Atlas of Cytopathology and Radiology

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To my husband, Rajeev Nayar—the wind beneath my wings.
To my parents, Tilak Raj and Sheila Bhalotra, for their undying encouragement, love, and support.
To my dear sisters, Anju and Sonia.
Ritu Nayar

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To my children, Amrita and Ranjit.
Ajit S. Paintal

To my children, Erich, Rachel, Mitchell, and Grace.
Albert A. Nemcek Jr.

Preface

The diagnostic services—pathology and radiology—are the cornerstone for supporting the delivery of high-quality healthcare by providing timely and accurate diagnosis. In this era of precision medicine, it has become increasingly important for these two services to work collaboratively in supporting our patients and clinical colleagues by informing and communicating the selection and interpretation of appropriate diagnostic tests, as well as obtaining adequate tissue for diagnosis, prognostication, and therapy at initial presentation and, if required, during disease progression/relapse. The importance of access to oncologic imaging and pathology expertise and technologies was highlighted at a recent workshop organized by the National Cancer Policy Forum—*Improving Cancer Diagnosis and Care: Patient Access to Oncologic Imaging and Pathology Expertise and Technologies* [1].

At our large teaching hospital, we are fortunate to have both cytopathology and interventional radiology expertise. Our teams have a close working relationship, with dedicated space for the cytopathology in interventional radiology, where biopsy review and decision-making, with discussion if warranted with the ordering physician, are done on a daily basis. Over the past three decades, we have built a state-of-the-art, collaborative, fine needle aspiration (FNA) and core biopsy service with immediate on-site adequacy evaluation and triage. This joint service provides the majority of primary cancer diagnosis and in advanced stage disease is the only pathology material on which all diagnostic and ancillary testing is done.

We previously published a monograph targeted toward our oncology colleagues, *Cytopathology in Oncology*, with the aim of "demystifying" cytopathology [2]. This current atlas is aimed at practicing cytopathologists and interventional radiologists and trainees in these areas. It is our pleasure to be able to share our experience with the readers of this atlas. We hope you will find it to be a useful reference for your practice.

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1 An Introduction to Radiology and Cytopathology Considerations in a Collaborative Biopsy Service

Ajit S. Paintal, Ritu Nayar, and Albert A. Nemcek Jr.

Interventional Radiology Fundamentals

Image-guided procurement of tissue or fluid for diagnostic purposes has become one of the most commonly performed procedures in medicine. Although the focus of this Atlas is cytologic analysis of tissue specimens, we would note that cytologic, biochemical, and microbiologic evaluation of fluids obtained in this manner is similarly important, and for the purposes of this text the term "biopsy" will be assumed to cover both settings.

The basic elements of image-guided biopsy are the following: a lesion or organ is identified as amenable and appropriate for biopsy; a method of imaging guidance is chosen; an approach to the lesion or organ is plotted; needle(s) or other devices are used to obtain tissue or fluid; and the material is processed and reviewed.

The target for biopsy is chosen when, on the basis of clinical radiological and/or endoscopic data, the target has potential clinical significance. While this would seem self-evident, it emphasizes that awareness of the imaging appearance of normal variants, pseudolesions, and typically insignificant manifestations of pathology such as focal hepatic steatosis, classic hepatic hemangiomas, and typical adrenal adenomas will minimize performance of unnecessary procedures. Biopsy of normal (or pathologically insignificant) tissues generally results in few complications. However, obtaining normal tissue may lead to the misperception that the operator is "missing" a lesion with biopsy attempts, possibly prompting additional attempts, each with inherent risk. Further, in certain scenarios, biopsy of normal tissue may carry a greater than average risk of complications. It has been suggested, for example, that biopsy of normal pancreas may increase the risk of subsequent pancreatitis [1].

Another consideration in choosing a target for biopsy is that less-invasive methods of obtaining a confident diagnosis are unavailable or unsuccessful. While diagnostic specificity on imaging is often elusive, properly chosen and performed imaging studies can establish a confident diagnosis in many instances. A corollary is that the operator should always evaluate imaging fully to look for the least risky intervention that is likely to obtain an answer (for example, biopsy of a subcutaneous nodule rather than a deep retroperitoneal lymph node).

A question to be answered by both the referring physician and the operator is whether plans for treatment or further investigation are likely to be strongly influenced by the biopsy results. Consider the setting of metastatic disease in a patient with a known primary malignancy. Pathologic analysis of the suspected metastases reinforces the use of potentially hazardous or debilitating therapy when metastatic disease is confirmed, and can alter workup and treatment when another diagnosis is established. Further, decision-making does not necessarily mandate tissue confirmation. Examples would include a patient with strong clinical and biochemical evidence of pheochromocytoma and a large adrenal mass (biopsy of which carries its own significant risks), or a cirrhotic patient with a liver mass with venous invasion, and a markedly elevated alpha-fetoprotein (highly diagnostic of hepatocellular carcinoma without the need for tissue) [2], or a patient who would not be treated regardless of the biopsy results. Image-guided biopsy is also unnecessary for patients who require surgical therapy for emergent clinical conditions caused by suspicious lesions that could be biopsied in the open setting. Progression/relapse of previously confirmed malignancies may require follow up biopsies for molecular testing and considerations for targeted therapy.

There should be both an advantage to imaging guidance and a reasonable chance that tissue or fluid can be obtained

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from the lesion/organ in question using some form of imaging guidance. For small, non-palpable focal lesions, the likelihood of success depends on many factors, with size becoming important especially at the lower limits of visibility [3, 4].

The literature is replete with studies that have evaluated the risks of percutaneous biopsy procedures [5–7], and in order to proceed with biopsy those risks need to be taken into account, communicated, and prepared for, and if the risks are considered prohibitive the biopsy should not be performed. There is, for example, a low but well-established potential for hemorrhagic complications of biopsy, even in patients with normal hemostasis, regardless of the lesion type or biopsy technique. Basic coagulation studies (international normalized ratio, platelet count) are generally obtained for all but superficial biopsies, with additional studies dependent upon the screening history and initial lab results. However, the correlation between bleeding risk and the results of routine coagulation studies is somewhat tenuous, and a good clinical history regarding bleeding risks should always be obtained [7, 8]. It is rare indeed that a biopsy needs to be performed emergently, and therefore every effort can usually be made to correct significant hemostatic abnormalities. Severe, uncorrectable coagulopathy is generally considered an absolute contraindication to biopsy, while the decision of whether and how to proceed in patients with milder abnormalities will depend on clinical circumstances. Occurrence of a complication during performance of a biopsy often limits the number of needle passes obtainable for biopsy, although in some cases on-site treatment (e.g. chest tube placement for pneumothorax incurred during lung biopsy) may allow the procedure to continue.

The operator also needs to account for the patient's ability to cooperate with the procedure. Biopsies in uncooperative patients are generally more risky and less likely to be successful. A careful pre-procedural explanation of the patient's role in the procedure (e.g. when and how to breath hold) is helpful. Use of local anesthesia is ubiquitous; pharmacologic analgesia and sedation are also useful in most cases, although use of these needs to be balanced against potential oversedation that may make lesion targeting more difficult and increase procedural risks.

Biopsy of specific tissue types, or needle paths through certain tissues, can also increase risks. Appropriate pre-procedural screening and planning can help minimize these risks. As an example, biopsy of lesions that elaborate vasoactive substances—pheochromocytomas, extra-adrenal paragangliomas, and carcinoid tumors—have been associated with severe and sometimes fatal blood pressure swings [9, 10]. When such tumors are suspected on the basis of clinical and/or radiologic findings, targeted biochemical screening should be performed. The operator should, by extension, become familiar with measures for treatment and prevention of such reactions.

Needle track seeding, although generally felt to be rare, almost certainly occurs with increased frequency for certain tumor types. One notable example is hepatocellular carcinoma, for which a meta-analysis estimated a not inconsiderable 2.7% incidence of needle track seeding, with a 0.9% incidence per year [11].

A variety of imaging methods are available for biopsy guidance, the most common currently being ultrasonography (percutaneous or endoscopic) and computed tomography (CT), with modalities such as fluoroscopy and magnetic resonance scanning less frequently used. The method chosen should portray the target well, and ideally allow the safest, technically easiest, and most reliable access. Cost, availability, personal preference/experience, and the potential need for ancillary procedures also enter these considerations. Ultrasound has advantages of real-time needle placement, portability, and relatively low cost; on the other hand, CT will often show lesions better than ultrasound, particularly if gas (as in lung biopsies) is in the path of the needle. Contrast agents may be useful in select CT cases and have begun to be investigated as a technique in ultrasound-guided biopsies (Fig. 1.1) [12]. Although still relatively early in development and not yet widely available, methods using "fusion" imaging (combinations of imaging methods, for example ultrasonography and nuclear medicine) [13] and guidance systems such as electromagnetic tracking [14] are likely to be applied more often in the future. Biopsy should be targeted toward that portion of the tumor most likely to yield diagnostic tissue. For example, lesions with necrotic centers are more profitably biopsied at their periphery, or functional imaging such as positron-emission tomography may direct the operator to more metabolically active portions of the lesion in question that are in turn more likely to yield diagnostic tissue.

In terms of devices used to procure diagnostic material, most are variations of needles, although other options such as biopsy forceps may also be useful. Even the simplest needle design may yield diagnostic material, although various tip alterations—cutting needles, semi-automated and fully automated core devices, and others—have been designed with the aim of improving yield [7]. Although an in-depth discussion is beyond the scope of this chapter, and although these divisions are somewhat arbitrary and subjective, the most basic division of needles is into smaller (around 21 to 26 gauge) devices that typically obtain fragmented tissue or aspirates of separated cells and larger (20 gauge and beyond) devices that obtain more tissue including true "cores" of tissue. Smaller devices are usually less painful for the patient and probably safer, although many studies show differences in complications only at the extreme ranges of needle size. Larger specimens generally translate to higher diagnostic

Fig. 1.1 Pathologist and radiologist reviewing patient CT scan in interventional radiology and discussing the case before beginning a lung biopsy procedure

yield, a factor that has become particularly important in recent years given the increasing focus on genomic/molecular analysis of tissue specimens for personalized medicine [15, 16]. Whereas, in the past, the primary goal of biopsy was establishment of a phenotypic diagnosis, requests are now made to characterize tumor genotypes and assess other biomarkers, and to do serial biopsies to assess response to therapy, monitor the progression of disease, and adjust therapy in response to the changing character of tumors. Indeed, this focus on obtaining larger quantities of "high quality" tissue for these purposes has raised a new set of questions applicable to image-guided biopsy that are currently the focus of intensive investigation: How often do we obtain adequate tissue for analysis? What strategies can be used to improve the yield of biopsy for such purposes (needle size, number of passes, presence of an on-site cytopathologist, correlation with functional imaging such as positron-emission tomography scanning)? And what is the cost of these strategies, both in terms of risk to the patient and monetary cost to both patient and society, especially when the benefit may be minimal or unpredictable? Further, will these considerations be rendered obsolete by emerging technologies such as "liquid" biopsy [17]?

Basic Cytopathology

Cytopathology differs from conventional histopathology in regards to specimen preparation, staining techniques, and common applications. Broadly speaking the two most common specimen types are aspiration biopsies and exfoliative specimens. Exfoliative specimens contain cells that have been shed from a surface. These cells may shed spontaneously, as in the case of a pleural effusion, or be removed mechanically, as in the case of a bronchial brushing, bladder washing, or cervical Pap test. These specimens are often prepared by making a direct smear of the specimen. Alternatively, the specimen may be centrifuged directly onto the slide in order to concentrate cellular material.

Fine needle aspiration (FNA) specimens, in contrast, are obtained by inserting a thin needle into an area of abnormal tissue and drawing cellular material into the needle with a combination of capillary action and suction. This material may be then expressed ("squirted") on to a glass slide and smeared or deposited into liquid medium. In contrast to a core biopsy, a macroscopic solid piece of tissue is not obtained in a fine needle aspiration.

Two types of stains are employed in most cytologic specimens. The Diff-Quik stain is commonly used on air-dried specimens and has the advantage of being rapid to perform; specimens can be stained and evaluated in a matter of minutes allowing real time intraprocedural feedback in regards to specimen adequacy and triage (see below). The Diff-Quik stain is excellent at highlighting extracellular material, such as stromal material and mucin as well as cytoplasmic detail. A drawback of this stain is that the combination of air drying and the opaque nuclear dye makes an assessment of fine nuclear detail very difficult.

The Pap stain, in contrast, requires alcohol fixation and a somewhat more complex set of processing steps. As such, this stain is less commonly employed in intraprocedural adequacy assessments ("Rapid Pap"). The main advantage of the Pap stain when combined with alcohol fixation is that it provides excellent nuclear preservation and detail. This fine

nuclear detail is vital in the diagnosis of a number of entities including pancreatic adenocarcinoma and papillary thyroid carcinoma.

In addition to using aspirate and exfoliative specimens to generate stained glass slides, cytologic material may also be collected in liquid media. This suspended material can then be used to either create additional slides, including cell blocks, for morphologic examination or for ancillary studies (see below).

There are a number of advantages and disadvantages in performing a fine needle aspiration vis-à-vis a core biopsy. One of the main strengths of a core biopsy is that typically more tissue is obtained. Recovering a greater quantity of tissue with each biopsy pass allows ancillary testing to usually be performed more reliably on core biopsy specimens than on aspirates. In addition, core biopsies are commonly placed directly into a formalin-based fixative and processed to generate formalin-fixed paraffin-embedded tissue (FFPE), the specimen type of choice for many ancillary tests. A final advantage of core biopsy is that an intact piece of tissue is obtained in contrast to the single cells and small groups of cells that are recovered in an aspirate specimen. The ability to examine a larger piece of tissue allows a more precise evaluation of the overall architecture of the tissue.

Fine needle aspirates of superficial lesions have the advantage of typically being less traumatic for patients than core biopsies. Also, they can be performed in a standard examination room and do not require a sterile room. Following the procedure, the patient typically only requires a small bandage for hemostasis. Another advantage of aspirate smears is that aspirate slides, either air dried or fixed in alcohol, provide superior preservation of fine cellular and nuclear detail relative to core biopsies.

A key advantage of FNA specimens is that in many cases, Diff-Quik–stained slides can be prepared and examined intra-procedurally. This allows an assessment of adequacy to be made and potential diagnoses to be communicated to the operator in real time. Using this feedback, material can be triaged appropriately for ancillary studies (microbiology cultures in the case of an inflammatory lesion versus molecular testing in the case of a malignancy, for example). Furthermore, the procedure can be confidently concluded once adequate material has been obtained without the morbidity of superfluous biopsy passes or the potential of an inadequate specimen and a repeat biopsy.

While intra-procedural adequacy assessments are typically most easily performed using aspirate specimens, in many cases core biopsies can be evaluated by tapping, rubbing, crushing, or otherwise exfoliating material from the core biopsies onto a glass slide before the piece of tissue is placed in formalin. The "touch" preparation glass slide can then be Diff-Quik–stained and evaluated in a similar fashion as an aspirate smear. In the case of fibrotic or extremely vascular lesions that do not yield tissue on aspiration, core biopsy with crush preparation provides a useful alternative means to obtain cytologic material, confirm adequacy and triage the tissue during the procedure (Fig. 1.2) [18].

In addition to morphologic assessment, material obtained from core biopsies and aspirate specimens can be used for a variety of ancillary studies. In the current paradigm, many malignancies are evaluated via immunohistochemistry. The general principle behind immunohistochemistry is that by

Fig. 1.2 Pathologist/cytotechnologist evaluating a biopsy for adequacy and triage with radiology physicians in interventional radiology