Fine-Needle Aspiration Followed by Core-Needle Biopsy in the Same Setting: Modifying Our Approach

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Key Words

Fine-needle aspiration · Core-needle biopsy · Combined approach · Rapid on-site specimen evaluation

Abstract

Fine-needle aspiration biopsy (FNAB) is a well-established initial diagnostic tool. However, in some instances limitations and shortcomings arise, making it insufficient for determining a specific diagnosis. Consequently, patients have to undergo another diagnostic procedure. The second procedure is either repeat FNAB, core-needle or open biopsy, and can be inconvenient and costly. In some centers, the FNAB is immediately followed by core-needle biopsy (CNB) in the same setting after assuring adequacy on the initial FNAB utilizing rapid on-site specimen evaluation (ROSE). It is argued that implementing such an approach will eventually have additional critical advantages that include the following: (a) it is more convenient to patients to have both procedures in one visit, (b) the tissue procured by both procedures will be more adequate, enabling cytopathologists to reach an accurate diagnosis, and (c) it is ultimately a cost-effective approach if we take into consideration the avoidance of a potential second more invasive diagnostic procedure. Since we

are living in an era of patient-centered medicine coupled with cost-cutting strategies, we present here a brief review of the topic with analysis of this alternative approach, review of the pertinent literature and shed light on a few scenarios that justify this approach.

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Introduction

Fine-needle aspiration biopsy (FNAB) is widely accepted as an initial diagnostic tool for almost all body lesions, benign or malignant. FNAB is usually obtained using 22- to 27-gauge needles and the procedure provides a sample for cytological examination, with possible cell block preparation. It is a simple and relatively noninvasive procedure which requires a skilled aspirator along with the routine use of syringes, needles and stains. Moreover, FNAB is a very safe technique with negligible complications [1, 2]. In most instances, and specifically for palpable lesions, FNAB does not need major preprocedure preparations and radiology guidance, so it can be performed in the clinic without reserving a place in the radiology unit or operating rooms.

FNAB with rapid on-site specimen evaluation (ROSE) provides an immediate assessment of adequacy and quick lesional diagnosis in most instances, which allows the clinicians to discuss the diagnosis with the patient without any delay. Furthermore, involvement of the cytopathology team with on-site evaluation ensures a proper clinical correlation and optimizes the handling of the specimen. When ROSE is utilized, it allows the provision of samples for ancillary studies, such as microbiological analysis, molecular studies, flow cytometry, cytogenetics, and sometimes electron microscopic studies. This triaging approach usually depends on the preliminary diagnosis performed utilizing ROSE [3, 4]. Nasuti et al. [5] demonstrated that the average nondiagnostic rate of FNAB dropped from 20 to 0.1% by the addition of on-site evaluation. Other investigators have documented a high accuracy rate of 96% of FNAB when on-site interpretation was performed during the procedure [5, 6]. In their analysis of CT-guided core biopsies of solid organs, Schoellnast et al. [7] demonstrated the critical importance of on-site assessment by cytopathologists. They concluded that FNAB without on-site cytopathological evaluation does not yield better sensitivity or specificity when compared to core-needle biopsy (CNB) alone.

The availability of ROSE is extremely important regardless of the specimen type. It can be very helpful whether the intended procedure is FNAB alone, CNB alone, or combined.

The introduction of the cell block technique increased the diagnostic accuracy of FNAB. The value of a cell block as complementary to cytological assessment is well established in many anatomical sites [8–11]. It essentially provides more tissue material that could be used for ancillary testing, such as polymerase chain reaction, fluorescent in situ hybridization and immunohistochemistry, consequently increasing the sensitivity and specificity of FNAB. In addition, the availability of a cell block provides more architectural details to the specimen (fig. 1). In their recent review, Jain et al. [12] provided a detailed description of the cell block technique in cytopathology with a comprehensive review of its preparative methods, utility in diagnosis and role in ancillary studies.

Despite these facts, FNAB occasionally falls short of providing adequate material to enable the cytopathologists to render an accurate and detailed comprehensive diagnosis. Adequate cytological diagnosis may not be given due to a small sample size, lack of cell block material for ancillary studies and the absence of a detailed architectural pattern. In these situations, a repeat FNAB, CNB

or open surgical biopsy may be necessary to obtain adequate tissue for a more specific and reliable diagnosis. In addition to its added cost, this process is time-consuming and is also inconvenient to the patient since it requires another procedure with exposure to either local or general anesthesia. To overcome these constraints, some centers currently perform CNB complementary to FNAB in a single diagnostic procedure. This review aims to address the potential benefits for modifying the diagnostic approach to encompass FNAB immediately followed by a CNB in one setting.

Limitations of FNAB

Although the increased sensitivity and accuracy of FNAB may decrease the need for CNB, FNAB may not provide adequate cellular or architectural details in certain types of lesions [11, 13]. Therefore, in a few circumstances, obtaining a tissue biopsy may be mandatory.

The diagnostic accuracy of FNAB may be variable depending on the skills and experience of the operator, hence it is really aspirator dependent. In some instances the amount of tissue obtained may not be sufficient enough to prepare a cell block, preventing the pathologist from performing the necessary diagnostic ancillary tests required for an accurate diagnosis. These include, but are not limited to, immunohistochemistry, microbiological analysis, and molecular and cytogenetic studies. For instance, in thyroid lesions, FNAB has some adequacy limitations whereby unsatisfactory rates have been reported to be between 4 and 21% [14–19], while the rate of indeterminate diagnosis is 3–18% even with ultrasound guidance [17, 18, 20]. The diagnostic sensitivity and specificity of ultrasound-guided FNAB of the thyroid are approximately 83 and 92%, respectively [21]. Although cell block preparation is not a routine step in thyroid aspiration cases, certain cases would benefit and the availability of cell block has the potential to limit the number of indeterminate interpretations and may provide material for molecular studies. However, other investigators, for whom the implementation of molecular analysis is characterized by a reasonable accuracy and availability in their institution, were successful in evaluating molecular studies on material obtained through fine-needle aspirates of thyroid [21–25].

In breast lesions, FNAB can be inconclusive in up to 30% of cases, with 20% being reported as inadequate and 10% being suspicious for malignancy [26]. This can be attributed to certain types of invasive ductal carcinoma, like

Fig. 1. Multiple cell blocks of different aspirates from different organs: mammary carcinoma (a), complex renal cyst that proved to be cystic nephroma (b), Warthin's tumor of parotid mass (c) and gastrointestinal stromal tumor through endoscopic ultrasound-

guided fine-needle aspiration (d). These cell blocks are as good as tissue biopsies exhibiting the appropriate features complementing the findings in the smears and are amenable to multiple ancillary studies.

scirrhous-type and lobular carcinoma which are sometimes difficult to diagnose by FNAB [2, 27, 28]. Although it is well known when evaluating mammary carcinoma that the axillary node status is best tackled by aspirate smears, FNAB alone in many cases cannot confirm that. Moreover, FNAB alone cannot confirm the presence of tumor invasion and cannot be used to differentiate between invasive and in situ neoplasia [29–31]. In addition, low-grade breast lesions, such as atypical ductal hyperplasia, low-grade ductal carcinoma in situ and tubular carcinoma, cannot be accurately diagnosed using this modality alone [32–35].

FNAB in many cases does not provide material to allow a full architectural evaluation which makes it difficult whenever the architecture is needed to make a specific diagnosis, such as certain types of lymphomas and benign nonneoplastic lung diseases (fig. 2). Besides, the relationship between the lesion and the surrounding tissues cannot be evaluated properly using an FNAB modality alone. One additional major limitation of FNAB is the inability to make an accurate interpretation for specific benign conditions in some organs. For instance, certain benign lymphoid lesions cannot be made accurately by FNAB, such as infectious mononucleosis and Castleman disease

Fig. 2. These images are from a 56-year-old male who presented with loss of weight and general weakness. He was found to have hepatomegaly and a PET scan (**a**) showed extensive infiltration by highly active nodules. FNAB was performed revealing numerous atypical

large lymphoid cells (Papanicolaou-stained smear; **b**) surrounded by many smaller bland-appearing lymphoid cells. A core biopsy followed by a laparoscopic wedge liver biopsy (**c**) was needed to make the diagnosis of T cell-rich B cell non-Hodgkin lymphoma.

[36, 37]. In one study aimed to assess the diagnostic value of CNB relative to FNAB in patients with pneumonia and mimics of pneumonia, which is a major differential diagnosis of lung masses, the authors found that a specific diagnosis was made in only 7 out of 41 patients (17%) with thoracic benign lesions [38].

In their study performed on FNAB of soft tissue lesions, Bennert and Abdul-Karim [39] showed that FNAB was unsatisfactory in 44 out of 117 cases (37%), of which 22 (50%) had a corresponding CNB diagnosis. CNB is more accurate than FNAB in diagnosing and subtyping soft tissue lesions. Table 1 summarizes the aforementioned limitations.

CNB as an Alternative to FNAB

CNB is obtained using large needles (14–18 gauge) and it primarily provides tissue for histological evaluation. In most cases where FNAB is indeterminate, CNB can help obtain a reliable histological diagnosis. This can easily be achieved by applying local anesthesia for those patients who are not surgical candidates or refuse surgery. Moreover, CNB provides an alternative option in situations where ROSE is not available, such as when there is a very busy pathology practice and in small primary care centers with no pathology services. In comparison to open surgical biopsy, CNB is less invasive and

Table 1. Limitations of FNAB

It is operator dependent and requires certain skills and experience to ensure adequate sampling
May not provide adequate material to prepare a cell block which limits the ability to perform diagnostic ancillary studies
Lack of architecture even with well-prepared cell blocks
Absence of the spatial relationship between the lesion and the surrounding tissues and inability to assess lesion capsular invasion by the tumor
Inability to specify a benign pathological process in some organs (benign lymphoid diseases, benign soft tissue lesions and nonneoplastic lung diseases)
Inability to differentiate invasive from in situ mammary carcinoma
Difficulty of assessing low-grade and borderline lesions in some organs (breast and soft tissue)
Certain types of lymphomas need tissue sampling

Table 2. Advantages of CNB as an alternative to FNAB

Less operator dependent (most radiologists and interventional radiologists are trained to perform the procedure)
Provides adequate material for histologic evaluation and to perform diagnostic ancillary studies
CNB enables assessment of the histological architecture and preserves the relationship with tissue surrounding the lesion, enabling the assessment of capsular and adjacent tissue invasion
CNB is superior to FNAB in specifying some benign pathological processes in some organs (benign lymphoid diseases, benign soft tissue lesions and nonneoplastic lung diseases)
Invasive and in situ mammary carcinomas can be easily differentiated by CNB
Better assessment of borderline and low-grade lesions, especially breast and soft tissue lesions
Immediate adequacy assessment and tissue triaging can be achieved by touch imprints of core tissue by a cytotechnologist on site, which makes it a convenient approach when a cytopathologist is not available

is usually done in a single pass that hopefully samples the lesion. In addition, CNB provides larger tissue samples compared to FNAB. If the needle successfully penetrates the nodule, CNB is less operator dependent and enables the assessment of the histological architecture and keeps the relationship to surrounding adjacent tissues avail-

Table 3. Shortcomings of CNB

Needs a radiologist and privileged clinician to perform the procedure
Needs local anesthesia that may be less convenient for the patient and clinician
More invasive than FNAB, with more complications such as bleeding, infection, tumor seeding, pneumothorax and others
Processing and preparation of the biopsy slides takes more time
More expensive than FNAB
More labor-intensive

able in most circumstances (table 2 summarizes the aforementioned points).

However, the performance of CNB has a few disadvantages, one being that it needs a radiologist or a clinician with such privileges to be available, which increases the cost of the procedure. Although CNB performed by experienced radiologists and others is a safe procedure, it is still more invasive than FNAB and has the potential of more serious complications, such as bleeding, infections and pneumothorax. One of the most serious complications of this procedure is malignant seeding of the tumor in the needle tract, which is less documented in FNAB [40–43]. In addition, local anesthesia is less convenient to both the patient and the clinician, and it takes a longer time to prepare for the procedure and to obtain the results. CNB is a more expensive procedure as it needs processing, cutting and staining. It was found that the cost of CNB is approximately 3 times more than FNAB alone [44]. Table 3 summarizes the shortcomings of CNB.

Approaching Masses by FNAB Immediately Followed by CNB (Explaining the Approach)

The patient needs to secure an appointment with the FNAB/CNB clinic or interventional radiology department. The procedural technique should be explained to the patient with emphasis on possible complications of the process, as a larger needle is used to obtain the biopsy, followed by acquiring appropriate signed consent. Initially, one FNAB pass is tried to make sure the lesion is targeted utilizing ROSE evaluation to assure proper sampling. If the first pass is adequate, and based on the initial impression, extra material can be taken for ancillary studies if needed (flow cytometry, culture and others). Finally,

Fig. 3. Algorithm of the fine-needle aspiration and core combined approach.

a CNB is obtained for further evaluation of the lesion. The entire process is performed in one setting with no additional inconveniences to both the patient or the operator of the procedure (fig. 3).

Advantages of the Combined Approach

Multiple studies have confirmed the effectiveness of the combined approach in increasing the accuracy of diagnoses of body lesions, especially small lesions [45–47]. Each technique (FNAB and CNB) plays a complementary role to the other in procuring satisfactory material for tis-

sue and ancillary studies, and to minimize the rate of false-negative and false-positive results. Although both procedures have comparable sensitivity and specificity rates for diagnosing malignant lesions, as has been proven by multiple studies, adding CNB to the FNAB procedure will improve the diagnostic yield in many body lesions. Furthermore, CNB is superior to FNAB for rendering a specific diagnosis for benign lesions and certain malignant processes [12, 48–50].

In their study on head and neck lesions, Kraft et al. [51] found that CNB was superior to FNAB in a few aspects – providing a specific diagnosis, identifying true neoplasms and detecting malignancy. In this study, the

Fig. 4. These images are from a 65-year-old male patient who was found to have an ill-defined lesion in the right lobe of the liver (**a**) by CT scan. CT-guided fine-needle aspiration revealed suspicious clusters of cells with a probable necrotic background (**b**). A core biopsy was immediately done which revealed a moderately to

poorly differentiated adenocarcinoma (**c**) which proved to be lung primary by immunohistochemistry, CK7+ and TTF-1+ (**d**). Note that the core on the right did not contain a tumor, while the one on the left did.

investigators compared the results obtained by CNB that was performed immediately before the surgical excision of the lesion and compared these with a prior FNAB diagnosis in 68 patients with head and neck masses. CNB was able to provide a specific diagnosis in 90 versus 66% obtained by FNAB. CNB was 100% accurate in identifying true neoplasms versus 93% identified by FNAB. They also reported that 99% of cases of malignancy were detected by CNB versus 90% detected by FNAB. However, the authors concluded that ultrasound and FNAB should remain the initial diagnostic tools for head and neck lesions. They also recommended utilizing the core biopsy approach as a substitute if FNAB fails to provide a diag-

nosis or in those patients where surgery is not an optimal option. Therefore, utilizing the combined approach in the same setting may provide us with optimum results.

Gong et al. [52] evaluated FNAB and CNB specimens of intrathoracic lesions. The authors compared the diagnostic accuracy of 362 FNABs and the concurrent CNB results that were performed in the same visit to the final diagnosis. The authors found that both FNAB and CNB had similar diagnostic accuracies for malignant tumors (85.1 and 86.7%, respectively), especially for malignant epithelial tumors. However, for nonepithelial malignant tumors like sarcomas and lymphomas, CNB yielded a better diagnostic accuracy than FNAB alone (96 vs. 77%, re-

Fig. 5. Images from a 54-year-old male patient who was found to have 2 lung lesions. The lesion on the right side (**a**, white arrow) was well-circumscribed while the one on the left side (**b**, white arrow) was ill defined.

spectively). They demonstrated that by reviewing the results of FNAB and CNB together, the diagnostic accuracy of malignancy improved from 85 and 86.7 to 95.2%. The same study showed a higher discrepancy in the diagnostic accuracy of FNAB and CNB in benign lung lesions. FNAB yielded a proper diagnosis in 40% of the benign cases, while 92% were diagnosed properly by CNB. The diagnostic accuracy increased to 96% by using both modalities together. These findings were supported by other studies emphasizing that CNB is superior to FNAB in diagnosing benign lung diseases [12, 48–50]. Thanos et al. [38] found that thoracic CNB provides a specific diagnosis in 87.5% of cases with pneumonia and mimics of pneumonia, compared to 20.83% diagnosed by FNAB. However, it is worth mentioning that recent studies have demonstrated success in the diagnosis and subtyping of lung carcinomas utilizing an FNAB approach alone [53–56].

Yang and Damron [57] confirmed the increased diagnostic accuracy of CNB over FNAB in musculoskeletal lesions, particularly in benign cases. This study, among others, emphasized that subclassification and grading of soft tissue lesions was achieved more accurately by CNB [57, 58]. In their soft tissue study, Bennert and Abdul-Karim [39] demonstrated that the unsatisfactory FNAB results of 22 cases were further clarified and specified by CNB (15 sarcomas, 2 fibromatosis and 5 benign lesions). Seven of the sarcoma cases that were diagnosed by FNAB were further subtyped by CNB. In their study that aimed to identify the diagnostic accuracy of FNAB and CNB in diagnosing desmoid tumors, Dalén et al. [59] showed that 35 out of 69 (50.7%) cases were diagnosed by FNAB and 24 out of 26 (92.3%) cases were diagnosed by CNB. These

findings confirm that CNB is more reliable than FNAB in diagnosing soft tissue lesions, and using the two modalities together would significantly improve the diagnostic accuracy in soft tissue lesions [39, 57, 59].

The sensitivity of diagnosing breast cancer in one study increased from 80% for FNAB alone and 88% for CNB alone to 100% when using both techniques together [60]. Since the utility of FNAB of the breast is on the decline and is being replaced by CNB in many institutions, Nassar [61], in her elegant review, emphasized the importance of FNAB of the breast and the utility of new modalities to help overcome its limitations when compared to CNB. She also reminded all of us in the field of cytology that utilizing new modalities in conjunction with fine-needle aspiration will potentially decrease the limitations of fine-needle aspiration alone. The incidence of inadequate specimens is lower in CNB than FNAB. In their study on nonpalpable breast lesions, Ibrahim et al. [62] demonstrated a high inadequacy rate for FNAB (58.7%). In another study on nonpalpable breast lesions, FNAB was inadequate in 22% of the cases [63].

Sung et al. [47] demonstrated that CNB and FNAB/CNB were significantly more accurate for diagnosing thyroid malignancies than FNAB alone, and that combined FNAB/CNB was more accurate for thyroid malignancy than CNB alone in small thyroid nodules of less than 1 cm. The authors suggested that adding CNB could reduce the nondiagnostic or atypical cells of undetermined significance/follicular lesion of undetermined significance cases of the Bethesda system for reporting thyroid cytology.

The current standard of care in the diagnosis and subtyping of lymphomas requires the utilization of morphol-

Fig. 6. CT-guided fine-needle aspiration of the lesion on the left side revealed large atypical cells with glandular differentiation (**a**) where the tumor was also seen on core biopsy (**b**). The tumor cells were immunoreactive for CK7 (**c**) and TTF-1 (**d**), confirming the primary nature of this adenocarcinoma.

ogy, immunophenotyping and molecular findings. As demonstrated by many, some of these features can be achieved by FNAB [64–67]. However, in some cases FNAB may not be adequate enough to provide all these requirements, mandating a core or open biopsy. Consequently, FNAB of lymph nodes provides adequate material for flow-cytometric immunophenotyping, while CNB allows the assessment of lymph node architecture and helps in the confirmation and subtyping of many lymphomas through immunohistochemistry [68–73]. In a large retrospective study aimed to evaluate the diagnostic accuracy of combined FNAB and CNB in diagnosing lymphomas, Amador-Ortiz et al. [68] demonstrated that 237 out of 263 cases were diagnosed and 193 (75%) cases

were completely subclassified (96.5% sensitive and 100% specific). The authors concluded that combined FNAB and CNB with ancillary studies provides a valuable alternative to excisional biopsies for the diagnosis of lymphoma. Other studies reported a higher diagnostic rate of lymphoma by CNB ranging between 80 and 90% [69–72]. In a recent comprehensive review, Dr. Caraway demonstrated the evolving role of FNAB in diagnosing lymphoproliferative disorders [74].

In a prospective study on 57 excised renal masses, Barwari et al. [75] demonstrated that combining FNAB and CNB in the evaluation of such masses improved the accuracy rate by about 3.5–14% when compared to FNAB or CNB alone. After surgical excision, the specimens were

Fig. 7. The lesion on the right side was also targeted by CT-guided FNAB followed by core biopsy and proved to be a benign hamartoma. Papanicolaou- (a) and Diff-Quik-stained smears (b); both showed myxoid and cartilaginous material, and the core had similar features.

examined in the pathology department where the urologist performed two CNBs using 18-gauge needles and subsequently performed FNAB using a 22-gauge needle before subjecting the specimen for routine and standard histological examination. Five pathologists participated in this study and all of them reached a consensus on the final histological diagnosis of these specimens. This consensus diagnosis was considered the final gold standard and reference diagnosis against which the accuracy of the FNAB and CNB interpretations were measured. They found that the diagnostic accuracy rate using CNB and FNAB together ranged from 89.5 to 98.2%, while for CNB alone was from 80.7 to 89.5% and for FNAB the accuracy ranged from 71.9 to 93%. In another study intended to evaluate the value of combined FNAB and CNB in the evaluation of small solid renal tumors, Li et al. [45] showed that the diagnostic accuracy for the combined procedure and for CNB was 100%, while it was 88% for FNAB.

In our routine daily practice we believe that the combined procedure helps to retain experience in the cytology of solid organs and provide maximum sensitivity and specificity. FNAB and CNB techniques should not be considered mutually exclusive, but as two different diagnostic modalities that complement one another [76–79]. We have encountered cases where the diagnostic material was only seen in the FNAB material, while in others it was more evident in the CNB material (fig. 4–7). Table 4 summarizes the advantages of the combined procedure. Therefore, and as shown by other investigators, the

Table 4. Advantages of the combined approach

Increases the accuracy of diagnosis, especially in small lesions
Provides more material for additional ancillary studies
Both FNAB and CNB are complementary to each other and allow better interpretation of morphology and architecture
Increases the sensitivity and the specificity of either approach alone
More convenient to the patient
More satisfaction for clinicians who are still hesitant to manage their patients based on cytological material alone
It builds greater experience in cytology for those pathologists who believe more in tissue diagnosis
It helps when there are very complex lesions, such as composite malignancies

utilization of both aspirate smears and core tissue biopsy material are complementary and have added value compared to either one alone [7, 13, 26, 29, 33, 35, 38, 39, 44–47, 50–52, 57–62, 68, 75–78].

The final argument that can be made against the combined approach is adding cost, especially in the current era of cost containment. An additional cost will be added when an additional core biopsy is performed, but on the other hand this approach will be cheaper than having a

second procedure, whether a repeat fine-needle aspiration or core biopsy. In addition, since 'patient-centered medicine' is a prime target of almost all health institutions, it makes tremendous sense to be able to provide a highly diagnostic procedure in one setting for our patients. Despite the fact that our current hospital is a ministry of health institution, we attempted to perform a cost analysis study to compare the cost of FNAB followed by a second CNB procedure at a later date to reach a better or more accurate diagnosis, and compared that to utilizing the combined approach in one setting. The result of our simple analysis was based on the assumption that if we had to bring 40% of our patients back for a CNB after an initial FNAB, and compared that with the combined approach in the same setting for those 40%, we found that the combined approach would create a cost saving of at least 17%.

Conclusions

The adoption of this combined diagnostic strategy of FNAB followed by CNB supplemented by on-site evaluation and immediate triaging by a pathologist is a cost-

effective approach that saves the patient unnecessary additional clinic visits and procedures, and reduces the number of false-negative results. It is easy to perform and time saving. Optimization of the diagnostic yield is highly dependent on an organized coordination among radiologists, pathologists and clinicians. Uniform guidelines for optimal tissue retrieval and triaging should be placed for each institution. We believe that the combined FNAB/CNB approach is reasonable and a logical technique, and we recommend its adoption as a diagnostic tool.

Acknowledgments

The authors thank Mr. Lambert T. Porter, section head of Quality and Strategic Planning (QSPA) at our hospital for his valuable help in the cost analysis.

Disclosure Statement

The authors declare no conflict of interest of any sort. No grants or funding were needed to complete this project.

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