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UPDATES AND INFORMATION FROM REX PATHOLOGY LABORATORY

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Thyroid Fine Needle Aspiration Biopsy - The Rex Experience

At any given time, somewhere between four and seven percent of the adult population in the United States has a clinically palpable enlargement of the thyroid gland (goiter). Before the advent of Fine Needle Aspiration Biopsy (FNA), the diagnostic armamentarium for evaluation of thyroid nodules included physical examination, thyroid function tests, and radionuclide scanning. During this time period, less than 25 % of surgically removed thyroid nodules were malignant. Today thyroid FNA is the most sensitive, specific and cost-effective test available for the diagnosis of thyroid malignancy. According to several large studies, a positive thyroid FNA will yield a neoplastic process at surgery at least 90% of the time while only 1-2% of individuals with a negative FNA will have a thyroid malignancy. The overall sensitivity of thyroid FNA averages 83% with an overall specificity of 92%[1].

Rex pathologists have interpreted thyroid FNA's for over 20 years. I recently reviewed our collective experience over the past twelve years (1993 through 2004). During that period the pathologists at Rex examined nearly three thousand Thyroid FNA cases. Endocrinologists submitted the majority of these FNA's with lesser numbers performed by radiologists (under ultrasound guidance), ENT surgeons, and general surgeons. 432 of these patients ultimately had thyroid surgery at Rex. A thyroid FNA to surgical excision correlation study was performed using these 432 cases. In 98 of the 432 cases (22.7%) the FNA prior to surgery was insufficient for diagnosis. The sensitivity for detection of neoplasm for the remaining FNA's was 93.2% with a specificity of 98% and an accuracy rate of 82%. These numbers compare quite favorably to those published in the literature. Table 1 lists pathologist-specific data.

In our experience, thyroid FNA's classified as insufficient for diagnosis fall into one of two categories: those that are truly too hypocellular for diagnosis and those that probably represent colloid nodules (benign nodular goiters) but have too few follicular cells present to meet the criteria for adequacy. The standard minimum criteria for an adequate thyroid FNA is the presence of at least six groups of at least ten follicular cells present on at least two slides. Many cases of colloid nodules, especially those with degenerative changes, will contain abundant colloid and hemosiderin-laden macrophages but will have relatively few follicular cells. In all insufficient cases we enumerate these elements in the microscopic description so that information is available for the clinician to decide whether the specimen is representative of the patient's condition (benign nodular goiter) or that the specimen is truly insufficient for diagnosis. When the FNA specimen contains colloid material and histiocytes but is insufficient only due to a paucity of follicular cells, malignancy is subsequently identified in less than 1% of cases. The percentage of subsequent malignancy is significantly higher if the FNA specimen is reported as acellular or contains no thyroid elements.

False positive thyroid FNA's are most often associated with either Hashimoto's thyroiditis or hyperplastic colloid nodules.

Table 1 - Statistical Data by Pathologist

Pathologist	% Cases Reviewed	Accuracy	False Negatives	False Positives	Sensitivity %	Specificity %
A	20	92	0	5	100	99
B	7	72	2	5	87	97
C	19	79	4	10	85	98
D	22	92	0	5	100	99
E	20	77	3	14	90	97
F	10	82	2	4	88	98
G	1	75	0	1	100	96
H*	3	100	0	0	100	100

Accuracy = TP +TN/(TP+TN+FP+FN)
Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

* Pathologist H is currently involved in contractual arbitration and is threatening free agency

Rex Pathology Associates, P.A.

Stephen V. Chiavetta, MD	(919) 784-3060	Keith V. Nance, MD	(919) 784-3286
Timothy R. Carter, MD	(919) 784-3058	Vincent C. Smith, MD	(919) 784-3056
John D. Benson, MD	(919) 784-3059	Rhonda Humphrey, Practice Manager	(919) 784-3063
John P. Sorge, MD	(919) 784-3062		

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Hashimoto's thyroiditis may produce cytologic changes mimicking papillary carcinoma (including nuclear grooves and nuclear clearing). Lymphocytic rich Hashimoto's thyroiditis may be difficult to distinguish from lymphoma. (Image 1 & Image 2) Hürthle cell nodules arising in Hashimoto's thyroiditis

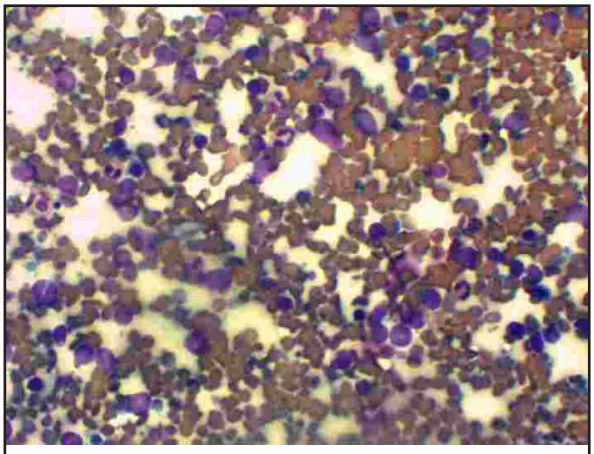


Image 1 - Thyroid FNA composed predominantly of large lymphocytes. Suspicious for large cell lymphoma.

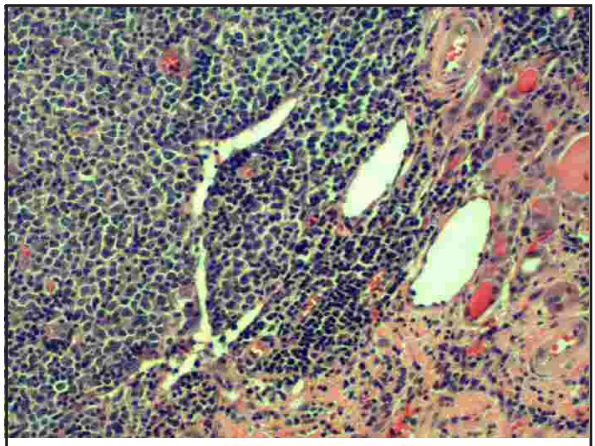


Image 2 - Resected thyroid gland following FNA (Image 1). Diffuse large B-cell lymphoma.

often produce cytologic changes suspicious for a follicular neoplasm. This problem is made even more complicated as both papillary carcinoma and lymphoma may arise in the setting of Hashimoto's thyroiditis. In cases where Hashimoto's thyroiditis is suspected on either clinical or laboratory grounds, such information should be conveyed to the pathologist interpreting the FNA. Hyperplastic colloid nodules may yield richly cellular specimens, which may be difficult to distinguish from follicular adenoma (or rarely follicular carcinoma) on cytologic grounds alone. In such a setting conservative excision (lobectomy) is recommended.

False negative thyroid FNA's occur almost exclusively in instances where a pathologist renders a diagnosis on a specimen that is of borderline adequacy. This is especially true in cases of cystic papillary carcinoma.

During the time period of the study there were an additional 630 thyroidectomy specimens for which there was no preceding FNA specimen. Interestingly, in only 238 of these 630 cases (37%) was a neoplastic process identified. This compares to a neoplastic detection rate of 77% for cases in which a FNA diagnosis suggesting neoplasm was followed by surgery. See Table 2 for a list of final surgical pathology diagnoses from the correlation study. Note that in many instances surgical intervention is deemed necessary for clinical reasons, despite a benign FNA diagnosis. Examples include nodules with lack of response to suppressive therapy as well as large goiters that must be removed due to mechanical obstruction or cosmetic concerns.

Table 2 - Distribution of Cases in Rex Thyroid Correlation Study (432 Cases)

Final Diagnosis	Number of Cases	(%)
Papillary Carcinoma	100	(23%)
Follicular Carcinoma	16	(3.7%)
Medullary Carcinoma	3	(0.7%)
Lymphoma	3	(0.7%)
Anaplastic Carcinoma	1	(0.2%)
Follicular Adenoma	86	(20%)
Hashimoto's Thyroiditis	49	(11.5%)
Nodular Goiter	174	(40%)

Overall our experience with thyroid FNA's has been quite positive. We welcome any suggestions as to ways to improve the process of evaluating and reporting these, or other, types of cytologic specimens.

For more information please contact Dr. Keith Nance at (919) 784-3286 or the Rex Cytology Department at (919) 784-3050.

Keith V. Nance, M.D.

Reference:

1. DeMay RM. Fine Needle Aspiration Biopsy of Thyroid in The Art & Science of Cytopathology. ASCP Press. Chicago. 1996.

Sentinel Lymph Node Mapping in Breast Carcinoma - The Rex Experience

Many aspects in the diagnosis and treatment of breast carcinoma have changed in the past 10-20 years. This discussion is primarily restricted to the assessment of axillary lymph node status, in particular sentinel lymph node mapping. By definition, the sentinel lymph node is the first lymph node to receive lymphatic drainage from the breast tissue. This procedure has been shown to accurately predict the status of the axillary basin, while reducing the morbidity compared to a full completion axillary dissection. Approximately 90-95% of sentinel lymph node procedures result in successful harvesting one or more sentinel lymph nodes[1]. The procedure is considered accurate at predicting the axillary lymph node basin in the vast majority of cases, but concern still lingers with so called "skip metastases" that may occur in less than 5% of cases[2]. Our thanks go to Michael Yarborough, MD, Jayne Byrd, BSN, RN, Julie Kreager, MD

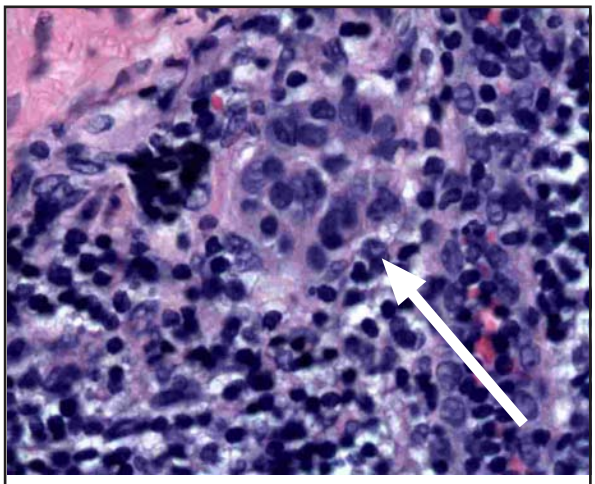
and Sabra McNeil, MD, who were instrumental in introducing this procedure at Rex in 1998.

Briefly, the process of axillary lymph node mapping in breast carcinoma cases involves administering a vital blue dye and radiocolloid material to the cancerous breast and biopsy of those axillary lymph nodes that are either blue and/or hot. Histopathologic assessment begins at the time of surgery with incising the sentinel lymph node(s) followed by examining touch imprint cytology preparations. If a touch imprint is positive, then the surgeon completes the axillary dissection. A negative touch imprint restricts the axillary lymph node removal to the sentinel lymph node(s) only. Frozen sections are best avoided, since a relatively large quantity of lymph node tissue is lost to the frozen sectioning process (due to facing the initial frozen section and subsequent refacing of the remaining tissue for permanent section). Subsequently the lymph nodes are evaluated by permanent section the following day. Sentinel lymph nodes judged to be negative by standard H&E sections are further evaluated by immunohistochemical staining for pan-cytokeratin, which increases the sensitivity for detection of metastatic carcinoma cells.

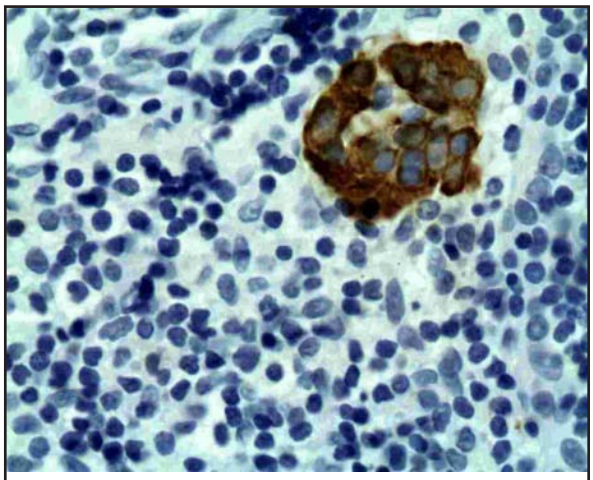
Although the sentinel lymph node histopathologic evaluation procedure at Rex parallels that performed at the Moffit Cancer Center in Tampa, FL - no national standard exists. Variations in all phases of the sentinel lymph node pathologic assessment have been reported, leading to difficulty in comparisons between studies. It is the author's personal view the process described above is the most efficient, cost effective way of assessing the axillary lymph node basin in breast cancer with the highest accuracy and least morbidity for the patient.

The introduction of immunohistochemical staining of the sentinel lymph node(s) has increased sensitivity of detecting smaller and smaller deposits of metastatic breast carcinoma, including isolated tumor cell clusters. By definition, tumor cell clusters are single cells or collections of presumably malignant cells that measure less than 0.2 mm in greatest dimension. Micrometastases are those clusters that measure between 0.2mm and 2 mm., whereas macrometastases measure greater than 2 mm in size. According to the AJCC, isolated tumor cell clusters are considered either N0(i-) or N0(i+) depending upon whether they are identified by immunohistochemical methods or not. Great care should be given to interpreting these cell clusters to exclude the possibility of passive transfer of benign epithelium into the sentinel lymph node(s), possibly secondary to the original biopsy. Considerable debate has also occurred over the significance of micrometastatic disease for similar reasons. However, the size of the micrometastatic deposits may be important for judging clinical significance, since a 1 mm immunohistochemical positive lesion may contain as many as 500,000 cells and suggests the potential for disease progression.[3]

However, the College of American Pathologists recommends H&E verification of immunohistochemically detected micrometastatic lesions, as H&E staining offers better cytologic detail in evaluating the cell clusters for morphologic features of malignancy.



H&E section of sentinel lymph node with isolated tumor cell cluster at arrow. Tumor cells difficult to distinguish from surround lymphocytes.



Stong positive cytokeratin immunostain of same isolated tumor cell cluster. Striking color contrast facilitates recognition (improving sensitivity), but suboptimal cytologic detail due to strong positive staining reaction.

I recently reviewed our experience with the sentinel lymph nodes during a six month period from September 2004 to February 2005. During this time, we received 107 sentinel lymph node cases with a total of 275 sentinel lymph nodes removed. In this study group, 29.9% of the cases had a positive sentinel lymph node. The average number of touch imprints per case was 2.6. The touch imprint interpretation agreed with the final diagnosis in 93.5% of the cases. The table below compares our performance to data from the Moffit Cancer Center collected over a six year study period in which 4905 lymph nodes from 2317 cases were analyzed.[4] Our most recent data correlates favorably with the Moffit Cancer Center experience and reiterates the universal difficulty with detecting isolated tumor cell clusters and micrometastases intraoperatively by imprint cytology at the time of the sentinel lymph node procedure. Some literature studies do not consider negative touch imprints in the setting of isolated tumor cell clusters or micrometastases to

be false negatives. If one adopts this definition, our sensitivity would improve to 82.8% and the negative predictive value would be 97.9%. The predictive value of a negative result reenforces the basic premise for this procedure, which is reducing the number of axillary dissections and thereby reducing morbidity without loss of staging accuracy.

Sentinel Lymph Node Evaluation by Touch Imprint Cytology

Performance	Rex 9/2004 - 2/2005	Moffit Cancer Center (6 year experience)
Sensitivity	58.1%	53.3%
Specificity	100%	99.5%
Accuracy	93.5%	85%

John P. Sorge, MD

References:

1. *Alberini JJ, Lyman GH, Cox C et al. Lymphatic mapping and sentinel lymph node biopsy in the patient with breast cancer. JAMA. 1996.276(22).1818-1822.*
2. *Rosen PP. Rosen's Breast Pathology Second Edition. Lippincott, Williams and Wilkins. 2001.960-961.*
3. *AJCC Cancer Staging Manual. Sixth Edition.Springer.2002.223-240.*
4. *Cox C, Centeno B, Dickson D et al. Accuracy of intraoperative imprint cytology for Sentinel Lymph Node Evaluation in the Treatment of Breast Carcinoma. A 6 Year Study. Cancer Cytopathology. 2004.105(1): 13-20.*

Lab Director Leaves

Ms. Sharon Logue resigned as Rex Healthcare Laboratory Director earlier this month to accept a position as Executive Laboratory Director for a hospital network in Atlanta, Ga. Sharon served as Lab Director at Rex for seven years. She focused on improving laboratory service to all areas of the hospital system and increasing Outreach business to offset the cost of inpatient testing. During her administration, point of care testing was expanded in the Special Care nursery, automated type and screens and electronic crossmatches were begun in the Blood Bank, and front end automation was implemented in the Core Laboratory. We will miss Sharon's aquarium, Graceland memorabilia, enthusiasm, and unique sense of humor. We wish her success in her new position. Elaine Patterson (Core Laboratory Manager) is serving as interim Laboratory Director at (919) 784-3054.

John Benson, MD

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Rex Healthcare Laboratory (919) 784-3040. Telephone extensions are: Pathologists' Direct Line (3063), Robin Ivosic (Customer Service and Outreach Manager 3053), Elaine Patterson (Core Lab, Blood Bank and Microbiology Manager 3054), Jackie Okoth (2nd and 3rd Shift Manager 4248), Diane Young (Anatomic Pathology Manager 3888).

Client Response Center (919) 784-6000 (phone) (919) 784-6299 (fax)