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Fine Needle Aspiration Biopsy and Comparison With Paraffin Section Results: A Prospective Cohort Study

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ABSTRACT

In this study, we investigated the diagnostic value of intraoperative fine needle aspiration biopsy (FNAB) to determine thyroid cancer in patients with multinodular goiter or solitary nodules/dominant nodules and the results from intraoperative FNAB and paraffin sections were compared in order to determine whether intraoperative FNAB could be an alternative to frozen section analysis.

40 patients were included in the study. During thyroidectomy, intraoperative FNAB was performed and results were classified as malign, benign and suspicious/indeterminate. FNAB and paraffin section results were compared in all patients and evaluated in terms of FNAB sensitivity, specificity, positive/negative predictive values and overall accuracy.

Among the 40 patients undergoing thyroidectomy, 7 were identified as thyroid cancer with paraffin section analysis. With intraoperative FNAB, two of the 40 patients were classified as malignant, three had suspicious lesions or extremely degenerated cells in which histopathologic evaluation was impossible. Diagnostic analysis of intraoperative FNAB for thyroid cancer revealed 33.33% sensitivity, 100% specificity and 94.59% overall accuracy. The positive and negative predictive values were 100% and 88.57% respectively.

Thyroid nodules found to be malignant as a result of FNAB were also found to be malignant in histopathological evaluation. However this was not the case for thyroid nodules found to be benign in FNAB. That is with FNAB some malignant nodules may be erroneously classified as benign. Therefore although FNAB has an important role in the management of thyroid nodules it is not sufficient in the detection of malignant cases.

Key Words: Thyroid, Nodules, intraoperative fine-needle aspiration biopsy

Introduction

Thyroid nodules with regard to both their diagnosis and treatment remain to be clinical and surgical challenges for the surgeon in their daily practice since nodular abnormalities of the thyroid are rather frequent. To avoid over and under treatment careful evaluation and accurate characterization of lesions are crucial. A better personalized diagnostic approach could be achieved through the use of various technologies such as ultrasound, thyroid scintigraphy and (when indicated) fine-needle aspiration biopsy (FNAB), in addition to more advanced methods including molecular testing. High-quality techniques and risk-based protocols have been reported to have great importance in all facets of the diagnostic approach to thyroid nodules (1, 2).

The most common surgical treatment indications for patients with multinodular goiter (MNG) or solitary nodule can be listed as: cancer or possibility of cancer, compression symptoms and cosmetic deformities (3). Planning an efficient treatment and sufficient excision/resection mainly depends on the differentiation between benign and malign thyroid nodules. Many diagnostic methods can be used for the differentiation however FNAB still maintains its importance as a primary preoperative diagnostic modality to evaluate thyroid nodules (4).

For preoperative cancer risk assessment of solitary nodules the usage of FNAB has great diagnostic value. However while evaluating the cancer risk of patients with MNG FNAB is well known to have lower sensitivity and this method may miss out on the diagnosis of up to 80% of cancers (5). As a consequence life-altering delays in diagnosis can occur for patients. Furthermore despite its importance as a swift on-demand analysis that can direct surgeons intraoperatively frozen section reportedly is losing its importance in endocrine surgery and thyroid tumors (6).

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In order to determine whether more efficient surgeries could be performed by the intraoperative detection of thyroid malignancies we designed this study with an aim to evaluate the diagnostic value of intraoperative FNAB for the diagnosis of thyroid cancer in patients with MNG or solitary nodules.

Material and Methods

A prospective cohort of all patients who underwent thyroid surgery for the treatment of multinodular or solitary thyroid nodules in the General Surgery Department was obtained. Approval was obtained from Ethics Committee to conduct the study.

Study Group: Patients hospitalized in our clinic with a diagnosis of multinodular or solitary thyroid nodules between the relevant dates were enrolled in the study given that they were suspected to have malignancy were aged between 15–67 years and had agreed to participate. Other patients were excluded from the study. The thyroid nodules of all patients were examined by ultrasound and intraoperative FNAB and frozen section results were recorded.

Fine Needle Aspiration Biopsy Procedure: For all patients the same surgical techniques were used and the thyroid gland was reached and explored through a midline incision. Dissection was started with the lobe which had the dominant nodule. Intraoperative FNAB was performed after entering the thyroid lobe with the dominant nodule. FNAB was performed from the largest nodule with a 21G needle on a 20 cc injector and cell material was aspirated 3 times. These materials were divided into 4 glass slides and air-dried. All of the materials were examined by the Medical Pathology Department.

Evaluation of the Results: Different classifications are available in the literature for FNAB analysis for our study we divided results into the following subgroups: "benign cytology", "malign cytology", "suspicious/indeterminate cytology", and "non-diagnostic". Also the results of paraffin section analysis were classified as "benign" and "malign" and FNAB outcomes were compared to the results of this analysis. Finally calculations were performed to assess the diagnostic accuracy of intraoperative FNAB with results for sensitivity, specificity, diagnostic accuracy and positive/negative predictive values.

Statistical Analysis: All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Data are given as mean ± standard deviation and range for continuous variables, and as frequency (percentage) for categorical variables. Categorical variables were analyzed with Fisher's exact test. $p<0.05$ values were accepted as statistically significant results.

Results

Forty patients who underwent thyroid surgery were included in this study. The mean age was 47.2 ± 13.4 (range 15-67) years. There were 33 female (82.5%) and 7 male (17.5%) patients. The mean age of males was 46 ± 8.9 years and the mean age of females was 47.5 ± 2.5 years ($p = 0.799$).

A total of 31 (77.5%) MNG cases and 9 (22.5%) solitary nodule cases were identified and their results were analyzed. Intraoperative FNAB results were classified as malign for only two patients (%5). The paraffin sections of both of these patients diagnosed with MNG had revealed the presence of follicular cancer. None of the solitary nodule cases were defined as malignant with FNAB. There were no non-diagnostic FNAB results. Three cases were reported as suspicious/indeterminate with intraoperative FNAB and those three cases were excluded from the final statistical analysis of diagnostic accuracy. The paraffin results of these three cases were reported as benign in two cases and papillary carcinoma in one. Six of the 31 patients diagnosed with MNG had conclusive findings for malignancy in paraffin section analysis. Among these six cases intraoperative FNAB had classified two as malign one as suspicious/indeterminate and three cases as benign. The remaining 25 cases were also reported to be benign in FNAB. Overall six (19.4%) of the MNG cases and 1 patient (11.1%) with solitary nodule were identified to have malignant lesions ($p = 0.567$).

According to FNAB results 35 cases (87.5%) were benign, 3 cases (7.5%) were suspicious/indeterminate and 2 cases (5%) were malign. In the 35 cases classified as benign with FNAB a total of four patients were determined to have carcinoma one patient with follicular carcinoma and 3 patients with papillary carcinoma. Therefore the percentage of false negativity was 66.67%. In the three suspicious/indeterminate cases (according to FNAB) paraffin section revealed that one patient had papillary carcinoma. Finally the two cases classified as malignant with FNAB were identified as follicular carcinoma with paraffin section results. In the diagnosis of thyroid

Table 1. Summary of Patients' Characteristics

Age (years)	47.2 ± 13.4
Gender	
Female	33 (82.5%)
Male	7 (17.5%)
Diagnosis	
Multinodular goitre	31 (77.5%)
Solitary nodule	9 (22.5%)
Result of fine-needle aspiration biopsy	
Benign	35 (87.5%)
Malignant	2 (5.0%)
Suspicious / indeterminate	3 (7.5%)
Result of paraffin section	
Benign	33 (82.5%)
Follicular carcinoma	3 (7.5%)
Papillary cancer	4 (10.0%)
Treatment	
Bilateral total thyroidectomy	32 (80.0%)
Thyroid lobectomy (right)	6 (15.0%)
Thyroid lobectomy (left)	2 (5.0%)

Data were given as frequency (percentage) for categorical variables and mean ± standard deviation for continuous variables

Table 2. Results of FNAB and Histopathological Diagnosis

	Paraffine section		
İntraoperative FNAB	Benign	Malignant	Fisher's Exact test, p value
Benign	31 (88.6%)	4 (5,4%)	
Malignant	0 (0%)	2 (100%)	6.716, 0.567
Suspicious/indeterminate	2 (66.6%)	1 (33.3%)	

cancer with intraoperative FNAB sensitivity, specificity and diagnostic accuracy were found to be 33.33%, 100% and 94.59% respectively. The positive and negative predictive values were 100% and 88.57% respectively. No false positivity was detected. (Table 1 and Table 2).

Discussion

The major problem after the detection of a nodule in the thyroid gland is to determine whether it is benign or malignant. The use of FNAB plays a crucial role in this determination and results can prevent unnecessary surgery or may aid physicians in the decision for the best surgical approach. In this study in which the accuracy of FNAB was examined relative to paraffin section results it was observed that all thyroid nodules found to be malignant via FNAB were indeed malignant with histopathological analysis however false negativity was high meaning that thyroid nodules that were in reality malignant (as a result of paraffin section) may be missed with FNAB. In addition although the limited number of cases with solitary nodules may have hampered statistical analysis the frequency of malignancy was not different between cases with MNG and solitary nodules.

In order for a diagnostic test to be preferred as a sole method of investigation (without the need for further tests) it is necessary to determine that the method has high accuracy. The role of FNAB in predicting histopathological diagnosis was examined in previous studies which report extreme variations in terms of diagnostic characteristics. In a meta-analysis aggregating studies on this subject Ospina et al. stated that in comparison to histopathological results FNAB had 5.6% sensitivity and 37.5% specificity in benign histopathology while it had 64.2% sensitivity and 99.3% specificity in malignant

histopathology when comparisons were performed according to a 4-category system (7). Machala et al. reported that FNAB had 60.3% sensitivity, 98% specificity, 2.0% false positive rate, 3.72% false negative rate, 89.5% accuracy (8). Sharma et al. determined 89.5% sensitivity, 98% specificity, 1.9% false positive rate, 10.5% false negative rate, 97% accuracy for FNAB in the assessment of thyroid nodules (9). In a retrospective study Ravetto et al. reported that FNAB sensitivity was in the range of 58.3–98% and specificity was in the range of 72–100% (10). Many studies have published similar results (11,12). In our study sensitivity was 33.3%, specificity was 100% and accuracy was 94.59% for FNAB. There was no false negative case. The low number of cases in our study may have led to low sensitivity value however it is also possible that the high number of benign cases disproportionately increased the accuracy value which may be a problem for many studies in this field. When the results of previous studies and our study were evaluated overall it was concluded that the utilization of FNAB as a solitary method of analysis would not be sufficient for the examination of thyroid nodules. In most of the studies on this topic (including ours) if a patient's result was suspicious/indeterminate with FNAB this data was excluded to ensure more reliable analysis of conclusive diagnostic outcomes however this is a limitation that must be noted even though it is a statistically sound approach since the inclusion of these cases would have increased sensitivity by grouping suspicious/indeterminate patients into the test-positive group. The current approach of the literature appears to be the most compelling method when it is kept in mind that further analyses must be performed in cases with inconclusive FNAB findings.

In the literature the results of FNAB have been classified and analyzed with different methods. It was observed that the 4-group classification system or the 6-group Bethesda classification were used in the majority of previous studies (13,14). The Bethesda classification divides the results of FNAB into 6 classes (non-diagnostic, benign, atypia of undetermined significance, suspicious for follicular neoplasm, suspicious for malignancy and malignancy) and includes treatment recommendations (15). After the Bethesda classification was put into use it was shown that the quality of reporting and the positive predictive values for malignancy increased and the number of unnecessary operations for benign nodules decreased (16, 17). However the meta-analysis by Ospina et al. demonstrates only marginal advantages with the Bethesda classification in comparison to the 4-group method especially in terms of sensitivity and specificity values for each classification group (7). This may be associated with the fact that both FNAB classification systems contain similar groups. Even so it is evident that the 4-group and Bethesda classifications will result in different distributions and heterogenous results. Therefore in this section the results of benign and malignant groups were examined independent of the classification system. In a study conducted in Turkey Ugurluoglu et al. found that 16% of thyroid nodule cases with benign FNAB results and 97% of those with malignant FNAB results were malignant according to histopathological examination (18). Reuters et al. detected malignancy in 25.7% of benign cases and 97.3% of malignant cases according to FNAB (19). Cavalheiro et al. reported that they detected 30–38% malignancy in groups that could not be classified as benign or malignant according to FNAB results (20). Ke et al. reported that cancer was detected in 14.2% of benign cases and 99.1% of malignant cases in their remarkable study that had drawn data from an astounding 13351 FNAB results (21). Additionally in many different studies it has been shown that malignancy was detected with a frequency of 2–17% in cases with benign FNAB results and 99-100% in cases with malignant FNAB results (22-25). In our study malignancy was found in 100% of those with malignant classification and 5.4% of those with benign classification. When the studies in the literature are evaluated in general it is seen that results similar to our study have been published. Additionally in a meta-analysis when compared with western countries it was claimed that FNAB detected malignancy at a lower rate in studies conducted in eastern countries (26). This may be due to the experience of the clinicians, the quality of the equipment used, the strength of healthcare systems, the amount of time that can be allocated per patient and many other factors. None of these conditions were evaluated in our study and previous studies.

While evaluating the thyroid nodule FNAB is indicated in the detection of suspicious image signs in ultrasonography with regard to the size of the thyroid nodule and the malignancy potential of the nodule is evaluated with the results of the FNAB procedure. According to the ATA guideline published in 2015 in the presence of multiple thyroid nodules, the probability of malignancy of each nodule is independent of other

nodules. Therefore if FNAB is indicated according to ultrasonography and nodule size it is recommended to perform FNAB separately in each indicated nodule (27). There are publications stating that patients with multiple thyroid nodules and patients with solitary thyroid nodules have the same risk of malignancy (28, 29). However when the cancer risk of each nodule is evaluated separately it has been reported that the cancer risk of solitary nodules is higher compared to multiple nodules however interestingly the total cancer risk from nodules is equal in each patient (30). Similar to previous studies malignancy was found to have a similar frequency in cases with MNG and those with solitary nodules however as mentioned previously the low number of cases with solitary nodules may have limited the accuracy of statistical analysis.

Owing to the improvements in surgical techniques and devices the duration of the operations and complication rates have decreased in thyroid nodules. However hoarseness due to nerve damage can still be seen after operations and lifelong drug use may be required due to hypothyroidism. If malignancy is not detected in the pathology results of patients who were operated on with a suspicion of cancer it is evident that unnecessary surgery was applied and may have caused complications to the patient in addition to the financial burden to the healthcare system. On the other end of the spectrum the health of patients with malignant nodules who were identified to have benign disease according to initial analyses are put at risk due to incorrect diagnosis and delayed treatment. Therefore before the decision of surgery or follow-up it is necessary to make a more accurate distinction between malignant"was examined in detail for this purpose in our study it was shown that it was not sufficient as a solitary method of analysis. Similarly in the literature it has been shown in many studies that FNAB alone is not sufficient for the accurate examination of thyroid nodules.

The main limitations of the study were that it was single-centered and included a small number of cases (especially the limited number of malignant cases and solitary nodules). For this reason it was not possible to carry out further analyses. Surgical experience in the FNAB procedure and pathologist experience in cytological examination may have affected the results. The diagnosis could not be confirmed by more than one pathologist in the study. The experience and skill of the surgeon during the biopsy process was also not evaluated. Another limitation is the lack of a universally-accepted FNAB classification system which limits comparability from study to study however this limitation is true for all studies in this field.

Thyroid nodules found to be malignant as a result of FNAB were also found to be malignant in histopathological evaluation. However this was not the case for thyroid nodules found to be benign in FNAB. That is some nodules that were malignant had been classified as benign with FNAB. Therefore although FNAB has an important role in the management of thyroid nodules it is not sufficient in the detection of all malignant cases. Our results support the opinion that FNAB cannot be utilized as a method that can single-handedly evaluate thyroid nodules.

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