بسم الله الرحمن الرحيم...
TNS

Thyroid nodule scoring system

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Sponsored by:
Nano Hesgarsazan Salamat Arya Co.
Thyroid Nodule Management
Thyroid Cancer Incidence

Although thyroid cancer currently ranks ninth with 568,000 cases, its incidence has increased dramatically in the last 20 years, and this increase has been faster and more than any other cancer. The incidence of thyroid cancer has increased worldwide especially due to developed cancer screening potentials in the countries. This change is largely related to an increased ability in detecting small clinically occult papillary cancers.

Radiological Thyroid Scoring

(2) ACR Thyroid imaging, Reporting and data systems (TI-RADS): white paper of the ACR TI-RADS committee.
Fine Needle Aspiration (FNA)

- The gold standard for thyroid nodules diagnosis is Ultrasound-guided fine needle aspiration (FNA). Diagnostic sensitivity of 83–98% and specificity of 70–92% is reported in the literatures for this process.

# The Bethesda system reporting thyroid cytopathology

<table>
<thead>
<tr>
<th>Category</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Non-diagnostic or inadequate</td>
</tr>
<tr>
<td>II</td>
<td>Benign</td>
</tr>
<tr>
<td>III</td>
<td>Atypia/follicular lesion of undetermined significance</td>
</tr>
<tr>
<td>IV</td>
<td>Follicular neoplasm or suspicious for follicular neoplasm</td>
</tr>
<tr>
<td>V</td>
<td>Suspicious for malignancy</td>
</tr>
<tr>
<td>VI</td>
<td>Malignant</td>
</tr>
</tbody>
</table>

Source: Cibas et al.\(^{(1)}\)

(4) The 2017 Bethesda System for Reporting Thyroid Cytopathology
Thyroid Nodule Management

Follow-up, Lobectomy, or Total thyroidectomy?!

Figure 38-14. Management of a solitary thyroid nodule based on Bethesda criteria. a = except in patients with a history of external radiation exposure or a family history of thyroid cancer; FNAB = fine-needle aspiration biopsy; AUS = atypia of unknown significance; FLUS = follicular lesion of unknown significance; FN = follicular neoplasm.

(5) Schwartz’s principles of surgery ninth edition by Charles brunicardi
Challenges in Thyroid Nodule Management
Atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS), occur in approximately 10–33.6% and 15–42% of all FNA samples, respectively. There is not convincing features or evidences to put AUS/FLUS directly in the benign or malignant category and therefore repeating FNA, molecular testing, and finally lobectomy would be the appropriate management for the patient according to the American Thyroid Association (ATA) management guidelines.

AUS/FLUS

• Nine different cytopathologic characteristics is defined for AUS/FLUS in the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) that the risk of malignancy in this classification (Bethesda III) differs in a wide range (about 6% to 48%). However, high percentage of inconclusive results (such as nondiagnostic or AUS/FLUS readings) occur in thyroid nodules with previous AUS/FLUS FNA (20%-49.1%).

• Also with repeat FNA, the diagnosis of indeterminate (AUS/FLUS) nodules will change to benign in about 40% to 58% of cases. However, in the lesions that are resected, malignancy rates are high. So, repeating FNA may result in uncertainty leading to unnecessary surgeries or misdiagnosis and not seem to be a satisfactory solution.

Follicular and Hurthle cell lesion

• Challenging and difficult for diagnosis in both FNA cytopathology and frozen-section histopathology in comparison to papillary thyroid carcinoma (with about higher than 90% accuracy in cytopathology). There is a risk of 15%-30% malignancy probability for suspected follicular neoplasm (FN) or Hurthle cell neoplasm (HCN) (Bethesda IV).

• Since only histopathological evidence of capsular and vascular invasion can confirm malignancy in follicular neoplasms, FNA cytology can not distinguish between benign and malignant tumors in HCN and FN cases. Surgery and histopathological diagnosis from surgical specimen is recommended for patients when FN or HCN is diagnosed in cytopathology.

Follicular and Hurthle cell lesion

- Intraoperative **frozen section pathology** for indeterminate (AUS/FLUS/FN, Bethesda III–IV) lesions thyroid nodule may not be **recommended** according to guidelines, which generally is too unspecific. These lesions may be challenges for radiologists and pathologists before surgery as well as for surgeons during the surgery.

- **Excision required nodules are still a challenge**


Electrical Impedance Spectroscopy (EIS) for real-time detection of excision-required breast lesions
Research Ethics Certificate

Approval ID: IR.TUMS.VCRREC.1398.892
Evaluated by: Vice-Chancellor in Research Affairs - Tehran University of Medical Sciences
Approval Date: 2020-02-04
Status: Approved

Proposal Title: Clinical trial of using standard spinal cannula for differentiation of benign and malignant lesions under sonography guidance to maximize accuracy of BI-RADS scoring and CNB, based on electrical impedance spectroscopy

Additional Information:

1. Although the proposal has been approved by the research ethics committee, meeting the professional and legal requirements is the sole responsibility of the PI and other project collaborators.
2. This certificate is reliant on the proposal/documents received by this committee on 2020-02-04. The committee must be notified by the PI as soon as the proposal/documents are modified.

Dr. Mohammad Ali Safari
Director of Institutional Research Ethics Committee
Vice-Chancellor in Research Affairs - Tehran University of Medical Sciences

Dr. Ehsan Shams Ghorabi
Secretary of Institutional Research Ethics Committee
Vice-Chancellor in Research Affairs - Tehran University of Medical Sciences
Tumor Detection Probe (TDP)

- Based on impedance spectroscopy
- Frequency range: 1 Hz to 1 MHz
- 0.4V amplitude constant voltage
- BI-RADS3 vs. BI-RADS4a
The electrical circuit model includes the main parts of the system and tissue electrical equivalent circuits in a series configuration.

In a biological environment, ions are the majority carriers and play an essential role in the characteristic of the impedance results. The model includes Faradic and diffusion processes, a double-layer capacitance, and an electrolyte resistance.

**Electrical Impedance Spectroscopy (EIS)**

\[ R_{CT}(\text{Charge transfer resistance}) = \frac{RT}{nF \Gamma_0} \]
\[ Z_{CPF}(\text{Constant phase element}) = \frac{1}{j\omega C_{\Gamma}} \]
\[ Z_{W}(\text{Warburg impedance}) = \frac{\sigma}{\sqrt{\omega}} (1 - j) \]
\[ \sigma = \frac{RT}{n^2F^2\sqrt{2}} \left( \frac{1}{C_0\sqrt{D_0}} + \frac{1}{C_R\sqrt{D_R}} \right) \]
Detection Method

(a) Graph: Shows the impedance phase (deg) and 10log(Ω) as a function of frequency (Hz) for different categories: Benign, Borderline, and Malignant.

(b) IPS Scale: Indicates the Impedance Phase Slope on a color-coded scale from -10 to +5.

(c) Images: Ultrasound and histological images of a breast tissue sample, showing a normal tissue pattern.

(d) Images: Ultrasound and histological images of a breast tissue sample, indicating a suspected abnormality.

(e) Images: Ultrasound and histological images of a breast tissue sample, showing a confirmed abnormality.

Legend:
- No need for Biopsy/Excision
- Required for Biopsy/Excision
Definition of Classification Features:

- \( Z_{1\text{KHz}} \): Impedance magnitude in the frequency of 1kHz
- IPS: Impedance Phase Slope in the frequency range of 100 kHz and 500 kHz
Human Model Study Results

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=138)</th>
<th>Benign (n=46)</th>
<th>Borderline (n=53)</th>
<th>Malignant (n=39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td>35.5±9.8</td>
<td>36.3±9.1</td>
<td>49.5±8.8</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;50</td>
<td></td>
<td>2 (4.35%)</td>
<td>2 (3.8%)</td>
<td>14 (35.9%)</td>
<td></td>
</tr>
<tr>
<td>35 to 50</td>
<td></td>
<td>19 (41.3%)</td>
<td>27 (50.9%)</td>
<td>23 (59%)</td>
<td></td>
</tr>
<tr>
<td>≤35</td>
<td></td>
<td>25 (54.3%)</td>
<td>24 (45.3%)</td>
<td>2 (5.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diameter (mm)</strong></td>
<td></td>
<td>25.8±21.8</td>
<td>28.4±17.8</td>
<td>29.4±18.5</td>
<td>0.076</td>
</tr>
<tr>
<td>&gt;30</td>
<td></td>
<td>10 (21.7%)</td>
<td>18 (34%)</td>
<td>12 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>&gt;20, ≤30</td>
<td></td>
<td>14 (30.4%)</td>
<td>15 (28.3%)</td>
<td>12 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>&gt;10, ≤20</td>
<td></td>
<td>13 (28.3%)</td>
<td>13 (24.5%)</td>
<td>12 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td></td>
<td>9 (20.6%)</td>
<td>7 (13.2%)</td>
<td>3 (7.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>BI-RADS</strong></td>
<td></td>
<td>0.00002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>9 (19.6%)</td>
<td>6 (11.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td>32 (69.5%)</td>
<td>42 (79.2%)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td>4 (8.7%)</td>
<td>5 (9.5%)</td>
<td>3 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>4c</td>
<td></td>
<td>1 (2.2%)</td>
<td>0 (0%)</td>
<td>13 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>22 (56.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>IPS</strong></td>
<td></td>
<td>1.1±2.1</td>
<td>-1.9±1.5</td>
<td>-3.5±1.6</td>
<td>1.4E-15</td>
</tr>
<tr>
<td>&gt;0</td>
<td></td>
<td>40 (87%)</td>
<td>3 (5.7%)</td>
<td>1 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>-2 to 0</td>
<td></td>
<td>2 (4.35%)</td>
<td>31 (58.5%)</td>
<td>2 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>≤-2</td>
<td></td>
<td>4 (8.7%)</td>
<td>19 (35.8%)</td>
<td>36 (92.3%)</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing TDP vs BI-RADS](image-url)
## Human Model Study Results

### Histopathology

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Total</th>
<th>True Positive</th>
<th>False Negative</th>
<th>True Negative</th>
<th>False Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDC, ILC</td>
<td>39</td>
<td>34 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DCIS, LCIS</td>
<td>4</td>
<td>4 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory carcinoma</td>
<td>1</td>
<td>0</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>38</td>
<td>38 (97.4%)</td>
<td>1 (2.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Boarderline and high-risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH</td>
<td>2</td>
<td>2 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Papillary lesions</td>
<td>13</td>
<td>13 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Benign phyllodes Tumor</td>
<td>5</td>
<td>5 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CCH and CCC(extensive area)</td>
<td>53</td>
<td>6 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Complex FA</td>
<td>17</td>
<td>16 (94.1%)</td>
<td>1 (5.9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cellular FA</td>
<td>5</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SA (complex or extensive area)</td>
<td>1</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IGM/mastitis</td>
<td>4</td>
<td>4 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50</td>
<td>50 (94.3%)</td>
<td>3 (3.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Benign</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>23</td>
<td>0</td>
<td>21 (87.5%)</td>
<td>2 (12.5%)</td>
<td>0</td>
</tr>
<tr>
<td>UDH, ULH</td>
<td>9</td>
<td>0</td>
<td>9 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CCC</td>
<td>7</td>
<td>0</td>
<td>5 (83.3%)</td>
<td>2 (16.7%)</td>
<td>0</td>
</tr>
<tr>
<td>FCC</td>
<td>46</td>
<td>2</td>
<td>0</td>
<td>2 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory process</td>
<td>2</td>
<td>0</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>SA (simple)</td>
<td>1</td>
<td>0</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>1</td>
<td>0</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>41</td>
<td>0</td>
<td>41 (89.1%)</td>
<td>5 (11.9%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Sensitivity: 95%
Specificity: 89%
Accuracy: 93%
Other TDP applications

Surgery guidance

Electrochemical treatment monitoring
Intraoperative real-time detection of excision-required Thyroid Nodules
Thyroid Nodule Scanning (TNS)

- This system records and analyses two electrical impedance features of $Z_{1kHz}$ and IPS of the nodules by Electrical Impedance Spectroscopy (EIS) between a metallic lead (ECG chest lead) had been attached on the skin of submental region and a G20 medical grade needle inserted to the targeted nodule.

- TNS is a precision impedance-based measurement system that calculates and analyses impedance magnitude and phase diagrams of an under test media in a two-electrode configuration. First a 0.4V alternating voltage signal is applied to the tissue by means of a two electrode probe that stimulates the tissue to produce a current response signal recorded by the system. Then the impedance magnitude is calculated by dividing the voltage to current signal amplitudes and impedance phase is defined according to phase shift of current against voltage signal.
Thyroid Nodule Scanning (TNS)

- Different electrode design
- Intra-Radiological scanning
- Intra-Operative Scanning
Thyroid Nodule Scanning (TNS): Ethics

Clinical Trial Protocol
Iranian Registry of Clinical Trials
17 Feb 2021

Clinical trial of Electrical Impedance Spectroscopy of Thyroid nodules for real-time discrimination of benign, atypical, and malignant lesions in patients candidate for surgery or biopsy

Protocol summary

Study aim
Differential of benign and malignant thyroid lesions in patients candidate for surgery and assistance in the diagnosis of lesions with non-diagnostic FNA and AUS.

Design
A pragmatic, single group, not blinded, not randomized, an intervention group, sample size 384 patients.

Settings and conduct
Considering inclusion and exclusion criteria, a double-layer sterilized G18-G22 needle is inserted into the solid mass or suspicious lymph node in the surgery room. Then a low power electrical signal of varying frequency is applied between the inner and outer needles of the probe. The electrical impedance is then measured and classification parameters are determined by analyzing phase and impedance diagrams for distinguishing benign and malignant thyroid lesions, metastatic lymph node detection, parathyroid tissue detection, and cancer type evaluation if possible (nodular, papillary, and follicular).

General information

Reason for update

Acronym

IRCT registration information
IRCT registration number: IRCT20190904044697N7
Registration date: 2021-02-16, 1399/11/28
Registration timing: prospective

Last update: 2021-02-16, 1399/11/28
Update count: 0
Registration date: 2021-02-16, 1399/11/28
Thyroid Nodule Scanning (TNS)

- Two parameters of impedance magnitude in frequency range of 1kHz ($Z_{1kHz}$) and Impedance Phase Slope in the frequency ranges of 100kHz to 500kHz (IPS) are then extracted as two impedance based features identifying intracellular, extracellular, and membranous abnormalities due to cancer developments.
Intraoperative TNS Results

- 48 detectable nodules in radiology
- 5 detectable nodules in surgery
- 1 undetectable nodules in radiology and surgery
- 36 normal thyroid/colloid goiter
  
  Total samples = 90

Sensitivity: 94%
Specificity: 87%
Accuracy: 91%
Intraoperative TNS Results in micro-PTC Nodules

- 18 nodules with micro-PTC involvement tested by TNS intra-operatively
- 12/18 were detectable in radiological evaluations
- 5/18 were detectable in surgical evaluations
- 1/18 was only detectable in permanent pathological evaluations
- 100% of micro-PTC nodules diagnosed positive by TNS
Thanks For your Attention
References


• (2) ACR Thyroid imaging, Reporting and data systems (TI-RADS): white paper of the ACR TI-RADS committee.

• (3) The 2017 Bethesda System for Reporting Thyroid Cytopathology

(4) Schwartz’s principles of surgery ninth edition by Charles brunicardi


