Introduction

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1.1 Introduction

Fine needle aspiration (FNA) is a reliable, minimally invasive, cost effective technique for obtaining samples from superficial and deep mass lesions for pathologic evaluation. Despite these advantages, physicians in the USA have been slow to embrace FNA as a primary diagnostic modality in the pediatric population. Obstacles to the acceptance and use of FNA include diagnostic challenges posed by the overall rarity and spectrum of tumors seen in children and adolescents, the experience and biases of clinicians and pathologists, and practical and technical considerations. Cytopathologists who are experienced in the performance and interpretation of FNAs may have limited familiarity with the spectrum and morphologic appearances of tumors seen in the pediatric population. Conversely, pediatric pathologists who are familiar with the histologic features and differential diagnosis of tumors encountered in children and adolescents often have little experience performing and/or interpreting FNAs. Likewise, clinicians who have extensive experience performing endoscopic or endobronchial ultrasound guided FNAs may have little experience with endoscopy or bronchoscopy of pediatric patients, and vice versa. These factors can impact the quality of the specimen and/or interpretation and lead to the need for a second procedure in order to arrive at a definitive diagnosis, thereby limiting the value of FNA as a diagnostic modality. Practical considerations include the cognitive and emotional maturity of the child or adolescent, and the need for immobilization, sedation, or anesthesia. Alone or in combination, these and other challenges and limitations have contributed to reluctance on the part of both pathologists and clinicians to promote the use of FNA as a primary diagnostic modality in the pediatric population. In contrast, exfoliative cytology is routinely used in the evaluation of cerebrospinal fluid and respiratory tract specimens from children and adolescents, and smears and crush preparations are standard methods for intraoperative assessment of pediatric central nervous system lesions.

1.2 Spectrum of Practice

The use of FNA as a primary diagnostic modality in the pediatric population varies with geographic location, practice setting, and clinical environment (Table 1.1) [1]. With respect to geographic

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Table 1.1 Factors influencing the use of FNA in the pediatric population

• Geographic location (resource-limited, resource-rich)
• Type of practice (academic, community)
• Presence of a free-standing pediatric hospital
• Organization of practice (subspecialty based or general pathology)
• Clinical environment (experience with and acceptance of FNA, referral patterns)
• Availability of physicians trained in performance and interpretation of fine needle aspiration
• Sensitivity and performance of fine needle aspiration (diagnostic vs. inadequate or non-diagnostic specimens, definitive or narrowed diagnoses that effectively guide management vs. nonspecific diagnoses/need for additional biopsy)

location, 86 % of the world's pediatric population lives in resource-limited or developing countries where malignancies in children and adolescents comprise a greater percent of all cancers and have a higher mortality rate than in the USA and Europe [2]. In countries where access to medical care, diagnostic imaging, and more invasive procedures such as core or excisional biopsy is limited, FNA is routinely used for the primary evaluation of suspected malignancies in the pediatric population and has proven to be an accurate diagnostic tool [3, 4]. In contrast, FNA is rarely used for the primary diagnosis of pediatric malignancies in the USA where there is widespread access to more invasive diagnostic modalities and where risk stratification and treatment are often based on histologic diagnosis.

Within the USA and other resource-rich countries, the volume of pediatric FNAs can also vary greatly in different practice settings. Clinicians who have had positive experiences with FNA as a diagnostic modality are more likely to consider referring patients for FNA or to recommend the use of FNA to their colleagues, than those who have had negative experiences. Acquisition of an adequate specimen, appropriate triage, and diagnostic expertise are all required for providing a high quality FNA service. Adequate samples can be obtained by pathologists, interventional radiologists, and/or clinicians with appropriate training and expertise in performing FNAs. However, within a given institution, the type(s) and availability of qualified physicians impacts whether FNAs are performed in inpatient and/or outpatient settings, or not at all, and whether the lesions sampled are superficial and/or deep. Appropriate triage of the specimen is essential when ancillary studies are needed for a definitive or narrowed differential diagnosis. Rapid on site evaluation (ROSE) not only allows assessment of adequacy, but also guides appropriate triage of the specimen. However, ROSE can be time consuming and is deemed economically impractical in some practice settings. The availability of pathologists and/or cytotechnologists to perform ROSE can have a significant impact on whether the procedure results in a definitive or narrowed differential diagnosis and thus, on the use of FNA rather than a more invasive core or open biopsy for the primary evaluation of a mass lesion in a child or adolescent. Finally, the expertise required for accurate cytologic diagnosis of pediatric lesions is more likely to be found in settings with subspecialty-trained cytopathologists and pediatric pathologists, and can have a positive impact on the use of FNA. In general, the key elements for the acceptance and successful use of FNA as a diagnostic modality in the pediatric population are more likely to be found in an academic institution than in a community hospital.

Geographic location and practice setting also influence the type and pathologic spectrum of pediatric lesions evaluated by FNA. In resource-limited countries, malignancies comprise the majority of lesions diagnosed by FNA [4], while in resource-rich countries benign processes predominate [1]. Moreover, in resource-limited countries, a greater proportion of malignancies diagnosed by FNA are primary and/or deep-seated tumors than in resource-rich countries. In the USA, primary cytologic diagnosis of malignancies is rare; rather, FNA is primarily used for the evaluation of superficial masses, the majority of which are benign and located in the head and neck [1]. It is important to note that this

pattern is observed even in institutions with robust pediatric FNA services and, in part, reflects the fact that Children's Oncology Group therapeutic protocols are based on histologic diagnosis and associated biologic studies require frozen or formalin-fixed tissue.

1.3 Diagnostic Considerations

Mass lesions in children and adolescents raise different diagnostic considerations than those in adults. In the pediatric population, malignancies are rare and comprised predominantly of hematolymphoid and central nervous system neoplasms. In contrast, in the adult population, cancer is common and epithelial neoplasms account for the vast majority of malignancies. Unlike in adults, small changes in age can significantly alter the differential diagnostic considerations in the pediatric population [5]. Table 1.2 lists the three most common types of malignancies in different age groups, and illustrates the changes observed with small increments of age. The types of tumors seen in a given anatomic site also vary with age. In the kidney, for example, mesoblastic nephroma is usually diagnosed in the first 3 months of life, whereas Wilms tumor is most common in children under 5 years of age, and renal cell carcinoma primarily affects adolescents. A variety of genetic syndromes are also associated with increased risk of developing certain pediatric tumors, as illustrated by the increased risk of Wilms tumor in children with Beckwith–Wiedemann, WAGR (Wilms tumor, aniridia, genitourinary malformation, and mental retardation), and Denys–Drash syndromes. Awareness of the types of tumors that arise at different ages in various anatomic locations and of the associations between genetic syndromes and certain types of tumors is important for accurate cytologic diagnosis of pediatric mass lesions.

Table 1.2 Cancer incidence by age group in children based on data from the Automated Childhood Cancer Information System ([5], adopted from ref. [2])

Age group	Tumor category
Infants (less than 1 y.o.)	#1: Sympathetic nervous system tumors
	#2: Leukemia
	#3: CNS tumors
Young children (1–4 y.o.)	#1: Leukemias
	#2: CNS tumors
	#3: Renal tumors
School-age children (5–9 y.o.)	#1: CNS tumors
	#2: Leukemias
	#3: Lymphomas
Older school-age children or young adolescents (10–14 y.o.)	#1: Lymphomas
	#2: Leukemias
	#3: CNS tumors
Older adolescents (15–19 y.o.)	#1: Lymphomas
	#2: Carcinomas
	#3: Germ cell tumors

In addition to these considerations, morphologic similarities between pediatric malignancies can pose diagnostic challenges. Many of the most common pediatric malignancies are small round blue cell tumors, while a variety of benign and malignant neoplasms have spindle cell morphology. Ancillary studies, such as immunoperoxidase stains, flow cytometry, fluorescence in situ hybridization, and/or other molecular tests, are usually required for definitive diagnosis, thereby making appropriate triage of these specimens critical. Treatments for many of these tumors vary considerably and thus, an accurate, specific diagnosis is essential. In contrast, for benign and low-grade spindle cell neoplasms for which treatment consists of surgical excision and for non-rhabdomyosarcomatous high-grade spindle cell sarcomas for which chemotherapy is the same, it may be sufficient to exclude certain entities and provide a narrowed differential diagnosis.

1.4 Conclusion

This book will provide a practical reference for pathologists evaluating cytologic specimens from pediatric patients. It is organized in an organ-based manner to address the spectrum of lesions seen in this population, and highlights important ancillary studies and differential diagnostic considerations.

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