasm. Studies have shown that they

arise from follicular epithelial cells with distinct biologic features and often produce thyroglobulin and concentrate radioiodine [3-6]. Further research of ITC is important because they have a more aggressive clinical course than conventional DTCs (follicular and papillary carcinomas), with a higher incidence of local recurrence, early cervical lymph node involvement, regional and distant metastases, most often in the bones and pulmonary tissue [4, 7]. Moreover, despite its moderate radioiodine avidity, the effect of radioiodine therapy often yields unsatisfactory results [3], and the management of ITC often requires additional external beam radiation [8].

Although different from conventional DTCs and exerting a more aggressive behavior, owing to its rarity, to date, the studies that delineate the

clinical and morphological characteristics of ITC are lacking. Moreover, numerous independent studies have defined several separate prognostic factors for overall survival, such as histotype per se, tumor size, stage of disease, vascular invasion, lymph node involvement, and the presence of distant metastasis [3, 8, 9]. However, the impact of each of these factors on survival remains controversial.

In the current study, we reviewed the pathologic and clinical characteristics of ten patients who had ITC and those who had papillary thyroid cancer (PTC) as controls, which is the most common form of DTC, and identify the prognostic factors associated with survival among patients with ITC, and proposed that multifocality might be able to predict the clinical outcome of patients with ITC.

### Materials and methods

#### *Patients*

After searching in pathology database at Tianjin Medical University Cancer Institute and Hospital from Jul 2007 to Nov 2010, ten patients with ITC were included in this study. All these ten ITC patients underwent total thyroidectomy and modified radical neck dissection. The clinical characteristics of ten ITC patients were summarized in **Table 1**. Besides, 2220 patients with PTC were included as control group. Almost all patients had total or near-total thyroidectomy; a few patients had subtotal thyroidectomy or thyroid lobectomy. Dissection of the central lymph node compartment was routinely performed.

#### *Histopathology and staging*

All surgical specimens were submitted to histopathologic evaluation and stained with hematoxylin and eosin. If required, immunostainings for thyroglobulin (Tg), calcitonin and thyroid tissue factor (TTF-1) were performed. All patients with insular thyroid cancer had their pathology re-reviewed at our institution. Tumor staging was based on the AJCC 7th edition TNM staging.

#### *Postoperative management and follow-up*

Follow-up was obtained in all patients by reviewing the clinical records. All patients were fol-

lowed up once or twice per year by US, chest X-ray, and/or computed tomography (CT) to screen for recurrence in the lymph nodes and distant organs, and the status of survival.

#### *Statistical analysis*

Statistical analysis was performed by SPSS 15.0 software (SPSS, Inc., Chicago, IL). The unpaired t-test was used to compare differences in time-independent continuous variables, and the chi-squared test was used for categorical data. The Kaplan-Meier method and the log rank test were used to determine significant prognostic factors.

### Results

#### *Patients and the clinical characteristics*

The clinical and pathologic characteristics of 10 ITC patients are summarized in **Tables 1** and **2**. As shown in **Table 1**, these ten ITC cases comprised 7 women and 3 men, with an average age of 46 years at the time of diagnosis (range, 16-69 years). Six patients were multifocal ITC. Of note, all these 6 multifocal ITC (mITC) showed cervical lymph node metastasis to the lateral compartment, while all the other four single focal/solitary ITC (sITC) had regional metastasis confined to level VI or even no cervical metastasis at all. In addition, five out of six multifocal ITC patients died of disease whereas all four (4/4) single loci ITC had long time survival (no less than 45 months). Four cases (4/10) showed retrosternal metastasis. Five patients (5/10) presented with distant metastasis at the time of diagnosis (four patients presented with lung metastasis and one patient had bone metastasis to right scapulae). A representative morphological appearance of ITC is presented in **Figure 1**.

**Table 2** summarized the clinicopathological characteristics of patients with ITC and papillary thyroid carcinoma (PTC). Two thousand two hundred and twenty PTC patients were included as controls. As shown in **Table 2**, the biological behavior of ITC was significantly different from that of PTC. The ITC group had more frequent retrosternal metastasis (40% vs. 7.5%,  $P=0.0006$ ), recurrent laryngeal nerve invasion (40% vs. 4.4%,  $P < 0.0001$ ), esophageal invasion (50% vs. 1.9%,  $P < 0.0001$ ), a higher proportion of distant metastasis (50% vs. 3.2%,  $P$

## Multifocality in ITC

**Table 1.** Clinicopathological characteristics of 10 cases of insular thyroid cancer

Case	Age	Gender	Multi-focality	Retrosternal metastases	Nodal metastases	Distant metastases	Outcome	Follow-up (mon)
1	45	F	N	N	N	N	LWD	45
2	16	M	Y	N	IV, VI	Lung	DOD	20
3	30	M	Y	Y	III, IV, VI	Bone	DOD	55
4	34	F	N	N	N	N	LWD	62
5	69	F	N	N	N	N	LWD	70
6	59	F	Y	Y	VI	Lung	LWD	78
7	50	F	Y	Y	IV, VI	N	DOD	6
8	63	F	N	N	VI	N	LWD	65
9	45	F	Y	N	II, III, IV, VI	Lung	DOD	30
10	49	M	Y	Y	II, III, IV, V, VI	Lung	DOD	35

Abbreviations: M, male; F, female; Y, yes; N, no; LVI, lymphovascular invasion; DOD, dead of disease; LWD, live with disease.

**Table 2.** Clinicopathological characteristics of study groups

Variable	ITC (n=10)	PTC (n=2220)	P
Gender			
M	3	539	0.9590
F	7	1681	
Multinodularity			
Present	6	551	0.0279
Absent	4	1669	
Retrosternal metastases			
Present	4	155	0.0006
Absent	6	2065	
Nodal metastases			
Present	7	1274	0.6281
Absent	3	946	
RLN invasion			
Present	4	94	< 0.0001
Absent	6	2126	
Esophageal invasion			
Present	5	41	< 0.0001
Absent	5	2179	
Distant metastases			
Present	5	68	< 0.0001
Absent	5	2152	
Vascular invasion			
Present	5	22	< 0.0001
Absent	5	2198	
Age	46±16	42±21	0.5531
Tumor diameter > 4 cm			
Present	6	77	< 0.0001
Absent	4	2143	

Abbreviation: RLN, recurrent laryngeal nerve; ITC, insular thyroid cancer; PTC, papillary thyroid cancer.

< 0.0001), and vascular invasion (50% vs. 1.0%,  $P < 0.0001$ ). While the presence of lymph node metastasis showed no significant difference.

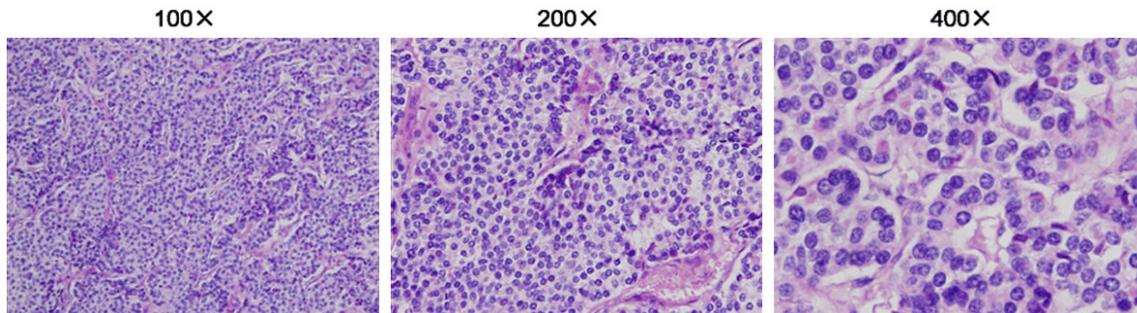
*ITC yields a worse overall survival than PTC patients*

For the survival analysis, 10 cases of ITC (5 deaths) were compared with 2220 cases of PTC (99 deaths). The median survival time for ITC was 45 months (range, 14.01-75.99 months), and survival rate at 5 years was 40%. All deaths were explained by tumor activity. The mean follow-up was 68 months, and the range was 3 to 89 months. The 5 year survival rate for PTC group was 95.9%. The disease specific survival at 5 years was significantly different between ITC and PTC patients, as shown in **Figure 2**.

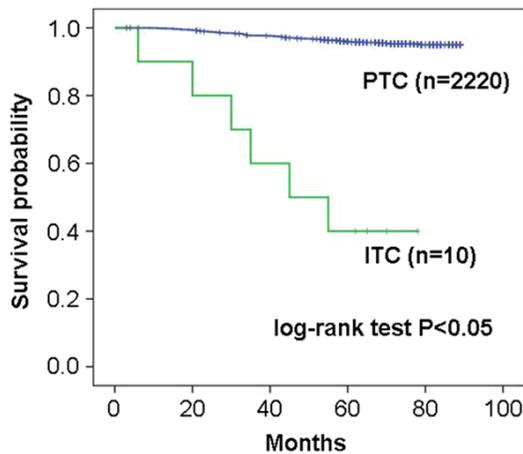
*Multiple nodularity might be a risk factor for disease specific death among ITC patients*

Although patients with ITC had a worsen prognosis compared with that of PTC, a deeper investigation into the survival of ITC patients was performed among these 10 ITC patients. Although patients with ITC are lacking in number to perform survival analysis, we still noticed that all the four sITC patients (4/4, 100%) have survived much longer (at least 45 months, 45-70 months) than those who have multinodularity (5/6, 83.3%, 6-78 months), as shown in **Figure 3**, which indicates that multinodularity might be a risk factor for poor prognosis for patients with ITC.

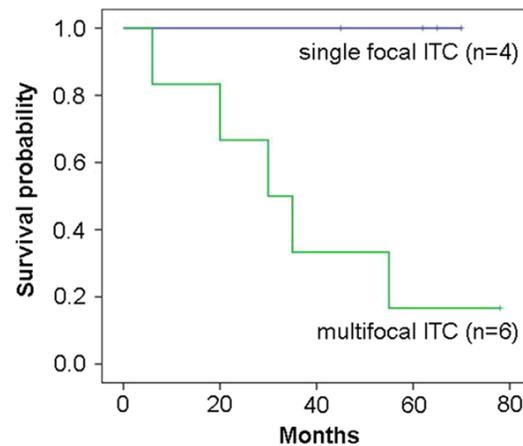
## Multifocality in ITC



**Figure 1.** Representative HE staining of insular thyroid cancer. Typical insular thyroid cancer showing nests and islets of small neoplastic cells surrounded by thin fibrovascular septa. 100 $\times$ , 200 $\times$  and 400 $\times$ , respectively.



**Figure 2.** Cumulative disease specific survival of patients with ITC and PTC (Kaplan-Meier plots).  $P < 0.05$ .



**Figure 3.** Cumulative survival of patients with ITC (Kaplan-Meier plots). Patients with single focal ITC (n=4) vs. multifocal ITC (n=6).

### Discussion

ITC is a clinically rare form of thyroid cancer. Accessible data were scattered and few studies have included patients more than twenty in number. The overall 5 year survival rate differs from study to study. It is believed that patients with localized ITC showed better prognosis than metastatic ITC patients. Our study revealed that the 5 year survival for ITC patients is 40%. This might be due to the relative advanced stage at the time of diagnosis in our study (5/10 patients were found to have distant metastasis at the time of diagnosis). In an up-to-now the largest cohort study, Kazaure and his colleagues reported that the overall 5-year OS was 61.9%, with the poorest prognosis being advanced ITC patients with distant metastasis when first diagnosed, and a favorable prognosis rounded to 90% in 5-year OS in patients with localized ITC [10]. This finding

indicates that advanced stage/metastatic ITC patients must have a poorer 5-year OS than 61.9%. Besides, Hiltzik et al reported that the overall OS for poorly differentiated thyroid cancer is 60%, with “extrathyroidal extension” and “tumor size” being independent risk factor for PFS [11]. Importantly, their study included three other subtypes of poorly DTC besides ITC. Another recent report including 17 ITC patients from Hod et al revealed that the 5-year overall survival rate is 83% [12]. Unfortunately, they did not provide the tumor size or TNM staging of these patients.

Some studies have reported in a recent study that no significant difference in prognosis was observed between patients with insular thyroid carcinoma and patients with widely invasive follicular thyroid carcinoma [13]. In a different study, it was found that the presence of an insular component (up to 90%) in either follicular

tumors or papillary tumors did not have an adverse effect on prognosis [14]. However, most researchers believed that insular variant of poorly differentiated thyroid carcinoma is an aggressive subtype of thyroid cancer with high propensity for local recurrence and distant metastases [8, 9].

Discrepancies in independent risk factors exist in various studies. Pellegriti reported that the histotype is an independent predictor of poor prognosis [8]. On the other hand, RAI therapy and distant metastasis were the two factors independently associated with survival of patients [12]. They reported that tumor size, extrathyroidal extension, distant metastasis, and total thyroidectomy but not multifocality were associated with the survival of patients with ITC in univariate analyses, however, in our study, multifocality might be an independent risk factor for disease-specific death, although more ITC patients are required for statistical analysis.

For a diagnosis of ITC, histological study must show an insular, solid, and/or trabecular growth pattern in more than 50% of the cell architecture (also called predominant ITC) [13], together with either convoluted nuclei, increased mitotic activity or tumor necrosis [15, 16]. Of note, it is essential to differentiate whether it is a predominant ITC (> 50% insular growth pattern), or differentiated thyroid cancer with only focal insular component since the extent/percentage of insular component might contribute to an increase of a poor prognosis. Rufini et al reported that, compared with variable focal insular component ( $\leq$  50% insular growth pattern), predominant ITC demonstrated a lesser frequency of disease-free outcome and a higher number of tumor-related deaths (41%), which is comparable with our result (5/10, 50%), than that of focal insular pattern (6.25%) [14]. In line with the above study, Sasaki et al also reported that the presence of an "insular component" is an independent aggressive prognostic factor for patients with DTC [17]. In our study, the ten patients were all predominant ITC and the overall survival significantly greater than that of the PTC strongly supports the notion that ITC should be considered as a separate entity. Moreover, the long time survival of patients diagnosed as "PTC with a focal insular pattern" even exerts a poorer prognosis than conventional PTC. Given that heterogeneity might

occur in one individual or even in one cancerous loci, a DTC diagnosis with focal ITC component might need careful and thorough sectioning when making pathological diagnosis.

In conclusion, the current study indicates that ITC is associated with a poorer patient outcome and must be considered a separate entity with respect to conventional PTC and therefore, warrant an initial aggressive treatment especially when ITC patients with multifocality.

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### Disclosure of conflict of interest

None.

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## Multifocality in ITC

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