

Fine-Needle Aspiration (FNA) Biopsy For Thyroid Nodules: Double-Edged Sword in Thyroid Cancer Treatment in China

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Abstract

Background: To compare the necessity between Fine-needle aspiration (FNA) biopsy and ultrasound examination in the diagnosis of different sizes of the thyroid nodules. Does the FNA biopsy have to do it all?

Methods: A retrospective analysis was performed to 8352 thyroid patients who underwent thyroid operations between 2011 and 2016 in our hospital.

Results: In FNA(+) group, the nodule was more smaller, the increment speed of the amount of operation increased more faster. In no FNA group, the increment speed decreased not obvious in nodules ≥ 10 mm sub-group, but tremendous in both nodules 5mm-10mm sub-group and nodules ≤ 5 mm sub-group no matter the nodules were malignant or benign. Over the six years, the total operation number increased, but operation of patients with nodules ≥ 10 mm decreased slightly and operation of patients with nodules < 10 mm increased markedly especially in nodules ≤ 5 mm sub-group. In no FNA group, to compare the malignancy or benign tumor after surgery between nodules 5mm-10mm sub-group and nodules ≥ 10 mm sub-group, $\chi^2=12.000$, $P=0.001$, and between nodules ≤ 5 mm sub-group and nodules ≥ 10 mm sub-group, $\chi^2=7.968$, $P=0.005$, but between nodules 5mm-10mm sub-group and nodules ≤ 5 mm sub-group, $\chi^2=0.669$, $P=0.414$. Further pairwise comparison showed, in nodules 5mm-10mm sub-group and nodules ≤ 5 mm sub-group, the probability of benign tumor was greater than nodules ≥ 10 mm sub-group.

Conclusions: In thyroid nodules ≥ 10 mm sub-group, there is no statistical difference between ultrasound diagnosis and biopsy. In nodules < 10 mm sub-groups, FNA biopsy has the great significance in the diagnosis to add more references for the subsequent treatment.

Background

At the beginning of the article, I will show you a small-scale survey questionnaire of 18 individuals among our colleagues including doctors and nurses. Question 1: if you find yourself a less than 1cm TI-RADS IVa (The thyroid imaging reporting and data system) nodule in ultrasound examination, your choice is FNA biopsy, surgery directory or follow-up? All the colleagues choose FNA biopsy. Question 2: if the FNA biopsy pathology showed thyroid cancer, your choice is surgery or follow-up? 17 colleagues choose surgery, one colleague said that she will think over.

FNA biopsy is recommended for nodules ≥ 10 mm in greatest dimension with high suspicion ultrasound pattern by American Thyroid Association (ATA) [1]. According to the literature review, the diagnostic accuracy of FNA biopsy for the thyroid nodules with different diameters was high, and the false positive rate was almost negligible[2]. When the interpretation is provided by an experienced pathologist who strictly followed the diagnostic guidelines, the cytohistologic correlation of the malignancy with postoperative outcome is very high. If a biopsied nodule is malignant on cytological examination, then according to the Bethesda system (The Bethesda System for reporting thyroid cytopathology) it is malignant in 97–99% of cases on final pathology. Though this recommendation is so reasonable, it is hard to practice in China. Even when the nodules < 10 mm, people also want to know their thyroid nodules are “good nodules” or “bad nodules”, and if doctors refused their “reasonable” requirement, sometimes, doctors should be in trouble. For extreme fear of cancers, once be diagnosed with thyroid cancer, the first choice of people are surgery besides the nodules is only 1mm. Strictly speaking, doctors can not guaranteed that small thyroid nodules must be safe. Metastases of lymph node in neck central area are the norm in thyroid microcarcinoma, distant metastases such like bone and lung are not rare in clinical practice[3–5]. So, big fishes and small fishes were captured in one fine fishing net. Happy endings of both patients and doctors.

We performed around 2000 cases of thyroid operations every year in The First Affiliated Hospital of Wenzhou Medical University, and over 1000 cases were thyroid malignant tumor. FNA was widely implemented since 2012 in the hospital. 2012 as the boundary, the distribution of thyroid operations changed. We will discuss the changing and put forward some thinking in this article.

Methods

A retrospective analysis was performed to identify all thyroid patients who underwent operations between 2011 and 2016 in Department of Surgical Oncology, The First Affiliated Hospital of Wenzhou Medical University. Totally 8571 patients were involved in this study including 8352 patients who underwent thyroid cancer operation. The preoperative examinations including FNA biopsy and ultrasound were compared and the detailed clinical data were summarized in Table 1–3. If patients have more than one nodules, the size was subjected to the biggest one. FNA biopsy were performed under the guidance of ultrasound in a two person team of a pathologist and a radiologist. The material was obtained by 25-gauge needles. The smears were fixed in 95% alcohol and stained with hematoxylin-eosin (HE). Each case consisted of at least two smears (more specimens were taken if there was scanty material). The material remaining in the aspiration needle was collected for molecular analysis. Ultrasound examinations of thyroid nodules in diagnosis were all carried out by the two experienced chief physicians of the department of ultrasound in our hospital. The patients' clinical data were obtained from the hospital's medical records.

Table 1
Nodule: FNA(+)

Variable	$\geq 10\text{mm}$			5mm-10mm			$\leq 5\text{mm}$			Total		
	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method
2011	278	---	---	54	---	---	22	---	---	354	---	---
2012	304	9.35%	9.35%	252	366.67%	366.67%	87	295.45%	295.45%	643	81.64%	81.64%
2013	326	17.27%	7.24%	298	451.85%	18.25%	147	568.18%	68.97%	771	117.80%	19.91%
2014	355	27.70%	8.90%	301	457.41%	1.01%	185	740.91%	25.85%	841	137.57%	9.08%
2015	344	23.74%	-3.10%	319	490.74%	5.98%	266	1109.09%	43.78%	929	162.43%	10.46%
2016	348	25.18%	1.16%	342	533.33%	7.21%	215	877.27%	-19.17%	905	155.65%	-2.58%
total	1955			1566			922			4443		
average increment speed	4.59%			44.65%			57.76%			20.65%		
In FNA(+) group, the average increment speed in different sub-groups was different. The nodule was more smaller, the increment speed increased more faster.												

Table 3
Nodule: No FNA & TI-RADS IVa-V (Surgery -patients of benign)

Variable	$\geq 10\text{mm}$			5mm-10mm			$\leq 5\text{mm}$			Total		
	benign	fixed basis	link-relative method	benign	fixed basis	link-relative method	benign	fixed basis	link-relative method	benign	fixed basis	link-relative method
2011	26	---	---	22	---	---	6	---	---	54	---	---
2012	18	-30.77%	-30.77%	11	-50.00%	-50.00%	2	-66.67%	-66.67%	31	-42.59%	-42.59%
2013	9	-65.38%	-50.00%	2	-90.91%	-81.82%	1	-83.33%	-50.00%	12	-77.78%	-61.29%
2014	11	-57.69%	22.22%	2	-90.91%	0.00%	0	-100.00%	-100.00%	13	-75.93%	8.33%
2015	6	-76.92%	-45.45%	1	-95.45%	-50.00%	0	-100.00%	0	7	-87.04%	-46.15%
2016	8	-69.23%	33.33%	2	-90.91%	100.00%	0	-100.00%	0	17	-68.52%	142.86%
total	78			40			9			134		
average increment speed	-21.00%			-38.10%			-100.00%			-20.64%		
In no FNA group, the average increment speed in different sub-groups was different. If the tumor was benign after surgery, the nodule was more smaller and the increment speed decreased more faster after ultrasound indicating TI-RADS IVa-V.												

The database was established on Excel 2007. Link relative ratio and fixed base relative were used to show increment speed of the consecutive patients from 2011 to 2016. Chi-square test was used to compare the malignancy or benign tumor after surgery in no-FNA biopsy group between different tumor size. Statistical analysis was conducted in SPSS 21.0. GraphPad Prism 7 was used for the drawing of the figure.

Results

In FNA(+) group, the number of patients who underwent thyroid operation increased in all sub-groups including nodules $\geq 10\text{mm}$, nodules 5mm-10mm and nodules $\leq 5\text{mm}$. In nodules $\geq 10\text{mm}$ sub-group, the growth was steady and slow, in the other sub-groups, the growth were rapidly especially in 2012. But in 2016, there was a significant decrease in nodules $\leq 5\text{mm}$ sub-group. In no FNA biopsy group, number of patients who underwent thyroid operation decreased in all sub-groups. In nodules $\geq 10\text{mm}$ sub-group, the decrease was not obvious. In the other two sub-groups, the decrease were distinct. (Fig. 1)

In FNA(+) group, the increment speed of the amount of thyroid operation in different sub-groups was different. The nodule was more smaller, the increment speed increased more faster. In nodules $\geq 10\text{mm}$ sub-group, the average increment speed was 4.59%. In the first two years except 2011, the fixed base relative increased more obvious. Since 2014, the fixed base relative tend to be stable. The link relative ratio fluctuated in the up and down 10%, but the growth showed a rising tendency overall. In nodules 5mm-10mm sub-group, the average increment speed was 44.65%. The fixed base

relative had an average increasing. The link relative ratio had an outbreak in 2012, and was stable over the next few years. In nodules $\leq 5\text{mm}$ sub-group, the average increment speed was 57.76%. The fixed base relative increased every year. The link relative ratio had an obvious increasing in 2012, and remained stable until there was a significant reduction in 2016. (Table. 1)

In no FNA biopsy group, the number of patients with smaller nodules decreased faster. If the tumor was malignant after surgery, the average increment speed was - 3.90%, -19.35% and - 33.54% respectively in nodules $\geq 10\text{mm}$ sub-group, nodules 5mm-10mm sub-group and nodules $\leq 5\text{mm}$ sub-group. If the tumor was benign after surgery, the average increment speed was - 21.00%, -38.10% and - 100.00% respectively in nodules $\geq 10\text{mm}$ sub-group, nodules 5mm-10mm sub-group and nodules $\leq 5\text{mm}$ sub-group. The overall average increment speed was - 4.42%, -20.50% and - 34.93% respectively in nodules $\geq 10\text{mm}$ sub-group, nodules 5mm-10mm sub-group and nodules $\leq 5\text{mm}$ sub-group. The change was not obvious in nodules $\geq 10\text{mm}$ sub-group, but tremendous in both nodules 5mm-10mm sub-group and nodules $\leq 5\text{mm}$ sub-group no matter the nodules were malignant or benign. (Table 2-4).

Table 2
Nodule: No FNA & TI-RADS IVa-V (malignant)

Variable	$\geq 10\text{mm}$ increment speed			5mm-10mm increment speed			$\leq 5\text{mm}$ increment speed			Total	increment speed		
	cancer	fixed basis	link-relative method	cancer	fixed basis	link-relative method	cancer	fixed basis	link-relative method		cancer	fixed basis	link-relative method
2011	582	---	---	211	---	---	54	---	---	847	---	---	---
2012	505	-13.23%	-13.23%	165	-21.80%	-21.80%	32	-40.74%	-40.74%	702	-17.12%	-17.12%	-17.12%
2013	488	-16.15%	-3.37%	127	-39.81%	-23.03%	15	-72.22%	-53.13%	630	-25.62%	-10.26%	-10.26%
2014	491	-15.64%	0.61%	118	-44.08%	-7.09%	16	-70.37%	6.67%	625	-26.21%	-0.79%	-0.79%
2015	455	-21.82%	-7.33%	89	-57.82%	-24.58%	5	-90.74%	-68.75%	549	-35.18%	-12.16%	-12.16%
2016	477	-18.04%	4.84%	72	-65.88%	-19.10%	7	-87.04%	40.00%	556	-34.36%	1.28%	1.28%
total	2998			782			129			3909			
average increment speed	-3.90%			-19.35%			-33.54%			-8.07%			
In no FNA group, the average increment speed in different sub-groups was different. If the tumor was malignant after surgery, the nodule was more smaller and the increment speed decreased more faster after ultrasound indicating TI-RADS IVa-V.													

Table 4
Nodule: No FNA & TI-RADS IVa-V (Surgery both malignant and benign)

Variable	$\geq 10\text{mm}$ increment speed			5mm-10mm increment speed			$\leq 5\text{mm}$ increment speed			Total	increment speed		
	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method		surgery	fixed basis	link-relative method
2011	608	---	---	233	---	---	60	---	---	901	---	---	---
2012	523	-13.98%	-13.98%	176	-24.46%	-24.46%	34	-43.33%	-43.33%	733	-18.65%	-18.65%	-18.65%
2013	497	-18.26%	-4.97%	129	-44.64%	-26.70%	16	-73.33%	-52.94%	642	-28.75%	-12.41%	-12.41%
2014	502	-17.43%	1.01%	120	-48.50%	-6.98%	16	-73.33%	0.00%	638	-29.19%	-0.62%	-0.62%
2015	461	-24.18%	-8.17%	90	-61.37%	-25.00%	5	-91.67%	-68.75%	556	-38.29%	-12.85%	-12.85%
2016	485	-20.23%	5.21%	74	-68.24%	-17.78%	7	-88.33%	40.00%	573	-36.40%	3.06%	3.06%
total	3076			822			138			4043			
average increment speed	-4.42%			-20.50%			-34.93%			-8.65%			
In no FNA group, the increment speed decreased not obvious in nodules $\geq 10\text{mm}$ sub-group, but tremendous in both nodules 5mm-10mm sub-group and nodules $\leq 5\text{mm}$ sub-group no matter the nodules were malignant or benign.													

If all malignant thyroid tumor with surgery put in one panel from 2011 to 2016, the total operation number increased, but operation of patients with nodules $\geq 10\text{mm}$ decreased slightly and operation of patients with nodules $< 10\text{mm}$ increased markedly especially in nodules $\leq 5\text{mm}$ sub-group. The average increment speed was - 0.83%, 9.33% and 23.91% respectively in nodules $\geq 10\text{mm}$ sub-group, nodules 5mm-10mm sub-group and nodules $\leq 5\text{mm}$ sub-group. (Table 5).

Table 5
No. of malignant tumor surgery: both FNA(+) and without FNA

Variable	≥ 10mm			5mm-10mm			≤ 5mm			Total		
	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method	surgery	fixed basis	link-relative method
2011	860	---	---	265	---	---	76	---	---	1201	---	---
2012	809	-5.93%	-5.93%	417	57.36%	57.36%	119	56.58%	56.58%	1345	11.99%	11.99%
2013	814	-5.35%	0.62%	425	60.38%	1.92%	162	113.16%	36.13%	1401	16.65%	4.16%
2014	846	-1.63%	3.93%	419	58.11%	-1.41%	201	164.47%	24.07%	1466	22.06%	4.64%
2015	799	-7.09%	-5.56%	408	53.96%	-2.63%	271	256.58%	34.83%	1478	23.06%	0.82%
2016	825	-4.07%	3.25%	414	56.23%	1.47%	222	192.11%	-18.08%	1461	21.65%	-1.15%
total	4953			2348			1051			8352		
average increment speed	-0.83%			9.33%			23.91%			4.00%		
Over the six years, the total operation number increased, but operation of patients with nodules ≥ 10mm decreased slightly and operation of patients with nodules < 10mm increased markedly especially in nodules ≤ 5mm sub-group.												

Table 6
No. of surgery patients without FNA but ultrasound showed TI-RADS IVa-V.

Variable	Nodule: No FNA & TI-RADS IVa-V (Surgery)							
	≥ 10mm		5mm-10mm		≤ 5mm		Total	
	cancer	benign	cancer	benign	cancer	benign	cancer	benign
2011	582	26	211	22	54	6	847	54
2012	505	18	165	11	32	2	702	31
2013	488	9	127	2	15	1	630	12
2014	491	11	118	2	16	0	625	13
2015	455	6	89	1	5	0	549	7
2016	477	8	72	2	7	0	556	17
total	2998	78	782	40	129	9	3909	134
Comparison of benign and malignant differences between different size nodules after operation								

In no FNA biopsy group, to compare the malignancy or benign tumor after surgery between nodules 5mm-10mm sub-group and nodules ≥ 10mm sub-group, $\chi^2 = 12.000$, $P = 0.001$, and between nodules ≤ 5mm sub-group and nodules ≥ 10mm sub-group, $\chi^2 = 7.968$, $P = 0.005$, but between nodules 5mm-10mm sub-group and nodules ≤ 5mm sub-group, $\chi^2 = 0.669$, $P = 0.414$. Further pairwise comparison showed, in nodules 5mm-10mm sub-group and nodules ≤ 5mm sub-group, the probability of benign tumor was greater than nodules ≥ 10mm sub-group. (Table. 6).

Discussions

Thyroid nodules are very common, which can be divided into benign and malignant tumors according to its nature. Different nodule properties lead to different treatment methods. However, due to the lack of early specific symptoms, it is not possible to effectively identify whether the nodules are benign or malignant [6]. Based on this, it is necessary to find an early and effective method for diagnosis. At present, there is still no unified clinical applicable standard for ultrasound examination in thyroid nodule diagnosis, and it is generally believed that the accuracy of ultrasound examination is high in the diagnosis of the nodule above 10 mm, but the accuracy of ultrasound examination is low in the diagnosis of the nodule below 5 mm [7]. In the recent years, In the diagnosis of thyroid nodular diseases, FNA biopsy under the guidance of ultrasound is of high accuracy, visibility, and avoid to damage the surrounding tissue and the important blood vessels. It can also promote the quality of the specimen by aspirating the nodules accurately [8]. Relevant medical studies have shown [9] that in the diagnosis of thyroid nodule, FNA biopsy has a higher accuracy in the surgical pathology examination. FNA biopsy is a reliable and fast method which is acknowledged as the golden standard in the evaluation of thyroid nodules.[10] With the BSRTC (Bethesda System for reporting thyroid cytopathology), established in 2007, the terminology being used in thyroid cytopathology was standardized which suggested cytopathology results shall be reported according to the six subgroups defined in this system.[11] In this study, FNA biopsy positive indicated thyroid cancer and the negative one indicated benign tumors. The thyroid imaging reporting and data system (TI-RADS) can perform standardized graded diagnosis of nodules [12]. Contrast-enhanced ultrasound is an advanced step from morphology to functional imaging.

Through low energy acoustic wave emission, it can be combined with pulse reverse harmonic imaging to present blood perfusion conditions under different physiological and pathological conditions [13]. In this study, the thyroid nodule contrast-enhanced ultrasound scoring method combined with conventional ultrasound TI-RADS classification was used to distinguish benign and malignant. TI-RADS IVa-V in ultrasound examination indicated suspicious malignant or cancer.

With people's attention to health and the continuous improvement of examination methods, the detection rate and the amount of thyroid operation increases year by year. Due to the safety, accuracy and convenience of FNA biopsy, more and more people choose to perform it when the ultrasound indicated thyroid nodules into TI-RADS IVa-V class, so as to further clarify the nature of the tumor before deciding whether to perform surgical operation. In this study, we found in the nodules $\geq 10\text{mm}$ sub-group, ultrasound is obviously better in distinguishing benign or malignant than in the other two sub-groups of small nodules. Because ultrasound is non-invasive, cheap, high accuracy, we can choose no FNA biopsy to reduce the economic burden of patients, and directly to decide whether to have surgery according to the results of ultrasound. In the sub-groups of nodules between 5-10mm and less than 5mm, the accuracy of ultrasound examination was low, while FNA biopsy was almost 100%. Therefore, it is necessary to choose FNA biopsy. According to previous reports in the literature, there were many cases about the small malignant thyroid nodules needed surgeries in different additions. Such as multiple lymphatic metastasis, close to the trachea or throat, infiltration of thyroid capsule, BRAF V600E gene mutation and so on[14–18]. At this time, if FNA biopsy shows benign, follow-up observation can be continued to avoid surgical trauma. When malignancy is shown, surgical operation is the best treatment to ensure the patient's health.

Conclusions

In thyroid nodules $\geq 10\text{mm}$ sub-group, due to the sensitivity of ultrasound, FNA biopsy though necessary, but it seems more like a routine. There is no statistical difference between ultrasound diagnosis and FNA biopsy. In nodules $<10\text{mm}$ sub-groups, FNA has the great significance in the diagnosis. As we know, small nodules are not the forbidden zone. Even small one less than 2mm can be obtained satisfactory cytological aspiration biopsy. We are more inclined to diagnose the small nodules less than 10mm by FNA which are suspected malignant by ultrasound, so as to add more references for the subsequent treatment. Of course, whether accepting surgical operation is decided by doctors and patients jointly.

Abbreviations

FNA Fine-needle aspiration

TI-RADS The thyroid imaging reporting and data system

ATA American Thyroid Association

HE hematoxylin-eosin

BSRTC Bethesda System for reporting thyroid cytopathology

Declarations

Ethics approval and consent to participate: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The study was approved by the ethics committee of the first affiliated hospital of Wenzhou Medical University (571-05).

Consent for publication All authors agree to publish the manuscript.

Availability of data and material All the figures and tables in our manuscript are original.

Competing interests The authors have no conflicts of interest to declare.

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Authors' contributions Jing Zhan and Bing-Luan Xie participated in data collection and statistical analysis. Yu-Jun Chen and Ye-Huan Liu drafted the manuscript. Shi-Xu Lv conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

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Figures

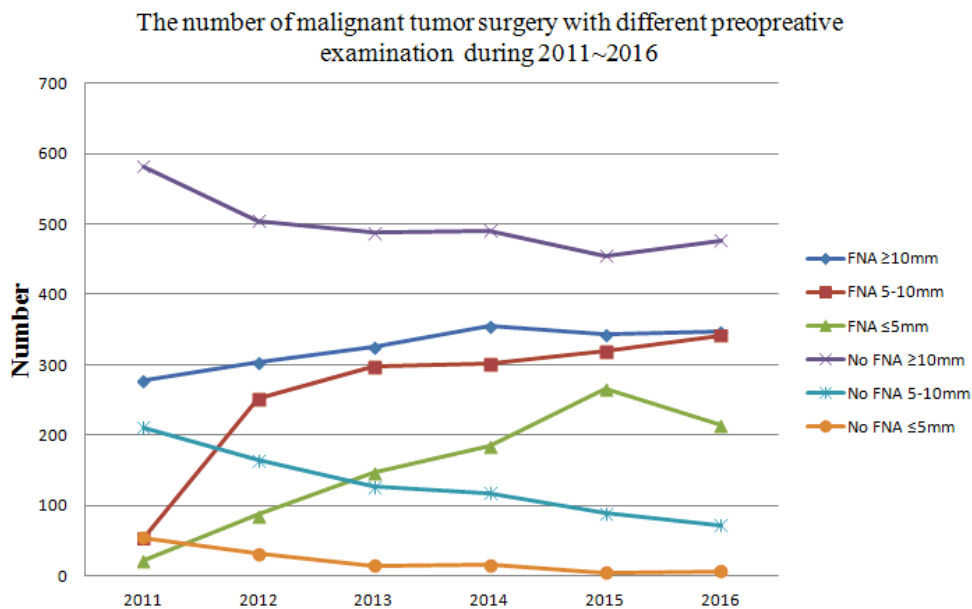


Figure 1

In FNA(+) group, the number of patients who underwent thyroid operation increased in all sub-groups including nodules $\geq 10\text{mm}$, nodules 5mm-10mm and nodules $\leq 5\text{mm}$. In nodules $\geq 10\text{mm}$ sub-group, the growth was steady and slow, in the other sub-groups, the growth were rapidly especially in 2012. But in 2016, there was a significant decrease in nodules $\leq 5\text{mm}$ sub-group. In no FNA biopsy group, number of patients who underwent thyroid operation decreased in all sub-groups. In nodules $\geq 10\text{mm}$ sub-group, the decrease was not obvious. In the other two sub-groups, the decrease were distinct. (Figure 1)