RESEARCH ARTICLE

Could Tumor Size Be A Predictor for Papillary Thyroid Microcarcinoma: a Retrospective Cohort Study

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Abstract

Background: Central lymph node metastasis(CLNM) is common in papillary thyroid microcarcinoma (PTMC). The aim of this study was to define the pathohistologic risk grading based on surgical outcomes. Materials and Methods: Statistical analysis was performed to figure out the optimal cut-off values of size in preoperative ultrasound images for defining the risk of CLNM in papillary thyroid microcarcinoma. Receiver operating characteristic curves (ROC) studies were carried out to determine the cutoff value(s) for the predictor(s). All the patients were divided into two groups according to the above size and the clinic-pathological and immunohistochemical parameters were compared to determine the significance of findings. Results: The optimal cut-off value of tumor size to predict the risk of CLNM in papillary thyroid microcarcinoma was 0.575 cm (area under the curve 0.721) according to the ROC curves. Significant differences were observed on the multifocality, extrathyroidal extension and central lymph node metastasis between two groups which were divided according to the tumor size by the cutoff values. Patients in two groups showed different positive rate and intensity of Ki67. Conclusions: The size of PTMC in ultrasound images are helpful to predict the aggressiveness of the tumors, it could be an easy predictor for PTMC prognosis and assist us to choose treatment.

Keywords: Papillary thyroid microcarcinoma - central lymph node metastasis - tumor size

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Introduction

Thyroid cancer incidence, stable until the early 1990s, has continuously and dramatically increased thereafter (Howlader et al., 2013; Guay et al., 2014). During the same period, most cancers have decreased and no cancer has increased as much as thyroid cancer. The US data reflect what occurred in most countries (Van et al., 2013; Ito et al., 2013) from both a quantitative and a qualitative standpoint. Specifically, the observed changes obvious characteristic. Nearly all the registered increase is limited to the papillary histotype and most increase related to tumors of small size (microcarcinomas, 1.0 cm maximum diameter) whose percentage increased to nearly 50% of all detected cancers. This means that papillary thyroid microcarcinoma (PTMC),defined as a papillary thyroid carcinoma (PTC) measuring 1 cm in maximal diameter, contributes the most increase. The incidence of PTMC has increased dramatically and it presents overall excellent prognosis that the overall 10-year survival rate associated with this malignancy is >90% (Wang et al., 2014). However, many current guidelines and recommendations regarding the optimal treatment strategy for PTMC remain controversial (Byar et al., 1979; Udelsman et al., 1996). The reason is that we could not accurately predict the aggressiveness of tumors before the operation. The aggressiveness of PTMC is associated with many factors, of which central lymph node metastasis (CLNM) is the most important one.

Someone reported that larger tumor size was associated with a significantly increased risk of CLNM, but which size would be the optimal values still remain controversial. Lim et al indicated it would be 0.7 cm (Lim et al., 2009), Zhang et al. (2012) indicated it would be 0.6 cm (Zhang et al., 2012) and Chang et al indicated it would be 0.5cm (Chang et al., 2015). As size of the tumor in ultrasound images is the most available preoperative parameters, we tried to make a study on the relationship between tumor size and CLNM.

The purpose of this study was to define the pathohistologic risk grading based on surgical outcomes. Statistical analysis was performed to figure out the optimal cut-off values of size in preoperative ultrasound images for defining the risk of CLNM in papillary thyroid microcarcinoma in order to guide individualized patient management. Receiver operating characteristic curves (ROC) studies were carried out to determine the cutoff value(s) for the predictor(s). Then we divided all the patients into two groups according to the above size and compared the clinic-pathological and immunohistochemical parameters to determine the clinical

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and pathological significance of findings.

Materials and Methods

A total of 359 patients who underwent thyroidectomy with routine CLND for PTMC at the department of general surgery, Shanghai General Hospital of NanjingMedical University, between January 2013 and December 2014 were enrolled in this study. Based on a review of our computerized database, the demographic information was collected.

The tumor size was defined as the maximum tumor diameter and determined digitally by ultrasound images, and they were equally to the pathological findings.

All the resection specimens were examined by two independent pathologists. The pathological parameters, such as multifocality, cervical lymph node metastasis, Hashimoto's thyroiditis(HT) and intensity of Ki67, were recorded. The tumor subtypes and lymph node stages were performed according to the American Joint Committee on Cancer TNM staging system (7th Edition)(Edge et al., 2010). Papillary microcarcinoma were defined as tumors with diameter ≤1.0cm at histological examination. The diagnosis of HT was based on histopathological findings. The immunohistochemical tests antibody for Ki67, was obtained from Gene Tech Company Limited, Shanghai, China.

All 359 patients underwent lobectomy+isthmectomy or total thyroidectomy with routine CLND, a resection of the primary tumor was sent for frozen section before performing CLND. Lobectomy+isthmectomy with ipsilateral CLND was performed in 285 patients because they had single lesions that were limited to the thyroid and clinically negative radiologic findings in the central lymph node, and total thyroidectomy with bilateral CLND was performed in 74 patients with clinically suspicious node metastasis or bilateral lesions. CLND was performed superiorly to the hyoid bone, laterally to the carotid sheath, inferiorly to the manubrium, and dorsally to the prevertebral fascia. The parathyroid glands were carefully preserved in situ, and the devascularized parathyroid glands were autotransplanted into the sternocleidomastoid muscle.

All the cases had been followed up to observe their circumstances of recurrence, metastasis and survival. The modes of follow up included letters, telephones, out-patient clinic and so on. The deadline was Oct 30, 2015.

Informed consent was obtained from all patients who donated their specimens, and all the experiments were approved by the hospital ethics committee.

Statistical analysis was performed to figure out the optimal cut-off values of size in preoperative ultrasound images for defining the pathological risk grading of papillary thyroid microcarcinoma. Receiver operating characteristic curves (ROC) studies were carried out to determine the cutoff value(s) for the predictor(s). Then we divided all the patients into two groups according to the above size and compared the clinic-pathological and immunohistochemical parameters to determine the clinical significance of findings.

Quantitative data were presented as mean±SD, and the t-test was used for comparison. The χ^2 test and Fisher exact test were used for comparison of the categorical data. Differences were considered statistically significant with p 0.05 using a two-tailed test. All statistical analyses were performed using SPSS Statistics version 20.0.0 for Macintosh (IBM, Armonk, NY, USA).

Results

The patient clinicopathological characteristics are summarized in Table 1. A total of 359 patients were included in this study. There were 87 men (24.2%) and 272 women (75.8%) with a mean age of 46.67 years, ranging from 16 to 81 years. The mean size of PTMCs was 0.58cm; of these patients, 72(20.1%) patients had PTMC with extrathyroidal extension. Multifocality was observed in 98 (27.3%) patients, and Hashimoto's thyroiditis was found in 74 (20.6%) patients. CLNMs were identified in 90 (25.1%)patients.

The ROC curves were carried out to predict the risk of CLNM and the optimal cut-off value of tumor size was calculated (Figure 1), which was 0.575 cm(area under

Table 1. Clinicopathological Characteristics (n= 359)

Characteristic	n(%)
Age(years)	46.67(16~81)
Tumor diameter(cm)	0.58
Gender	
Male	87(24.2)
Female	272(75.8)
Multifocality	
No	261(72.7)
Yes	98(27.3)
Central lymph node matastasis	
No	269(74.9)
Yes	90(25.1)
Extrathyroidal extension	
No	287(79.9)
Yes	72(20.1)
Hashimoto's thyroiditis	
No	285(79.4)
Yes	74(20.6)

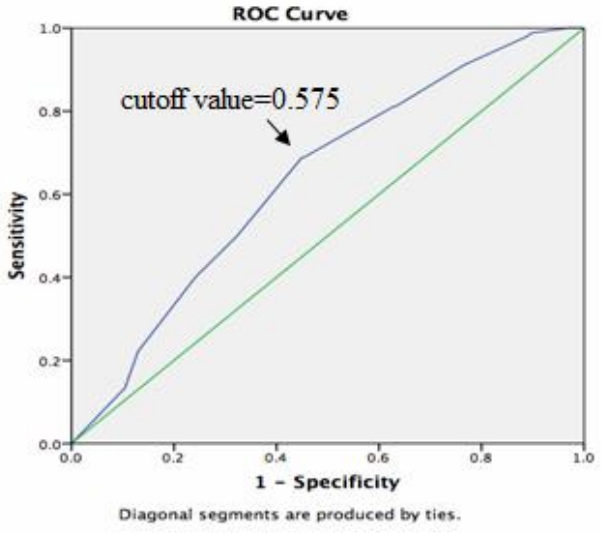

Figure 1. Receiver-operating Characteristic (ROC) Curves for Predicting the Risk of CLNM

Table 2. Analysis of Clinical and Pathological Characteristics of Ptmc with Different Groups Devided by Cut-Off Values of Tumor Size

	Group I (size≤0.575) n=176	Group II (size>0.575) n=183	RR	Values	*P*
gender(male/female)	36/140 (20.5%/79.5%)	51/132 (27.9%/72.1%)		χ^2=2.686	*P*=0.101
Multifocality	37 (21.0%)	61 (33.3%)	0.63	χ^2=6.851	*P*=0.009
Central Lymph node metastasis	28 (15.9%)	62 (33.9%)	0.47	χ^2=15.424	*P*<0.001
Extrathyroidal extension	17(9.7)	55(30.1)	0.32	χ^2=23.276	*P*<0.001
HT (+)	38(21.6%)	36(19.7%)	1.1	χ^2=0.202	*P*=0.653
Ki67 (+)	122 (69.3%)	153 (83.6%)	0.83	χ^2=10.219	*P*<0.001
age	46.52±11.65(y)	46.81±12.57(y)		t=0.228	*P*=0.820
Ki67 expression intensity	2.93±3.96(%)	3.96±3.20(%)		t=-2.715	*P*=0.007

the curve 0.721). The cutoff value of tumor size was statistically correlated with the risk of CLNM (p<0.01).

All the patients were divided into two groups (Group I and Group II) according to the tumor size by the cutoff values. Then the clinic-pathological and immunohistochemical parameters were compared. Based on table 2, it showed there were no statistically significant differences between two groups on the gender, age and coexisting with HT. Significant differences were observed on the multifocality, extrathyroidal extension and central lymph node metastasis between two groups. Patients in Group II showed a higher positive rate of Ki67 and higher expression intensity of Ki67 as compared to Group I.

Follow up

The follow-up time was 10~34months, and mean time was 19.6months. There were 358 cases survived in 359 PTMC patients, including 2 cases which were found ipsilateral recurrence after surgery in 30 and 32monthes respectively, one male and one female, and their tumor diameters were 0.7cm and 0.8cm respectively(both >0.575cm). The only case of death was because of the unexpectedly cardiovascular disease.

Discussion

The incidence of PTMC has increased dramatically in recent years and CLNMs are relatively common in PTMC patients. PTMC is a special kind of subtype of thyroid carcinoma, accounting for up to 30% of all the differentiated thyroid carcinoma cases(Riemann et al., 2009). Occuring rate in female is significantly higher than men, reported in the literature, mostly in the 3:1 In our study group of cases the male to female ratio is about 1:3.13. PTMC usually considered an excellent prognosis (Jeon et al., 2009), but its biological behavior is a kind of mature cancer, and part of the PTMC biological behavior is poor, which can be manifested as cervical lymph node metastasis and recurrence, distant metastasis and even cause death (Zafon et al., 2010). Several studies have demonstrated that CLNMs are observed in about 24.3-64.1% of patients with PTMC (Roh et al., 2008; Lim et al., 2009; Yuan et al., 2015). In this study, the incidence of CLNMs in patients with PTMC was 25.1%.

However, many current guidelines and recommendations regarding the optimal treatment strategy for PTMC remain controversial. Someone think that CLND is unnecessary, because the reported mortality rates of PTMC range from 0% to 1%, and CLND provides no survival benefit (Appetecchia et al., 2002), CLND may increase the frequency of perioperative complications as well (Wada et al., 2003). However, other studies demonstrated that the risk of recurrence significantly increased in PTMC patients with CLNM(Chow et al., 2003). In addition, some investigators have showed that the operations for recurred lymph nodes in PTC increased the risk of postoperative complications(Vini et al., 2003) . Furthermore, CLND is helpful to assess the accurate staging of lymph node (Levin et al., 1992).

The reason for all these arguments is we could not accurately predict the aggressiveness of tumors before the operation. We supposed may be only parts of the PTMC patients need CLND. There are many ways we can predict the aggressiveness of PTMC, whilethe size of the tumor in ultrasound images is the easiest available predictors. In our study, we found the cutoff value of tumor diameters by ROC curve. Then we defined two groups by the diameter(0.575 cm) and compared many risk factors between two groups. Significant differences were observed on the multifocality, extrathyroidal extension, central lymph node metastasis, the positive rate of Ki67 and the intensity of Ki67 between two groups. Ki67 is a kind of DNA binding protein which presents in proliferating cell nuclear and been closely related with cell proliferation. There is a correlation between the expression of Ki67 and the metastasis and the prognosis in PTMC.

Above result showed that the PTMC with the diameter >0.575cm is more aggressive than those with the diameter ≤0.575cm. And the result excluded gender and age which might be the interference factors. So maybe we can call these tumors with the diameter ≤0.575cm micromini carcinoma. It suggested that the tumors with the diamerter >0.575cm may be more susceptible to recurrence and metastasis after surgery. That was a group of high-risk patient population, who needed close follow-up in order to intervent early.

Nowadays, most increase is due to cancers of small size is certainly true and a possible consequence of more sensitive diagnostic procedures. This increase occurred in spite of a more frequent early diagnosis and timely treatment of small tumors, a practice that should have decreased the number of large cancers. We may face more situation of tumor size ≤0.575cm in the future and more studies needs to be done.

In conclusion, the size of PTMC in ultrasound images are helpful to predict the aggressiveness of the tumors, it may become an easy predictor for PTMC prognosis and assist us to choose treatment. Due to the limited number of patient into the group and follow-up time, it need further increasing sample and long-term follow-up to confirm the conclusion. In the future, we will do more works on this subject. We will follow up these patients and create disease-free survival (DFS) curves to determine the clinical significance of the above findings.

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