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

Lei Liu¹*, Dapeng Li²*, Hailing Wang³, Xiaoyong Yang², Yang Yu², Ming Gao²

¹Department of Otorhinolaryngology, Tianjin Third Central Hospital, Tianjin, China; ²Department of Thyroid and Neck Tumor, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China; ³Department of Diagnostic and Therapeutic Ultrasonography, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China; ⁴Key Laboratory of Cancer Prevention and Therapy, Tianjin, China. *Equal contributors.

Received July 25, 2015; Accepted August 26, 2015; Epub September 1, 2015; Published September 15, 2015

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 carcinoma (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
Multifocality in ITC

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 followed 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

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

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

Table 2. Clinicopathological characteristics of study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>ITC (n=10)</th>
<th>PTC (n=2220)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>3</td>
<td>539</td>
<td>0.9590</td>
</tr>
<tr>
<td>F</td>
<td>7</td>
<td>1681</td>
<td></td>
</tr>
<tr>
<td>Multinodularity</td>
<td>6</td>
<td>551</td>
<td>0.0279</td>
</tr>
<tr>
<td>Present</td>
<td>4</td>
<td>1669</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>4</td>
<td>155</td>
<td>0.0006</td>
</tr>
<tr>
<td>Retrosternal metastases</td>
<td>4</td>
<td>2065</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6</td>
<td>1274</td>
<td>0.6281</td>
</tr>
<tr>
<td>Absent</td>
<td>7</td>
<td>946</td>
<td></td>
</tr>
<tr>
<td>Nodal metastases</td>
<td>7</td>
<td>41</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Present</td>
<td>3</td>
<td>2179</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>5</td>
<td>41</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Esophageal invasion</td>
<td>5</td>
<td>68</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Present</td>
<td>5</td>
<td>2152</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>5</td>
<td>22</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>5</td>
<td>2198</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5</td>
<td>46±16</td>
<td>0.5531</td>
</tr>
<tr>
<td>Absent</td>
<td>6</td>
<td>42±21</td>
<td></td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>5</td>
<td>77</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Present</td>
<td>4</td>
<td>2143</td>
<td></td>
</tr>
</tbody>
</table>
| 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 worsened 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

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

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×, 200× and 400×, 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).
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 (≤ 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.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC), No. 81402392, 81272782, 81472580, 8150-2322; Tianjin High School Science & Technology Fund Planning Project, No. 20110127; TJMUCH Foundation for Young Investigators, No. B1317.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Ming Gao and Yang Yu, Department of Thyroid and Neck Tumor, Tianjin Medical University Cancer Institute and Hospital, Huan Hu Xi Rd., Hexi Distr., Tianjin, China. Tel: 0086-22-23340123-3150; E-mail: gaoming68@aliyun.com (MG); nkyuyang@126.com (YY)

References


[5] Chao TC, Lin JD, Chen MF. Insular carcinoma: infrequent subtype of thyroid cancer with ag-


