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Spectrum of pediatric tumors diagnosed by fine-needle aspiration cytology

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Abstract

Pediatric tumors differ markedly from adult tumors in their nature, distribution, and prognosis. In this 10-year retrospective study, we present our experience with fine-needle aspiration (FNA) in pediatric patients 18 years of age and younger and correlate relationship between gender with organ, diagnosis, malignancy, and age. In our study, FNA material of pediatric tumors or masses with 18 years aged and younger were analyzed retrospectively.

All FNAs in pediatric patients during this time period were identified and analyzed for age, gender, cytologic diagnosis, and site of aspiration. A total 1000 FNAs were performed from January 2007 to October 2015 in 499 children. Regardless the gender, the most frequently aspirated organ was lymph node, comprising 129 of the 499 cases followed by thyroid (112), neck cyst (79), and parotid (35) cases. The majority of the cases were diagnosed as benign lesions (436 of 499 cases). Other 63 cases comprising 40 female and 23 male cases had malignant lesions. There was significant age difference between people with or without malignancy. In malignant cases, there was a significant difference between the age on males and females. In regard to gender and diagnosis, cytologic diagnosis was stratified into 9 broad diagnostic categories: lymphadenitis, benign and malignant thyroid, cyst contents, benign breast, benign and malignant salivary, and negative for malignancy.

In conclusion, our study supports the use of FNA cytology (FNAC) in lesions of various anatomic sites in the children less than 18 years old. As a simple, minimally invasive, and rapid procedure, cytopathologists can reliably utilize FNAC in children. The mean age of children receiving a malignant diagnosis was significantly higher than that of benign lesions. The mean age of malignancy in boys is significantly lower than that of girls with malignancy.

Abbreviations: FNA = fine-needle aspiration, FNAC = fine-needle aspiration cytology.

Keywords: benign lesions, fine-needle cytology, malignancy, organ frequency, pediatric tumors

1. Introduction

Pediatric tumors differ markedly from adult tumors in their nature, distribution, and prognosis.[1] Pediatric patients represent a unique study population with regard to spectrum and frequency of disease. Although only 2% of all malignant tumors occur in infancy and childhood, cancer is the leading disease related cause of death among children in the world.[2] Fine-needle aspiration cytology (FNAC) of the tumors is well accepted as a diagnostic procedure in the adult population. FNAC has been recently recommended as a technique for accurate evaluation and diagnosis of childhood.[3–6] It has been shown to be a safe, with minimal trauma, and cost-effective diagnostic method that notably typically lacks the need for sedation or general anesthesia in compared to surgical biopsy.[1] Despite these reported benefits, FNA as a diagnostic tool is still far less universally accepted in pediatric patients than in adults.[7] To our knowledge there is only 1 report analyzing all FNAs, both benign and malignant, performed at a large medical center in children 12 years of age and younger.[7]

Previous publications have more narrowly focused on FNA of specific anatomic sites or of particular disease entities. In this 10-year retrospective study, we present our experience with FNA in pediatric patients 18 years of age and younger and correlate relationship between gender with organ, diagnosis, malignancy, and age. Additionally, the diversity of lesions that can occur in the pediatric patients was investigated.

2. Materials and methods

Computer-generated searches were performed in the archives of the Pathology Departments of Dr Daneshbod Lab during the period January 2007 to October 2015. In our study, FNA material of pediatric tumors or masses with 18 years aged and younger were analyzed retrospectively.

All FNAs in pediatric patients during this time period were identified and analyzed for age, gender, cytologic diagnosis, and site of aspiration.

Editor: Sergio Gonzalez Bombardiere.

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:6(e5480)

Received: 10 March 2016 / Received in final form: 6 October 2016 / Accepted: 1 November 2016

http://dx.doi.org/10.1097/MD.0000000000005480

Aspirations were performed by cytopathologists using 25- or 27-gauge needles. The aspirated material was expelled onto glass slides and smeared. The smears were fixed immediately in 95% ethanol and stained by the Papanicolaou method or air-dried and stained with modified Giemsa. Cytologic diagnosis was classified into different diagnostic categories.

Nondiagnostic specimens were considered technically unfeasible (i.e., technical failures), the patients with recurrent lesions, and they were lost to follow-up were excluded from the study.

2.1. Statistical analysis

Data management was done by using the Statistical Package for Social Sciences (SPSS version 22). Descriptive statistics were used to gender, organ, diagnosis, and malignancy frequencies, age histogram and analysis of these frequencies with gender. Age difference between malignant/benign cases and sex difference between malignant/benign cases were analyzed by using *t* tests, and Chi-square, respectively.

2.2. Ethics statement

The Ethics Committee and the authors' institutional review board of Shiraz Molecular Pathology Research Center (Shiraz, Iran) approved the study. The author group collected written informed consent from all the patients.

3. Results

A total 1000 FNAs were performed from January 2007 to October 2015 in 499 children who ranged in age from 4 months to 18 years (mean, 11.51 ± 5.41 years). Out of the patients 268 (53.7%) cases were female and 231 (46.3%) were male. The mean age of male and female patients was 9.72 ± 5.47 and 13.06 ± 4.86 years (Fig. 1A and B). The patients were classified in 4 age groups; 0 to 5 (76 cases, 15.2%), 5 to 10 (102 cases, 20.4%), 10 to 15 (129 cases, 25.9%), and 15 to 18 (192 cases, 38.5%) years old (Table 1).

Regardless the gender, the most frequently aspirated organ was lymph node, comprising 129 of the 499 cases (25.9%) followed by thyroid including 112 cases (22.4%), neck cyst including 79 cases (15.8%) and parotid including 35 cases (7.0%) (Fig. 2A). Lymph nodes and thyroid were most frequently aspirated organs in male and female patients, respectively.

Cytologic diagnosis was stratified into 9 broad diagnostic categories: lymphadenitis, benign and malignant thyroid, cyst contents, benign breast, benign and malignant salivary, and negative for malignancy (Table 2) (Fig. 3A). Lymphadenitis and

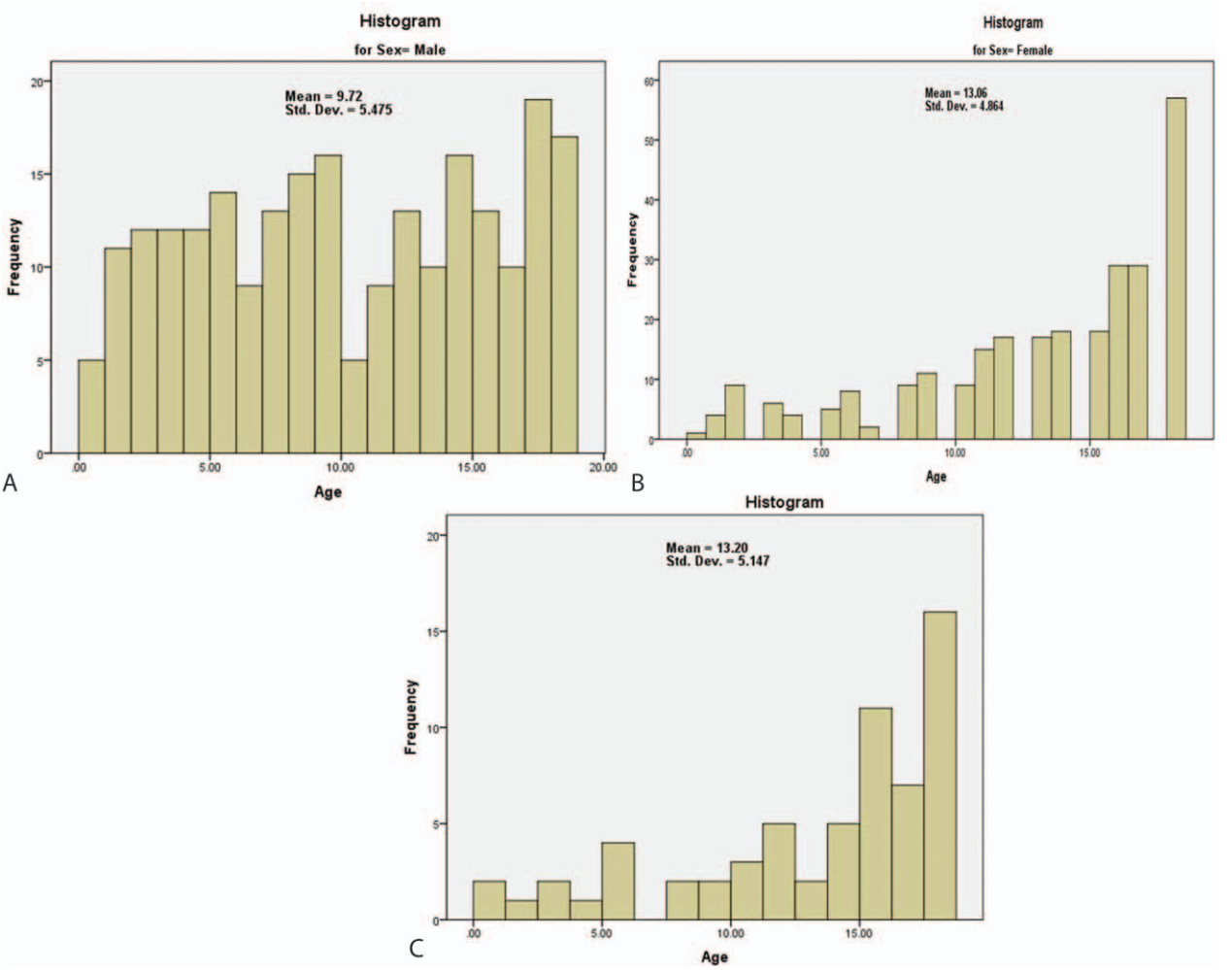

Figure 1. (A and B) Age histogram in male and female patients, (C) age histogram in malignant diagnoses.

Table 1

Incidence rates for cancers and benign lesions in regard to age and cytologic diagnosis.

Diagnostic code	Age				Total
	0–5	6–10	11–15	16–18	
1	36 (19.8%)	52 (28.6%)	46 (25.3%)	48 (26.4%)	182
2	4 (20%)	1 (5%)	7 (35%)	8 (40%)	20
3	0 (0.0%)	0 (0.0%)	1 (100%)	0 (0.0%)	1
4	1 (1.1%)	7 (7.4%)	39 (41.1%)	48 (50.5%)	95
5	14 (26%)	18 (33.3%)	10 (18.5%)	12 (22.2%)	
6	0 (0.0%)	0 (0.0%)	3 (11.1%)	24 (88.9%)	27
7	6 (13.6%)	7 (15.9%)	10 (22.7%)	21 (47.7%)	44
8	0 (0.0%)	1 (5.6%)	4 (22.2%)	13 (72.2%)	18
9	15 (25.9%)	16 (27.6%)	9 (15.5%)	18 (31%)	58
Total	76 (15.2%)	102 (20.4%)	129 (25.9%)	192 (38.5%)	

The code number, 1–9, is defined according to Table 2.

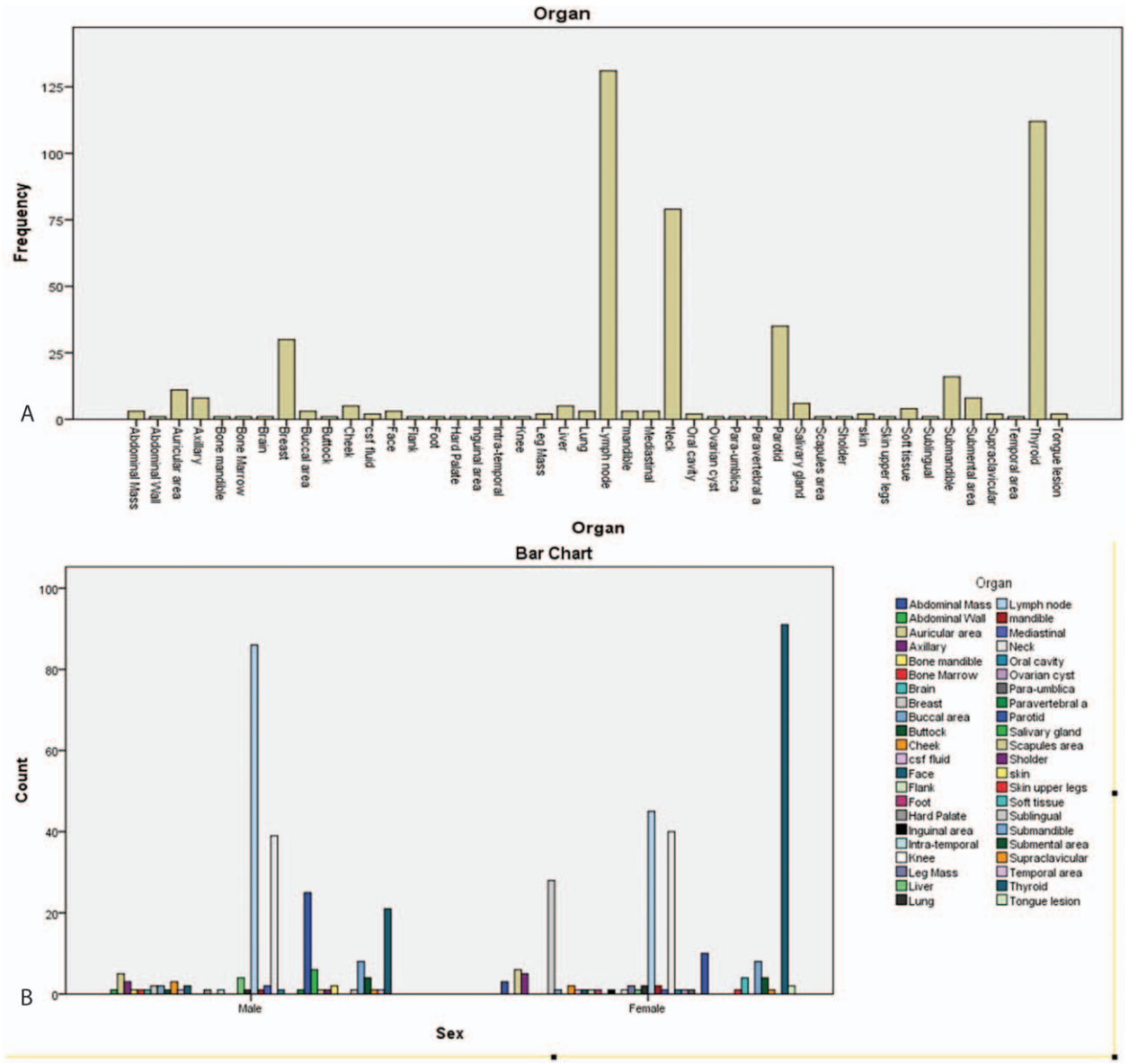

Figure 2. (A) Organ frequency regardless to the gender. The most frequently aspirated organ was lymph node followed by thyroid including neck cyst and parotid cases. (B) Organ frequency in male and female patients.

Table 2

Nine broad diagnostic categories was made by FNAC diagnosis.

Label as	Diagnosis	Surgical follow-up
1. Lymphadenitis (granuloma, necrotizing)	Essentially normocellular marrow	Persistent; Hodgkin lymphoma; tuberculosis; infectious mononucleosis; localized leishmania lymphadenitis
	Reactive lymphoid hyperplasia	
	Reactive follicular hyperplasia	
	Reactive lymphadenitis	
	Reactive lymphadenopathy	
	Suggestive of reactive lymphadenitis	
	Consistent with reactive lymphadenitis	
	Reactive lymph node with few atypical large cells	
	Reactive changes	
	Giant cell granulomatous lymphadenitis	
	Few atypical cells are seen	
	Necrotizing granulomatous	
	Necrotizing suppurative lymphadenitis	
	Suggestive of granulomatous lymphadenitis	
	Necrotizing granulomatous lymphadenitis	
	Granulomatous lymphadenitis	
	Consistent with granulomatous lymphadenitis	
	Necrotizing lymphadenitis	
	Necrotizing suppurative lymphadenitis	
	Suggestive of suppurative lymphadenitis	
	Acute suppurative lymphadenitis	
	Suggestive of suppurative lymphadenitis	
2. Benign salivary gland lesion	Suggestive of suppurative chronic sialoadenitis	Basal cell adenoma; mixed tumor, sialoadenitis
	Suggestive of acute suppurative sialoadenitis	
	Salivary gland neoplasm, suggestive of recurrence of basal cell adenoma	
	Salivary gland neoplasm, pleomorphic adenoma (mixed tumor)	
3. Malignant salivary gland tumor	Highly suspicious for recurrence of mucoepidermoid carcinoma	Mucoepidermoid carcinoma
4. Benign thyroid lesion	Chronic lymphocytic thyroiditis	Hashimoto thyroiditis; colloid nodular goiter; benign follicular nodule; simple or hemorrhagic cyst; chronic thyroiditis
	Benign, consistent with chronic lymphocytic (Hashimoto) thyroiditis	
	Benign, chronic lymphocytic thyroiditis	
	Nodular goiter with chronic lymphocytic thyroiditis	
	Benign follicular nodule (colloid nodular goiter)	
	Benign follicular nodule (colloid nodular goiter with cystic degeneration)	
	Nodular goiter	
	Cystic colloid goiter	
	Suggestive of epidermoid cyst	
	Adenomatous goiter with focal chronic lymphocytic thyroiditis	
	Benign follicular nodule (adenomatous goiter)	
5. Cyst	Suggestive of thyroglossal duct cyst	Abscess; thyroglossal duct cyst; branchial cleft cyst; epidermal inclusion cyst; inflammation; surgical remove
	Suggestive of thyroglossal cyst with inflammatory process	
	Acute inflammatory process	
	Severe acute inflammation and abscess formation	
	Inflammatory process	
	Benign cyst	
	Suggestive of branchial cleft cyst	
	Suggestive of epidermal inclusion cyst	
	Infected Epidermoid Cyst depidermoid cyst	
	Nonneoplastic cystic lesion	
	Epidermal inclusion cyst	
	Consistent with infected epidermal inclusion cyst	
6. Benign breast	Fibroadenoma	Fibroadenoma; fibrocystic change; benign breast tissue
	Suggestive of fibroadenoma	
	Fibroadenoma with foci of fibrocystic change	
7. Positive for malignancy	Positive for malignancy	Lymphoma; Hodgkin lymphoma; T-ALL; metastatic sarcoma
	Suspicious for malignancy	

Label as	Diagnosis	Surgical follow-up
	Small round cell tumor	
	Positive for malignancy, Hodgkin lymphoma	
	Suspicious for Hodgkin lymphoma	
	Highly suspicious for lymphoma	
	Positive for malignancy, lymphoma	
	Positive for malignancy, according to cytomorphology and IHC suggestive of high grade sarcoma	
	Positive for malignancy, spindle cell	
	Metastatic osteosarcoma	
	Suspicious for histocytosis-X	
8. Malignant thyroid	Positive for malignancy, thyroid papillary carcinoma	Papillary thyroid carcinoma; metastatic carcinoma
	Positive for malignancy, metastatic thyroid papillary carcinoma	
	Suspicious for papillary carcinoma	
	Positive for malignancy, suspicious of papillary.	
	Highly suspicious for thyroid papillary carcinoma in base of lymphocytic thyroiditis	
9. Negative for malignancy	Only fat with 1 atypical cell cluster	Hemangioma; lipoma; hematoma; Sjogren syndrome; hematolymphoid
	Lipoma	Lesions
	Probably hematoma	
	Suggestive of hematoma	
	Suggestive of benign vascular lesion	
	Not suitable for diagnosis	
	Suspicious of benign mesenchymal	
	No malignant cell is seen	
	Negative for malignancy	
	Sjogren syndrome	
	Suggestive of hemangioma	

ALL = acute lymphoblastic leukemia, FNAC = fine-needle aspiration cytology, IHC = immunohistochemistry.

benign thyroid were frequently detected in male and female patients, respectively (Fig. 3B).

The majority of the cases were diagnosed as benign lesions (436 of 499 cases, 87.37%). Other 63 cases comprising 40 female and 23 male cases had malignant lesions. There was no significant sex difference between people with or without malignancy ($P > 0.05$). Organ frequency in malignant cases is shown in Fig. 4.

Regardless the gender, the mean age of children receiving a benign diagnosis was 11.26 ± 5.41 years, while the mean age for malignant diagnoses was 13.20 ± 5.14 years. There was significant age difference between people with or without malignancy ($P < 0.01$). The highest malignant cases were found in children with over 15 years old (Fig. 1C).

In regard to gender, the mean age of malignancy in male and female patients was 10.81 ± 5.60 and 14.56 ± 4.37 years, respectively. In malignant cases, there was a significant difference between the age on males and females ($P < 0.01$).

4. Discussion

The primarily aim of this study was to consider our experience with FNA in pediatric patients 18 years of age and younger and correlate relationship between gender with organ, diagnosis, malignancy, and age. The utility of FNA in children has been illustrated in numerous studies.[8–10] However, to our knowledge, there is no report detailing the application of FNA cytology to lesions of several anatomic sites in the pediatric population. The majority of our cases, children presented with persistently enlarged lymph nodes followed by thyroid and neck lesions. Since lymph nodes and thyroid were most frequently aspirated organs in male and female patients in this study, lymphadenitis and benign thyroid were frequently detected in male and female patients, respectively. Pediatric head and neck lesions are common, and as illustrated in this series most represent reactive lymphoid proliferations. In the most of cases, children present with persistently enlarged lymph nodes after a trial course of antibiotics.[11] Thyroid nodules < 1 cm are rarely biopsied unless or more suspicious ultrasound criteria are found, or if there is a concerning clinical history, including previous neck irradiation, previously diagnosed thyroid cancer or an increased calcitonin level.[12]

The patients were classified in 4 age groups and the average age-specific incidence rates for each of the 4 calendar periods of observation show dissimilar and much higher cancer rates for the oldest (15–19 years of age) age groups than the youngest (0–5) and 2 intermediary age (5–10 and 10–15) groups. Regardless the gender, the mean age of children receiving a benign and malignant diagnosis was 11.26 ± 5.41 and 13.20 ± 5.14 years, respectively. There was significant age difference between people with or without malignancy. The highest malignant cases were found in children with over 15 years old. The most malignant cases of our patients were lymphoma and thyroid cancer. The most common cancer in children ages 0 to 14 are acute lymphocytic leukemia, brain and central nervous system, neuroblastoma, and non-Hodgkin lymphoma, hence, the most common cancers among adolescents ages 15 to 19 are Hodgkin lymphoma, thyroid carcinoma, and lymphoma.[13] Since most of our patients were diagnosed as thyroid cancer (Table 1), the highest malignancies were detected in children over 15 years old. In regard to gender, the mean age of malignancy in male was lower than that of female patients (10.81 ± 5.60 years vs 14.56 ± 4.37 years). There was a significant difference between the age on boys and girls with malignancies. Some of these differences may reflect the different types of cancers that occur in male compared to female in this age group.[14] For example, boys have somewhat higher rates of Hodgkin lymphoma for children younger than

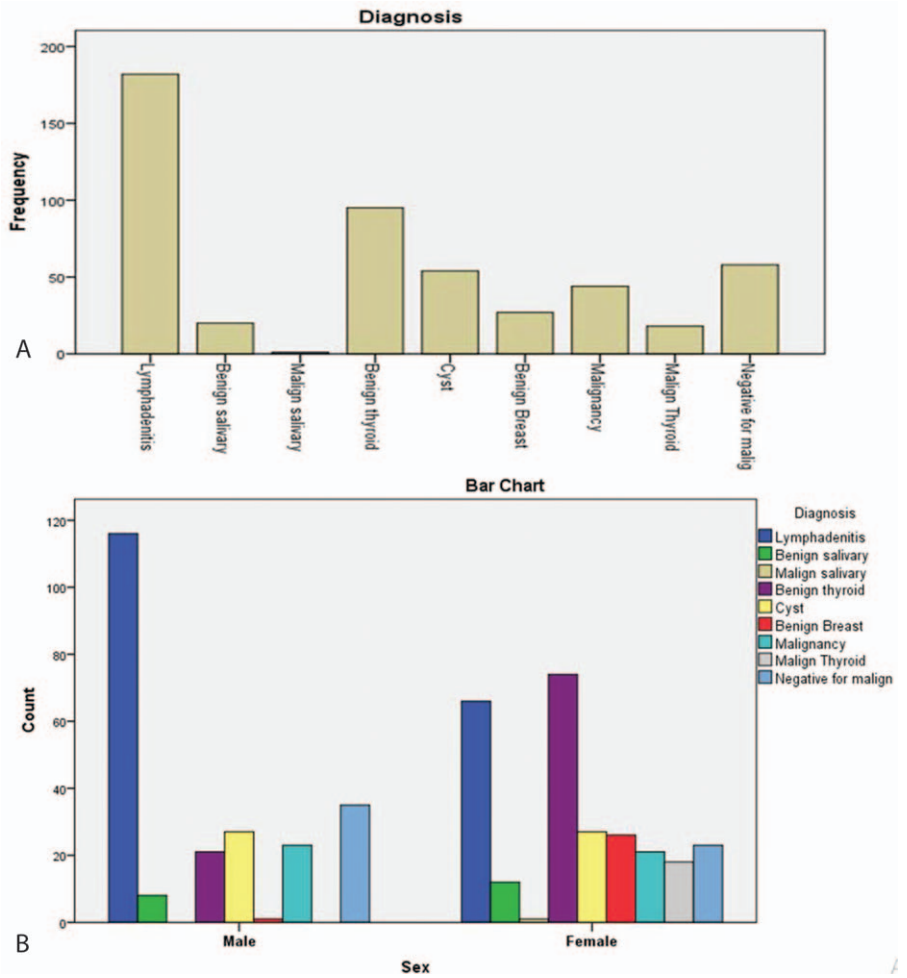

Figure 3. (A) Cytologic diagnosis was stratified into 9 broad diagnostic categories regardless to gender. (B) Lymphadenitis and benign thyroid were frequently detected in male and female patients, respectively.

15 years of age, but girls have higher rates for adolescents, 15 to 19 years of age.[15]

In the present study the majority of cases were identified with benign lesions. The male-to-female ratio was 1:1 in patients with benign nodule versus 1:1.7 among those with malignancies. Although, for all sites combined, malignancy rate was generally higher for females (40 cases) than male (23 cases) during the 10-year period, there was no significant sex difference between people with or without malignancy.

Both thyroid nodules and cancer were detected in 19 (95 of 499) and 28.5 (18 of 63) percent of our patients. We found higher incidence of thyroid cancer than that of benign thyroid lesions by using FNA and all thyroid cancer were detected in girls. Unlike our results, it has been shown that odds of malignancy is 4.2 times higher for men versus women.[16] Both thyroid nodules and cancer are less common in children than adults, but the risk of malignancy in thyroid nodules is much higher in children.[17] It has been demonstrated that FNA cytology valuable tool to discriminate benign from malignant nodules in pediatric patients.[18]

Hypocellularity, degenerated tumor cells, necrosis, and epithelial hyperplasia are some of the factors that may be encountered in evaluating a difficult smear, mimicking atypical or malignant lesions. The false-negative cases in FNAC, although few, are commonly due to poor tumor localization, poor sampling technique, and the presence of a well-differentiated histology of the tumor. Small tumor size and nonpalpable masses

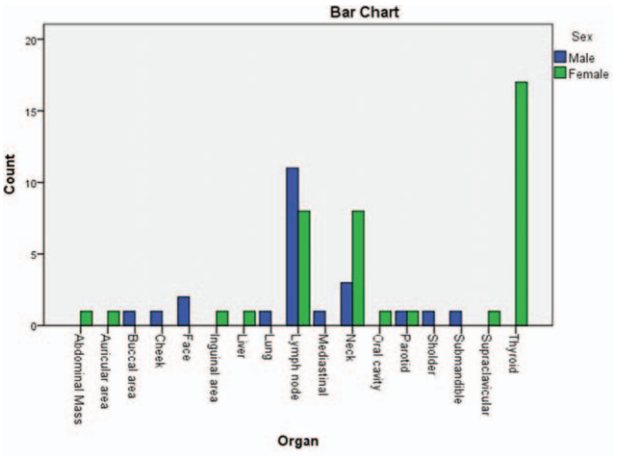

Figure 4. Site or location frequency in malignant cases. Thyroid and lymph node were dominant malignant organ in girls and boys, respectively.

lesions are also commonly associated with false-negative and aspirate inadequacy. FNA for head and neck masses has also several limitations. Failure to establish an accurate diagnosis may be because of sampling error. In these circumstances, repeat aspiration is suggested, and excisional biopsy may be considered.[19] This study has focused on spectrum of FNA in pediatrics. There are many papers on accuracy, sensitivity, and specificity which already confirmed FNA as useful.[20–23]

In conclusion, our study supports the use of FNAC in lesions of various anatomic sites in the children less than 18 years old. As a simple, minimally invasive, and rapid procedure, cytopathologists can reliably utilize FNAC in children. Regardless the gender, the mean age of children receiving a malignant diagnosis was significantly higher than that of benign lesions.

The mean age of children receiving a malignant diagnosis was significantly higher than that of benign lesions. The mean age of malignancy in boys is significantly lower than that of girls with malignancy and the malignancy mostly occurs in the children over 15 years old.

Acknowledgment

The authors would like also to thank Dr K. Daneshbod and Shahrekord University for their help.

References

[1] Ahmed H, Elmubasher MB, Salih RA, et al. Fine needle aspiration cytopathology of pediatric lymphadenopathy among Sudanese children. Asian Pac J Cancer Prev 2013;14:4359–63.
[2] Li J, Thompson TD, Miller JW, et al. Cancer incidence among children and adolescents in the United States, 2001–2003. Pediatrics 2008;121: e1470–7.
[3] Rapkiewicz A, Thuy Le B, Simsir A, et al. Spectrum of head and neck lesions diagnosed by fine-needle aspiration cytology in the pediatric population. Cancer 2000;111:242–51.
[4] Razack R, Michelow P, Leiman G, et al. An interinstitutional review of the value of FNAB in pediatric oncology in resourcelimited countries. Diagn Cytopathol 2012;40:770–6.
[5] Viswanathan S, George S, Ramadwar M, et al. Evaluation of pediatric abdominal masses by fine-needle aspiration cytology: a clinicoradiologic approach. Diagn Cytopathol 2010;38:15–27.
[6] Alam K, Khan R, Jain A, et al. The value of fine-needle aspiration cytology in the evaluation of pediatric head and neck tumors. Int J Pediatr Otorhinolaryngol 2009;73:923–7.
[7] Cole C, Wu HH. Fine-needle aspiration in pediatric patients 12 years of age and younger: a 20-year retrospective study from a single tertiary medical center. Diagn Cytopathol 2014;42:600–5.
[8] Howell L. Changing role of fine-needle aspiration in the evaluation of pediatric masses. Diagn Cytopathol 2001;24:65–70.
[9] Dave B, Shet T, Ramadwar M, et al. Cytological evaluation of head and neck tumors in children—a pattern analysis. Diagn Cytopathol 2006;34: 434–46.
[10] Layfield L, Glasgow B, Ostrzega N, et al. Fine needle aspiration cytology and the diagnosis of neoplasms in the pediatric age group. Diagn Cytopathol 1991;7:451–61.
[11] Oguz A, Karadeniz C, Temel EA, et al. Evaluation of peripheral lymphadenopathy in children. Pediatr Hematol Oncol 2006;23:549–61.
[12] Jakowski J, DiNardo LJ. Advances in head and neck fine-needle aspiration and ultrasound technique for the pathologist. Semin Diagn Pathol 2015;32:284–95.
[13] Steliarova-Foucher E, Stiller C, Lacour B, et al. International Classification of Childhood. Cancer 2005;103:1457–67.
[14] Howlader N, Ries LAG, Mariotto AB, et al. Improved estimates of cancer specific survival rates from population based data. J Natl Cancer Inst 2010;102:1–5.
[15] Rangel M, Cypriano M, de Martino Lee ML, et al. Leukemia, non-Hodgkin's lymphoma, and Wilms tumor in childhood: the role of birth weight. Eur J Pediatr 2010;169:875–81.
[16] Anderson T, Atalay MK, Grand DJ, et al. Management of nodules with initially nondiagnostic results of thyroid fine-needle aspiration: can we avoid repeat biopsy? Radiology 2014;272:777–84.
[17] Buryk M, Simons JP, Picarsic J, et al. Can malignant thyroid nodules be distinguished from benign thyroid nodules in children and adolescents by clinical characteristics? A review of 89 pediatric patients with thyroid nodules. Thyroid 2015;25:392–400.
[18] Hobbs H, Bahl M, Nelson RC, et al. Applying the Society of Radiologists in Ultrasound recommendations for fine-needle aspiration of thyroid nodules: effect on workup and malignancy detection. AJR Am J Roentgenol 2014;202:602–7.
[19] Paulo M, Maribel L, Puay-Hoon T, et al. Fine needle aspiration cytology of the breast: the nonmalignant categories. Patholog Res Int 2011;2011:547580.
[20] Iacob A, Zazgyva A, Ormenisan A, et al. Effectiveness of fine-needle aspiration cytology in the diagnosis of lateral cervical nonthyroid tumors. Medicine (Baltimore) 2016;95:e4448.
[21] Negahban S, Shirian S, Khademi B, et al. The value of ultrasound-guided fine-needle aspiration cytology by cytopathologists in the diagnosis of major salivary gland tumors. J Diagn Med Sonogr 2016;32:92–9.
[22] Daneshbod Y, Daneshbod K, Khademi B. Diagnostic difficulties in the interpretation of fine needle aspirate samples in salivary lesions. Acta Cytol 2009;53:53–70.
[23] Khanlari M, Daneshbod Y, Shaterzadeh Yazdi H, et al. Discrepancy of target sites between clinician and cytopathological reports in head neck fine needle aspiration: did I miss the target or did the clinician mistake the organ site? Cancer Med 2015;4:1374–80.