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Central echogenic areas in thyroid nodules: Diagnostic performance in prediction of papillary cancer

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ABSTRACT

Purpose: To determine the diagnostic performance of the "central echogenic area" sonographic finding in differentiating papillary carcinomas from benign nodules and to how this finding may be used to improve fine needle aspiration(FNA) technique/utilization.

Materials and methods: We retrospectively analyzed ultrasound guided FNAs of thyroid nodules between 1 and 3 cm for central echogenic areas. 92 patients (evenly distributed benign vs papillary carcinoma) were evaluated by a blinded reader for areas of non-shadowing homogenously echogenic centers within the nodules and correlated with FNA proven pathologic diagnosis. A selection of nodules with the central echogenic area finding were selected for further slide review to establish a pathologic basis for the finding.

Results: Diagnostic performance of the "central echogenic area" feature in papillary thyroid cancers was 52.2% sensitive and 91.3% specific for papillary thyroid carcinoma with a PPV of 85.7% and NPV of 65.6%. There was a significant correlation with a $p < 0.01$ between the central echogenic area finding and papillary carcinoma. On pathologic slide review, nodules with central echogenic areas consistently demonstrated a central scar with conglomerate fibrosis and very few viable cells.

Conclusion: Despite its relatively low sensitivity, the central echogenic area finding is highly specific for papillary carcinoma of the thyroid and can be a useful sonographic finding in decisions regarding FNA. Additionally, due to the paucity of cells and high density of conglomerate fibrosis, central echogenic areas should be avoided during FNA to decrease the chance of an inadequate sample collection.

1. Introduction

Nodules within the thyroid are an extremely common finding and have an estimated prevalence of 19–68% in adult patients [1,2]. Although nodules are common, only a small minority of these nodules (1–15%) are proven to be malignant [3–5]. The relatively low prevalence of cancerous nodules shifts the clinical impetus away from nodule detection and rather towards identification of features that help determine which nodules require further evaluation by fine needle aspiration (FNA) and ultimately surgical excision for definitive treatment. The first step recommended by all consensus guidelines in determining whether further procedures are required is a dedicated thyroid ultrasound [2,3,6,7]. Ultrasound has been shown to be the imaging modality of choice in thyroid evaluation due to the ability to non-invasively visualize nodule morphology and characterize internal architecture with exquisite high resolution that typically exceeds all other imaging modalities. Thyroid ultrasound is also advantageous because it is a low-cost imaging modality that does not use ionizing radiation.

Many sonographic features of thyroid nodules have been well- studied and are used clinically to evaluate nodules for malignancies. Sonographic features commonly used in clinical practice include taller than wide shape, presence of microcalcifications, predominantly solid composition, hypoechoic appearance, and nodule margins [7–10]. However, as ultrasound technology advances and image resolution have improved, we have found that some malignant nodules often demonstrate a central echogenic area. This feature has not been previously described but may be a helpful sonographic finding that should increase suspicion for malignancy in thyroid nodules.

In a majority of sonographic pattern based approaches to thyroid nodules, echogenic (hyperechoic) appearance compared to adjacent thyroid has traditionally been considered to be suggestive of benignity [6,11,12]. However because central echogenic areas could potentially be confused for "echogenic nodules," the latter more suggestive of benignity, we sought to study this previously undescribed sonographic finding in more detail. Moreover, recent studies have demonstrated a correlation between nodule fibrosis and malignancy [13]. Thus, a

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dedicated evaluation of this more nuanced sonographic appearance is merited. The purpose of this study was to determine whether non-shadowing echogenic areas contained *within* thyroid nodules seen on high resolution ultrasound studies can be used to identify potential papillary carcinomas of the thyroid.

2. Materials and methods

Standard Institutional Board Review approval was obtained from our research compliance office prior to implementation of this study. The patient cohort in this study was comprised of every patient who underwent ultrasound guided fine needle aspiration (FNA) between January 2010 and December 2015 by the Stanford Department of Radiology. We retrospectively reviewed electronic medical records to obtain pertinent patient information including study dates, sex, age, FNA proven pathologic diagnosis, and prior ultrasound records.

All ultrasound studies were generated by trained sonographers using either the Siemens S2000 (Siemens Medical Solutions, Mountain View, CA) or GE Logiq E9 (GE Healthcare, Waukesha, WI). Images were obtained with patients positioned supine and slightly hyperextended necks. Transverse and longitudinal images using grayscale imaging with color or power Doppler imaging when necessary were evaluated in each study. High resolution scans were necessary to evaluate for discrete central echogenic areas and because of this, 12–18 MHz frequencies were used exclusively when evaluating thyroid nodules. All studies were checked and interpreted by board-certified radiologists at the time of the examination to ensure image quality and adequacy.

From the initial patient cohort, patients with follicular carcinomas were excluded because diagnosis requires surgical excision regardless of imaging findings. Anaplastic carcinomas were excluded because they are upstaged to T4 under current ATA guidelines and are usually not surgical candidates [14]. Nodules measuring < 1 cm were excluded from this study because surgical management is not recommended even in the setting of known carcinoma [15] [16]. Likewise, solid nodules that measured > 3 cm at their greatest diameter were not included in the cohort because most current guidelines recommend biopsy regardless of suspicious sonographic features [7,14,11]. The final nodule population selected was a size matched control set including all remaining papillary carcinomas and equivalent benign nodules. Size matched controls were selected from all nodules not previously excluded due to size or pathologic diagnosis. Controls were randomly selected using the random number (RAND) generating function in Microsoft Excel (Version 1711; Microsoft, 2016) from a selection of nodules that had measured lengths with in 0.1 mm of the 2 largest dimensions and 0.2 mm of the third measured dimension.

All ultrasound images were evaluated by a board-certified radiologist (R.B.J) with more than 25 years of experience reading sonographic studies of the thyroid. Our reader was blinded to the pathologic diagnosis, the ratio of malignant vs benign nodules within the study, and original image interpretations. Each nodule was evaluated retrospectively on a Centricity picture archiving and communication system workstation (GE Healthcare) with Barco color monitors (Barco Inc, Kortrijk, Belgium) with either 2-megapixel 1600 × 1200 or 2.3-megapixel 1920 × 1200 resolution.

Each nodule was evaluated for the central echogenic area feature in a binary manner (present vs absent). Nodules were evaluated in transverse and longitudinal images including looped cine clips taken prior to FNA biopsy. The central echogenic area feature was defined as a non-shadowing homogenous echogenic area (excluding microcalcifications) that is centrally located within a relatively hypoechoic nodule (Fig. 1). A minimum size cutoff of 0.3 mm was applied to the central echogenic area definition to limit the inclusion of artefactual variations in echogenicity as echogenic areas. There is no maximum size criteria for a central echogenic area but it should be completely surrounded by the remaining nodule and should not abut the adjacent normal thyroid parenchyma (Fig. 2).

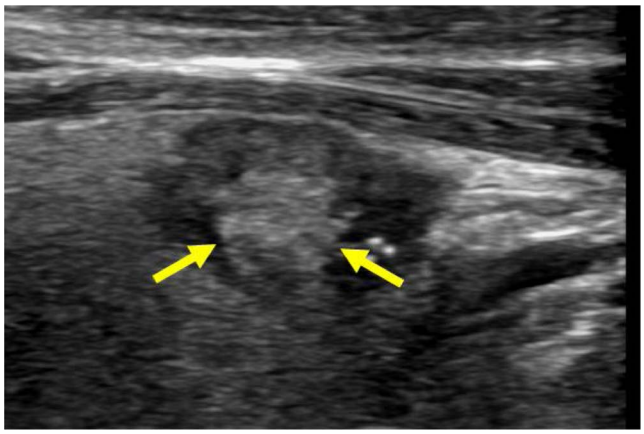

Fig. 1. 58 year old woman with papillary carcinoma. Longitudinal ultrasound of the right thyroid demonstrating a non-shadowing area of isoechoic tissue centrally located within a nodule (arrow) consistent with the central echogenic area finding.

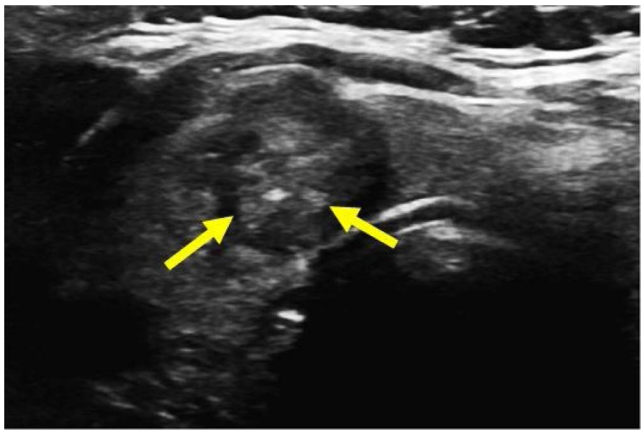

Fig. 2. 33 year old woman with papillary carcinoma. Transverse ultrasound of the isthmus demonstrating an example of the central echogenic area (arrow) with a non-uniform hypoechoic rim circumferentially around the nodule.

A random subset of nodules found to demonstrate the central echogenic area was selected for further pathologic evaluation. The nodules were selected randomly from all nodules demonstrating a central echogenic area with no preference given for nodule size or pathologic diagnosis. The sample nodules that underwent surgical resection were examined microscopically using formalin-fixed, paraffin embedded tissue sections routinely hematoxylin-eosin stained and assessed at a 40× and 100× magnification by a board-certified pathologist (AJG).

Statistical analysis was completed using SPSS (SPSS, version 24.0 for Windows; SPSS, Chicago, Ill). The central echogenic area feature was evaluated for association with malignant tissue diagnosis vs benignity. FNA proven diagnosis was used as the reference standard to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A significant difference was defined as a P value less than 0.05. A chi squared and Fisher exact test were used for comparison of the categorical variable. Additionally, a logistic regression analysis method was performed to evaluate the central echogenic area finding as a predictor for malignancy ($P < 0.05$) and the associated odds ratio.

3. Results

Between January 2010 to December 2015 a total of 1181 patients under went ultrasound guided FNA of the thyroid by Stanford's Department of Radiology. These patients had 765 nodules that