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Dielectric Properties for Differentiating Normal and Malignant Thyroid Tissues

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The incidence rate of thyroid cancer has increased greatly during the last few decades, and highly sensitive and specific methods for early diagnosis and prognostic evaluation remain lacking. In this study, we investigated a novel approach based on microwave theory to detect thyroid cancer.

Material/Methods: Freshly excised thyroid tissues (n=236) from 48 patients were identified as normal or malignant using histology. Each sample was measured for effective dielectric permittivity and effective conductivity (0.5–8 GHz). The means of each of these parameters of the normal and malignant groups were compared.

Results: The effective dielectric permittivities of normal and malignant thyroid tissues were 24.026±1.951 to 17.950±1.648 and 69.782±2.734 to 57.356±1.802, respectively. Also, as a function of frequency, the effective conductivities of normal and malignant thyroid cancer were 0.8395±0.2013 to 1.8730±0.0979 and 1.8960±0.5024 to 9.7461±0.9349 (S/m), respectively. The mean effective dielectric permittivities and effective conductivities of normal thyroid tissues were significantly lower than that of thyroid cancer tissues.

Conclusions: Measuring the effective dielectric permittivity and effective conductivity of excised thyroid tissues may be a new and viable method to determine malignancy in thyroid cancer.

MeSH Keywords: **Early Detection of Cancer • Microwaves • Parathyroid Neoplasms**

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Background

The incidence rate of thyroid cancer has increased rapidly in recent years, with a projected estimate for the year 2017 of 56 870 new cases and 2010 deaths in the United States [1]. Conventional methods of diagnosing thyroid cancer are ultrasonography, fine-needle aspiration biopsy, and computed tomography [2], but each of these methods has limited low sensitivity and specificity, indeterminate results, or imposes a radiation hazard [3]. Therefore, early diagnosis of thyroid cancer remains a challenge, with many patients undergoing surgical resection for what eventually proves to be a benign condition. Improving the accuracy of early diagnosis of thyroid cancer could reduce the number of unnecessary procedures. New, non-invasive diagnostic approaches with higher sensitivity and specificity are urgently needed.

Microwaves are alternating current in the frequency range of 300 MHz to 300 GHz [4]. This frequency range is especially useful for biomedical detection and treatment, being a compromise between the demands for shallow penetration and high spatial resolution. Previous studies have investigated the dielectric properties of microwaves for the ability to differentiate normal and malignant breast [5–7], cervical neoplasia [8], prostate [9], and bladder [10] tissues. However, for the thyroid, the investigated dielectric spectrum has included frequencies only in the KHz or several MHz range [11,12]. The prospective study of Stojadinovic et al. [13] measured the electrical impedance spectroscopy of thyroid nodules from 50 to 20 000 Hz, and reported that the positive and negative predictive values of malignant thyroid nodules were 83% and 79%, respectively. Despite the safety, ease of use, and possible diagnostic value of using this technique to differentiate various thyroid tissue types, the accuracy and robustness remain low.

Because microwave frequencies are non-ionizing and exhibit reasonable penetration, diagnostic methods in thyroid cancer based on differences in dielectric properties may be both achievable and harmless. It is reasonable to suppose that microwaves may even be suitable for mass surveys for thyroid cancer. However, available data regarding thyroid tissue within the microwave band is almost nil.

To determine whether microwave parameters have potential diagnostic value in thyroid cancer, the present large-scale study investigated the dielectric properties of freshly excised thyroid tissues, comparing groups of normal and malignant tissues as determined by pathology.

Material and Methods

Object of study

The Ethics Committee of Sichuan Provincial People's Hospital approved this study. The study sample included 236 freshly excised thyroid tissues obtained from 48 patients undergoing thyroidectomy at Sichuan Provincial People's Hospital. All the specimens were stored in heated, sealed, and insulated containers to minimize desiccation, and were transported to the measurement location.

Pathological examination

The pathological examination was performed in accordance with the hospital's standard protocol. Typically, a pathologist paged one of the engineers responsible for conducting the measurements as soon as the specimens arrived. To confirm the histological type, samples were stained with hematoxylin and eosin (H&E). Within 2 h, the microwave parameters of the samples from the pathology department were measured, as described below.

Original data acquisition

After H&E staining, the pathologist assisted us to cut 1 piece off each specimen, with the following shape criteria: with at least 1 side approximately flat (to avoid an air gap between the sample and the aperture of the coaxial line), and a minimum square area of the flat side at least 5–6 times that of the coaxial aperture. Since the aperture was ~10.2 mm^2, the edges of the square flat face were >7.8 mm. In addition, the minimum thickness of the tissue sample from the chosen side to the opposite side was >2 mm [14–17].

To obtain the scattering (S) microwave parameter of each sample (i.e., S_1, S_2... S_n), a coaxial probe was connected to a Vector Network Analyzer (VNA, Rohde & Schwarz R&S; Figure 1). The reference parameter S_0 was measured when the probe was open to the air. All the frequency bands of the S-parameters ranged from 0.5 GHz to 8 GHz.

Data de-embedding

Using the VNA, the first step was calibration for the point between the VNA and the coaxial probe. The S-parameters (S_1, S_2... S_n) were saved to ASCII files (*.CSV) using the viewer software of the VNA (ZVH viewer, R&S, version V1.44). The ASCII files were imported into MATLAB (version 2014A). S_1, S_2... S_n were subtracted from the reference S0 to calibrate and remove information related to the coaxial probe. After de-embedding the data in this way, the S-parameters of the samples were exported into SNP files.

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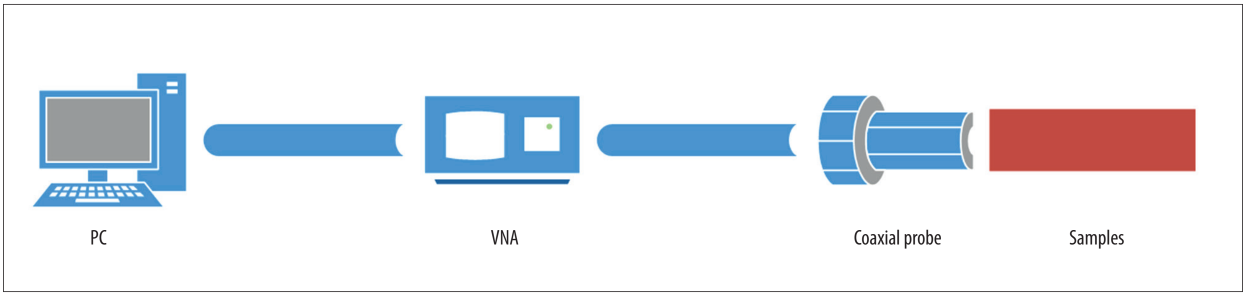

Figure 1. Schematic of measuring system.

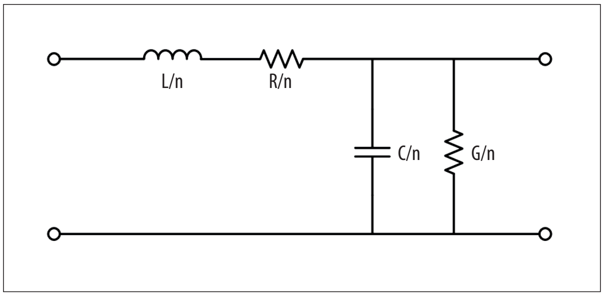

Figure 2. One cell of the transmission line model.

Modeling

In microwave theory, any material that can transport electromagnetic fields can transmit microwaves. We modeled the cells of the samples as a series of transmission lines (Figure 2), with n number of cells (in this case n=2, 4, or 8). The components inductance (L) and capacitance (C) represent energy storage, and resistance (R) and conductance (G) constitute energy loss [4].

Modeling entailed importing the SNP files into the Advanced Design System (Agilent Technologies, Version 2015), in which a transmission line was designed to fit the S-parameter from each SNP File. The L, C, R, and G values for each sample are then recorded.

Measurement results

When we obtained the values of the model parameters, we applied the following formulations from microwave theory:

$Z^* = \sqrt{{R + j\omega L}/{G + j\omega C}}$ and, $Z^* = Z_0 \cdot \sqrt{{\mu_0 \cdot \mu_r}/{\varepsilon_0 \cdot \varepsilon_r^*}}$ where Z^* is the complex characteristic impedance of the sample; R is resistance; j is the imaginary unit; ω is the angular frequency; L, G, and C are defined as above; Z_0 is the complex characteristic impedance of air; μ_0 is the permeability of vacuum; μ_r is the relative permeability of the sample (for the human body, equal to 1); ε_0 is the permittivity of vacuum; and ε_r^* is the complex relative dielectric permittivity.

Given that Z_0=377 Ω, ε_0=8.854 × 10^{-12} F/m, μ_0=4ϖ × 10^{-7} N/A^2, and ω=2π×frequency, we could calculate the complex relative dielectric permittivity (ε_r*) of each sample. According to dielectric physics and microwave theories, we also know that:

$\varepsilon_r^* = \varepsilon' - j \cdot \varepsilon'' = \varepsilon' - j \cdot \frac{\sigma_{eff} / \varepsilon_0}{\omega} = \varepsilon_{eff} - j \cdot \frac{\sigma_{eff}}{\omega \cdot \varepsilon_0}$, where ε' and ε'' are the real part and imaginary parts of ε*, respectively; and εeff is the effective dielectric permittivity and σ_{eff} is the effective conductivity. Both εeff and σ_{eff} are real numbers. Thus, εeff and σ_{eff} of each sample could be calculated from ε* as a function of frequency.

Statistical analysis

All data were analyzed using SPSS 13.0 software (SPSS, Chicago, IL, USA). Measured data are depicted as mean ± standard deviation and compared by multivariate repeated-measures analysis of variance. A statistical difference of *P*<0.05 was considered significant.

Results

Histology-based group criteria

We categorized the tissue groups as normal or malignant based on the WHO classification criteria applied to the histology slides.

To minimize uncertainty when determining the composition of tissues within the probe's sensing volume, we established the criteria for categorizing tissue groups based on histology slides (Figure 3). We had a histopathologic diagnosis of 138 pieces of normal tissues and 98 pieces of papillary thyroid cancer conducted by 2 experienced pathologists. The diagnosis was made according to the NCCN Clinical Practice Guidelines in Oncology.

Effective dielectric permittivity and effective conductivity of normal thyroid tissue and thyroid cancer as a function of frequency

The mean effective dielectric permittivity was calculated as a function of frequency for both normal and malignant thyroid tissues (Figure 4A, 4B, respectively). From 0.5 to 8 GHz, the

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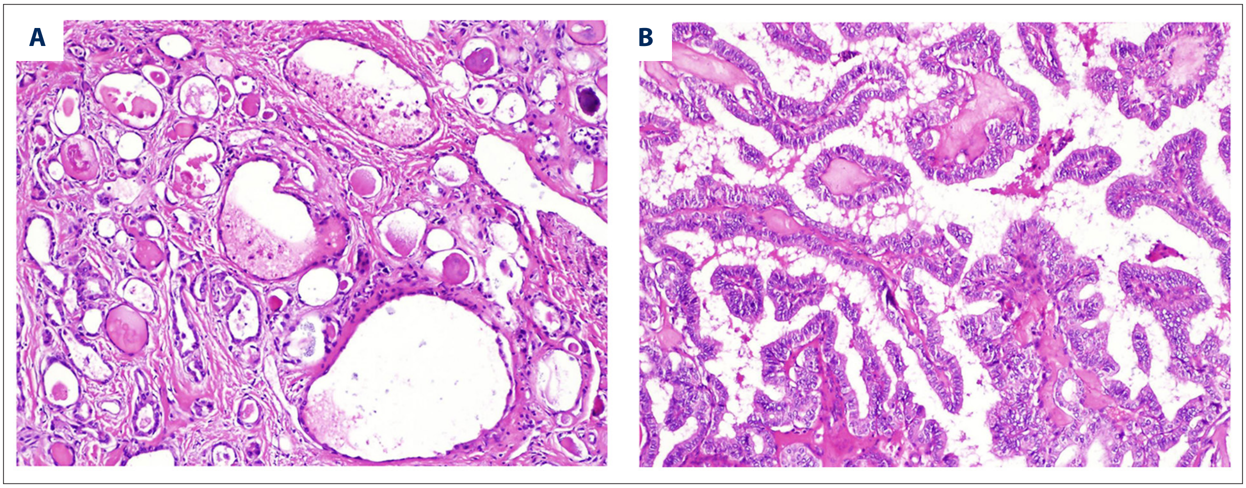

Figure 3. H&E staining of (**A**) normal thyroid tissue, (**B**) papillary thyroid cancer.

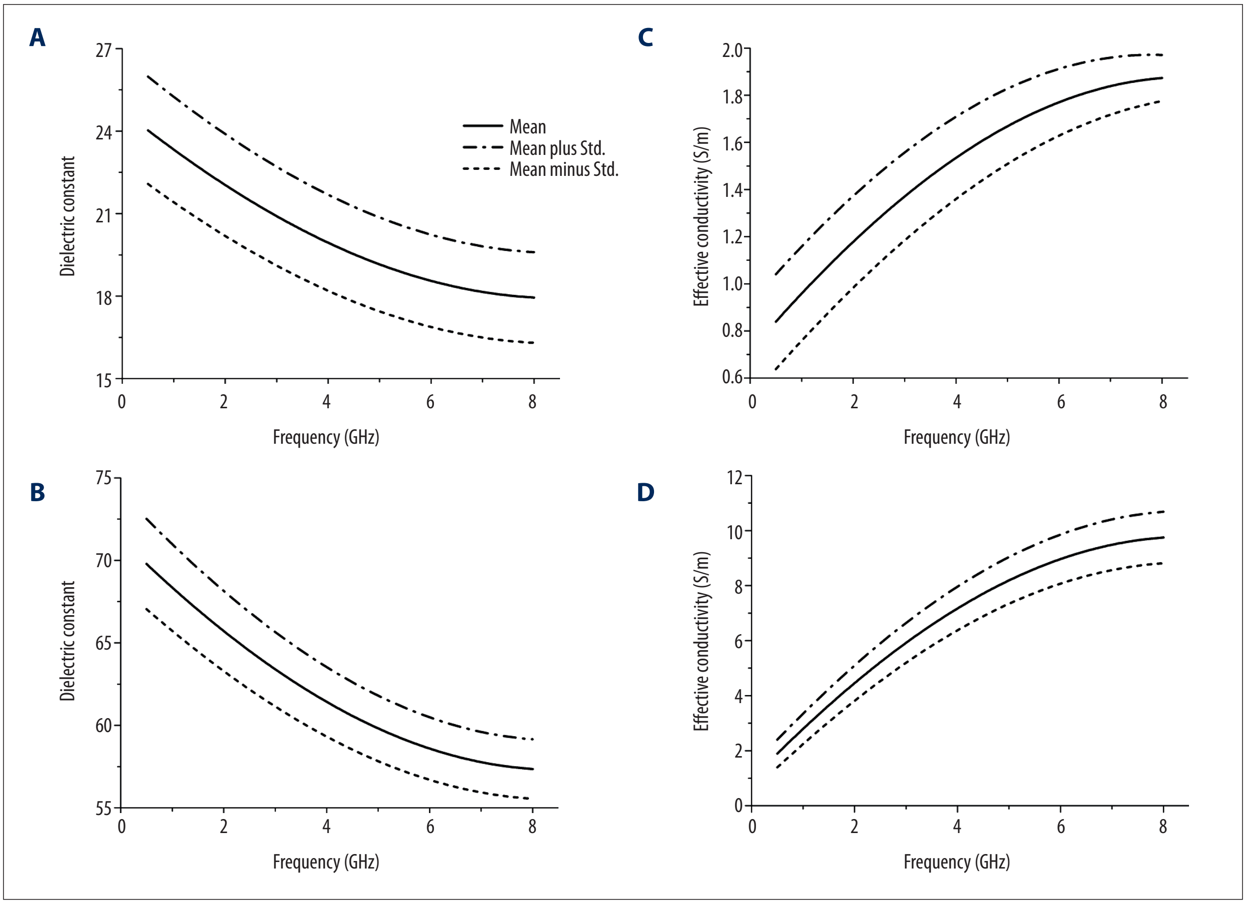

Figure 4. Dielectric constant or effective conductivity as a function of frequency. (**A, B**) Dielectric constant of (**A**) normal thyroid tissue and (**B**) thyroid cancer. (**C, D**) Effective conductivity of (**C**) normal thyroid tissue and (**D**) thyroid cancer (201 sample points).

effective dielectric permittivity of normal thyroid tissues varied from 24.026±1.951 to 17.950±1.648, and that of thyroid cancer from 69.782±2.734 to 57.356±1.802. These variations in the effective dielectric permittivity differed significantly between the normal and cancer tissues ($P<0.05$).

The mean effective conductivity was also calculated as a function of frequency for both normal and malignant thyroid tissues (Figure 4C, 4D, respectively). From 0.5 to 8 GHz, the effective conductivity of normal thyroid tissues varied from 0.8395±0.2013 to 1.8730±0.0979 S/m, and that of thyroid

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Table 1. Microwave parameters of 2 thyroid tissue types at low (0.5 GHz), middle (2 GHz, 4 GHz, 6 GHz) and high (8 GHz) frequencies.

		0.5 GHz	2 GHz	4 GHz	6 GHz	8 GHz
ε_{eff}	Normal	24.026±1.951	22.040±1.852	19.919±1.746	18.550±1.677	17.950±1.648
	Cancer	69.782±2.734	65.716±2.429	61.379±2.103	58.581±1.894	57.356±1.802
	P	0.0003	0.0002	0.0002	0.0002	0.0002
σ_{eff}, (S/m)	Normal	0.840±0.201	1.178±0.195	1.538±0.174	1.771±0.142	1.873±0.098
	Cancer	10.896±0.502	4.455±0.643	7.198±0.795	8.970±0.892	9.746±0.935
	P	0.0243	0.0014	0.0009	0.0002	0.0000
Re(Z*), (Ω)	Normal	74.254±3.577	46.645±3.511	27.287±1.458	20.152±0.755	16.756±0.404
	Cancer	30.561±0.671	23.798±1.660	12.346±0.667	8.818±0.422	7.262±0.333
	P	0.0017	0.0025	0.0008	0.0001	0.0000
Im(Z*), (Ω)	Normal	11.392±0.948	28.308±1.266	22.811±1.131	18.290±0.711	15.677±0.416
	Cancer	15.749±0.287	15.958±0.571	10.968±0.508	8.300±0.368	6.971±0.303
	P	0.0103	0.0009	0.0007	0.0002	0.0000

ε_{eff} – effective dielectric permittivity; σ_{eff} – effective conductivity; Re(Z*) – real part of impedance; Im(Z*) – imaginary part of impedance; p – cancer group compared with normal group.

cancer from 1.8960±0.5024 to 9.7461±0.9349 S/m. These variations in the effective conductivity differed significantly between the normal and cancer tissues (*P*<0.05).

To be more specific, the microwave parameters of 2 thyroid tissue types at low (0.5 GHz), middle (2GHz, 4GHz, 6GHz), and high (8 GHz) frequencies were described and compared (Table 1). It was obvious that the effective dielectric permittivity and effective conductivity of thyroid cancers significantly differed from those of normal tissues at low, middle, and high frequencies.

Real and imaginary part of impedance of normal thyroid tissue and thyroid cancer

The real and imaginary part of impedance of 2 thyroid tissue types at low (0.5 GHz), middle (2GHz, 4GHz, 6GHz), and high (8 GHz) frequencies were also described and compared (Table 1). It was obvious that real and imaginary part of impedance of thyroid cancers significantly differed from those of normal tissues at low, middle, and high frequencies (*P*<0.05).

Discussion

This study investigated the feasibility of applying microwave theory to differentiate malignant thyroid cancer from normal thyroid tissues. The dielectric properties (effective dielectric permittivity and effective conductivity) of 236 thyroid tissues from 48 patients were determined. It was found that the normal and malignant tissues differed significantly with respect to both of these parameters.

Previous relevant research has sought to differentiate normal and malignant cells based on differences in proliferation, cytoskeleton, metabolism, and other functional categories. It is believed that the electrical properties of cells vary as a result of these differences [18, 19]. A previous report [20] showed that electrical impedance signal features were useful to distinguish between malignant and benign thyroid nodules. In the present study, we also investigated the real part and the imaginary part of complex microwave impedance of 2 thyroid tissue types at low (0.5 GHz), middle (2GHz, 4GHz, 6GHz), and high (8 GHz) frequencies and found that there were significant differences in all 3 kinds of frequencies. When only P values were taken into account, there seemed to be no significant difference between impedance and permittivity and conductivity, but there were some differences in physical significance. Impedance is defined as the frequency domain ratio of the voltage to the current. In KHz and MHz frequency bands, it is not hard to define and measure the voltage and current; thus, the impedance is more convenience to use. Therefore, the frequencies used in most previously published papers using impedance for thyroid cancer diagnosis have been in the KHz or MHz range [11,12,20], but in the GHz band, theories and instruments only focus on the electromagnetic wave. Thus, the voltage and current are difficult to define, so we chose permittivity and conductivity, which are macroscopic manifestations of microscopic physical mechanisms and are more comprehensive and convenient to use. However, there are no data

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in the literature related to the effective dielectric permittivity or effective conductivity. Our present results did not indicate so great a fold-change between normal and malignant thyroid tissues. This may be due, at least partly, to the relative lack of adipose tissue surrounding the thyroid; therefore, there is less water and there are lower dielectric properties.

When measuring the dielectric parameters of any material, there must be stable and continuous contact with the dielectric probe. This is easiest when the material tested is soft or liquid. Some probes that are suited for hard materials are not recommended for measuring the dielectric properties of softer human tissues.

Compared to conventional diagnostic modalities such as immunohistochemistry, microwave detection has the advantages of being fast, easy to use, and low-cost. Recently, several new diagnostic and treatment methods have emerged [21,22]. Microwave theory is very promising for early diagnosis and strategizing treatment in thyroid cancer, but the present study does have some limitations. For example, only the dielectric properties of normal and malignant tissues were measured, and we did not include a sufficient number of benign samples because very few patients with suspected benign lesions underwent surgery. In addition, although previous researchers have reported that the temperature and fibroconnective content of tissues may affect the dielectric properties [23], we did not analyze these parameters, and this calls for further investigation.

Conclusions

In this study, H&E staining was used as the criterion standard to confirm the histological type of the tissue as normal thyroid or malignant thyroid cancer. The microwave parameters (effective dielectric permittivity and effective conductivity) were measured from 0.5 GHz to 8 GHz with 201 sample points. Each of the microwave parameters were measured in both groups of tissues over the same frequency range and compared. It was determined that both the effective dielectric permittivity and effective conductivity of the 2 groups were significantly different. Based on these differences, thyroid cancer could be differentiated from normal thyroid tissue. This suggests that these microwave parameters may be a viable method to use in diagnosis of thyroid cancer.

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