Journal of Surgical Research 171, 650–656 (2011)
doi:10.1016/j.jss.2010.05.031

Intraoperative Detection of Thyroid Carcinoma by Fourier Transform Infrared Spectrometry

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Submitted for publication January 26, 2010

Background. **Fourier transform infrared (FTIR) spectroscopy is a powerful tool for distinguishing cancerous tissue from normal one. Our aim in this study was to establish tissue discriminant analysis for thyroid malignancy and benign samples intraoperatively using FTIR spectroscopy.**

Methods. **Seventeen papillary thyroid cancer and 43 nodular goiter tissues were obtained and underwent FTIR spectroscopy scanning intraoperatively. Nine peak positions were identified and assigned. Peak position values and wave intensity ratios were measured in every single spectrum. Data of malignant and benign groups were compared and equations of canonical discriminant analysis were established.**

Results. **Peak positions of P1640, P1240, P1550, and peak intensity ratios of I3375/I1460, I1640/I1460, I1400/I1460, I1550/I1080, I1080/I1460, and I1640/I1550 of thyroid papillary carcinoma group are significantly different from nodular goiter group. The sensitivity, specificity, and accuracy rate of the discriminants are 83.3%, 95.2%, and 91.67%, respectively.**

Conclusion. **FTIR spectroscopy technique in combination with canonical discriminant analysis method can achieve fast and accurate discrimination for malignant and benign thyroid nodules during operation**

Key Words: **FTIR; thyroid tumor; canonical discriminant analysis.**

INTRODUCTION

Thyroid nodules are common. The prevalence of palpable thyroid nodules has been estimated to be 4% of the population [1]. Thyroid cancer accounts for almost 1% of all malignancies [1, 2]. Papillary thyroid cancer is the most common subtype of thyroid cancer. In 95% of cases, thyroid cancer presents as a solitary thyroid nodule [3].

Prompt and accurate diagnosis is crucial for the prognosis of thyroid cancer. The value of preoperative diagnostic methods such as ultrasonography, computed tomography, and thyroid scanning in the evaluation of thyroid nodules is limited and, therefore, they are not commonly practiced [4]. Fine-needle aspiration (FNA) is the primary diagnostic procedure in diagnosing thyroid malignancy and guides surgeons on patient selection for thyroidectomy in U.S. and European countries. Reported accuracy rate exceeds 80% according to most studies [5]. However, patients with negative FNA findings do not necessarily undergo surgery and are often considered in statistical analysis. This may lead to bias in many reported sensitivity of FNA. Tee *et al.* reviewed published literature from 1966 to 2005 and found that FNA could miss up to a third of all thyroid malignancy [6].

The final diagnosis relies on the gold standard of histopathologic diagnosis. However, this method is a time-consuming process, which involves fixation, dehydration, embedding, slicing, and the complex process of histochemical staining technique. The diagnosis depends on the pathologist's subjective judgment and experience. Moreover, it is limited to the area being examined and requires extensive human observations to

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0022-4804/$36.00

recognize both the constitutive histologic entities and the pathologic states. Great emphasis is placed on finding diagnostic methods that may enhance the ability to differentiate between benign and malignant tissues, to make fast and accurate decisions during operation, and to avoid performing unnecessary extensive procedures or repeated operations.

The generation and progression of cancer manifest themselves at the molecular level before morphologic changes take place, which can not be detected by conventional techniques, such as CT scanning or even pathologic examination. Fourier transform infrared (FTIR) spectroscopy, on the other hand, is sensitive to changes in molecular compositions and structures. With the absorption of electromagnetic radiation in the middle infrared range (from 4000 cm^{-1} to 400 cm^{-1} wave numbers), FTIR spectroscopy has been proven to be a powerful tool to detect changes at the molecular level [7–9]. It permits the rapid collection of spectrum obtained from millimeter-sized samples, which in principle, can be scanned to provide biochemical signatures of tissue samples that associate with the generation and progression of malignancy. FTIR spectroscopy has been utilized to detect carcinoma of several types of organs [10–14].

The purpose of our study was to explore the possibility of establishing a quick and accurate diagnostic method by intraoperative application of FTIR spectroscopy and differentiate malignancy from benign thyroid nodules.

MATERIALS AND METHODS

Tissue Collection

Sixty patients with thyroid nodules underwent surgery in our hospital from November, 2006 to March 2007. The average age of patients was 46 ± 15 y (range, 18–77 y). Preoperative diagnoses were made based on thorough history inquiry of patients, complete physical examination of head and neck, and auxiliary tests including serology, biomedical tests, and the report of ultrasonography. Generally, a mass in the cervical anterior region is the most common symptom. If the mass is single, solid, and unilateral, combined with necessary image technology, the patient is strongly recommended to have surgery. Tissue samples for FTIR scanning were obtained from the center of the thyroid nodules during operation, and were immediately (within 3 min at maximum) prepared to approximately 1.0 cm × 1.0 cm × 0.5 cm in size and mounted on ATR detection plate attached to FTIR spectroscopic equipment without special sample pretreatment. All tissue samples were scanned for spectra intraoperatively. Each scan took approximately 1–2 min. After scanning, the same tissue samples were then processed as paraffin embedded blocks and sent to pathologists for pathologic diagnosis. Forty-three of these patients were histopathologically diagnosed with nodular goiter, while 17 were papillary thyroid cancer. The study was approved by ethical committee of Peking University Health Science Center, and all participants gave their written, informed consents to the study.

FTIR Measurement

Thyroid tissue samples were measured using attenuated total reflection (ATR) equipped with a liquid-nitrogen-cooled mercury cadmium telluride detector (Fourier transform infrared spectrometer, WQF-660; Beijing RuiLi Analytical Apparatus Corp., Beijing, China). Mid-infrared radiation was passed to and from the ATR accessory. Spectra were measured at a resolution of 4 cm^{-1} and 32 scans was co-added to achieve an acceptable signal-to-noise ratio, with wave number ranging from 4000 cm^{-1} to 800 cm^{-1}. Background spectrum was recorded before scanning every sample tissue and was subtracted from sample spectrum automatically to eliminate atmospheric effects.

Data Processing

A total of 60 spectra were obtained, baseline corrected, straight-line generated, and smoothed using a 9-point moving average with the aid of OMNIC E.S.P. ver. 5.0 software (Nicolet Instrument Co., Madison, WI, USA). For each spectrum, data of selected peak positions and wave intensity ratios were measured and recorded. Test of normal distribution and variance of homogeneity were performed in all parameters, including nine peak positions and 12 relative wave intensity ratios. For normal distributed data, *t*-test was adopted to examine the differences between the two groups, while for non-normal distributed data, Mann-Whitney U test was performed. Canonical discriminant analysis (CDA, SPSS release 11.0.0; Chicago, IL) was carried out to distinguish benign thyroid tissue from thyroid cancer. Stepwise method was applied to choose variables of peak positions and intensity ratios that contribute most to the discriminant function. Two discriminant equations were established. Sensitivity (true positives/[true positives + false negative]), specificity (true negatives/[true negatives + false positives]), accuracy (true positives + true negatives/total evaluations), and positive predictive value (true positive/[true positive + false positive]) of CDA were calculated for FTIR data. Pathologic findings of thyroid specimens as gold standard were compared with the CDA classification later. Cross validation was employed to evaluate the discriminating power of CDA.

RESULTS

Pathologic Examination

Surgically removed thyroid tissues were fixed in formalin and sent to pathologists for diagnosis immediately after FTIR spectroscopy scanning. Seventeen papillary thyroid carcinoma and 43 nodular goiters were pathologically diagnosed.

FTIR Spectrum Scanning

Table 1 is the preliminary assignment of FTIR bands of thyroid samples. Figure 1 shows the typical FTIR spectra of nodular goiter and papillary thyroid cancer. Differences of band shifts and intensity ratio variances were noted in the spectra between benign and cancerous group; however, any single peak position or wave intensity ratio change (such as the cancer peak) could not sufficiently distinguish the two groups.

Statistical Results

Comparisons of Peak Positions and Wave Intensity Ratios Between Two Groups

Student *t*-test for normal distributed data and Mann-Whitney U test for non-normal distributed data were carried out. Peak intensity of I1460 is relatively stable