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Clinical predictors of lymph node metastasis and survival rate in papillary thyroid microcarcinoma: analysis of 3607 patients at a single institution



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ABSTRACT

Background: The treatment of papillary thyroid microcarcinoma (PTMC) patients is controversial, as PTMC is often found incidentally and its prognosis is quite good. Because lymph node metastasis (LNM) is one of the main predictors of recurrence and impacts the survival rate of PTMC patients, this study aims to retrospectively identify the clinical factors that increase the risk of LNM and/or recurrence and can then be used to separate clinically unfavorable PTMCs from the rest and to help guide their treatment accordingly. Methods: Clinical and pathologic data were collected from 3607 patients diagnosed with PTMC at Shanghai Renji Hospital between 2005 and 2015. Univariate and multivariate analyses were performed to identify the clinical predictors of LNM and survival rates were calculated by using the Kaplan—Meier method.

Results: Our univariate and multivariate analyses show that age of <45 y (P < 0.01), gender of male (P < 0.01), tumor diameter >0.7 cm (P < 0.01), and multifocality (P < 0.01) significantly increase the risk of central LNM. However, clinical factors, such as LNM, age, gender, multifocality, and operation range, do not affect the 10-y disease-free survival rate (P > 0.05). Conclusions: Clinical factors, such as gender of male, age of <45 y, multifocality, and tumor size >0.7 cm, suggest a higher risk of LNM; however, they do not affect PTMC patients' 10-y disease-free survival rate. We recommend ipsilateral lobectomy to PTMC patients. For PTMC patients with higher LNM risk, preoperative central and lateral cervical lymph node imaging examination should be emphasized, and lymph node dissection is recommended. The range of dissection should be determined based on the imaging results.

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Introduction

The incidence of papillary thyroid carcinoma (PTC) in China increased from 10.4 per 100,000 people in 2000 to 96.8 per 100,000 in 2010. As a result, new PTC cases increased 35.3% year after year in that period. In the United States, more than 56,000 new cases were reported in 2015 alone. The increase in

the incidence of PTC is mainly due to early detection of papillary thyroid microcarcinoma (PTMC), which is defined as carcinoma ≤ 1 cm in the greatest dimension. This observation emphasizes the importance for clinicians to direct their focus toward a more accurate diagnosis and treatment plan.

The clinical features of PTMC occur at a higher incidence in females and young patients (aged <45 y) with a tendency

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toward multifocal growth and cervical lymph node metastasis (LNM).3 Because no consensus exists regarding the natural history of PTMC, the recommended treatment ranges from observation alone to total thyroidectomy (TT) with radioactive iodine ablation.4 For example, Oda et al.5 suggested that low-risk PTMC patients might be treated nonsurgically, with close observation and follow-up. However, Hay et al.6 recommended thyroid lobectomy of the affected side on PTMC patients, although they suggested that a more extensive surgical range would likely increase the incidence of complications. Yet from another angle, studies by Pacini et al. showed that PTMC had all the biological characteristics of malignant tumors and reported that the highest LNM rate was up to 50%. Meanwhile, ipsilateral thyroid lobectomy and lymph node (LN) dissection in selective areas fulfill the basic requirements of tumor-free principle. However, the 2015 Guidelines of the American Thyroid Association (ATA) do not recommend LN dissection in the central area to PTMC patients without clear evidence of existing LNM.^{8,9} These aforementioned divergent recommendations of treatment demonstrate that for different PTMC patients, individualized treatment plans should be developed according to their individual clinical factors.

This study aims to retrospectively identify the clinical factors that increase the risk of metastasis or recurrence and to calculate patients' 10-y tumor-free survival rate. Consequently, higher risk PTMCs could be identified to receive more aggressive treatment.

Methods

The clinical data (Table 1) of the PTMC patients who underwent thyroid surgical treatment in our department between January 2005 and January 2015 were analyzed retrospectively. The patient inclusion criteria are as follows: (1) a postoperative paraffin section-based pathologic diagnosis of papillary thyroid carcinoma, (2) a maximum tumor diameter \leq 1 cm, and (3) long-term residence in Shanghai, which facilitated the postoperative follow-up. A total of 3607 patients meet the inclusion criteria. Among them are 3513 cases of nonincidental PTMC and 94 cases

Table 1 $-$ General characteristics of 3607 PTMC patients.			
Characteristic	Number	Average value	Median
Gender			
Male	868 (24.1%)		
Female	2739 (75.9%)		
Tumor multifocality			
Solitary lesion	2932 (81.3%)		
Multifocal growth	675 (18.7%)		
Age (y)			
<45	1416 (39.3%)	47.5 ± 12.0	49
≥45	2191 (60.7%)		
Diameter (cm)		0.6 ± 0.3	0.6
Incidental PTMC	94 (2.6%)	0.4 ± 0.4	0.3
Nonincidental PTMC	3513 (97.4%)	0.6 ± 0.3	0.6

of incidental PTMC. PTMCs detected by postoperative pathologic examination of surgical specimens resected for benign thyroid diseases are defined as incidental. PTMCs detected by preoperative fine-needle aspiration cytology (FNAC) or frozen section during surgery are defined as nonincidental.

Patients whose maximum tumor diameter was ≥ 0.5 cm received FNAC when suspicious lesions were observed by ultrasonography. Patients who had malignant nodules in unilateral lobe confirmed by FNAC or intraoperative frozen section underwent ipsilateral thyroid lobectomy + LN dissection in the central area during surgery. Patients who had nodules in bilateral lobes (one or more nodules were confirmed malignant by FNAC or frozen section) underwent TT + LN dissection in the central area. Patients who had lateral LNM confirmed by FNAC underwent TT + LN dissection in the central area + selective lateral LN dissection (levels II, III, and IV). Incidental PTMC patients underwent ipsilateral subtotal thyroidectomy. After the initial operation, patients whose maximum tumor diameter was \leq 0.5 cm did not receive further operation. Patients whose maximum tumor diameter was >0.5 cm underwent phase II surgery, which entails resection of residual thyroid + LN dissection in the central area.

For patients who were pathologically confirmed to have lateral cervical LNM and patients whose tumor extended beyond the thyroid gland, routine I¹³¹ treatment was administered. All PTMC patients received suppressive therapy with oral Euthyrox postoperatively, and their TSH levels were maintained between 0.1 and 0.5 mlU/L. Thyroglobulin level was used to evaluate for recurrent or persistent disease in the patients who underwent TT, especially in the patients who have lateral cervical LNM and whose tumor extended beyond the thyroid gland.

The patients were followed up every 3 mo for the first 3 y, every 6 mo for the fourth and fifth years, and every 12 mo for the subsequent years. The follow-ups mainly include the serological examination of thyroid function and B-ultrasound examination of the thyroid and cervical LNs. When suspicious lesions were observed by ultrasonography, FNAC specimens were obtained to determine whether thyroid and/or cervical LNM had occurred. A progression-free state is defined as the absence of cancer as demonstrated by ultrasonography and (if necessary) pathological examination by using fine needle aspiration. Postoperative complications are not included in the definition of disease, which refers only to the presence, recurrence, or metastasis of cancer.

SAS statistical software, V8 edition, is used for data analysis and graph generation. The statistical methods used mainly include the t-test and χ^2 test. Relative risks (odds ratio [OR] values) and confidence intervals (CI) are determined by logistic regression, and the survival rate analysis is conducted using the Kaplan–Meier method.

Result

Surgical treatment of 3607 patients was illustrated in Figure 1. Seventy-three patients received radioactive iodine after operation. The shortest follow-up interval for the 3607 patients is 25 mo, and the longest follow-up interval is 138 mo, with an average follow-up period of 68 mo. In all, 68.9% of patients were followed up for more than 5 y.

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