Evaluation of the Role of Magnetic Resonance Spectroscopy in the Diagnosis of Follicular Malignancies of Thyroid

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Objectives: To evaluate role of magnetic resonance spectroscopy in differentiating benign from malignant follicular nodules.

Design: Prospective study.

Setting: Department of Surgery in collaboration with Department of Radio Diagnosis, Maulana Azad Medical College, Delhi, India.

Patients: Twenty-five patients with a solitary thyroid nodule with follicular etiology.

Interventions: Magnetic resonance spectroscopy was carried out in all the cases, and its findings were compared with the final diagnosis based on histopathological examination of sample obtained at surgery.

Main Outcome Measures: Choline peak detected on MRS.

Results: There were 17 benign cases, 16 follicular adenomas, and 1 colloid goiter. Of the 17 benign cases, only 1 showed choline peak; however, all 8 follicular carcinoma cases showed prominent choline peak. Hence, the sensitivity is 100% while the specificity is 94.11%.

Conclusion: Magnetic resonance spectroscopy may prove to be a sensitive diagnostic tool in differentiating follicular adenomas from carcinomas.

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Hypothyroid Nodules Are a Common Clinical Entity; Present in 4% to 7% of the General Population. The vast majority of these nodules are benign, with only 5% of all solitary nodules proving to be malignant. Fine-needle aspiration cytology is an excellent diagnostic modality for papillary cancers, medullary cancers, colloid goiter, and lymphoma, with an accuracy of as high as 97% in expert hands, but it has limitations such as pain, risk of hematoma formation, indeterminate cytology, and inability to differentiate between benign and malignant follicular lesions. Computed tomography and magnetic resonance imaging may give an accurate assessment of the goiter size and its mediastinal extension and relation to the major structures in head and neck but cannot be relied on for differentiating benign from malignant lesions.

A noninvasive diagnostic imaging technique that can accurately predict malignancy in thyroid nodules will be useful in thyroid evaluation. Magnetic resonance spectroscopy (MRS) is the only noninvasive modality capable of measuring chemicals/metabolites in the human body. These are measured by their different magnetic frequencies or chemical shifts. This technique has been used as a diagnostic modality for various cancers. Limited literature is available about its in vivo use for thyroid lesions.

The present study was carried out to evaluate the role of MRS in differentiating benign follicular lesions from malignant ones, which cannot be done by any other established diagnostic modality.

Methods: The present study was conducted in the Department of Surgery in collaboration with the Department of Radio Diagnosis, Maulana Azad Medical College, New Delhi, India. This study was approved by the ethical committee of the institution. Patients who fulfilled the following 3 criteria were included in the study: presenting with solitary thyroid nodule, euthyroid status, and fine-needle aspiration cytology (FNAC) findings suggestive of follicular etiology.
A total of 25 such patients who presented to the surgical outpatient department from February 2007 to April 2009 were enrolled in the study. Patients with multiple nodules, hypothyroid/hyperthyroid status determined biochemically, or FNAC findings suggestive of findings other than follicular etiology were excluded from the study. Patients were also excluded if they were pregnant, had an electrically powered implanted device (eg, pacemaker), or had previously diagnosed cancer of the head or neck. Informed consent was taken from all the patients. A detailed medical history and clinical examination of all patients was performed. All patients underwent indirect laryngoscopy, x-ray of the soft tissue of the neck, anteroposterior and lateral view, and routine hematological investigations.

Magnetic resonance spectroscopy was carried out on a 1.5-T superconductive system (Siemens Magnetom, Erlangen, Germany) with gradient strength of 33 mT/m. A fast scout scan in sagittal, axial, and coronal planes was obtained. A voxel size of 10 to 20 mm, depending on the size of the lesion, was placed on the lesion, and its position was checked in all the 3 planes. The scan technique used was the point-resolved spectroscopy single-voxel technique. The sequence parameters used were echo time, 136 milliseconds and time to repetition, 2000 milliseconds, with sampling number 512, averaging 16, and average scan time of 4.26 minutes. It was followed by water suppression pulses to be followed by data acquisition. Choline peak was specifically looked for. Fisher exact test was applied and P value calculated.

RESULTS

A total of 25 patients were enrolled in the study. The female to male ratio was 16:9. The mean age of the patients was 42.2 years (range, 23-62 years). Histopathological findings were compared with MRS findings. There were 17 benign cases, 16 follicular adenomas, and 1 colloid goiter. Of the 17 benign cases, only 1 showed choline peak; however, all 8 follicular carcinoma cases showed prominent choline peak. The height of the choline peak depends on the amount and nature of tissues under the voxel. Of 8 follicular carcinoma cases, 2 were widely invasive and 6 minimally invasive. The choline peak was higher in cases of widely invasive malignancies (Figure, A) than minimally invasive ones (Figure, B). Sixteen of the 17 benign cases did not exhibit the characteristic choline peak (Figure, C). The correlation analysis of MRS with histopathology is depicted in the Table. The sensitivity of this technique is 100%, while the specificity is 94.11%, with a positive predictive value of 88.88% and negative predictive value of 100% (P < .001 indicated statistical significance).

COMMENT

The normal thyroid gland is impalpable. The term goiter (the Latin is guttur, meaning the throat) is used to describe generalized enlargement of the thyroid. A solitary thyroid nodule is defined as a palpable, discrete
swelling in an otherwise apparently normal gland. The prevalence of palpable thyroid nodules varies from 4% to 7%, increases with age, and is greater in women and those who have been exposed to radiation. The importance of solitary thyroid nodule lies in the risk of neoplasia compared with other thyroid swellings. Some 15% of isolated swellings prove to be malignant, and an additional 30% to 40% are follicular adenomas. The remainder are nonneoplastic, largely consisting of areas of colloid degeneration, thyroiditis, or cysts.

While the vast majority of these lesions are benign, the exclusion of thyroid malignancy remains a significant diagnostic problem. The patient's age, sex, and tumor size and the presence of multiple nodules all influence the relative risk of malignancy, but currently, a diagnosis can only be made using tissue material examined either cytologically or histologically. Fine-needle aspiration cytology, although accurate in differentiating papillary, medullary, and anaplastic carcinomas, is generally unable to differentiate benign from malignant follicular neoplasms.

Historically, follicular carcinoma is considered the second most common malignancy of the thyroid gland, with a reported incidence of 5% to 20%. However, LiVolsi and Asa10 and DeMay et al11 reported a much lower incidence of this malignancy (1%). This decrease in incidence of follicular carcinoma has been attributed to changing diagnostic criteria, an increase in incidence of papillary carcinoma, and the addition of iodine to our diet.10,11

Tumors that are arbitrarily designated as follicular adenomas and follicular carcinomas are indistinguishable in terms of clinical, radiological, and gross pathological features. In most cases, the cellular components of both types of tumors have the same histomorphology. In such tumors the criterion for malignancy is the finding of capsular or vascular invasion at the periphery of the neoplasm. This requires surgical removal of the entire tumor and extensive laboratory examination that is rarely complete. For example, an average of 8 paraffin blocks is recommended to adequately examine the perimeter of a follicular tumor.11 As such, the diagnosis of malignancy depends very much on sampling and is, at times, pure chance. Even when the entire tumor capsule is examined, it is still not always possible to absolutely discriminate benign and malignant follicular neoplasms. Different pathologists may classify the same lesion as either an atypical adenoma or an encapsulated follicular carcinoma. Thus, while the treatment of such tumors may be the same, the decision as to whether a patient has thyroid cancer may become a matter of the majority opinion.

Ultrasoundography, an important modality in the treatment of patients with thyroid nodules, has little discriminatory value in distinguishing benign from malignant lesions. Although most thyroid cancers appear solid, hypoechoic, and without a peripheral ring on ultrasonography, exceptions are common. Computed tomography and magnetic resonance imaging allow rapid and accurate assessment of the size of a goiter, its extension into the mediastinum, and its relationship to and impingement on major structures within the chest and neck. It can also identify mediastinal masses as thyroidal in origin, eliminating the need for further invasive testing. However, their accuracy in differentiating benign from malignant lesions is usually low.

Magnetic resonance spectroscopy is the only noninvasive technique capable of measuring chemicals/metabolites within the body.12 The metabolites are measured using their slightly different magnetic frequency or chemical shifts. Because in many pathological processes metabolic changes precede anatomic changes during disease progression and treatment, MRS offers a method for early detection of new disease and can influence the therapeutic success or failure. The nuclei with odd numbers of protons/neutrons such as H1, P31, C13, and F19 are commonly observed in MRS, as they have a magnetic moment and thus interact with external field.

An extremely important observation was made in the early 1970s by Damadian,14 who found that the relaxation times of water protons in malignant tissues were longer than those of nonmalignant tissues. He suggested that this represented a qualitative difference between normal and malignant cells and that MRS might be used to diagnose malignancy. The concept that malignant cells produce a large number of H1 magnetic resonance–visible molecules, few of which are observable in healthy tissues, has been explored as a diagnostic modality for cancer of the human uterine cervix, colon, rectum, breast, and prostate.

Literature about MRS application for thyroid lesions is limited. All of the studies done initially were ex vivo; either MRS was performed on FNAC specimen or on tissues obtained at surgery.15-17 In one study,13 MRS was carried out over tissue obtained at the time of surgery from 53 patients undergoing partial or total thyroidectomy for solitary thyroid nodule. When compared with histological diagnosis, 1H MRS distinguished normal thyroid tissue from invasive papillary, anaplastic, and medullary carcinoma with P < .001, negative predictive value of 100%, and specificity of 52%.

In another study,16 results of MRS of FNAC specimens were compared with MRS of tissue specimens obtained from 70 patients after surgery. The study showed that the sensitivity of MRS in excluding thyroid malignancy in a solitary thyroid nodule based on assessment of fine-needle biopsy is 95% compared with 100% in tissue. Our last publication7 was the only in vivo study showcasing the usefulness of MRS in solitary thyroid nodules.

In this study, we focused on follicular lesions because in follicular pathologies, the available diagnostic modalities cannot differentiate between benign and malignant lesions. A total of 25 patients were included in this study who presented to us with FNAC-proven follicular thyroid nodule. Findings of MRS were compared with histopathology of thyroid specimens obtained at surgery. There were 8 malignant cases and 17 benign ones. Choline peak was specifically looked for. It was observed that presence or absence of choline peak correlated well with presence or absence of malignant foci within the nodule (sensitivity, 100%; specificity, 94.11%).

Importance of choline peak has been proved earlier by few centers in cases of carcinoma of the breast.18,19 The choline peak at 3.22 ppm is mainly due to glycerophosphocholine and glycerophosphoethanolamine that form phospholipids of the cell membranes. The choline content rises in malignancy because of rapid multiplication and proliferation of cells. The height of the choline peak
depends on the amount and nature of tissues under voxel. If there is more necrotic tissue under the voxel, there will be a prominent lactate peak, seen at 1.33 ppm, as a result of anaerobic glycolysis.

To date, no in vivo study has been published that evaluates the role of MRS in follicular neoplasms. This study is an attempt to evaluate the role of MRS in differentiating genuinely benign from truly malignant follicular neoplasms.

The high sensitivity and specificity seen in this study may be because of a small sample size. Nonetheless, this marks a new beginning in our pursuit of an ideal diagnostic tool for follicular thyroid nodules.

Follicular thyroid nodules always pose a diagnostic dilemma. Currently available diagnostic modalities fail to differentiate follicular adenomas from carcinomas. Magnetic resonance spectroscopy may prove to be a useful noninvasive diagnostic tool in carrying out this differentiation and may add to the diagnostic algorithm.

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