Cancer Management and Research

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ORIGINAL RESEARCH

High Risk Thyroid Nodule Discrimination and Management by Modified TI-RADS

This article was published in the following Dove Press journal:
Cancer Management and Research

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Objective: Thyroid cancer is the most common primary malignant disorder of the thyroid. We aimed to illustrate the modified TI-RADS report system for differentiating malignant thyroid nodules from benign ones, and especially its role in the management of high risk nodules.

Methods: In this retrospective study, 5,162 healthy individuals who underwent thyroid ultrasound according to modified TI-RADS from January 2014 to December 2014 were enrolled and followed up during the whole 5 years, and the medical data were investigated and reviewed.

Results: The total detection rate of thyroid nodules was 39.40%. The total detection rate of thyroid cancer was 0.66%. Most thyroid cancers were single-shot, located at unilateral, at early clinical stages, without lymph node metastases, and with low recurrence risk. All patients had thyroid papillary carcinoma, except one thyroid medullary carcinoma. Based on modified TI-RADS classification, at the end of 5 years follow-up, more changes of thyroid nodules grade status were observed in grades 4a and above. The higher the grade status, the more malignant advances were occurred. The modified TI-RADS report system played an instructional role in adding medical treatment choice and decision for clinicians.

Conclusion: The modified TI-RADS report system plays an important role in thyroid benign and malignant nodule identification and management.

Keywords: thyroid cancer, thyroid nodules, high-risk nodules, thyroid ultrasound, TI-RADS report system

Introduction

Although thyroid nodule is the first thyroid sign of thyroid cancer, only 7–15% of the nodules are malignant, while most of them are benign. Hence, the primary goal in thyroid cancer diagnosis is to distinguish the malignant lesions from the benign ones.[1] For the advantages such as non-invasive technique, high sensitivity, ease of operation, good repeatability, and so on, ultrasonography is the first-line imaging modality for thyroid nodule detection, because it is non-invasive, highly sensitive, and repeatable.

In the late 2000s, the concept of Thyroid Imaging Reporting and Data System (TI-RADS), based on a quantitative scoring system, was introduced, and its format has been evolving and developing constantly.[2] Currently, the three widely recognized quantitative scoring systems are the American College of Radiology (ACR) TI-RADS, the Korean Society of Thyroid Radiology (KSThR) TI-RADS, and the American Thyroid Association (ATA) TI-RADS. In view of their critical role in thyroid nodule management, more improved TI-RADSs have emerged.[3,4] The

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http://doi.org/10.2147/CMAR.S284370

modified TI-RADS based on the ACR TI-RADS scoring system was sponsored by Wang et al.[5] The modified TI-RADS was composed of seven ultrasound features in identifying benign and malignant thyroid nodules, such as the nodular texture, nodular echo type, morphology, border, calcification, blood flow signal, and lymph node metastasis.

For most clinical management of malignant tumors, early detection, timely monitoring, and scientific treatment are crucial to improve the prognosis and reduce mortality. However, overdiagnosis of micro and favorable prognosis thyroid cancers are of no benefit of the patients and the society, but this is not true for advanced stage thyroid cancers as well as poor prognosis pathological types.[6,7] In China, more scholars still insist that the incidence and mortality of thyroid cancer have increased.[8] Though general population based screening of thyroid cancer is not recommended, distinction of malignant thyroid nodules from benign ones and reasonable management of high-risk thyroid nodules remain key problems which need to be resolved. Concerning the identified high-malignant risk nodules, there are still several problems that need to be explored, such as how to carry out scientific hierarchical management, how to avoid over-treatment, how to avoid delayed treatment, and how to choose the best treatment time window.

In this study, we aimed to assess the value of a modified TI-RADS report system in thyroid benign and malignant nodules distinguishment and malignant nodules and high malignant risk thyroid nodules management. Fortunately, it may also provide reliable data for high-risk thyroid nodule management.

Patients and Methods

Patients

In this retrospective study, a total of 5,196 participants, who provided informed consent and underwent thyroid ultrasound detection in the Department of Cancer Prevention Center in Tianjin Medical University Cancer Institute and Hospital from January to December 2014, were investigated in the next 5-year follow-up. The inclusive criteria were: a) underwent the thyroid gland examination by ultrasound technology; b) repeated the two aforementioned examinations at least once each year during the 5-year follow-up period except or until they had surgical treatment; c) all data on thyroid gland examination, surgical treatment, and pathology diagnosis were available; and d) no previous history of thyroid cancer or surgery treatment. Finally, 5,162 individuals were enrolled in this study with the loss rate of 0.65% (34/5196). The exclusive criteria were lost to follow-up due to death or other reasons. This research project was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital. All patients provided informed consent to participate in this study and publish the images in this submission. Written consent was obtained from each patient.

Modified TI-RADS Report System

Thyroid gland nodules status was detected by ultrasound equipment Philips iU22 and reported based on modified TI-RADS by physicians with the qualifications of the attending physician or advanced. Modified TI-RADS graded general thyroid gland pathology as 0–6 according to the risk of thyroid cancer from low to high. In grades 0–3, the malignant risk of thyroid nodules is extremely low, less than 5%; while the malignant risk of thyroid nodules in grade 4 and above increases sharply, and the final risk is 100%, because thyroid nodules in grade 6 are all pathologically confirmed thyroid cancer. For patients with thyroid nodules at different risk grades, clinicians give different medical management or were advised no attention, medical observation, regular follow-up visits with different frequencies, and even surgical operations. The detailed malignant risk grades and medical suggestion were as shown in Table 1.

In the modified TI-RADS, the evaluation criteria were nodular texture, nodular echo type, morphology, border, calcification, blood flow signal, and lymph node metastasis status. ACR TI-RADS Grade 4, where the benign and malignant nodules can easily overlap, in this modified TI-RADS, was further divided into grade 4a, 4b, and 4c, as shown in Figure 1. In each patient with more than one nodule, only the highest grade of nodules was registered and monitored.[5]

Thyroid Cancer Risk Classification

To assessment the value of modified TI-RADS in thyroid cancer diagnosis and identification of benign and malignant nodules, we divided the individuals into two groups as the low risk group and high risk group based on the risk of thyroid cancer. According to the modified TI-RADS, individuals with thyroid nodules graded 1–3 were identified as the low-risk group of thyroid cancer, while individuals graded 4a–6 were identified as the high-risk group of

Table 1 Malignant Risk of Thyroid Nodules Reported by Modified TI-RADS and Corresponding Medical Suggestion

Grade	Malignant Risk	Medical Suggestion
0	No abnormalities in ultrasound in clinically suspected cases, including additional examinations, such as for thyroiditis	No medical treatment needed
1	Normal thyroid or cystic nodules without further follow-up	Medical observation
2	Benign nodules with no obvious signs of malignancy	Re-inspection every 1–2 years
3	Nodules may be benign with malignancy risk less than or equal to 5%	Re-inspection every 6 months to 1 year, and seek medical attention once changed
4	Suspected malignancy requiring surgery or fine-needle aspiration biopsy before surgery	
4a	The proportion of malignancy is 6–45%	Re-inspection within 3–6 months or consult outpatient department of head and neck surgery
4b	The proportion of malignancy is 46–75%	Re-inspection within 3 months or to visit outpatient department of head and neck surgery
4c	The proportion of malignancy is 76–95%	Visit outpatient department of head and neck surgery
5	Malignant nodules with clear lymph node metastasis	Visit outpatient department of head and neck surgery and seek further treatment
6	Malignant nodules confirmed by biopsy pathology	Conventional medical care followed surgical treatment

thyroid cancer. During the 5-year follow-up, with the growth and changes of thyroid nodules, the TI-RADS grading also changed accordingly, and some nodules progressed from low-risk nodules to high-risk nodules. We registered the grading in the last follow-up as final grade.

Thyroid Cancer Diagnosis

According to the latest grade reported by modified TI-RADS and clinicians' suggestions, some patients received surgical treatment. After surgical resection, the samples were immediately fixed by paraformaldehyde and followed by paraffin sectioning and HE staining and observed under a microscope of 400×. Then, pathological diagnosis was made by two double-blinded qualified pathologists. Finally, the pathological diagnosis was the only criterion for thyroid cancer diagnosis. On the basis of pathological diagnosis, the size, number of lesions, peripheral invasion, and lymph node metastasis status were recorded.

Clinical Staging Criteria and Risk of Recurrence for Thyroid Cancer

The clinical staging of thyroid cancer patients depends on the patient's age, tumor size, degree of local invasion, lymph node metastasis, and distant metastasis. These were based on the American Joint Committee on Cancer (AJCC) seventh Edition (2017) thyroid cancer TNM staging and AJCC 8th edition differentiated thyroid cancer TNM staging criteria.[9] Risk of recurrence of thyroid papillary carcinoma was divided into three groups as low-risk, middle-risk, and high-risk groups, according to the stratification criteria for risk of recurrence of differentiated thyroid cancer.[10] Regarding the risk of recurrence of thyroid medullary carcinoma, as the high-risk recurrence was determined by its own pathological features, it was enrolled in the high-risk group.

Statistical Analysis

Statistical Package of the Social Sciences (SPSS) software version 20.0 was applied for statistical analysis of the recorded data. The continuous variables were analyzed by *t*-test, and the statistical significance was defined as $P<0.05$ (two sided). Univariate and multivariate logistic regression analyses were performed using the logistic regression model.

Results

Patient Characteristics

A total of 5,162 individuals were enrolled in this study, of which 2,638 were males and 2,524 females. Their ages ranged from 20–80 years, with the median age being 48 years.

Thyroid Nodule and Thyroid Cancer Detection Rate

Based on modified TI-RADS classification of thyroid ultrasound, the detection rate of thyroid nodules was 39.40% (2,034/5,162) and of high-risk nodules was 1.43% (74/5,162). At the end of the 5-year follow-up, 34 cases of thyroid cancer were diagnosed, and the total detection rate of thyroid cancer was 0.66% (34/5,162) individuals in Table 2.

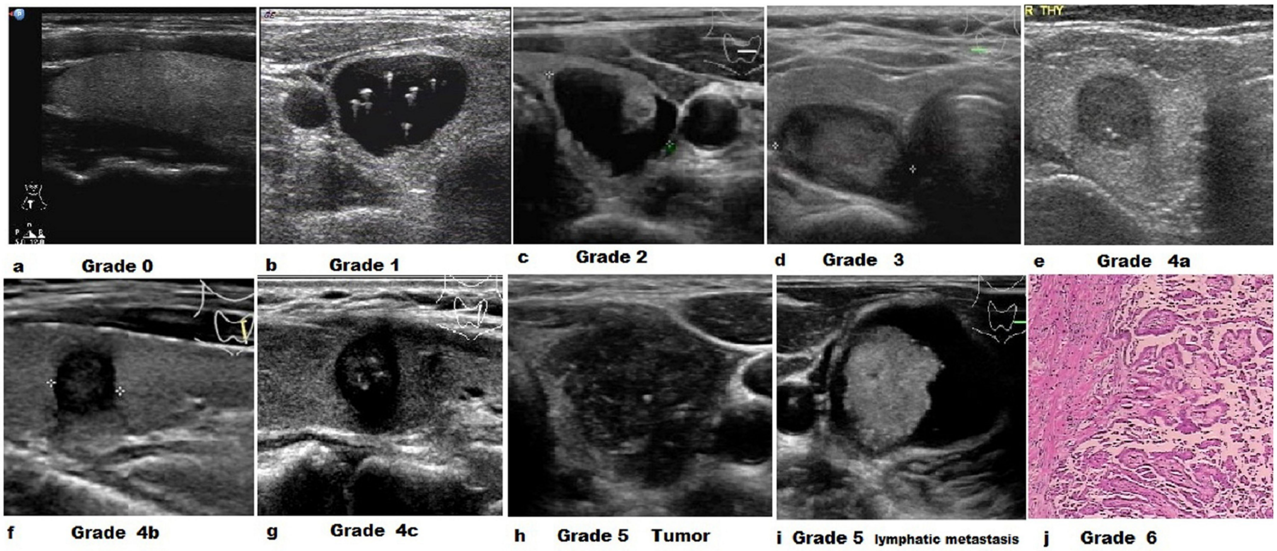

Figure 1 The classification standard for modified TI-RADS system. (**A**) Grade 0 by improved TI-RADS system; (**B**) Grade 1 by improved TI-RADS system; (**C**), Grade 2 by improved TI-RADS system; (**D**) Grade 3 by improved TI-RADS system; (**E**) Grade 4a by improved TI-RADS system; (**F**) Grade 4b by improved TI-RADS system; (**G**) Grade 4c by improved TI-RADS system; (**H**) Thyroid nodules, Grade 5 by improved TI-RADS system; (**I** and **H**) Lymphatic metastasis, Grade 5 by improved TI-RADS system; (**J**) Thyroid papillary cancer under microscope by 400×, Grade 6 by improved TI-RADS system.

Clinical Characteristics of the Thyroid Cancer Patients

During the 5-year follow-up, 29 (of 74) individuals with high-risk nodules and five (of 1,960) individuals with low-risk nodules voluntarily received gradual surgical treatment. Most of the nodules were single-shot, without lymph node metastases, at early clinical stages, and in the low-risk group. Thirty-three cases were thyroid papillary carcinoma and only one case was thyroid medullary carcinoma, as shown in Table 3.

Table 2 Incidence of Thyroid Nodules and Detection Rate of Thyroid Cancer Between Males and Females

Item	Male	Female	Total	χ^2	*P*
Thyroid nodules				52.750	*0.000
Negative	1,726	1,402	3,128		
Positive	912	1,122	2,034		
Detection rate (%)	34.57	44.45	39.4		
High risk nodules					
Negative	2603	2485	5088	0.435	0.559
Positive	35	39	74		
Detection rate (%)	1.33	1.55	1.43		
Thyroid cancer				0.224	0.731
Negative	2,622	2,506	5,131		
Positive	16	18	34		
Detection rate (%)	0.61	0.71	0.66		
Total	2,638	2,524	5,162		

Note: *P<0.05 is statistically significant.

Effect of Age on Thyroid Nodules Incidence and Thyroid Cancer Incidence

To describe the effect of age on thyroid nodules and thyroid cancer, 5,162 patients were teamed as age. As the results show, the incidence of both thyroid nodules and high risk nodules gradually increased with age (Figure 2A and B). This demonstrated that thyroid cancer patients are mainly concentrated in the 30–39 and 50–59 year olds, there was no obvious found distribution rule (Figure 2C). It is difficult to evaluate the relationship between thyroid cancer and age due to small samples size. But we still found that the high risk nodules incidences were also increased as age (Figure 2B). Next, the ages of the high risk group patients (54.29±14.54 years old) was higher than the low risk group patients (46.24 ±13.74 years old) (P<0.001) (Figure 2D). In the high risk group, the age of the patients undefined pathological diagnosis (60.27±13.20 years old) was higher than the patients with defined pathological diagnosis (45.81±12.03 years old), there was statistically significance (P<0.001) (Figure 2E).

Diagnosed Thyroid Cancer in Different Grades Reported by Modified TI-RADS

Based on the final preoperative grading of patients with thyroid cancer, the diagnostic ability of modified TI-RADS for thyroid cancer was evaluated by comparing

Table 3 Clinical Characteristics of the Thyroid Cancer Patients

Clinical Characteristics	**n**
Items	
Gender	
Male	16
Female	18
Age (Mean±SD years old)	45.81±12.03
Tumor Character	
Size	
≤1	27
>1 and ≤2	7
Number	
Single	28
Multiple	6
Location	
Unilateral	28
Bilateral	6
Pathological type	
Papillary carcinoma	33
Medullary carcinoma	1
Lymph node metastasis	
No	20
Yes	14
N1a	10
N1b	4
Clinical stage	
I	29
III	4
IVa	1
Risk of recurrence	
Low risk group	18
Middle risk group	13
High risk group	2
Modified TI-RADS Before surgical Treatment	
3	5
4a	14
4b	7
4c	6
5	2
Surgical time distribution	
1st year follow-up	18
2nd year follow-up	5
3nd year follow-up	8
4th year follow-up	2
5th year follow-up	1

the diagnosed thyroid cancer percentages in each of the risk grades. Grade 0 represents healthy or with no signs of thyroid cancer, and grade 6 represents a postoperative patient who has been diagnosed, so these two grades are no longer to be compared. There were no diagnosed thyroid cancer cases in Grade 0 to Grade 2, there were five (of 102) diagnosed cases in Grade 3, 14 (of 52) cases in Grade 4a, seven (of nine) cases in Grade 4b, six (of six) cases in Grade 4c, and two (of two) cases in Grade 5 in order. Figure 2F shows that the diagnosis percentages of Grade 0–3 thyroid cancer were relatively lower, science Grade 4 to Grade 5, thyroid cancer diagnosis percentages were gradually increased, including the sub-grades of Grade 4. The diagnosis of thyroid cancer percentages increased with the risk classification by modified TI-RADS; the higher the grade the higher the malignant risk.

The Dynamic Alterations of TI-RADS Grades for Thyroid Nodules

During the 5-year follow-up, along with growth of thyroid nodules themselves, the modified TI-RADS classification status was also changed. From a holistic perspective, in the low risk nodules group, the individuals' proportion was unchanged in Grade 1, decreased by 0.13% (2/1514) in Grade 2, and decreased by 4.00% (4/100) in Grade 3, in the high risk nodules group, individuals' proportion decreased by 20.83% (10/48) in Grade 4a, decreased by 86.67% (13/15) in Grade 4b, and decreased by 100% (5/5) in Grade 4c, was unchanged in Grade 5, and increased in 34 cases in Grade 6, as shown in Table 4. From an individual perspective, the individuals' thyroid nodules grade status was unchanged in Grade 1; however, the nodules' grades enhanced to higher or declined to lower by one or more grades in Grades 2–6 as follows: decreased by 0.26% (4/1514) and increased by 0.13% (2/1514) in Grade 2, decreased by 6% (6/100) and increased by 2% (2/100) in Grade 3, decreased by 39.58% (19/48) and increased by 4.17% (2/48) in Grade 4a, decreased by 60.00% (9/15) and increased by 13.33% (2/15) in Grade 4b, decreased by 160% (8/5) and increased by 60% (3/5) in Grade 4c, decreased in two cases and increased in five cases in Grade 5 and 34 cases of thyroid cancer patients in Grade 6, as showned in Table 5. All together, as times went by, changes frequency decreased year by year, with a decrease of 93.75% (45/48) of nodules that

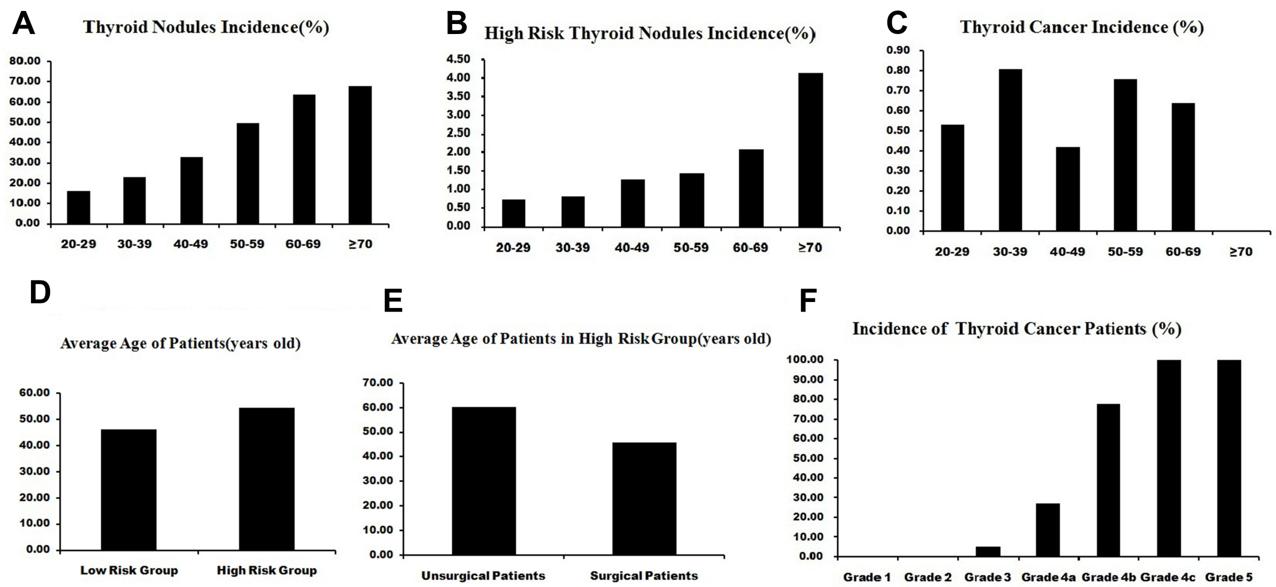

Figure 2 The incidence of thyroid nodules and thyroid cancer among patients (**A**) incidence of thyroid nodules among different age teams; (**B**) incidence of high risk nodules among different age teams; (**C**) incidence of diagnosed thyroid cancer among different age teams; (**D**) thyroid cancer incidence in each grade by the modified TI-RADS; (**E**) comparison with the average ages between the low risk group and the high risk group (*P*<0.001); and (**F**) comparison with the average age between undiagnosed and diagnosed thyroid cancer patients in the high risk group (*P*<0.001).

advanced from lower grade to higher grader and the remaining 6.25% (3/48) improving from higher grade to lower grade; more frequent changes were observed in high-risk nodules than low-risk nodules.

Discussion

Under the dual background of global increasing and over-diagnosis and treatment of thyroid cancer, early diagnosis of thyroid cancer, differentiation of benign and malignant nodules, and management of high-risk nodules are important issues of cancer prevention and treatment. In this study, we found that the modified TI-RADS played an important role in the identification of benign and malignant nodules, monitoring of high-risk nodules, and clinical treatment decision-making.

Table 4 Thyroid Nodules Detection by Ultrasonography Reported by Modified TI-RADS System During the 5-year Follow-Up

Modified TI-RADS Grades	Initial Diagnosis	1st Year	2nd Year	3rd Year	4th Year	5th Year
0	3,128	3,128	3,128	3,128	3,128	3,128
1	352	352	352	352	352	352
2	1,514	1,513	1,513	1,513	1,512	1,512
3	100	95	96	96	96	96
4						
4a	48	42	41	39	39	38
4b	15	12	8	3	2	2
4c	5	1	0	0	0	0
5	0	1	1	0	0	0
6*	0	18	23	31	33	34

Note: *Grade 6: Malignant nodules confirmed by biopsy pathology.

The incidence of thyroid cancer is globally prevalent, such as in South Korea, France, Italy, Canada, and the US.[11,12] Although China does not rank first, the incidence of thyroid cancer has been increasing in recent years.[13,14] However, this may be mainly caused by the application of ultrasound technology in thyroid cancer screening, which is controversial and not recommended internationally.[15] Regardless of thyroid cancer screening, it neesd to be discussed early what we should do about high risk thyroid nodules detected intentionally or unintentionally, should we just ignore them, manage them normatively, or carry out surgical treatment and other effective treatments actively? Hence, to answer these questions, there are still lots of clinical studies to do, and scientific management of high risk thyroid nodules deserves further study.

The concept of TI-RADS was introduced in the late 2000s, and the three main TI-RADS grading systems included ACR TI-RADS, ATA TI-RADS, and KSThR TI-RADS, followed by a variety of similar and derived TI-RADSs.[2,3] Among them, ACR TI-RADS has shown good agreement with FNA and is recommended for clinical

Table 5 Thyroid Nodules Changes with Modified TI-RADS Grades During the 5 Year Follow-Up

Follow-Up Time	Modified TI-RADS Grades	n
1st year		
	2 to 3	1
	2 to 4a	2
	3 to 2	1
	3 to 6*	5
	4a to 2	1
	4a to 4b	1
	4a to 4c	1
	4a to 6*	5
	4b to 4c	1
	4b to 6*	3
	4c to 5	1
	4c to 6*	5
2nd year		
	2 to 3	1
	4a to 2	1
	4a to 4b	1
	4b to 4c	1
	4b to 6*	3
	4c to 5	1
	4c to 6*	1
	5 to 6*	1
3rd year		
	4a to 6*	7
	5 to 6*	1
4th year		
	4a to 6*	1
	4b to 6*	1
5th year		
	4a to 6*	1

Notes: *Grade 6: Malignant nodules confirmed by biopsy pathology.

diagnosis of benign and malignant thyroid nodules.[16] As the TI-RADSs could facilitate the effective interpretation and communication of thyroid ultrasonography findings among referring physicians, cytopathologists, and even the managers in charge of thyroid nodule management, so more focus has been exercised on the improvement of TI-RADSs to utilize them in clinical practice.[17] In this study, modified TI-RADS by Wang et al[5] based on ACR TI-RADS was used for identification of benign and malignant thyroid nodules. ACR TI-RADS Grade 4, where the benign and malignant nodules can easily overlap, was further divided into Grade 4a, Grade 4b, and Grade 4c, according to the malignancy evaluation signals, including nodular texture, nodular echo type, morphology, border, calcification, blood flow signal, and lymph node metastasis. Modified TI-RADS grades classification criteria, details and corresponding medical suggestion were described above in Table 1 and Figure 1 and certified by our research data.

According to our data, the total detection rate of thyroid cancer in individuals who underwent physical examination was 600.54 per 100,000 at the end of the 5-year follow-up in Table 2. When it comes to the highest incidence of thyroid cancer in South Korea, this detection rate is staggering. Hence, the incidence and mortality of thyroid cancer is bound to cause our concern. In our opinion, Tianjin was an iodine-rich city of China, being adjacent to the Bohai Sea, so that the special geographical conditions might have increased the risk of thyroid cancer. Therefore, the identification and scientific management of high-risk nodules are indispensable parts of thyroid cancer prevention and treatment.

The incidence of thyroid nodules gradually increased with age. Thyroid cancer patients are mainly concentrated in the 30–39 years old team and 50–59 years old team. There was no obvious found distribution rules, so further analysis were done to explain it in Figure 2. First, we found that the high risk nodules incidence were increased as age, and at the same time, high risk group patients was older than the low risk group patients ($P<0.001$), it seems that more and more high risk nodules were distributed among younger patients. Second, not all of the high risk patients accepted surgical treatment and pathology diagnosis, the surgical patients were younger than the nonsurgical patients ($P<0.001$), more younger patients with high risk nodules preferred to choose surgical treatment, and most older patients with high risk nodules rejected surgical treatment and lacked a pathology diagnosis.

As the results showed in Table 3, most of the diagnosed thyroid cancers were papillary thyroid carcinoma, single-shot, located unilaterally in the thyroid glands, without lymph node metastases, at early clinical stages, and in the low-risk group. We diagnosed most thyroid cancers at an early stage. Nearly all of them were well-differentiated papillary thyroid carcinoma, except one patient with medullary thyroid carcinoma. As we known, there are four main types of primary thyroid cancer: papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and undifferentiated thyroid carcinoma and their subtypes. Additionally, there are other types of malignant thyroid tumors, including primary and secondary thyroid lymphoma and metastatic cancer. Pathological classification of thyroid cancer and clinical staging at the time of consultation are the most important factors affecting the prognosis of thyroid cancer patients. Due to the limitations of ultrasonography and modified TI-RADS, we cannot predict thyroid cancer pathology types, we cannot distinguish whether they were well-differentiated, poorly differentiated, or undifferentiated. However, we can through the modified TI-RADS dynamic monitoring high-risk nodules risk level changes, growth speed, lymph node metastasis, and the peripheral tissues invasion, etc. On this basis, we can initially determine the clinical stage of patients, so clinicians can formulate a diagnosis and treatment plan according to the patient's age, health, medicine resource allocation through scientific and rational management of high-risk nodules to maximize patient survival benefit.

As the results show in Figure 2F, modified TI-RADS grading system is a reliable predictor of thyroid cancer risk. The higher the grade, the higher the percentage of thyroid cancer diagnosed. In addition, in the intensive part of modification compared to ACR TI-RADS in Grade 4, the diagnosis rate of thyroid cancer increased gradually among Grade 4a, Grade 4b, and Grade 4c, which further demonstrated the feasibility and reliability of the improvement. Compared with the traditional ACR TI-RADS, the modified TI-RADS can provide stronger support for clinicians' treatment decisions and enable patients to benefit more.

The most important core of high risk nodules management is to seek a reliable mean for dynamic monitoring. In this study, the dynamic monitoring of high risk thyroid nodules was carried out by ultrasound and reported by modified TI-RADS. During the 5-year follow-up, modified TI-RADS played a critical role in thyroid nodules risk reassessment and clinicians treatment choices. As the results showed in Tables 4 and 5, we found that constant growth of thyroid nodules themselves affected the risk characters status, the risk grades of nodules also changed correspondingly. Compared to the low risk group, the frequency of changes was higher in high risk nodules group. As times went by, changes in frequency decreased year by year, most of the nodules advance from lower grade to higher grader and less of them get better from higher grade to lower grade, most of the risk nodules advanced and were finally diagnosed as thyroid cancers. Therefore, it was necessary to monitor nodules changes, especially with high risk and medical suggestions at just way. Generally, for nodules in the low-risk group, we suggested observation or routine review without excessive concern. However, for the high-risk nodules, with the increase of risk level, the time for reexamination is constantly shortened. Patients in Grade 4a and Grade 4b were more concerned and monitored closely. Patients in Grade 4c and Grade 5 were even decisively recommended surgical treatment. However, it is necessary to make a balance according to patients' individual intention, age, physical condition, risk aversion, and benefit, so as to make patients get the maximum benefit.

Therefore, we insisted that thyroid nodules of Grade 0–3 are in a low risk group of thyroid cancer, while nodules of Grade 4–6 are in a high risk group of thyroid cancer; additionally, the latter group should be focused upon during thyroid nodule management according to the risk-degree instructing specific monitoring frequency and treatment scheme. We suggested that nodules of Grade 4a and 4b could still be benign and need closer monitoring. However, nodules of Grade 4c or 5 are more likely to be malignant and accompanied with lymph node metastasis, so they needmore clinical attention and relatively early treatment. Modified TI-RADS further refines the stratification of ACR TI-RADS Grade 4, where the benign and malignant nodules can easily overlap, which has an impact on clinical treatment.

The only diagnosed medullary thyroid carcinoma was in Grade 3 as the modified TI-RADS, it is just the rapidly growth aroused our attention during follow-up. Therefore, dynamic change itself may be another important factor. Since the modified TI-RADS is still a static descriptive system, rapid growth, an important malignant feature, needs to be dynamically monitored. The condition of rapid growth can be included in the classification standard by comparing the size between the nearest two times. In the future, the modified TI-RADS may need more improvement and supplement. In this study, our results could not completely elucidate the viewpoint. Hence, more modifications of the TI-RADS status of high-risk nodules are needed in the future, which is the large sample size and multi-center research.

Among the various available methods of thyroid cancer diagnosis, ultrasound diagnosis is recognized as the first method, which is superior to CT, MRI, etc. In clinical work, thyroid clinical palpation is the most economical and practical method, but it is largely limited by the size of thyroid nodules, especially for nodules below 1.0 cm in diameter, so its detection rate is extremely low in health examination individuals with micro-nodules. Similarly, fine needle aspiration cytology diagnosis (FNAC) is also limited by the size of nodules. When applied in micro-nodules, it will increase the risk of puncture failure, the incidence of complications, and a false negative rate in thyroid cancer diagnosis.

In addition, in the era of molecular diagnostics, we strive for molecular diagnostic indicators for thyroid cancer. At present, there are a variety of diagnostic molecular markers, such as RET-PTC, RAS, and BRAF (V600E) mutations, Galectin 3, and so on.[18] These novel molecular-based management strategies for thyroid nodules and thyroid cancer are the most exciting developments in this unprecedented era of molecular thyroid-cancer medicine. So, in the future, we consider choosing appropriate molecular markers for inclusion in our guidelines.

In our study, modified TI-RADS played a critical role in high-risk thyroid nodule identification, monitoring, and management. It facilitated the refinement and improvement of ACR TI-RADS diagnostic criteria, improvement of the diagnostic level of thyroid cancer, better management of high-risk nodules, and works well on thyroid cancer prevention.

Conclusions

The incidence of thyroid nodules and thyroid cancer is high and may be expected to increase in the future in China and especially in Tianjin, which is an iodine-rich city. The ultrasound technology including its modified TI-RADS report, which has the advantages of reproducibility, non-invasiveness, and high specificity and preciseness of modified TI-RADS, plays a crucial role in the identification, monitoring, and follow-up of high risk thyroid nodules.

At present, there is no uniform standard for TI-RADS in the diagnosis and treatment of thyroid cancer, which is the biggest limitation in its application worldwide. The TI-RADS used in our study, which is based on the current ACR TI-RADS, is modified depending on the clinical experience in thyroid cancer diagnosis enrolled related tumor indexes. With the wide application of modified TI-RADS, more data will be supplemented. We believe that in the near future, there will be a unified standard both in China and around the world, which will have a considerable clinical value.

Data Sharing Statement

All data generated or analysed during this study are included in this article. All the data during the current study are available from the corresponding authors Menghui Li and Juntian Liu on reasonable request.

Ethics Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Tianjin Cancer Institute and Hospital research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. And all patients had provided informed consent to participate in this study and publish their pathological and ultrasonography images as represented figures.

Consent for Publication

All the individuals have signed the informed consent and were committed to testing samples and results which could be used in nonprofit medical research without disclosing any information related to the identity of the subject.

Acknowledgments

Thanks to all the colleagues in the cancer prevent department of Tianjin Medical University Cancer Institute and Hospital in the process of the project.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; Menghui Li took part in drafting; Lijuan Wei and Fangxuan Li took part in revising; Yanyan Kan, Xiaofeng Liang, and Huan Zhang took part in critically reviewing the article; Juntian Liu gave final approval of the version to be published; all the authors have agreed on the journal to which the article has been submitted; and all the authors agree to be accountable for all aspects of the work. All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This work in the Department of Cancer Prevent Center is partially funded by grants from National Natural Science Foundation of China (81502309 and 81602926).

Disclosure

The authors report no conflicts of interest for this work.

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