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ORIGINAL ARTICLE

PREOPERATIVE FINE-NEEDLE ASPIRATION CYTOLOGY VERSUS FROZEN SECTION IN THYROID SURGERY

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Aim: ***To assess diagnostic accuracy of preoperative fine-needle aspiration (FNA) compared to that of frozen-section examination (FSE) in the management of thyroid surgery.***
Methods: ***This is a retrospective review of 34 patients who underwent thyroid surgery between 2003-2005 at King Abdulaziz University Hospital. FNA and FSE were taken form all patients. FNA and FS sensitivity, specificity, positive and negative predictive values, accuracy were calculated versus permanent section.***
Results: ***FNA results were 29 (85.3%) benign, 3 (8.8%) malignant, and 2 (5.9%) suspicious. FSE diagnosis was benign in 28 (82.4%), deferred in 2 (5.9%), and malignant in 4 (11.8%). Diagnosis of malignancy in suspicious deferred cases was 50%. Sensitivity, specificity, positive, negative predictive values, and accuracy for FNA versus FSE were 33.3% versus 50.0%; 89.7% versus 92.9%, 25.0% versus 50.0%; 92.9% versus 92.9%; 84.4% versus 87.5%..***
Conclusion: ***FSE showed higher sensitivity, specificity, positive predictive value, and accuracy when compared to FNA. In patients with FNA revealing thyroid pathology, the extent of thyroidectomy must be established by FSE. Reliance on FSE lowers the possibility of unnecessary surgery and the need for additional surgery. However, increased costs for operative time and the pathologist needed for routine FSE negate any substantial benefit in patients' outcome.***

Keywords: ***Thyroidectomy, permanent section histopathology, accuracy.***

INTRODUCTION

Thyroid nodules (TN) are common. About 50% of the general population have incidental thyroid nodules found on autopsy[1] while 4–7% have clinically palpable nodules.[2] It is estimated that approximately 5% - 10% of TN are malignant,[3] therefore ability to distinguish benign from maligant nodules is vital in order to avoid unnecessary operations. Frozen section examination (FSE) has allowed surgeons to make rapid intraoperative diagnosis of excised specimens for over 100 years. FSE in thyroid surgery is used to make intraoperative pathological diagnosis of malignancy in thyroid nodules at time of hemithyroidectomy. Positive diagnosis denotes complete thyroidectomy, thus avoiding reoperation.[4]

The advent of fine needle aspiration (FNA) in 19525[5] revolutionized the management of TN and replaced much of the need for FSE. FNA has gained acceptance as the most accurate diagnostic assessment in the management of TN.[6] Literature supports the effectiveness of FNA in improving diagnostic yield for thyroid cancer[6] while reducing the

number of thyroidectomies performed for TN.[6] Because sensitivity of FNA in detecting thyroid cancer is high (67–98%),[7] cost, time involved, needs special instruments required in performing FSE have rendered it out of favour.[8]

However, operative planning basing on FNA alone is handicapped by a 20–30% rate of indeterminate cytological findings (suspicious or follicular cells)[9] where cytology is unable to reliably differentiate malignant from benign aspirates. Presence of indeterminate cytological

findings reduces specificity of FNA to 44%.[10] Furthermore, there is a 15−20% incidence of inadequate sampling as well as the theoretical concern of false positive cytology.[4] Many surgeons use intraoperative FSE to confirm diagnosis of FNA and guide thyroidectomy extent.[11] However, both FNA and FSE are associated with false positive and false negative diagnosis.[12]

The aim of this study was to examine the role of FNA and FSE in predicting malignant permanent section (PS) histopathology in patients with operative thyroid diseases. Sensitivity, specificity, positive and negative predictive values, and accuracy for both FNA and FSE were compared to assess their utility in thyroid surgery.

PATIENTS AND METHODS

This retrospective study included 34 patients who underwent thyroid surgery in the Surgical Department at King Abdulaziz University Hospital, Jeddah, Saudi Arabia between 2003 and 2005. Informed consent for surgery was obtained preoperatively in all cases. Patients who underwent thyroidectomy for management of non-thyroid pathology were excluded. The study was performed with the approval of the Ethical Committee at King Abdulaziz University Hospital.

Patients were analyzed in regard to age, sex, operation type, FNA, FSE and histopathology results. Preoperative FNA as described by Loewhagen et al.[13] with (22–25 gauge) disposable needles without local anesthesia was performed in all patients, who underwent neck ultrasonography for confirming thyroid lesions. Material was prepared by various cytopathologists who were present during the procedure. One slide was evaluated immediately to confirm specimen adequacy. Smears showing a minimum of six clusters of epithelial cells with more than 20 cells in each cluster were considered adequate. In patients with initial inadequate smears, reaspiration was performed. Smears were spread on standard glasses slides, air-dried, and stained by heamotoxylin-eosin. Specimens were blindly reviewed by an experienced cytologist. FNA result was classified into: malignant; benign; and suspicious. A finding of suspicious was made for FNA in which "follicular neoplasm" was considered in cytopathologic diagnosis or FNA results showed cellular changes suggestive of, but not diagnostic for, carcinoma.

Intra-operative FSE was done in all patients. Tissue slices were cut in cryostat (-21°C) at 6 μm and stained with haematoxylin-eosin. FSE diagnosis was made by experienced pathologists and classified into: malignant; benign; and deferral (FSE in which follicular neoplasm or "Hurthle cell tumor" was reported because these diagnoses could be reflective of either benign or malignant lesion). Permenant section (PS) histology demonstrating vascular and/or capsular invasion would be required to confirm presence of malignancy. When FSE confirmed malignancy, hemithyroidectmy would be converted to total thyroidectomy. When FSE showed benign or indeterminate findings, completion thyroidectomy would not proceed, final histology would then determine subsequent - management. PS analysis was performed in all cases using hematoxylin-eosin stain.

Statistical analysis: Data were expressed as mean and SD or percentage using SPSS version 12. Difference and correlations between parameters were done using Chi Square and Sperman tests. A $p<0.05$ were considered significant. Sensitivity, specificity, positive predictive, negative predictive values, and accuracy were calculated with respect to histopathology.

RESULTS

Table 1. Shows characteristics of patients who underwent thyroid operations. There was a significant predominance of females over males. Clinical diagnosis of diseases were mulinodular giotre, solitary thyroid nodule, malignant suspecious, or simple diffused enlargement of thyroid (n=7,20.6%,n=24, 70.6%,n=2, 5.9%,n=1 2.9%). Thyroid function tests were normal in all participants. Thyroid surgery were total lobectomy (n=10,29.4%), subtotal thyroidectomy (n=8,23.5%), hemithyroidectomy (n=7,20.6%), total/ near total thyroidectomy (n=5,14.7%), and nodulectomy (n=4,11.8%), with no significance diference between them. Post operative wound status was not followed in (n=18,52.9%) of the patients, and was clean in (n=16, 47.1%), with no significant difference ($p>0.05$).

The lesion of thyroid was either benign (n=29, 85.3%) or malignant (n=5, 14.7%) with significant difference between them. Benign lesions were mostly multinodular goiter with degenerative changes, followed by follicular adenoma, adenomatous hyperplasia; Hashimoto's thyroiditis; and calcified infected cyst (n=12, 35.3%, n=10, 29.4%, n=3, 8.8%, n=3, 8.8%, n=1, 2.9%). Malignant tumors were papillary, follicular, or medullary carcinomas (n=3, 8.8%,n=1, 2.9%,n=1, 2.9%).Cytopathological results of FNA showed benign diagnosis in 29 (85.3%) cases, that was uncorrected in 3 [false negative; 1 (2.9%) papillary carcinoma, 1 (2.9%) follicular carcinoma, 1 (2.9%) medullary carcinoma] by PS. FNA showed 2 (5.9%) suspicious findings, PS interpreted them as benign in 1 (2.9%) case (follicular adenoma) and malignant in 1 (2.9%) case (papillary carcinoma). FNA cytology indicated malignant diagnosis in 3 (8.8%) cases, but PS assessment was benign in 2 of them [false positive; 1 (2.9%) (multinodular goiter with degenerative changes, 1 (2.9%) follicular adenoma]). FSE showed benign diagnosis in (n=28, 82.4%), which was corrected by PS in 26 cases (true negative) and as malignant in 2 (5.9%) [false negative; 1 (2.9%) papillary carcinoma, 1 (2.9%) medullary

carcinoma]. Deferred diagnosis was made in 2 (5.9%), which was interpreted in PS as benign in 1 (2.9%) case (follicular adenoma), malignant in 1 (2.9%) case (papillary carcinoma). In malignant diagnosed patients (n=4), 2 (5.9%) cases were correct by PS (true positive) and benign in 2 (5.9%) [false positive; 1 (2.9%) ,multinodular goiter with degenerative changes, 1 (2.9%) follicular adenoma] Table 2.

(Fig. 1) lists FSE results for 34 patients with FNA biopsies that were classified as benign, suspicious, or malignant. In benign diagnosed patients (n=29) with FNA, FSE was also interpreted as benign in 28, and malignant in 1 case (2.9%). Meanwhile, suspicious (n=2) and malignancy (n=3) cases diagnosed by FNA were also diagnosed as deferral (n=2) and malignancy (n=3) by FSE.

Table 3. Shows cross tabulation between type of operation performed and histopathology results. Subtotal thyroidectomy was performed in 8 (23.5%) cases [2 (5.9%) multinodular goiter with degenerative changes; 3 (8.8%) follicular adenoma; 1 (2.9%) adenomatous hyperplasia; 1(2.9%) Hashimoto's thyroiditis; and 1 (2.9%) papillary carcinoma]. Total or near total thyroidectomy was performed in 5 (14.7%) cases [2 (5.9%) multinodular goiter with degenerative changes; 2 (5.9%) papillary carcinoma, and 1 (2.9%) follicular adenoma]. Total lobectomy was performed in 10 (29.7%) cases [3 (8.8%) multinodular goiter with degenerative changes; 3 (8.8%) follicular adenoma; 1 (2.9%) adenomatous hyperplasia; 1(2.9%) Hashimoto's thyroiditis; 1 (2.9%) follicular carcinoma; and1 (2.9%) medullary carcinoma]. Hemithyroidectomy was performed in 7 (20.6%) cases [2 (5.9%) multinodular goiter with degenerative changes; 2 (5.9%) follicular adenoma; 1 (2.9%) adenomatous hyperplasia; 1 (2.9%) Hashimoto's thyroiditis; and 1 (2.9%) calcified infected cyst]. Nodulectomy was performed in 4 (11.8%) cases [3 (8.8%) multinodular goiter with degenerative changes; and 1 (2.9%) follicular adenoma].

It was found that sensitivity, specificity, PPV, NPV, and accuracy for FNA and FSE were (33.3% versus 50.0%; 89.7% versus 92.9%; 25.0% versus 50.0%, 92.9% versus 92.9%, and 84.4% versus 87.5%, respectively) Tables 4a,b.

Table 1. Demographic and clinical characteristics, type of operations of the patients.

Variables	Patients (n=34)
age (years) (mean ±SD)	36.5±10.3
range	(22.00-64.00)
Male/female (numbers; %)	5 (14.7%) / 29 (85.3%)
Initial diagnosis (numbers; %)	
Mulinodular goitre	7 (20.6%)
Solitary nodule	24 (70.6%)
Malignant suspecious	2 (5.9%)
Simple diffused	1 (2.9%)
Thyroid function (numbers; %)	
Normal	34 (100%)
Type of operation (numbers; %)	
Total lobectomy	10 (29.4%)
Subtotal thyriodectomy	8 (23.5%)
Hemithyroidectomy	7 (20.6%)
Total/near total thyroidectomy	5 (14.7%)
Nodulectomy	4 (11.8%)
Postoperative wound status (numbers; %)	
Not followed	18 (52.9%)
Clean wound	16 (47.1%)
Significance	p>0.05

Table 2. Cross tabulation between fine needle aspiration (FNA) and frozen section examination (FSE) results with definitive histological diagnosis.

Histopathology	FNA			FSE		
	Benign	Suspicious	Malignant	Benign	Deferred	Malignant
Benign (n=29, 85.3%)						
Multinodular goiter with degenerative changes						
(n=12, 35.3%)	11 (32.4%)	-	1 (2.9%)	11 (32.4%)	-	1 (2.9%)
Follicular adenoma (n=10, 29.4%)	8 (23.5%)	1 (2.9%)	1(2.9%)	8 (23.5%)	1 (2.9%)	1(2.9%)
Adenomatous hyperplasia (n=3, 8.8%)	3 (8.8%)	-	-	3 (8.8%)	-	-
Hashimoto's thyroiditis (n=3, 8.8%)	3 (8.8%)	-	-	3 (8.8%)	-	-
Calcified infected cyst (n=1, 2.9%)	1(2.9%)	-	-	1 (2.9%)	-	-
Malignancy (n=5, 14.7%)						
Papillary carcinoma (n=3, 8.8%)	1(2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)
Follicular carcinoma (n=1, 2.9%)	1(2.9%)	-	-	-	-	1 (2.9%)
Medullary carcinoma (n=1, 2.9%)	1(2.9%)	-	-	1 (2.9%)	-	-
Total (n=34, 100%)	29 (85.3%)	2 (5.9%)	3 (8.8%)	28 (82.4%)	2 (5.9%)	4 (11.8%)

% total number of cases

Table 3. Cross tabulation between type of operations and permenant histopathology results.

Histopathology	Operation type				
	Subtotal thyroidectomy	Total or near total thyroidectomy	Total lobectomy	hemithyroidectomy	nodulectomy
Benign (n=29, 85.3%)					
Multinodular goiter with degenerative Changes (n=12, 35.3%)	2 (5.9%)	2 (5.9%)	3 (8.8%)	2 (5.9%)	3 (8.8%)
Follicular adenoma (n=10, 29.4%)	3 (8.8%)	1 (2.9%)	3 (8.8%)	2 (5.9%)	1 (2.9%)
Adenomatous hyperplasia (n=3, 8.8%)	1 (2.9%)	-	1 (2.9%)	1 (2.9%)	-
Hashimoto's thyroiditis (n=3, 8.8%)	1 (2.9%)	-	1 (2.9%)	1 (2.9%)	-
Calcified infected cyst (n=1, 2.9%)	-	-	-	1 (2.9%)	-
Malignancy (n=5, 14.7%)					
Papillary carcinoma (n=3, 8.8%)	1(2.9%)	2 (5.9%)	-	-	-
Follicular carcinoma (n=1, 2.9%)	-	-	1 (2.9%)	-	-
Medullary carcinoma (n=1, 2.9%)	-	-	1 (2.9%)	-	-
Total (n=34, 100%)	8 (23.5%)	2 (14.7%)	10 (29.4%)	7 (20.6%)	4 (11.8%)

% total number of cases

Table 4a. Statistics formula used.

Outcome measure	Formula
Positive predictive value	TP/TP+FP
Negative predictive value	TN/TN+FN
Sensitivity	TP/TP+ FN
Specificity	TN/TN+FP
Accuracy	TP+TN/TP+TN+FP+FN

TP, true positive; TN, true negative; FP, false positive; FN, false negative.

Table 4b. Results of fine needle aspiration (FNA) and frozen section examination (FSE) in differentiating between benign and malignant thyroid lesions.

Results	FNA cytology	FSE
True positive (number)	1	2
True negative (number)	26	26
False positive (number)	2	2
False negative (number)	3	2
Sensitivity (%)	33.3%	50.0%
Specificity (%)	89.7%	92.9%
Positive predictive value (%)	25.0%	50.0%
Negative predictive value (%)	92.9%	92.9%
Accuracy (%)	84.4%	87.5%

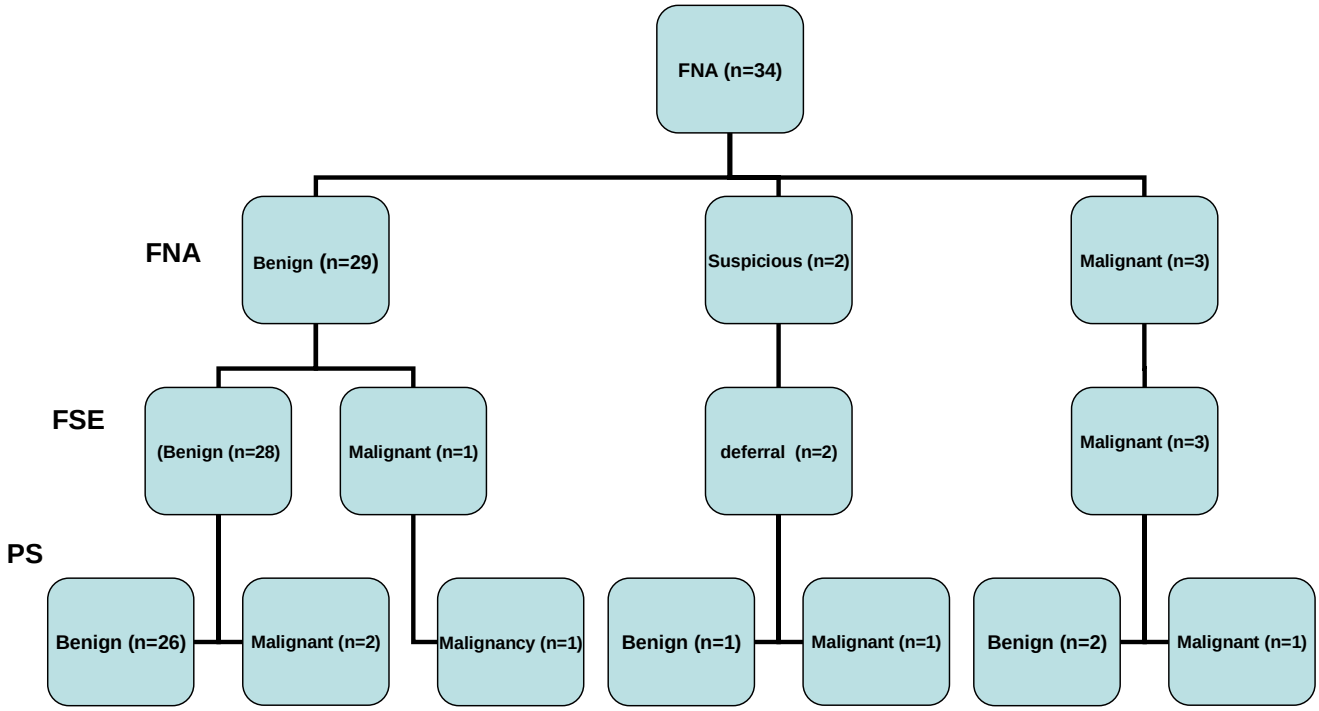

Fig 1. Permanent Section (PS) histopathology results in 34 patients with both fine needle aspiration (FNA) and frozen section Examination (FSE) biobsies classified as bengn, suspicious and malignancy.

DISCUSSION

Clinical assessment of thyroid malignancy by physical examination and thyroid ultrasonography is not completely reliable.[14] the optimal operative approach for thyroid cancer is to treat it definitively by a single operation. The goals of FNA and FSE are twofold: first to identify benign disease and reduce unnecessary thyroid resections, and second to identify malignancy and avoid increased costs and operative risks with total thyroidectomy. Although the goals are clear, roles and indications are controversial.[15]

FNA biopsy proved to differentiate between benign and malignant thyroid nodule, and therefore represented choice technique in management of such patients.[16] In this series, sensitivity, specificity, and accuracy of FNA were 33.3%, 89.7%, 84.4%. Previous studies reported FNA sensitivity (80%-93.5%);[8,17,18] specificity (56%-97%);[8,17,18] and accuracy (79.6%-94%).[8,17] Based on our results, the chance of a correct positive discovery of carcinoma on histopathologic analysis in suspicious FNA was 50% (diagnosed as papillary carcinoma). Malignancy rate in diagnosed suspicious FNA patients in nodular thyroid disease is generally reported to be 16%-54%.[19,20]

FNA results are affected by how the given study' author(s) chooses to define and/or classify suspicious FNA results. Inclusion of suspicious FNA with clearly malignant FNA increases the sensitivity, while decreasing the specificity and accuracy of FNA.[19] In the present study, suspicious cases were considered separately. FNA technique varied among individuals; disciplines which decreased sensitivity. In our hospital, FNA of thyroid and results interpretation were performed by different cytopathologists. A high incidence of unsatisfactory aspirates usually occurs when cytopathologists who make diagnosis do not perform the FNA and therefore unable to judge specimen adequacy at time of procedure.[20,21] Lack of the development and honing of the skills neccessary to

FNA and inadequate speciemen are important influences on unsatisfactory rate.[12,20]

In 1982 Hamberger et al.,[22] proved that with the introduction of FNA, the number of TN patients who underwent thyroidectomy decreased from 67% to 43%; and the rate of diagnosis of thyroid cancer increased from 4% to 29%. In the present study, PPV of FNA was 25.0% which is lower than what has been reported by others (37.7-100%).[21,20] The 2 cases (5.9%) false positive results obtained in this study were (n=1, 2.9% multinodular goiter with degenerative changes,n=1, 2.9% follicular adenoma). PPV depends on technique, physicians experience, and interpretation. NPV for FNA in this series was 92.9%, higher than that reported by others (69.2-97.1%).[20-22] Mayo Clinic reported false positive of 0.7% in 439 benign cytological aspiration.[23] In our series, (n=3,8.8%) false negative cases were reported (n=1,2.9% papillary carcinoma, n=1, 2.9% follicular carcinoma, n=1,2.9% medullary carcinomas).Sampling error contributed to false-negative FNA or follicular and papillary carcinoma which cannot be diagnosed by cytology.[20]

To solve these problems, the utilization of touch smears (intraoperative) FNA has been suggested[25] as more time-efficient, more cost-effective, and more accurate than FSE. Multanen et al.[26] reported accuracy of FNA improved from 41% to 52% with ultrasound guidance. Although FNA may help with patients selection, this technique is not usually useful in determining the extent of thyroid resection when benign aspirates were obtained.[27,18] Accordingly, we believe that routine FSE where benign cytology has been obtained, allows for a better informaed diagnosis.

Many surgeons use intraoperative FSE to confirm diagnosis FNA.[11] The sensitivity, specificity, and accuracy of FSE reported in this study were (50.0%, 92.9%, 87.5%) respectively. In previously reported findings, sensitivity of FSE was (60%-93%),[10,22,24] specificity was (97% - 100%),[8,18] and accuracy was (92% -97%).[8,18] In the present study, deferral FSE results were excluded from calculations. Higher accuracy has been reported when deferral diagnoses have been excluded from calculations.[8,18] In this study, deferral, cases showed malignancy in the histopathology of 1 (50.0%) of 2 cases. In literature, FSE deferral rate reported to be 16% to 50%.[8]

In this study, FSE showed PPV of 50.0%, NPV 92.9%. The 2 (5.9%) false negative cases were diagnosed by histopathology as papillary and medullary carcinomas. This false interpretation was possibly due to loss of nuclear morphological details caused by freezing tissue and tumor encapsulation resembling follicular adenoma.[20] The inability of FSE to differentiate follicular carcinoma from adenoma is well recognized, and is considered to be due to sampling errors, inadequate fixation, and/or artifact freezing.[28] A recent study found that the FSE sensitivity for follicular cancer was 17%.[29]

In our series, 2 (5.9%) cases [1 (2.9%) follicular, and 1 (2.9%) papillary cancers] were successfully identified by FSE. 3 patients (8.8%) underwent second operations because of 2 false negative findings and 1 deferred FSE. Only 2 (5.9%) false positives,[1 (2.9%) multinodular goiter with degenerative changes and 1 (2.9%) follicular adenoma] received excessive thyroid surgery based on FSE. FSE was specific in detecting one case (2.9%) of malignancy (follicular carcinoma) which was completely missed by FNA; total thyroidectomy was performed, thus saving the patient from a second completion thyroidectomy procedure. Our data showed that FSE appears unnecessary when FNA finding is positive, but FSE is useful in determining the extent of surgery when the FNA report is suspecious.[37] Negative FNA and FSE results must be treated with caution because false negatives have been noted.[30]

Some authors have found no difference in sensitivity, specificity, or accuracy between FSE and FNA,[8,18] and recommended against routine FSE use due to cost-ineffectiveness.[8] Several studies showed that generally misleading data may be obtained from FSE.[31] Others suggested FSE may be less sensitive than FNA, but more specific.[32] Some authors argued that all FNA diagnoses of "follicular neoplasm" warrant FSE intra-operatively,[33] while others have argued that FSE should be reserved for patients with persistently non nondiagnostic FNA, incidental TN found at surgery, and/or confirmation of metastases.[27,8] High specificity and accuracy of FSE makes it safe to proceed to definitive surgery in the event of a malignant FSE report. This position is also supported by others.[8,15]

In conclusion, FNA has been demonstrated to be a non-sensitive diagnostic technique and to have lower specificity, more positive predictive value, greater accuracy than frozen section in malignant thyroid diseases at our institution. Negative FNA should not prevent an operation indicated by clinical factors. Routine use of frozen section analysis is warranted. With reliance on FSE as intraoperative guide of thyroid surgery, unnecessary extensive surgery and second operations can be reduced. Any thyroid surgeon must be aware of the efficacy of his or her institution in pathologic interpretation. This study, emphasizes the importance of a specialist team approach to ensure optimal management of operable thyroid diseases.

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