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Original Article

Fine needle aspiration cytology in pediatric tumors: a low-cost, high-accuracy diagnostic tool for resource-limited settings

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Abstract: Introduction: Fine needle aspiration cytology (FNAC) is gaining popularity in diagnosing pediatric tumors because of ease of performance, easy reproducibility, and low morbidity. However, literature on its efficacy in resource-limited settings is lacking. Hence, the present study evaluated the diagnostic accuracy of FNAC in pediatric tumors in a North Indian center where ancillary diagnostic techniques are unavailable. Materials and methods: This was a four-year retrospective and 1-year prospective study. Both direct and radiology-guided FNAs were performed in children under 14 years. Cytomorphologic diagnoses were compared with the corresponding histopathologic diagnoses, wherever available, and the concordance rates determined. The diagnostic accuracy of FNAC for pediatric tumors was assessed using sensitivity, specificity, and positive and negative predictive values. Results: The present study included 125 cases of pediatric tumors, of which 65 were benign and 60 were malignant. The most common site of involvement was the head and neck. The most common benign pediatric tumor was pleomorphic adenoma, while the most common malignant tumor was non-Hodgkin lymphoma. The overall cytologic-histopathologic concordance was high (96.3%), with an overall sensitivity and specificity of 95.65% and 96.88%, respectively. Conclusions: FNAC is a highly sensitive and specific technique for diagnosing pediatric tumors, with a high histopathologic concordance, even in resource-limited setups where advanced ancillary techniques are unavailable. Nevertheless, additional ancillary techniques can complement FNAC to improve this diagnostic accuracy further.

Keywords: Fine needle aspiration cytology, pediatric tumors, benign tumors, malignant tumors, cytology, childhood tumors

Introduction

Childhood tumors are rare, accounting for less than 2% of all cancer cases in developed countries [1, 2]. The annual incidence of childhood cancer exceeds 200,000 worldwide. Of these, more than 80% are contributed by the developing world [3]. Several types of cancers are unique to the pediatric age group. Carcinomas, which are more frequently seen among adults, are sporadic among children [4]. A sizeable population-based registry study covering significant regions of the world found that the incidence rates were higher in boys than girls with a few exceptions. Female preponderance was observed for renal, epithelial, germ cell, and gonadal tumors. Differences also exist in the age-wise distribution of various pediatric and adolescent tumors. In children under 4 and 5-14 years, leukemia was the most common tumor, followed by central nervous system (CNS) tumors. In ages 15-19 years, lymphomas were the most common malignancies, followed by epithelial tumors and malignant melanoma [5].

Pediatric tumors show significant racial differences, being more common in Caucasians as compared to African-Americans. Overall, Hispanic children have a lower risk of cancer as compared to non-Hispanic Whites. Asians have a lower incidence than Whites, especially for

CNS tumors, neuroblastoma, and Wilms tumor [6]. There is also a considerable variation in the geographic distribution of pediatric tumors. For instance, the incidence of childhood Hodgkin's disease is relatively high among children of developing countries in Latin America and the Middle East. The highest incidence of Burkitt lymphoma is found in a broad geographic band of tropical Africa compared to any other region of the world [7]. The standardized incidence rate of childhood cancers in India ranges from 38 to 124 per million children per year, and the incidence is higher in males than in females. Leukemia constitutes 25% and 40% of childhood cancers in India and is the most common pediatric cancer. Lymphomas are the second most common, exceeding CNS tumors, and Hodgkin lymphoma is more common than non-Hodgkin's lymphoma [2].

Fine needle aspiration cytology (FNAC) is a widely acknowledged and generally accepted technique for evaluating and diagnosing mass lesions in adult patients. However, it has been receiving acceptance among clinicians for diagnosing tumors in the pediatric population. FNAC is generally considered a safe, rapid, and minimally invasive procedure with good patient acceptance [8]. However, the literature on its efficacy in resource-limited setups is sparse. Hence, the present study was performed at a tertiary care center in North India to study the distribution patterns and the cytomorphologic features of pediatric tumors by fine-needle aspiration cytology and to assess the reliability of FNAC in establishing an accurate diagnosis employing cyto-histopathologic correlation.

Materials and methods

Study design

The present study was done at a tertiary care hospital in Northern India. This center caters to a population size of approximately 900,000. This was a four-year retrospective and one-year prospective study. In the prospective study arm, patients were evaluated bad on history, chief complaints, physical examination, radiography, and clinical diagnosis. Patients screened positive on clinical examination and/or radiologic evaluations were sent for FNAC. FNAC was performed with a 21-gauge fine needle.

Inclusion criteria

Children aged less or equal to 14 years, with clinical or radiologic features indicative of a tumor, were included. The 0-14-year age group was chosen in accordance with the International Agency for Research (IARC) on cancer guidelines, which define children as being up to 14 years of age [9].

Exclusion criteria

Children with contraindications to FNAC, i.e., bleeding diathesis, were excluded.

Clinicoradiologic details

Data on age and gender were recorded. In the retrospective part, the FNAC records from the cytopathology archives were screened for the presence of tumors in this age group. The surgical histopathology database was then searched for the corresponding histopathologic diagnoses for the cases with a cytologic tumor diagnosis in the selected population. Data on age, gender, cytologic findings, and histopathology reports were recorded for all the included cases.

Fine needle aspiration cytology

With the patient in a comfortable position on the couch, the lesion was grasped with two fingers of one hand. The overlying skin was prepared by applying an antiseptic solution. Aspiration was done with a 21 Gauge needle advancing into the center of the tumor using quick and smooth motion. Suction was applied while the needle was moved back and forth within the lump using short, quick strokes. The aspirate was expressed on the slides, and 4 to 6 smears were prepared. Direct percutaneous FNAC was performed for superficially located pediatric tumors. Ultrasound-guided or computerized tomography-guided FNAC was performed for deep-seated tumors like those in the mediastinum or the retroperitoneum. Fixation for Hematoxylin and Eosin (H&E) staining and Papanicolaou staining was done in 70% ethyl alcohol. For May Grunwald Giemsa (MGG) staining, smears were air-dried.

Cytomorphologic examination

The stained smears were examined microscopically by two independent pathologists and diagnosed cytomorphologically. Various cytomorphologic features of all pediatric tumors were analyzed in detail, including the adequacy of the aspirate, cell arrangement, cellular mor-

Table 1. Age and gender distribution of pediatric tumors noted in the present study (n=125)

Characteristic	Number of patients (n)	Percentage (%)
Gender		
Male	68	54.4
Female	57	45.6
Age group		
11-14 years	73	58.4
6-10 years	23	18.4
1-5 years	26	20.8
<1 year	3	2.4

phology, nuclear features, cytoplasmic characteristics, and smear background.

Histopathologic examination

Surgical biopsies/specimens were processed for histopathologic examination using standard histopathological techniques [10]. An attempt was made to ascertain the concordance between cytological and histopathological examination wherever the subsequent histopathological diagnosis was available.

Data analysis

The concordance between the cytological and histopathological diagnoses was calculated as a percentage. The diagnostic discrimination of FNAC in pediatric tumors was assessed by calculating sensitivity, specificity, positive predictive value, and negative predictive value. All statistical analysis was done using Epi Info version 6.0.

Results

The present study included 125 cases of pediatric tumors in the age group of 0-14 years. Of these, 75 cases were retrieved retrospectively, and 50 cases were included prospectively. The mean age of patients in this study was 10.2 years. The youngest patient was nine months old, and the oldest was 14. Most cases (58.4%) were in the 11-14-year age group. Males were more cfrequent than females in all age groups except in the 11-14-year age group, where females were predominant. Out of a total of 125 cases, 65 (58%) were benign and 60 (48%) were malignant (**Table 1**).

Among the benign tumors, pleomorphic adenoma (n=12) was the most common, contributing to 18.5% of all benign cases. Fibroadenoma, hemangioma, and lipoma together constituted around 50.7% of the benign cases. Among the malignant tumors, hematolymphoid malignancies (n=25) were the most common, contributing 41.6% of all malignant cases, followed by malignant small round cell tumors (n=21), which accounted for 35% of all the cases. Amongst the individual cytologic diagnoses, pleomorphic adenoma was the most common pediatric tumor, accounting for 9.6% (n=12) of all the cases. Fibroadenomas, lipomas, and hemangiomas each accounted for 8.8% of all cases. Non-Hodgkin lymphoma (NHL) was the most common malignant tumor in our study, accounting for 8.0% (n=10) of all cases, followed by Hodgkin lymphoma (HL) (n=8; 6.4%) (**Table 2**).

Region-wise distribution of benign and malignant pediatric tumors showed the predominance of tumors in the head and neck region with 28.8% of the cases. In contrast, the least common sites were the thorax, chest wall, and mediastinum, involved in 5.6% of the cases. In the head and neck region, 27 (21.6%) cases were benign, and 9 (7.2%) were malignant tumors. The most common benign tumor was pleomorphic adenoma; the most common malignant tumors were the malignant small round cell tumors (MSRCTs). Abdominal, back, pelvic, and genitourinary regions had 16 (12.8%) malignant and 5 (4.0%) benign tumors. The most common tumors in these regions were malignant small round cell tumors, accounting for 8 (38.1%) cases. Fibroadenoma was the only breast tumor observed in the present study, accounting for 11 (8.8%) cases (**Table 3**).

The corresponding histopathologic diagnoses were available for 55 (44%) cases. On comparing the cytologic diagnoses with the corresponding histopathologic diagnoses, we observed that the cytological diagnoses were concordant in 53 (96.4%) cases. A cyto-histopathologic discordance was observed in 2 (3.6%) cases (**Table 4**). We noted an overall sensitivity and specificity of 95.65% and 96.88%, respectively. The positive predictive value of FNAC was 95.65%, and the negative predictive value was 96.88%, with an overall accuracy of 96.36% (**Table 5**).

Table 2. Various benign and malignant pediatric tumors observed in the present study (n=125)

Cytologic diagnosis	Patients in the present study (n=125) (%)
Benign tumors (n=65)	
Pleomorphic adenoma	12 (9.6)
Fibroadenoma	11 (8.8)
Hemangioma	11 (8.8)
Lipoma	11 (8.8)
Benign nerve sheath tumor	9 (7.2)
Lymphangioma	9 (7.2)
Xanthoma	2 (1.6)
Hematolymphoid tumors (n=25)	
Non-Hodgkin lymphoma	10 (8.0)
Hodgkin lymphoma	8 (6.4)
Acute lymphoblastic leukemia	4 (3.2)
Myeloid sarcoma in acute myeloid leukemia	1 (0.8)
Langerhans cell histiocytosis	2 (1.6)
Malignant small round cell tumors (n=21)	
Ewing Sarcoma	5 (4.0)
Neuroblastoma	5 (4.0)
Wilms tumor	3 (2.4)
Rhabdomyosarcoma	2 (1.6)
Hepatoblastoma	1 (0.8)
Retinoblastoma	1 (0.8)
Malignant small round cell tumor-not otherwise specified	4 (3.2)
Malignant germ cell tumors (n=9)	
Yolk sac tumor	4 (3.2)
Embryonal carcinoma	1 (0.8)
Malignant germ cell tumor - not otherwise specified	4 (3.2)
Others (n=5)	
Papillary carcinoma thyroid	3 (2.4)
Liposarcoma	1 (0.8)
Osteosarcoma	1 (0.8)

Table 3. Regional distribution of benign and malignant pediatric tumors in the present study (n=125)

Location	Benign	Malignant	*P* Value
Head & neck	27 (21.6%)	9 (7.2%)	<0.0001
Chest wall, thorax, and mediastinum	3 (2.4%)	4 (3.2%)	
Abdomen, back, and pelvis	5 (4%)	16 (12.8%)	
Breast	11 (8.8%)	0	
Extremities	19 (15.2%)	10 (8%)	
Lymph Nodes	0	21 (16.8%)	

Discussion

The present study included all pediatric tumors except brain and spinal cord tumors. Most tumors were noted to occur in the 11-14-year age group. Infants constituted only 2.4% of the study group. This is in accordance with the results of Maheshwari et al. and Yaris et al., who also reported the 11-14 years as the most predominant age group [11, 12]. The reason for such predilection is unknown; however, it has been suggested that the growth spurt and increased metabolic activity may be the predisposing factors. The other reason may be that many children in this age group are subject to child labor in developing countries and may be exposed to carcinogens [12].

Table 4. Cytologic-histopathologic correlation observed in the present study

		Histopathology		Total
		Benign	Malignant	
Cytology	Benign	22	1	23
	Malignant	1	31	32
Total		23	32	55

Table 5. Diagnostic discrimination of fine-needle aspiration cytology in the present study

Statistic	Value	95% Confidence intervals
Sensitivity	95.65%	78.05% to 99.89%
Specificity	96.88%	83.78% to 99.92%
Positive Predictive Value	95.65%	76.13% to 99.35%
Negative Predictive Value	96.88%	82.00% to 99.53%
Accuracy	96.36%	87.47% to 99.56%

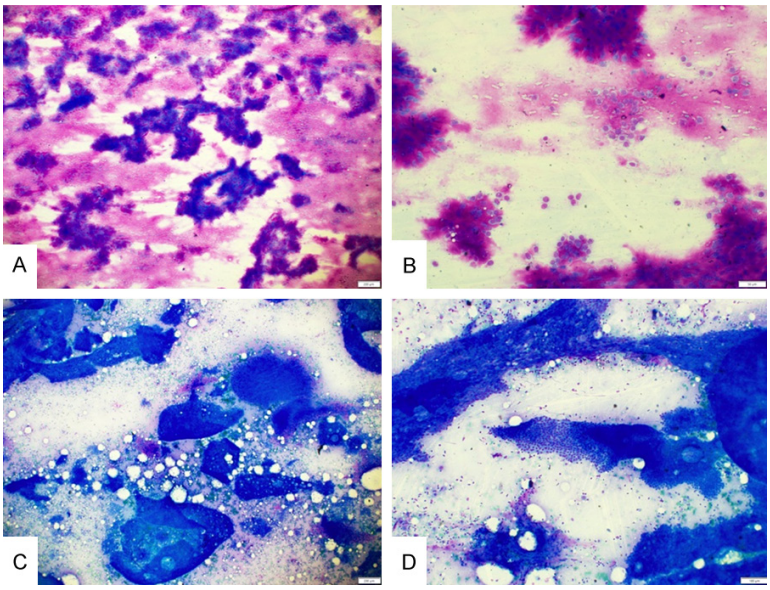

Figure 1. (A, B) Pleomorphic adenoma: Fine needle aspiration smear showing clusters of epithelial and myoepithelial cells in the background of abundant chondromyxoid stroma (May Grunwald Giemsa; A: 4×, B: 20×); (C, D) Fibroadenoma: Fine needle aspiration smear showing multiple sheets and branching clusters of benign ductal epithelial cells with bare bipolar myoepithelial nuclei and stromal fragments in the background (May Grunwald Giemsa; C: 4×, D: 10×).

In the present study, the male-to-female ratio was 1.2:1. Males were more commonly affected in all age groups, except in the 11-14-year age group, where females were more commonly affected. These findings are consistent with the previous studies. Maheshwari et al. reported a male-female ratio of 2:1 in their study [11], and Shakoor et al. reported a male-female ratio of 1.5:1 in their study [13]. The predominance of pediatric tumors in males may be because of rapid growth and larger body size in males, which increases their risk of cancer [14]. Furthermore, males are at increased risk of cancer-initiating events like loss of tumor suppressor genes or gain of oncogene function, whereas females may be more resistant to these events [15].

Head and neck tumors were the most common tumors in the present study (28.8%), followed by musculoskeletal tumors (23.2%), lymph node tumors (16.8%), abdomen, back, and pelvic tumors (16.8%), and breast tumors (8.8%). Chest wall, mediastinal, and thoracic tumors were the least common (5.6%). These results are similar to previous studies wherein authors observed the head and neck region as the most common site and the thorax as the least common site for pediatric tumors [16].

In the present study, there were 125 tumors, of which 65 (52%) were benign, and 60 (48%) were malignant, with a benign:malignant tumor ratio of 1.08:1. Maheshwari et al. reported a benign:malignant ratio of 2.8:1, whereas it was 1.2:1 in the study by Drut et al. [11, 17]. The most common tumor in the present study was pleomorphic adenoma, followed by fibroadenoma, lipoma, and hemangioma. The cytologic smears in cases of pleomorphic adenoma were cellular and showed variable admixtures of benign epithelial and myoepithelial cells embedded in abundant fibrillary chondromyxoid stroma. The smears in cases reported as fibroadenoma demonstrated multiple sheets and branching cohesive clusters of benign duc-

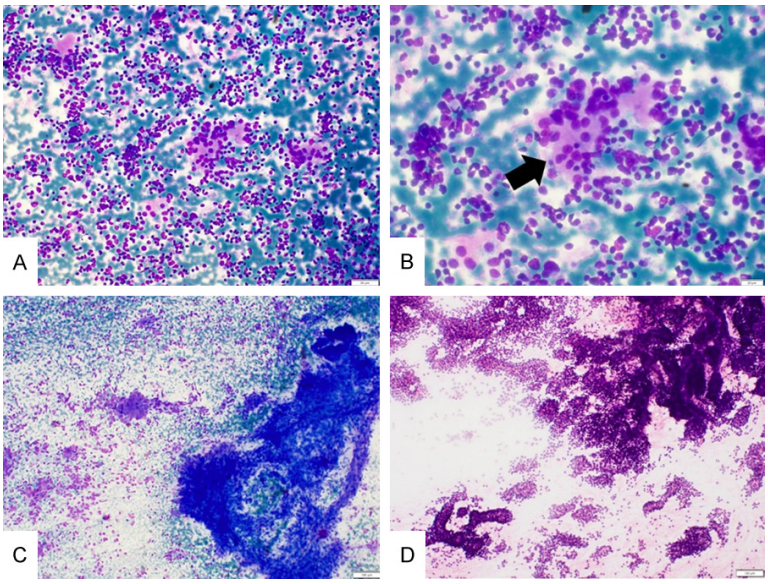

Figure 2. (A, B) Neuroblastoma: Fine needle aspiration smear showing singly scattered small round tumor cells with pinkish fibrillary material (neuropil) in the background as well as in the center of Homer-Wright rosettes (arrow) (May Grunwald Giemsa; A: 20×, B: 40×); (C, D) Wilms tumor: Fine needle aspiration smear showing singly scattered blastemal cells with cohesive papillary clusters of epithelial cells and loose mesenchymal fragments (C: May Grunwald Giemsa; 10×) (D: Hematoxylin and eosin; 10×).

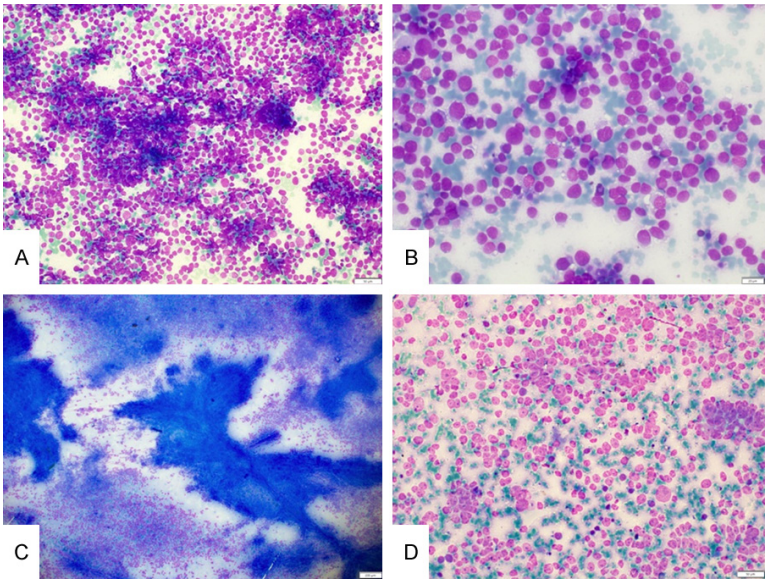

Figure 3. (A, B) Ewing sarcoma: Fine needle aspiration smear showing predominantly singly scattered small round tumor cells with mild pleomorphism, fine chromatin, inconspicuous nucleoli and scant cytoplasm with some showing cytoplasmic vacuolations (May Grunwald Giemsa; A: 20×, B: 40×); (C, D) Rhabdomyosarcoma: Highly cellular fine needle aspiration smear showing singly scattered round tumor cells with mild to moderate anisonucleosis, fine chromatin, occasional prominent nucleoli, and scant to vacuolated cytoplasm (May Grunwald Giemsa; C: 4×, D: 20×).

tal epithelial cells with many bare bipolar myoepithelial nuclei in the background (**Figure 1**).

Among the malignant tumors, the hematolymphoid tumors (n=25; 41.6%) were the most common, followed by malignant small round cell tumors (n=21; 35%). Among the hematolymphoid tumors, NHL (n=10) was the most common, followed by HL (n=8) and infiltration by acute lymphoblastic leukemia (n=4) (**Figure 2**). The common MSRCTs encountered in this study included Ewing sarcoma and neuroblastoma (n=5), followed by Wilms tumor (n=3) and rhabdomyosarcoma (n=2) (**Figures 3**, **4**). Among the least common malignant tumors, there were 3 cases of papillary carcinoma thyroid and 1 case each of liposarcoma and osteosarcoma (**Figure 5**). These findings are similar to those observed by other researchers in the literature [18, 19].

In the present study, histological diagnosis was available for correlation in 55 (44%) of the 125 cases. Of these, the cytological diagnosis was found to be in concordance with the histological diagnosis in 53 (96.4%) cases. A cytohistological mismatch was observed in 2 (3.6%) cases. The concordance rates in different studies range from 95% to 98%, similar to that noted in the present study [11, 16, 17] (**Table 4**). The discordant cases included one case reported as an NHL on cytology, which was found to be reactive lymphoid hyperplasia on subsequent histopathologic examination, and one case reported as benign nerve

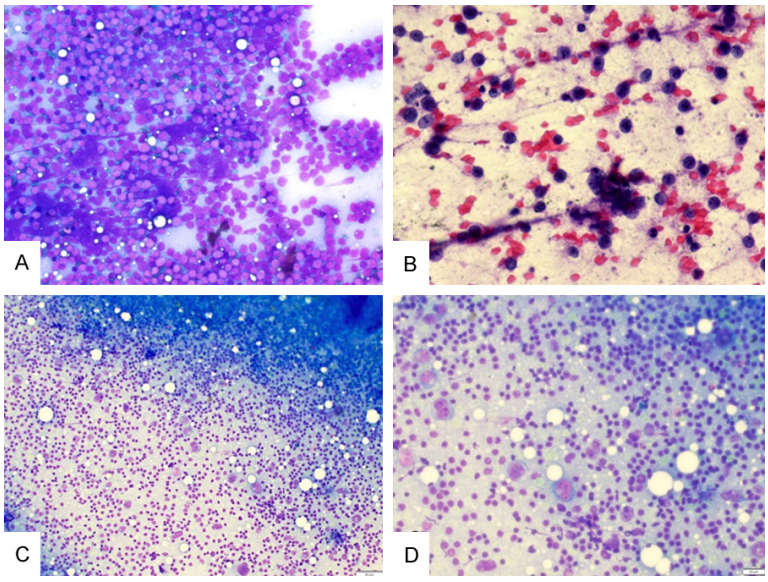

Figure 4. (A, B) Lymphoblastic lymphoma (non-Hodgkin lymphoma): Fine needle aspiration smear showing high cellularity with monomorphic population of atypical lymphoid cells with high nucleo-cytoplasmic ratio, open chromatin, variably conspicuous nucleoli, and scant cytoplasm (May Grunwald Giemsa; 20×) (D: Hematoxylin and eosin; 40×); (C, D) Hodgkin lymphoma: Fine needle aspiration smear showing scattered mononuclear, binucleated, and multinucleated Reed-Sternberg cells in a background showing reactive lymphoid cells with scattered eosinophils (May Grunwald Giemsa; C: 20×, D: 40×).

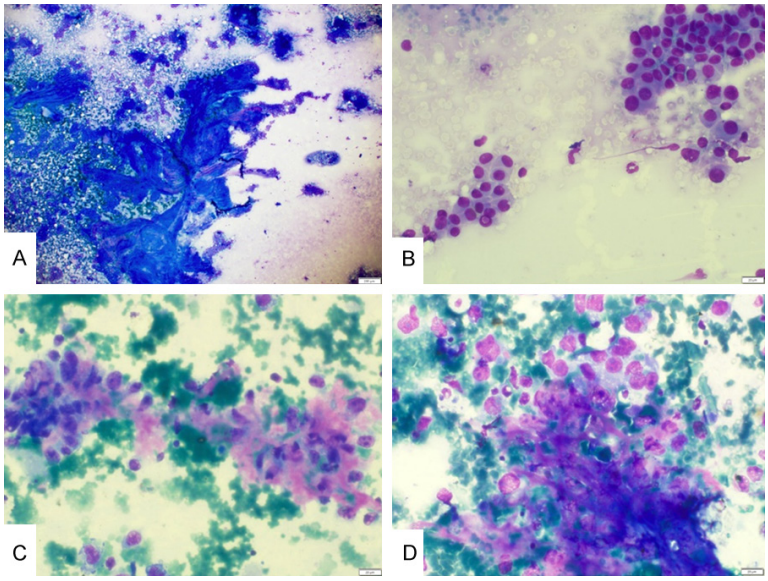

Figure 5. (A, B) Papillary thyroid carcinoma: Fine needle aspiration smear showing papillae and sheets of thyroid follicular cells with nuclear enlargement, pale to fine chromatin, inconspicuous nucleoli, longitudinal nuclear grooving, and intranuclear pseudoinclusions (May Grunwald Giemsa; A: 4×, B: 40×); (C, D) Osteosarcoma: Fine needle aspiration smear showing highly pleomorphic tumor cells associated with lacy eosinophilic osteoid (May Grunwald Giemsa; 40×).

sheath tumor on cytology, which was reported as a spindle cell sarcoma on subsequent histopathologic examination.

The overall sensitivity and specificity of FNAC in the present study were 95.65% and 96.88%, respectively. The positive predictive value of FNAC was 95.65%, and the negative predictive value of FNAC was 96.88%, with an overall accuracy of 96.36% (**Table 5**). These results are similar to those documented by previous studies in the literature [11, 15, 17, 20].

FNAC has been slow to gain popularity for the diagnosis of pediatric mass lesions as compared to adults because of the rarity of pediatric tumors, morphologic overlap with many tumors, lack of awareness of the characteristic cytomorphologic features, non-representative/inadequate sampling, and unavailability of specific ancillary diagnostic techniques [21-23]. The results of the present study indicate that FNAC is a highly precise, cost-beneficial diagnostic method with low morbidity and can replace histopathological diagnosis in many cases [24]. Furthermore, the use of ancillary diagnostic techniques, including immunocytochemistry, flow cytometry, fluorescence in situ hybridization, and next-generation sequencing, can enable pathologists to give definitive diagnoses in most of these cases [22]. The sensitivity and specificity of FNAC in pediatric lesions have approached 93% and 100%, respectively, in experienced centers. The results

of this study show that with adequate training, resource-limited setups can also strive to achieve diagnostic rates comparable to those of experienced centers.

The strengths of this study include a large sample size (over a study period of 12 months), which was representative of the majority of pediatric tumors. However, the limitations include the retrospective nature of one arm of the study and the fact that cyto-histologic correlation was available for only 44% of the cases. Despite limitations, nonetheless, this study shows that FNAC can be used as a reliable and safe diagnostic tool for pediatric tumors in resource-limited settings.

Conclusions

FNAC is an effective, reliable, and safe diagnostic modality for evaluating pediatric tumors in resource-limited settings. It has the distinct advantages of ease of procedure, rapid diagnosis, no need for anesthesia, and minimal complications. It gives excellent predictive results for benign tumors and a majority of malignant tumors. However, poorly differentiated and primitive tumors may be challenging to diagnose accurately based on cytomorphology alone. The cytological results should be carefully interpreted and confirmed using ancillary diagnostic tests and/or histopathological examination for such tumors.

Disclosure of conflict of interest

None.

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