

ORIGINAL ARTICLE

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The impact of the frozen section analysis on surgical strategy in nodular thyroid diseases

 Mehmet Turan Cicek¹,  Emrah Gunduz¹,  Tuba Bayindir¹,  Sumeyye Gunduz²,  Hasan Gokce³,  Yuksel Toplu¹

¹Inonu University, Faculty of Medicine, Department of ENT Surgery, Malatya, Turkey

²Inonu University, Faculty of Medicine, Department of Family Medicine, Malatya, Turkey

³Inonu University, Faculty of Medicine, Department of Pathology, Malatya, Turkey

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Abstract

In this retrospective cross-sectional study we aimed to investigate of the impact of frozen section analysis (FSA) on the surgical strategy in nodular thyroid diseases. The patients who underwent thyroidectomy (n=293) were analyzed retrospectively and 138 of 293 who had intraoperative FSA results included to the study. All these patients (n=138) also had fine needle aspiration biopsy (FNAB). The patients (n=138) were divided to 5 groups; Group 1 (n=32), Group 2 (n=22), Group 3 (n=12), Group 4 (n=17) and Group 5 (n=55). Twelve of these patients who were reported as “follicular neoplasia” in FSA were excluded from the study. According to the results of FSA (n=126), 48 patients were reported as malignant, whereas 78 patients were benign. The permanent sectional pathological examination (n=126), 57 patients were reported as malignant and 69 were benign. The sensitivity of FSA was found 78.9% and the specificity was found 95.6%, respectively. Also, FSA affected the surgical strategy correctly in 111 (88.1%) and incorrectly in 15 patients (11.9%). As a conclusion of this study we found that frozen section analysis significantly affects the surgical strategy especially in patients whose surgical strategy cannot be determined by FNAB.

Keywords: Frozen Section Analysis, thyroid nodule, fine needle aspiration cytology, Bethesda diagnostic category

Introduction

While the prevalence of palpable thyroid nodules is 4-7% in the adult population living in regions without iodine deficiency, this ratio is higher 2-3 times in endemic regions with iodine deficiency and the prevalence is up to 15-67% with high resolution ultrasonography. Although most of the nodules are benign, there is a 5-15% incidence of malignancy [1,2]. Therefore, accurate and differential diagnosis of these nodules are very important. In recent years, the diagnosis of thyroid nodules is based on the anamnesis and physical examination findings along with the ultrasonographic findings, and fine needle aspiration biopsies (FNABs) can be done with high accuracy [3]. Fine needle aspiration biopsy (FNAB) is the first procedure in the diagnosis of nodules with high sensitivity and specificity in differentiating nodules as benign

or malignant [4]. Also, FNAB is a simple, cheap, reproducible, minimally invasive and easily tolerated procedure and low risk of complications are the advantages of this technique. However, there are disadvantages such as; inability to distinguish between follicular adenoma and carcinoma, 10-20% of suspicious results, 2-21% of inadequate material and morphological tissue defects in recurrent FNABs [1,5]. Despite the numerous good practical guidelines and effective results of FNAB in thyroid nodule pathologies, the importance and the impact of some other methods such as frozen section analysis (FSA) is still controversial [6,7]. Frozen section analysis is a rapid intraoperative examination that involves the freezing of the surgical tissue fragment and classically used to determine intraoperative surgical extension with a different perspective. Frozen section analysis serves to determine the surgical strategy for preventing unnecessary total thyroidectomies and/or incomplete surgical resection in uncertain nodules in thyroid surgeries and provides to perform accurate surgeries in one step. Although guiding in intraoperative decision and diagnosis, the technique has disadvantages in terms of experienced pathologist requirement and cost-effectivity [8-10].

*Corresponding Author: Tuba Bayindir, Inonu University, Faculty of Medicine, Department of ENT Surgery, Malatya, Turkey
E-mail: tpbayindir@gmail.com

Due to the lack of a definitive diagnostic test for the thyroid nodules, both pre-operative and intraoperative diagnostic tests should be

used to make the right surgical desicion [11]. In this study, we aimed to investigate the role and impact of FSA in determining the surgical strategy by assisting FNAB.

Materials and Methods

Two hundred ninety three (n=293) patients who underwent thyroidectomy surgery in Inonu University Department of Otorhinolaryngology between January 2016 and April 2019 were retrospectively analyzed and found that 138 of these cases had intraoperative FSA result. All these patients who underwent intraoperative FSA also had FNAB in the pre-operative period, which performed under ultrasound guidance by the same radiology department and cytological diagnoses by the same pathology department.

This study was approved by the Inonu University Institute’s Committee on Human Research and the medical Ethics Committee under the reference number 2020/665.

The pre-operative FNAB results of these patients were categorized according to the Bethesda classification [12]. According to the Bethesda classification, the patients (n=138) were divided to 5 groups; despite recurrent FNABs, 32 patients were reported as non-diagnostic or unsatisfactory diagnosed (Group 1, Bethesda 1, n=32); 22 patients were reported as benign, but the suspicion of malignancy according to clinical and USG findings (Group 2, Bethesda 2, n=22); 12 patients were reported as atypia of undetermined significance despite recurrent FNABs (Group 3, Bethesda 3, n=12), 17 patients were reported as follicular neoplasia (Group 4, Bethesda 4, n=17) and 55 patients were reported as suspicious for malignancy (Group 5, Bethesda 5, n=55). Frozen section analysis were done intraoperatively to all these patients. Twelve of these patients who were reported as “follicular neoplasia” in FSA were excluded from the study. And the definitive diagnosis was left to permanent histopathological examination in these patients. Remaining 126 patients were included to the study.

Patients with malignant cytology in FNAB report (Bethesda 6) underwent total thyroidectomy, and patients who received benign diagnosis and did not have a risk of malignancy, unilateral thyroidectomy was performed and no additional diagnostic procedure was required for surgical decision in these group of patients in our department. Therefore, routinely, FSA was not performed in these patients and these patients were not included to the study (n = 155) (Figure 1).

Patients diagnosed as malignancy (such as Papillary/Follicular Cancer) with intraoperative FSA reports underwent total thyroidectomy and patients with benign diagnosis underwent unilateral thyroidectomy.

We aimed to investigate the sensitivity and specificity of FSA for the diagnosis of malignancy and the impact on defining the surgical strategy, by comparing the FSA results with the results of permanent histopathological tissue diagnosis. In addition, the benefit of FSA in the diagnosis of malignancy was examined by comparing with FNAB reports according to Bethesda diagnostic categories.

All datas (age, gender, FNAB, FSA and permanent tissue histopathological diagnosis results) were analyzed in the excel-based data program. The effect of FSA on the surgical strategy in the direction of FNAB was investigated using “diagnostic test performance criteria (sensitivity, specificity, overall accuracy rate, positive predictive value and negative predictive value)”.

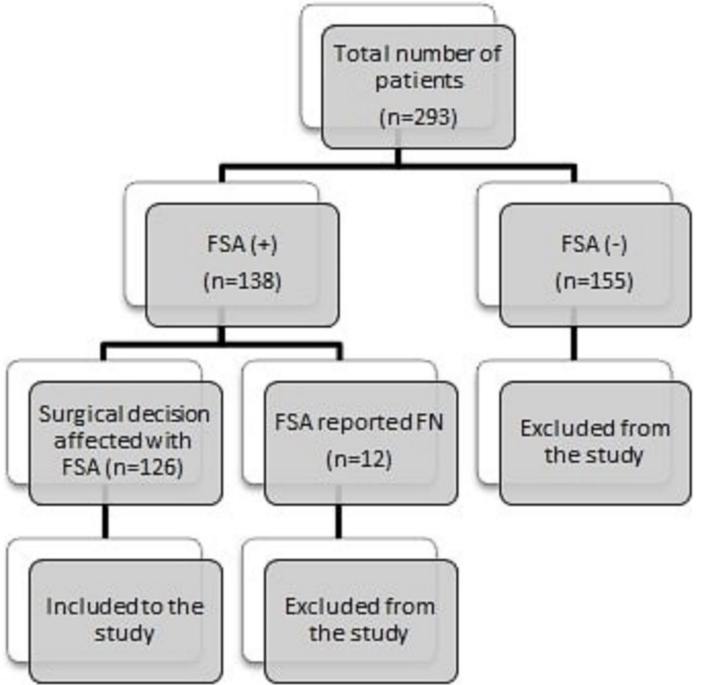


Figure 1. Selection criterias of the study group

Results

Of the 126 patients, 83 were female and 43 were male. The average age was 45 (17-74) years. As a result of FSA, 48 of the patients were reported as malignant and 78 as benign. In the permanent tissue histopathological diagnosis, 57 patients were reported as malignant and 69 as benign. It was observed that three patients who were reported as malignant in FSA were reported as benign in the permanent histopathological tissue diagnosis and 12 patients who were reported as benign were found to be malignant in the permanent histopathological tissue diagnosis (Table 1).

Table 1. Comparison of permanent histopathological tissue diagnosis with FSA

		Permanent histopathological tissue diagnosis		
		Malign	Benign	Total
FSA	Malign	45	3	48
	Benign	12	66	78
	Total (n)	57	69	126

In Group 1 (Bethesda 1 n=28); 22 patients were reported as benign and 6 patients as malignant (papillary cancer) in FSA. It was observed that papillary carcinoma was reported in 3 of 22 patients and benign was reported in 1 of 6 patients in permanent tissue histopathological diagnosis.

In Group 2 (Bethesda 2 n=20); 15 patients were reported as benign and 5 patients as malignant (papillary cancer) in FSA. It was observed that papillary carcinoma was reported in 3 of 15 patients and benign was reported in 1 of 5 patients in permanent tissue histopathological diagnosis.

In Group 3 (Bethesda 3 n=11); 10 patients were reported as benign and 1 patient as malignant (papillary cancer) in FSA. It was observed that follicular carcinoma was reported in 1 of 10 patients, while the only patient reported as malignant was also reported as malignant in permanent tissue histopathological diagnosis.

In Group 4 (Bethesda 4 n=16); 12 patients were reported as benign and 4 patients as malignant (3 papillary cancer, 1 follicular cancer) in FSA. It was observed that the permanent tissue histopathological diagnosis was not different from the results in the FSA in all patients.

In Group 5 (Bethesda 5 n=51); 19 patients were reported as benign and 32 patients as malignant (31 papillary cancer, 1 follicular cancer) in FSA. It was observed that papillary carcinoma was reported in 5 of 19 patients, benign was reported in 1 of 31 patients in permanent tissue histopathological diagnosis.

According to diagnostic test performance criterias of FSA;

In Group 1 sensitivity was 62.5%, specificity was 95%, positive predictive value (PPD) was 83.3% and negative predictive value (NPD) was 86.3%, respectively. FSA results affected the

surgical strategy correctly in 24 (85.7%) patients, and incorrectly in 4 (14.2%). Three of 4 patients required complementary thyroidectomy according to the results of permanent tissue histopathological diagnosis, whereas only one patient underwent total thyroidectomy unnecessarily.

In Group 2 sensitivity was 57.1%, specificity was 92.3%, PPD was 80% and NPD was 80%. FSA results affected the surgical strategy correctly in 16 patients (80%) and incorrectly in 4 (20%) patients. Three of 4 patients required complementary thyroidectomy according to the results of permanent tissue histopathological diagnosis and one patient underwent unnecessary total thyroidectomy.

In Group 3 sensitivity was 50%, specificity was 100%, PPD was 100% and NPD was 90%. FSA results affected the surgical strategy correctly in 10 patients (90.9%) and incorrectly in 1 patient (9.1%). This patient required complementary thyroidectomy according to the results of permanent tissue histopathological diagnosis.

In Group 4 all of these diagnostic test performance criterias of FSA were 100%. In this group, FSA affected the surgical strategy correctly 100%.

In Group 5 sensitivity was 86.1%, specificity was 93.3%, PPD was 96.8% and NPD was 73.6%, respectively. FSA results affected the surgical strategy correctly in 45 patients (88.2%) and incorrectly in 6 patients (11.8%). Five of these 6 patients required complementary thyroidectomy, whereas only one patient underwent unnecessary total thyroidectomy.

Comparison of FNAB, FSA and permanent tissue histopathological diagnosis results (Table 2) and diagnostic test performance criterias of FSA of all groups were summarized in the tables (Table 3).

Table 2. Comparison of FNAB, FSA and permanent tissue histopathological diagnosis

	FNAB	FSA	Permanent tissue histopathological diagnosis
Group 1	Non-diagnostic (n=28)	Benign (n=22)	Benign (n=19) PC (n=3)
		PC (n=6)	Benign (n=1) PC (n=5)
Group 2	Benign (n=20)	Benign (n=15)	Benign (n=12) PC (n=3)
		PC (n=5)	Benign (n=1) PC (n=4)
Group 3	Atypia of undetermined significance (n=11)	Benign (n=10)	Benign (n=9) FC (n=1)
		PC (n=1)	PC (n=1)
Group 4	Follicular neoplasia (n=16)	Benign (n=12)	Benign (n=12)
		PC (n=3)	PC (n=3)
		FC (n=1)	FC (n=1)
Group 5	Suspicious for malignancy (n=51)	Benign (n=19)	Benign (n=14) PC (n=5)
		PC (n=31)	Benign (n=1) PC (n=30)
		FC (n=1)	FC (n=1)
Total	126		
PC: Papillary carcinoma, FC: Follicular carcinoma			

Table 3. Diagnostic test performance results of FSA

	Sensitivity (%)	Specificity (%)	PPD (%)	NPD (%)
Group 1	62.5	95	83.3	86.3
Group 2	57.1	92.3	80	80
Group 3	50	100	100	90
Group 4	100	100	100	100
Group 5	86.1	93.3	96.8	73.6

Table 4. Comparison of FSA sensitivity, specificity and the effect on the surgical strategy

	Sensitivity (%)	Specificity (%)	Effect on Surgical Strategy (%)
Bethesda 1	62.5	95	85.7
Bethesda 2	57.1	92.3	80
Bethesda 3	50	100	90.9
Bethesda 4	100	100	100
Bethesda 5	86.1	93.3	88.2

As a result, in the study group (n=126) diagnostic test performance criteria was used to analyze FSA results statistically. The sensitivity of FSA was found 78.9%, the specificity was found 95.6%. However, the overall accuracy rate was found 88.1%. The PPD was found 93.7% and NPD was found 84.6%.

Discussion

The diagnosis of malignancies in thyroid nodules can be done by histopathological evaluation. The purpose of diagnostic procedures such as ultrasonography, FNAB and FSA are to detect malignancy in thyroid nodules pre-operatively or intraoperatively and to make thyroid surgeries in one step [1,2]. In nodular thyroid diseases, according to the result of FSA, preferred approach is total thyroidectomy for malignancy and hemithyroidectomy for benign diagnoses. Besides, FSA provides total thyroidectomies in one step, hemithyroidectomy decision due to FSA result can prevent the patient from living with life-long thyroid hormone therapy and decrease serious complications such as permanent hypothyroidism and recurrent nerve damage. Despite the successful results of FNAB, many surgeons still consult to intraoperative FSA in suspicious cases [9, 13, 14].

In our study, the impact of FSA in determining the surgical strategy was examined in accordance with FNAB proper to Bethesda classification. The patients were separated to six categories favorably to Bethesda classification. According to the results of FNAB, in Bethesda 6 group our surgical strategy was determined as total thyroidectomy, so that we did not apply FSA in this group. Besides, the risk of malignancy in the Bethesda 6 group has been found to be high as 96% in the literature [14]. Thus, patients in the Bethesda 6 group were not suitable for the purpose of the study and excluded.

According to the results of this study, the role of FSA in determining malignant nodules was found lower than its role in determining benign nodules. It was observed that FSA determined 45 of 57 malignant nodules and 66 of 69 benign nodules correctly, which diagnosed by permanent tissue histopathological diagnosis. With these findings, sensitivity was found as 78.9% and specificity as

95.6% for FSA. Similar to our results, in a metaanalysis, with 21 studies and 4970 patients, FSA sensitivity was found as $71 \pm 13\%$ and the specificity was $99 \pm 1.2\%$ [7].

In our study group (n=126), surgical decision identified according to the FSA results independently from FNAB. The results were compared with permanent tissue histopathological diagnosis results and found that FSA affected the surgical strategy in 111 patients (88.1%) correctly. Complementary thyroidectomy was needed in 12 of 15 patients whose surgical strategy was determined incorrectly with FSA and unnecessary total thyroidectomy was performed only in three patients. With these results, the false positivity of FSA was found 4.3% and the false negativity was 21.1%.

When the Bethesda groups examined separately, it was observed that the most important contribution of FSA in determining the surgical strategy was in the follicular neoplasia (Bethesda 4) and suspicious for malignancy (Bethesda 5) groups, respectively. In other groups, the sensitivity of the FSA was found lower, but similar to each other. The specificity was high in all groups (Table 4).

In Bethesda 4 group, all patients had the right surgical decision with FSA results. Although the results in our study for follicular lesions are similar to the literature, this high rates of FSA on correct diagnosis can be correlated with the low sample sizes.

Miller et al., reported that FSA decreases the number of complementary thyroidectomies and decreases the cost in Bethesda 4 group. Also, the sensitivity and specificity of FSA in Bethesda 2 group was found lower and the contribution on the surgical strategy was found insignificant [15]. Cheng et al., reported that the benefit of FSA to surgical strategy was found to be lower for patients with benign cytology. And they recommended FSA for Bethesda 5 group, but noted that FSA is not necessary in Bethesda 6 group [16]. We did not include Bethesda 6 group to our study because our surgical strategy would not change according to the FSA result. And similar to Cheng et al., our results showed the benefit of FSA to surgical strategy in Bethesda 5 group.

FSA has some advantages over FNAB in terms of pathologist in the diagnosis of thyroid nodules. First, the surgeon delivers a macroscopic specimen in FSA, while a small liquid specimen is delivered to the pathologist for examination in FNAB [4,7]. This may also explain the excess of non-diagnostic results in FNAB. Therefore, it seems reasonable to refer to the FSA in determining the surgical strategy in uncertain results in FNAB.

There were some limitations of our study. The study has a high n of patients (126) but is difficult to generalize. Interpretation of frozen section is pathologist specific, so results in one institution may be hard to replicate in another. In addition, there are 5 categories reported, but some of these categories (Group 3 and Group 4) are small, with n=16 or 11.

With the results of these study, we considered that FSA is a diagnostic method with high specificity and prevents unnecessary total thyroidectomies effectively. Although its sensitivity is not as high as specificity, FSA has made a great contribution in the one-step process of total thyroidectomies. And our results were found to be compatible with the literature. FSA is an intraoperative diagnostic method complementary to FNAB in selected cases. FSA significantly impacts the surgical strategy and reduces unnecessary or complementary thyroid surgery in patients whose surgical strategy can not be determined by FNAB.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

The study was conducted retrospectively. The files of the patients were scanned. No data or images were used to identify patients. The ethics committee of the study was obtained from the Ethics Committee of Health Sciences Non-Interventional Clinical Researches. Decision no: 2020/665.

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