Review and Conclusions – Final Draft
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Committee I: Indications and Pre-FNA Requirements

A. Indications for performing an FNA of a thyroid nodule discovered by palpation

Review:

Every patient with a palpable thyroid nodule is a candidate for fine needle aspiration (FNA) and should undergo further evaluation to determine if an FNA is warranted.[1-3] Thyroid nodules detected by palpation are usually at least 1.0 cm in dimension[4,5] and are therefore potentially clinically significant. Before a decision is made to perform an FNA, a complete history should be obtained; a physical examination directed to the thyroid gland and cervical lymph nodes should be performed; and a serum thyrotropin level (TSH) and thyroid ultrasound (US) should be obtained.[1,3,6-8]

Significant history or physical examination findings that increase the likelihood of malignancy include a family history of thyroid cancer, prior head and neck or total body irradiation, rapid growth of the nodule, a very firm or hard nodule, hoarseness or vocal cord paralysis, ipsilateral cervical lymphadenopathy, and fixation of the nodule to surrounding tissues.[1,3,6,9,10]

Patients with a normal or elevated serum TSH level should proceed to a thyroid US to determine if an FNA needs to be performed (see section B below); those with a depressed serum TSH should have a radionuclide thyroid scan, the results of which should be correlated with the sonographic findings.[1,3,6,7,11] Functioning thyroid nodules in the absence of significant clinical findings do not require an FNA because the incidence of malignancy is exceedingly low.[12] A nodule that appears either iso- or hypo-functioning on radionuclide scan should be considered for FNA based on the US findings (see section B below).[1-3]

Contraindications to thyroid FNA are very few: an uncooperative patient and a severe bleeding diathesis. In such circumstances appropriate medical consultation should be sought prior to the FNA.[13-15] The most significant (but extremely rare) complication of thyroid FNA, limited to a few case reports and small series, is intrathyroidal hemorrhage and acute upper airway obstruction.[16]

Extrapolating from recommendations for endoscopic US-guided FNA, it is usually possible to perform an FNA on a patient who is taking standard doses of aspirin, other non-steroidal anti-inflammatory drugs (NSAIDS), or prophylactic low molecular weight heparins (LMWH).[3,14,17,18] Nevertheless, consideration should be given to stopping LMWH at least 8 hours before the procedure.[19] In patients taking therapeutic doses of warfarin or heparin/LMWH, performing a thyroid FNA is controversial but can be done.[18,19] There are no data on the safety of FNA in patients taking anti-platelet medications like Plavix® (clopidogrel bisulfate). A reasonable approach is to stop the medication for 3-5 days with agreement from the prescribing doctor. If this cannot be done safely, an FNA may be performed using the smallest needle possible and limiting the number of passes performed. In this scenario, US guidance may be preferable so that the surrounding small vessels can be visualized and avoided.

Conclusions:

1. Before biopsying a patient with one or more thyroid nodules discovered by palpation, a serum TSH level should be measured and an US examination performed.
2. If the serum TSH level is depressed, the findings of a radionuclide thyroid scan should be correlated with those of US examination. If the nodule of interest is hot, an FNA is not indicated.
3. If the serum TSH is normal or elevated, an US examination should be performed to determine if sonographic criteria for FNA are met (see section B below). If so, the nodule should be biopsied.
4. An FNA may be contraindicated if the patient is uncooperative.
5. An FNA may be contraindicated if the patient has a severe bleeding diathesis.

B. Indications for performing an FNA of a thyroid nodule discovered via imaging

Review:

A nodule not previously suspected or discovered clinically but detected by an imaging study is considered an incidental nodule ("incidentaloma"). Whether or not a nodule has been detected clinically depends on the expertise of the person performing the clinical examination (if one was done), the size and mobility of the patient's neck, and the size and location of the nodule.

Incidentalomas detected by ^{18}FDG-PET are unusual (2-3% of all PET scans) but have a higher risk of cancer (14-50%) compared to the background incidence.[20-28] A focal ^{18}FDG-PET-avid thyroid nodule is much more likely to be a primary thyroid cancer than metastatic disease to the thyroid, even in patients with an extrathyroidal malignancy. Many ^{18}FDG-PET-avid lesions that are not papillary cancer are follicular or Hurthle cell neoplasms. Therefore, a focal nodule that is ^{18}FDG-PET-avid is an indication for FNA. This applies only to focal lesions. Diffuse increased uptake on ^{18}FDG-PET does not warrant FNA unless thyroid sonography detects a discrete nodule.

All focal hot nodules detected on sestamibi scans and confirmed by US to be a discrete nodule should undergo FNA. Thyroid incidentalomas detected on sestamibi scans have a high risk of cancer (22-66%).[29-33] Many that are not papillary cancer are follicular neoplasms.

Incidentalomas detected by US (such as carotid Doppler scans or scans done for parathyroid disease) have a cancer risk of approximately 10-15% (0-29%)[34-46] and should undergo dedicated thyroid sonographic evaluation. Lesions with a maximum diameter greater than 1.0-1.5 cm should be considered for biopsy unless they are simple cysts or septated cysts with no solid elements. FNA may also occasionally be replaced by periodic follow-up for nodules of borderline size (between 1.0-1.5 cm in maximum diameter) if they have sonographic features that are strongly associated with benign cytology.

A nodule of any size with sonographically suspicious features should also be considered for FNA. Sonographically suspicious features include:

- microcalcifications
- hypoechoic solid nodules

- irregular/lobulated margins
- intra-nodular vascularity
- nodal metastases (or signs of extracapsular spread)

This latter approach is controversial because it includes patients with microcarcinomas, in whom a survival benefit following an FNA diagnosis has not been documented. Nevertheless, the American Thyroid Association,[1] the Academy of Clinical Thyroidologists[34] and a collaborative effort of the American Association of Clinical Endocrinologists and the Associazione Medici Endocrinologi[47] make this recommendation (Table 1). There are several reasons for this approach. A nodule that has suspicious sonographic features may not be malignant. If the nodule is benign by FNA, the patient can be reassured, and subsequent follow-up can be less frequent. On the other hand, if the FNA reveals that the nodule is malignant, surgery is generally recommended. The natural history of micropapillary carcinomas, however, is not well understood. Most remain indolent, as implied by the 13% prevalence of micropapillary cancers in the United States at autopsy examination.[48] A minority follow a more aggressive course; this subgroup might be identified by sonographic evidence of lateral cervical node metastases, tumor multifocality, extrathyroidal invasion, or cytopathologic features that suggest a high-grade malignancy.[49] The development and application of even more sensitive and specific markers of aggressive potential (including molecular and genetic markers) may one day facilitate triage of patients with a microcarcinoma.

There are few direct data on the cancer risk of thyroid incidentalomas detected by computed tomography (CT) or magnetic resonance imaging (MRI). They are seen in at least 16% of patients evaluated by neck CT or MRI.[50] The risk of cancer in one study was predicted at 10%, but it included only a limited number of patients who went on to FNA.[51] CT and MRI features can not determine the risk of malignancy, except in very advanced cases that are unlikely to be incidental. Until more data are available, incidentalomas seen on CT or MRI should undergo dedicated thyroid sonographic evaluation. Any nodule with sonographically suspicious features (see above) should be considered for FNA. In addition, lesions that have a maximum diameter greater than 1.0-1.5 cm should also be considered for FNA.

As discussed in section A, serum TSH levels may influence the decision to perform an FNA on an incidentaloma. Given the infrequency with which TSH levels are depressed, the decision to perform an FNA need not be delayed if the patient is undergoing sonography and the results are not available.

It may not be feasible or advisable to perform an FNA for all incidentalomas. There are too many, the costs and strain on the medical system would be too great, and such a practice would ultimately lead to needless surgery on many benign lesions. The goal in dealing with incidentalomas is to avoid FNA as best possible for nodules likely to be benign, while maximizing the number of malignant nodules that are diagnosed. The consensus in the literature and among professional societies specializing in thyroid diseases is that incidentalomas should undergo sonography and only those that have suspicious sonographic features, exceed a certain size (1.0-1.5 cm), or have clinical risk factors should undergo FNA. Given the imperfect ability of clinical factors to predict the risk of cancer, and the unavoidable overlap in sonographic features between benign and malignant nodules, any recommendation will result in some missed cancers and some FNAs of benign lesions.

Table 1 Indications for Thyroid FNA: Recommendations of Other Professional Societies			
ACT*	**ATA****	**AACE***	**SRU****
<10 mm FNA if clinical risk factors	<10 mm FNA if clinical risk factors or malignant US features	<10 mm FNA if clinical risk factors or suspicious US features	<10 mm No recommendation
5-10 mm FNA if suspicious US features			>10 mm FNA if microcalcifications
10-20 mm FNA most nodules. May defer FNA if benign US features			>15 mm FNA if solid with coarse calcifications
>20 mm FNA all	>10-15 mm FNA all	>10 mm FNA all	>20 mm FNA if mixed solid & cystic or cystic with mural nodule

ACT – Academy of Clinical Thyroidologists
ATA – American Thyroid Association
AACE – American Association of Clinical Endocrinologists
SRU – Society of Radiologists in Ultrasound[38]

* Nodule size not specified as maximum or mean
** Nodule size refers to maximum dimension

Conclusions:

1. All focal ^{18}FDG-PET-avid lesions should undergo FNA.
2. All hot nodules detected on sestamibi scans should undergo FNA.
3. Incidentalomas detected by US should undergo a dedicated thyroid sonographic evaluation.
4. Until more data are available, incidentalomas seen on CT or MRI should undergo a dedicated thyroid sonographic evaluation.
5. Any nodule with sonographically suspicious features should be considered for FNA.
6. Lesions with a maximum diameter greater than 1.0-1.5 cm should be considered for FNA.

C. Indications for performing a thyroid FNA using palpation for guidance

Review:

Palpation-guided FNA can be performed with high levels of success in specific circumstances.[2,52-54] In the setting of a new, palpable thyroid enlargement without a definable nodule on sonography, the decision to perform a biopsy or not still depends to a large degree on the sonographic appearance of the thyroid. If the thyroid is truly enlarged but is normal in echogenicity and echotexture, then malignancy is so unlikely that a biopsy is not necessary. On the other hand, if the enlarged thyroid is hypoechoic and heterogeneous/coarsened, then the differential includes lymphocytic thyroiditis (most commonly), and, rarely, uncommon malignancies like lymphoma and anaplastic cancer, as well as amyloid goiter. In such a case, an US-guided FNA may be warranted depending on the size of the thyroid, the degree of left to right asymmetry, other sonographic features, or based on clinical or laboratory findings.

The benefits of palpation-guided FNA of thyroid nodules are its reduced cost in comparison to US-guided FNA as well as its logistical efficiency: the practitioner can perform the procedure without an US machine or assistance from other practitioners. In the evaluation of individual patients with nodular disease, there are occasions when either palpation or US-guided FNA of a thyroid nodule are reasonable to perform. Published data from one study, however, confirm that US evaluation changes the management in 63% of patients with palpable thyroid nodules.[55] Thus, when thyroid nodules do not fulfill the criteria below, or when practitioners trained in palpation-guided aspiration are not readily available, US-guided FNA should be preferred.

Conclusions:

A palpation-guided FNA can be considered in the following scenarios:

1. A thyroid nodule >1cm in diameter has been confirmed via US examination of the thyroid. The sonographic examination is important because physical examination can be imprecise in determining nodule size and its origin from the thyroid rather than adjacent tissues.[56]
2. The thyroid nodule is discrete and readily identified on physical examination. Importantly, a diffuse or asymmetric goiter without a discrete nodule on physical examination should preclude palpation-guided FNA in lieu of US-guided FNA.
3. The nodule is primarily solid (<25% cystic) on US examination.[57,58]
4. The patient has no other head or neck illnesses or prior head or neck surgery that may affect the thyroid anatomy.
5. A prior non-diagnostic biopsy of the nodule has not occurred. In such cases, an US-guided FNA should be performed.[59]
6. Obtaining US guidance for FNA is logistically difficult or not readily available.

D. Indications for performing a thyroid FNA using ultrasound for guidance

Review:

Ultrasound guidance for FNA of the thyroid gland is useful in the combined evaluation of the thyroid nodule, as it simultaneously allows detailed examination of the remainder of the thyroid gland, characterization of the nodule (solid, cystic, well-circumscribed, irregular, calcifications, vascularity, size, etc.), and accurate placement of the aspiration needle in the nodule of interest. The advantages of US guidance include a decreased rate of insufficient or inadequate cytology specimens in several studies in which these were compared.[52,53,60-62] US also allows sampling from solid areas of partially cystic lesions, accounting for some increase in adequacy.[63] Not all studies show a difference in adequacy and accuracy, or show a difference only for smaller lesions.[60,64]

US findings such as irregular margins, microcalcifications, intra-nodular vascularity, and the characteristics of other occult thyroid nodules can be used by the clinician to identify nodules at risk that should be sampled.[45,65,66] US guidance can also provide additional information for patients who have had benign or non-diagnostic (i.e., insufficient cells/colloid) results from palpation-guided FNA.[61,62] Re-evaluation of patients using US-guided FNA for those with initially benign or non-diagnostic results can lead to the reclassification of a substantial portion of patients and diagnose more cancers.[61,62] Finally, there are US-specific findings that can be used to inform the results of the US-guided FNA (e.g., the benign sonographic appearance of a unilocular cyst explains why only cyst fluid was obtained by FNA).

Both palpation-localized and US-guided thyroid FNA are widely practiced. Several studies have shown, however, that US-guided FNA is a more sensitive technique than palpation-guided assessment.[53,60,67]

Conclusions:

1. US guidance should be used to aspirate nodules that are not palpable.
2. US guidance should be used to aspirate nodules that have an appreciable (>25%) cystic component.
3. US guidance should be used if a prior aspiration contained insufficient cells/colloid for interpretation (“nondiagnostic” result).
4. US guidance for thyroid FNA may be used as an alternative to palpation localization because it permits the operator to:
    a. be certain that the nodule of interest is aspirated by direct imaging,
    b. be sure that a discrete nodule is present before aspiration, and
    c. avoid passing the needle into critical structures in the neck.

E. The informed consent form for thyroid FNA

Review:

Informed consent is the communication process between a patient and physician that results in the patient’s agreement to undergo a particular procedure or treatment.[68-74] For the purposes of the following discussion, the procedure is a thyroid FNA.[75]

The principle of informed consent is rooted in medical ethics, [76] codified as a legal principle,[77] and based on the assertion that a competent person has the right to determine what is done to her or him.[68-74] In the informed consent process, the physician informs a patient about the risks and benefits of a proposed therapy or procedure and allows the patient to decide if the therapy or procedure should be undertaken.[78] Informed consent in the research setting differs considerably from informed consent in a clinical context.[79]

In reality, all medical care, including the procuring of all laboratory tests, requires informal informed consent, except when the patient is incompetent to make a decision or gives up the right to provide it.[68-74] Formal procedures of obtaining consent, such as the signing of a consent form, following the exchange of information and a patient-physician communication, are only undertaken in some circumstance, such as prior to major invasive procedures or surgery.[68,80,81] Legislation regulating the conditions under which consent must be obtained vary greatly by state.[68,72,73] Thus, providers (e.g., pathologists, radiologists, surgeons, endocrinologists, etc.) who perform FNA need to design informed consent policies and forms based on state regulations. In essence, there is a lack of standardization of national informed consent policy that determines exactly when and how informed consent is obtained.

National organizations like the American Medical Association (AMA) have provided general guidelines of informed consent.[73] The AMA recommends that the following be disclosed and discussed with the patient:

1. The patient's diagnosis, if known;
2. The nature and purpose of a proposed treatment or procedure;
3. The risks and benefits of a proposed treatment or procedure;
4. Alternative options (regardless of their cost or the extent to which these options are covered by health insurance);
5. The risks and benefits of the alternative treatment or procedure;
6. The risks and benefits of not receiving or undergoing a treatment or procedure.[73]

The AMA Code of Medical Ethics establishes informed consent as an ethical obligation of physicians.[73] Failure to obtain adequate informed consent renders a physician liable for negligence or battery and constitutes medical malpractice.[68]

Although it has been suggested that improved informed consent policies could result in improvements in the patient-physician relationship, patient compliance, patient trust of the healthcare system, and patient safety (by providing information that could reduce medical error),[82] this hypothesis has not been definitively proved.

Many informed consent procedures are incomplete.[68,69] In addition, less than 50% of the population understands commonly used medical terms, resulting in a "health literacy" problem that limits patients in their attempts to understand information.[83-87] Several studies have focused on insufficiencies in procedures to obtain informed consent. Braddock et al. created a 3-tier evaluation procedure, in which the completeness of the informed consent discussions differed depending on the complexity of the decision.[70] Basic decisions (e.g., laboratory test ordering) require discussing the clinical nature of the decision and the evaluation of patient preferences. Intermediate decisions (e.g., medication changes) require a moderate depth of discussion and include adding a discussion of alternative treatments, including the risks and benefits of these alternatives

and an assessment of patient understanding. Complex decisions (e.g., undergoing an operative procedure) require a discussion of the uncertainties associated with the procedure, in addition to the components listed previously.

Providing written information, which is also discussed during the informed consent process, may increase comprehension.[88-91] This information, however, must be provided in a manner that is clearly understood by the patient. Hooper et al. found that patients with a high school education understand only 16% of all consent forms.[92,93] Jubelirer et al. reported that, in a study of adult cancer patients, most had a reading level between 10^{th} and 11^{th} grade.[84] Jubelirer et al. recommended that consent forms be written at 3 grade levels below the highest level of education of the specific patient.[84]

For thyroid FNA, a consent form should be patient friendly and written so that the patient fully understands the procedure. Patient comprehension of thyroid FNA forms has not been rigorously studied. Potential complications should be listed on consent forms but written in a manner understandable to all patients. Concepts such as false-negative and false-positive proportions need to be discussed and written in terms that a patient understands; simply listing such numbers likely would not benefit most patients.

Currently, informed consent is receiving a great deal of attention, and a number of studies researching informed consent have been performed. The Agency for Healthcare Research and Quality (AHRQ) identified the challenge of addressing shortcomings such as missed, incomplete or not fully comprehended informed consent, as a significant patient safety opportunity.[68,71,82] Thus, informed consent policies are evolving.

Conclusions:

1. Informed consent materials, including written documents, if used, should describe the FNA procedure and potential risks and complications.
2. The possibility of a hematoma, the most frequently occurring complication, should be mentioned.
3. Information should be presented in a manner to facilitate patient understanding.
4. It might be useful to mention the possibility of a non-contributory result.
5. Estimates of accuracy, such as false-negative or false-positive proportions, are not mandatory and should be considered only if the practitioner believes they would facilitate patient comprehension.

F. Information required on the requisition form that accompanies a thyroid FNA

Review:

Federal regulations in the United States require that certain identifying information be provided to laboratories with all specimens submitted for laboratory testing.[94] These include:

- name and address of person requesting the test
- patient's name or unique identifier
- patient's gender
- patient's age or date of birth

- name of the test to be performed
- specimen source
- date of specimen collection
- 'any additional relevant information'

The purpose of this discussion is to consider what 'additional relevant information' a laboratory needs to properly evaluate a thyroid FNA specimen.

With regard to the already required patient age, the risk of malignancy may be greater in individuals that are older (over age 60), and the risk is likely greater in younger individuals (children, generally under age 20). Risk is also increased in men.[95-97] Papillary hyperplasias occur in children that can be confused with papillary thyroid cancer.[98]

The location of the nodule (right vs. left; isthmus; upper pole, mid-pole, lower pole, etc.) should be specified on the requisition form to permit correlation with sonographic findings and subsequent histopathologic examination (if applicable). Such identification is often necessary because patients often present with multiple nodules (some but not all of which may be biopsied), or they may develop other nodules over time.

There is, at best, an imperfect correlation between the size of a nodule and the likelihood of malignancy, but larger nodules (>4cm) may be associated with a higher malignancy risk, and therefore size should be included.[99]

Benign cytologic changes that mimic malignancy, particularly papillary carcinoma, occur in some patients with autoimmune (Hashimoto's) thyroiditis. If not alerted to this history, a misdiagnosis can occur.[100,101] Furthermore, nuclear alterations may be seen in patients with a history of I-131 therapy (for hyperthyroidism) or external radiation.[102-104] In some patient with Graves' disease, an FNA of a nodule may include pleomorphic cells from the extra-nodular Graves' thyroid parenchyma that can be a pitfall in cytologic interpretation.[105]

It is important to note a personal history of malignancy because metastatic tumors to the thyroid can mimic the appearance of a primary thyroid neoplasm. Metastatic renal cell carcinoma mimics a follicular neoplasm; melanoma can mimic medullary carcinoma; metastatic lung cancer can mimic anaplastic carcinoma of the thyroid. Cytologists should be alerted to the possibility of a metastatic tumor in any patient with a history of malignancy.

Approximately 15% of medullary thyroid cancers are familial (familial MTC or MEN2a or 2b). Knowledge of family history can alert the pathologist to the possibility of medullary carcinoma. In addition, recent data show that papillary thyroid cancer can also be familial,[106] and thus knowledge of such family history can alert the pathologist to consider papillary carcinoma.

The following information can be useful to the cytologist but is considered optional on the requisition form.

- *Additional clinical history*
  - *Prior FNA.* Morphologic alterations due to a prior FNA can affect cytologic interpretation.[107]
  - *Concurrent levothyroxine therapy*. Levothyroxine (LT4) use can alter follicular cell morphology. Such altered morphology can be encountered in an FNA obtained because of nodule growth while a patient is taking LT4.

Nodules that yield a more cellular benign specimen may demonstrate more colloid and degenerative changes after LT4 therapy.[108]

- *TSH level***.** If a patient has Hashimoto's hypothyroidism or Graves' disease, cytologic findings can be affected. A lower serum TSH level is also associated with a lower risk of thyroid cancer.[96]
- *Results of ultrasound examination*
  - US characteristics of the nodule
  - US characteristics of surrounding extra-nodular thyroid
  - presence of other nodules
  - location of nodule

US characteristics associated with malignancy include microcalcifications, hypoechogenicity, irregular margins, and increased vascularity.[45] Predominantly cystic nodules may be less likely to be malignant.[109] US imaging of the surrounding extra-nodular thyroid may indicate that Hashimoto's (lymphocytic) thyroiditis is present, which, as noted above, can cause benign cytologic changes that mimic malignancy. Although the risk of cancer for an individual patient is the same whether he/she has a single or multiple nodules, the risk of malignancy per nodule is lower if multiple nodules are present.[109] The lower parathyroid glands may be contiguous to the thyroid at its lower poles. Therefore, what is imaged as a lower pole hypoechoic thyroid nodule may be a parathyroid gland.

- *Results of nuclear medicine imaging studies (functioning or not functioning).* In general, a nodule that functions on an I^{123} scan should not undergo FNA.[38,47,110]

Conclusions:

At a minimum, the following data should appear on the requisition form that accompanies a thyroid FNA to the laboratory:

1. Usual required data for lab test submission (see above)
2. Location of the nodule
3. Size of the nodule
4. History of hypothyroidism, autoimmune thyroiditis, or a positive test for antithyroid antibodies
5. History of Graves' disease
6. History of I^{131} or external radiation therapy
7. Personal history of cancer
8. Family history of thyroid cancer

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Committee II: Training,credentialing and re-credentialing for the performance of a thyroid FNA

A. Training and credentialing for the performance of a thyroid FNA

Review:

Historically the procurement of FNA specimens has not been listed as a separate credential in most institutions outside of departments of radiology and pathology. Presumably this is because the FNA procedure itself carries very low morbidity, particularly when applied to superficial lesions. In recent years there has been a trend towards using more detailed lists of procedures on credentialing documents. Because the level of proficiency in FNA procurement has considerable impact on the accuracy of the test and can result in missed or delayed cancer diagnoses, a separate credential in FNA procurement may be considered. A number of ACGME accredited training programs in various specialties include requirements for training in FNA procurement.

Measuring proficiency in FNA procurement ideally would include monitoring the frequency of inadequate material leading to missed diagnoses. This approach is difficult because it requires large numbers of cases and access to long term reliable follow-up on all cases, not just those referred to surgery soon after FNA. Instead, rates of unsatisfactory samples are more often used as a measure for the level of proficiency.

Conclusions:

Complete residency/fellowship training including FNA procurement or equivalent training in an alternative setting should suffice for initial credentialing.

For re-credentialing, documentation of the number of total FNA procedures per year, for an individual provider, in combination with a documented unsatisfactory sample rate (<10%) is a conservative measure of proficiency. For credentialing purposes, cyst contents that may be categorized as “non-diagnostic” due to a lack of follicular cells , should not be considered “ unsatisfactory” samples.

B. Training for the performance of thyroid FNA via palpation and ultrasound guidance.

Review:

In 1982 Van Herle demonstrated that FNA of a palpable mass in the thyroid gland should be the initial test performed to establish a diagnosis and to guide clinical management.[1] Since then FNA has become widely used in the USA. Subsequent reports reflect similar results from various settings and countries.[2-28] (Table 1.) These reports, including specimens collected via palpation and ultrasound, show wide variability in the rate of non-diagnostic/unsatisfactory specimens (0-41%) and in suspicious findings/ follicular lesions (4.3-42%). These diagnostic categories necessitate additional testing and/or surgery. There is a dearth of data on actual false negative rates because most

patients in published series do not have surgical follow-up or long term clinical follow-up. Furthermore, population based cancer registries typically are not available for long term, reliable follow-up data or are not utilized.

Most of the studies included in Table 1 include information on the medical specialty of the operators collecting the samples (last column). In the 5 studies with the lowest combined non-diagnostic and suspicious/follicular rates, all or a substantial portion of the specimens were procured and interpreted by the same physician. These studies concurrently reported definitively benign diagnoses in over 80 percent of cases. Another observation is that most large studies(those with more than 1000 cases reported) show better results than did smaller studies.

TABLE 1

1st Author (Years)	Country	Benign Dx	Mal Dx	Susp/Follic	Non-Dx/ Unsat	Susp/ Follic + Non-DX	Total Sites	Operators
Waisman, manuscript in preparation (2000-2004)	USA	90.4%	3.2%	4.5%	1.9%	6.4%	1055	CP,RAD,SURG,ENDO,US, PALP
Ko, *et.al.* (1999-2001)	Korea	83.3%	7.3%	4.3%	5%	9.3%	1613	CP, PALP
Ravetto *et. al.* (1980-1997)	Italy	87.2%	3.3%	7.9%	1.6%	9.5%	37,895	CP, PALP
Werga, *et. al.* (1992-1996)	Sweden	92.2%	3.3%	4.6%	6% (0%†)	10.6% (4.6%†)	3958	CP, PALP
Danese *et. al. (1998)*	Italy	-	-	5.3%	6.2%	11.5%	9,683	US, PALP, ENDO, RAD
Yang, *et.al.* (1994-1998)	USA	82.1%	4.4%	12.8%	0.7%	13.5%	1135	RAD,US,CP
Tsou, *et.al.* (1990-1996)	Taiwan	68.5%	16.1%	11.8%	3.5%	15.3%	254	CLIN, RAD, PALP, US
Khurana, *et. al.* (1998)	USA	72.3%	10.1%	13.5%	3.4%	16.9%	119	RAD, US, CT, CP
Jogai, *et.al.* (1998-2003)	Kuwait	61.9%	20.3%	15.1%	2.6%	17.7%	192	CP, PALP
Ljung, manuscript in preparation 1993-2003	USA	75%	7.1%	14.4%	3.5%	17.9%	1387	CP, PALP
Schmiege, *et. al.* (2000-2005)	USA	89.6%	5.0%	13.8%	5%	18.8%	240	CP, RAD, PALP, US
Malle, *et. al.* (< 2006)	Greece	64%	16%	16%	4%	20%	459	PALP (Smears and liquid prep)
Carmeci, *et. al.* (1991-1996)	USA	74%	4%	7.6%	13.9%	21.5%	497	ENDO,PATH, SURG,PALP, US,CT
Raab, *et.al.* (2003-2005)	USA	72.2%	3.2%	18.0%	5.8%	23.8%	1543	CLIN RAD
Lerma, *et.al.* (2005)	Spain	72%	3.5%	12.5%	12%	24.5%	167	PALP
Baloch, *et. al*. (1997-1999)	USA	63.2%	10.1%	21.7%	5%	26.7%	313	ENDO, US, CP
Tollin, *et.al.* (1994-1998)	USA	72%	1%	23%	4%	27%	93	ENDO, US, CP
Liel, *et.al.* (1979-1996)	Israel	68%	4%	16%	11%	27%	849	ENDO, PALP
De Vos Tot Nedereen Copell (2001)	Nether-lands	59.3%	13%	7.7%	20%	27.7%	810	PALP

1st Author (Years)	Country	Benign Dx	Mal Dx	Susp/Follic	Non-Dx/Unsat	Susp/ Follic + Non-DX	Total Sites	Operators
Solymosi, *et. al.* (1993-1994)	Hungary	64%	7%	20%	9%	29%	513	PALP
Gharib, *et. al.* (1982-1994)	USA	63.75%	4.25%	17%	15%	32%	~12,000	ENDO, PALP
Tambouret, *et. al.* (1993-1997)	USA	60%	8%	17%	15%	32%	290	RAD, US, CT
Yassa et. al 1995-2005 In press	USA	60%	4%	23%	13% (7%†)	36% (30%†)	3,589	ENDO, US
Amrikachi, *et. al.* (1982-1998)	USA	60%	3.4%	7.2%	29.5%	36.7%	6226	SURG, ENDO, PALP
Jones, *et. al.* (1995-2001)	USA	56%	6%	22%	16%	38%	445	
Burch, *et. al.* (1990-1993)	USA	57%	3%	9%	31%	40%	504	ENDO, CT, PALP
Sclabas, *et. al.* (1991-2002)	USA	22%	32%	42%	5%	47%	240	US
Eedes, *et.al.* (2002)	USA	---	----	---	(13%)+ (33%)*	NA	331	PALP, SURG, ENDO, US, CT, CP
Scurry, *et. al (2000)*	Australia	31%	1%	27%	41%	68%	401	ENDO, SURG, PALP

NM=Nuclear Medicine, SURG=Surgeon, CT=Cytotech Present, US=Ultrasound Guided, PALP=Palpable, CP=Cytopathologist, RAD=Radiologist, ENDO=Endocrinologist, CLIN= Other/non-specified Clinician
+with and * without adequacy check at sampling time
†based on repeat sampling

In recent years a number of publications analyzed the underlying factors contributing to success in reaching a useful diagnosis in FNA as applied to the thyroid gland and other organs. [26, 28-35] Several issues raised in most of these reports include the inherent inability of cytologic specimens to assess capsular and vascular involvement in follicular lesions, difficulties with predominantly cystic lesions, and the importance of expertise in interpreting specimens. The root cause of about half of diagnostic failures was unsatisfactory samples. Most remaining failures were due to either short comings in interpretation of adequate samples, or pathologists issuing diagnoses on samples with inadequate material. [13, 17, 29, 34] Thus unsatisfactory specimens were the cause or a contributing factor in the majority of failed diagnoses.

Two reports described successful interventions for improving FNA non-diagnostic/inadequate sample rates of palpable lesions.[36-37] Pre-intervention the unsatisfactory rates were 43% and 29%. In both reports pre-intervention FNA biopsy was performed by the physician who originally detected the mass. Samples were sent to a laboratory for processing and interpretation. The intervention in both reports consisted of the establishment of a FNA clinic wherein a small number of physicians both collected and interpreted the samples. The post-intervention unsatisfactory rates were 9% in both studies. Another report compared FNA unsatisfactory rates between cytopathologist (12%) and non-cytopathologist collected samples (32%). [38] This report found no improvement in unsatisfactory rates when immediate examination for adequacy was provided to non-cytopathologists by a cytotechnician.

The replacement of palpation-guided FNA with ultrasound-guided FNA for palpable lesions has been reported as a way to decrease the unsatisfactory rate. In two studies,[56, 57] the palpation-guided FNAs were performed by many physicians whereas all the ultrasound guided FNAs were performed by a single radiologist. The decrease in unsatisfactory rates were impressive, from 46.8 to 15.6 % in one report and 16 to 7 % in the second. In two other reports where the same physicians did FNAs guided by palpation or by ultrasound, the decrease in non-diagnostic rates were modest, 8.7 to 3.5 % and 32 to 21 % [5, 18]. In the latter report by Cesur, [18] the improvement was confined to lesions <15 mm. It is not clear whether the decrease in unsatisfactory rates in some studies was due to the use of ultrasound or a single better trained operator with more experience. The observation that switching to ultrasound-guided FNA while at the same time concentrating the procedure in the hands of a single operator produced better results than when the same operators performed both palpation and ultrasound-guided FNA would indicate that the proficiency of the operators played a significant role in the marked decrease in unsatisfactory rates. This conclusion is further supported by the fact that five of the published studies listed in the table above (3, 4, 2, 9, 11) reported unsatisfactory rates of 6 percent or less using palpation to guide the needle. It should be pointed out that no studies to date compare palpation guided FNA to ultrasound guided FNA on the same nodules. Ultrasound guided FNA in the above referenced studies are on the average performed on smaller nodules than are palpation guided FNA. Prospective studies controlling for operator proficiency and size and image findings of nodules are needed to know the true impact of ultrasound guidance on the accuracy of FNA of palpable nodules.

Two reviews of thyroid FNA state that the procurement of the samples is not as easy as generally perceived and stress the importance of obtaining an adequate sample in order for the test to be useful.[39-40] Suen makes the recommendation that “the procedure is carried out by a core group of dedicated physicians”.[41] In a 2003 editorial Kocjan discussed many of the problems with the current practice of FNA and stressed the importance of training in specimen collection and preparation regardless of the specialty of the operator.[42]

A recent publication on the teaching of procedural skills indicates that the most important factor for mastering procedures is focused training with appropriate feedback by expert practitioners.[49] The previously widely held belief that simply performing a large number of procedures, produces excellence does not appear to be true. [35] Given these observations it doesn’t make sense to advocate that a specific number of procedures should be performed without specifying the circumstances.

Reports comparing the effectiveness of specific, defined training strategies for FNA sampling are lacking in the literature. Such studies would be helpful in order to optimize training of operators in various settings and specialties.

Several options are available for the preparation and processing of FNA specimens, including smears, cell blocks and liquid based monolayer preparations. The teaching of technically excellent smear preparation is an imperative component of thyroid FNA training regardless of medical specialty. The preparation of high quality smears is imperative for on –site adequacy assessment and for subsequent sample evaluation if smears are utilized. Several studies, have compared conventional smearing techniques with LBC for thyroid samples. [43-48 , 11, 58, 59]. Proponents of conventional

smears feel that further study is needed before LBC can be considered as an acceptable replacement for smears. LBC can not be used for rapid on-site assessments or on-site adequacy evaluations.

Some authors have advocated using cellblocks instead of smears when expertise in smear preparation is lacking. In our experience, cell block material in most cases is much less informative than well prepared conventional smears. Although a cellblock can be a valuable complement to direct smears in select cases, for example when special stains are required.

A recent study compared FNA using conventional smears with core needle biopsy [60] .The rate of unsatisfactory specimens for FNA was 30 percent compared to core biopsy at 18 percent. When combined the unsatisfactory rate was 11 percent. The authors also concluded that core needle biopsy was less sensitive, especially for papillary carcinoma. An associated editorial suggested combining the techniques. However, serious concerns about complications from core biopsies in the thyroid gland were raised and illustrated by one of the presenters at the Oct 22-23 2007 NIH conference. Further training in sampling and smear preparation technique should improve the unsatisfactory rate of FNA smears to the point where core biopsy would be equivalent at best. Physicians who both procure and interpret FNA specimens, benefit from the ongoing prompt feedback on the quality of their specimens which provides a strong incentive to work on improving and maintaining high quality samples. Physicians with training in FNA interpretation have the opportunity to immediately examine the aspirates for adequacy and to provide a diagnosis on site. This feedback enables the operator to collect additional samples in order to achieve diagnostic material and limit the number of samples collected in a given case. There is also an opportunity to triage material for special studies. For example, in cases when high vascularity dilutes the specimen or immunohistochemistry is needed, a cell block can be prepared. Similarly material can be collected for cell surface marker analysis by flow cytometry when features suggesting lymphoma are found. On-site adequacy evaluation can be provided by cytopathologists or cytotechnologists for endocrinologists or radiologists that perform FNA. On-site evaluation of the specimen adequacy has lessened the percent unsatisfactory specimens and limited the number of passes in per nodule sampled. [53, 54] In all but one of these reports on-site evaluation of the specimens was one of several factors reported to improve accuracy but was not calculated as a separate factor. [52] One report found on-site evaluation helpful in minimizing unsatisfactory samples only for less experienced radiologists procuring samples.[55] At the very least, it appears that on-site evaluation serves as an important educational tool for the physician performing the FNA in providing immediate feed back on the quality of the specimen.

The physician procuring the sample has first hand access to the clinical presentation of the patient which can be helpful in the final interpretation of the specimen. Elements helpful in this regard are firmness of the mass, diffuse enlargement vs. multi-nodular gland, one mass vs. multiple masses, degree of resistance to needle and gross appearance of the aspirate and the smear (especially as to the presence or absence of gross colloid).

Most physicians who both collect and interpret FNA specimens have cytopathology fellowship or equivalent training and typically have extensive ongoing experience collecting at least several hundred FNA samples per year. Physicians who

collect but do not interpret FNA samples, may collect fewer samples and may have difficulty mastering the technique and maintaining expertise once obtained.

A detailed instructional video on FNA technique as well as smear preparation techniques is available on-line, sponsored by the Papanicolaou Society of Cytopathology at: http://www.papsociety.org/fna.html

Conclusions:

1. There is wide variability in the ability to achieve useful and correct diagnoses based on thyroid FNA whether using palpation or ultrasound guidance.

2. There is widespread acknowledgement that interpretation of FNA specimens is challenging and requires special training. However, there is a common misconception that FNA procurement is so easy to learn that it requires little or no training beyond reading a description of the technique or observing or performing a few procedures.

3. The majority of diagnostic problems are due to inadequate sampling and preparation of samples. Thus, effective training in sampling and sample preparation is likely to improve the diagnostic accuracy of FNA regardless of mode of guidance.

4. Training in smear preparation is an integral component of any training program in FNA technique regardless of medical specialty.
5. Studies where the same physician both collects, prepares and interprets the specimens tend to report better results. There are also reports with good results when procurement and interpretation are carried out by a trained team of physicians, including an experienced on site cytopathologist.

6. Studies reporting larger numbers of cases tend to report better results.

7. All samples regardless of procurement and processing should be interpreted in a specific clinical framework.

C. Suggested components in an FNA training program:

a. Studying of illustrated texts, a DVD or similar teaching aid with moving images that explain the principles and show all required tasks including sampling and specimen preparation techniques in detail. The DVD should be kept by the trainee for future reference. Lectures and demonstrations can also be helpful. A detailed instructional video on FNA technique as well as smear preparation techniques is available on-line, sponsored by the Papanicolaou Society of Cytopathology at: http://www.papsociety.org/fna.html

b. Bench practice under supervision to learn basic needle manipulation and to master different techniques of preparing samples. Bovine liver works well and is a safe and readily available material for training. Timely and precise placement of the needle tip under ultrasound guidance can be practiced with a model (for example turkey breast with a "target" inserted between the muscles or commercially available practice materials).

c. Sampling of thyroid nodules guided either by palpation or ultrasound. (If with ultrasound guidance prior adequate training in ultrasound imaging is necessary, such training is beyond the scope of this document). The procedure should be done under the direct supervision of a proficient and experienced operator. In addition, the trainee should examine all resulting specimens in order to provide feedback regarding the success or failure in sampling and preparing a given specimen.

d. It is difficult to stipulate a specific number of samples that should be collected before training is complete. Program directors must verify that a trainee has achieved proficiency in FNA sampling and specimen preparation technique.

In our experience, a crucial factor in training an operator to a high level of proficiency is exposure to relatively easy targets initially and relatively challenging targets as higher levels of proficiency are reached. Clearly trainees need to work on challenging cases in order to master the technique. The number of cases needed in training is dependent on the available case mix and progress on the part of the trainee. One should expect at least 90% diagnostic specimens before completion of training.

D. Future improvement of training:

Virtual reality tools have been developed to train physicians particularly in endo/laparoscopic procedures. Similar tools can be developed to train physicians in successful FNA technique.

Finally, in America, it is not likely that one physician will perform all of the steps involved in all thyroid aspiration biopsies. Thus, we must set standards for each step in the process, assure continuity of the process through all steps, and provide ongoing assessment of the results to maintain the confidence of our patients and those who underwrite medical care.

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Committee III: Techniques for Thyroid FNA

A. Aspiration devices, needles and methods
Review:

Needles

A wide variety of needles of varying lengths and diameters are available for FNA use (Figure 1). A large majority of those posting comments at the website exclusively use 25-27 gauge needles for their initial biopsies.

Figure 1 (Adapted from Sigma-Aldrich Co @ http://www.sigmaaldrich.com/Area_of_Interest/Research_Essentials/Chemicals/Key_Resources/Technical_Library/Needle_Gauge_Chart.html)

Needle	Nominal O.D.		Nominal I.D.	
Gauge	mm	inches	mm	inches
10	3.4040	0.1340	2.6920	0.1060
11	3.0480	0.1200	2.3880	0.0940
12	2.7690	0.1090	2.1590	0.0850
13	2.4130	0.0950	1.8030	0.0710
14	2.1080	0.0830	1.6000	0.0630
15	1.8290	0.0720	1.3720	0.0540
16	1.6510	0.0650	1.1940	0.0470
17	1.4730	0.0580	1.0670	0.0420
18	1.2700	0.0500	0.8380	0.0330
19	1.0670	0.0420	0.6860	0.0270
20	0.9020	0.0355	0.5840	0.0230
21	0.8130	0.0320	0.4950	0.0195
22	0.7110	0.0280	0.3940	0.0155
23	0.6350	0.0250	0.3180	0.0125
24	0.5590	0.0220	0.2920	0.0115
25	0.5080	0.0200	0.2410	0.0095
26	0.4570	0.0180	0.2410	0.0095
27	0.4060	0.0160	0.1910	0.0075
28	0.3560	0.0140	0.1650	0.0065
29	0.3300	0.0130	0.1650	0.0065
30	0.3050	0.0120	0.1400	0.0055
31	0.2540	0.0100	0.1140	0.0045
32	0.2290	0.0090	0.0890	0.0035
33	0.2030	0.0080	0.0890	0.0035

Most solid phase biopsies utilize 27 to 22 gauge needles that equates to outside diameters of 406 - 711 microns and inside diameters of 191 - 394 microns.[1] Follicular cell nuclei on smear preparations are similar to the diameter of red blood cells or lymphocytes, around 8-10 microns.[2, 3] Thus, the commonly used needles would have internal diameters better than 20 – 50 times that of a follicular cell nucleus. Since three dimensional follicles average around 200 microns, but vary considerably, these commonly used needle sizes often allow passage of intact individual follicles or even small stromal-epithelial fragments (‘mini-cores’) on many FNA smears.[4] Given that the

risk of a hemorrhagic complication reasonably bears some relationship to increasing needle diameter, one approach is to begin the biopsy sequence with the smallest diameter needle that in one's experience is usually effective (25-27 gauge). The resulting unstained slide can be visually assessed for colloid and tissue fragment content, with progression to larger needle sizes if needed. This approach is supported by one study of 123 patients biopsied with 23 and 27 gauge needles that found no significant difference between the two sizes of needles in the adequacy of material obtained.[5] That report also recommended using both sizes noting that 'the number of dry passes is lower with the larger needle, but the diagnostic quality of the aspirate may be better with the smaller one'. In a study of needle sizes in the diagnosis of lung caner, Unver found, however, that 18, 22, and 25 gauge needles had no significant differences in diagnostic yield or cell type concordance.[6]

Needles come in two basic bevel styles.[7] For FNA purposes, the long or regular bevel needles are the best, are the most commonly available, and are the typical needles used for intramuscular injections. The angle of the long bevel needle is 14 degrees or less. The arrow in **Figure 2** is 9 degrees, a common value.

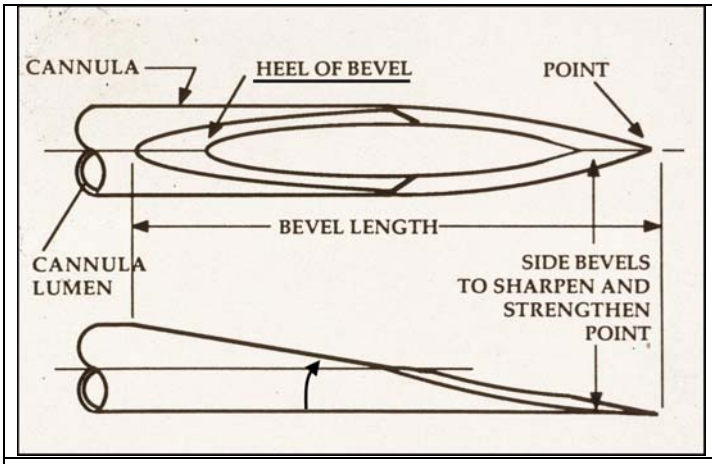

Figure 2. Long bevel needle

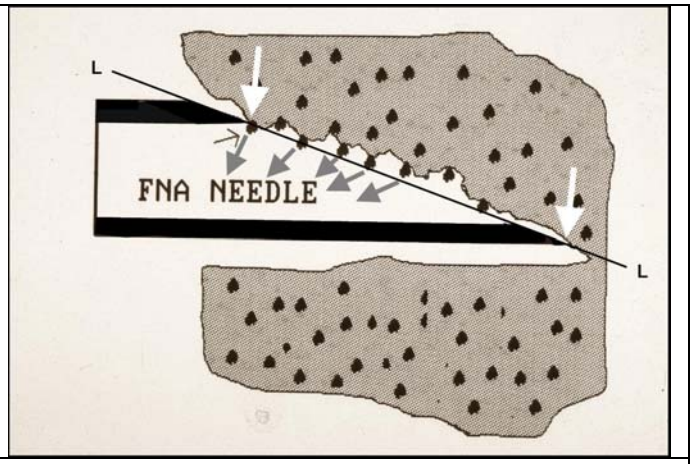

Figure 3. Needle heal cutting action

Because of this relatively narrow angle, these long bevel needles are relatively "side looking" and thus are perfect for thyroid sampling as the trailing edge of the needle bevel can act in a guillotine-like fashion as the needle is advanced forward, harvesting the soft epithelial component and relatively avoiding the accompanying stromal component (Figure 3). Just as the 9° bevel of the leading edge of the needle is a very effective cutting device (right white arrow), the trailing edge (left white arrow) is also equally effective for effective cutting (line L cuts the parallel lines of the needle cylinder at equal angles). The cellular yield is maintained within the needle core by a combination of forward movement of the needle and the suction-like effect of surface tension induced capillary action, which is relatively high in these smaller diameter needles.

In contrast, the two other needle bevel styles, grouped together as short bevel, have a much greater angle and are usually used for intradermal use. Since they open nearly perpendicular to the direction of needle travel, they are not generally used in FNA sampling. In addition, the short bevel needles tend to become occluded by normal tissue such as muscle prior to reaching the thyroid target. This is due to the larger bevel angle

that is closer to a core needle with a 90 degree bevel compared to a long bevel at 14 degrees or less.

Larger gauge needles are often needed to drain viscous colloid cysts. Specifically, for straight pipes, such as a FNA needle, the resistance is inversely proportional to the diameter of the pipe. Twenty, 14 and 10 gauge needles have internal diameters of 0.584, 1.600, and 2.690 millimeters, respectively. These diameters are generally sufficient to allow full evacuation of all but the most viscous of colloid cyst contents, and are atraumatic when preceded by adequate anesthesia. As will be discussed below, a standard 34 inch flexible IV extension tube can be used to join the vacuum producing pistol syringe holder and these larger needles.

Aspiration Devices

There are a variety of syringe holders. Among the oldest and most widely used pistol grip like holders is the Cameco [Precision Dynamics Corp., San Fernando, CA] as shown in the opening chapter of the late Dr. Josef Zajicek's classic FNA textbook.[8] Wide experience in both the Swedish and the American models have show this to be an excellent instrument allowing the aspirator to both direct the biopsy and supply negative pressure with one hand, with the other hand immobilizing the target and assessing needle depth of penetration.

In 1986 Zajdela suggested a novel approach to needle biopsy, using a bare needle without syringe or negative suction.[9] The Zajdela technique relies on the forward motion of the needle as well as the surface tension induced capillary action within the core of the needle which can be quite strong, particularly in small diameter needles. The formula showing how smaller diameter needles have a greater capillary effect is included in his original paper. Later on Cajulis validated the effectiveness of this approach showing that FNA both with and without aspiration provided adequate cells for diagnosis and special studies.[10] Moreover, their results show that, when both aspiration and non-aspiration techniques are used in the evaluation of a given nodule, they had an additive effect.

There are more recent studies of aspiration versus non-aspiration in needle biopsy. In a series of 200 patients with thyroid nodules scored for blood, number of cells obtained and preserved architecture, no statistically significant differences were found with or without aspiration.[11] In another study of 150 patients with thyroid gland enlargement, diagnostically superior specimens were obtained significantly more frequently by the non-aspiration techniques.[12] In a meta-analysis of 4 cross over trials, an odds ratio favored non-aspiration but the difference was not significant.[13]

Based as much on favorable clinical experience as in these studies, many FNA practitioners adopted the Zajdela technique for the first biopsy sample. Also, the visual impact to the patient is less with this technique since the physician can approach the patient with the needle concealed in the palm of the hand versus the larger visual cross section of the pistol grip syringe holder. With or without anesthesia, the first biopsy using the Zajdela methods can often be obtained with so little impact that patients occasionally ask, "Was that the biopsy?" In addition, "spinning" or variably oscillating the needle around its long axis in a clockwise-counterclockwise manner during the forward motion has been suggested. With spinning the rotational velocity vector slightly increases the effective forward velocity of the needle. Also, the circular rotation adds a

shearing component to the cutting action of the trailing edge of the needle, an action that may improve cellular yield.

With the advent of ultrasound directed biopsies of smaller and often non-palpable nodules, the pistol grip syringe holder may seem more cumbersome and awkward in contrast to its great utility in conventional palpable thyroid nodules. The Tao instrument [Tao and Tao Technology, Carmel, IN] seeks to bridge this gap by being small and gripped much like a pencil, but still able to provide the element of suction during the course of the biopsy.[14] The main drawback to the Tao device (http://www.taoaspirator.com/) is its lack of a simple means of quickly relieving any residual vacuum at the end of the biopsy prior to withdrawing the needle. That residual vacuum, although small, is often more than sufficient to draw the specimen into the syringe, a major impediment for a more rapid specimen recovery and slide smearing. In a like manner, the Inrad aspiration biopsy syringe gun [Inrad, Inc., Kentwood, MI] has been presented as offering some advantages over the Tao device (http://www.inrad-inc.com/main.htm).

There is a potential solution to the awkward size and mass of the pistol-grip-syringe-needle instrument in the ultrasound directed sampling of small targets. One can interpose a plastic disposable IV tube extension between the pistol-grip-syringe and the needle. This is a simple modification of an earlier suggested method which utilized a butterfly IV needle and its attached plastic tubing.[15] Thus the biopsy physician can have the delicate tactile feel of the Zajdela technique holding just the needle with one hand while having a second had free to isolate the lesion or manipulate the ultrasound probe while suction is applied by an assistant holding the pistol grip as needed. A single IV tube extension can mate any already available needle in the inventory of the FNA clinic to the syringe holder without the expense of having to have butterfly IV needles in an array of sizes. Also the relatively short length of the butterfly needle can be insufficient for deep posterior nodules or for patients with thick necks.

Methods

There are a variety of methods for proceeding with manual and ultrasound directed FNA sampling. The Stanley and Lowhagen textbook nicely combines the Swedish and the American approaches to FNA biopsy in Chapter 1 “Equipment, Basic Techniques, and Staining Procedures”[1] Descriptions of smearing techniques along with detailed illustrations have been published.[16] Additional reviews can be found in current cytopathology text books.[17] The Pap Society’s web site (http://papsociety.org/) also offers study aids applicable to thyroid FNA, including a detailed instructional video outline all aspects of FNA including sample preparation (http://www.papsociety.org/fna.html). Available as down-loadable PDF files from its Guidelines tab are “Optimal Smear Preparation Techniques” (http://papsociety.org/guidelines/Smears_handout_distribution.pdf) and “Pathologist Performed Ultrasound Guided FNA” (http://papsociety.org/guidelines/us_SanDiego_cut_handout_distribution.pdf). Videos of FNA technique can also be downloaded for free via Google™.

These concepts are presented briefly in the following figures. The specimen character or location determines the technique needed as outlined in **Figure 4. Figures 5 and 6** present the one step technique for semisolid or viscous samples, whereas **Figures 7 and 8** demonstrate concentration techniques for a fluid sample.

Figure 4

Character	Technique
Semisolid	One step
Thin watery	Two step
Fluid in hub	Snap
Fluid in syringe	Pop

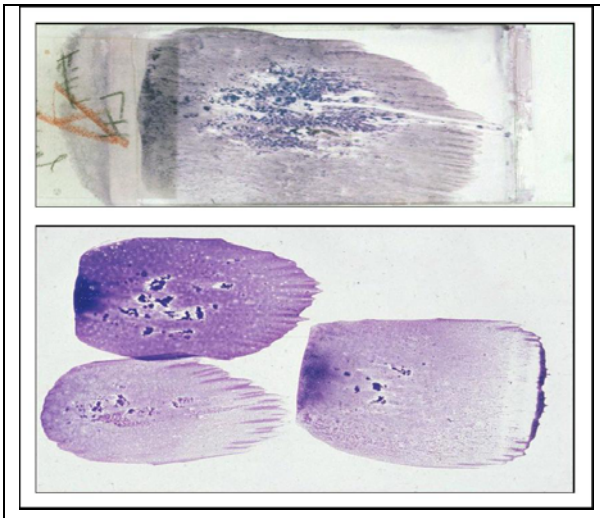

Figure 5. 1 step technique smear

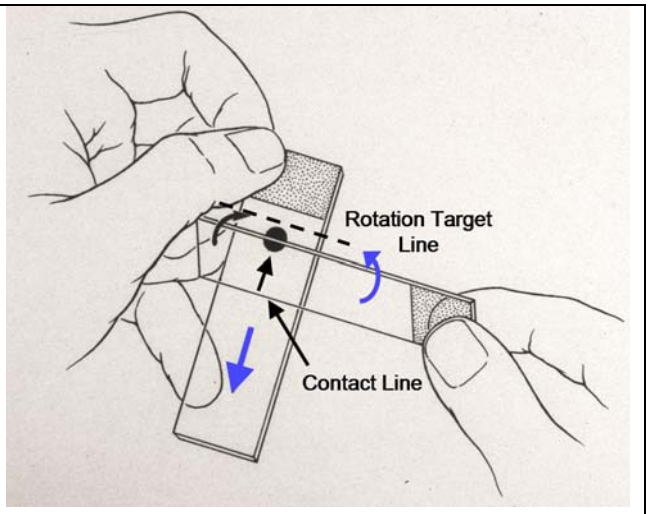

Figure 6. 1 step technique method

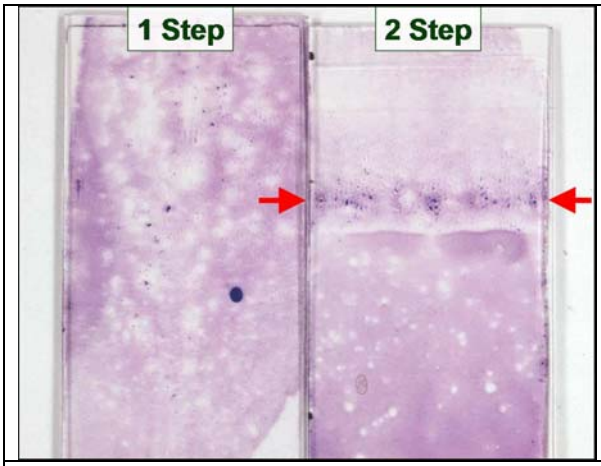

Figure 7. 1 step and 2 step smears

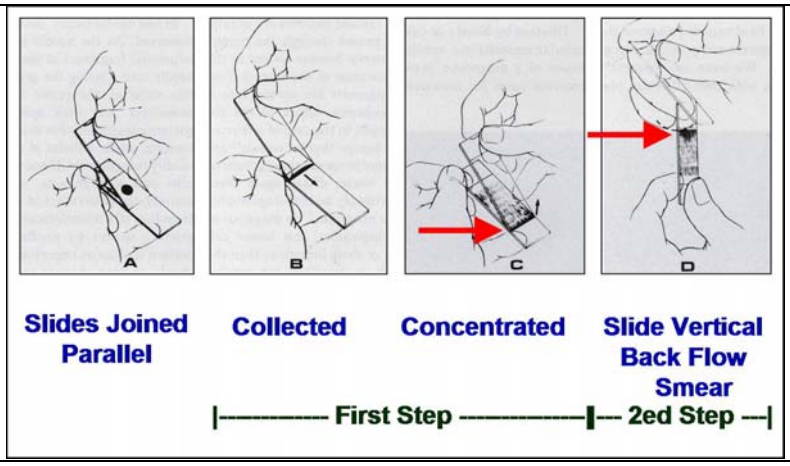

Figure 8. 2 step smearing technique

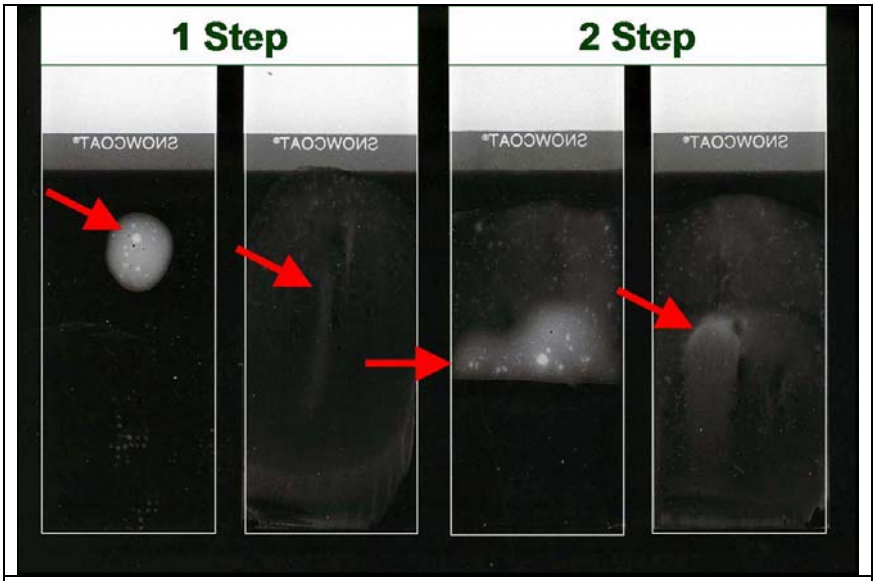

Figure 9. Smear practice material, 1 step and 2 step examples

Reasonably realistic smearing practice materials can be prepared utilizing a suspension of any of the readily available hand lotions. Lubriderm for normal skin (Pfizer, Morris Plains, New Jersey), when gently swirled with water, disperses into small droplets of opaque white tissue-like fragments within a watery background. Swirling rather than shaking is recommended since the latter tends to produce bubbles. By incorporating less or more water into this mixture, one can mimic the semi-solid material appropriate for a one-step technique, as opposed to more watery material appropriate for a 2-step technique as illustrated in **Figure 9**. This material remains relatively stable for an hour or so and can be transferred to small bottles with eyedropper dispensers so that one can produce a precise and appropriate sized droplet on a slide for demonstration purposes. Although the classic calf liver model is excellent for practicing the biopsy method (discussed below), the relatively fibrous content of aspirated calf liver fragments does not correspond well to the tissue from thyroid FNA, and thus this lotion suspension method is recommend for smearing practice.

These conventional smearing techniques, which were perfected by the early 1970s, now have a world wide experience of over 35 years and provide the basis for which the vast majority of thyroid FNA criteria now in use have been developed. These techniques, as presented in illustrations given above, may seem complex to the inexperienced. Yet they are in fact quite easily learned as one practices them with someone experienced in proper smear preparation.

Due to poor or absent teaching of these techniques and the subsequent poor quality smear production has led some to non-smear techniques such as cell blocks and liquid based preparations. These alternatives to smears add technical costs not associated with direct smears and may limit the higher definitive diagnostic ability of good quality direct smears for inexperienced cytopathologists in LBC presentation.

There are a variety of readily available materials for training and practice in FNA collection. One easy practice source for the FNA biopsy technique is a portion of liver wrapped in several layers of latex examining gloves. In particular, calf's liver has a relatively soft parenchyma that nicely approximates aspiration biopsy collection.

To perform an FNA, in brief, the skin is cleansed only with a simple alcohol preparation since the needle sizes are generally those of an intramuscular injection or blood drawing. Accordingly, there is no need for elaborate sterile draping. When larger needles (18 gauge or larger) are used to evaluate a viscous cyst, an iodine preparation in a non-iodine allergic patient may be a reasonable additional safeguard. If anesthesia is used, a half cubic centimeter of local anesthetic slowly delivered into the subcutaneous fat through a 30 gauge needle (readily available through dental supply outlets) provides rapid, comfortable anesthesia as long as the agent is delivered into the subcutaneous fat without the formation of a dermal wheal. The use of anesthesia is discussed further under Agenda Item B.

By visual or US means the needle is quickly introduced into the nodule with a series of advance-withdraw motions, the excursions of which are carefully maintained within the target over a brief time; 2-5 seconds on the first sample is usually a good starting point for most thyroid nodules. Some benign thyroid nodules are sufficiently rich in colloid and limited in vascularity to allow a somewhat longer sampling time. The presence of blood in the needle hub is indicative of too long a needle dwell time in the nodule so that sampling process has been changed from the desired collection of the more viscous colloid and cellular material to a sampling of the considerably less viscous capillary blood, which preferentially enters the needle. Rapid (3 excursions per second) sampling motions with brief dwell time within the nodule may diminish bloody dilution and obscuration. Production of 1-2 slides per biopsy reflects an appropriate dwell time. The consistent production of over 3 or more slides per biopsy suggests an overly long dwell time and risks bloody dilution and/or obscuration.

Some tumors are exquisitely vascular, such as hyperactive nodules, microfollicular neoplasia, and some metastatic carcinomas, notably renal cell carcinoma. Such tumors present a contest between successful tissue sampling versus capillary blood sampling. Fortunately a simple modification of the basic biopsy is usually effective. First, since these lesions are usually hypercellular, vacuum is usually not needed and may even be counter-productive. For such hypervascular nodules, the Zajdela technique is ideal. Secondly, the dwell time within the nodule must be greatly reduced. To do this the patient is advised that the biopsy will be very rapid so as not to be surprised, expecting the smooth gentle motion of the initial FNA sample. The needle is gently place through the skin and comes to rest just outside of the thyroid and nodule. When ready, the physician proceeds with one or two extremely rapid but fully controlled thrusts before it is withdrawn and the smears rapidly made. Again the needle tip excursions are only allowed within the volume of the targeted area. The speed of the needle advancement greatly augments the ability of the sharpened metal at the trailing edge of the needle's bevel to act in an efficient cutting fashion, rendering multiple epithelial fragments into the core of the needle before the injured capillaries can release much in the way of blood. Because of localized release of capillary blood at a prior biopsy site, subsequent biopsies are obtained from geographically different areas to the greatest degree possible.

If US guidance is used, the needle must <u>never</u> be passed through a layer of US gel on the skin since this gel produces a serious obscuring precipitation on Wright's staining. Rather the point of skin entry is identified by placing an ultrasound dense object under the probe, such as a ball point pen. When centered over the target, the site of the pen's tip is inked with a surgical skin marker. Once the needle is within the skin, the probe

with its gel is applied, the target acquired, and the biopsy performed. When the needle is withdrawn, often US gel will coat its outside surface. This US gel can be completely removed by simply wiping gauze from needle hub to needle tip.

Following the biopsy, the biopsy site is gently compressed with manual pressure for about a minute and then a small bandage applied to protect the patient's clothing. For most patients normal activities can immediately be resumed at the discretion of the physician.

Conclusions:

1. Commonly available 27-25 gauge needles are best used for thyroid FNA starting with the smallest diameter needle and increasing needle size as needed; larger diameter needles reserved for drainage of viscous colloid cyst contents.
2. The native suction provided by surface tension within smaller diameter needles often make devices for additional suction unnecessary.
3. When suction is needed, such as in the drainage of cystic contents, a section of IV tubing interposed between the needle held by the physician and the aspiration device as held by an assistant allows for near normal tactile sense and needle mobility that approaches that of the Zajdela technique. A syringe in an aspiration device is also useful.
4. The basic principles of thyroid FNA are the same whether the needle is inserted into the lesion by manual or ultrasound guidance. Cellular material is obtained by the cutting action of the trailing edge of the needle (heel of the bevel) and is retained in the needle core by forward motion and capillary tension.
5. As a starting point, a dwell time of 2-5 seconds within the nodule with 3 forward and back oscillations per second often maximizes cellular yield, minimizes bloody artifacts, and efficiently produces 1-2 slides per biopsy pass.
6. Readily available and easily learned smearing techniques allow the aspirated material to be best presented on the slides for optimal fixation, staining, and microscopic assessment. Failure or any significant flaw in smearing technique can limit or totally hinder microscopic evaluation, irrespective of how much material was obtained during the biopsy phase of the FNA.

B. The role of anesthesia for palpable and nonpalpable FNA and guidelines for its use

Review:

There are no good published data on the use of topical anesthesia in thyroid FNA. Most authors, however, recommend no local anesthetic for palpable nodules.[18] However, the trend with other FNA physicians, particularly as they acquire experience in the effective anesthetic techniques described below, has been to offer local anesthesia to all patients.

Discussing superficial FNA in general, the National Committee for Clinical Laboratory Standards (NCCLS), in their publication (GP20-A2, Volume 23, Number 27), clearly states that most of these FNAs can be performed without local anesthetic for three main reasons: 1) injection of a local anesthetic can cause more pain than the FNA itself; 2) infusion of the anesthetic agent can obscure anatomic detail and make the target lesion/mass difficult to palpate; 3) local anesthetic may cause degeneration and loss of cellular morphology.

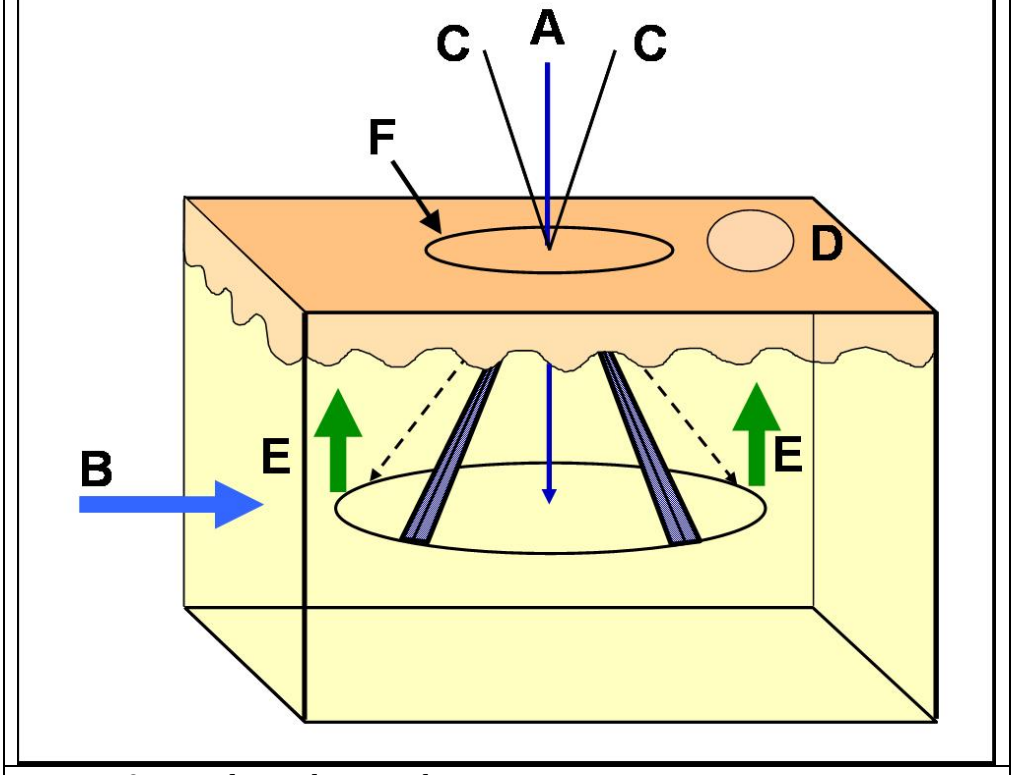

Figure 10. Local anesthesia technique.

Excellent anesthesia for thyroid FNA is obtained by injecting between 0.5-1.5 cc of 2% lidocaine with or without epinephrine 1:100,000. The ultra thin 30-32 gauge needles minimize discomfort during the initial skin puncture. These are available as disposable items for use with a reusable tubex injector, and are readily obtainable through dental supply outlets.

As demonstrated in Figure 10, the needle goes directly down through the skin (A) into the upper subcutaneous fat plane (B). Approximately half the total desired amount to be delivered is slowly infiltrated into the outermost portion of the subcutaneous fat to avoid a wheal. The remaining half of the desired anesthetic volume is administered as the needle is progressively withdrawn and repositioned into sequential quadrants (C) in the same fat plane (B).

The standard 2% Lidocaine tubex unit contains 1.8 ml of anesthetic agent. As a general guideline, one can place about a third of the total tubex volume during the first phase of injection and a second third of the tubex volume is equally distributed into the perimeter quadrants. This will deliver about 1.2 cc of anesthetic agent, which almost always is sufficient, but 0.6 cc remains should further administration be needed.

During both the first and the second phases of the anesthetic injection, introducing counter irritation, such as tapping or rubbing the skin adjacent to the injection site with one's finger (D), is quite helpful. During the next minute or so the anesthetic back infiltrates into the dermis (E) leading to a slowly evolving zone of excellent anesthesia (F). After approximately one minute or so, one has about a 1 cm area of completely numb skin.

Normally cutaneous anesthesia as described here is all that is necessary to provide for a painless thyroid FNA. Rarely a patient may encounter pain upon capsular penetration. In such a case, one should consider anesthetizing the anterior part of the thyroid capsule through which the biopsy needle will pass. Such capsular tenderness can certainly be the case for subacute thyroiditis. Additionally it may be seen in other conditions, such as chronic thyroiditis as well as patients who have an acute process such as intrathyroidal hemorrhage, infarction, or cyst leakage. With good quality ultrasound equipment one can easily visualize the small 30 gauge needle either directly, or as a distinctive zone of soft tissue distortion. Under this visualization an additional third of a tubex is applied just above the surface of the thyroid capsule. Adequate capsular anesthesia generally develops in 2-5 minutes.

The duration of local anesthesia after the initial injection lasts long enough and a repeat injection is rarely, if ever, needed. With epinephrine the anesthetic effect lasts 0.5-1.5 hours. At these low doses lidocaine is safe and only rare instances of allergic reactions have been reported.

Alternative numbing methods used by some include an ice pack placed on the proposed FNA site before the procedure, 4% lidocaine spray and Lidocaine gel.
Conclusions:

1. In some practitioners' experience thyroid FNAs are well-tolerated and are not associated with significant discomfort or pain for the well prepared patient. These physicians feel that local anesthesia prior to FNA is not need.
2. Other physicians, particularly as they gain experience with proper anesthetic administration techniques, feel that properly administered local anesthesia renders the biopsy painless, and offers patients comfort and piece of mind, resulting in an overall more pleasant experience. These FNA physicians use local anesthesia for all thyroid FNAs.
3. Thus, the use or non-use of local anesthesia is within the judgment and discretion of the FNA physician with the concurrence of the informed patient.
4. For deep, non-palpable thyroid nodules that may require more time and probing to reach the nodule, and for all biopsies using needles other than a fine needle, local anesthesia is recommended.
5. Local anesthetic of choice is 1-2% lidocaine with or without 1:100,000 epinephrine.
6. Inject about 0.5 – 1.5 cc of the anesthetic utilizing 30 gauge needle and inject slowly into the subcutaneous fat (not the reticular dermis) and allow allowing the anesthetic to back infiltrate the dermal nerves, avoiding rather than make a painful intradermal wheal.

C. Influence of thyroid lesion location, size and imaging characteristics on FNA sampling technique

Review:

Nodule Location

The location of a nodule will potentially exclude the option of palpation guided biopsy. Posterior lobe nodules that are deep in the neck and difficult to feel benefit from ultrasound guidance. The location of the nodule (right lobe, left lobe, isthmus, upper or lower pole) does not appear to affect the rate of non-diagnostic thyroid FNAs performed under US guidance.[19] Alexander, et. al. analyzed in detail 189 non-diagnostic thyroid FNAs, and the only factor on multivariate analysis that proved to be an independent predictive factor of non-diagnostic specimens was the cystic content of the nodule.[19]

Nodule Size

Large nodules should be aspirated in 2 or more locations depending on the size of the lesion to insure adequate sampling of potentially heterogeneous composition. See Committee I: Indications for discussion of the influence of nodule size on decision to biopsy.

Nodule Imaging Characteristics.

The most critical aspect influencing the FNA sampling technique and the rate of non-diagnostic FNAs is the presence of cystic change within a nodule.[19-22]Frates, et. al. have now recommended not biopsying nodules > 75% cystic by volume, due to the extremely low yield of carcinoma within these nodules.[23, 24] Alexander, et. al., in an analysis of 189 patients with non-diagnostic thyroid FNAs, found that the percent of cystic change was the single most important variable in determining a non-diagnostic FNA result.[19] The fraction of specimens that demonstrated non-diagnostic FNAs increased with the greater cystic content of the nodule. Solid nodules had an 8% non-diagnostic rate, which increased to 12% if the nodule was 25 - 50% cystic, 25% if the nodule was 50 - 75% cystic, and 36% if it was > 75% cystic. As such, a key feature of the ultrasound FNA technique stressed by numerous authors is that only the solid mural components of the nodule should be biopsied. Additionally, areas of the nodule with suspicious calcifications should be targeted. Thus, the advantage of ultrasound is the ability to determine with accuracy the nodule location, size and characteristics therefore insuring that the appropriate solid or suspiciously calcified area of the nodule is sampled.[25-27]

Conclusions:

1. Nodule location in the posterior lobes deep in the neck and difficult to feel should be aspirated with ultrasound guidance.
2. Large nodules should be aspirated 2 or more times in different locations to insure adequate sampling of potentially heterogeneous nodules.
3. Thyroid cysts should be drained and any residual solid component visible on ultrasound should be subjected to biopsy.
7. Suspicious calcifications identified on ultrasound should be targeted.

D. The role of ultrasound guidance in FNA of a palpable thyroid nodule

Review:

Fine needle aspiration biopsy of palpable thyroid nodules historically has been guided by palpation (P-FNA), a technique widely utilized by pathologists and endocrinologists. However, recently US guidance for FNA (US-FNA) of palpable thyroid nodules has been advocated as a means to reduce the rate of non-diagnostic aspirates due to insufficient sample for interpretation, and to reduce the rate of false negative interpretations.[19, 25-31] The indications for use of ultrasound in the aspiration of palpable nodules is covered by Committee I.

Reports on the clinical utility of ultrasound in FNA of palpable thyroid nodules has largely centered on the experience of radiologists and endocrinologists.[19, 25-31] However, Redman, et. al. reported that pathologists had the highest diagnostic yield in their diverse group of physicians performing FNAs of thyroid nodules.[32] There is no inherent reason why pathologists should not be able to use ultrasound guidance for thyroid FNAs as effectively as radiologists and endocrinologists. Any pathologist who presently sees patients and routinely performs quality FNA sampling of palpable thyroid nodules can easily incorporate US examination and guidance as an augmentation to the biopsy procedure. The trend for pathologist-based FNA clinics to utilize US is just beginning. Ultrasound gives the pathologist a new dimension in patient care, one that the interested pathologist can easily obtain. Ultrasound imaging greatly augments physical diagnosis and guides the needle for better targeting of palpable thyroid nodules (see agenda item C above).

There are some very practical reasons that now allow an FNA pathologist to add US imaging to their practice. With expanding patient directed heath screening services, nodules that the pathologist is being asked to sample are becoming ever smaller. In addition, given the falling cost of US equipment to around $20-40,000 for a good bedside portable system with printer, monitor, and ever improving image quality, US direction is now affordable in an active FNA clinic setting. There are excellent instructional courses given by various professional societies, such as the American Association of Clinical Endocrinologists (http://www.aace.com/) and the American Institute of Ultrasound in Medicine (http://www.aium.org/).

Conclusions:

1. Ultrasound may be utilized as a tool for the FNA of palpable thyroid nodules by all physicians who perform thyroid FNA.
2. Pathologists are encouraged to use ultrasound guidance for FNA of palpable thyroid nodules.
3. See Committee I conclusions for indications of ultrasound use in the setting of palpable thyroid nodules.

E. The role of core biopsy for palpable and non-palpable thyroid nodules

Review:

Large CNB provides tissue fragments for conventional histologic examination. Its use was more prevalent in the past, but was subsequently replaced by FNA.[33] There are two main types of large CNB, Vim-Silverman needle and Tru-Cut needle, which utilize 14-gauge needles. Large needle aspiration technique is similar to FNA, but uses considerably larger needles (16-18 gauge). Most clinicians utilizing CNB are now using a

modern spring-loaded core biopsy, single-action and double action devices. The double action spring loaded needles (i.e. Monopty or Biopty gun), are those in which the spring-activated stylet, containing a biopsy specimen slot, and cutting cannula (outer blade) are fired in rapid succession.[34, 35] The biopsy is actually obtained from tissue 1-3 cm deeper than the pre-triggering cutting notch position (depending on distance of throw). After firing, the stylet tip is correspondingly deeper than in the specimen. This mechanism discourages their use in the vicinity of vulnerable structures or for the biopsy of very small lesions.[35] A short throw device (11 mm excursion) is, therefore, preferred, so that when the system is fired the cutting cannula is propelled only a given controlled distance. This decreases the risk of penetrating large cervical vessels, esophagus, nerve, or trachea.[36] The single action spring activated needle, i.e. Temno needle, uses a similar but non-advancing cutting action. The needle is triggered only when the stylet and biopsy notch have been manually extended. Before triggering, the biopsy notch is situated at the exact site of the intended target. During the cutting action, only the blade slides over the cutting notch but the actual stylet tip does not advance further into the specimen.[35] FNA is performed with 23-27 gauge needles utilizing the aspiration or non-aspiration technique.

Utility of large needle biopsies

Wang, et. al., using a 14-gauge Vim-Silverman needle, reported a 90% satisfactory rate and 90% accuracy rate on 906 thyroid biopsies over a 20 year period.[37] Some limitations, however, included inability to sample nodules less than 1 cm in size, or nodules deep in the thoracic inlet due to difficulty of sampling and the potential of hemorrhage. In 1981, Ashcraft and Van Herle extensively reviewed the literature, evaluating 9161 cases of thyroid FNA and 553 large needle biopsies, and concluded that the diagnostic accuracy, sensitivity and specificity for FNA were comparable to both CNB and large needle aspiration, but FNA was superior due to its safety, reliability and cost effectiveness.[38] Colacchio, et. al. compared 300 FNA to 225 Tru-cut CNB and found similar results.[39] The Vim-Silverman needle procedure has been abandoned, while Tru-cut needle is still in use.[33] Perhaps the most important impediment to the use of the Vim-Silverman needle in North America has been a case report by Crile and Vickery[40] of tumor implantation of a thyroid carcinoma into the skin after its use.[38] Subsequently Wang, et. al. described one case of an implantation after Vim-Silverman-needle biopsy of a metastatic renal cell carcinoma to the thyroid. Large CNB such as Tru-cut needles or large aspiration needles have not become a standard procedure for several reasons, including relatively increased risk of complications, high proportion of unsatisfactory samples, and difficulty of performing the biopsies on lesions smaller than 1.5 cm or those located in poorly accessible sites.[36] Routine use of CNB, in the past, has also not been advocated because of concern for increased patient discomfort and anxiety with little or no difference in its diagnostic value compared to FNA.

Utility of modern core needle biopsies

There is limited literature regarding the use of modern biopsy needles in thyroid, but so far it suggests that it is safe. This is due to the use of single action spring activated needles, which are believed to result in a lesser amount of trauma. In an excellent study, Screaton, et. al. assessed the safety, yield, and accuracy of US-guided CNB (US-CNB) of thyroid, utilizing 16-18 gauge needles.[41] They evaluated 209 CNB from 198 patients,

with histologic followup on 83 patients, and clinical followup (6-60 months) on 126 patients with non-neoplastic diagnoses. Patients were referred to CNB after repeated non-diagnostic FNAs, indeterminate follicular lesion diagnoses (66%), or nonpalpable nodules (34%) with no previous FNA. In separating benign from malignant cases, they achieved sensitivity, specificity, diagnostic accuracy, and non-diagnostic rates of 96%, 89%, 92% and 5%, respectively. The authors concluded that US-CNB is a safe outpatient procedure with a high diagnostic yield, that often obviates surgery for patients in whom FNA findings are recurrently "unsatisfactory".[41] Taki, et. al. evaluated the efficacy of US-CNB of 74 cases, using an 18-gauge double spring activated needle.[36] They achieved 84% sensitivity, 95% specificity, and 91% diagnostic accuracy, however, better results were achieved in thyroid lesions larger than 10 mm. Renshaw and Pinnar compared the adequacy and accuracy of US-guided FNA and CNB in 377 patients who underwent both tests.[42] The adequacy rate for CNB was significantly higher than that of FNA (82% vs. 70%), but the combined adequacy of both methods was significantly higher than either test alone (88%). Although it was associated with higher adequacy rate, in their series, CNB appeared to be less sensitive than FNA, especially in the detection of papillary carcinoma.[42]

FNA diagnostic accuracy and limitations

FNA is characterized by a high diagnostic accuracy rate, reported in the range of 90-100%.[43, 44] It is a safe, inexpensive and easily performed procedure that is associated with minimal patient discomfort. Major limitations of FNA include the difficulty to distinguish hypercellular non-neoplastic nodules from a follicular neoplasm, and the difficulty to obtain an adequate specimen on some occasions. False positive diagnoses make up less than 1% of cases, and are mostly due to over-interpretation of reparative and reactive nuclear changes as papillary thyroid carcinoma (PTC). False negative rates range from 1 to 11%, and are mostly due to unsatisfactory specimens.[45] Sampling errors, interpretation errors and cystic neoplasms, especially PTC, account for most of the other false negative cases.[34]

FNA vs. CNB in diagnosing follicular neoplasms

For all practical purposes, FNA cannot distinguish between follicular adenoma and follicular carcinoma.[46] Histologic confirmation is needed in such cases in order to demonstrate capsular and/or vascular invasion.[47] This limitation, however, is also true for CNB. Boey, e. al. found that core biopsy was not able to distinguish between adenomatous hyperplasia and follicular neoplasm, when they evaluated 167 consecutive patients with both FNA and drill-needle biopsy.[48] In previous studies, Silverman, et. al. and Miller, et. al., have shown that large needle biopsies, similar to FNA, cannot separate benign from malignant non-papillary follicular lesions.[49, 50] Wang, et. al. demonstrated, when they examined 906 thyroid biopsies using 14-gauge Vim-Silverman needle, that similar to FNA, sparsely cellular specimens occurred with colloid goiters, and that there was difficulty in differentiating follicular neoplasms, especially hypercellular adenoma from follicular carcinoma, and lymphocytic thyroiditis from lymphoma.[37] Carpi, et. al. used large needle aspiration (16-18 gauge needles), rather than CNB, in 114 patients with palpable nodules.[51, 52] They found that lesions with pure microfollicular architecture, compared to mixed micro-macrofollicular lesions, were more likely to be neoplastic (33% vs. 6%) and more likely to be malignant (22% vs. 4%).[51, 52] Miller, et. al. indicated that the addition of large needle biopsy to FNA

provided diagnostic material in some cases diagnosed as “unsatisfactory” by FNA.[53] In addition, 50% of cases interpreted as cellular neoplasms by FNA were revised to a benign diagnosis by large needle biopsy.[53] Using specific cytologic criteria (nuclear enlargement and architectural disarray), Kini, et. al. reported a 75% FNA accuracy rate in diagnosing follicular carcinoma.[54] Most other studies, however, could not reproduce such accuracy. On histologic followup, FNA diagnosis of “follicular neoplasm” is associated with approximately 20% risk of malignancy and 70-80% risk of neoplasia.[55-57]

FNA vs. CNB in unsatisfactory specimens

Ultrasound has been shown to significantly improve sensitivity and specificity of thyroid FNA, as well as reduce the unsatisfactory rate, compared to freehand (non-US guided) FNA.[47] The literature reveals unsatisfactory/non-diagnostic freehand FNA rates ranging from 5 to 43%.[34, 58] “Unsatisfactory’ specimens may be associated with difficult to palpate lesions and lesions that are extremely vascular, cystic, or fibrotic.[47, 59-61] The adequacy of FNA is also highly dependent on the skill and experience of the operator. Several authors have advocated the use of US-guidance in association with FNA or CNB, in order to improve the diagnostic accuracy of thyroid sampling.[30, 31, 62] Baloch, et. al. evaluated the role of repeat FNA in “unsatisfactory” and “indeterminate for follicular neoplasm” cases from 50 patients with surgical followup.[63] Repeat FNA under US guidance retrieved diagnostic material in 80% of those cases. Repeat FNA, however, should be performed at least 3 months after initial FNA, to prevent post-FNA reparative atypia, which can be mistaken for malignancy.[63]

Harvey, et. al. compared the use of US-CNB (79 cases) to FNA (266 cases) with and without US-guidance.[34] They found CNB to produce an adequate specimen more often than FNA (87% vs. 60%), but was not any more accurate than US-guided FNA. CNB and FNA with image guidance had higher sensitivity than non image guided FNA alone (100% vs. 61%). The authors also appreciated that the major difficulty, in both FNA and CNB, was assessing cellular follicular lesions, as neither technique was able to definitively diagnose or exclude follicular carcinoma.[34] Mehrotra, et. al. compared 141 freehand FNA to 121 US-guided 20-gauge True cut needle biopsies.[58] Although US-CNB had a lower unsatisfactory rate (16%) compared to FNA (47%), 91% of patients had satisfactory repeat US-CNB following initial unsatisfactory freehand FNA, compared to 47% of patients who had repeat US-guided FNA. The authors found repeat CNB under US guidance to be a useful tool in repeat thyroid nodule sampling, even if the nodules were clinically palpable.[58] Karstrup, et. al. assessed US-guided FNA in combination with US-CNB in the evaluation of solitary or dominant thyroid nodules from 77 patients, using 21-gauge FNA and 18-gauge CNB (single action spring activated biopsy system).[64] When used alone, FNA and CNB had satisfactory rates of 97% and 88%, respectively, but showed a 100% satisfactory rate when used in combination. Diagnostic accuracy of both methods showed no significant difference. The authors concluded that CNB was justified in selected patients who had previous unsatisfactory FNA or discrepancy between FNA and clinical findings, but did not find it justifiable to routinely use CNB in the initial evaluation of thyroid nodules.[64] In a prospective study, Quinn, et. al. reported better results using US-guided spring activated one stage automated CNB(20-21 gauge), compared to FNA, in 102 patients.[65] Best results, however, were obtained with combined use of both techniques. Thyroid nodules ranged in size from

7mm to 62 mm, and all patients tolerated the CNB well. These 20-21 gauge spring action needles were found to be small enough for use on nodules in the 10-20 mm range, in contrast to the Tru-cut needles which were usually used for larger nodules.[65]

Without utilizing image guidance, Pisani, et. al. compared 136 freehand FNA to 32 CNB (20-21 gauge), and where 29 patients had both procedures done.[66] They found CNB to be associated with a much higher rate of unsatisfactory specimens (38%) compared to FNA (4%), and that CNB provided no advantage over FNA in diagnostic accuracy. In addition, not all patients tolerated the CNB procedure as well as FNA.[66] Silverman, et. al. compared FNA (309 patients) to large needle and CNB (23 patients), and found no significant differences in diagnostic accuracy.[49] The unsatisfactory rate for tissue biopsies was 15 % compared to 0% for FNA. Boey, et. al., in a prospective study of 167 patients, found FNA to be superior to high-speed drill CNB because of its higher diagnostic yield (93% vs. 52%).[48] Liu, et. al. simultaneously performed freehand FNA and Tru-cut CNB on 100 patients with palpable nodules.[67] Both specimen types were adequate in 95 % of cases, and showed similar sensitivity, specificity and diagnostic accuracy. The authors concluded that no one method was superior to the other, however, both techniques were complimentary.[67] Broughan, et. al. also attained higher diagnostic accuracy and lower false negative results when used FNA and 18-gauge Tru-cut CNB in combination.[68]

Complications of CNB

Complications such as tumor implantation along the biopsy track, hemorrhage, and recurrent laryngeal nerve injury have been described only in older literature, and were associated mainly with non-image guided large bore needles.[37, 38, 40, 69] Two such cases of needle tract implantation (seeding) are cited in the literature.[38] There are rare reports of needle tract seeding with FNA using 22-gauge needles or larger, but none with 23-gauge needles or smaller.[70] There has been a rare report of hemorrhage following large needle biopsy, requiring urgent neck exploration.[68] Limitations of CNB include the need for local anesthesia, local discomfort, and decreasing patient acceptance of repeat biopsies. Because of the above reasons, there has been declining interest in performing CNB.[49]

Conclusions:

1. FNA remains the best technique available, to date, for the initial evaluation of thyroid nodules. The slight increase in diagnostic accuracy obtained by CNB is outweighed by ease of use, cost effectiveness, and less patient discomfort associated with FNA.
2. US-guided CNB should not be seen as a competitor of FNA, but rather as a complementary investigational tool.
3. In the recent literature CNB of thyroid appears to be well tolerated and has low incidence of complications.
4. CNB under US guidance and utilizing modern needles may be advantageous in cases rendered “unsatisfactory” by FNA, but offers no additional diagnostic value in separating cellular hyperplastic nodule from follicular adenoma and follicular carcinoma. One potential disadvantage of CNB is that a larger needle has a greater chance for damage to surrounding structures and bleeding.

5. CNB, especially in small pathology practices and community hospital settings where cytopathology expertise may not be available, provides a tissue sample for histologic examination.

F. Advantages and disadvantages to various specialists performing FNA of palpable thyroid nodules

Review:

Thyroid FNA is performed primarily by endocrinologists, radiologists, surgeons and pathologists.[45, 71] The majority of these physicians have had variable amounts of formal training and clinical experience in the performance of thyroid FNA during residency, fellowship or postgraduate continuing medical education (CME). There is a virtual absence of thyroid FNA literature supporting residency and fellowship training resulting in procedural and clinical competency compared with published articles on an analogous activity: breast FNA.[72-74]

Subsequent postgraduate training, clinical activity and experience in thyroid FNA is also highly variable based on the individual physician's interest, institution or office type of practice, credentialing, accessibility, community awareness and referral patterns. Essentially no physician performing thyroid FNA in any setting or practice (with the exception of some radiologists) have had a comprehensive and systematic evaluation of competency including ultrasound imaging and utility in diagnostic or real time ultrasound selection of nodules for unguided thyroid FNA or ultrasound guided FNA, number of thyroid FNAs performed per year, proficiency in acquiring satisfactory cytologic specimens and slide preparation. CME programs in thyroid FNA are available, but the longitudinal validation and certification of thyroid FNA activity, proficiency, quality assurance and recertification in thyroid FNA are voluntary at this time and available only from subspecialty organizations.

A literature review of thyroid FNA does support two specific tenets:

1. Ultrasound guided thyroid FNA (UGFNA) significantly improves sensitivity and specificity and should be utilized for not only previously unsuccessful thyroid FNA procedures, but also in the initial performance of thyroid FNA in nodules which are non-palpable or difficult to palpate, are located posteriorly, have a large cystic or multiple cystic compartments or are located within a diffuse or multinodular goiter.[24, 75, 76]
2. On-site smear assessment improves specimen adequacy and an on-site diagnostic evaluation enhances service.[47, 77] Thus, begs the question: Who should perform thyroid FNA?

Conclusions:

1. Currently, the ideal physician to perform thyroid FNA in an institutional or office practice should be one who is experienced and has repeatedly demonstrated appropriate judgment in nodule selection, technical excellence, and proficiency in obtaining aspirate material and preparing slides.
2. For ultrasound guidance of FNA for either non-palpable or palpable nodules, this physician must have ultrasound imaging availability, ultrasound diagnostic skills and the capability to perform UGFNA.
3. Based on availability, it is preferable to have an on-site assessment of the aspirate specimens for adequacy, and if possible, a diagnostic evaluation.

G. Optimal preparation of FNA material for routine evaluation and ancillary studies, and the role of immediate assessment

Review:

Optimal Tissue Preparation of aspirated tissue from solid and cystic nodules

For aspirations performed by cytopathologists, pathologists, or clinicians *with* immediate access to the cytopathology laboratory the following is recommended:

Solid and semi-solid material:[78]

Air-dried and alcohol fixed smears should be prepared for Romanowsky (Diff Quik, Wright- Giemsa, Wright stains) and Papanicolaou staining, respectively. Direct smears can be processed alone or with a supplemental liquid based cytology (LBC) or cellblock prepared. Liquid based processing can be utilized alone or as a supplement to direct smears. Direct smears, however, are essential for immediate on-site interpretation and adequacy assessments.

Cyst fluid

One or two air-dried smears (immediate interpretation)

Cytospins or liquid based (SurePath, ThinPrep) preparations

Cellblock if cyst fluid clots or contains minute fragments of tissue[79, 80]

For aspirations performed by clinicians *without* immediate access to cytopathology laboratory, communication with the laboratory is essential. Clinicians skilled in smear preparation may perform smears for transport. Alternatively or in addition to smears, the aspirated material should be collected using a transport method that is appropriate for the cytopreparation to be used. The following is recommended for material collected from both solid and cystic lesions:

Collection of material in liquid preservative as directed; Examples

RPMI, balanced saline (cytospins)

Formalin (cellblock)

Liquid base collection vials (Surepath, ThinPrep)

While liquid based preparations have demonstrated utility in gynecologic (cervical) cytology such that they have virtually replaced conventional smears, the same has not yet been conclusively demonstrated in aspiration cytology. However if clinicians “off site” perform FNAs, such that transportation to a cytology or reference laboratory is required then collection of aspirated material in a liquid medium is reasonable. For clinicians and radiologists not trained in smear technique, rinsing the needle in a liquid (see above) is easy and allows the laboratory to handle the preparation and staining.[81-86]

The low cost, ease of preparation and interpretation of a good quality smear by an experienced FNA physician and pathologist is difficult to improve upon. As such, the optimal preparation for samples with easy access to the laboratory, as stated above, is direct smears. Direct smears are also essential for immediate assessment. Unfortunately, there is a wide range of expertise in both specimen collection and smear preparation. In addition, thyroid FNA has moved from aspiration of mostly large, easily palpable nodules without ultrasound guidance to smaller, non-palpable or difficult to palpate nodules requiring ultrasound guidance. Training in quality smear preparation has not followed the training in utilization of ultrasound guidance for most clinicians who perform thyroid FNA. As such, many laboratories use LBC for thyroid FNAs, either in addition to smears

or as the sole preparation method.[87-89] For institutions using LBC as the sole means of specimen preparation, pathologists' knowledge of the alterations in cellular appearance is essential for accurate interpretation.[83, 88, 90, 91]

Conflicting results have been obtained regarding the relative rate of unsatisfactory specimens. There are data that show no significant difference between the adequacy rates of LBC and smears;[85] higher adequacy rates with smears[81, 92] and higher adequacy rates with LBC.[87]

With regard to diagnostic accuracy of LBC, some studies have shown LBC to be similar to conventional smears.[85, 87, 90, 91, 93, 94] Other studies have shown a trend in favor of increased accuracy when smears are used rather than LBC,[81, 83, 85] but the differences were not statistically significant, and, in some, a split-sample study design was used: smears were prepared first and LBCs were made from the residue, placing the LBC at a disadvantage.[81, 83] Other comparative studies examined fewer than 100 cases and thus suffer from small sample size.[82, 92] The study by Werga,et.al[95] is one that demonstrates a high definitive diagnostic rate of 78% for papillary cancer using direct smears. This study from Scandinavia analyzes FNAs of palpable thyroid nodules without guidance by highly experienced physicians with great skill in procurement as well as smear technique. Such a skilled group needs to perform a study comparing direct smears with LBC. In addition, however, cytological interpretations must be by highly experienced pathologists in both smears and LBC , and the gold standard histopathology needs to be interpreted by the same pathologists using the same criteria for nodule classification. When all of these variables are controlled for, then the study will be one that can accurately address the superiority of one preparation technique over the other.

Optimal routine preparation of aspiration material for ancillary studies

Currently ancillary studies in thyroid FNA predominantly involve immunocytochemistry or flow cytometry. If the clinical suspicion or presentation suggests lymphoma or if an immediate assessment reveals a lymphoproliferative pattern that warrants further evaluation then material should be collected for flow cytometry. The most common collection fluids are RPMI or balanced saline solution. Material can be collected by needle rinses for residual material from each pass or, more preferable, by placing one to two dedicated passes directly into the transport fluid. The most reliable and reproducible immunocytochemistry results are obtained from cellblock sections made from one or more dedicated passes. Immunocytochemistry may be performed on unstained (and even destained) air-dried or alcohol fixed smears but appropriate controls and dilutions must be used to insure accuracy of the staining result. Cytospins and liquid based preparations may also be utilized but with the same caveat.[96]

The role of immediate assessment

Immediate assessment is controversial. Some laboratories employ it routinely for all thyroid FNAs as it may decrease complications and improve triage of tissue.[19, 78, 82, 97-100] Others have found that immediate assessment has little impact on patient care, and any benefits are outweighed by its costs and burden on the laboratory.[101-103]

Immediate evaluation of material will allow the opportunity to obtain more tissue if needed for diagnosis, have directed pass(es) for cellblocks and /or ancillary studies which may necessitate fresh, unfixed material(flow cytometry), sterile material for microbiology.

Most patients, and certainly physicians, are cognizant that the majority of immediate assessments by (cyto)pathologists are quite accurate. Thus, in the clinic setting physicians use this preliminary information to discuss further treatment options or follow up with their patients during that office visit.

Conclusions

1. Optimal Routine Preparation:
   For aspirations performed by cytopathologists, pathologists, or clinicians *with* immediate access to cytopathology laboratory
      Solid and semi-solid material
         Air-dried and alcohol fixed smears should be prepared for Romanowsky (Diff Quik, Wright- Geimsa, Wright stains) and Papanicolaou staining, respectively.
         Needle rinses and/or dedicated pass for LBC or cellblock preparation if needed.
      Cyst fluid
         One or two air-dried smears (immediate interpretation)
         Cytospins or liquid based (Surepath, ThinPrep) preparations
         Cellblock if cyst fluid clots or contains minute fragments of tissue
   For aspirations performed by clinicians *without* immediate access to cytopathology laboratory
      Smears may be performed
      Collection of material in liquid preservative as directed
         RPMI, balanced saline (cytospins)
         Formalin (cellblock)
         Liquid base collection vials (Surepath, ThinPrep)
2. Optimal Tissue Preparation for Ancillary Studies
      Flow Cytometry
         RPMI or balanced saline for flow cytometry or cytospins for immunocytochemistry
      Immunocytochemistry
         Formalin fixed cell button for cell block
3. Immediate Assessment is optimal.

H. Management of adverse reactions during and after the procedure, and the need for verbal or written post-procedural instructions.

Review:

Multiple literature sources reporting on vast clinical experience in thyroid FNA describe thyroid FNA as being very well tolerated as it is in other superficial sites. The incidence of complications increases with increasing needle size.[18, 104-106] For superficial fine needle aspiration minor complications similar to blood drawing occur and are typically restricted to local pain and slight ecchymosis.

Pain and ecchymosis at Biopsy Site

Local pain or bruising can be treated with an ice pack. Readily accessible ice packs that produce cold temperatures with crushing are commercially available. Tylenol is recommended.

Hematoma

Small asymptomatic hematomas are common and resolve without treatment. There are at least two case reports of significant hematoma post FNA.[107-109] The case of Noordzji is detailed and instructive. He found a large hematoma after needle biopsy with a 25 gauge needle in a patient without coagulopathy.[109] A hematoma developed two hours after the procedure and required operative drainage. It manifest with increasing pain, swelling, ecchymosis, and dyspnea. CT scanning identified a 7 cm hematoma with tracheal deviation. At surgery an active bleeding site on the thyroid capsule required ligation. For FNA of deep lesions, those using large bore needles (>23 gauge), and especially core needle biopsy post-procedure observation of at least 30 minutes is recommended. Direct pressure to the biopsy site after biopsy is also recommended for both unguided and guided biopsies. This can be accomplished by either the patient or an assistant if available.

Vasovagal Reactions

Vasovagal reactions can be quite scary, especially if the patient experiences seizure-like activity with uncontrolled flailing of arms and legs. The best approach for a vasovagal reaction of simple light-headedness and clammy hands, is to first reassure the patient that the feeling will pass. With seizure-like activity, insuring that the patient is secure on the table is the first priority. Recline the patient to the supine position if not already there and apply a cold compress to the forehead. Having a juice, a soda and/or crackers is also helpful. In most instances, the reaction lasts only 2-3 minutes, however, the patient may not feel "normal" for quite some time and should be counseled in that regard.

Infection

Infection is an uncommon complication of FNA even in patients with immunocompromise.[105] Nishihara has reported a case of S. Aureus infection in a cystic nodule in a patient with atopic dermatitis after FNA. Symptoms developed four days after fine needle aspiration.[110] Nishihara notes opportunistic thyroid infections are uncommon but typically occur in patients with preexisting thyroid abnormalities (especially cysts), patients with local (ex. atopic dermatitis) or general (ex. DM,TB,HIV) immunocompetence issues. Wu recommended alcohol for routine skin prep and iodine prep for “deep site” FNA.[105] The author feels if skin hygiene is poor, iodine skin prep is best.

Recurrent laryngeal nerve paralysis

A feared complication of any perithyroidal procedure is RLN paralysis which is manifest by paralytic dysphonia and dysphasia. While several large FNA series have failed to report on RLN paralysis, Tomoda’s work is an impressive review of over 10,000 FNA’s with 23 gauge needle with documentation of four patients with vocal cord paralysis, a rate of .036%.[106, 111] Tomoda found voice change typically occurred one to two days after FNA procedure, and that all cases were transient with average resolution in four months.[111] Hulin notes in a case report of a patient with FNA induced RLN paralysis increased fibrosis around the RLN at surgery with increased difficulty of surgical dissection.[107] It is this author's experience that if cystic fluid in a thyroid lesion, through either FNA or trauma, leaks out of the thyroid cyst into surrounding structures, subsequent dissection can be very challenging. All clinicians involved in pre-op thyroid FNA need to be aware that increased surgical difficulty may result from aggressive or excessive FNA biopsies.

Tumor seeding

Given the frequency with which thyroid FNA is performed, it appears this complication is exceedingly rare though not zero.[70, 112] Strict adherence to standard FNA procedure including release of suction with needle removal, and use of an appropriate small gauge needle, must be

assumed. Wu, in a review of FNA of multiple sites including thyroid, notes that worldwide literature review as of 2004 has revealed a total of 12 cases of tumor seeding referable to FNA.[105] Wu found increased risk with larger gauge needle (19-21 gauge), and virtually no risk with 23 gauge or smaller. The majority of reported cases regarded lung and prostate biopsy.[105]

Post procedure guidelines

An empiric 30 minute observation period post procedure to observe for progressive swelling and ecchymosis has been advocated.[105] It is of note that the rare clinical reports of hematoma generally document onset of symptoms several hours after the procedure. Local pain or bruising can be treated with an ice pack. Readily accessible ice packs that produce cold temperatures with crushing are commercially available. Tylenol pain reliever is also recommended. Restrictions on activity are generally not necessary. Instructions to seek medical attention should sudden rapid swelling or unrelenting pain is recommended. An information sheet reviewing the expected minor discomfort, ecchymosis, important signs to watch for and an emergency contact number should be given to all patients.

Conclusions

1. Cold packs and Tylenol are recommended for pain at the biopsy site.
2. Apply direct pressure to the biopsy site to reduce the potential for bruising and hematoma.
3. Alcohol cleansing of the skin is adequate for simple, palpable biopsy. Unclean skin, or biopsies of deep sites warrants iodine skin prep to reduce the risk of infection.
4. Reduce excessive number of biopsies and aggressive biopsy technique of cystic thyroid nodule to reduce the risk of cyst fluid leakage into the neck.
5. Utilize a 23 gauge needle or smaller to reduce the risk of tumor track seeding.
6. Written post-procedural guidelines with an emergency number is recommended.

I. Optimal number of passes for a solid and cystic lesion

Review

The number of passes can vary considerably. The number of passes relates to how many passes are necessary to obtain an adequate specimen. A variety of factors can influence adequacy rates **(Table 1**).

Table 1. Factors that can affect adequacy rates

1. Operator's skill
2. Nature of the nodule (size, location, cystic, fibrotic, etc)
3. Gauge of the needle
4. Whether the needle is aspirated or only capillary suction is used
5. The number of passes
6. Other technical factors
7. The criteria for adequacy
8. The patient's tolerance of the procedure

Unfortunately, in general, the factors that are easiest to adjust (i.e. gauge of the needle) have less impact on adequacy than factors that are much more difficult to adjust (i.e. whether the nodule is cystic.[5, 32, 34, 113-119]

Adequacy is discussed further elsewhere (Agenda Item 10). However, in brief, the goal of an adequate specimen is to ensure that the sensitivity of the aspirate is sufficiently high to allow clinical follow-up of negative aspirates without the need for additional tissue sampling. Because some if not many of these lesions progress slowly, clinical follow-up may be problematic as a gold standard unless it is obtained over very long time periods. Histologic follow-up is problematic since many lesions with a negative FNA will not be resected. Core needle biopsy performed at the same time as aspiration may be one way of overcoming this problem.[42, 67, 120] In addition, the histologic gold standard has changed over time, as more lesions are now being classified as follicular variants of papillary carcinoma, and the reproducibility of this diagnosis on histologic material is poor.[121, 122] Most studies report sensitivity for malignancy between 90 and 100%. Studies that have reported sensitivity of 80% or lower have suggested that negative aspirates need to be repeated or steps performed to increase the sensitivity, suggesting that sensitivities in this range are not sufficient for patient care.[123, 124] It has been noted that the false negative samples are more likely to be scant and suboptimal, from lesions that are known to be difficult to obtain a representative sample, such as cystic papillary carcinoma, or from lesions with overlapping cytologic features such as the follicular variant of papillary carcinoma.[22, 113-119, 124-126] On the other hand, in some settings with very high sensitivity, it has been noted that extremely scant samples (with as few as 10 cells) may also be deemed adequate without lowering the sensitivity if they lack Hurthle cell change or any atypia.[127] While increasing the number of passes may affect the sensitivity if scant specimens are the problem, the impact of the number of passes on lesions with overlapping cytologic features is not as clear.

The effect of the number of passes on adequacy rates and sensitivity for malignancy using histologic follow-up are shown in **Table 2** below.

Table 2. Performance characteristics for unselected Thyroid FNA series and # of passes

Reference	# cases	# cases with histologic fu	Sensitivity (%)*	Adequacy (%)$	# passes
Suen[128]	331	79	94	96	1 or more
Hamaker[129]	116	41	95	86	2-3
Boey[120]	384	384	96	84	3-4
Anderson[130]	562	373	94	79	1
Hawkins[106]	1399	415	86	98	At least 2
Goellner[131]	6300	382	98	80	1-4
Hamburger[132]	1380	258	100	75%	2-8
Hamburger[126]	888	159	100	75	At least 6
Caraway[133]	394	150	94	82	3-5
Gharib[104]	10,971	984	94	79	Usually 2 up to 6
Hanbidge[5]	123	0	NA	87	4
Baloch[125]	662	140	98	89	Average of 2
Liu[67]	100	100	100	99	2
Poller[134]	156	75	100	76	3 or more
Ravetto[135]	37895	4069	92	98	Usually 2
Baloch[97]	313	77	100	95	2 or more
O'Malley[102]	121	11	NA	78	2-12, mean 4-7
Baloch[63]	3007	101	NA	92%	2-4
Eedes[101]	311	0	NA	86	2-6
Harvey[34]	266	22	68	60	1-3
Redman[32]	693	0	NA	96	1-11, mean 3.2-5.4

* sensitivity for malignancy, atypical and above as the diagnostic threshold, histologic fu cases only
$ includes both nondiagnostic and nonspecific, and cases
b core biopsy fu

The median sensitivity is 96% (range 68-100%) and the median adequacy rate is 86% (range 60-99%).
Using the data in Table 2, one can demonstrate neither the sensitivity nor the adequacy is strongly correlated with the maximum number of passes reported (correlation = -.5 and .2, respectively). Indeed, sensitivity is also not strongly correlated with adequacy rates (.37). This suggests that other factors listed in Table 1, or problems with determining sensitivity listed in paragraph 2 have larger impacts on both sensitivity and adequacy rates than the number of passes. Importantly, when changes have been made to have

more stringent adequacy rates within a single study, where these factors are more controlled for, the sensitivity has always increased.[124, 132]

Similarly, in every single study in which different numbers of passes has been compared (and presumably, the other factors listed in Table 1 are controlled for) the more passes performed (up to 12) the higher the adequacy rate, see Table 3.[32, 101, 132]
Table 3 Adequacy Rate in relation to # of passes

# of passes

Reference	1	2	3	4	5	6	7	11
[132]	36	65	77	87	95	98	100	
[32]	5	29	52	69	82	94	97	100
[101]		37	90	98	99	99		

There is not enough data reported to assess the role of the number of passes on sensitivity within individual studies. From discussions at the October meeting, it was felt that the small incremental increase in adequacy reported beyond 5 passes did not out-weight the potential increased morbidity and trauma associated with additional passes, and, as such, the consensus among all specialists in attendance was to stop at 5 passes.

The literature shows that it is more difficult to obtain an adequate sample from a cystic lesion.[5, 32, 34, 113-119] However, there is no information suggesting that increased number of passes in a cystic lesion is more effective at increasing the adequacy than increasing the number of passes for solid lesions.

Conclusions:

1. It is not possible to define a specific number of passes that should be used in every setting.
2. If immediate adequacy assessment is not available, between 2 and 5 passes are a reasonable number of passes to perform to try and ensure an adequate sample.
3. There is no justification to recommend a different number of passes for a cystic lesion, unless the criteria for adequacy are different.
4. A reasonable guideline is as follows:
    a. FNAs with rapid interpretation available: 2 biopsies from different areas of the lesion with a representative slide stained for adequacy. No more tissue is needed if 1. a cyst is completely drained and no residual mass is identified, 2.a specific malignancy is identified (and no ancillary tests are deemed necessary), or 3. if the aspirate appears adequate. Additional biopsies are recommended if 1. there is a residual mass after draining a cyst, 2. cellularity is inadequate or, 3. to enrich a sample for cellblock, flow cytometry or electron microscopy.
    b. FNAs without a rapid interpretation available: 2-5 biopsies from different sites with representative tissue from each pass smeared on a slide (or 2) and the remaining rinsed into a collection tube with transport fluid without fixative (unless delay in immediate processing is expected).

J. Adequate FNA samples from a solid lesion and cystic lesion

Review:

Given that the purpose of thyroid FNA is to provide clinically useful information regarding the need for surgery, the FNA sample must be adequate enough for interpretation that yields a low false negative rate. Patients whose tumors are not detected by FNA experience delayed treatment, and once excised, have a higher rate of vascular and capsular invasion, and are two-fold more likely to have persistent disease at follow-up.[136] To avoid unnecessary surgery, the FNA sample must be adequately representative of the lesion. A thyroid FNA that is persistently inadequate will result in surgery.[19, 137]

Adequacy defines the quality and quantity of a sample, a definition that varies not only with respect to the site sampled, but also with respect to the type of lesion sampled. As noted by the Papanicolaou Society of Cytopathology (PSC) Guidelines for the Examination of FNAs from thyroid specimens, the cellularity of a specimen is influenced by the intrinsic nature of the lesion.[138] Although FNA can be quite diagnostic of papillary, medullary and anaplastic carcinoma, large cell lymphoma, colloid nodule, and Hashimoto's thyroiditis, in the context of a follicular nodule, FNA is a screening triage tool used to distinguish between those nodules that require surgery and those that do not. It is in this context that the definition of adequacy in thyroid FNA is controversial.

The quality aspect of thyroid FNA is not controversial. An FNA specimen must be of good quality and "technically" adequate for interpretation. The FNA sample must be well-preserved and well-prepared with tissue that is adequately stained and readily interpretable.

The quantity aspect of adequacy in thyroid FNA is quite a controversial issue, one that is non-standardized and inconsistently used by pathologists between and within institutions. One reason the controversy and inconsistency exists is due to the application of a single definition of adequacy to all types of thyroid specimens, both solid and cystic, and outside of the clinical context of the lesion. As such, adequacy will be discussed in the clinical context of the specimen type.

Solid Nodules

…..with cytological atypia

As is true with all cytology specimens, the identification of any cytological atypia warrants an interpretation, even if descriptive. Such a specimen should never be interpreted as "unsatisfactory", rather as "Satisfactory but limited by scant cellularity" with a description of the atypia. In a study by Renshaw, all 16 of 80 unsatisfactory thyroid aspirates with malignant histological follow-up demonstrated cytological atypia suggestive of papillary carcinoma on review.[127] Those aspirates with sufficient cellular quality and quantity to be diagnostic of a particular malignancy will be interpreted as positive. The experience and expertise of the cytopathologist will affect the "quantity" issue in this case.

…..with inflammation

Accuracy in the diagnosis of thyroiditis generally relies on the presence of both an inflammatory infiltrate accompanied by thyroid follicle cells.[139] No set number of

follicle cells has been established for adequacy in this setting, however. Although a general rule of adequacy can be imposed on all types of thyroid specimens, given the well recognized variability in the histological counterpart to thyroiditis of all types and the often paucicellular follicle component of most, a strict rule for a certain number of follicle cells on FNA may result in a high number of unnecessary thyroid resections. Some cases of Hashimoto's thyroiditis may produce only an exuberant population of lymphocytes and no follicle cells. Should such a case be deemed inadequate and unsatisfactory? Or is a reasonable approach one that highlights that "Evaluation limited by absent follicular component" with a recommendation for clinical correlation and potentially repeat aspirate for flow cytometry analysis to rule out lymphoma? Is not the presence of an inflammatory infiltrate with multinucleated giant cells and fibrous tissue fragments sufficient to support the clinical impression of subacute thyroiditis? Are any follicle cells really necessary? Not according to the study by Shabb.[140]

…..with abundant colloid

The presence of abundant thick or watery colloid that covers a significant portion of the surface of a slide and is readily identified as colloid (and not serum or protein) is a reliable sign of benignity and not a feature reported to be associated with malignancy.[138, 141, 142] Aspiration of colloid nodules will produce variable amounts of follicle cells, frequently quite few. The recognition of abundant colloid should override the requirement of a set number of follicular cells as the false negative rate of such an aspirate approaches zero. As such, cytological interpretation should be reported as "negative or benign " and "consistent with a colloid nodule" , not "unsatisfactory" or "nondiagnostic".[143]

… .follicular proliferation with less than abundant colloid

The number of follicle cells that will allow for an accurate classification of a solid thyroid nodule is variable and non-standardized. Some advocate for not counting cells at all.[144] Goellner's early seminal studies on thyroid FNA used an adequacy criteria of 5-6 groups with at least 10 well-preserved follicle cells, even in aspirates with abundant colloid.[32, 131, 145] With these criteria, the false negative rate at his institution was <1%. His unsatisfactory rate, however, was 20%. Kini required the presence of at least six to eight clusters of thyroid follicle cells on every two smears with a total of six smears prepared from six different sites of every thyroid nodule. These strict criteria also led to a high unsatisfactory rate of 20%.[139] Nguyen required the presence of 10 large clusters of follicle cells with at least 20 cells each when counted from all available smears.[146] In his study of 1631 thyroid aspirates, the false negative rate was 9%. Do 5-10 groups of follicle cells with a flat honeycombed pattern exclude the possibility of follicular carcinoma? The study by Deshpande would say not entirely.[141] This pattern predominated in almost 18% (5/18) of the follicular carcinomas in his study. From the majority of these studies in which adequacy is clearly defined and the false negative rate determined, it seems that the minimum criteria for adequacy is 5-6 follicle groups each with at least 10 cells, but each case must be evaluated in the context of the clinical and radiological information available.

Thyroid cysts

Thyroid cysts are most commonly a result of cystic degeneration of an adenomatous nodule. The risk of malignancy in a thyroid cyst is low, 1- 4% in simple, non-complex cysts aspirates.[21, 24, 38, 147] The risk rises to 14% in mixed solid and

cystic nodules, large cysts (>3cm) and recurring cysts.[143] Of aspirated cysts, only about 1% of cysts are malignant.[38, 146] Given the extremely low potential of a false negative rate in such aspirates, to classify all thyroid cysts with few to no follicle cells “unsatisfactory” (an interpretation indicating that no information at all is available from the aspirate) as some suggest[104] does not seem to be in the best interest of patient care.[131, 148] An interpretation of "cyst fluid only" is more informative indicating that a cyst was aspirated albeit nonspecific to etiology. The clinical-radiological correlation that would lead to further evaluation of a nodule with few to no follicular cells can be done by the clinician. Classifying these cases as “limited” due to the absence or scantiness of a follicular component is a reasonable approach that will not force the clinician to resample a clinically benign cystic lesion.[102, 138, 143, 144]

Conclusions:

1. All thyroid FNAs must be technically adequate with well-preserved and well-prepared tissue for interpretation.
2. Any cytological atypia precludes the interpretation of inadequate and, although adequacy can be deemed “limited”, an interpretation of the atypia must be rendered.
3. An interpretation of an inflammatory process such as thyroiditis does not require a minimum number of follicle cells.
4. An interpretation of a colloid nodule in which there is abundant, thick colloid present on the slide(s) does not require a minimum number of follicle cells.
5. In solid nodules producing a follicular cell population with less than abundant colloid, a minimum number of 5-6 groups with a least 10 cells, preferably on a single slide, is recommended.
6. Thyroid cysts with little to no follicular cells should be interpreted as "cyst fluid only" under the heading "non-diagnostic" and not unsatisfactory". An optional recommendation for correlation with the cyst size and complexity and a disclaimer that a cystic carcinoma cannot be entirely excluded may be added.

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Committee IV: Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions.

Following includes the proceedings of the National Cancer Institute Thyroid (NCI) FNA Committee IV. The task of this committee was to explore, discuss and put forth a suggested scheme for thyroid FNA diagnostic terminology and cytomorphologic criteria that can be helpful in the diagnosis of various thyroid lesions. As one of the committee member stated "*that this document has all the virtues and flaws of a committee document*", however, it is an endeavor and outcome of many back and forth communications between committee members and "passionate" comments posted on the NCI website and vocalized at the NCI Thyroid FNA State of the Art Conference in Bethesda, Maryland.

A. Diagnostic terminology/classification scheme for thyroid fine-needle aspiration (FNA) interpretation.

Fine-needle aspiration has proven to be an effective management tool in patients with thyroid nodules.[1-28] Its main purpose is to provide a rational approach to management and determine the correct surgical procedure when surgery is required. At present no standard exists for reporting of thyroid FNA specimens. [22, 29, 30] Several classification schemes have been suggested by various authors based on personal/institutional experiences and clinical organizations including Papanicolaou Society, American Thyroid Association and American Association of Clinical Endocrinologist. [22, 31, 32] (Table 1) In a recent survey of pathologist and clinicians on the perceptions of diagnostic terminology and cytopathology reporting of thyroid FNA showed a discord between pathologists and clinicians.[1]

Table 1: Thyroid FNA Classification Schemes

Papanicolaou Society of Cytopathology Task Force on Standards of Practice– 1997[2]	**1. Inadequate / Unsatisfactory** **2. Benign** **3. Atypical Cells Present** **4. Suspicious for Malignancy** **5. Malignant**
Diagnostic Terminology Scheme Proposed by American Thyroid Association (2006)[3]	**1.Inadequate** **2. Malignant** **3. Indeterminate** ■ **Suspect for neoplasia** ■ **Suspect for carcinoma** **4.Benign**
Diagnostic Terminology Scheme Proposed by American Association of Clinical Endocrinologists & Associazione Medici Endocrinologi - 2006[4]	**1. Benign** **2. Malignant or Suspicious** **3. Follicular neoplasia** **4. Non-diagnostic or Ultrasound suspicious**

Many studies favor a tiered system for classifying thyroid FNA; this ranges from 3-6 (or more) diagnostic category schemes. The most favored one is a six category diagnostic scheme consisting of benign, lesion (atypia) of undetermined significance, follicular neoplasm, suspicious, malignant, and unsatisfactory. [1, 5-7] With regard to the reporting of "risk of malignancy" for each diagnostic category this is generally considered to be optional.

Conclusions: There is general support for the utilization of a tiered classification system. The reporting of malignancy risk is considered optional or can be communicated verbally.

Potential Tiered Classification Scheme (as summarized in Table 2):

1. **Benign**
    a. Low risk of malignancy.
    b. This category includes but not limited to following terms:
        i. Nodular goiter
        ii. Chronic lymphocytic thyroiditis
        iii. Hyperplastic / adenomatoid nodule in goiter
    c. Patients with a benign nodule are followed by clinical and periodic radiologic examination and some patients may undergo repeat FNA due to increase in the size of nodule.
2. **Follicular Lesion / Atypia of Undetermined Significance**
    a. This is a heterogeneous category that includes cases that cannot be classified as either Benign or Follicular Neoplasm.
    b. The findings are not convincingly benign, yet the degree of cellular or architectural atypia is not sufficient for an interpretation of "Follicular Neoplasm" or "Suspicious for Malignancy".
    c. Some of these cases are placed in this category because of a compromised specimen (e.g. low cellularity, poor fixation, obscuring blood).The spectrum of cases that deserve this categorization will be illustrated in the on-line atlas which will be accessible through the website ***thyroidfna.cancer.gov and www.papsociety.org***
    d. Risk of malignancy 5 - 10%.
    e. This group can benefit from repeat FNA and correlation with clinical and radiologic findings.
    f. This is an optional category. The authors encourage minimizing its use.
3. **Follicular-Neoplasm / Suspicious for Follicular Neoplasm**
    a. Low to intermediate risk of malignancy 20-30%.
    b. This category applies to ***non-papillary*** follicular patterned lesions/neoplasms and Hurthle cell lesions / neoplasms.
    c. A majority of studies have shown that up to 20% of the thyroid lesions classified as such are found to be malignant on surgical excision (the predictive value / relative risk of this diagnosis can be included in the report. This percentage may be higher in Hurthle cell lesions if the nodule is equal to or larger than 3.5 cm in greatest dimension.
    d. Other diagnostic terms for this category are:

i. Micro-follicular proliferation / lesion
ii. Suggestive of neoplasm
iii. Follicular lesion

e. Most patients with this diagnosis undergo lobectomy/hemithyroidectomy and a definite diagnosis (adenomatoid nodule vs. adenoma vs. carcinoma) is rendered on surgical pathology examination.
f. The alternative term "Suspicious for Follicular Neoplasm" is acceptable. Some laboratories prefer it for its clarity and for risk-management reasons: approximately 25% of these nodules will turn out not to be neoplasms.

4. Suspicious for Malignancy

a. This term can be used as:
i. Suspicious for papillary carcinoma (a majority of cases in this group (50-75%) are found to be follicular variant of papillary carcinoma).
ii. Suspicious for medullary carcinoma (applies to cases in which there is limited specimen to perform confirmatory immunostains for calcitonin. The cytology report should include a note to assay serum calcitonin levels to confirm cytologic impression).
iii. Suspicious for other malignancies
1. Suspicious for lymphoma (may include recommendation to repeat FNA with flow cytometry).
2. Suspicious for metastatic / secondary tumor of thyroid.
iv. Suspicious for neoplasm because of total necrosis of lesional cells (eg. anaplastic carcinoma).

5. Malignant

6. Nondiagnostic.

a. Specimen processed and examined, but non-diagnostic due to:
i. Limited cellularity
ii. No follicular cells
iii. Poor fixation and preservation

b. A repeat FNA can be recommended.

Table 2: Potential Tiered Classification Scheme

Suggested Categories	Alternate Category (s) terms*	Risk of Malignancy**
Benign		<1%
Follicular lesion of undetermined significance	Atypia of undetermined significance R/O Neoplasm Atypical follicular lesion Cellular Follicular Lesion	5-10%
Neoplasm	Suspicious for Neoplasm	20-30%
Suspicious for Malignancy		50-75%
Malignant		100%
Non-diagnostic	Unsatisfactory	

***These terms can be used instead of the suggested category terms (based on website responses and NCI meeting attendees); ** Data collected from literature[29, 32-41]**

B. Diagnostic terminology for benign / non-neoplastic conditions

The diagnostic terminology for the benign thyroid lesions used in the literature includes nodular goiter; chronic lymphocytic thyroiditis; hyperplastic /adenomatoid nodule and colloid nodule ***(The term "colloid nodule"*** *though not favored* ***can be used in cases that show abundant colloid, however, the specimen should fulfill criteria of cellular adequacy for thyroid FNA interpretation. If a nodule has been aspirated repeatedly and the repeat FNA contains mostly colloid and few follicular cells, then the term can be used "suggestive of colloid nodule").***[8-12] **See also Agenda Item F and committee III document.**

Conclusions:

- **The term "Benign" may also apply to neoplastic lesions (adenoma). Other terms instead of "Benign" that can be used:**
  - **Negative for malignancy**
  - **Non-neoplastic**
- **Based on formal discussions the majority of respondents in a group of pathologists and clinicians prefer the term "Benign" .**

C. Diagnostic terminology for benign lesions

See Agenda Item A

D. Diagnostic terminology for potentially malignant / suspicious lesions

See also Agenda Items A (diagnostic categories 4) and E

This category deserves a separate diagnostic term such as suspicious for malignancy.[13-29] The term suspicious for papillary carcinoma can also be placed in this category. The use of intra-operative consultation has been suggested in these cases because if a definite diagnosis can be rendered in the operative setting (e.g., frozen section and intraoperative cytology), the surgeon can perform the definitive procedure in one stage, however, this is still debatable.[30-35]

Conclusions:

- The term "suspicious" is favored for potentially malignant lesions.

E. Diagnostic terminology for neoplastic / malignant lesions.

The terms that have been suggested to diagnose neoplastic lesions in instances when one is not able to differentiate between benign and malignant (i.e. cellular adenomatoid nodule, follicular adenoma and follicular carcinoma) include: follicular lesion, follicular proliferation, follicular neoplasm (follicular and Hürthle), as well as "rule out, suspicious of, suggestive of and cannot exclude" follicular lesion/neoplasm.[7, 13-29, 36-53] As noted this diagnosis is most often used in cases of follicular patterned lesions of the thyroid which include cellular adenomatoid nodule, follicular adenoma and carcinoma, and follicular variant of papillary thyroid carcinoma. The cytological examination cannot differentiate between benign and malignant follicular lesions, since that distinction is dependent upon documentation of capsular and/or vascular invasion.[54]

Likewise, the dependency upon cytologic atypia in follicular and Hürthle cells for the distinction between a benign and malignant lesion has not proven to be a reliable criterion.[12, 27, 55] A number of benign conditions such as thyroiditis, post treatment effects and adenomatoid nodules can show marked cellular atypia.[56-59] Any diagnostic term that indicates "follicular neoplasm" should only be used when a surgical excision is recommended to differentiate between an adenoma and carcinoma (based on invasive characteristics). Some clinicians believe that these cases should be re-aspirated for definitive diagnosis,[60-66] while others believe that repeat FNA is only helpful in non-diagnostic and atypical cases due to limited cellularity and poor cellular preservation.[61] Repeat FNA carries its own risk of reparative atypia of follicular cells being mistaken for a neoplastic / malignant lesion. It is recommended that repeat FNA should be performed mainly in cases diagnosed as "follicular lesion of undetermined significance" after 3-months of first FNA to avoid atypical reparative changes.[67] See also Committee I document.

The malignant thyroid lesions *that* can be classified on cytology include: papillary carcinoma and its various variants, medullary carcinoma, anaplastic carcinoma, lymphoma, poorly differentiated carcinoma and metastases.[11, 68]

Conclusions

- Follicular patterned lesions may be divided into two categories:
    - Follicular lesion or atypical cells of undetermined significance: Potential candidate for repeat FNA (Also see Committee I document)
    - Follicular neoplasm or suspicious for follicular neoplasm: Potential surgical candidate
- Potential terminology for follicular-patterned neoplasms:
    - The most commonly used terminology is follicular neoplasm or lesion.
    - The term cellular follicular lesion may be used.
    - Further attempting sub-classification are the terms follicular lesion, favor hyperplasia, follicular lesion, hyperplasia vs. neoplasm and follicular lesion, favor neoplasm.
- For the diagnosis of malignant lesions the diagnostic criteria are well described and illustrated in the literature. Papillary carcinoma diagnosis is based on nuclear features and architecture (to define variants) and diagnosis of medullary carcinoma is based on cytomorphology and immunostains for calcitonin and thyroglobulin.

F. Morphologic criteria for benign & non-neoplastic conditions

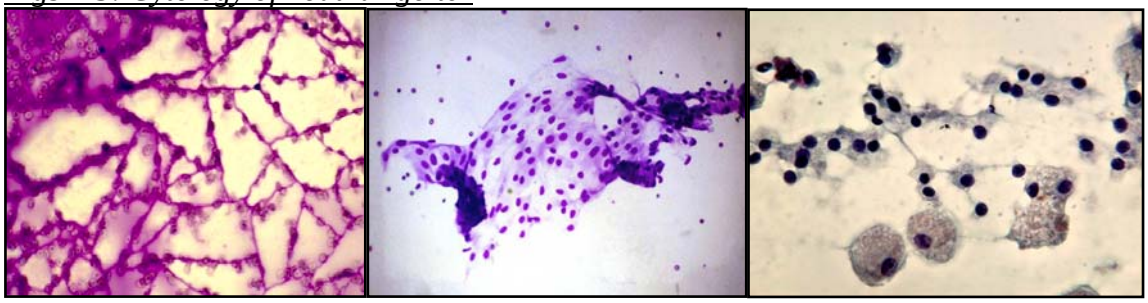
The following morphologic criteria have been described in the literature.

Nodular Goiter

The term goiter encompasses both nodular and diffuse enlargement of the thyroid, and can be applied to benign and hyperplastic processes or a process of unknown etiology. Clinically this disease of the thyroid can be divided into toxic and

non-toxic variants depending upon the clinical symptoms and thyroid function tests (hypothyroid, euthyroid, or hyperthyroid).[12, 69]
The cytology specimen from a goiter (depending upon the preparation method) is characterized by:

Figs 1-3: Cytology of nodular goiter

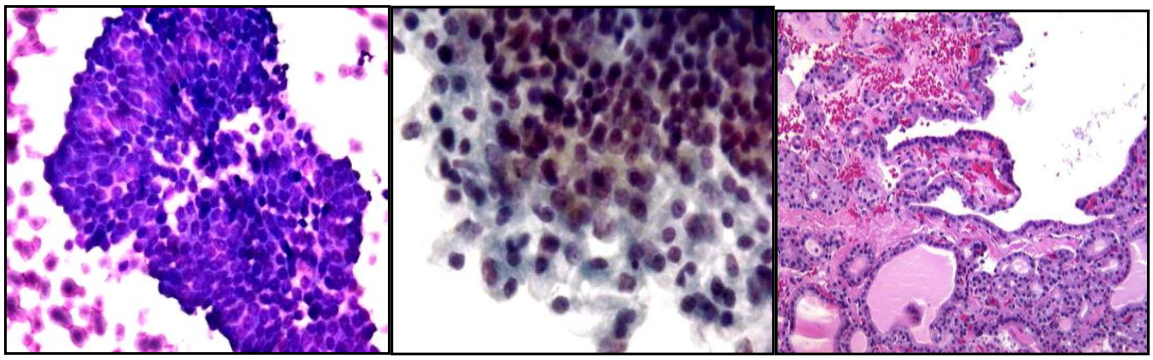


- **Abundant watery colloid (usually appears bluish-pink magenta in color and shows a "chicken wire" artifact due to air-drying in smears stained with Romanowsky stain).**
- **Follicular cells appear small, round to oval in shape with dark nuclei and are arranged in monolayer sheets, groups with follicle formation or as single cells.[11, 70] The cytoplasm is usually scant in follicular cells and can show numerous, small blue-black granules.[70] In the cytology literature these granules are termed as "paravacuolar granules"; electron microscopic and histochemical studies have shown these to be lysosomes containing hemosiderin and lipofuscin pigments. Though, common in nodular goiter these granules can also be observed in malignant lesions of thyroid.**
- **In some cases of nodular goiter, especially the ones with cystic changes, the follicular cell groups may assume a spindled shape and appear similar to cells growing in "tissue culture"**
- **Macrophages, usually filled with hemosiderin granules are also noted; however, their number depends upon the presence or absence of degenerative changes or a cystic component.[70, 71]**

The aspirates of hyperplastic/adenomatoid nodules will show:

- **Cellular specimen as compared to that of goiterous nodules with cystic change. Due to their cellularity these aspirates can be mistaken for a follicular neoplasm.**
- **Admixture of follicular cells and Hurthle cells arranged in monolayer sheets in a background of watery colloid and macrophages. Nuclear overlapping and crowding is a rare finding in these specimens.[70-72]**

Figs 4-6: Cytology and Histology of Hypeperplastic / Adenomatoid Nodule



Diffuse Toxic Goiter (Graves' Disease)

Graves' disease (GD) is an autoimmune thyroid disorder characterized by hyperthyroidism; diffuse thyroid enlargement, exophthalmos and less commonly pretibial myxedema. The patient's serum contains autoantibodies, which stimulate the thyrotropin receptor and have been termed as thyroid-stimulating immunoglobulins (TSI).[12, 69, 73]

The patients with GD usually do not undergo FNA because diffuse enlargement of thyroid seen in GD is not an indication for FNA. Only GD patients with solitary nodules, which are cold on radioiodine scan, are selected for FNA.

- **The aspirates of GD are usually cellular and show similar features to hyperplastic goiter. One may also observe lymphocytes and oncocytic cells.**
- **Enlarged follicular cells arranged in loosely cohesive groups with prominent nucleoli and ample eosinophilic cytoplasm.**
- **Occasionally the cells may display focal nuclear chromatin clearing and rare intranuclear grooves; however, other diagnostic nuclear features of papillary carcinoma are absent.[74-77]**

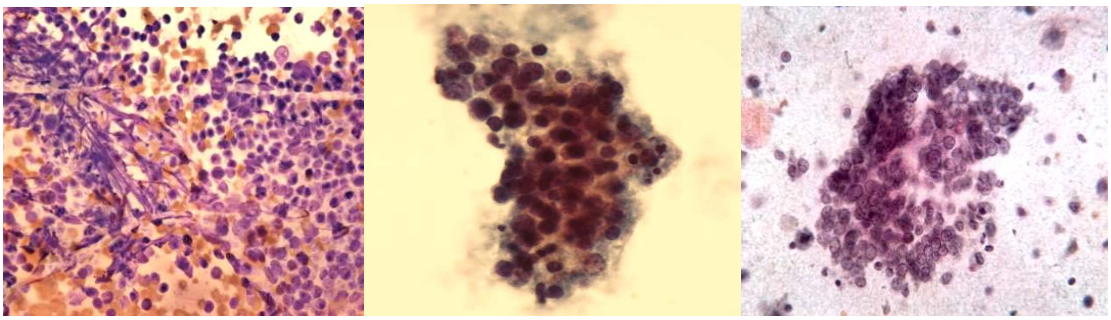
Autoimmune Thyroiditis

Hashimoto first described this condition in 1912. It is characterized by follicular atrophy with Hurthle cell metaplasia and diffuse lymphocytic infiltration. It is more common in women; with a female to male ratio of approximately 10:1. The patients usually have circulating antibodies to the thyroglobulin, thyroid peroxidase (microsomal antigen), colloid antigen and thyroid hormones. In addition, there is increased prevalence of HLA-DR5 and a strong family history of autoimmune disorders, especially Graves' disease.[69]

The FNA is usually performed in patients with chronic lymphocytic thyroiditis who present with distinct nodules that are cold on thyroid scan. [78-80]

The specimens from such cases usually show:

Figs 7-9: Cytology of chronic lymphocytic thyroiditis



- **Scant colloid, Hürthle cells, follicular cells, lymphocytes and few plasma cells.**
- **The lymphocytes are usually seen in the background, percolating between cell groups and in some cases one may see an intact lymphoid follicle.**
- **The Hürthle cells may display nuclear atypia and similarly follicular cells may show some chromatin clearing and nuclear grooves; however, they maintain round shape and demonstrate prominent nucleoli. Hence, one should refrain from interpreting these changes as malignant.[39, 78, 80]**
- **Papillary carcinoma arising in the background of thyroiditis is seen as a separate population, devoid of lymphocytic infiltrate and with appropriate nuclear features.[12, 81]In some specimens of lymphocytic thyroiditis there may be a preponderance of Hurthle cells, leading to a diagnosis of Hurthle cell neoplasm. This diagnosis should only be entertained in cases that display a separate monotonous population of Hürthle cells devoid of lymphocytic infiltrate.**
- **An extensive lymphocytic infiltrate can appear monotonous and mistaken for malignant lymphoma arising in lymphocytic thyroiditis.[57-59, 82] If lymphoma is suspected it is advisable that an aliquot of specimen be submitted for flow cytometry to confirm the morphologic suspicion. (See also accompanying document by Clark et al)**

G. Morphologic criteria for potentially neoplastic lesions

See Agenda Items F and H.

H. Morphologic criteria for neoplastic lesions.

1. Follicular-Patterned Neoplasms

<u>Cytology of Follicular-Patterned Neoplasms:</u>

Fine-needle aspiration (FNA) cannot distinguish between benign and malignant non-papillary follicular and Hurthle cell lesions. Both benign and malignant lesions appear similar in cytologic specimens. [83]

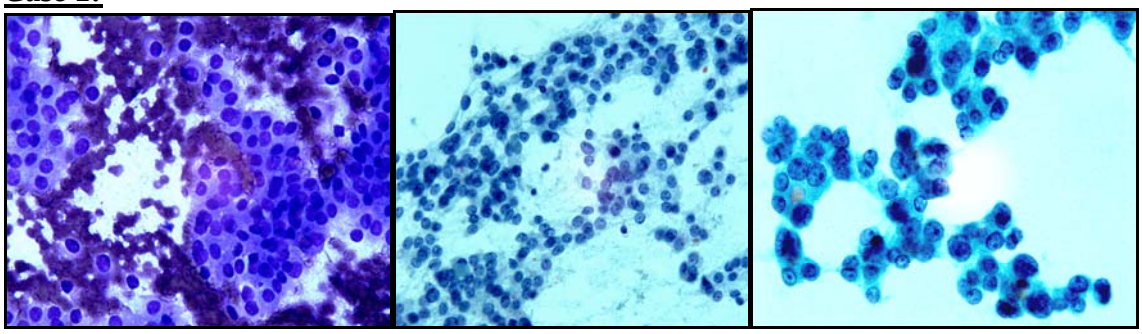
Follicular neoplasm

As mentioned above this term encompasses both benign and malignant tumors; i.e. follicular adenoma and carcinoma. The diagnostic terminology such as “follicular neoplasm” reflects the limitations of thyroid cytology,[84, 85], since the diagnosis of follicular carcinoma is only based on the demonstration of capsular and/or vascular invasion.[13, 14, 16-19, 26, 27, 38] Several authors have shown that, at most, only 20% -30% of cases diagnosed as “follicular neoplasm” are diagnosed as follicular carcinoma on histological examination and a majority is composed of follicular adenomas and cellular adenomatoid nodules.[7, 28, 51]

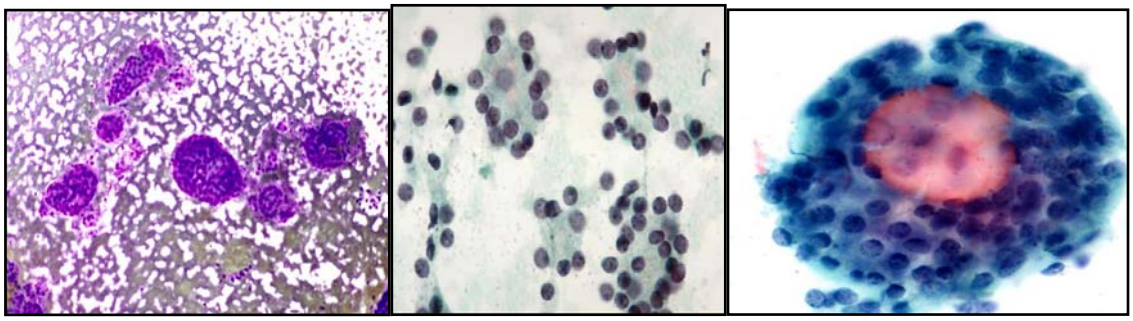
The FNA of a follicular neoplasm usually shows:

Figs 10-15: Cytology of follicular neoplasm / suspicious for follicular neoplasm

Case 1:



Case 2:



- Hyper-cellular as compared to most aspirates of nodular goiter and demonstrates a monotonous population of follicular cells with minimal or absent background colloid.
- The cells are usually arranged in three dimensional groups and microfollicles with prominent nuclear overlapping and crowding.
- Some cases may show nuclear atypia; however, this is not a diagnostic criterion of malignancy, since benign nodules can also show nuclear atypia.[14, 16, 18]
- It has been suggested that the presence of microfollicles in an FNA specimens is diagnostic of a follicular lesions neoplasm (adenoma or carcinoma).[43, 86-89]. A microfollicle is defined as <15 cells arranged in circle that is at least two-thirds complete.[90]
- Some authors have even proposed the term ***micro-follicular lesion***. However, various studies have shown that diagnosis of microfollicles suffers from inter observer variability and even aspirates of normal thyroid and hyperplastic / adenomatoid nodules can show microfollicles. [90] Others have suggested that the

diagnosis of follicular neoplasm should only be made when a thyroid FNA specimen demonstrates a monotonous cell population arranged in cohesive groups with nuclear overlapping and crowding in a background of thick instead of watery colloid.[14, 28]

Hurthle cell neoplasm

The term Hürthle cell neoplasm of the thyroid denotes a set of tumors, which are composed exclusively or predominantly of follicular cells with eosinophilic cytoplasm, enlarged, round nuclei with prominent nucleoli.[91-93] *According to new WHO classification of thyroid tumors the term "oncocytic" is preferred as to "Hurthle cell".*[94] The Hürthle cell is derived from follicular epithelium and ultrastructurally shows numerous large mitochondria filling the cells. Originally the cell described by Hürthle in 1894 is now believed to represent para-follicular or C cells; whereas Askanazy provided the correct description in 1898 of these cells in thyroid as oxyphil cells. Immunohistochemical studies have shown that these cells produce thyroglobulin and lack calcitonin. [91, 95]

Hürthle cells are not specific to any pathology affecting the thyroid gland: they can be found in nodular goiter, chronic lymphocytic thyroiditis, long standing hyperthyroidism, in the thyroid of elderly persons and in the thyroid of patients who have received radiation to the head and neck region. [91, 93, 96, 97] In these conditions the Hürthle cells are seen as isolated cells affecting only a few follicles as a metaplastic change or poorly circumscribed un-encapsulated nodules. This presentation of Hürthle cells can be very prominent in chronic lymphocytic thyroiditis, as such most believe it is a degenerative/atrophic change of follicular cells.[98]

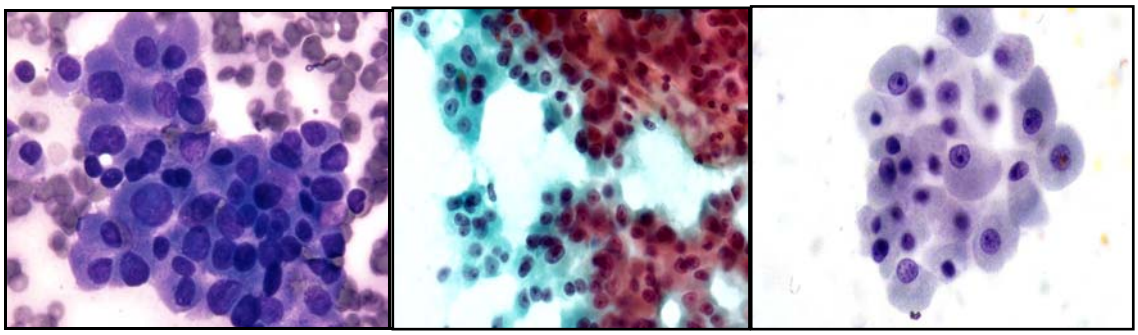
Some authors classify Hürthle cell neoplasms into a separate category of thyroid tumors.[99, 100] These lesions have a higher prevalence of aggressive histologic and biologic features, since approximately 35% in major reported series fulfill criteria for malignancy.[99] Hürthle cell carcinomas show a greater inclination towards regional lymph node and distant metastases than follicular carcinomas and unlike other follicular derived carcinomas Hürthle cell carcinomas rarely take up radioactive iodine avidly, making their clinical treatment difficult.[91-93, 98, 100] In addition, recent molecular techniques have shown significant differences in the genetic alterations between Hürthle cells and other follicular derived neoplasms.[101-105]

Clinical features of Hürthle cell neoplasms

The mean reported age of patients for adenomas and carcinomas is the same and ranges from 46 to 50 years. Hurthle cell neoplasms occur in both sexes equally. However, male patients show an overall lower frequency of Hürthle cell but a higher reported percentage of carcinomas.[91, 98, 106]Similar to non-papillary follicular lesions, the diagnosis of Hurthle cell malignancy is solely dependent upon demonstration of capsular and/or vascular invasion. Thus, FNA cannot differentiate between Hurthle cell adenoma and carcinoma. [107, 108]

FNA specimens of Hürthle cell lesions (benign and malignant) usually show:

Figs 16-18: Cytology of Hurthle cell neoplasm



- Cellular aspirate comprising one cell population of Hürthle cells in a background of minimal colloid.
- Cells can be arranged in monolayer sheets, follicular groups or as scattered single cells. [109] Some authors have suggested that cellular dispersion leading to single cells is more common in aspirates of Hurthle cell carcinoma than adenoma; however, this observation has failed to stand the test of time.[98, 109] Cellular dispersion is more due to smearing technique rather than an indication of malignancy.
- Cellular atypia is also commonly observed in Hurthle cell lesion; this can be seen in the form of random nuclear enlargement, multi-nucleation, cellular pleomorphism and prominent nucleoli. Some authors have shown this to be a diagnostic cytologic feature of Hürthle cell carcinoma. However, marked cellular atypia can occur in aspirates of Hurthle cell nodules arising in a background of lymphocytic thyroiditis, Graves' disease and also in Hurthle cell lesions which have been previously aspirated.[110, 111]

  Recently some authors have suggested that FNA specimens of neoplastic Hurthle cell lesions usually show intra-cytoplasmic lumens and transgressing vessels.[112, 113]

Follicular Variant of Papillary Carcinoma: Please refer to section on malignant lesions of the thyroid, papillary carcinoma and its variants (section I)

I. Morphologic criteria of malignant lesions

The well-differentiated thyroid carcinomas are the commonest form of malignant thyroid tumors. They are more common in young adults, whereas, the less differentiated and anaplastic tumors of the thyroid are prevalent in older age.

The well-differentiated thyroid tumors behave in an indolent manner and have an excellent prognosis. The 5-year survival rates range between 90-95%. The anaplastic carcinoma of the thyroid commonly occurs in older individuals and carries a dismal prognosis.[69]

Papillary Thyroid Carcinoma

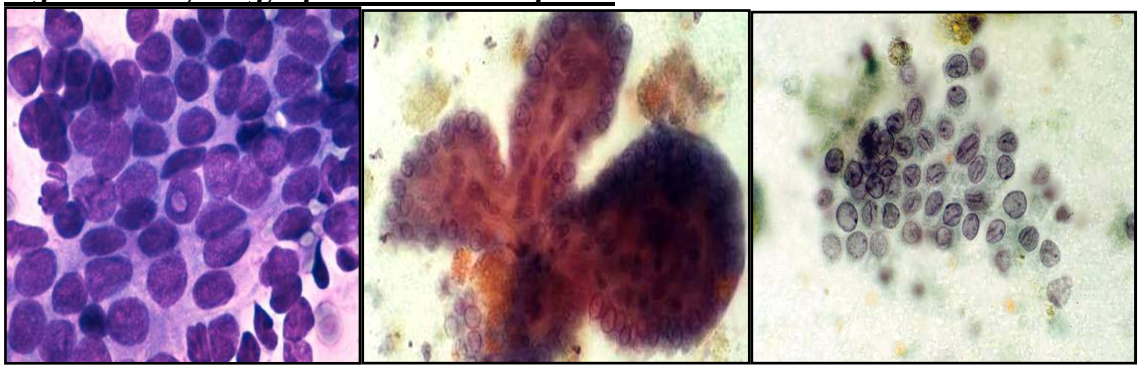
Papillary carcinoma is the most common form of thyroid malignancy. Up to 80% of thyroid malignancies diagnosed in non-endemic goiter regions are classified as papillary thyroid carcinoma. It usually presents before the age of 40 years and is more frequent in women than in men. It is the most common form of pediatric thyroid cancer. Papillary thyroid carcinoma behaves in an indolent fashion with a prolonged disease free survival and high probability of cure. However, some histologic variants of papillary carcinoma behave in an aggressive manner with distant metastasis and can be the cause

of death. Papillary thyroid carcinoma most commonly metastasizes via lymphatics, however, vascular invasion can also be seen .[69]

Cytology of Papillary Thyroid Carcinoma (PTC) and its variants

PTC is the only thyroid malignancy that is diagnosed on the basis of its nuclear morphology regardless of cytoplasmic features, growth pattern, special stains and immunohistochemical markers. This holds true for a majority of cases of PTC. However, some variants of PTC may pose some diagnostic difficulties.[11, 114, 115]

Figs 19-21: Cytology of classic variant of PTC



- The FNA specimen of PTC is usually cellular and shows tumor cells arranged in papillary groups, three-dimensional clusters or as single cells; most of the specimens display a combination of all three patterns.
- The smear background may show colloid, nuclear or calcific debris, macrophages and stromal fragments.
- The colloid in PTC is usually thick and is found as round to oval deposits. In Romanowsky stained preparations it can appear dark pink to magenta in color. In some cases this colloid can show thick “ropy” streaks connecting multiple cell groups. Some authors have termed this “bubble gum / chewing gum colloid”. [11]
- Macrophages can be seen in variable numbers; the amount of macrophages in a given FNA specimen of PTC is proportional to the cystic component of the tumor
- Stromal fragments appear as strings of eosinophilic material either surrounded or totally devoid of cells.[11]The “hallmark” feature for diagnosis of PTC is the nucleus.
- The individual tumor cells are enlarged and are mainly oval in shape; however one may also encounter round cells.
- The cytoplasm usually appears eosinophilic in Romanowsky stained preparations but is usually indistinct in alcohol fixed Papanicolaou stained preparations.[11] This also holds true for monolayer preparations (Thin-Prep®, SurePath®, etc).
- The nuclei show elongation, membrane thickening, chromatin clearing, grooves and inclusions. The nucleoli are usually small and eccentric. In a majority of cases the nuclear grooves traverse the entire longitudinal axis of nucleus, whereas, in some cases they can appear as sort invaginations of the nuclear membrane.
- Nuclear inclusions can be of varying sizes and number and occupy a central or an eccentric position within the nucleus. The margins of nuclear inclusions are usually sharp and distinct and can form part of the nuclear membrane.

Intranuclear inclusions should not be just clear holes in the nucleus but should reflect the color of the cytoplasm of that cell showing thru.[11, 72, 114] Intranuclear grooves and inclusions can be seen in other benign and malignant conditions of thyroid. These include Hashimoto's thyroiditis, nodular goiter, hyalinizing trabecular adenoma, Hürthle cell tumors and medullary carcinoma. Some authors believe that hyalinizing trabecular tumors are not adenomas, but rather variants of PTC and those Hurthle cell tumors with nuclear features of PTC are oncocytic variants of PTC.[116, 117] Clearly, the diagnosis of PTC should be based upon all of the above mentioned features rather than a single feature.[118, 119]

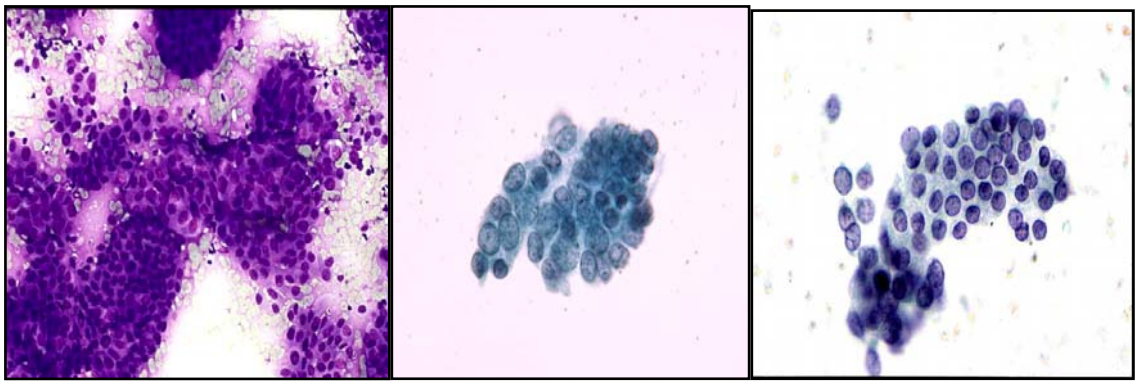
Table 3; Papillary Carcinoma Diagnostic Cytologic Features [11, 120-126]

Major Diagnostic Criteria	Minor Diagnostic Criteria
Enlarged, oval and irregular nucleus	**Papillary cytoarchitecture**
Eccentric and often multiple micro-nucleoli	**Syncytial monolayers**
Fine, pale chromatin	**Dense squamoid cytoplasm**
Longitudinal nuclear grooves	**"Bubble-gum" colloid**
Intranuclear pseudo-inclusion	**Psammoma bodies**
	Multinucleated giant cells
	Histiocytoid cells
	Cellular swirls

Papillary thyroid carcinoma can range in size from less than or equal to a centimeter, defined as microcarcinoma, to a large tumor mass with infiltration into surrounding neck structures

Follicular variant of papillary carcinoma (FVPTC): Similar to histologic diagnosis the cytologic interpretation of FVPTC can also be difficult. Some cases, due to a paucity of nuclear features of PTC, can be mistaken for hyperplastic nodules. The smears from FVPTC usually show:

Figs 22-24: Cytology of follicular variant of papillary thyroid carcinoma (FVPTC) (this case was diagnosed as suspicious for FVPTC)

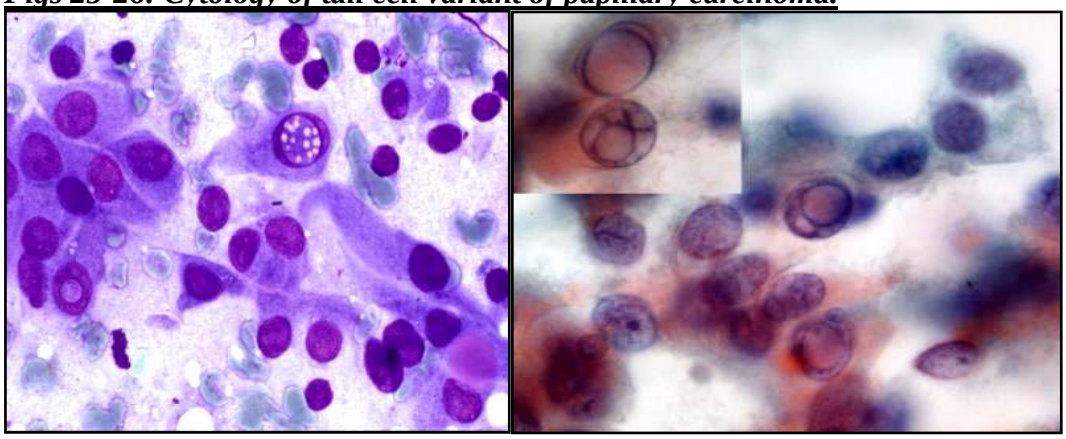


- Tumor cells arranged in monolayer sheets and follicular groups in a background of thin watery colloid.
- Thick colloid can also be present in varying proportions, however, much less as compared to classic PTC.
- The individual tumor cells show nuclear elongation, chromatin clearing and thick nuclear membranes; however, nuclear grooves and inclusions are very scarce. Nonetheless, chromatin clearing and nuclear membrane thickening is always seen in these cases. Cytoplasmic eosinophilia has been reported in cases of FVPTC. [22, 24, 36, 37, 44, 46, 47, 49, 50, 52, 87, 127]

It has been suggested that if a thyroid FNA specimen focally shows cells with nuclear elongation, chromatin clearing and grooves but lacks nuclear inclusions, it may be diagnosed such as "follicular derived neoplasm with features suspicious for PTC". In a review of these cases up to 70% reported as suspicious for PTC category turned out to be follicular variant of papillary carcinoma.

Tall cell variant of papillary carcinoma is an aggressive form of PTC and can be associated with multiple local recurrences, distant metastases and even death. Due to this aggressive biologic behavior it is prudent that this variant of PTC be diagnosed correctly in thyroid FNA specimens. Cytology specimens of this tumor usually show:

Figs 25-26: Cytology of tall cell variant of papillary carcinoma.



- Elongated cells with sharp cytoplasmic borders, granular eosinophilic cytoplasm and variably sized nuclei with nuclear features of papillary carcinoma.

- The nuclear features of papillary carcinoma are usually abundant in aspirates of tall cell variant as compared to that of classic PTC. Thus, nuclear grooves and inclusions are readily identifiable.
- Some authors have reported the presence of intraepithelial neutrophils in aspirates from cases of tall cell variant of PTC. This tumor can be confused with Hürthle cell tumors on cytology due to cytoplasmic eosinophilia. However, the nuclear features should help in differentiating between these two tumors.[128-132]

Warthin-Like variant of PTC derives this peculiar designation due to its morphologic resemblance to "Warthin tumor" of salivary glands.

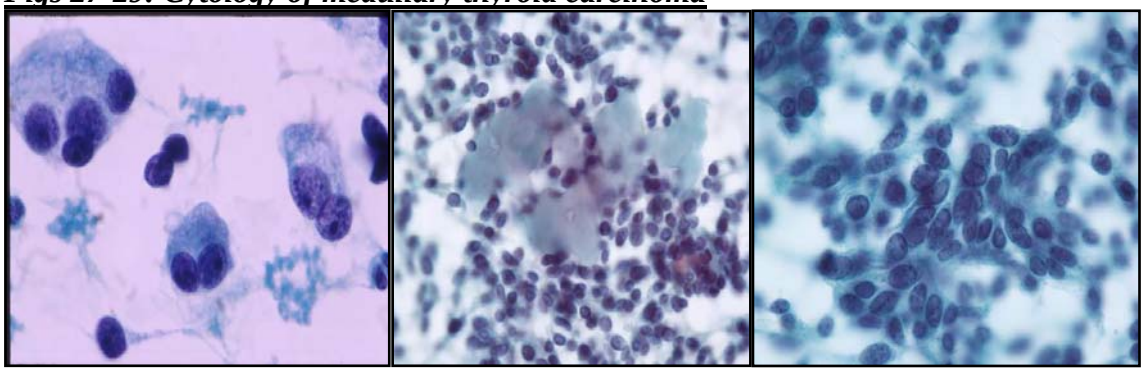
- These tumors can show papillary fragments or cellular groups infiltrated by a lymphocytes and plasma cells.
- The individual tumor cells display oncocytic cytoplasm and nuclear features of PTC.
- Aspirates from this form of PTC can be mistaken for chronic lymphocytic thyroiditis; however, the tumor cells have distinct PTC nuclei and do not resemble Hurthle cells.[81, 133, 134]

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) originates from the C-cells of the thyroid and constitutes about 10% of all malignant thyroid tumors. This thyroid tumor has drawn the interest of many due to its clinical presentation, familial origin, and association with other neuroendocrine lesions and morphologic spectrum. [69]

The FNA specimens from MTC can show a varied morphologic pattern similar to that seen in surgical pathology specimens. The majority of MTC cases show:

Figs 27-29: Cytology of medullary thyroid carcinoma



- A cellular aspirate consisting of round to oval cells arranged mainly as single cells or loosely cohesive groups.
- The individual tumor cells show abundant eosinophilic granular cytoplasm; up to 20% of cells will demonstrate fine granules in Romanowsky-stained preparations.
- The nuclei are usually eccentric giving rise to a plasmacytoid appearance to tumor cells.
- The nuclear chromatin is similar to that seen in neuroendocrine tumors; salt and pepper type with inconspicuous nucleoli.
- Intranuclear inclusions and multinucleated cells can also be seen.

- In some cases of MTC the tumor cells are can assume a “spindle shape” and appear mesenchymal in origin.
- Amyloid may be observed as acellular material in the form of strings or as round to oval shaped fragments; it can be seen surrounded by tumor cells or separate from them. It can be distinguished from the thick colloid of papillary carcinoma by performing a Congo-red stain.
- In cytology specimens the diagnosis of MTC can be confirmed by performing immunostains for calcitonin and thyroglobulin.
- In cases with limited cellularity it is advisable to have serum calcitonin levels performed on the patient to confirm the diagnosis of MTC.[11, 135] The differential diagnosis of medullary carcinoma in FNA specimens includes: Hürthle cell neoplasm, papillary carcinoma, metastatic neuroendocrine tumors and plasmacytoma. Hürthle cells usually show prominent nucleoli, lack a neuroendocrine chromatin pattern and cytoplasmic granules. Papillary carcinoma cells exhibit classic nuclear features and are negative for calcitonin and positive for thyroglobulin. A detailed family and clinical history is helpful in the diagnosis of medullary carcinoma, as this diagnosis has implications for other members of the family.[89, 136] The diagnosis of medullary carcinoma must be established by performing immunostains for calcitonin and calcitonin gene related peptide (CGRP). Medullary carcinoma also stains positive for carcinoembryonic antigen (CEA), chromogranin and synaptophysin. [89] (See accompanying article in this issue by Clark et al).

Anaplastic carcinoma

Anaplastic carcinoma of the thyroid is one of the most aggressive and fatal human tumors. It usually presents in older individuals and is more common in regions of endemic goiter. The aspirates from anaplastic carcinoma usually do not pose any diagnostic difficulties; they can be readily classified as malignant due to extreme cellular pleomorphism and obvious malignant features. The specimens can show:

- Epitheloid and spindle shaped tumor cells, and osteoclast type giant cells with marked cellular pleomorphism and anaplasia in a background of inflammation and necrosis.
- The tumor cells are usually infiltrated by neutrophils.[11, 137-139] Some cases of anaplastic carcinoma are associated with extensive necrosis and sclerosis, which can give rise to a non-diagnostic specimen on FNA.
- It is advisable that if a thyroid aspirate in an older patient shows a necrotic and inflammatory background with rare pleomorphic cells, one must include anaplastic carcinoma in the differential diagnosis.[12]
- By immunohistochemistry the anaplastic carcinoma cells are thyroglobulin negative and are positive for vimentin; they may be positive for cytokeratins. (See also committee V document).

Conclusions

- For the diagnosis of malignant lesions the diagnostic criteria are well described and illustrated in the literature.

- A papillary carcinoma diagnosis is based on nuclear features and architecture (to define variants) and the diagnosis of medullary carcinoma is based on cytomorphology and immunostains for calcitonin and thyroglobulin.

G. Specimen adequacy for epithelial lesions (see Committee III document)
H. Report format and potential use of recommendations/disclaimers (see Committees I & VI document)

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Committee V: Utilization of ancillary studies in thyroid FNA

A. **Indications for ancillary studies on thyroid FNAs**.

Review:

The indications for ancillary studies on thyroid FNAs are based largely upon the cytomorphologic features of the FNA sample. However, the clinical setting should also be factored into this decision, particularly a family history of thyroid cancer, a history of other cancer, or a rapidly growing, firm nodule. Most of these ancillary studies are aimed at the characterization of suspected carcinoma and rely on the identification of proteins specifically associated with various lesions. A more controversial area involves the utilization of ancillary studies to re-classify an indeterminate or suspicious FNA into a benign or malignant category or to refine the risk of malignancy within this category.

Conclusions:

The indications for ancillary studies on thyroid FNAs include:

1. Suspected medullary carcinoma.
2. Suspected anaplastic carcinoma.
3. Suspected metastatic carcinoma.
4. Suspected lymphoma.
5. Suspected parathyroid lesion
6. Suspected metastatic thyroid carcinoma to lymph node.
7. Indeterminate/Suspicious FNA

B. Specific ancillary studies to be performed for each of these indications.

Review:

The ancillary studies with the widest utility involve the detection of specific proteins using immunologic techniques, typically immunohistochemistry on cell block preparations. Immuno**cyto**chemistry may also be utilized, but protocols should be carefully validated for this type of specimen since reactivity may differ from that of standard paraffin-embedding cell blocks when using various other cytologic preparations (eg. smears, cytospins, monolayers, etc).

In cases of suspected medullary carcinoma, an immunohistochemical panel of calcitonin, thyroglobulin, CEA, and chromogranin should be employed to distinguish medullary carcinoma from neoplasms derived from the follicular epithelium. In addition, clinicians should consider obtaining a serum calcitonin level since most patients with medullary carcinoma have an elevated serum calcitonin level. This is particularly important if there is insufficient FNA sample for ancillary studies.[1-8]

Anaplastic carcinoma is often apparent based on its pleomorphic cytomorphology and aggressive clinical presentation. Its IHC profile is not very useful since anaplastic carcinoma often lacks TTF-1 and thyroglobulin staining. However, IHC for pan-

cytokeratin may be utilized to distinguish anaplastic carcinoma from sarcomas. The clinical setting may also raise the possibility of a metastatic lesion.[9-14]

Although rare, the most common metastases to the thyroid arise from primary carcinomas of the kidney, lung, breast, colon, or malignant melanoma. The clinical history and presentation is obviously important in determining the appropriate ancillary studies. One may initially employ TTF-1 IHC to narrow the primary site to thyroid (or lung), followed by further IHC characterization as indicated.[15]

Flow cytometric immunophenotyping is the standard for the characterization of suspected lymphoma in FNA samples from lymph nodes. This standard also applies to suspected lymphoma in thyroid FNAs. One challenging area is in the setting of Hashimoto's thyroiditis. Not all cases of Hashimoto's thyroiditis should be automatically sent for flow cytometric immunophenotyping. The indication should be based on additional cytomorphologic or clinical features that raise the suspicion of lymphoma. In addition, immunophenotyping results from thyroid FNA samples should be interpreted with caution since Hashimoto's thyroiditis may yield κ/λ ratios that are skewed beyond normal values associated with reactive lymph nodes[16].

Parathyroid tissue can be extremely difficult to distinguish from thyroid tissue based on cytomorphologic features alone. Consequently, the possibility of a parathyroid lesion is often raised by the radiographic image or clinical features. In this setting, IHC for TTF-1, PTH, and chromogranin may distinguish thyroid tissue from parathyroid. Neither the IHC nor the cytomorphology should be utilized to distinguish normal from abnormal parathyroid tissue. Chemical detection of PTH levels in FNA samples has been utilized in isolated cases, and may be considered following careful assay validation[17-22].

The identification of metastatic thyroid carcinoma to a lymph node in patients with a known history of thyroid carcinoma may not require any ancillary studies beyond the cytomorphology of the FNA sample. However, in cases of a metastatic carcinoma of unknown primary, IHC for TTF-1, calcitonin, and thyroglobulin may be useful in identifying a thyroid primary site. Several studies have suggested that chemical assays for thyroglobulin on the FNA sample are useful in identifying metastatic PTC when the cytomorphology is equivocal or non-diagnostic[23-26]. Such approaches should be implemented with caution since clinical management of patients with benign or indeterminate lymph node FNAs containing detectable thyroglobulin remains undefined.

The management of patients with an indeterminate/suspicious thyroid FNA remains problematic, so ancillary studies that would permit re-classification into a benign or malignant category would benefit these patients and clarify their management. Several different molecular markers exist that have been associated with thyroid carcinomas. These include several proteins (galectin-3, Cytokeratin-19, HBME-1), chromosomal translocations (*RET*/PTC, *PAX8*/*PPARG*), and genetic mutations (*BRAF*, *RAS*). This review focused on molecular markers that have proven efficacy for the stated indication, i.e. the re-classification of indeterminate/suspicious FNAs based on the application of a molecular test to this type of FNA. Application of molecular techniques to other specimen types, such as resected thyroid nodules, was not considered in our discussion. The specificity of several markers for thyroid carcinoma is very promising, but limited evidence precludes a recommendation for their widespread clinical use.

Conclusions:

1. Suspected medullary carcinoma.
    a. IHC panel (calcitonin, thyroglobulin, CEA, chromogranin)
    b. Serum calcitonin
2. Suspected anaplastic carcinoma.
    a. IHC for pan-cytokeratin
3. Suspected metastatic carcinoma.
    a. IHC for TTF-1 (If TTF-1 negative, then expand IHC panel based on cytomorphology and clinical setting to identify primary)
4. Suspected lymphoma.
    a. Flow cytometric immunophenotyping
5. Suspected parathyroid lesion
    a. IHC for TTF-1, PTH, chromogranin.
    b. May consider PTH level assessment on FNA sample.
6. Suspected metastatic thyroid carcinoma to lymph node.
    a. IHC for TTF-1, thyroglobulin, calcitonin
    b. May consider thyroglobulin level assessment on FNA sample.
7. Indeterminate/Suspicious FNA
    a. Insufficient evidence for a specific recommendation.

C. Sample preparation for each type of ancillary study

Review:

Pre-analytical sampling and processing protocols as well as variables are very important in the interpretation of results from any ancillary studies. The relatively limited cellularity of thyroid FNAs raises challenges for any ancillary study. Also, the material obtained for cytomorphologic analysis should not be compromised by the ancillary study. For IHC analysis, most studies have utilized cell block preparations from a portion of the FNA sample. In some cases, entire passes are dedicated to the cell block preparation. Immuno**cyto**chemistry may also be considered, but laboratories should carefully validate their reagents based on specimen preparation type. Ancillary studies to detect genetic alterations may require dedicated passes and special processing protocols depending on the analyte (DNA or RNA) and the methodology (FISH, PCR, RT-PCR). Standardized protocols with clinical validation may be required before nucleic acid-based ancillary studies can be recommended. Flow cytometric immunophenotyping of suspected lymphoma requires live cells suspended in a supportive medium, preferably from at least one dedicated pass.

Conclusions:

1. IHC. Cell block preparation from an FNA sample, preferably including at least one dedicated pass.
2. Flow cytometry. Live cells suspended in a supportive medium, preferably from at least one dedicated pass.

3. Other (nucleic acids). No conclusion at this time.

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VI. Committee VI: Post FNA Testing and Treatment Options

A. Follow up of "non-diagnostic" FNA results.

Review:

A universally accepted approach to "non-diagnostic" (unsatisfactory) thyroid FNAs is still lacking but the American Thyroid Association (ATA) has proposed a set of strategies which appear widely accepted.[1] The following strategy is based partially on their publication along with proposals discussed at the NCI State of the Science Conference in October of 2007.

Non-diagnostic aspirates may be due to the qualitative or quantitative nature of the material recieved.[2] Clearly, aspirates distorted by abundant blood or otherwise technically compromised because of smearing, fixation or staining artifacts are non-diagnostic. The quantitative aspect of specimen adequacy is more controversial. It is clear that smear cellularity depends on several factors including the aspirator's skill and the intrinsic nature of the thyroid nodule. The cellularity is most germane for adequacy assessment of cystic and partially cystic thyroid nodules. All thyroid cysts should be completely drained and the cyst wall sampled. Specimens obtained from cystic nodules may yield two types of specimens. One in which the material is composed of pure colloid without an epithelial component. The second type is watery fluid in which are dispersed a number of histiocytes and histiocyte-like cells with varying degrees of nuclear atypia. Aspirates composed of pure colloid and lacking a cellular component can be considered benign rather than "non-diagnostic." Aspirates of cysts containing blood and histiocytes, but no epithelial cells need correlation with ultrasound findings.[3] If ultrasound examination discloses suspicious areas, these aspirates should be considered "non-diagnostic." Cystic lesions yielding "non-diagnostic" aspirates should undergo repeat FNA either with or without ultrasound guidance. When repeat FNA yields a "non-diagnostic" aspirate, close clinical follow-up or surgery has been recommended by the ATA. Solitary nodules that are repeatedly "non-diagnostic" on fine-needle aspiration have an unknown risk of malignancy, but it is probably between 5 and 10 percent. The choice of clinical or surgical follow-up in nodules with repetitively "non-diagnostic" results is left to the discretion of the clinician. Many cystic nodules contain only central colloid surrounded by a thin rim of follicular epithelium and even when drained and the cyst wall sampled, little or no follicular epithelium is obtained. These cysts are at very low risk for harboring malignancy and their precise follow-up has been controversial.

Surgical resection of these nodules will result in a high percentage of non-neoplastic specimens which do not require surgery for therapeutic reasons. Hence, many authors have recommended that management of these cysts in reliable patients is best achieved by clinical/non-surgical follow-up. Other authors point to the low, but real incidence of cystic papillary carcinoma in these cystic nodules. Based on this low incidence of carcinoma, they recommend surgical resection of the nodule following two "non-diagnostic" aspirations. Timing of repeat FNA has not been established, but 6-18 months appears to be a reasonable interval.

The American Thyroid Association recommends that solid nodules associated with a "non-diagnostic" smear should be reaspirated with ultrasound guidance, and if

repeat aspirates remain “non-diagnostic,” surgery should be strongly considered.[1] Others have suggested that the repeat aspirates should be performed with pathology assistance whenever possible.[2] Some authors recommend that solid nodules less than 1 cm associated with a “non-diagnostic” repeat aspirate should be followed by ultrasound and only undergo surgical resection if enlargement is documented on repeat ultrasound examinations.[3]

Conclusions:

1. Cystic lesions with an initial “non-diagnostic” aspirate should undergo a repeat FNA if ultrasound examination demonstrates suspicious areas. The repeat FNA should be under ultrasound guidance and when possible intraprocedural review of the aspirated material by a cytopathologist is optimal. When repeat FNA yields non-diagnostic material, correlation with family history and close clinical and ultrasonographic follow up should be performed.

2. Solid nodules associated with “non-diagnostic” aspirates should be reaspirated with ultrasound guidance and whenever possible, intraprocedural review by a pathologist. If repeat smears are “non-diagnostic,” surgery should be strongly considered. If the patient is considered reliable and likely to return for clinical follow up and the nodule is 1 cm or less in size, close clinical follow up with ultrasound examination is a reasonable alternative to surgery. When growth of the nodule is detected during ultrasound surveillance, excision appears appropriate.

3. In general a waiting period of at least 3 months should elapse between the initial non-diagnostic aspirate and reaspiration. If suspicion of a carcinoma is high based on clinical or ultrasonographic findings a shorter waiting period may be appropriate in some cases.

B. Follow up of “benign” FNA results

Review:

Fine needle aspirates yielding a diagnosis of benign include the categories; nodular goiter, multinodular goiter, colloid goiter and Hashimoto’s thyroiditis. The precise management of these benign and non-neoplastic entities has varied over time and between institutions. Because patients with multiple thyroid nodules have the same risk of malignancy as those with only a single nodule, follow up of patients with multiple nodules should be the same as those with a solitary dominant nodule. Certain ultrasonographic characteristics indicate a higher likelihood of malignancy including microcalcification, hypoechogenicity in a solid nodule and intranodular hypervascularity.[4,5] These nodules may require more frequent clinical and ultrasonographic follow up after a benign diagnosis is rendered by fine needle aspiration. Cytologically benign thyroid nodules require careful clinical follow up due to the 5%

false negative rate associated with FNA of these lesions.[6,7] The false negative rate may be higher with FNAs directed by palpation than by ultrasound examination.[8-10] Thus, cytologic diagnoses obtained by palpation directed FNA may require closer clinical follow up than those diagnoses obtained from ultrasound-guided FNAs.

Options for follow up of benign nodules by FNA have included reaspiration, suppressive therapy and clinical follow up with repeat ultrasound examination. Routine medical suppressive therapy to confirm a benign cytologic diagnosis remains controversial. Multiple randomized trials have shown that thyroid hormone suppression may result in a decrease in nodule size for patient populations with borderline low iodine intake.[11-13] The data are less convincing in populations ingesting sufficient iodine. Also, rare examples of thyroid hormone suppression of papillary and follicular carcinomas have been reported. From these data, it is unclear that thyroid suppressive therapy is a reliable test for confirmation of a benign cytologic diagnosis of a solitary or dominant thyroid nodule.

Cytologically benign nodules can be followed clinically with interval ultrasound examination. These nodules may be reaspirated or surgically removed when significant changes in size occur. Ultrasonography appears to be the best technique for detection of changes in nodule size.[14] Unfortunately, there is no general agreement as to what a significant increase in size of a nodule is that necessitates reaspiration or surgical resection. The American Thyroid Association has suggested that a 20% increase in nodule diameter with a minimum increase in two or more dimensions of at least 2 mm is a reasonable definition for significant change in nodule size.[1]

The American Thyroid Association has recommended clinical follow up of cytologically benign and easily palpable nodules to occur at 6-18 month intervals. When nodules are not readily palpable, their recommendation is for serial ultrasound examinations at 6-18 month intervals following the initial FNA.[1] When there is evidence for nodular growth either by palpation or ultrasonography, repeat FNA should be performed, preferably under ultrasound guidance.[1]

Conclusions:

1. Thyroid nodules cytologically diagnosed as benign require careful clinical follow up. Easily palpable thyroid nodules may be followed clinically at 6-18 month intervals. Nodules which are not readily palpable should receive serial ultrasound examinations at 6-18 month intervals. The total duration of the follow up period is not fully defined, but should be at least 3 to 5 years.
2. If a 20% increase in nodule diameter or a minimum of a 2 mm increase in two dimensions is detected either by palpation or ultrasonography, repeat fine needle aspiration is appropriate. Repeat FNA should also be performed if ultrasound abnormalities (irregular margins or central hypervascularization) develop. The repeat fine needle aspiration should be performed under ultrasound guidance. The attendance of a pathologist at the reaspiration procedure is optimal whenever possible to assure adequate sampling.

3. At this time, hormone suppressive therapy cannot be recommended as a diagnostic maneuver for confirmation of benignity in a cytologically benign thyroid nodule.
4. Ethanol ablation may be considered in selected patients.

C. Follow up of "follicular lesion/atypical/borderline" FNA results

Review:

A variety of terms are employed by laboratories to convey uncertainty about the significance of thyroid cytologic findings. Such changes do not rise to the level of a significant concern for a follicular neoplasm meriting lobectomy (see section D below), nor do they fit a "suspicious for malignancy" interpretation (see E below). Because of some (usually focal and/or mild) cytologic or architectural atypia, neither can such cases be reliably called benign. A variety of diagnostic headings are used to report such cases. These include "atypical follicular lesion," "cellular follicular lesion," and "indeterminate". (The term "indeterminate" has also been used by some laboratories to mean "follicular neoplasm" as discussed in section D below.) The term "atypical/borderline" will be used for the remainder of this discussion.

The lack of agreement on terminology for this category has led to variability in the percentage of these lesions which are malignant. In a majority of series, approximately 5-10% of the indeterminate category are malignant neoplasms with the remaining 90-95% being adenomas or dominant nodules of a multinodular goiter.[15,16] Other authors have reported a 20-30% malignancy rate in "indeterminate" cases. Given that this diagnostic category is associated with low specificity and a low positive predictive value, the appropriate follow up or therapy for this category remains controversial. Some authorities have recommended repeat FNAs, repeat ultrasound scans, or repeat radio-nucleotide uptake studies. Some reports have suggested the use of liquid-based cytology and immunocytochemistry to improve diagnostic accuracy.[17-23]

Radiological correlation may also be helpful in improving the overall positive predictive value of the "atypical/borderline" category. Besides increasing size, ultrasonographic features such as hypoechogenicity, irregular nodular border, calcifications and abnormalities of vascularization all favor a malignant diagnosis.[24,25]

Although no consensus has been reached concerning the value of iodine^{123} scans, it may be useful in selected cases. In cases cytologically designated as "atypical/borderline," and when the serum TSH level is low or below normal the referring clinician may consider an iodine^{123} scan. If the scan is "hot", clinical follow-up with a repeat FNA in 3-6 months is appropriate. If the scan is "cold", the patient may be referred for surgery. In patients who are suboptimal operative candidates, close clinical follow-up with repeat ultrasound to detect an increase in nodule size, abnormalities of vascularization or the presence of calcification can be performed to increase the diagnostic accuracy of the "atypical/borderline" category.

The utility of outside "expert" consultation is debatable, but in some patients where reaspiration is not easily attainable, expert consultation may be a reasonable alternative to reaspiration or surgery.

Conclusions:

1. Outside expert cytopathology consultation may be considered in cases with an "atypical/borderline" cytologic diagnosis.
2. In general, a conservative approach is recommended. After a single "atypical/borderline" interpretation, a repeat FNA should be considered in 3 to 6 months. If the repeat FNA is "atypical/borderline" or worse, a surgical consultation should be considered.

D. Follow up of an FNA diagnosis of "Neoplasm (Follicular)"

Review:

This category has in some reports been termed "Suspicious for Neoplasm." The category of "Neoplasm" generally refers to follicular neoplasms with the majority being adenomas. The category is associated with a 20-30% incidence of malignancy.[1] Because of the relatively high incidence of malignancy associated with this diagnostic category, operative intervention has been recommended.[1]

Conclusions:

1. Patients with a diagnosis of "Follicular Neoplasm" or "Suspicious for Follicular Neoplasm" should be referred to a surgeon for operative exploration. Usually a lobectomy is performed followed by histologic examination of the lesion for capsular and/or vascular invasion. In some cases, total thyroidectomy may be performed. The choice between lobectomy and total thyroidectomy depends on a variety of factors including the presence or absence of nodules in the contra-lateral lobe and the characteristics of the index nodule combined with the age of the patient.
2. There is little support in the literature for frozen section evaluation to intraoperatively separate follicular adenoma from follicular carcinoma. The majority of the discussants at the NCI Conference did not recommend intraoperative frozen section analysis. The surgeon may, however, elect to have intraoperative frozen section evaluation of the nodule performed. If capsular or vascular invasion is documented, total thyroidectomy may be performed. When capsular or vascular invasion is not identified the operation is completed by lobectomy.
3. When frozen section is not utilized, the initial surgery is limited to lobectomy. If subsequent histologic examination discloses capsular or vascular invasion, the diagnosis of follicular carcinoma is made. Depending on the discretion of the surgeon, the histiopathologic characteristics of the carcinoma and the clinical status of the patient reoperation and total thyroidectomy may be performed.

E. Follow up of FNA's with a diagnosis of "suspicious for malignancy".

Review:

In the majority of cases where this category is used, the cytopathologist is concerned that the nodule may represent a papillary carcinoma, but insufficient criteria are present for a definitive diagnosis.[15] Less commonly, other malignancies such as medullary carcinoma are included in this category. Approximately 50-75% of lesions placed in the category are malignant.[15]

Conclusion:

1. Patients with an FNA diagnosis of "Suspicious for Malignancy" should be referred to a surgeon for consideration of thyroid lobectomy. Subsequent operative intervention depends on intraoperative or post operative histologic review. Intraoperative frozen section may be of significant aid in determining the extent of surgery when a definitive diagnosis of papillary carcinoma is made by frozen section evaluation. Because of an increased risk of malignancy in this category, total thyroidectomy should be considered in patients with large tumors (>4 cm), when marked atypia is seen on FNA and in patients with a family or personal history of radiation exposure. Patients with bilateral nodular disease or those who prefer to undergo bilateral thyroidectomy to avoid the possibility of future thyroid surgery on the contralateral lobe should be considered for total thyroidectomy.[1]

F. Follow up of "malignant" FNA results

Review:

This category refers to the histopathologic entities of papillary cancer, medullary carcinoma, lymphoma and anaplastic cancer. Little controversy exists that a positive cytologic diagnosis of malignancy in a thyroid nodule should be followed by a referral for surgery. In many cases a definitive type of carcinoma can and should be cytolocially diagnosed. Controversy exists as to the optimal surgical therapy for papillary carcinoma. The decision to perform lobectomy or total thyroidectomy is at the discretion of the surgeon and depends on a number of factors including size and subtype of papillary carcinoma, patient age and health status. The ATA recommends total or near-total thyroidectomy if any of the following are present: primary carcinoma is more than 1 to 1.5 cm in size, contralateral thyroid nodules, regional or distant metastases, patient history of radiation to head or neck or a first degree relative with differentiated carcinoma of the thyroid. Patient age over 45 may also favor total thyroidectomy. However, if the cytology suggests metastatic cancer, a search to identify the primary site is required so that unnecessary thyroidectomy can be avoided. The most common metastatic tumors are renal cell carcinoma, metastatic lung carcinoma and metastatic adenocarcinoma of the breast.

Conclusions:
1. The cytologic diagnosis of malignancy in the thyroid nodule should result in the referral of the patient for surgical consultation.
2. Whenever possible, the type of carcinoma present should be stated in the cytologic diagnosis.

3. It is mandatory that metastatic carcinoma be excluded whenever possible before surgical intervention is undertaken.
4. In certain clinical situations, surgical intervention may initially be simple lobectomy or lobectomy with intraoperative frozen section examination to determine if total thyroidectomy should be performed. When frozen section examination confirms the presence of a primary thyroid carcinoma, total thyroidectomy may be performed.[1] If frozen section is equivocal, the operative procedure is ended with a lobectomy and further therapy is based on the findings of permanent sections.[1]
5. Depending on the patient's clinical status and the characteristics of the malignancy, total thyroidectomy may be performed for a cytologic diagnosis of papillary carcinoma.
6. Controversy exists as to whether total thyroidectomy or unilateral lobectomy should be performed in some cases of papillary carcinoma. The selection of lobectomy versus thyroidectomy depends on the evaluation of the patient's clinical status and the size and nature of the papillary carcinoma present. Papillary carcinomas under 1-1.5 cm in size and without unfavorable prognostic features may best be treated by simple lobectomy. Larger carcinomas and especially those over 4 cm in size should, in most cases, undergo total or near total thyroidectomy.
7. If total thyroidectomy is performed, it may be accompanied by a central compartment dissection. For patients with large bulky disease or recurrent laryngeal nerve dysfunction, preoperative cross-sectional imaging should be considered as well as ultrasound imaging for lateral neck nodal disease.

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