Prospective Trial Evaluating Electrical Impedance Scanning of Thyroid Nodules Before Thyroidectomy

Final Results

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Background: Electrical impedance scanning (EIS) identifies tissue impedance changes associated with malignancy. Methods to distinguish benign from malignant thyroid nodules, particularly in patients with indeterminate cytology are lacking.
Purpose: To determine the diagnostic accuracy of EIS in the preoperative evaluation of thyroid nodules.
Patients and Methods: From September 2002 to December 2006, 216 patients underwent thyroid fine needle aspiration (FNA) and EIS prethyroidectomy in this prospective cohort study. EIS, either positive or negative for malignancy, was correlated with final histopathology. A focal bright spot over a thyroid nodule correlating with increased conductivity and/or capacitance >25% baseline sternocleidomastoid muscle impedance defined positive EIS. Study endpoints were EIS accuracy, sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV). This study has been registered in the National Institutes of Health's public trials registry at ClinicalTrials.gov. The registration number is NCT00571077.
Results: EIS correctly diagnosed 96 of 110 patients with malignant and 75 of 106 patients with benign dominant thyroid nodules: Sn = 87%, Sp = 71%, PPV = 76%, NPV = 84%: overall EIS accuracy = 79%. Pretest cancer probability of 51% (110 of 216) increased to 76% (96 of 127) post-EIS, and preoperative use of EIS would result in a significant reduction (71%, 75 of 106) in number of operations performed for benign nodules. EIS performance was similar for 109 patients with indeterminate FNA: Sn = 83%, Sp = 67%, PPV = 61%, NPV = 87%, accuracy = 73%. Pretest probability of cancer increased from 39% (42 of 109) to 61% (35 of 57) post-EIS. The use of EIS would result in a significant reduction (67%, 45 of 67) in the number of purely diagnostic thyroidectomy for indeterminate FNA.
Conclusion: EIS shows promise in differentiating thyroid nodules. Further EIS hardware and software optimization is warranted to improve upon the already favorable negative predictive value in indeterminate thyroid nodules.

(*Ann Surg* 2008;247: 843–853)

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ISSN: 0003-4932/08/24705-0843
DOI: 10.1097/SLA.0b013e318165c757

The incidence of thyroid cancer in the United States is rising faster than any other malignancy[1] and has nearly doubled in the past 3 decades. This change is largely attributable to an increased ability to detect small, clinically occult papillary cancers,[2] as evidenced by the stable or improving mortality rate from thyroid cancer during this same time period. The prevalence of clinically apparent thyroid nodules is approximately 5% to 10% and the prevalence is as high as 67% on ultrasonography.[3,4] Approximately 20% to 30% of patients with thyroid nodules undergoing fine needle aspiration (FNA) will have indeterminate cytology. This, along with the modest 20% incidence of cancer in these patients means that the majority of them will undergo nontherapeutic thyroid resection, making cautious use of diagnostic testing to limit inappropriate investigations imperative.[5,6]

As the majority of patients with indeterminate FNA cytology have benign nodules, operations are undertaken primarily with diagnostic intent. This underscores the need for more accurate and less invasive methods to differentiate benign and clinically inconsequential low-risk malignant nodules from those that indeed stand to benefit from resection. Color Doppler sonography with quantitative analysis of tumor vascularity in conjunction with conventional ultrasonographic assessment of echogenicity, halo, microcalcifications, and tumor size is undergoing feasibility testing as a means of differentiating malignant from benign solid thyroid nodules in the preoperative setting.[7–10] The enhanced predictive value of this combined technique is achieved by compromising diagnostic sensitivity.[11] Preliminary studies suggest that the predictive value of ultrasonography may be enhanced significantly through the application of ultrasound thyroid elastography.[12,13] The application of F18-FDG positron emission tomography (PET) has shown high sensitivity for the diagnosis of malignancy in thyroid nodules demonstrating indeterminate cytology on preoperative FNA; however, the low specificity of the technique limits its utility.[14,15]

Cellular changes alter the flow of electrical current through living tissue, and differences in cellular electrical signature between malignant and nonmalignant tissue have been identified and studied extensively since the 1920s.[16] Electrical impedance scanning (EIS) devices are designed to measure tissue impedance characteristics and identify irregularities in conductance and capacitance that are associated with increased levels of cellular activity and malignant transformation.[17] Introducing a known, low-level, biocompatible, alternating current to the body via a handheld electrical signal generator, directing the signal through the measured tissue, and collecting the signal via a noninvasive surface probe achieve EIS measurements.

Prospective studies support the safety, feasibility, and diagnostic accuracy in detecting differences in the bioelectrical signature of benign and malignant tissue through body surface measurements of suspicious skin lesions and lymph nodes, and breast abnormalities using EIS.[18–26] Data from an earlier pilot study evaluating the clinical performance of impedance scanning for thyroid nodules requiring resection indicated that EIS is a safe, rapid, real-time, and noninvasive imaging modality with predictive value sufficient to make it an important adjunct to FNA, particularly in the setting of indeterminate cytology.[27] Presented here are the final results of that prospective, observational cohort trial conducted to determine the diagnostic accuracy of EIS in the preoperative diagnosis of thyroid nodules.

METHODS

Clinical Trial Design

A prospective single arm observational cohort trial addressing the utility of thyroid EIS in the preoperative assessment of patients scheduled to undergo thyroidectomy was conducted under the participating medical centers' institutional review board approval from September 2002 to December 2006. All subjects enrolled into the study voluntarily agreed to participate and gave written informed consent.

Thyroid EIS Examination

EIS of the thyroid was performed before scheduled thyroidectomy using the T-Scan 2000ED [TransScan Medical (Mirabel), Austin, TX). The T-Scan 2000ED consists of a handheld thyroid probe (held by the examiner) and a handheld metal cylinder (held by the patient), both connected to a computer and monitor. An EIS examination requires the placement of a conducting gel on the flat surface of the thyroid probe and on the metal cylinder used to transmit electrical current.

The metal cylinder was held in the seated (upright at approximately 45 degrees) patient's hand. A low-level biocompatible (alternating current) electrical signal (1.0–2.5 volts, maximum current 5 mA) was transmitted from the cylinder to the subject's body. The electrical circuit was completed when the handheld flat multiarray thyroid probe covered with ultrasound conducting gel was placed on the surface of the neck overlying the thyroid gland. The probe has a flat circular measuring surface with 3.5 cm diameter, on which is centered an 8×8 planar array of 2×2 sq mm electrodes. The detection surface is therefore 16×16 mm, which is covered with ultrasound conducting gel and placed on the surface of the neck overlying the thyroid gland for surface measurement of thyroid nodule impedance. Each skin surface probe sensor element measured relative distribution and alteration of the applied electrical current passing through the thyroid tissue.

Current flowed up the arm and across the neck induced by a potential difference between the metal cylinder (reference electrode) and thyroid scan probe (measuring electrode at ground potential). This device isolated the thyroid for EIS. Uniform conductivity and capacitance is characteristic of normal or benign thyroid tissue and is represented by homogeneous gray scale conductivity and capacitance maps or "images" on the T-Scan 2000ED system display monitor. Benign thyroid nodules demonstrate similar conductivity and capacitance (or impedance) to normal thyroid tissue.

A focal disturbance in electrical field distribution (disruption of parallel lines of electrical current) by a malignant tumor due to its increased conductivity and, or capacitance (or decreased impedance) appears as a focal bright white spot on the T-Scan 2000ED gray scale impedance map. Skin surface lesions or artifacts (incomplete probe contact, insufficient conducting gel, rib, clavicular head) can appear as white spots as well and were taken into account and correlated with specific localization of the thyroid nodule in question to arrive at appropriate surface recordings of thyroid impedance.

Preliminary EIS examination of the thyroid was performed to correlate skin changes (nevi, biopsy scars, skin tags, etc) that may produce false positive white spots on the impedance map display. Baseline measurements of conductivity and capacitance were obtained from the proximal sternocleidomastoid muscle in all patients. Thereafter, focused EIS examination was conducted with T-Scan 2000ED in high-resolution targeted mode over the area of interest corresponding to the sonographic or palpable thyroid abnormality.

The recordings of each thyroid lobe and isthmus were performed in a predetermined sequence in accordance with the real-time image acquisition technique (frequency range, 50–20,000 Hz). As the scan was being performed, conductivity and capacitance data were presented as a real-time, gray-scale, surface impedance map at a frequency of 1100 Hz on the computer monitor.

The impedance map acquired in targeted mode is an anatomic image that identifies the location of a lesion. Air bubbles and areas of poor contact were eliminated in order for the computer to accept the imaged thyroid sector data. When an adequate artifact-free "image" was obtained, the examiner was prompted by the device to press the record button on the probe, and the image was recorded. Conductivity and capacitance were recorded over palpable nodules or those seen by ultrasound, as well as areas of focal bright spots on the thyroid gland. The T-Scan 2000ED "images" and data obtained as part of the thyroid EIS examination were stored in a computerized database. Experienced examiners (experienced thyroid surgeons) performed and interpreted the thyroid EIS examinations. To optimize nodule localization, examiners reviewed the sonographic and FNA data before the EIS examination. Interpretation of the EIS data was done at the end of the EIS examination so investigators were blinded to the histopathology results and operative findings but not to the ultrasound and cytology data.

The change in conductivity and capacitance from baseline was calculated as the difference in conductivity and capacitance between the proximal sternocleidomastoid muscle and the thyroid nodule, respectively. Time to complete EIS of the thyroid gland was 5 to 15 minutes.

Definition of a Positive Finding on Thyroid EIS Examination

EIS was either positive or negative for malignancy and was correlated with final histopathology. The definition of a positive finding was established in a previous learning group-training data set.[27] A focal bright spot over a thyroid nodule correlating with increased conductivity (decreased impedance) and/or capacitance >25% baseline sternocleidomastoid muscle impedance, which could not be attributed to a local artifact, defined positive EIS. Focal bright spots that were not palpable or evident by ultrasound were correlated with final histopathology.

Safety Evaluation

All study subjects enrolled in this clinical trial were evaluated for device-related adverse events, including cardiac, neurologic, dermal, thermal, or allergic reactions or events. They were also queried whether they felt any discomfort or pain or experienced any other adverse reaction or sensation during the examination.

Primary Study Endpoints

This study was conducted with the primary aim to determine the diagnostic accuracy of EIS in the preoperative diagnosis of thyroid nodules. Study endpoints included accuracy, sensitivity, specificity, and positive and negative predictive values of thyroid EIS in patients scheduled for thyroid resection. Decision to perform thyroidectomy was made by the operating surgeon on the basis of standard clinical, radiologic, or cytologic factors. These factors included but were not limited to enlarging nodule on thyroid suppression; solid nodule in a patient with prior cervical radiation exposure, with Graves disease or family history of thyroid cancer; nodules with positive, indeterminate or suspicious cytology; and those with suspicious ultrasound characteristics, namely peripheral vascularization, microcalcifications, irregular margin, marked hypoechogenicity, and a shape that was taller than it was wide.

Eligibility Criteria

Adult males and nonpregnant females (age >18 years) with primary thyroid nodules, 5 mm or more in diameter who were scheduled to undergo thyroid surgery were eligible for this trial provided that they had not undergone thyroid biopsy or needle aspiration of the thyroid nodule ≤4 weeks before thyroid EIS. Written informed consent was obtained from each patient before study procedures.

Study Interventions

Study participants were scheduled for thyroid resection before study enrollment and the majority (96%) underwent prior FNA of the thyroid before providing informed consent for this prospective observational cohort study. Focused EIS examination was conducted with T-Scan 2000ED in high-resolution targeted mode over the area of interest corresponding to the sonographic or palpable thyroid abnormality. Study subjects then underwent thyroid lobectomy or total thyroidectomy, as indicated by the primary pathology. The findings of thyroid EIS were not used to alter surgical management; therefore, the operative plan was not affected by participation in this clinical trial. Thus, findings at operation, not EIS results, were the basis on which extent of resection was decided. FNA aspirate and tissue diagnosis was rendered by experienced cytologists and pathologists, respectively. Results of thyroid EIS (positive or negative for malignancy) were compared with the gold standard of permanent-section histopathology.

Our approach to indeterminate thyroid nodules is diagnostic lobectomy/isthmusectomy with completion of total thyroidectomy at the time of incident operation for unequivocal signs of malignancy (papillary thyroid carcinoma) on frozen section analysis. Otherwise, completion thyroidectomy at a second operation for final histopathology diagnosis of malignancy is undertaken. In select cases of small, minimally invasive cancers having low potential of metastases and no indication for adjuvant radioiodine therapy, lobectomy/isthmusectomy alone is sufficient.

Data and Statistical Analysis

Assuming a probability of 50% for finding malignant disease in the study population, a sample size of 200 would allow the sensitivity and specificity to be estimated to within ±10% with 95% confidence. Differences in baseline characteristics were evaluated using Fisher exact test (2-tailed) for categorical variables and the Wilcoxon rank sum test for continuous or ordinal data. Results of thyroid EIS (positive or negative for malignancy) were compared with the gold standard of permanent-section histopathology. Diagnostic accuracy of thyroid EIS was described by calculating sensitivity, specificity, positive predictive values, and negative predictive values together with 95% confidence intervals for these proportions. Continuous data were presented as either medians with ranges or means with standard deviations (±SD). Logistic regression was used to compute the relationship among clinical, sonographic, and pathologic parameters, and EIS diagnostic accuracy. Significance was determined at the $P \leq 0.05$ level (2-tailed). Statistical analyses were carried out using SPSS statistical software (version 13.0, SPSS, Inc., Chicago, IL).

RESULTS

Study Population

This study was initiated in September 2002. Enrollment ended in December 2006. Two hundred forty-four patients were assessed for eligibility and enrolled; 216 completed the study protocol. Twenty-eight patients were excluded. One was ineligible for study, 3 could not complete the thyroid EIS for technical reasons, and 24 did not undergo thyroid operation at the designated study sites. Flow of study participants through each stage of the trial is demonstrated in Figure 1.

Two hundred sixteen patients (mean age 47.3 years ± 15.8 SD) with 1 or more thyroid nodules underwent EIS before thyroid lobectomy and isthmusectomy (24.5%) or total thyroidectomy (75.5%). The majority of patients were female (78.7%), and clinically and chemically euthyroid (80.6%), Table 1. There were no reported, device-related cardiac, neurologic, dermal, thermal, or allergic reactions or serious adverse events in this study.

Of the 216 patients, 207 had preoperative FNA of a dominant thyroid nodule. FNA was negative, positive, and indeterminate for malignancy in 13.9%, 28.7%, and 50.4% of patients, respectively (Table 1, Fig. 2). All patients having FNA underwent operation. Approximately 3% (6 of 207) of fine needle aspirates in this study were unsatisfactory, and only 1 of the 62 patients with positive aspirates (1.6%) proved to be a false positive cytology in a patient with Hashimoto thyroiditis. There were 30 patients with negative FNA cytology. There was a 73% concordance between EIS and FNA (22 of 30 patients). Of the 8 patients with discrepancy noted between FNA and EIS findings (FNA−/EIS+), 3 (38%) had cancers and 5 were benign (false positives). Of the

TABLE 1. Baseline Characteristics of 216 Patients

Electrical Impedance Scanning Before Thyroidectomy	Patients (N = 216)
Characteristic	N (%)
Patient age, yr	
Median	47
Range	18–85
Gender	
Male	46 (21.3)
Female	170 (78.7)
Thyroid status before operation	
Euthyroid	174 (80.6)
Hyperthyroid	26 (12.0)
Hypothyroid	16 (7.4)
Fine needle aspiration result	
Inadequate	6 (2.8)
Not done	9 (4.2)
Negative	30 (13.9)
Positive	62 (28.7)
Indeterminate	109 (50.4)
Extent of operation	
Lobe/isthmusectomy	53 (24.5)
Total thyroidectomy	163 (75.5)
EIS conductivity	
Mean ± SD	265.3 ± 167.5
Median (range)	224.0 (53.0–1146.0)
EIS capacitance	
Mean ± SD	438.6 ± 126.5
Median (range)	431.0 (122.0–871.0)

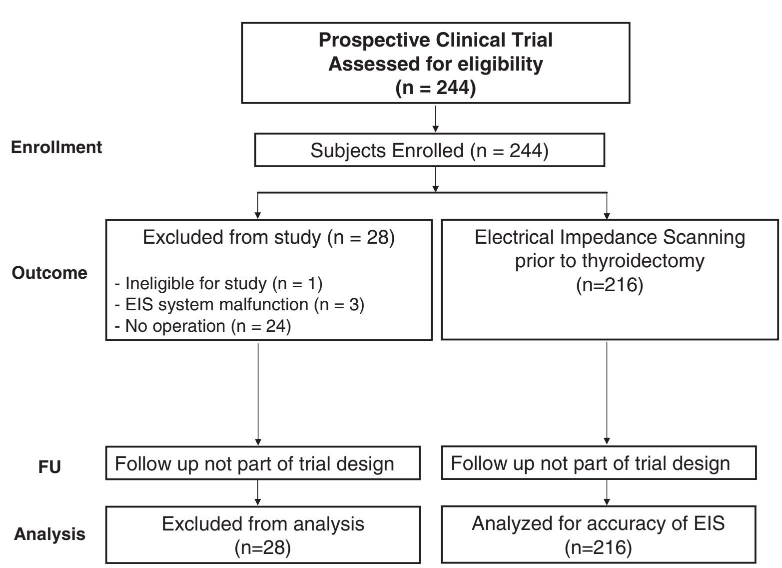

FIGURE 1. Flow of participants in a prospective observational cohort study evaluating diagnostic accuracy of EIS in the preoperative diagnosis of thyroid nodules.

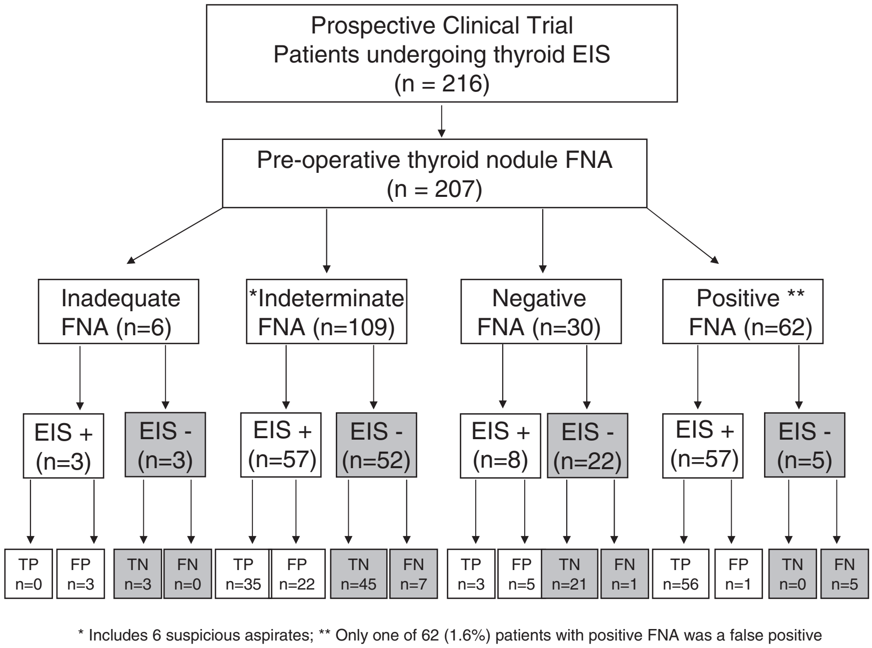

FIGURE 2. Distribution of EIS algorithm performance among 207 of 216 study participants that underwent fine needle aspiration of a thyroid nodule followed by thyroid EIS before thyroidectomy. TP, true positive; TN, true negative; FP, false positive; FN, false negative. Only 1 of the 62 patients with positive FNA (1.6%) proved to be a false positive cytology in a patient with Hashimoto thyroiditis.

TABLE 2. Thyroid Histopathology Correlated With EIS Results Among 216 Patients

Histopathology	False Negative	False Positive	True Negative	True Positive	Total
Thyroiditis (Graves or Hashimotos)	0	0	13 (100%)	0	13
Multinodular goiter	0	11 (28.9%)	27 (71.1%)	0	38
Hyperplasia or adenomatous nodule	0	17 (30.9%)	38 (69.1%)	0	55
Medullary thyroid carcinoma	3 (60.0%)	0	0	2 (40.0%)	5
Min. invasive follicular carcinoma	3 (50.0%)	0	0	3 (50.0%)	6
Widely invasive follicular carcinoma	0	0	0	10 (100%)	10
Papillary thyroid carcinoma	8 (9.0%)	0	0	81 (91.0%)	89

22 concordant (FNA−/EIS−) cases, only 1 of 22 had cancer (5%, false negative).

Per-Patient Analysis of EIS Performance

The results of preoperative EIS were analyzed on a per-patient and per-nodule basis. There were 293 nodules among 216 patients, mean size 23.4 (SD 16.2) mm. EIS diagnosis was correct in all patients with thyroiditis (n = 13) and widely invasive follicular carcinoma (n = 10) and in over 90% of patients with papillary thyroid carcinoma (n = 89). Diagnostic accuracy of EIS was poor (≤50%) in patients with minimally invasive follicular or medullary thyroid carcinoma (Table 2).

Predictive value of EIS is demonstrated in Table 3. EIS correctly diagnosed 96 of 110 patients with malignant and 75 of 106 patients with benign dominant thyroid nodules yielding sensitivity of 87.3% and specificity of 70.8%. The negative and positive predictive value of EIS in these patients was 84.3% and 75.6%, respectively. Overall EIS accuracy on a per-patient basis was 79.2%. Hence, the pretest probability of cancer of 50.9% (110 of 216) using standard criteria for operation increased to 75.6% (96 of 127) post-EIS, and the preoperative use of EIS would result in a significant reduction (70.8%, 75 of 106) in the number of nontherapeutic thyroid operations.

Per-Nodule Analysis of EIS Performance

There were 293 nodules with a mean size 23.4 (SD 16.2) mm. The characteristics of these nodules are shown in Table 4. The majority of nodules were mobile (89.8%) on examination and solid (75.1%) in nature by thyroid ultrasound. Accuracy of EIS according to histology of the dominant thyroid nodule is shown in Figure 3. When all 293 nodules were analyzed, EIS performance remained stable: sensitivity = 85.2%, specificity = 73.6%, negative predictive value = 82.8%, positive predictive value = 77.0%, and accuracy = 79.5%.

EIS Performance in Patients With Indeterminate FNA

Of 109 patients 42 (38.5%) with indeterminate FNAs had malignancy apparent on final histopathology: medullary (n = 3), minimally invasive (n = 4) and widely invasive (n = 8) follicular, and papillary (n = 27) carcinoma. Of 109 patients 80 (73.4%) with indeterminate

TABLE 3. Predictive Value and Accuracy of EIS in 216 Patients With Benign and Malignant Thyroid Nodules

Characteristic	Thyroid Cancer	Benign Thyroid Nodule	Total	EIS Predictive Value and Accuracy
EIS positive	96	31	127	PPV = 96/127 (75.6%) 95% CI: 67%–82%
EIS negative	14	75	89	NPV = 75/89 (84.3%) 95% CI: 75%–91%
Total	110	106	216	Accuracy = 171/216 (79.2%) 95% CI: 73%–84%
EIS sensitivity	96/110 (87.3%) 95% CI: 80%–92%			
EIS specificity		75/106 (70.8%) 95% CI: 61%–79%		
Conductivity	278.5 ± 171.4	251.6 ± 163.1		$P = 0.239$
Capacitance	452.4 ± 130.9	424.3 ± 120.7		$P = 0.103$
Δ Conductivity	89.7 ± 147.9	44.1 ± 115.9		$P = 0.013$
Δ Capacitance	74.7 ± 102.4	43.2 ± 96.4		$P = 0.021$

EIS indicates electrical impedance scanning; PPV, positive predictive value; NPV, negative predictive value; Δ = change from baseline; conductivity and capacitance, Δ conductivity and Δ capacitance represent mean values ± SD.

TABLE 4. Baseline Characteristics of 293 Nodules Among 216 Patients

Characteristic	Nodules (N = 293) N (%)
Mean size ± SD determined by ultrasound	23.4 ± 16.2 mm
Median	19.5 mm
Range	0.5–82.0 mm
Anatomic location	
Isthmus	12 (4.1)
Left lobe	123 (42.0)
Right Lobe	158 (53.9)
Appearance by ultrasound	
Simple cyst	5 (1.7)
Complex cyst	16 (5.5)
Mixed solid cystic	42 (14.3)
Solid	220 (75.1)
Unknown	10 (3.4)
Mobility on examination (26 nonpalpable)	
Fixed	4 (1.4)
Nonpalpable	26 (8.9)
Mobile	263 (89.8)

dominant thyroid nodule were correctly diagnosed with preoperative EIS (Fig. 2).

EIS performance was not significantly different for the 109 patients with indeterminate cytology who underwent FNA of a dominant thyroid nodule: sensitivity = 83.3%, specificity = 67.2%, negative predictive value = 86.5%, positive predictive value = 61.4%, and accuracy = 73.4% (Fig. 2). The 7 false negative EIS cases in patients with indeterminate FNA consisted of minimally invasive follicular (n = 2), medullary (n = 1), and papillary thyroid carcinoma (n = 4).

The pretest probability of cancer in the 109 patients with indeterminate FNA was 42 of 109 (38.5%). This probability increased to 61.4% (35 of 57) post-EIS, and the preoperative use of EIS would result in a significant reduction (67.2%, 45 of 67) in the number of purely diagnostic thyroid operations.

Change in conductivity and capacitance from baseline differed significantly ($P < 0.05$) in patients with benign and malignant dominant thyroid nodules (Table 3). Logistic regression analysis of clinical covariates (gender, age, thyroid hormone status, nature and size of thyroid nodule, tumor grade) did not identify a single variable predictive of EIS diagnostic accuracy ($P > 0.2$ for all comparisons).

DISCUSSION

Clinically apparent thyroid nodules are encountered frequently. Widespread use of high-resolution ultrasound increases further the incidence of clinically relevant thyroid nodules. Consequently, diagnostic FNA is being performed increasingly for the evaluation of thyroid nodules. In our experience, FNA cytology has a high diagnostic accuracy and remains the most practicable test relied on for the initial evaluation of thyroid nodules. However, the efficacy of FNA for the differential diagnosis of follicular and Hurthle cell neoplasms remains imperfect at best. Because the majority of detected thyroid nodules are benign, and cytology, even in the best hands, is indeterminate in nearly a third of fine needle aspirates, the frequency of diagnostic or nontherapeutic thyroid resection is ever increasing. The application of a noninvasive and accurate diagnostic adjunct to FNA for differentiating benign from malignant thyroid nodules is warranted.

One such promising technological adjunct is impedance scanning. Our previous experience with EIS of the breast served as the launch point for a small-scale feasibility study applying the EIS probe for the detection of malignant thyroid nodules.[25,26,28] In that pilot study, we were able to

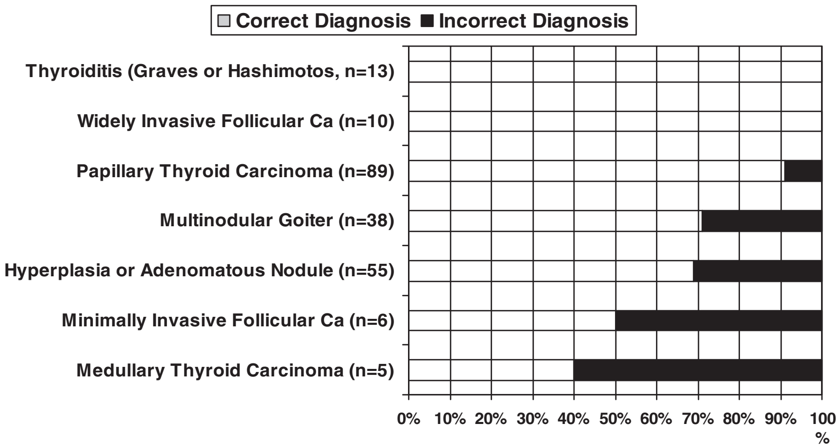

FIGURE 3. Diagnostic accuracy (horizontal axis, %) of preoperative thyroid EIS according to final (postoperative) thyroid histopathology (vertical axis). Gray and black bars represent correct and incorrect ESI diagnosis, respectively.

detect 6 of 7 thyroid cancers.[28] Using the TransScan 2000ED platform, a prototype EIS device designed specifically for thyroid examination was developed. Hence, an existing technology was modified for a novel and specific indication. Because the primary aim of this thyroid EIS platform was the detection of specific thyroid nodules identified either by clinical examination or ultrasound, we elected to implement focused EIS examination in high-resolution targeted mode over the area of interest corresponding to the palpable or sonographic thyroid abnormality and chose not to use the screening mode EIS for the whole gland as we used for patients with breast cancer. The definition of threshold values for the differentiation of benign from malignant thyroid nodules and the standardization of thyroid EIS were attained on a test cohort of 64 patients.[27]

The results of a prospective observational cohort trial herein extend and validate the findings of the previous pilot studies. The current study was conducted to determine the diagnostic accuracy of EIS in the preoperative assessment of thyroid nodules for patients in whom thyroidectomy was indicated based on standard selection criteria for operation. The results of preoperative EIS were compared with histopathology. EIS correctly diagnosed 87% of patients with malignant and 71% of patients with benign dominant thyroid nodules. Overall EIS accuracy on a per-patient basis was 79%. Hence, the pretest probability of cancer of 51% using standard criteria for operation increased to 76% using EIS, and the preoperative use of EIS would result in a significant reduction in the number of purely diagnostic thyroid operations. The findings of this study support the safety, feasibility, and diagnostic utility of this minimal risk, rapid, and real-time technology in patients with thyroid nodules.

When the analysis was extended to all 293 nodules (per-nodule analysis), EIS performance remained stable with a sensitivity of 85% and a specificity of 74%. The negative predictive value of EIS (83%) in the current study is important and clinically relevant because it would contribute to more confident surgical decision making. Device specificity, however, is not of sufficient magnitude to allow EIS to serve as a stand-alone replacement test for ultrasound or FNA. The data indicate that incorporating EIS as an adjunct to current clinical diagnostic tests such as ultrasound and FNA, particularly for indeterminate nodules, would most likely decrease significantly the number of nontherapeutic thyroid operations. We attempted to correlate EIS findings with patient or thyroid nodule-specific characteristics; however, the analysis proved unrevealing. The impact of thyroid metabolic function, as reflected by serum TSH abnormalities on EIS performance, is yet to be determined.

The histology of the underlying thyroid pathology had a major impact on EIS accuracy. All patients with inflammatory conditions were correctly diagnosed as benign by EIS examination, and all patients with widely invasive follicular carcinoma were correctly identified as malignant before operation. Diagnostic accuracy of EIS is favorable (91%) in patients with papillary carcinoma; however, this finding is less meaningful given the much higher accuracy of FNA in this group of patients. A small cancerous thyroid lesion, on the other hand, in a patient with multinodular goiter may be difficult to diagnose using standard diagnostic tests.[29] The accuracy of EIS examination exceeded 70% in patients with multinodular goiter in the present study, suggesting that EIS may be contributory to the detection of cancers within a goitrous gland. Conversely, patients with minimally invasive follicular cancers or patients with medullary carcinoma of the thyroid may not benefit from an EIS examination given the poor accuracy of EIS for both pathologic subgroups. The favorable biology of minimally invasive follicular cancers and the rarity of medullary cancer and availability of other accurate diagnostic tests (eg, FNA, serum calcitonin, etc) counterbalance the inaccuracy of EIS for these tumor types. Finally, the differentiation of adenomatous or hyperplastic thyroid lesions from cancers is imperative; however, FNA has limited utility in this regard. That EIS can identify adenomatous lesions as benign in approximately 70% of patients indicates the role of EIS in this diagnostic dilemma.

Ultrasound and fine needle aspirate cytology form the principal basis of current practice guidelines for the diagnostic evaluation of solitary thyroid nodules and nodules within a multinodular goiter. Diagnostic thyroid scan (^{99m}Tc-pertechnetate scintigraphy) can differentiate "cold" nodules associated with higher malignancy risk from other lesions with higher uptake and lower cancer risk. However, the low specificity of thyroid ^{99m}Tc-pertechnetate scintigraphy (20%–

25%) limits its clinical applicability to the evaluation of thyroid nodules.[30] 99mTc-sestamibi scintigraphy has also been evaluated for the differential diagnosis of thyroid nodules, and the results of various studies are inconsistent, showing broad ranges of sensitivity and specificity and overall diagnostic accuracy.[31–33] The widespread application of F18-FDG positron emission tomography for the extent of disease evaluation in patients with various malignancies has produced a unique diagnostic dilemma: what to do with the asymptomatic, clinically occult, thyroid incidentaloma detected by F18-FDG PET. The sensitivity of focal uptake on F18-FDG PET scan of the thyroid is consistently high; however, the limited specificity of this approach impedes the adoption of this technique into clinical practice for the preoperative assessment of indeterminate thyroid nodules.[14,15,34–36]

In addition to thyroid scintigraphy, Doppler ultrasound, magnetic resonance imaging, and molecular analysis of fine needle aspirates are other adjunctive modalities being studied to improve the ability to determine risk of malignancy in indeterminate dominant thyroid nodules. The presence of intranodular vascular spots and microcalcifications seen by Doppler ultrasound increases the risk of malignancy, but the absence of these findings does not entirely rule out malignancy.[37] Thyroid nodular flow patterns, peripheral in benign versus central in malignant nodules, as well as higher vascular resistive index measured by color Doppler ultrasound may predict malignancy but, again, cannot rule out its presence in indeterminate thyroid nodules.[38] Magnetic resonance imagining may improve diagnostic accuracy in thyroid imaging; however, the experience is limited to several small scale studies.[39,40]

Combined ultrasound with visual analysis of power color flow Doppler patterns has high predictive value for malignancy in indeterminate or suspicious thyroid nodules, but the increased predictive value of this technique is limited by poor diagnostic sensitivity.[11] Color Doppler ultrasound with quantitative analysis of tumor vascularity, on the other hand, has shown improved diagnostic accuracy over visual analysis of Doppler flow patterns. Sensitivity, specificity, and overall diagnostic accuracy for dominant thyroid nodules <2 cm in size with a normalized vascular index >0.14 or weighted index >0.24 is approximately 70%, 100%, and 85%, respectively.[8] Hence, Color Doppler ultrasound with quantitative analysis tumor vascular index determination provides incremental and significant diagnostic accuracy over ultrasound alone and over combined ultrasound with qualitative analysis of intranodular vascular patterns by color flow Doppler.[7–11]

A promising addition to conventional cytologic analysis of fine needle aspirates may be the reverse transcription polymerase chain reaction (RT-PCR). Real-time quantitative RT-PCR assays for thyroid-cancer related genes might be a new frontier in the diagnosis and risk assessment of thyroid malignancy. A number of groups have attempted to identify a set of optimal molecular markers for that purpose and to optimize RT-PCR reactions on cytologic specimens.[41–44] Much diversity of candidate genes and interassay variability exists making reproducibility of results a significant diagnostic challenge. Therefore, high throughput molecular analysis by RT-PCR of FNA aspirates, although promising, currently has limited value in the diagnosis of malignancy of the thyroid gland when applied to indeterminate cytologic specimens.

An important consideration of diagnostic adjuncts to the current standard of practice for the assessment of thyroid nodules is diagnostic performance in the subset of patients with indeterminate findings. EIS performance was not signif-

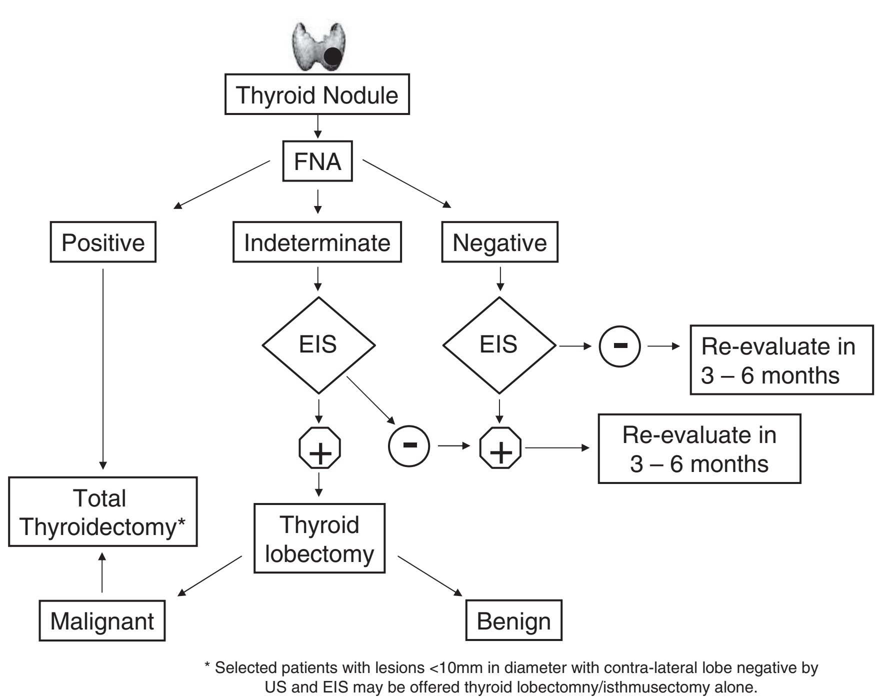

FIGURE 4. Clinical pathway incorporating diagnostic thyroid EIS. False negative diagnosis occurs in 10% of patients undergoing thyroid FNA, and false negative rate of EIS in patients with indeterminate cytology is 17%. Hence, patients with negative FNA/positive EIS and indeterminate FNA/negative EIS should be reassessed in 3 to 6 months. As the false positive rate of EIS in patients with indeterminate nodules is 33%, patients with indeterminate FNA/positive should undergo thyroid lobectomy to avoid overtreatment.

icantly different for patients with indeterminate cytology in the present study. The pretest probability of cancer among the patients with indeterminate FNA increased significantly post-EIS, and the preoperative use of EIS would result in a significant reduction (67%) in the number of nontherapeutic thyroid operations.

The results of the current validation trial support the incorporation of EIS in the preoperative decision making in patients being considered for thyroid resection of indeterminate thyroid nodules. As EIS may overlook some cancers in the indeterminate group, it is best considered an adjunct to ultrasound-guided FNA in the management of thyroid nodules (Fig. 4). In the case of positive needle aspirate, total thyroidectomy is generally recommended irrespective of EIS findings. However, for small subcentimeter nodules positive for papillary carcinoma by FNA, the contralateral lobe may be screened by ultrasound and EIS. If the contralateral lobe is negative for signs of malignancy using this combined ultrasound plus EIS diagnostic method, thyroid lobectomy and isthmusectomy is a reasonable surgical treatment approach.

For patients with dominant thyroid nodules showing benign cytology and negative EIS the likelihood of cancer is extremely low and routine observation by annual ultrasound and physical examination is safe (Fig. 5). False negative diagnosis occurs in 10% of patients undergoing thyroid FNA, and false negative rate of EIS in patients with indeterminate

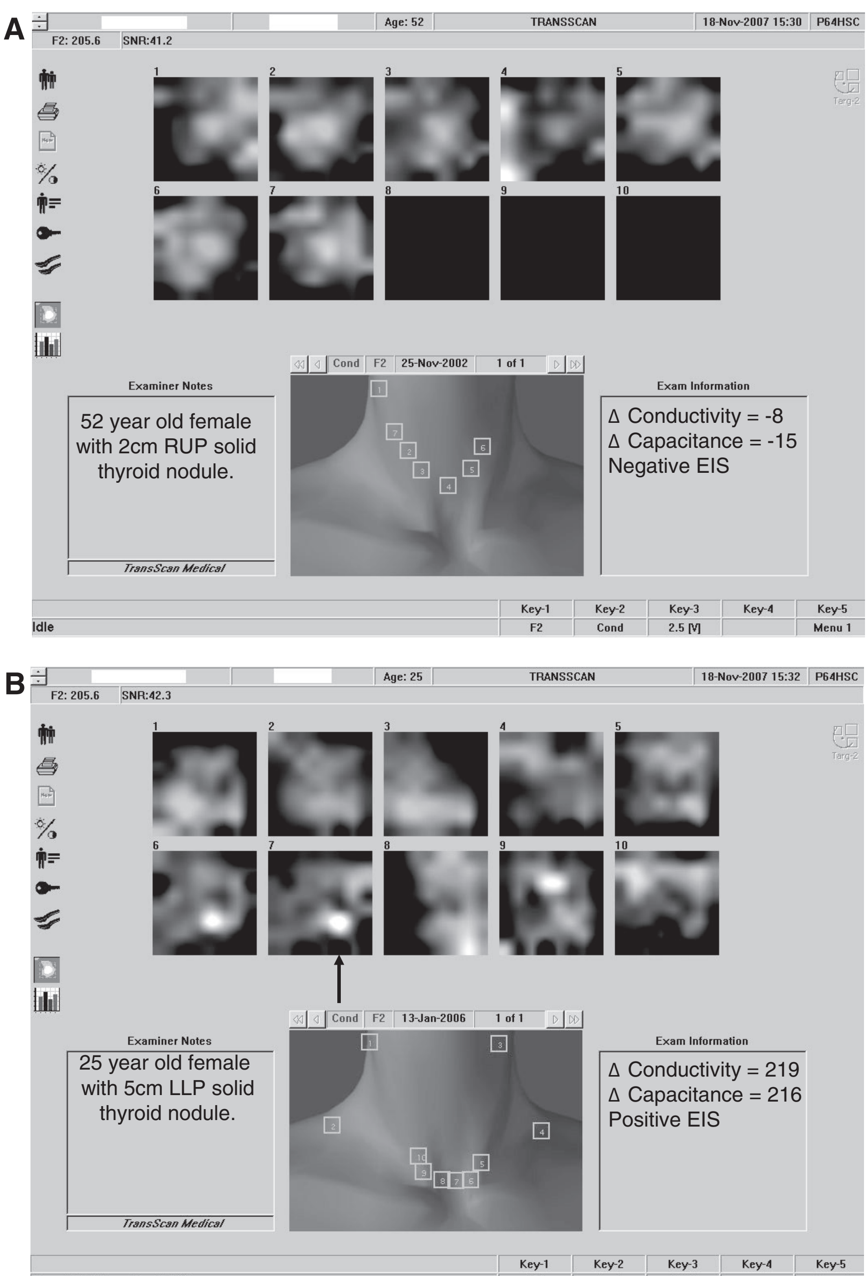

FIGURE 5. A, 52-year-old woman with a 2-cm solitary right upper pole thyroid nodule and negative EIS. B, 25-year-old woman with 5-cm solid left lower pole thyroid nodule. Arrow points to hot spot in left lower pole associated with significant increase in conductivity and capacitance relative to baseline, which indicate positive EIS.

cytology is 17%. Hence, patients with negative FNA and positive EIS, as well as those with indeterminate FNA and negative EIS may be considered for short interval follow-up and reexamination in 3 to 6 months; however, definitive recommendations await the results of larger, prospective observational trials. Up to 38% of patients with indeterminate cytology have underlying thyroid cancer. For these patients, indeterminate FNA cytology should be followed by thyroid EIS. For those having positive EIS, diagnostic lobectomy/isthmusectomy is recommended to avoid over treatment given the 33% false positive rate of EIS in patients with indeterminate FNA. Completion thyroidectomy is recommended in patients with indeterminate cytology and positive EIS found to have malignant tumors 1 cm or larger typically by permanent histology.

The addition of a noninvasive, inexpensive diagnostic modality such as EIS may improve the diagnosis of thyroid nodules and reduce the rate of nontherapeutic thyroidectomy. However, the results of this trial must be interpreted with caution because the study was conducted in 2 medical centers specializing in thyroid surgery and imaging. All EIS examinations as well as interpretations of impedance maps were performed by surgeons experienced not only in thyroid surgery but also in EIS. Therefore, further evaluation of this technology in the context of a large-scale clinical trial is imperative before widespread implementation of thyroid EIS.

The fact that EIS was performed by examiners not blinded to the ultrasound and FNA data may also bias the results. However, given that this modality was being studied as an adjunct to existing diagnostic modalities and not as a stand-alone diagnostic modality, we thought it best to perform the EIS examination with full preoperative data available to the examiner. In the group of patients with intermediate FNA findings, diagnostic performance of EIS remained consistent, suggesting that not blinding the examiners to the cytology data on EIS performance was not a confounding factor. Further, independent review of 40% of electrical impedance scans with concealment of clinical, cytologic, and pathologic data in this study indicated 28 concordant positive EIS and 49 concordant negative EIS examinations (concordance = 77 of 82 = 93.9%). There were 5 (6%) discordant findings, upstaging from EIS negative (initial review) to positive (blinded review). All 5 discordant cases represented changes in prediction from true negative to false positive EIS according to final histopathology results. FNA results in these patients were as follows: 2 negative, 2 indeterminate, and 1 positive. This suggests small but acceptable interobserver variability that is not consistent with significant bias.

The indeterminate thyroid nodule remains a formidable diagnostic challenge. The addition of improved techniques to existing modalities to expand the ability to distinguish benign from malignant thyroid nodules is imperative to reduce the need for purely diagnostic thyroidectomy. This prospective observational cohort trial was conducted to establish the diagnostic accuracy of a promising adjunct, namely EIS, to the present standard in the preoperative evaluation of thyroid nodules. The findings of this study support the safety, feasibility, and diagnostic utility of this minimal risk, rapid, and real-time technology in patients with thyroid nodules.

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