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Review

The Role of Frozen Section Examination in Thyroid Surgery

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Abstract

In endocrine pathology, frozen section (FS) examination is most commonly used for the intraoperative evaluation of thyroid and parathyroid tumors, as well as cervical lymph nodes. In the past, frozen section was considered a fundamental tool in thyroid surgery. However, with advancements in preoperative ultrasound and fine-needle aspiration biopsy (FNAB), there have been increasing queries about its routine use due to the improved preoperative diagnosis. Nowadays, while the use of FS during thyroidectomy has decreased, it is still used as an additional method for different purposes intraoperatively. FS may not always provide definitive results. If FS will alter the surgical plan or extent, it should be applied. Routine FS is not recommended for evaluating thyroid nodules. But in addition to FNAB, if FS results may change the operation plan or extent, they can be utilized. FS should not be applied for thyroid lesions smaller than 1 cm, and the entire lesion should not be frozen for FS. For the assessment of thyroid nodules, the use of FS is recommended based on the Bethesda categories of FNAB. In Bethesda I category nodules, FS may contribute to distinguishing between malignant and benign lesions and guide surgical treatment. In Bethesda II nodules, where the malignancy rate is low, the performance of FNAB and FS can be compared, but it's not recommended due to the lack of a significant contribution to the surgical strategy. The sensitivity of FS in Bethesda III and IV nodules is low; its contribution to the diagnosis is limited, and it does not provide an apparent benefit to treatment; therefore, it is not recommended. In Bethesda V nodules, FS can effectively confirm the malignancy diagnosis, contribute to the surgical strategy, and reduce the possibility of completion thyroidectomy, and accordingly, it is recommended for use. Nonetheless, in Bethesda V nodules with a benign FS report, the malignancy rate remains high, so it should not be used to rule out malignancy. In Bethesda VI nodules, the performance of FS is lower or comparable to FNAB and does not significantly contribute to the treatment strategy; hence, it is not recommended. Particularly in patients with papillary thyroid cancer, intraoperative FS can be effective in detecting extrathyroidal extension and can assist the surgeon in determining the extent of thyroid surgery and central neck dissection. FS has high sensitivity and specificity in evaluating the lymphatic status of the central region intraoperatively and can be used to determine the extent of central compartment node dissection. During thyroidectomy, FS examination can be used in recognizing parathyroid tissue and distinguishing it from fatty tissue, thymus, thyroid, lymph nodes, especially in differentiating metastatic lymph nodes.

Keywords: Bethesda classification, FNAB, frozen section

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In endocrine pathology, frozen section (FS) examination is often used to evaluate thyroid and parathyroid tumors, as well as cervical lymph nodes, intraoperatively.[1] However, thyroid frozen section examination is not as clear as commonly believed. In an interinstitutional study conducted by the American College of Pathologists in 1994, after skin, breast, the female genital system, and metastatic lymph nodes, the thyroid and parathyroid glands became the fifth

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most discordant anatomical site in frozen section diagnoses.[2] In the past, frozen examination was considered as a fundamental tool in thyroid surgery.[3] Today, due to significant advancements in ultrasound (US) technology, which serves as the gold standard for evaluating the morphology of thyroid nodules, detailed descriptions of nodular morphology can be provided.[3] Over the past two decades, various risk stratification systems based on US characteristics of thyroid nodules have been developed to assess the risk of thyroid cancer. These systems have become fundamental tools in the management of thyroid nodules. Their primary aim is to reduce unnecessary fine-needle aspiration biopsies (FNABs), prevent the oversight of clinically significant thyroid cancers, and personalize the treatment of patients with thyroid nodules.[4] FNAB plays a crucial role in the assessment of nodules based on US characteristics. While reducing the rate of unnecessary surgeries for benign thyroid nodules, FNAB enables appropriate surgical triage in patients with thyroid cancer. The malignancy rate for nodules surgically excised before routine FNAB was around 14%, but with current FNAB practice, it has risen over 50%. To standardize the terminology and other aspects related to FNAB, the Bethesda system has been developed for reporting thyroid cytopathologies.[5] This system has gained widespread acceptance and significantly contributed to establishing a common language among cytopathologists in FNAB assessment. Improvements in US and FNAB have notably contributed to evaluating thyroid nodules and surgical planning. Consequently, questioning the routine use of intraoperative FS examination has been increasingly common. In fact, some pathologists do not recommend FS examination for evaluating thyroid nodules due to diagnostic limitations, freezing artifacts, and the superiority of permanent assessment.[6,7] In the future, the increased usage and widespread implementation of molecular testing in FNAB samples will further enhance preoperative diagnosis and potentially decrease the rate of FS examination in thyroid nodules.[8] This situation will lead FS to be an additional complementary tool to obtain information about tumor size, focality, lymph node involvement, or extracapsular growth. Despite the increasing evidence regarding the technical and diagnostic limitations of intraoperative FS examination in the literature, it continues to take place in thyroid surgery.[9] However, in current literature, it is generally not recommended to routinely perform FS for the evaluation of thyroid nodules.[10,11] Frozen section may not always provide a definitive result. In today's practice, FNAB is the primary diagnostic tool for the preoperative evaluation of thyroid nodules. FS can be utilized if the frozen results, in addition to FNAB, are expected to alter the surgical plan or the extent of the operation.[12] In cases of multinodular goiter, unless there are suspicious features in the macroscopic appearance of a nodule, frozen section should not be performed. For lesions smaller than 1 cm, frozen section should be avoided. Additionally, it is particularly important to completely refrain from freezing an entire lesion. Tissue alterations due to frozen section procedures can render the diagnosis nearly impossible in permanent sections.[1]

The role of FS examination in thyroid surgery will be examined under four main headings.

A. The Role of Frozen Section Examination in the Evaluation of Thyroid Nodules

B. Frozen Section Examination in the Assessment of Extrathyroidal Spread of Thyroid Malignancies

C. Frozen Section Examination in the Evaluation of Suspicious Lymph Nodes

D. Frozen Section Examination in the Assessment of Intraoperative Parathyroid Tissue

A. The Role of Frozen Section Examination in the Evaluation of Thyroid Nodules

An argument regarding the use of FS in thyroid nodules has persisted for the past 50 years. In a meta-analysis encompassing studies predating the Bethesda classification, FNAB and FS results were compared between follicular lesions, non-follicular lesions, and unspecified lesions. In follicular lesions, FNAB demonstrated significantly higher sensitivity (69% vs. 21%) compared to FS, with similar NPV (negative predictive value) (84% vs. 73%), markedly lower specificity (60% vs. 99%), and PPV (positive predictive value) (35% vs. 86%). Although FS seemed to exhibit higher specificity and PPV for follicular lesions compared to FNAB in this analysis, its limited practical applicability due to low sensitivity has been emphasized in daily practice.[13] Non-follicular lesions showed similar findings between FNAB (where FNAB with a diagnosis of papillary cancer was considered test positive, excluding follicular lesion/neoplasm diagnoses but including suspicious for papillary cancer in other categories considered test negative) and FS: sensitivity (67% vs. 66%), specificity (95% vs. 98%), PPV (positive predictive value) (94% vs. 96%), and NPV (negative predictive value) (79% vs. 84%). As nuclear features are diagnostic for papillary cancer in both FNAB and FS, it was emphasized that FS does not offer any advantage over FNAB for papillary cancer.[13] In studies that did not distinguish between non-follicular and follicular lesions, frozen section was found to be superior to FNAB in every parameter. However, the researchers emphasized that this could be misleading because, for FNAB, positive or suspicious categories for carcinoma were taken as test positive without distinguishing

papillary cancer or follicular lesions. In the assessment of non-follicular and follicular lesions, it was highlighted that FNAB showed significantly different specificity (60% vs. 95%) and PPV (positive predictive value) (36% vs. 67%) for follicular lesions and papillary carcinomas. Also, the different PPV values for frozen section (86% vs. 96%) made interpreting these findings challenging.

The researchers in this meta-analysis have stated that FS contributes minimally to improving the diagnostic accuracy of thyroid FNAB.[13] Bethesda classification has led to studies with varied outcomes regarding the use of FS in thyroid nodules. In a cohort study by Mallick et al.,[14] during a period when molecular tests were used, they highlighted that FS altered intraoperative management in only 2.1% of cases. Due to this minimal impact on altering thyroid surgeries and the associated increase in cost and time without providing significant benefits, they do not recommend its routine use. In another study where routine FS is not recommended, it is emphasized that due to its low sensitivity in Bethesda III and IV nodules and comparable performance to FNAB in Bethesda II, V, and VI nodules, its use is not suggested. However, it has been emphasized as an option for Bethesda I nodules, as it might contribute to surgical management.[11] In another study, it was noted that the routine use of intraoperative FS in patients undergoing diagnostic lobectomy for nodules larger than 4 cm could result in a reduction in healthcare utilization. Additionally, it was emphasized that avoiding FS in patients with follicular lesions could lead to additional cost savings.[15] Cost-effectiveness is a crucial factor in the utilization of methods, as costs can vary from one country to another. In a center in the United States, the impact of routine FS during thyroid lobectomy on diagnosing clinically significant thyroid cancer was found to be limited. As a result, routine FS has been excluded for cost-effectiveness purpose.[16] In the Canadian healthcare system, it has been reported that the routine use of FS is cost-effective even without considering non-monetary costs such as patient anxiety, emotional stress, and productivity loss due to a second surgical procedure.[17] In China and many other Asian countries, FS is still routinely used. In recent years, in a large series where both FNAB and FS were routinely performed in China when nodules considered malignant or suspicious for malignancy in FNAB, were confirmed as malignant in final pathology, the concordance was reported as 90.3%, with a sensitivity of 90.7%, specificity of 85.2%, PPV of 98.8%, and NPV of 40.4%. The model demonstrating the highest diagnostic concordance was found to be the use of FNAB with selective FS (applying FS in Bethesda I-V nodules and avoiding FS in Bethesda VI nodules due to a very high malignancy rate of 99.2%). This model showed a concordance of 96.9%, sensitivity of 97.3%, specificity of 92%, PPV of 99.4%, and NPV of 71.6%, demonstrating significantly better diagnostic performance than FNAB alone (the net reclassification index (NRI)=0.135, 95% CI 0.103-0.167, p<0.001). According to this model, 32% of patients required FS, and compared to FNAB alone, FS correctly reclassified 18.2% of patients. Researchers have recommended this model for diagnostic accuracy and medical efficiency.[7] In a recent multicenter study conducted in Europe, where FS was liberally used in a target-oriented manner, the application rate of FS in a tertiary center in Germany was 35.7%. This rate, while similar to the recommendation from the previous study in China, is lower overall in Europe and detected as 22%. In a European center, where FS is liberally utilized in a target-oriented manner, the sensitivity of FS was higher compared to centers with lower FS usage (75% vs. 63.5%, RR 1.2, 1.2 to 1.3; p<0.040), indicating its utility in guiding appropriate surgical decisions in thyroid surgery. Although the malignancy rate was higher in the center, where FS was selectively used (21.3% vs. 12.2%; p<0.001), it explicitly decreased the need for completion thyroidectomy (8.1% vs. 20.8%, RR 0.4, 0.2 to 0.7; p<0.001).[9] In the United States, centers where the usage of FS is lower (less than 10% of cases), also draw attention.[18]

The Role of Frozen Section Examination According to Bethesda Categories

I. Nondiagnostic (Bethesda I):

Approximately 15% of FNABs take part in this category. After their initial Bethesda I FNAB, the malignancy risk in nodules surgically excised, ranges between 5-20%. Repeat FNAB is recommended if the initial FNAB result is Bethesda I, and in 60-80% of cases, the repeat FNAB results in a diagnostic category.[19,20] If the second FNAB also yields a nondiagnostic result, surgical resection is recommended.[21] Especially in cases with Bethesda I FNAB and with a surgical indication, an intraoperative FS can be utilized.[18] It has been reported that FS significantly contributes to the interpretation of nodules in Bethesda I category.[22] In the evaluation of 252 nodules where both FNAB and FS were assessed, 70 (27.8%) nodules were categorized as Bethesda I, and malignancy was detected in 13 (18.6%) of these nodules upon final pathology. FS examination identified 9 out of these 13 malignant nodules (69%). Researchers have underlined the indispensable role of FS in the assessment of nodules categorized as Bethesda I, stating that it enhances diagnostic quality.[23] In a study evaluating thyroid nodules using both FNAB and FS in over 3800 patients, among the 75 nodules categorized as Bethesda 1, 32 (42.7%) were identified as malignant upon final pathology. From these

32 nodules, FS examination reported 29 (90.1%) as malignant, 1 (3.1%) as suspicious for malignancy, and 2 (6.2%) as benign or indeterminate. Among the 43 nodules labeled as benign, 41 (95.3%) were reported as benign or indeterminate, and 2 (4.7%) were identified as suspicious for malignancy.[7] In a study evaluating 272 patients who underwent both FNAB and FS examinations, 21 nodules were categorized as Bethesda I. According to the final pathology, 19 nodules were benign, and 2 were malignant, resulting in a malignancy rate of 9.5%. While FS examination correctly classified 19 benign nodules and 1 malignant nodule, it misclassified 1 malignant nodule as benign (false negative). For nodules in the Bethesda I category, FS examination yielded a sensitivity of 50%, specificity of 100%, positive predictive value of 100%, negative predictive value of 95%, and concordance of 95.2% in categorization. Researchers have reported that routine FS application in Bethesda I category nodules could improve surgical management.[11] The evidence in the literature indicates that FS examination can significantly contribute to distinguishing between malignancy and benignity in Bethesda I category nodules and can impact surgical planning.

II. Benign (Bethesda II):

%70 of FNABs fall within the benign category.[19] In general, although nodules in the benign category in FNAB have a low risk of malignancy, different malignancy rates have been reported in Bethesda II category in studies where FS examination was evaluated. Roychoudhury and colleagues identified 2 malignancies (3.9%) in the final pathology, among 51 nodules with a FNAB Bethesda 2 classification. FS was able to detect one of these cases, while the other case was among those left for paraffin examination. The researchers stated that FS examination in nodules categorized as Bethesda II did not lead to significant changes in treatment and did not recommend the use of FS in this category.[22] Cohen et al.'s study[24] revealed that among 149 patients categorized as benign (Bethesda II) in FNAB, 11 (7.4%) were identified as malignant in the final pathology. During FS examination, only 1 (0.7%) of these malignancies was detected, while the other 10 cases were reported as benign. FS did not significantly enhance the malignancy diagnosis in FNAB-categorized Bethesda II nodules and failed to diagnose most of the malignancies. In another study, among 44 nodules with Bethesda 2 FNAB classification, 7 (16%) were determined as malignant in the final pathology. During FS examination, 2 (29%) of these nodules were identified, while 5 (71%) were later identified as malignant in final pathology. Among these 44 nodules, FS reported 29 (66%) nodules as descriptive and left 15 (34%) as indeterminate for further paraffin section examination. The malignancies detected by FS only led to a transition from hemithyroidectomy to total thyroidectomy in just 5% of cases with FNAB Bethesda II classification. This study also highlighted the low malignancy detection rate of FS and its rare alteration of surgical strategy.[18] Among 116 nodules classified as Bethesda II in FNAB, malignancy was detected in 20 (17.2%) upon final pathology examination. During FS examination, of the malignant nodules, 12 (60%) were identified as malignant, 3 (15%) as suspicious for malignancy, and 5 (25%) as benign or indeterminate. Among the 96 nodules reported as benign in the final pathology, 1 (1%) was suspicious for malignancy, and 95 (99%) were reported as benign or indeterminate. Researchers stated the contribution of FS usage diagnostic accuracy in nodules categorized as Bethesda I, II, III, IV, and V towards.[7] Some studies have observed a higher-than-expected rate of malignancy; however, these series involved operated patients who underwent FS examination. As a result, they did not encompass all nodules classified as Bethesda II, mainly because a significant portion of Bethesda II nodules does not undergo surgery. Generally, the malignancy rate is low in this category.[20] Although FNAB does not definitively exclude the risk of malignancy, the false-negative rate in the Bethesda II category is low, typically ranging from 0% to 3%.[25] In this category, due to the low probability of malignancy risk and changing the surgical strategy, FS is generally not recommended as it is unlikely to make a significant contribution.

III. Atypia Of Undetermined Significance (Bethesda III):

10-15% of FNABs fall within the Bethesda III and IV categories.[19] In adults, the malignancy risk in nodules classified as Bethesda III and undergoing surgical resection averages around 22% (range: 20-32%). This percentage might be relatively higher than the overall malignancy risk of the entire Bethesda III category, including nodules that were not resected.[20] Posillico et al.[26] conducted a retrospective assessment of 120 patients with Bethesda III classification in FNAB. Among these, 62 patients underwent total thyroidectomy without FS based on ultrasound and clinical characteristics, while 58 patients were scheduled for lobectomy or total thyroidectomy with FS. Among the 58 nodules where FS was applied, 11 (19%) were found to be malignant in final pathology. Of these, FS provided descriptive results for 37 nodules (64%), and 21 nodules (36%) were left for paraffin examination. Out of the descriptive results, 33 were benign (32 true negative, 1 false negative), and 4 were malignant (true positive). Out of the 11 malignant nodules, 4 (36.4%) were identified by FS. FS demonstrated a sensitivity of 36.4%, specificity of 100%, a PPV of 100%, a NPV of 87%, and a concordance of 88%. The researchers noted that in 36 (62%) of patients who underwent FS, the examination influenced the decision for surgery. They highlighted the high specificity and PPV of FS, suggesting

its reliability in diagnosing malignancy in unilateral thyroid disease and its potential assistance in determining the extent of thyroidectomy in 62% of cases. However, due to the low sensitivity observed in the study, the results are subject to debate, as FS might only prevent the need for completion thyroidectomy in approximately one-third of malignant cases.[26] Cotton et al.[27] retrospectively evaluated data from patients diagnosed with follicular lesions before the Bethesda classification and those diagnosed with Bethesda III and IV nodules after the Bethesda classification, who were planned for lobectomy and FS. Among the 65 patients diagnosed with a follicular lesion in FNAB, malignancy was detected in 6 (9.2%) in the final pathology, and FS identified 3 of them (50%), leading to a change in the surgical approach in 3 patients (4.6%) out of the total 65. The sensitivity was determined as 50%, specificity as 100%, PPV as 100%, and NPV as 95%. Out of the 45 patients diagnosed with Bethesda III, malignancy was detected in 5 (11.1%) based on final pathology, and FS could identify 1 of them (20%). In 1 patient out of the 45 (2.2%), the surgical approach was altered. The sensitivity was determined as 20%, specificity as 100%, PPV as 100%, and NPV as 91%.[27] False-positive FS results were not detected in follicular lesions or the Bethesda III category. Researchers emphasized the limited utility of FS in both pre-Bethesda follicular lesions and post-Bethesda III categories.[27] In another study, among 296 patients with Bethesda III FNAB who underwent thyroid surgery, FS examination was performed in 56 (19%) cases. Out of these, 16 (28.6%) were found to be malignant upon final pathology. Within the FS results, 38 cases (68%) were left inconclusive for paraffin sectioning, where 6 were malignant (all true positives) and 12 were benign (all true negatives) in the final pathology. FS detected 6 of these malignant lesions, leading to a change in the surgical strategy in 6 out of 56 cases (10.7%). However, it was emphasized that FS did not significantly impact altering treatment in Bethesda III nodules.[22] Overall study findings support the limited contribution of FS in evaluating Bethesda III nodules, suggesting that it does not significantly contribute to altering treatments.

IV - Follicular Neoplasm (Bethesda IV):

Estimated risk of malignancy in this category is % 30 (range: % 23-34).[20] In Kennedy and Robinson's study,[18] 139 patients underwent surgery with FS for thyroid nodules, and 50 of them had Bethesda IV nodules according to preoperative FNAB. However, in the final pathology results, 31 (62%) of the patients were reported as benign and 19 (38%) as malignant. In FS examination; 13 (26%) patients were reported as benign, 4 (8%) as malignant, 26 (52%) as suspicious for follicular neoplasm and 7 (14%) as suspicious for malignancy. The researchers stated that in the majority of patients except non-diagnostic and non-malignant cases, patient results did not support the rationality of FS according to the study.[18] In another study; by Roychoudhury et al.,[22] FS was applied to 57 (58%) patients among 99 patients underwent surgery due to Bethesda IV nodule in FNAB. Malignancy was detected in 18 nodules (31.6%). FS was applied to 57 nodules, and 48 (85%) were left for paraffin section examination. 4 (7%) were diagnosed as malignant, 5 (8.8%) as benign, and 22.2% of the malignant nodules could be detected by FS. There was a change in intraoperative treatment with FS in only 3 (5.3%) of 57 cases in the Bethesda IV category. The researchers emphasized that the results did not have a significant impact on the treatment of Bethesda IV nodules and did not support its application in these nodules. In the study by Goemann et al.,[11] including 272 patients with FNAB and intraoperative FS, 80 nodules were reported as Bethesda III and IV categories. In the final pathology, 12 (15.6%) of these nodules were reported as malignant, while 68 as benign. In the FS examination, 77 nodules were reported as benign (96.2%) and 3 (3.8%) as malignant. 9 (75%) of the malignant lesions were reported as benign (false negative) by FS. In this group of patients, sensitivity was determined as 25%, specificity as 100%, PPV as 100%, NPV as 88.3%, and accuracy as 88.7%. The results of the study do not support the routine use of FS for Bethesda categories III and IV due to its low sensitivity. Therefore, the researchers emphasized that the application of FS may not be accurate enough to guide the intraoperative management of thyroidectomies in these categories, as a high rate of false positive results would be expected. Before the Bethesda classification, in a meta-analysis including 1531 cases of 23 studies conducted between 1982 and 2007, the sensitivity of FS in follicular lesions was found as 21+23%, specificity 99+2.4%, PPV 86+26%, NPV 83+16%. The researchers concluded that the low sensitivity of FS in follicular lesions significantly limits its applicability in daily practice and that it may contribute minimally to the diagnostic relevance of FNAB. As a result, they did not recommend the use of FS in follicular neoplasia.[13] Many studies were published about using FS in follicular neoplasia after this meta-analysis. In 2019, Grisale and Sanabria reported a meta-analysis including 46 studies between 1991 and 2018, about using FS in Bethesda IV nodules. The sensitivity was determined as 43%, specificity 100%, PPV 62.9%, and NPV 87.7%. The researchers stated FS had moderate diagnostic performance in follicular neoplasia and its contribution was limited for making decisions intraoperatively. Researchers recommended avoiding the routine use of FS in these patients.[28] FS should not be routinely recommended to evaluate malignancy in lesions with follicular patterns. In nodules with a follicular

pattern, capsular and lymphovascular invasion cannot be evaluated with FS. Nowadays, some of the follicular pattern tumors are follicular variant papillary cancer or noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Moreover, it is difficult to evaluate the entire capsule in FS, and distinguishing this lesion from others is challenging since FS artifacts mask nuclear features. Additionally, FS examination of nodules with Bethesda IV FNAB prolongs the operating time, increases the burden on the pathology department, and is not cost-effective. It causes a negligible effect on the decrease in delayed completion thyroidectomy rates. Increasing the use of genetic tests in Bethesda IV nodules will further reduce the use of FS.[29] Moreover, the systematic usage of FS may make the final pathological diagnosis more difficult and less accurate. A comprehensive evaluation of the entire capsule of follicular lesions is mandatory to demonstrate any capsular or vascular invasion, which is the hallmark of malignancy. FS is performed on a fresh, unfixed thyroid sample, which is then formalin-fixed and embedded in paraffin for the final pathological examination. Therefore, performing FS results in a more fragmented thyroid sample; this may lead to difficulties in orienting and cutting the sample after detection and may compromise the detection of signs of capsular invasion.[30] However, there are also rare studies stating that FS has a more appropriate diagnostic performance than FNAB.[31]

In conclusion, due to its low diagnostic performance, FS should not be recommended as a routine intraoperative test to evaluate malignancy in lesions with a thyroid follicular pattern to determine the extent of initial surgery.[29] At present, it is generally accepted that FS should not be used in nodules in the Bethesda IV category.

V - Suspicion for Malignancy (Bethesda V):

Estimated risk of malignancy in this category is 74% (range: 67-83%). The "Suspicious for malignancy" category (Bethesda V) is very heterogeneous. It is used when the cytomorphologic features of thyroid FNAB are suggestive of papillary thyroid carcinoma, medullary thyroid carcinoma, lymphoma, or another malignant neoplasm but are quantitatively and/or qualitatively insufficient for a definitive malignancy diagnosis. Most cases in this category are classified as "suspicious for papillary thyroid carcinoma." Some of the cases in this category increase the possibility of the follicular variant of papillary thyroid carcinoma or the follicular variant of NIFTP. For this subgroup, the addition of an optional note explaining that "cytomorphological features are suspicious for a follicular variant of papillary thyroid carcinoma or its silent type NIFTP" may be considered. Performing less aggressive surgeries such as lobectomy instead of total thyroidectomy could be more appropriate in these situations.[20] In the study by Roychoudhury et al.,[22] FS examination was performed on 27 (47%) of 57 nodules with Bethesda V FNAB, and malignancy was detected in 26 nodules (96.3%) in the final pathology. In FS, 18 nodules (66%) were reported as malignant (all of them true positive), and the diagnosis of 9 (34%) nodules was left to paraffin section. The researchers emphasized that FS makes a significant contribution to the planning of surgical treatment in patients diagnosed with Bethesda V. In the study evaluating the use of FS in nodules with Bethesda V and Bethesda VI FNAB, 287 (93.8%) of 306 nodules in the Bethesda V category were found to be malignant. In FS, 260 (84.9%) nodules were reported as malignant, 14 (4.6%) as suspicious for malignancy, and 32 (10.5%) as benign or indeterminate. The malignancy rates of these results in the final pathology were found to be 100%, 64.3%, and 56.3%, respectively.[32] In another study, 647 (97.3%) of 665 Bethesda category V nodules were detected as malignant. 608 (91.4%) nodules were reported as malignant, 19 (2.9%) as suspicious for malignancy, 38 (5.8%) as benign or indeterminate in FS. The malignancy rates of these results in the final pathology were found to be 100%, 89.5%, 57.9%, respectively. In both studies, FS in Bethesda V nodules was effective in confirming the diagnosis of malignancy. More than half of the nodules reported as benign as a result of FS were malignant, showing that FS cannot completely exclude the possibility of malignancy. Therefore, it should not be used to exclude malignancy. In another study, malignancy rates in final pathology in Bethesda II, III, IV, V categories were found to be 7.4%, 14%, 29%, 84%, respectively, and malignancy detection rates with FS in categories were 0.7%, 3%, 1.1%, and 42%, respectively. In this study, the contribution of FS to the diagnosis of malignancy is a total of 4% in all categories. When Bethesda V category is excluded, the contribution of FS to the diagnosis in all other categories is only 1.9%. In final pathology, 43 (51.8%) of 83 malignant tumors were follicular variant papillary cancer, and only 3 (7%) of them could be diagnosed with FS. The researchers stated that the role of FS examination in the evaluation of thyroid nodules is limited and that it is most useful for nodules diagnosed with Bethesda V FNAB. They also emphasized that the diagnosis of the follicular variant of PTC with FS is still difficult.[24] In a study including 65 patients with Bethesda V, the malignancy rate in final pathology was 61.5%, and 45% of them were detected intraoperatively with FS. Specificity and PPV were 100%, sensitivity was 83%, and NPV was 95%. Total thyroidectomy was indicated in 9% of the patients, and findings that would cause conversion from lobectomy to a total thyroidectomy with FS were detected in 83%. The researchers concluded that in this category, the number of

completion thyroidectomies can be reduced with FS leading to reduced use of healthcare resources.[33] However, there are also studies reporting that the performance of FS in the Bethesda V category is comparable to FNAB and that it does not have a significant contribution to surgical planning.[11] In fact, there are studies reporting that since the diagnostic relevance of FNAB is significantly higher than FS in Bethesda V and VI categories, FS may not be used in these categories.[31] FS may contribute to confirming malignancy when determining the surgical strategy for nodules with FNAB in the Bethesda V category.

VI - Malignant (Bethesda VI):

The risk of malignancy in nodules in the Bethesda VI category is on average 97% (range: 97%-100%) in adults.[20] In a recent large study, the malignancy rate in Bethesda VI category nodules in FNAB is high as 99.7%. In addition, the risk of false negativity in FS is 4%, and its diagnostic accuracy is lower than FNAB.[7] In fact, there are studies in which FS is not recommended in nodules with Bethesda VI FNAB because FS may result in 10% false negative results.[32] Similar to these studies, many other studies have shown that FS does not contribute to the diagnostic relevance of FNAB.[11,22,23,31] According to studies in the literature, it appears that the rate of malignancy is high in nodules with FNAB in the Bethesda VI category. In addition, it is not recommended to use FS in this category as it will not have a significant effect on the diagnosis of malignancy and treatment.

B. Frozen Section Examination in Assessment of Extrathyroidal Extension of Thyroid Malignancy:

Extrathyroidal extension may be a negative prognostic factor in thyroid cancer. It may not be possible to detect limited or microscopic extrathyroidal extension with preoperative imaging methods. In particular, microscopic extrathyroidal extension can only be detected by pathological microscopic examination.[34] The number of studies on the effectiveness of FS in extrathyroidal extension is limited in the literature. First of all, Park et al.[35] studied the effectiveness of FS in evaluating extrathyroidal extension in papillary thyroid cancer. Extrathyroidal extension was reported by FS examination in 54 (20%) of 268 cases of papillary thyroid cancer, and extrathyroidal extension was confirmed in 53 of them in the final pathology. Extrathyroidal extension was detected in 80 patients (30%) in the final pathology. FS had a sensitivity of 66%, a specificity of 99%, a PPV of 98%, and an NPV of 87%. In another study, where microscopic extrathyroidal extension was 27.5% in papillary thyroid cancer, it was reported that intraoperative FS could detect microscopic extrathyroidal extension with 100% sensitivity and specificity in all cases.[34] Both studies reported that intraoperative FS can be used to detect extrathyroidal extension in papillary thyroid cancer, and FS can assist the surgeon in determining the extent of thyroid surgery and central dissection. FS examination can be used to evaluate extrathyroidal spread, especially if the treatment plan will change in patients with papillary thyroid cancer.

C. Frozen Section Examination in the Evaluation of Suspicious Lymph Nodes:

Lymph node metastasis is common in differentiated thyroid cancer, especially in papillary thyroid cancer. Lymph node metastasis spreads first to the ipsilateral paratracheal lymph nodes and then to the contralateral lymph nodes. Afterwards, it spreads to the lateral neck compartments.[36] Ipsilateral central neck metastasis is among the risk factors for contralateral central metastasis, and the risk of bilateral central metastasis is high in patients with unilateral central metastasis.[37] Lim and colleagues evaluated 252 patients with papillary thyroid cancer who underwent total thyroidectomy and bilateral central neck dissection, and the ipsilateral central dissection material was examined with FS. Central metastasis was detected in 53% of the patients, and central metastasis was detected in 49% of the patients by FS examination of the ipsilateral central region. Bilateral central metastases were detected in 35 (26%) of 134 patients with central metastases. FS for ipsilateral central region had a sensitivity of 92%, a specificity of 99%, a PPV of 99%, and an NPV of 84%. For quantitative analysis of the central region, the authors reported that FS is a useful tool for the unilateral central region with high sensitivity and specificity in the precise intraoperative evaluation of the lymphatic status of the central region.[38] Central metastases were detected in 21 of 48 patients with unilateral papillary cancer and no preoperative lymph node metastases (15 unilateral central metastases, 6 bilateral central metastases). It was revealed that ipsilateral central zone FS could appropriately predict the lymph node status of 43 patients (27 nodes negative, 16 nodes positive), but could not detect 5 lymph node metastases (3 of them micrometastases). The sensitivity of FS examination of ipsilateral central lymph dissection material in predicting central node metastasis was determined as 80.7%, specificity as 100%, and overall accuracy as 90%. It has been reported that FS examination of ipsilateral central zone material is an appropriate method for predicting lymph node metastasis in clinical node-negative patients and can be used to determine the extent of central zone node dissection.[38] In fact, routine ipsilateral central dissection and FS examination may be a valid alternative to prophylactic bilateral central neck dissection, as it predicts the central region lymph node status

and reduces morbidity.[39,40] Additionally, if there is a suspicious lymph node during thyroidectomy, this lymph node can be removed, and FS examination can be used to evaluate whether it is a metastasized lymph node.

D. Frozen Section Examination for the Evaluation of Intraoperative Parathyroid Tissue:

During thyroidectomy, FS examination for the parathyroid gland is performed to confirm whether a tissue is parathyroid or not and to distinguish tissue that may be parathyroid from fatty tissue, thymus, thyroid, lymph node, especially metastatic lymph node.[1] FS performed to determine parathyroid tissue is an extremely reliable way to determine tissue type with a high accuracy rate.[41] However, separating parathyroid tissue from surrounding adjacent tissues may be difficult due to freezing artifacts. Shidham et al.[42] suggested that before freezing the tissue sent for FS, 2 imprint preparations should be prepared from the tissue, and their intraoperative cytological examination would be an important aid to FS examination in distinguishing parathyroid tissue from other tissues. To distinguish parathyroid from nonparathyroid tissue, FNAB can be applied to the relevant tissue in situ or ex vivo, and rapid PTH measurement can also be performed from this aspiration. It has been reported that this method is a fast, simple, noninvasive method with a short learning curve and is an alternative to FS examination.[43] During thyroidectomy, effort should be made to preserve the parathyroid glands in situ with their vascular pedicle. If its vascularity cannot be preserved or its vascularization is thought to be impaired after dissection, it should be excised for autotransplantation. The parathyroid gland may be intracapsular within the thyroid and may have no vascular pedicle. If they become dusky after separation from the thyroid, they should be removed for autotransplantation. In addition, the removed thyroid sample should be carefully examined for unintentionally removed parathyroid. If a tissue that may be parathyroid is seen on the sample, it should be separated from the sample and kept on ice in physiological saline or in a moist gauze for autotransplantation. To confirm that the autotransplanted tissue is parathyroid, a small piece should be sent for FS examination and autotransplanted after FS examination confirms that it is parathyroid.[44] When performing central dissection in thyroid cancers, effort should be made to protect the parathyroid glands with a vascular pedicle. If the vascularity of the parathyroids is impaired, they must be removed for autotransplantation. In particular, it should be investigated on the operating table whether there is a parathyroid in the removed central tissue. Suspicious parathyroid glands should be completely cleared of surrounding nodal tissue. In particular, it must be ensured that the surrounding tissue is cleanly separated from the malignant tissue. A small piece of this removed tissue is sent for FS examination. FS examination confirms whether the tissue is parathyroid tissue. It can also provide information about whether this tissue is malignant and whether the surrounding malignant tissue invades the parathyroid tissue.[45] This tissue should be transplanted after confirming that it is parathyroid by FS. If there is suspicious malignant infiltration in the tissue under FS examination, this tissue should not be autotransplanted. Since a very small tissue is sent from the parathyroid gland for FS examination, the biggest danger is cutting and consuming the tissue while sectioning. To reduce this risk, careful sectioning is important.[1]

Disclosures

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