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The correlation between ultrasonographic features, bFGF, and the local invasiveness of thyroid papillary carcinoma

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Abstract

The present study aimed to investigate the correlation between ultrasonographic features, basic fibroblast growth factor (bFGF), and the local invasiveness of papillary thyroid carcinoma (PTC).

A total of 350 samples of thyroid nodules were collected. Routine ultrasonography was performed before the operation and routine pathological diagnosis and bFGF detection were performed after the operation.'

These 350 samples of thyroid nodules included 90 samples of nodular goiter, 36 samples of focal thyroiditis, and 224 samples of PTC. A total of 326 thyroid nodules were examined for bFGF. The results revealed that the difference in the expression of bFGF between the benign and malignant groups was statistically significant ($P < .05$) and the difference in the positive expression of bFGF between the invasive and non-invasive PTC groups was statistically significant ($P < .05$).

Whether the shape of PTC is regular or not and whether there is micro-calcification in PTC and other ultrasonographic features, the size and location of the lesions and the age of the patient help make a preliminary prediction of local invasiveness before the operation. Postoperative detection of bFGF is helpful for further risk assessments of PTC.

Abbreviations: bFGF = basic fibroblast growth factor, PTC = papillary thyroid carcinoma, TI-RADS = thyroid imaging reporting and data system.

Keywords: basic fibroblast growth factor, carcinoma, invasiveness, thyroid, ultrasound

1. Introduction

The thyroid gland is an endocrine organ in the anterior region of the neck in the human body. In recent years, the incidence of thyroid carcinoma has increased yearly and thyroid carcinoma has become the world's fastest rising malignant tumor.[1] In China, the incidence of thyroid carcinoma is also increasing.[2] The reasons are complicated, 1 of which is the extensive application of high-frequency ultrasound and the ultrasound-guided fine needle aspiration biopsy,[3] allowing for early diagnosis of many asymptomatic thyroid carcinomas. Papillary carcinoma is the most common histopathological type in thyroid carcinoma and accounts for approximately 90% of all thyroid carcinomas[4] with the characteristics of low invasiveness and a good prognosis. Invasive thyroid carcinoma can reduce the 10-year survival rate of patients;[5] its prognosis is significantly different from that of non-invasive thyroid carcinomas. Invasive thyroid carcinoma refers to a thyroid carcinoma in which the tumor tissue invades and penetrates the glandular membrane and invades the tissues and/or organs surrounding the gland to varying degrees. Furthermore, its lymph node metastases occur early and distribute widely, its distant metastases are more than those of non-invasive thyroid carcinoma, and the scope of surgical resection is also larger.

The thyroid gland is at a superficial location and has a homogeneous internal structure. A satisfactory sonogram can be obtained by high-frequency ultrasound. Therefore, ultrasound plays an important role in the diagnosis and differential diagnosis of thyroid carcinomas, especially papillary carcinomas. Common ultrasound findings of papillary thyroid carcinomas (PTC) are as follows: most patients present a single nodule, especially those with a diameter of ≤1cm; aspect ratio is >1; solid; extremely low echoes; irregular shape; blurred boundaries; and internal micro-calcification. When the capsule is invaded, the strong echoes of the capsule are blurred or interrupted and a swollen lymph node can be observed in the neck if the patients have lymph node

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metastases. This study analyzed the ultrasound findings of 350 thyroid nodules to investigate whether there is a correlation between an ultrasound sonogram of PTC and the local invasion of PTC.

The risk assessment for thyroid carcinomas is based on the following factors: age, gender, tumor size, number of lesions, and the presence of extra-glandular invasion and lymph node metastasis, while other factors are still controversial. Basic fibroblast growth factor (bFGF) is a multifunctional regulatory peptide; it induces new capillary growth and acts as a potent mitogen to stimulate mitosis and proliferation. There is a small amount of bFGF in the cytoplasm of normal thyroid follicular epithelial cells, however, there is no bFGF on the basement membrane. Therefore, bFGF is not expressed in normal thyroid tissues.[6] In the present study, the detection of bFGF was performed on surgical specimens that met the inclusion criteria to observe the difference in the expression of bFGF between benign and malignant thyroid nodules and the difference in expression of bFGF between invasive and non-invasive PTC, in order to obtain more indicators of postoperative risk assessments of PTC.

2. Materials and methods

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Affiliated Tumor Hospital of Xinjiang Medical University. Written informed consent was obtained from the participants.

2.1. Patients

The present study was a prospective study. A total of 350 consecutive patients that met the inclusion criteria were enrolled from December 2017 to January 2019. All of these patients were treated in our hospital due to thyroid nodules confirmed by operation pathology. In the present study, local invasiveness is defined as the invasion of adenocarcinoma to the capsule and/or the surrounding tissues and organs. Among these patients, 78 patients were male and 272 patients were female. The age of these patients ranged within 22 to 77 years old, with an average age of 46.61 ± 10.24 years old. All patients underwent surgery within 1 week after the ultrasound examination in our hospital. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Affiliated Tumor Hospital of Xinjiang Medical University. Written informed consent was obtained from the participants.

Inclusion criteria: The criteria included patients without a history of radiotherapy of the head and neck, a history of thyroid surgery, a history of treatment with thyroid-related drugs, a history of use of bFGF-related medical supplies and patients with thyroid papillary carcinomas confirmed by postoperative pathology in the malignant group. All cases were operated on in our hospital and ultrasound and pathological examinations were completed.

Pathological findings of PTC:

(1) ground glass-like cell nuclei, nucleus pseudo inclusions, nuclear sulcus, and enlarged nuclei;
(2) neoplastic nipples;
(3) some granulosomes.

Exclusion criteria: patients with a thyroid nodule of <0.5 cm or >3.0 cm in diameter, who were excluded from this study is related to the limitation of real-time shear wave elastic imaging (SWE). It is impossible to accurately measure the shear waves of these 2 sizes of nodules using SWE. Besides, patients with a non-papillary type of thyroid carcinoma were excluded, as well as patients with an invalid bFGF test result.

For multiple nodules of the thyroid, 1 of them was chosen as the research object. The inclusion criteria of thyroid nodules are as follows: Nodules with the highest risk of malignancy classified by preoperative ultrasound Thyroid Imaging Reporting and Data System (TI-RADS); for those had both benign and malignant nodules, suspected malignant nodules were chosen; for the nodules similar in the sonogram, and those with the largest diameter were selected.

2.2. Instruments and methods

2.2.1. Routine ultrasound examination. A Supersonic Imaging Aixplore ultrasound diagnostic apparatus with line array probes and frequencies of 4 to 15 MHz and equipped with a storage hard drive was used in the study.

The ultrasonic TI-RADS classification is based on the Kwak TI-RADS method.[7] It includes the following signs of malignancy for diagnosis of thyroid carcinoma: solid component, hypoechogenicity, marked hypoechogenicity, microlobulated or irregular margins, microcalcifications, and taller-than-wide shape. As the number of suspicious ultrasound features increased, the fitted probability and risk of malignancy also increased.

The Kwak TI-RADS method is a common diagnostic system and its classification is as follows:

TI-RADS 1: normal thyroid tissue;
TI-RADS 2: benign lesion;
TI-RADS 3: no suspicious ultrasound features;
TI-RADS 4a: one of the above malignant features has been found;
TI-RADS 4b: two of the above malignant features have been found;
TI-RADS 4c: three or 4 of the above malignant features have been found;
TI-RADS 5: all the malignant features have been found.

2.2.2. Detection method of bFGF. Reagents: Anti-FGF2 antibody is a rabbit monoclonal antibody (100 μL in each tube). Detection steps: All patients enrolled in this study were tested for bFGF, which was completed in the molecular laboratory of our hospital. The specimens were fixed with 3.7% neutral formaldehyde, paraffin embedded tissue sections (3–4 μm thick, attached to a charge slide) and stained with Benchmark automatic immunohistochemistry (Roche, Switzerland) to perform detectionof bFGF using streptavidin-perosidase (SP) method. In the IHC protocol of SP method, primary antibody of bFGF (catalog number: ab92337, Abcam) was added and incubated in refrigerator at 4°C overnight, and the color development degree was mastered under the microscope. The selection, preparation, and interpretation of the specimens' results were completed in the Pathology Department.

Interpretation of bFGF results: bFGF is expressed in the cytoplasm and membrane when there are brownish-yellow particles in the above parts of cells. Moreover, the cells are determined as positive or no positive cells. A positive cell percentage of $<25\%$ was defined as (−), a positive cell percentage of$\geq 25\%$ and $<50\%$ was defined as (+), a positive cell percentage of$\geq 50\%$ and $<75\%$ was defined as (++), and a positive cell percentage of $\geq 75\%$ was defined as (+++).

Table 1

The expression of bFGF in 326 thyroid nodules (patients, %).

bFGF expression	Pathological diagnosis			χ^2 value	*P* value
	Focal thyroiditis	Nodular goiter	Thyroid papillary carcinoma	74.836	<.001
Negative	17 (47.2)	15 (16.7)	24 (12.0)		
+	13 (36.1)	47 (52.2)	38 (19.0)		
++	6 (16.7)	24 (26.7)	50 (25.0)		
+++	0	4 (4.4)	88 (44.0)		

Because +++ of the focal thyroiditis was 0, combined the data in the focal thyroiditis and nodular goiter when chi-square test was applied.
Compared focal thyroiditis with nodular goiter when the +++ row was excluded, $\chi^2=11.658$, $P<.01$.
bFGF = basic fibroblast growth factor.

2.3. Statistical analysis

SPSS19.0 was used for data statistical analysis. All the counting data were expressed as n (%). The Chi-square test was used for comparison between groups. A *P* value of less than .05 was considered as statistical significant difference.

3. Results

Surgical pathological results. A total of 350 thyroid nodules were surgically resected in our hospital. The pathological results reveal that nodular goiter was present in 90 (25.7%) patients, focal thyroiditis in 36 (10.3%) patients, and PTC in 224 (64%) patients. In the benign group, lesions were found in the left lobe in 59 (46.8%) patients, lesions were found in the right lobe in 50 (39.7%) patients, and lesions was found in the isthmus in 17 (13.5%) patients. Among these patients, a single lesion was found in 41 (32.5%) patients and multiple lesions were found in 85 (67.5%) patients. In the malignant group, lesions were found in the left lobe in 87 (38.8%) patients, lesions were found in the right lobe in 111 (49.6%) patients, and lesions were found in the isthmus in 26 (11.6%) patients. Among these patients, a single lesion was found in 163 (72.8%) patients, multiple lesions were found in 61 (27.2%) patients, and 113 (50.4%) patients had cervical lymph node metastases.

The expression of bFGF was detected in 350 specimens after the routine acquisition and obtaining the results of the pathological diagnosis. The Department of Pathology and the Molecular Laboratory of our hospital completed the bFGF detection. Finally, there were 326 patients that met the experimental criteria and our findings achieved satisfactory results (Table 1). Results of bFGF expression detection in 126 patients in the benign group: 32 (25.4%) patients had a negative expression, 60 (47.6%) patients had a (+) expression, 30 (23.8%) patients had a (++) expression, and 4 (3.2%) patients had a (+++) expression. The difference in bFGF expressions between the benign group and the malignant group was statistically significant. That is, the number of bFGF positive cells was higher in the malignant group than in the benign group and the trend of positive expression levels was reversed in the benign group and the malignant group (Table 1). The difference in bFGF expressions between focal thyroiditis and nodular goiter was statistically significant ($P < .05$) That is, nodular goiter had more positively expressed cells and the number of positive cells of the 2 decreased with the increase in a positive level.

BFGF expression detection results in 200 patients with PTC: 24 (12%) patients had a negative expression, 38 (19%) patients had a (+) expression, 50 (25%) patients had a (++) expression, and 88 (44%) patients had a (+++) expression. According to whether the tumor invaded the capsule and/or surrounding tissues and organs, these patients were divided into 2 groups: local invasive and non-invasive PTC groups. The overall difference between the 2 groups was not statistically significant ($P>.05$, Table 2). Statistical analysis of 176 cases of bFGF positive expression showed that there was a statistically significant difference in the trend test of bFGF positive expression between 2 groups ($P<.05$) (Table 3). These results suggested that the number of bFGF positive cases in the invasive PTC group increased with the elevated expression level, but not in the non-invasive group (Fig. 1).

In 224 PTC patients, 44 patients were male and 180 patients were female. The difference in gender between the local invasive and non-invasive PTC groups was not statistically significant ($P>.05$). Patients in the present study were divided into 2 age groups with the threshold of 50 years old; 160 patients were younger than 50 years old and 64 patients were over 50 years old. The difference in age between the 2 groups was statistically significant ($P<.05$). Ultrasound findings of PTC (Fig. 2) and local invasiveness were tested using a Chi-square test. These results are presented in Table 4.

Table 2

The expression of bFGF molecules in 200 patients in the local invasive and non-invasive papillary thyroid carcinoma groups (patients, %).

bFGF expression	Pathological diagnosis		χ^2 value	*P* value
	Locally invasive	Locally noninvasive		
Negative	14 (12.3)	10 (11.6)	6.969	.073
+	15 (13.2)	23 (26.7)		
++	28 (24.6)	22 (25.6)		
+++	57 (50.0)	31 (36.1)		

Linear-by-Linear Association value = 3.024, $P=.082$.
Bfgf = basic fibroblast growth factor.

Table 3

The expression of bFGF molecules in 176 patients with positive expressions in papillary thyroid carcinomas (patients, %).

bFGF expression	Locally invasive	Locally noninvasive	χ^2 value	*P* value
+	15 (15.0)	23 (30.3)	6.942	.031
++	28 (28.0)	22 (28.9)		
+++	57 (57.0)	31 (40.8)		

Linear-by-Linear Association value = 6.696, $P=.010$.
Bfgf = basic fibroblast growth factor.

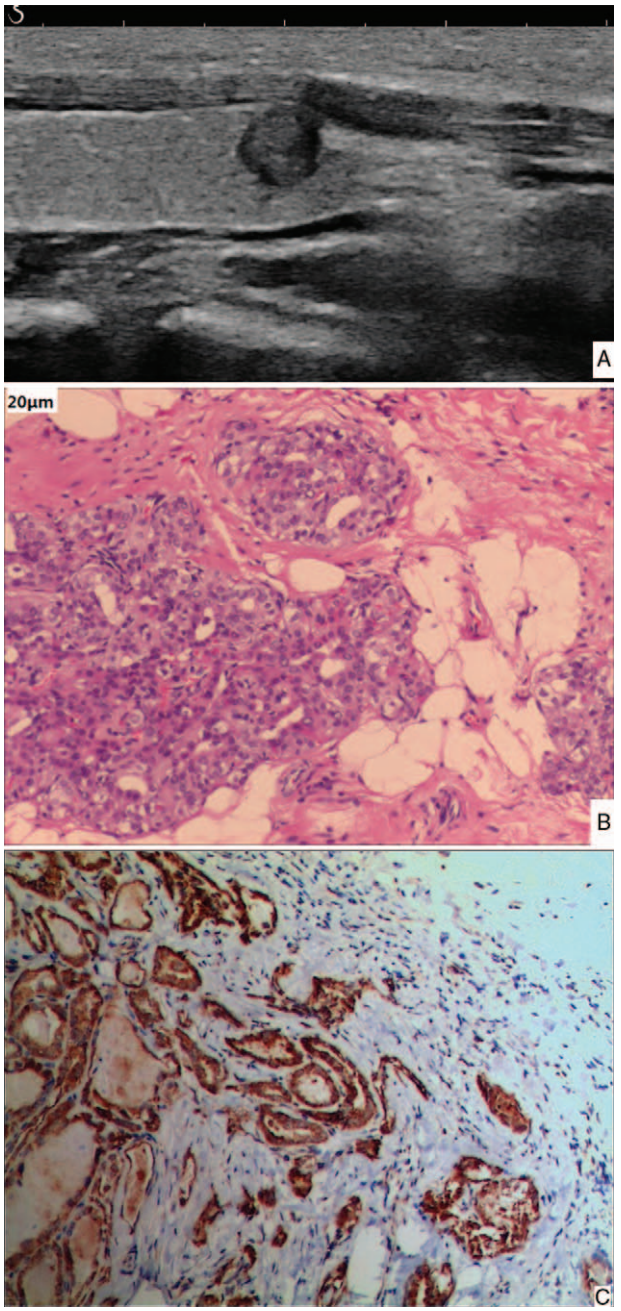

Figure 1. A 29-yr-old female patient has a small papillary carcinoma at the left lobe of the thyroid gland, the size is approximately 0.7 × 0.6 cm. A is an ultrasonogram, which reveals that the nodule is adjacent to the anterior ridge of the capsule and the continuity is interrupted. B is the pathology (H & E, × 100), which reveals that the carcinoma invades the surrounding fat tissue. C is bFGF × 100, the cytoplasm is strongly positive (+++) in papillary thyroid carcinomas and negative in the surrounding normal thyroid tissue.

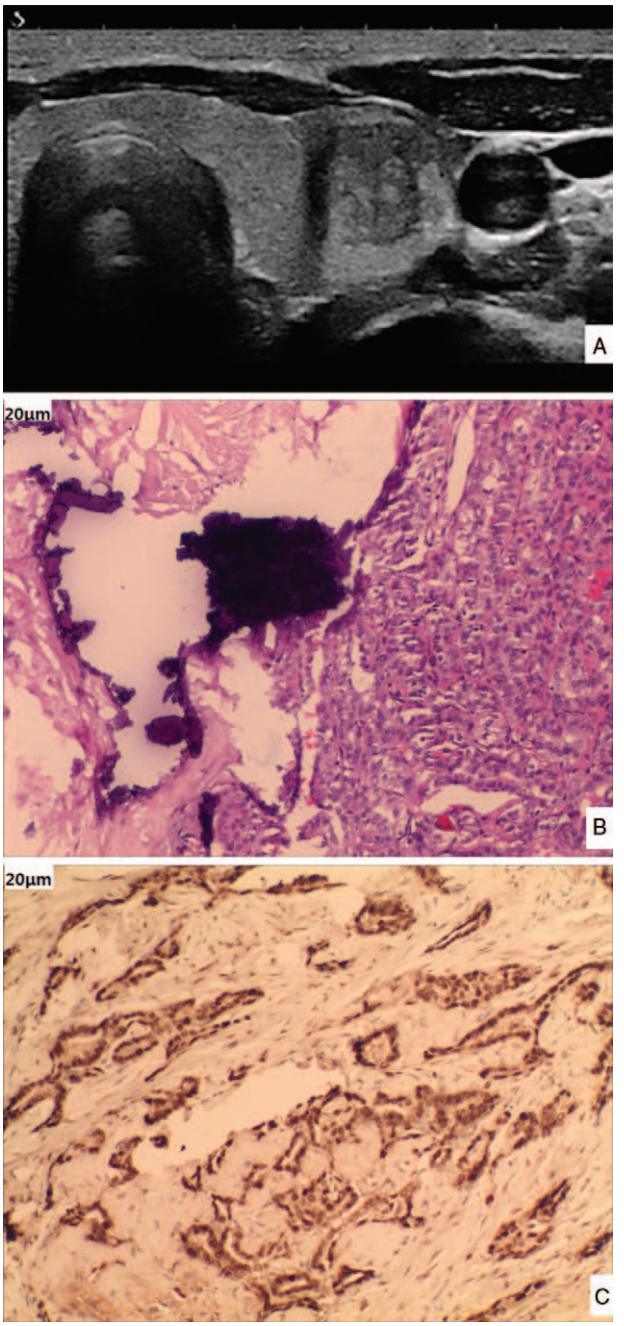

Figure 2. A 32-yr-old female patient has a papillary carcinoma at the left lobe of the thyroid gland. A is an ultrasonogram, which reveals that the nodule does not invade the capsule, the size is approximately 1.5 × 0.9 cm. B is the pathology (H& E, × 100), which reveals that focal calcification can be observed. C is bFGF × 100, the cytoplasm is strongly positive (+++) in papillary thyroid carcinomas and negative in the surrounding normal thyroid tissue.

4. Discussion

PTC is a type of tissue that has the best prognosis in malignant thyroid tumors; the 5-year survival rate is up to 97%.[8] However, invasive thyroid carcinoma increases the risk of the recurrence and metastasis of thyroid carcinomas. Therefore, an evaluation of PTC from multiple aspects is helpful in assessing the prognosis and guiding postoperative follow-ups and subsequent treatments.

Studies have revealed that bFGF was strongly expressed in human PTC and mainly presented in the cytoplasm of cancer cells.[9] The positive expression rate of bFGF in thyroid carcinoma tissues was significantly higher than in adjacent normal thyroid tissues. The result suggested that bFGF expression was correlated to the malignant behavior of thyroid carcinomas.[10] The results of the present study revealed that the difference in the expression of bFGF between the benign and

Table 4

The correlation between local invasiveness and ultrasound findings in 224 patients with papillary thyroid carcinomas (patients, %).

Ultrasound manifestation	Locally invasive		χ^2 value	*P* value
	Yes (%)	No (%)		
Maximum diameter				
≥0.5∼<1.0	51 (54.3)	108 (83.1)	22.581	<.001
≥1.0∼<2.0	36 (38.3)	20 (15.4)		
≥2.0∼≤3.0	7 (7.4)	2 (1.5)		
The location of lesions				
Left lobe	30 (31.9)	57 (43.8)	6.164	.046
Right lobe	48 (51.1)	63 (48.5)		
Isthmus	16 (17.0)	10 (7.7)		
Obscure boundary				
Yes	83 (88.3)	112 (86.2)	0.223	.691
No	11 (11.7)	18 (13.8)		
Internal echo				
Very low	75 (79.8)	108 (83.1)	0.395	.600
Low or other	19 (20.2)	22 (16.9)		
Aspect ratio >1				
Yes	52 (55.3)	70 (53.8)	0.048	.892
No	42 (44.7)	60 (46.2)		
Irregular				
Yes	60 (63.8)	53 (40.8)	11.605	.001
No	34 (36.2)	77 (59.2)		
Internal calcification				
Microcalcification	55 (58.5)	44 (33.8)	18.939	<.001
Crude calcification	8 (8.5)	5 (3.8)		
No	31 (33.0)	81 (62.3)		

Bfgf = basic fibroblast growth factor.

malignant groups was statistically significant. In the PTC group, patients with the percentage of bFGF-positive cells of >50% accounted for 69% of all patients, while in the benign lesions group, patients with the percentage of bFGF-positive cells of <50% accounted for 73% of all patients. The results of the study revealed that thyroid carcinomas were often accompanied by calcification and fibrosis. This may be 1 of the reasons for the significant difference in the bFGF expressions between benign and malignant thyroid lesions. BFGF is 1 of the polypeptide factors with a wide range of biological functions in the body, which can directly act on tumor cells to promote these cells to secrete various proteolytic enzymes and collagenases, thereby promoting tumor metastasis and infiltration. PTC reflects the correlation between bFGF expression and PTC metastasis that is different in the expression level of bFGF in metastatic and non-metastatic.[11] In the present study, in the cases of locally invasive PTC, the higher the positive expression level of bFGF, the more patients with a positive expression of bFGF. In the sample of patients that presented no evasion in the capsule, the number of positive expressions of bFGF was not significantly changed with the increase in positive expression levels. A previous report pointed out that the positive expression rate of bFGF was significantly higher in thyroid carcinomas than in normal thyroid glands, which was significantly higher in the undifferentiated carcinoma group than in papillary carcinoma group. The rate of bFGF was also significantly higher in metastatic papillary carcinomas than in non-metastatic patients.[12,13] High expression of bFGF can promote tumor metastasis. Therefore, bFGF detection can be used as an indicator for assessing the biological behavior and prognosis of thyroid carcinomas.[14]

In the present study, among the 224 PTC patients who met the inclusion criteria, the number of women was approximately 4 times that of the male participants, which was consistent with the epidemiological findings of thyroid carcinomas.[15] Furthermore, gender differences are not correlated to PTC local invasiveness. In the PTC group, the proportion of patients with invasive thyroid carcinomas was 57.8% in the over 50-year-old age group and only 35.6% in the under 50-year-old age group. This difference was statistically significant. Therefore, it is considered that PTC patients over 50 years old are more likely to develop aggressive carcinomas than those under 50 years old. Age is 1 of the key factors that have been closely related to the prognosis of thyroid carcinomas. Sharen G et al concluded in their retrospective analysis that,[16] in the population over 60 years old, although the detection rate of thyroid carcinomas was lower than that of young and middle-aged populations, its malignancy was higher and the prognosis was poorer than that of young and middle-aged patients with thyroid carcinomas.

Tumor size is a well-defined factor associated with the aggressiveness of thyroid carcinomas. The present study revealed that with the increase in the volume of the PTC nodule, the risk of local invasiveness in thyroid carcinomas increases. Falvo L. has reported that,[15] the nodule with a diameter of >1.5 cm indicates a poor prognosis. In the 224 PTC patients in the present study, the tumors in the isthmus in 16 patients (16/26, 61.5%) were invasive carcinomas; the difference was statistically significant compared to thyroid carcinomas in the bilateral lobes. The thyroid isthmus is located in front of the trachea and has a small space; the cancerous nodules break through the capsule and invade the surrounding tissues relatively easily. Even if the carcinoma in the thyroid isthmus is small, it can develop into an invasive carcinoma with lymph node metastasis. Therefore, special attention should be paid to malignant lesions occurring in the thyroid isthmus. It is also advisable to make use of a partial magnification function to explore its relationship with the adjacent capsule and the surrounding tissues.

Calcification has a certain correlation with thyroid carcinomas. The malignant risk of thyroid nodules with calcification is as high as 59.2%.[17] In addition, micro-calcification is closely correlated to PTC.[18] Therefore, as 1 of the typical ultrasound signs of thyroid carcinomas, micro-calcification is of great significance in the thyroid TI-RADS classification. Pathology suggests that the cause of micro-calcification in thyroid carcinomas may be as follows: active and disordered metabolism of malignant tumor cells, depositions of phosphate and other calcium salts in the intercellular substance,[19] and autocrine growth of tumor cells.[20] A previous study revealed that the presence of psammoma bodies revealed by pathology suggested a poor prognosis[21] and pathological psammoma bodies were micro-calcifications that were revealed by ultrasound. Bu Kyung Kim et al consider that[18] PTC with micro-calcifications revealed by ultrasound has more unfavorable pathological features than PTC without micro-calcification and the former is more invasive than the latter. This is in line with the results of the present study.

The regular shape of the ultrasound definition includes a circle; a quasi-circular shape, an ellipse, and a large and shallow lobular shape, shapes that are not in any particular form are also included in the irregular shapes. In the present study, sonograms of 224 patients with PTC were analyzed. Locally invasive PTC was more likely to present with an irregular shape than non-invasive PTC, which is consistent with the growth characteristics of malignant tumors. Generally, as the tumor volume continues to increase, the characteristics of the tumor invasive growth become more significant (edge burr sign or horn-shaped protrusions) and invasive growth makes the shape more irregular. Differences in other ultrasound features of PTC such as taller-than-wide shape, blurred boundaries, internal echo, and the posterior echo attenuation between the local invasive and non-invasive PTC groups were not statistically significant.

There are also some limitations in our study. Our sample size remains limited, and the sample size needs to be expanded for further confirmation. Herein, bFGF is the target of this study, but whether other indicators can play a role in the identification of PTC remains to be further studied. In addition, whether these indicators can indicate the prognosis also needs more investigation. There are still shortcomings in the quantitative aspects of diagnosis of ultrasound. In the future study, quantitative tools and methods will be applied in the evaluation of PTC.

As the most commonly used imaging method in the diagnosis and screening of thyroid carcinomas, ultrasound can be used to preliminarily predict the invasiveness of PTC before surgery. When the nodule has a diameter of ≥1 cm, internal calcification, and an irregular shape or is located in the isthmus, the lesion is predicted to have a relatively high risk of invasiveness. The detection of bFGF expression in postoperative specimens can further evaluate the invasiveness of PTC, which indicates its risk and provides a better evaluation of diagnosis and identification.In the future study, the sample size will be expanded to further explore the value of bFGF in the risk assessment of thyroid cancer.

Author contributions

Jia was responsible for collecting cases, data analysis and writing articles; Wu Xiulan is responsible for the collection case, case follow-up; Zhang Yinhua was responsible for pathological film reading and molecular detection; Ma Binlin negative surgical assessment of thyroid cancer; Ma Fucheng is responsible for project guidance, quality control and article writing.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

[2] Yang L, Zheng RS, Wang N, et al. Analysis of incidence and mortality of thyroid cancer in China, 2013. Zhonghua Zhong Liu Za Zhi 2017; 39:862–7.

[3] Lee KL, Chen TJ, Won GS, et al. The use of fine needle aspiration and trends in incidence of thyroid cancer in Taiwan. J Chin Med Assoc 2018;81:164–9.

[4] Lee SH, Roh JL, Gong G, et al. Risk factors for recurrence after treatment of N1b papillary thyroid carcinoma. Ann Surg 2019;269: 966–71.

[5] Hamzany Y, Soudry E, Strenov Y, et al. Early death from papillary thyroid carcinoma. Am J Otolaryngol 2012;33:104–8.

[6] Daa T, Kodama M, Kashima K, et al. Identification of basic fibroblast growth factor in papillary carcinoma of the thyroid. Acta Pathol Jpn 1993;43:582–9.

[7] Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules:a step in establishing better stratification of cancer risk. Radiology 2011;260:892–9.

[8] Song H, Mosci C, Akatsu H, et al. Diagnostic 123I whole body scan prior to ablation of thyroid remnant in patients with papillary thyroid cancer. Clin Nucl Med 2018;43:705–9.

[9] Liang H, Zhong Y, Luo Z, et al. Assessment of biomarkers for clinical diagnosis of papillary thyroid carcinoma with distant metastasis. Int J Biol Markers 2010;25:38–45.

[10] Tian XF, Zhang XW, Chen RX, et al. Clinical significance of expression of VEGF and bFGF in thyroid carcinoma. Chinese Journal of Surgery 2004;42:864–6.

[11] de Araujo-Filho VJ1, Alves VA, de Castro IV, et al. Vascular endothelial growth factor expressionin invasive papillary thyroid carcinoma. Thyroid 2009;19:1233–7.

[12] Zhao WX, Yang YH, Chen DL. Expression of basic fibroblast growth factor and fibroblast growth factor receptor Relate to Invasion and Metastases in Thyroid Carcinoma. Journal of Fujian Medical University 2002;36:286–9.

[13] Tian XF, Zhang XW, Chen RX, et al. Clinical significance of exoression of bFGF in thyroid carcinoma. Chinese Journal of Laboratory Diagnosis 2004;8:246–7.

[14] Sebag F, Vaillant-Lombard J, Berbis J, et al. Shear wave elastography: a new ultrasound imaging mode for the differential diagnosis of benign and malignant thyroid nodules. J Clin Endocrinol Metab 2010;95:5281–8.

[15] Falvo L, Catania A, D'Andrea V, et al. Prognostic importance of histologic vascular invasion in papillary thyroid carcinoma. Ann Surg 2005;241:640–6.

[16] Sharen G, Zhang B, Zhao R, et al. Retrospective epidemiological study of thyroid nodules by ultrasound in asymptomatic subjects. Chin Med J (Engl) 2014;127:1661–5.

[17] Khoo ML, Asa SL, Witterick IJ, et al. Thyroid calcification and its association with thyroid carcinoma. Head Neck 2002;24:651–5.

[18] Kim BK, Lee EM, Kim JH, et al. Relationship between ultrasonographic and pathologic calcification patterns in papillary thyroid cancer. Medicine (Baltimore) 2018;97:e12675.

[19] Xiao X, Li L. The significance of thyroid calcification for diagnosis of thyroid carcinoma. Chinese Journal of Current Advances in General Surgery 2017;20:897–9.

[20] Das DK, Sheikh ZA, George SS, et al. Papillary thyroid carcinoma: evidence for intracytoplasmic formation of precursor substance for calcification and its release from wellpreserved neoplastic cells. Diagn Cytopathol 2008;36:809–12.

[21] Cai YF, Wang QX, Ni CJ, et al. The clinical relevance of psammoma body and Hashimoto thyroiditis in papillary thyroid carcinoma: a large case-control study. Medicine (Baltimore) 2015;94:e1881.