

Techniques for Thyroid FNA: A Synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference

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The National Cancer Institute (NCI) sponsored the NCI Thyroid fine-needle aspiration (FNA) State of the Science Conference on October 22–23, 2007 in Bethesda, MD. The 2-day meeting was accompanied by a permanent informational website and several on-line discussion periods between May 1 and December 15, 2007 (<http://thyroidfna.cancer.gov>). This document summarizes matters addressing manual and ultrasound guided FNA technique and related issues. Specific topics covered include details regarding aspiration needles, devices, and methods, including the use of core needle biopsy; the pros and cons of anesthesia; the influence of thyroid lesion location, size, and characteristics

on technique; the role of ultrasound in the FNA of a palpable thyroid nodule; the advantages and disadvantages of various specialists performing a biopsy; the optimal number of passes and tissue preparation methods; sample adequacy criteria for solid and cystic nodules, and management of adverse reactions from the procedure. (<http://thyroidfna.cancer.gov/pages/info/agenda/>) Diagn. Cytopathol. 2008;36:407–424.

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The authors of this document comprised Committee III. The charge of this committee was to evaluate the utilization of various techniques in thyroid FNA. This area was further subdivided into several discussion topics, designated A–J in the discussion that follows. (<http://thyroidfna.cancer.gov/pages/info/agenda/>). This is a summary of the “Review and Conclusions” of the subject matter that this committee analyzed based on several parameters: literature reviews limited to English language publications dating back to 1995 using PubMed as the search engine with key words determined by the committee members; online forum discussions (<http://thyroidfna.cancer.gov/forums/default.aspx>), and formal interdisciplinary discussions held at the October 2007 conference. This is not a “standards of practice” guideline, nor is it endorsed as such by the National Cancer Institute.

The success of fine-needle aspiration biopsy (FNAB) in the evaluation of thyroid nodules is directly related to a low false-negative rate (FNR) and high true positive rate (TPR), and, thus, appropriate triage of patients to surgery. A low FNR is dependent on high quality samples that are obtained by technically-skilled operators who obtain and prepare samples that are representative of the lesion with sufficient quantity and quality for accurate interpretation. A high TPR is dependent on quality interpretations that follow established criteria for adequacy and specific entities. This committee addresses FNAB technique of the

thyroid and issues related to specimen adequacy, processing, and adverse reactions.

Aspiration Devices, Needles, and Method

Needles

A wide variety of needles of varying lengths and diameters are available for FNA use (See Fig. 1. at <http://thyroidfna.cancer.gov>). A large majority of biopsy physicians exclusively use 25- to 27-gauge needles for the initial biopsy which equates to outside diameters of 406–508 μm and inside diameters of 191–241 μm .¹ Follicular cell nuclei on smear preparations are similar to the diameter of red blood cells or lymphocytes, around 8–10 μm .^{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 μm , 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 materials 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 cancer, Unver et al. found 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° or less with 9° a common value. 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 (see Figs. 2 and 3 at <http://thyroidfna.cancer.gov>). Just as the 9° bevel of the leading edge of the needle is a very effective cutting device, the trailing edge is also equally effective for effective cutting. The cellular yield is maintained within the needle core by a combina-

tion 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, short bevel needles 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° bevel compared with a long bevel at 14° or less.

Larger gauge needles are often needed to drain viscous colloid cysts. Specifically, for straight pipes, such as an FNA needle, the resistance is inversely proportional to the diameter of the pipe. Twenty-, fourteen-, and ten-gauge needles have internal diameters of 0.584, 1.600, and 2.690 mm, 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-in.-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, 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 shown 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 et al. 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 and Sneige 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 nonaspiration 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 nonaspiration techniques.¹² In a meta-analysis of four cross over trials, an odds ratio favored nonaspiration 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 is a technique utilized mainly by endocrinologists. It has been theorized, that with spinning the rotational velocity vector may slightly increase 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. This premise has not been scientifically proven.

With the advent of ultrasound directed biopsies of smaller and often nonpalpable 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 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.

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 hand 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 Papanicolaou Society's website (<http://papsociety.org/>) also offers study aids applicable to thyroid FNA. Available as downloadable 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 the technique can also be downloaded for free via Google™ and The Papanicolaou Society's web site (<http://papsociety.org/>), located specifically under the PSCO Guidelines as "Optimal FNA Technique" (<http://www.papsociety.org/fna.html>).

These concepts are discussed in detail with illustrations available at <http://thyroidfna.cancer.gov>.

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. Because of poor or absent teaching of these techniques and the subsequent poor quality smear production, in addition to the absence of ready access to the cytopathology laboratory of some aspirators, have 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.

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 (three 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 three 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, a vacuum is usually not needed and may even be counterproductive. For such hypervascular nodules, the Zajdela technique is ideal. Second, 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 ultrasound guidance is used, the needle must never 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 ultrasound gel will coat its outside surface. This ultrasound gel can be completely removed by carefully swiping gauze downward 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. An empiric 30-min observation period post procedure to observe for progressive swelling and ecchymosis has been advocated (see section on adverse reactions).

Conclusions

1. Commonly available 27- to 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 three 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.

The Role of Anesthesia for Palpable and Nonpalpable FNA and Guidelines for its Use

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 On the other hand, 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.

Excellent anesthesia for thyroid FNA is obtained by injecting between 0.5 and 1.5 ml of 2% lidocaine with or without epinephrine 1:100,000. The ultra thin 30- to 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 1, 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 ml of anesthetic agent, which

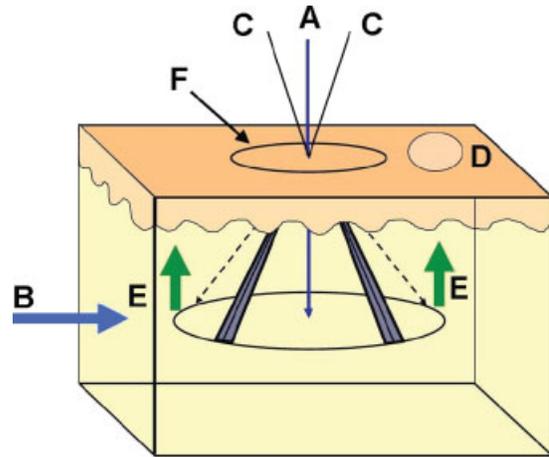


Fig. 1. Steps in cutaneous anesthesia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

almost always is sufficient but 0.6 ml 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 ~1 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 min.

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 hour. 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 needed.
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 peace 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 ml of the anesthetic utilizing 30-gauge-needle and inject slowly into the subcutaneous fat (not the reticular dermis) allowing the anesthetic to back infiltrate the dermal nerves, avoiding rather than making a painful intradermal wheal.

Influence of Thyroid Lesion Location, Size, and Imaging Characteristics on FNA Sampling Technique

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 nondiagnostic 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 two or more locations depending on the size of the lesion to insure adequate sampling of potentially heterogeneous composition. At least one biopsy per unique area by ultrasound is reasonable. See accompanying discussion in the article in this issue by Cibas et al.

Nodule Imaging Characteristics

The most critical aspect influencing the FNA sampling technique and the rate of nondiagnostic 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 nondiagnostic 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 nondiagnostic FNAs increased with the greater cystic content of the nodule. Solid nodules had an 8% nondiagnostic 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 nodules should be aspirated with ultrasound guidance.
2. Large nodules should be aspirated two 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. Suspicious calcifications identified on ultrasound should be targeted/sampled.

The Role of Ultrasound Guidance in FNA of a Palpable Thyroid Nodule

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 localization 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} Indications for the use of ultrasound localization in the aspiration of palpable nodules are covered in the accompanying article in this issue by Cibas et al.

Reports on the clinical utility of ultrasound in FNA of palpable thyroid nodules has largely centered on the expe-

rience 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 localization 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, not just for thyroids but for the sampling of other body sites as well. With expanding patient directed health screening services, nodules that the pathologist is being asked to sample are becoming increasingly 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.

The Role of Core Biopsy for Palpable and Nonpalpable Thyroid Nodules

The use of large core needle biopsies such as Vim-Silverman needles and Tru-Cut needles (14–18 gauge) was more prevalent in the past, but was subsequently replaced by FNA.³³ This was mostly due to reports of relatively increased risk of complications, increased patient discomfort and anxiety, and little or no difference in its diagnostic value compared to FNA.^{33–37} Most clinicians utilizing core needle biopsy (CNB) are now using a modern spring-loaded core biopsy, single-action or double action devices. 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. 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.^{38,39} The biopsy is actually obtained from tissue 1–3 cm deeper than the pretriggering cutting notch position (depending on distance of throw). This mechanism discourages their use in the vicinity of vulnerable structures or for the biopsy of very small lesions, therefore, a short throw device (11-mm excursion) is preferred.^{37,39} The single action spring activated needle, i.e. Temno needle, uses a similar but non-advancing cutting motion. The needle is triggered only when the stylet and biopsy notch have been manually 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.³⁹

Screaton et al. assessed the safety, yield, and accuracy of 209 US-guided CNB (US-CNB) of thyroid, utilizing 16- to 18-gauge needles.⁴⁰ Patients were referred to CNB after repeated nondiagnostic FNAs, indeterminate follicular lesion diagnoses, or nonpalpable nodules with no previous FNA. They achieved sensitivity, specificity, diagnostic accuracy, and nondiagnostic 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.”⁴⁰ Taki et al. evaluated the efficacy of US-CNB of 74 cases, using an 18-gauge double spring activated needle.³⁷ 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.⁴¹ 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%). Also, CNB appeared to be less sensitive than FNA, especially in the detection of papillary carcinoma.⁴¹

For all practical purposes, CNB, similar to FNA, cannot distinguish between follicular adenoma and follicular carcinoma.^{42,43} Boey et al. found that CNB was not able to distinguish between adenomatous hyperplasia and follicular neoplasm, when evaluated 167 consecutive patients with both FNA and drill-needle biopsy.⁴⁴ Harvey et al., compared FNA with CNB, when assessed cellular follicular lesions, and found neither technique to be able to definitively diagnose or exclude follicular carcinoma.³⁸ Other studies have shown that large needle biopsies could not separate benign from malignant nonpapillary follicular lesions, or lymphocytic thyroiditis from lymphoma.^{34,45,46}

Harvey et al. compared the use of US-CNB (79 cases) to FNA (266 cases) with and without US-guidance.³⁸ 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%). 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).⁴⁷ When used alone, FNA and CNB had satisfactory rates of 97 and 88%, respectively, but showed a 100% satisfactory rate when used in combination. 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.⁴⁷ In a prospective study, Quinn et al. reported better results using US-guided spring activated one stage automated CNB(20–21 gauge), compared with FNA, in 102 patients.⁴⁸ Best results, however, were obtained with combined use of both techniques.

Without utilizing image guidance, Pisani et al. compared 136 FNA with 32 CNB (20–21 gauge), including 29 patients who had both procedures done.⁴⁹ 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.⁴⁹ 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%).⁴⁴ Liu et al. simultaneously performed freehand FNA and Tru-cut CNB on 100 patients with palpable nodules.⁵⁰ 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.⁵⁰

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.^{34-36,51} Two such cases of needle tract implantation (seeding) are cited in the literature.³⁶ There has been a rare report of hemorrhage following large needle biopsy, requiring urgent neck exploration.⁵² Limitations of CNB include the need for local anesthesia, local discomfort, and decreasing patient acceptance of repeat biopsies.⁴⁵

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 potential complementary investigational tool. When cytopathology expertise is not available, CNB provides a small tissue sample for histologic examination.
3. CNB of thyroid utilizing modern needles, especially single action spring activated needles, appears to be well tolerated and has low incidence of complications.
4. CNB under US guidance 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.

Advantages and Disadvantages to Various Specialists Performing FNA of Palpable Thyroid Nodules

Thyroid FNA is performed primarily by endocrinologists, radiologists, surgeons, and pathologists.^{53,54} 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.⁵⁵⁻⁵⁷ Please see the accompanying article in the issue by Ljung et al. which deals specifically with training and credentialing for the performance of thyroid FNA.

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 nonpalpable or difficult to palpate, are located posteriorly, have a large cystic or multiple cystic compartments or are located within a diffuse or multinodular goiter.^{24,58,59}
2. On-site smear assessment improves specimen adequacy and an on-site diagnostic evaluation enhances service.^{43,60} 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 nonpalpable 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.

Optimal Preparation of FNA Material for Routine Evaluation and Ancillary Studies, and the Role of Immediate Assessment

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 suggested.

*Solid and semisolid material.*⁶¹ Air-dried and alcohol-fixed smears should be prepared for Romanowsky (Diff Quik, Wright- Giemsa, Wright stains) and Papanicolaou staining, respectively.

Liquid-based processing can be utilized either alone or as a supplement to direct smears. Likewise, direct smears can be processed alone or with a supplemental LBC or cellblock prepared. Direct smears, however, are essential for immediate assessment.

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.^{62,63}

For aspirations performed by clinicians without immediate access to cytopathology laboratory communication with the laboratory is essential. If the clinician is trained in smearing techniques, he/she can directly prepare smears which can be air-dried or spray fixed with an ethanol based fixative and then forwarded to the cytopathology laboratory. Alternatively or in addition to smears, depending upon the practice patterns utilized by the clinicians and the cytopathology laboratory, material can be collected using a transport method that is appropriate for the cytopreparation to be used. Material can be collected in the following liquid based preservatives:

RPMI, balanced saline (cytospins)

Formalin (cellblock)

Liquid-based 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. For clinicians and radiologists not trained in smear techniques, rinsing the needle in a liquid (see above) is easy and reasonable and allows the laboratory to handle the preparation and staining.⁶⁴⁻⁶⁹

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, nonpalpable 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.⁷⁰⁻⁷² For institutions using LBC as the sole means of specimen preparation, pathologists' knowledge of the alterations in cellular appearance is essential for accurate interpretation.^{66,71,73,74}

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 smears⁶⁸; higher adequacy rates with smears^{64,75} and higher adequacy rates with LBC.⁷⁰

With regard to diagnostic accuracy of LBC, some studies have shown LBC to be similar to conventional smears.^{68,70,73,74,76,77} Other studies have shown a trend in favor of increased accuracy when smears are used rather than LBC,^{64,66,68} 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.^{64,66} Other comparative studies examined fewer than 100 cases and thus suffer from small sample size.^{65,75} The study by Werga et al.⁷⁸ 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

The role of ancillary studies in thyroid FNA is discussed in detail in this issue in the accompanying article by Filie et al. 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.⁷⁹

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.^{19,61,65,80-83} Others have found that immediate assess-

ment has little impact on patient care, and any benefits are outweighed by its costs and burden on the laboratory.⁸⁴⁻⁸⁶

Immediate evaluation of material allows 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 semisolid material. Air-dried and alcohol-fixed smears should be prepared for Romanowsky (Diff Quik, Wright-Geimsa, Wright stains) and Papanicolaou staining, respectively.

Direct smears can be processed alone or with a supplemental LBC or cellblock prepared. Direct smears, however, are essential for immediate assessment. Liquid based processing can be utilized either alone or as a supplement to direct smears.

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 prepared if the clinician is skilled in smear preparation technique.

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 (See accompanying article by Filie et al.).

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 optional.

Management of Adverse Reactions During and After the Procedure, and the Need for Verbal or Written Postprocedural Instructions

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.^{18,87–89} 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.^{90–92} The case of Noordzji and Goto is detailed and instructive. He found a large hematoma after needle biopsy with a 25-gauge needle in a patient without coagulopathy.⁹² A hematoma developed 2 hours after the procedure and required operative drainage. It manifested 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 CNB postprocedure observation of at least 30 minute is recommended. Direct pressure to the biopsy site after biopsy is also recommended for both unguided and US-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 minute, 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 that are immunocompromised.⁸⁸ Nishihara has

reported a case of *S. Aureus* infection in a cystic nodule in a patient with atopic dermatitis after FNA. Symptoms developed 4 days after fine needle aspiration.⁹³ Nishihara notes that opportunistic thyroid infections are uncommon but typically occur in patients with preexisting thyroid abnormalities (especially cysts), or in patients with local (ex. atopic dermatitis) or general (e.g., DM, TB, HIV) immunocompetence issues. Wu recommended alcohol for routine skin prep and iodine prep for “deep site” FNA.⁸⁸ 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 and coworker’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 0.036%.^{89,94} Tomoda found voice change typically occurred 1–2 days after FNA procedure, and that all cases were transient with average resolution in 4 months.⁹⁴ Hulin and Harris 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.⁹⁰ 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.^{95,96} 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 and Burstein 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.⁸⁸ 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.⁸⁸

Postprocedure Guidelines

An empiric 30-minute observation period post procedure to observe for progressive swelling and ecchymosis has been advocated.⁸⁸ 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.

Optimal Number of Passes for a Solid and Cystic Lesion

The number of passes for an adequate thyroid FNA 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 I). 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).^{5,32,38,97-103}

Adequacy is discussed further in Agenda Item J. However, in brief, the goal of an adequate specimen is to insure 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. CNB performed at the same time as aspiration may be one way of overcoming this problem.^{41,50,104} 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.^{105,106} Most studies report sensitivity

Table I. 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

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.^{107,108} 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.^{22,97-103,108-110} 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.¹¹¹ 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 II. The median sensitivity is 96% (range 68–100%) and the median adequacy rate is 86% (range 60–99%).

Using the data in Table II, one can demonstrate neither the sensitivity nor the adequacy is strongly correlated with the maximum number of passes reported (correlation = -0.5 and 0.2 , respectively). Indeed, sensitivity is also not strongly correlated with adequacy rates (0.37). This suggests that other factors listed in Table I, or problems with determining sensitivity listed in paragraph two 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.^{108,116}

Similarly, in every single study in which different numbers of passes has been compared (and presumably, the other factors listed in Table I are controlled for) the more passes performed (up to 12) the higher the adequacy rate (See Table III at <http://thyroidfna.cancer.gov>). 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

Table II. Performance Characteristics for Unselected Thyroid FNA Series and No. of Passes

Reference	No. of cases	No. cases with histologic F/U	Sensitivity (%) ^a	Adequacy (%) ^b	No. of passes
Suen and Quenville ¹¹²	331	79	94	96	1 or more
Hamaker et al. ¹¹³	116	41	95	86	2-3
Boey et al. ¹⁰⁴	384	384	96	84	3-4
Anderson and Webb ¹¹⁴	562	373	94	79	1
Hawkins et al. ⁸⁹	1,399	415	86	98	At least 2
Goellner et al. ¹¹⁵	6,300	382	98	80	1-4
Hamburger et al. ¹¹⁶	1,380	258	100	75%	2-8
Hamburger and Husain ¹¹⁰	888	159	100	75	At least 6
Caraway et al. ¹¹⁷	394	150	94	82	3-5
Gharib et al. ⁸⁷	10,971	984	94	79	Usually 2 up to 6
Hanbidge et al. ⁵	123	0	NA	87	4
Baloch et al. ¹⁰⁹	662	140	98	89	Average of 2
Liu et al. ⁵⁰	100	100	100	99	2
Poller et al. ¹¹⁸	156	75	100	76	3 or more
Ravetto et al. ¹¹⁹	37,895	4,069	92	98	Usually 2
Baloch et al. ⁸⁰	313	77	100	95	2 or more
O'Malley et al. ⁸⁵	121	11	NA	78	2-12, mean 4-7
Baloch et al. ¹²⁰	3,007	101	NA	92%	2-4
Eedes and wang ⁸⁴	311	0	NA	86	2-6
Harvey et al. ³⁸	266	22	68	60	1-3
Redman et al. ³²	693	0	NA	96	1-11, mean 3.2-5.4

^aSensitivity for malignancy, atypical and above as the diagnostic threshold, histologic fu cases only.

^bIncludes both nondiagnostic and nonspecific, and cases b core biopsy F/U (follow-up).

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.^{5,32,38,97-103} 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 paradigm is as follows:
 - a. FNAs with rapid interpretation available: two 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: two to five biopsies from different sites with representative tissue from each pass smeared on a slide (or 2) and the remaining tissue rinsed into a collection tube with transport fluid without fixative (unless delay in immediate processing is expected).

Adequate FNA Samples from a Solid Lesion and Cystic Lesion

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, a higher rate of vascular and capsular invasion, and are two-fold more likely to have persistent disease at follow-up.¹²¹ 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.^{19,122}

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.¹²³ 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.¹¹¹ 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.¹²⁴ 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 inflam-

matory 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.¹²⁵

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.^{123,126,127} 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 FNR of such an aspirate approaches zero. As such, when the follicular component is less than generally considered adequate (see below), the cytological interpretation should be reported as "negative or benign" and "consistent with a colloid nodule," not "unsatisfactory" or "nondiagnostic."¹²⁸

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 nonstandardized. Some advocate for not counting cells at all.¹²⁹ Goellner and coworker'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.^{32,115,130} With these criteria, the FNR 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%.¹²⁴ Nguyen required the presence of 10 large clusters of follicle cells with at least 20 cells each when counted from all available smears.¹³¹ In his study of 1,631 thyroid aspirates, the FNR was 9%. Do 5–10 groups of follicle cells with a flat honeycombed pattern exclude the possibility of follicular carcinoma? The study by Deshpande et al. would say not entirely.¹²⁶ 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 FNR 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 cyst aspirates.^{21,24,36,132} The risk rises to 14% in mixed solid and cystic nodules, large cysts (>3 cm)

and recurring cysts.¹²⁸ Of aspirated cysts, only about 1% of cysts are malignant.^{36,131} Given the extremely low potential of a FNR in such aspirates, to classify all thyroid cysts with few to no follicle cells as “unsatisfactory” (an interpretation indicating that no information at all is available from the aspirate) as some suggest⁸⁷ does not seem to be in the best interest of patient care.^{115,133} 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.^{85,123,128,129}

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 of “nondiagnostic” 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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TECHNIQUES FOR THYROID FINE-NEEDLE ASPIRATION

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