

From Mount Sinai to Mount Scopus: Differences in the Role and Value of Fine Needle Aspiration for Evaluating Thyroid Nodules

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ABSTRACT: **Background:** Fine needle aspiration is the main diagnostic tool used to assess thyroid nodules.

Objectives: To correlate FNA cytology results with surgical pathological findings in two teaching medical centers across the Atlantic.

Methods: We retrospectively identified 484 patients at Hadassah Hebrew University Medical Center, Jerusalem and Mount Sinai Hospital, New York, by means of both preoperative FNA cytology and a final histopathological report. Results compared FNA diagnosis, histological findings and frozen section results (Mt. Sinai only).

Results: The sensitivity value of FNA at Hadassah was 83.0% compared with 79.1% at Mt. Sinai (NS). Specificity values were 86.6 vs. 98.5% ($P < 0.05$), negative predictive value 78.7 vs. 77.6% (NS) and positive predictive value 89.7 vs. 98.6% ($P < 0.05$), respectively. "Follicular lesion" was diagnosed on FNA in 33.1% of the patients at Hadassah and in 21.5% at Mt Sinai ($P < 0.005$) with a malignancy rate of 42.5 vs. 23.1% ($P < 0.05$), respectively. Frozen section was used in 190 patients at Mt. Sinai (78.5%) with sensitivity and specificity values of 72.3% and 100%. Frozen section results altered the planned operative course in only 6 patients (2.5%). Follicular carcinoma was diagnosed in 12 patients at Hadassah vs. 2 patients at Mt. Sinai ($P < 0.05$).

Conclusion: The sensitivity of FNA at the two institutions was comparable. While malignancy on frozen section is highly specific, it should be used selectively for suspicious FNA results. Follicular lesions and the rate of malignancy in such lesions were more common at Hadassah, favoring a more aggressive surgical approach.

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prove to be cancerous. This low malignancy rate led to the development of fine needle aspiration in 1960 in Sweden in an attempt to better assess thyroid nodules. Since its first presentation, FNA of suspicious palpable or ultrasonographically detected nodules has gained wide acceptance [1]. Ultrasound-guided biopsy further improved the yield and accuracy of the procedure and it is now widely used. This technique is especially useful for small or non-palpable suspicious nodules [2,3]. With the appropriate technique and interpretation by an experienced cytopathologist, the reported FNA accuracy approaches 90% [4]. This approach has led over the years to a substantial decrease in the number of unnecessary thyroidectomies performed for benign disease and a concomitant increase in the yield of cancer found in surgically excised specimens [5]. This improvement in diagnosis underlines the importance of communication between the pathologist and the surgeon. Pathologists will usually classify aspiration samples into four categories: malignant, benign, non-diagnostic or indeterminate, and follicular. The first two categories are easily dealt with by surgeons. A malignant finding on FNA carries a specificity rate of over 90% and is considered an indication for thyroidectomy. Benign lesions on FNA carry a sensitivity rate of 80–85% and justify observation unless other risk factors are present, such as age, size of the lesion, tracheal deviation and respiratory symptoms [4]. The reported malignancy rates for FNA-detected follicular lesions are 20–40% [4–8] and thus pose a frustrating challenge for pathologists, surgeons and patients. Some institutions use an intraoperative frozen section to assess the malignant potential of such follicular lesions with a specificity rate of 95–100% [9–13]. The purpose of this study was to compare the utility and correlation of FNA cytology results and surgical pathology findings in two medical teaching centers across the Atlantic*.

PATIENTS AND METHODS

A retrospective computer search of all unilateral and bilateral thyroidectomies performed at Hadassah-Hebrew University Medical Center in Jerusalem, Israel between January 1994

Thyroid nodules are common in the general population, occurring at a rate of approximately 20%–30% on ultrasound examination; however, only 5% of all thyroid nodules

FNA = fine needle aspiration

*The Hadassah data were previously published [13].

Table 1. Hadassah Medical Center FNA results compared with final histopathology

FNA vs. Pathology			FNA		
			Malignant	Benign	Follicular lesion
Final histopathology	Malignant	Papillary ca	67	7	20
		Follicular ca	–	1	11
		Micro ca	11	8	3
	Benign	Normal	–	–	–
		Goiter	4	55	23
		Adenoma	2	4	20
		Thyroiditis	3	–	3
	Total		87	75	80

Table 2. The Mount Sinai School of Medicine FNA results compared with final histopathology

FNA vs. Pathology			FNA			
			Malignant	Benign	Follicular lesion	Suspicious
Final histopathology	Malignant	Papillary ca	63	12	7	13
		Follicular ca	–	–	2	–
		Micro ca	9	7	3	6
	Benign	Normal	–	7	–	1
		Goiter	–	32	13	5
		Adenoma	1	20	24	7
		Thyroiditis	–	7	3	–
	Total		73	85	52	32

and December 2004 identified a total of 242 patients with both preoperative FNA cytology and a final histopathological report. A similar search identified 242 patients at the Mount Sinai School of Medicine in New York, USA, operated between November 2002 and October 2006. Data were obtained for FNA diagnosis, patient age and gender, findings on ultrasound, frozen section results (only at Mt. Sinai) and final histopathology findings. Thyroidectomies with no preoperative FNA reports were excluded.

FNA reports of papillary carcinoma were considered malignant and all such patients underwent a total thyroidectomy. FNA results of normal thyroid tissue, colloid goiter, and non-diagnostic reports were all considered benign. Some patients with benign FNA results underwent total or partial thyroidectomy for other specific indications, such as large or retrosternal goiters, compression or tracheal deviation, enlarging nodules, “cold” nodule on radionuclide scintigraphy, patient preference, and malignancy diagnosed on frozen section.

Two important differences in evaluating FNA results were identified between the two institutions. First, at Hadassah an

FNA result suspicious of malignancy was considered to predict a high yield of malignancy and all patients with such a report were recommended to undergo total thyroidectomy. However, at Mt. Sinai such a report was considered as only moderate risk for malignancy and therefore an intraoperative frozen section was performed to more accurately assess the nodule. Second, patients diagnosed with follicular lesions on FNA were treated differently in the two institutions. At Hadassah the patients were presented with the option of either a unilateral or a bilateral thyroidectomy. For those patients who chose to undergo an initial unilateral thyroidectomy and the final pathology report proved the lesion to be malignant, completion to total thyroidectomy was subsequently accomplished. At Mt. Sinai, because of the relatively low risk of malignancy of such lesions, the patients were offered the option for an intraoperative frozen section. Patients with malignant results on frozen section underwent total thyroidectomy while a benign pathology resulted in unilateral thyroidectomy only. It is important to emphasize that in both institutions the patients were given detailed explanations of the advantages and disadvantages of all procedures and were fully involved in the decision making, hence not all cases fit this exact algorithm.

Frozen sections were performed at Mt. Sinai only and according to the surgeon's discretion. The results were reported as malignant or benign. Final pathology in both institutions was defined as benign for normal thyroid, adenoma, goiter and thyroiditis. All carcinomas were considered malignant, including papillary micro-carcinomas, equal to or less than 1 cm in diameter.

To identify differences between groups for specific variables, statistical analysis was performed using the chi-square test. Statistical calculations were completed using statistical software SPSS version 11.5 (SPSS, Inc., Chicago, IL, USA) and a P value < 0.05 was considered to represent statistical significance for all comparisons. This study was approved by the Institutional Review Board of the Mount Sinai School of Medicine.

RESULTS

Of the 242 patients in each institution there was a predominance of females. The male to female ratio at Hadassah-Hebrew University Medical Center was 1:5.2 vs. 1:3.1 at Mount Sinai School of Medicine. The mean age was 43 years (range 16–82) and 50 years (range 15–84) respectively. Bilateral thyroidectomy was performed in 154 patients (63.6%) at Hadassah and in 144 (59.5%) at Mt. Sinai. Of the patients initially undergoing unilateral thyroidectomy, 25% required completion to total thyroidectomy at Hadassah vs. 12.2% at Mt. Sinai ($P < 0.05$).

The detailed correlation between FNA and final pathology results at Hadassah and Mt. Sinai are presented in Tables 1 and 2, respectively. Of the patients with a benign FNA result 21.3% had malignancy on final pathology at Hadassah and 22.3% at Mt. Sinai for a sensitivity of 83.0% vs. 79.1% (NS).

Of the patients with a malignant result on FNA 10.3% had a benign pathology result at Hadassah and only 1.4% at Mt. Sinai for a specificity of 86.8% vs. 98.5% ($P < 0.05$). The overall accuracy was 84.6 vs. 87.3% (NS), the negative predictive value of a benign FNA was 78.7 vs. 77.6% (NS), and the positive predictive value of a malignant FNA was 89.7 vs. 98.6% ($P < 0.05$), respectively. The incidence of follicular lesion on FNA at Hadassah was 33.1 vs. 21.5% at Mt. Sinai ($P < 0.005$). The incidence of malignancy found on final pathology in such lesions was significantly higher at Hadassah, 42.5 vs. 23.0% ($P < 0.05$). Similarly, the overall incidence of follicular carcinoma was significantly higher at Hadassah, 5.0 vs. 0.8% ($P < 0.05$).

No frozen section was used at Hadassah while intraoperative frozen section was performed at Mount Sinai School of Medicine in 190 cases (78.5%). Of the 114 patients with a benign result on frozen section 29 (25.4%) were found to have carcinoma on final pathology (9 patients with PMC) for a sensitivity of 72.4%. Of these 29 patients 20 underwent total thyroidectomy at the time of the initial procedure according to the surgeon's decision, 5 patients required subsequent completion to total thyroidectomy, and 4 patients with PMC were observed with no further surgical procedure.

A malignant result reported on frozen section was confirmed in all 76 patients on final pathology for a specificity of 100% (13 patients with PMC). The overall accuracy for frozen section was 84.7%, the negative predictive value of a benign frozen section 74.6%, and the positive predictive value of a malignant frozen section 100%. Of the 84 patients with an FNA result of follicular lesion or suspicious for malignancy 12 patients declined frozen section and underwent initial total thyroidectomy. In the remaining 72 patients frozen section proved 55.5% sensitivity and 100% specificity. Frozen section altered the operative decision in only 6 patients (2.5%). These patients had benign FNA and malignant frozen section reports and underwent total thyroidectomy. Malignancy was confirmed by histopathology in all of these cases.

DISCUSSION

Although thyroid nodules are common (20–30%) in the general population on ultrasound examination, only about 5% of these nodules will ultimately prove to be malignant [5]. Primary evaluation of thyroid nodules includes a detailed history and physical examination. Risk factors for malignancy include male gender, age younger than 30 or above 60, history of radiation to the neck, or family history of thyroid cancer [14]. Rapid increase in nodule size, dyspnea, dysphagia, hoarseness, or Horner's syndrome is worrisome, but these findings are not specific for malignancy. On examination of the neck, attention to the firmness, mobility and size of the

nodules as well as adherence to surrounding structures and the presence of lymphadenopathy are important clues, but again, they lack specificity for malignancy. Thyroid function tests or radionuclide scintigraphy can determine whether the nodule is functional but it is far less cost-effective, specific and sensitive compared to fine needle aspiration [7]. FNA is the single most important diagnostic test in the initial workup of a patient with a thyroid nodule. High resolution ultrasonography is a useful tool for assessing nodules and improving both the sensitivity and specificity of FNA [15]. Approximately 60% of FNAs are classified as benign (range 53–90%), 4% as malignant (range 1–10%), 17% represent insufficient sampling (range 15–20%), and approximately 20% are classified as follicular lesions (range 7–36%) [5,16].

A review of some of the larger series in the literature reveals a wide range of FNA sensitivity and specificity values. In 1993 Gharib and Goellner [6] reviewed the results of 18,183 FNAs and found a mean sensitivity and specificity of 83% and 92% respectively. Baloch et al. [4] reported a sensitivity and specificity of 92% and 84% in 662 patients, and Hamburger [7] reported a sensitivity and specificity of 85% and 80%.

At both the Hadassah-Hebrew University Medical Center and the Mount Sinai School of Medicine the sensitivity rate was similar and in the range reported in the literature. However, specificity was significantly higher at Mt. Sinai, reaching 98.5%. It is our opinion that this difference is related to issues already mentioned in the Methods section. First, at Hadassah the FNA malignancy category includes both “definitely malignant” and “suspicious for malignancy.” This wide definition of “positive” FNA causes an increase in the false positive rate and consequently decreases the specificity, as was also demonstrated in other studies [7,12]. Second, the liberal use of intraoperative frozen sections at Mt. Sinai decreases the false positive results and increases the specificity. This is also reflected in the smaller number of patients requiring completion to total thyroidectomy at Mt. Sinai. Third, the inclusion of PMC as malignancy results in the relatively lower sensitivity at both institutions. It is unclear whether FNA really reflects these small, mostly incidental, lesions. The definition of PMC as malignancy, the need for surgical intervention in selected cases, and the extent of surgery required is still under debate [17]. However, we chose to define PMC as malignant owing to cases in which lymph node involvement was present in patients with primary PMC. The accuracy reported by other studies with smaller numbers of FNA ranges from 70% to 97%, depending on both the skill of the individual performing the biopsy and the cytopathologist interpreting it [4-7].

The diagnosis by FNA of follicular lesions is inherently problematic because of the need for tissue rather than cells for accurate and reliable determination of malignancy. The entire lobe containing the neoplastic lesion must be removed and examined for vascular or capsular invasion and cellular

PMC = papillary micro-carcinomas

characteristics to prove malignancy. Many studies have tried to determine risk factors for malignancy prior to surgery. Suggested risk factors include male gender, age, nodule size, and cytological characteristics such as nuclear appearance, cytoplasmic morphology and atypia. Even molecular genetic techniques were tried but none has yet been widely accepted [18-20]. Malignancy is actually found in only 20% of the nodules classified as follicular lesions on FNA (range 15–30%) [4-7], and less than 15% of the nodules presenting as follicular lesions on FNA will turn out to be follicular carcinomas on final pathology. Both the incidence of follicular lesions on FNA (33.1%) and the incidence of malignancy in such lesions (42.5%) were all higher at Hadassah than in other reported series and significantly higher than at Mt. Sinai. Moreover, the incidence of follicular carcinoma at Hadassah was significantly higher than at Mt. Sinai. The reasons for this difference are not readily apparent, although the variance may be secondary to referral patterns and to pathologists' interpretation (minimally invasive versus widely invasive follicular carcinoma) [5-7]. A diet low in iodine was also suggested to play a role in the incidence of follicular carcinoma [21,22], although we are not aware of such a deficiency in our population. The assumption that immigration to Israel from regions close to Chernobyl and the associated higher rate of malignancy was not supported by a demographic analysis of the population at Hadassah. In both institutions the number of previous biopsies, age over 45, and gender did not correlate with malignancy.

The utility of intraoperative frozen section to help assess malignancy in a suspected thyroid nodule has been tested in several studies. Recent studies demonstrated a very high specificity rate (95–100%) and a much lower sensitivity (50–87%). Overall accuracy rates vary from 81.4 to 98.7% [8-11]. In our study frozen sections were performed only at Mt. Sinai, with similar specificity (100%), sensitivity (72.4%) and accuracy (84.7%). The high rate of false negative results led surgeons to examine the use of frozen section in selected patients. Chen and co-workers [8] examined the usefulness of the frozen section technique in patients with follicular lesions and reported that 87% of the frozen sections rendered no useful information and 5% gave inaccurate results. A subsequent randomized prospective study with similar results reaffirmed the recommendation to avoid frozen section in patients with follicular lesions [23]. When evaluating the Mt. Sinai frozen section results for follicular lesions and suspected malignancy, the sensitivity was even lower at 55.6% but the specificity remained 100%. According to the literature, frozen section did not alter the planned operative course in more than 11% [9-12] and in our experience it did so in only 2.5%.

Although frozen section was not used at Hadassah while it was used extensively at Mt. Sinai, the sensitivity results of FNA are comparable. The difference in specificity between the institutions can be attributed to the wide definition of malignancy

and not necessarily to the use of frozen section at Mt. Sinai. It does seem that frozen section has only a limited role in patients with a malignant or benign result on FNA. Our data showed that a malignant result on FNA has a very high specificity rate. Such a result should not be disregarded, and performing a frozen section should not alter the planned operative procedure. Our data further show that routine frozen section after a benign FNA result is not indicated unless a clinical intraoperative suspicion of malignancy rises. We support those who recommend a very selective use of frozen section in patients with suspicious malignancy on FNA. The role of frozen section in patients with follicular lesions on FNA differs between institutions, countries and rates of malignancy in the general population. It is important to emphasize that intraoperative examination of the thyroid gland and surrounding soft tissue adds more information for operative planning and can avoid unnecessary frozen sections.

When interpreting the results of our study it is important to consider the limitations of the study. Entry criteria included only patients who underwent thyroidectomy, while patients with benign FNA who were never referred to surgery were not included. Furthermore, both institutions are referral centers for thyroid surgery, and these two factors explain the high rate of malignancy in these two groups of patients. It is also somewhat difficult to compare the two institutions as the approach to "suspicious malignancy" on FNA is different: At Hadassah it is considered malignant and treated as such, whereas at Mt. Sinai it is routinely further investigated by frozen section. This, as mentioned above, had an influence on the rate of specificity. There are some clear differences in the occurrence of follicular lesions and follicular carcinomas with more of both occurring at Hadassah. We are also aware of the different population and referral patterns, all of which add to the complexity of this study.

CONCLUSIONS

Fine needle aspiration plays a key role in evaluating thyroid nodules, with comparable sensitivity between the two institutions in our study. A malignant FNA result proved more specific at Mt. Sinai than at Hadassah. While malignancy on frozen section is highly specific and should not be overlooked, it should be used selectively for suspicious FNA results. Follicular lesions and the rate of malignancy in such lesions are more common at Hadassah and thus favor a more aggressive approach.

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