The Ongoing Debate In Thyroid Surgery: Should Frozen Section Analysis Be Omitted?

OZER MAKAY, GOKHAN ICOZ, BARIS GURCU, YESIM ERTAN*, MUGE TUNCYUREK*, MAHIR AKYILDIZ AND ENIS YETKIN

Ege University, School of Medicine, Department of General Surgery, 35100 Bornova, Izmir, Turkey
*Ege University, School of Medicine, Department of Pathology, 35100 Bornova, Izmir, Turkey

Abstract. Controversies concerning the role of frozen section (FS) have been a matter of debate. The aim of this study was to identify the role of FS analysis in intraoperative decision making and analyze the effect of the cost in detecting thyroid malignancies in Turkey. Out of 214 consecutive patients who had been operated on for thyroid cancer between January 1996 and August 2004, 178 patients were evaluated retrospectively. All 178 patients were subjected to FS. Intraoperative FS correctly identified the pathology as malignant in 58.4% of patients. A true-positive FS result changed the surgical strategy in 30 (27.6%) cases False negative FS lesions were defined histologically as papillary microcarcinoma in 54%, follicular variant of papillary cancer in 18% and follicular cancer in 8% of cases. The sensitivities of FNAB and intraoperative FS in thyroid cancer patients were 22.5% and 58.4%, respectively. False negative FS results increased the cost for each informative FS from €25 to €42.7. Despite limitations, results of this study reject the idea that the role of FS is becoming limited. We recommend routine frozen section in the operative assessment of thyroid nodules. Omitting FS may be suggested only in cases with a FNAB revealing malignancy.

Key words: Thyroid cancer, Frozen section, Thyroidectomy

(Since the management of the thyroid nodule has a wide spectrum, determining the nature of the nodule is of utmost importance in the management of the disease [1]. Aggressive surgery plays an important role in the treatment of thyroid cancer; it facilitates detection and ablation of metastatic disease with radioactive iodine, allows for monitoring of thyroglobulin levels, treats residual disease of the contralateral lobe in cancer with multicentricity, decreases the risk of recurrence and it provides longer survival [2]. The extent of surgery still remains controversial [3]. While developments and controversies in thyroid surgery are ongoing, the benefit of frozen section (FS) has been a matter of debate between experts [1, 4–10].

The aim of the present study is to answer the following questions;

– Can frozen section analysis provide more accurate information in nodular disease?
– Do frozen section results affect intraoperative decision making or is frozen section useless?
– What is the effect of the cost of frozen section analysis in detecting thyroid malignancies in Turkey?

Materials and Methods

During the period from January 1996 to August 2004, a total of 2378 patients underwent surgical treatment for thyroid disease at a university teaching hospital in Izmir, Turkey. Data were obtained retrospectively from 214 consecutive patients who had been operated on for thyroid cancer during this period. Of these, a total of 178 patients (148 women and 30 men with a mean age of 48.8 ± 13.5 years) who were subjected to FS, were enrolled in the study. Patients with whom FS was not carried out were excluded from the study. Cases were also excluded if they had previous
thyroid surgery; had a recurrent cancer or had evidence of distant metastasis. Multinodular disease without a dominant nodule did not routinely undergo fine needle aspiration biopsy (FNAB). Operative reports and hospital records were reviewed.

FNAB findings were graded as benign, malignant, suspicious (indeterminate) or inadequate, while intraoperative FS results were classified as benign, malignant or suspicious. Samples showing cellular atypia or suggestive of follicular lesions were included in the suspicious (indeterminate) category. If the FNAB showed malignancy it did not divide papillary or follicular cancer.

For intraoperative FS analysis, the specimen was macroscopically examined and then serial sections were performed and examined from the macroscopically most suspicious nodules at the Department of Pathology. Specimens were evaluated by one of the staff pathologists. Reoperations for completion thyroidectomy were performed in patients with a false negative FS result, whose TSH levels did not rise and were between reference ranges. The cost of both surgery and FS was calculated by means of governmental refunding fees to nationwide hospitals.

Preoperative ultrasonography, scintigraphy, thyroid hormone assessment and indirect laryngoscopy were performed on all patients before operative intervention. Indications for the thyroid surgery at our institution were clinical suspicion of malignancy, compressive symptoms or obvious cosmetic problems, even if FNAB results were negative. Our routine operative strategy for thyroid nodules was to perform a loboisthmectomy, a sub-total (remnant thyroid tissue was intended to be between 2–4 g), a near-total thyroidectomy (leaving less than 2 g of tissue if necessary to preserve parathyroid tissue or protect the recurrent laryngeal nerve) or a total thyroidectomy based on the results of preoperative tests, intraoperative exploration and frozen section analysis. Both lobes and the isthmus were carefully evaluated for the presence of any gross disease.

The results of FNAB and FS were compared with the final histopathological diagnosis. Sensitivity of FNAB and FS in thyroid cancer patients was calculated as the proportion of patients with a positive FNAB and FS results among all patients with malignancy (the sum of true-positive and false-negative results) on final histological examination. Statistical analysis was performed by means of the Chi² test.

**Results**

All 178 patients in this study were confirmed to be malignant based on final pathology. There were 10 (5.6%) loboisthmectomies performed and 13 (7.3%) sub-total, 27 (15.2%) near-total and 128 (71.9%) total thyroidectomies. Functional lymph node dissection was added in 5 patients with medullary cancer. Table 1 concentrates on the pathology results of the study group. Papillary cancer was the most common type of malignancy. A total of 106 patients underwent FNAB before surgery. In other words, the sequential use of both techniques (FNAB and FS) occurred in 59.6% of patients. Results of FNAB and FS were compared and summarized in Table 2 and 3.

A total of 51.9% false negative FNAB lesions were defined histologically as papillary microcarcinoma in 19 (34.5%), follicular variant of papillary cancer in 4 (7.2%) and follicular cancer in 8 (14.5%) cases. When the FNAB result was determined as malignant, it accurately reflected the final histology in 22.6% of patients. The intraoperative FS correctly identified the pathology as malignant in 104 (58.4%) patients, whereas it indicated no malignancy (benign + suspicious results)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>(#)</th>
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<tbody>
<tr>
<td>Papillary microcancer</td>
<td>49</td>
</tr>
<tr>
<td>Papillary cancer</td>
<td>104</td>
</tr>
<tr>
<td>Follicular cancer</td>
<td>16</td>
</tr>
<tr>
<td>Medullary cancer</td>
<td>5</td>
</tr>
<tr>
<td>Anaplastic cancer</td>
<td>2</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>178</td>
</tr>
</tbody>
</table>

**Table 2.** Comparison of preoperative FNAB and FS results in 178 thyroid cancer patients

<table>
<thead>
<tr>
<th>FNAB</th>
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<th>%</th>
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<tr>
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<td>1.7</td>
</tr>
<tr>
<td>benign</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>suspicious</td>
<td>24</td>
<td>13.5</td>
</tr>
<tr>
<td>malignant</td>
<td>24</td>
<td>13.5</td>
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<table>
<thead>
<tr>
<th>FS</th>
<th>n = 178</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>benign</td>
<td>49</td>
<td>27.6</td>
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<tr>
<td>suspicious</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>malignant</td>
<td>104</td>
<td>58.4</td>
</tr>
</tbody>
</table>

Table 1. Final histologic diagnoses in 178 patients with thyroid cancer
in 74 (41.6%) patients. Among the malignancies diagnosed with FS, 7 (6.8%) were follicular carcinoma, 89 (86.4%) were papillary carcinoma, 3 (2.9%) were medullary carcinoma, 2 (1.9%) were anaplastic cancers, 1 (1%) was a non-Hodgkin lymphoma and 1 (1%) was a primary squamous cell carcinoma. False negative FS lesions were defined histologically as papillary microcarcinoma in 54%, follicular variant of papillary cancer in 18% and follicular cancer in 8% of cases. The frequency of papillary microcarcinoma was 17.4% in the correctly diagnosed group.

In the statistical analysis, the sensitivities of FNAB and intraoperative FS in thyroid cancer patients were 22.5% and 58.4%, respectively. When suspicious findings were included in the malignant group, because of the effect on surgical strategy, the sensitivity of the study in both FNAB and FS increased. Sensitivities according to this calculation were 45% for FNAB and 72% for FS. When papillary cancers were compared with papillary microcarcinomas, a remarkable difference was reflected in the sensitivity rates for FS, which were 68.3% and 36.7%, respectively.

When FNAB was determined as benign (56 of 106 patients), which was the most preoperative cytological finding, FS determined 17 benign and 30 malignant patients. In other words, as with FNAB, FS failed to detect cancer in 16.5% of the patients. Meanwhile, a true-positive FS result changed the surgical strategy in 30 (27.6%) cases. We also examined the value of FS in patients with a suspicious FNAB result. Analysis in this subgroup revealed 79.2% malignant, 8.3% suspicious and 12.5% benign results by FS. Altogether, 9 (12%) of the 75 patients with a benign or suspicious FS result had a follicular carcinoma. Nevertheless, 9 of the 79 patients with a benign or suspicious FNAB result had a follicular carcinoma. There were no false positive FS lesions.

This study demonstrated a solitary nodule in 38 (21.3%) cases, multinodular goiter in 129 (62.5%) cases and Graves’ disease in 11 (6.2%) cases. Comparison of patients with a solitary nodule to patients with multinodular goiter revealed no significant difference (60% versus 52%) in the sensitivity of FS (p>0.05).

The cost of both surgery and FS was analyzed. At Ege University Hospital, Izmir, the mean charge of each FS was €25, while the cost of thyroidectomy was €500. Since 104 of the 178 FS results were informative, the cost for each informative FS increased to €42.7.

Twenty-five (14%) patients had a completion thyroidectomy, because they had a loboisthmectomy, a sub-total or a near-total thyroidectomy performed during their initial operation. Unfortunately, FS results were false-negative in these patients, influencing the decision to perform a less aggressive surgery than total thyroidectomy.

### Discussion

The present study has included all surgically treated thyroid cancers where FS was carried out between 1996 and 2004. Although there are many reports concerning FS in thyroid surgery, the role of intraoperative FS in thyroidectomy is still a subject of controversy. On one hand there is strong evidence that FS diagnosis is accurate for processing a high volume of surgical pathology cases and may avoid surgical over- and under-treatments and the need for a second operation [5, 9, 11, 12], while on the other hand it is believed that the role of FS is becoming increasingly limited and has no substantial benefit in patient outcome [4, 10, 13]. One of the main goals of intraoperative FS is to identify which patient has malignancy, to avoid the increased costs and operative risks associated with a completion surgery [13].

In this series, FS identified 103 of 178 cancers, while FNAB identified only 24 of 106 carcinomas. We designated the sensitivity of FS analysis as 58%. This rate was similar to those of some other studies in the literature [1, 6, 13, 14]. The inability to diagnose papillary microcarcinoma, follicular variant of papillary carcinoma and follicular carcinoma intraoperatively with FS...
was the major factor accounting for the low sensitivity of FS. The sensitivity of intraoperative diagnosis of malignancy depends on the type of thyroid carcinoma as previously reported by Leteurtre et al. [15]. Intraoperative frozen section analysis of follicular neoplasms rarely renders informative information and is still problematic due to the difficulty of differentiating follicular adenoma from carcinoma [16–18]. A diagnosis of follicular carcinoma is not possible on FNAB alone, and the contention that FS can discriminate follicular adenoma from carcinoma is a central point of debate. Meanwhile, LiVolsi et al. suggest that frozen section is of no value in the intraoperative diagnosis of lesions diagnosed on FNAB as “follicular neoplasm” or “Hurthle cell neoplasm” because the characterization of these lesions requires detailed analysis of the tumor capsule for the demonstration of capsular and/or vascular invasion [18].

Gharib and Goellner stated that FNAB has emerged as the most direct accurate diagnostic procedure to differentiate benign from malignant thyroid nodules [19]. High rates of false-negative FNAB results are expressed to be unacceptable, since there must be low false-negative and low false-positive rates to play a reliable role in thyroid cancer [1]. Grant et al. reported a false-negative rate of 0.7% out of 642 patients [20]. The sensitivity rate of FNAB in the present series is of concern, since it is inferior to that generally reported in the literature. One of the reasons is that microcarcinomas actually were incidentally found. Another possible reason for such a low accuracy is that it can be caused by sampling errors, misinterpretations in patients with microcarcinoma and follicular variant of papillary cancer or varying FNAB techniques between disciplines.

Should routine use of FS be omitted as Hamming et al. suggested in their study [21], or should it not? Bugis et al. reported that FNAB is complementary to FS [22], while McHenry et al. suggested in their series that FS should be restricted to cases with an indeterminate result or a report with follicular pathology [16]. In our study, when FNAB was graded as benign, FS results were reported as malignant in 29 patients. These FS findings resulted in changing the initial surgical strategy that had been based on preoperative evaluation (including FNAB) in 16% of patients, which is not a low percentage that can be overlooked. This is one of the main reasons why FS should not be omitted in detecting thyroid malignancies. Another reason is that FS analysis in patients with a benign FNAB had a remarkable benefit, since 55 (31%) patients had a cancer with a false negative FNAB.

Cost savings should be considered. FS analysis represents additional cost. That is why some authors suggest that FS can be avoided to reduce the duration and cost of the operation [23–25]. In our study, the cost per useful FS analysis was €42.7, which was absolutely not higher than the cost of a second operative intervention. We believe that the operative time will not increase the cost, since FS analysis only prolongs surgery about 25 to 30 minutes per procedure. One study reported a decrease in the number of reoperations as a result of routine FS analysis, which led to an estimated saving of 40% [5]. Since the costs of both FS analysis and operative intervention differ greatly between countries [5, 10, 26], we believe that this issue needs individualization for each country. There is limited information available regarding the clinical and cost results of FS in thyroid cancer in Turkey. One recently published paper from our country concentrated on the value of FS analysis in patients with nodular disease [27]. Information about the cost analysis was lacking in that study.

A trial of 197 patients with multinodular disease evaluated the utility of FS for ruling out malignancy [7]. That study found that the sensitivity of FS was 19%. Authors concluded that FS should not be used routinely in the management of multinodular disease. In this series, a solitary or multi-nodular disease revealed no significant difference in terms of FS sensitivity (60% versus 52%).

A good working relationship between the surgeon and the pathologist and the capability to establish a more definitive diagnosis will provide highly accurate frozen section results and spare a patient from a completion surgery [28]. Highly resourceful settings are required to improve the results of both FNAB and FS.

Unfortunately, the weak point of our retrospective study is that it is not possible to calculate specificity and accuracy, since only patients with malignancy were reviewed. Nevertheless, no interpretations could be made concerning the effect of FS in altering the surgical management. No data can be offered about the larger population with benign disease. Whether the cost of all of these negative FS results would change the cost analyses data will be studied.

To conclude, despite limitations, results of this study reject the idea that the role of FS is becoming limited. We recommend routine frozen section in the operative
assessment of thyroid nodules, leading to decreased patient anxiety and avoidance of the cost of a completion surgery. It also permits the surgeon to a more radical surgery. Omitting FS may be suggested only in cases with a FNAB revealing malignancy. New cytopathological strategies are mandatory for a better identification of microcarcinoma, follicular variant of papillary cancer and follicular cancer.

References


