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

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Research

Keywords: fine needle aspiration (FNA) biopsy, thyroid nodules

DOI: https://doi.org/10.21203/rs.3.rs-477528/v1

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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(+), 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 ≥10mm sub-group, but tremendous in both nodules 5mm-10mm sub-group and nodules ≤5mm 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 ≥10mm decreased slightly and operation of patients with nodules <10mm increased markedly especially in nodules ≤5mm sub-group. In no FNA group, to compare the malignancy or benign tumor after surgery between nodules 5mm-10mm sub-group and nodules ≥10mm sub-group, χ²=12.000:P=0.001, and between nodules ≤5mm sub-group and nodules ≥10mm sub-group, χ²=7.968:P=0.005, but between nodules 5mm-10mm sub-group and nodules ≤5mm sub-group, χ²=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.

Conclusions: In thyroid nodules ≥10mm sub-group, there is no statistical difference between ultrasound diagnosis and biopsy. In nodules <10mm 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, you 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 ≥10mm 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 <10mm, 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 | ≥ 10mm | Increment speed | 5mm-10mm | Increment speed | ≤ 5mm | Increment speed | Total | Increment speed |
|----------|--------|-----------------|----------|-----------------|-------|-----------------|-------|-----------------|
| surgery  |        | fixed basis     | link-     | relative method | 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 2
Nodule: No FNA & TI-RADS IVa-V (Surgery -patients of benign)

| Variable | ≥ 10mm | Increment speed | 5mm-10mm | Increment speed | ≤ 5mm | Increment speed | Total | Increment speed |
|----------|--------|-----------------|----------|-----------------|-------|-----------------|-------|-----------------|
| benign   |        | fixed basis     | link-     | relative method | 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 ≥ 10mm, nodules 5mm-10mm and nodules ≤ 5mm. In nodules ≥ 10mm sub-group, the growth was steady and slow, in the other sub-groups, the growth was rapidly especially in 2012. But in 2016, there was a significant decrease in nodules ≤ 5mm sub-group. In no FNA biopsy group, number of patients who underwent thyroid operation decreased in all sub-groups. In nodules ≥ 10mm 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 ≥ 10mm 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 ≤ 5mm 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 ≥ 10mm sub-group, nodules 5mm-10mm sub-group and nodules ≤ 5mm sub-group. The change was not obvious in nodules ≥ 10mm sub-group, nodules 5mm-10mm sub-group and nodules ≥ 5mm sub-group. The overall average increment speed was - 4.42%, -20.50% and - 34.93% respectively in nodules ≥ 10mm sub-group and nodules ≤ 5mm sub-group. If the tumor was benign after surgery, the average increment speed was - 21.00%, -38.10% and - 100.00% respectively in nodules ≥ 10mm sub-group, nodules 5mm-10mm sub-group and nodules ≤ 5mm sub-group. The overall average increment speed was - 3.90%, -19.35% and - 33.54% respectively in nodules ≤ 10mm sub-group, nodules 5mm-10mm sub-group and nodules ≥ 5mm sub-group. (Table 2–4).

| Variable | ≥ 10mm | increment speed | 5mm-10mm | increment speed | ≤ 5mm | 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    | -13.23%         | 211     | -5.73%         | 54    | -2.90%         | 847   | -9.95%         |
| 2012     | 505    | -16.15%         | 165     | -21.80%        | 32    | -40.74%        | 702   | -17.12%        |
| 2013     | 488    | -15.64%         | 127     | -23.03%        | 15    | -53.13%        | 630   | -10.26%        |
| 2014     | 491    | -15.64%         | 118     | -7.09%         | 16    | -6.76%         | 625   | -0.97%         |
| 2015     | 455    | -21.82%         | 89      | -24.58%        | 5     | -68.75%        | 549   | -12.16%        |
| 2016     | 477    | -18.04%         | 72      | -19.10%        | 7     | 40.00%         | 556   | 1.28%          |
| total    | 2998   | -18.04%         | 782     | -19.10%        | 129   | 3909           | 556   | 1.28%          |

In no FNA group, the increment speed decreased not obvious in nodules ≤ 5mm sub-group no matter the nodules were malignant or benign.

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.

| Variable | ≥ 10mm | increment speed | 5mm-10mm | increment speed | ≤ 5mm | 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    | -13.98%         | 233     | -24.46%        | 60    | -43.33%        | 901   | -18.65%        |
| 2012     | 523    | -18.26%         | 176     | -24.46%        | 34    | -43.33%        | 733   | -18.65%        |
| 2013     | 497    | -17.43%         | 129     | -26.70%        | 16    | -52.94%        | 642   | -12.41%        |
| 2014     | 502    | -24.18%         | 120     | -6.98%         | 16    | 0.00%          | 638   | -0.62%         |
| 2015     | 461    | -48.50%         | 90      | -25.00%        | 5     | -68.75%        | 556   | -12.85%        |
| 2016     | 485    | -20.23%         | 74      | -17.78%        | 7     | 40.00%         | 573   | 3.06%           |
| total    | 3076   | -20.23%         | 822     | -34.93%        | 138   | 4043           | 573   | 3.06%           |

In no FNA group, the increment speed decreased not obvious in nodules ≥ 10mm sub-group, but tremendous in both nodules 5mm-10mm sub-group and nodules ≤ 5mm 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 ≥ 10mm decreased slightly and operation of patients with nodules < 10mm increased markedly especially in nodules ≤ 5mm sub-group. The average increment speed was - 0.83%, 9.33% and 23.91% respectively in nodules ≥ 10mm sub-group, nodules 5mm-10mm sub-group and nodules ≤ 5mm sub-group. (Table 5).
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 cytology 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.

### Table 5

| Variable | ≥ 10mm | increment speed | 5mm-10mm | increment speed | ≤ 5mm | 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     | 860    | -5.93%         | 265     | -5.36%         | 76    | -5.36%         | 1201   | -5.36%         |
| 2012     | 809    | -5.93%         | 417     | 57.36%         | 119   | 56.58%         | 1345   | 11.99%         |
| 2013     | 814    | -5.36%         | 425     | 60.38%         | 162   | 113.16%        | 1401   | 16.65%         |
| 2014     | 846    | -1.63%         | 419     | 58.11%         | 201   | 164.47%        | 1466   | 22.06%         |
| 2015     | 799    | -7.09%         | 408     | 53.96%         | 271   | 256.58%        | 1478   | 23.06%         |
| 2016     | 825    | -4.07%         | 414     | 56.23%         | 222   | 192.11%        | 1461   | 21.65%         |
| total    | 4953   | -0.83%         | 2348    | 9.33%          | 1051  | 23.91%         | 8352   | 4.00%          |
| average  | -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

| Variable | Nodule: No FNA & TI-RADS IVa-V (Surgery) |
|----------|------------------------------------------|
|          | ≥ 10mm | 5mm-10mm | ≤ 5mm | Total |
| cancer   | 582    | 118      | 67    | 767   |
| benign   | 26     | 11        | 2     | 39    |
| cancer   | 505    | 118      | 11    | 634   |
| benign   | 18     | 11        | 2     | 31    |
| cancer   | 488    | 127      | 2     | 617   |
| benign   | 9      | 12        | 1     | 22    |
| cancer   | 491    | 118      | 2     | 615   |
| benign   | 11     | 11        | 1     | 23    |
| cancer   | 455    | 89       | 1     | 543   |
| benign   | 6      | 9         | 0     | 15    |
| cancer   | 477    | 72       | 2     | 551   |
| benign   | 8      | 7         | 0     | 15    |
| total    | 2998   | 782      | 40    | 3909  |
| 10mm     | 9      | 7         | 0     | 16    |
| 5mm-10mm | 86      | 7         | 0     | 93    |
| ≤ 5mm    | 40      | 7         | 0     | 47    |

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).
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 ≥ 10mm 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 ≥ 10mm 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 <10mm 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.

**Funding:** Not applicable.

**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
In FNA(+) group, the number of patients who underwent thyroid operation increased in all sub-groups including nodules ≥10mm, nodules 5mm-10mm and nodules ≤5mm. In nodules ≥10mm 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 ≤5mm sub-group. In no FNA biopsy group, number of patients who underwent thyroid operation decreased in all sub-groups. In nodules ≥10mm sub-group, the decrease was not obvious. In the other two sub-groups, the decrease were distinct. (Figure 1)