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Clinical Decision Making for Surgery using Ultrasound Characteristics of the Thyroid Nodules Classified as Category III (AUS/FLUS) in the Era of Molecular Tests

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Abstract

It has been suggested that they a gene-expression-classifier (GEC) would be worth to be used if there is low suspicion for thyroid cancer in patients with atypia of undetermined significance / follicular lesion of undetermined significance (AUS/FLUS).In our recent study among 153 patients with AUS/FLUS who underwent surgery, malignancy rate for nodules without any worrisome ultrasound features (low suspicion category) was 0%.

GEC test had a false negative rate (FNR) of 5.5% for AUS/FLUS patients, and 43% of AUS/FLUS patients have been assumed to be benign on GEC. If GEC was performed on AUS/FLUS patients with low suspicion category (35 patients) in our series, the volume of thyroidectomy would be reduced from 153 to 138 resulting in a 10% decrease with a FNR of 5.5%. If AUS/FLUS nodules with low suspicion category would not have undergone surgery, thyroidectomy volume would be reduced from 153 to 118 resulting in a 23% decrease with a FNR of 0%. These findings show that our approach has apparent advantage over the use of GEC.

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Introduction

The ongoing interest on molecular tests for atypia of undetermined significance or for follicular lesion of undetermined significance (AUS/FLUS) category of thyroid nodules continue to be alive [1]. Burman KD and Wartofsky L [1] stated that molecular analysis should be considered in the case of thyroid fine-needle aspiration results that are interpreted as AUS/FLUS or follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN). The recently updated American Thyroid Association (ATA) guidelines suggest that molecular testing may be useful after consideration of clinical and radiologic findings and after a discussion with the patient regarding the advantage and disadvantage of such an approach [2]. Therefore, I wished to make an example of such an approach by applying the radiologic findings for patients with AUS/FLUS nodules before decision for surgery, and discussed the advantage of our approach over the use of gene expression classifier (GEC), and mutational tests. In our recent study among 4,312 nodules that underwent fine needle aspiration biopsy (FNAB), 504 (11.7%) had AUS, 30% of nodules (153 of 504) with atypia of undetermined significance (AUS) underwent surgery with a malignancy rate of 23% (153 patients with nodules which were classified as AUS underwent surgery with a malignancy rate of 23%) [3]. Microcalcification, irregular margin, solid structure, and hypoechogenicity on ultrasound, an increased vascularization of the nodule on Doppler ultrasound were found to be the significant predictive risk factors for malignancy. Predictive indices generated by the combination of risk factors revealed that malignancy rate for predictive index 0 (without any predictive risk factor) was 0%, whereas it was 12% for predictive index 1 (with one predictive risk factor), 38% for index 2 (with two predictive risk factors), 52% for index 3 (with three predictive risk factors, and 100 for index 4 (with four or more predictive risk factors). Briefly, malignancy rate for nodules without any worrisome sonographic features was 0% (low suspicion category), 12% with one sonographic risk factor (intermediate suspicion category) and 53% with two or more sonographic risk factors (high suspicion category) [3]. The potential effect of GEC for AUS is calculated by assuming that 43% of AUS patients would be benign on GEC [4]. If GEC was performed on AUS/FLUS patients in our series [3] and an estimate of 43% benign profile was applied, the volume of thyroidectomy would be reduced from 153 to 87 resulting in a 43% decrease with a false negative rate of 5.5% [5]. If our predictive indices had been used, AUS/FLUS nodules with predictive risk index 0 (low suspicion category) would not have undergone surgery, and thyroidectomy volume would be reduced from 153 to 100 resulting in a 35% decrease

with a false negative rate of 0%. If patients with predictive risk indices 0 and 1 (low and intermediate suspicion categories) had not undergone surgery, thyroidectomy volume would be reduced to 57 resulting in a 63% decrease with a false negative rate of 5.2%. These findings show that our method of predictive risk indices has apparent advantage over the use of GEC. Burman and Whartofsky [1] also suggested that they would tend to use a GEC if there is low suspicion for cancer and tend to consider mutational analysis if the clinical or radiologic features raise the suspicion for cancer and the likelihood of referral for thyroidectomy is higher. GEC test had a positive predictive value (PPV) of 38% (percentage of malignant nodules with positive test result) and a false negative rate of 5.5% (percentage of malignant nodules with negative test results) for AUS/FLUS patients [5]. 2015 ATA guidelines classified thyroid nodules according to sonographic patterns as high, intermediate, low, very low and benign and estimated the risk of malignancy as > 70-90%, 10-20%, 5-10%, < 3%, and < 1%, respectively (Table 6 of ATA guidelines) [2]. Our predictive risk indices also classify the nodules into low, intermediate and high suspicion categories [3]. We recommend observation for patients with predictive index 0 category (low suspicion category) with an expected false negative rate of 0%. For patients with nodules with predictive index 1 (intermediate suspicion category) who are candidates for surgery and had 12% malignancy risk, we offer surgery or observation consulting with the patient. We recommend surgery for patients with predictive indexes 2, 3, and 4 (high suspicion category) with a PPV of 53%. Therefore, we suggest to classify AUS/FLUS nodules into three categories using predictive indices generated by ultrasound risk factors for thyroid cancer and to observe low suspicion category without GEC or any other mutational tests. If available and evaluated as cost-effective, GEC could help triage the high risk nodules within the predictive index 1 (intermediate suspicion category) to surgery and mutational analysis could be considered for high suspicion category. Available markers for gene mutation analysis (MT-7, ThyroSeq) that utilize a "Rule-In" cancer method report that between 6-28% of cases of malignancy lack a mutation of one of the included markers thereby leading to a false negative result. While gene mutation testing paradigm has not yet been validated in prospective, multi-center clinical trial, gene expression classifier (GEC) was validated for clinical utility with a large, prospective, multicenter study and has been marketed as a "rule out" test with sufficient reliability to defer surgery in AUS/FLUS patients [4]. However, cost-effectiveness of GEC testing was not validated [4]. While cost effectiveness of molecular testing is controversial, our model of predictive indices is cheap, available in every clinic and cost-effective.

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