Solid tumors in Turkish children: a multicenter study

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Background: **This paper presents a detailed incidence study on childhood solid tumors comprising a histopathology-based documentation of benign and malignant lesions.**

Methods: **The Ankara Pediatric Pathology Working Group collected databases of pediatric solid tumors from six pediatric reference centers in order to analyze the incidence, distribution and some epidemiologic characteristics of the tumors and to establish a multicenter database for further studies. A five-year retrospective archive search was carried out. Excluding epithelial tumors of the skin, leukemia, lymphoreticular system neoplasias, metastatic tumors, and hamartomas, 1362 solid tumors in 1358 patients were classified according to age, sex, localization, histopathology and clinical behavior.**

Results: **The male/female ratio was 0.9; 14.8% (201) of the patients belonged to 0-1 year age group, 20.7% (281) to 2-4 years, 25.9% (352) to 5-10 years, 22.2% (301) to 11-14 years, and 16.4% (223) to 15-18 years. Among all tumors, 708 (52.0%) were malignant, 645 (47.4%) benign tumors, 2 (0.1%) borderline tumors, and 2 (0.1%) unknown behavioral tumors. Malignant tumors were found in 50.2% (357) of female patients and in 54.0% (349) of male patients. A balanced distribution between benign and malignant entities among children under 18 years was observed. Comparison between the age groups revealed malignant cases outnumbered benign cases under 4 years of age while benign tumor numbers increased after 10 years of age. The most common entities in the malignant group were of sympathetic nervous system origin, while soft tissue tumors far outnumbered the others in the benign group.**

Conclusions: **We conclude that the cancer patterns of children in the Ankara region mostly resemble with those of the western population. This study provides useful information on the diagnosis of solid tumors in children and highlights variations in cancer incidence in different age groups.**

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Original article

Introduction

Nonlethal genetic damage lies at the heart of carcinogenesis. It involves primarily four classes of normal regulatory genes [growth promoting protooncogenes, growth inhibiting tumor suppressor genes, genes regulating programmed cell death (apoptosis), and genes involving in DNA repair] which are the principal targets of genetic damage. Epigenetics is another rapidly expanding field that focuses on stable changes in gene expression that are not accompanied by changes in DNA sequence and that are mediated primarily by DNA methylation, histone modifications and RNA interference. The importance of the epigenetic mechanisms in cancer development is only beginning to be understood, and it is believed that epigenetic inactivation may be at least as common in human cancers as mutational events.

Up-to-date statistics on cancer occurrence and

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outcome are essential for the planning and evaluation of programs for cancer control. In Turkey, 150 000 adult cancer cases are expected every year, whereas approximately 2500-3000 cancer cases are expected for the 0-14 age group.[1] The cancer frequency in children under the age of 15 is between 110 and 150 per million. Compared to adults, cancer is observed less frequently in children; 0.5% of all cancer cases are detected in children under the age of 15. Despite the rarity of malignancies in children, their study has provided important insights into normal cellular growth regulation and cancer development. The classification of cancer in children is based on morphological findings and not, as in adults, on the organ where the primary tumor is localized. According to the International Classification of Childhood Cancer (ICCC), childhood cancers are studied under 12 main groups (Table 1).[2]

Despite a number of clinical epidemiological studies on childhood cancer, histopathology-based documentation studies are limited in the literature.[3] This paper presents a detailed incidence study on childhood solid tumors comprising a documentation of benign as well as malignant lesions. The Ankara Pediatric Pathology Working Group collected databases of pediatric solid tumors from six reference pediatric centers in order to analyze the incidence, distribution and some epidemiologic characteristics of tumors, attempting to establish a multicenter database for further studies. Patients with leukemia and lymphoma were excluded from the study to prevent inaccurate estimation of the overall incidence data, because some of these specimens were evaluated outside the pathology laboratories for diagnostic purposes. A detailed incidence study was accomplished and the results were compared with the reported data with an emphasis on pediatric solid tumors.

Table 1. International classification of childhood cancers (ICCC-3, 2005)[2]

1. Leukemias, myeloproliferative diseases and myelodysplastic diseases
2. Lymphomas and reticuloendothelial neoplasms
3. CNS and miscellaneous intracranial and intraspinal neoplasms
4. Neuroblastoma and other peripheral nervous cell tumors
5. Retinoblastomas
6. Renal tumors
7. Hepatic tumors
8. Malignant bone tumors
9. Soft tissue and other extraosseous sarcomas
10. Germ cell tumors, trophoblastic tumors and neoplasms of gonads
11. Other malignant epithelial neoplasms and malignant melanomas
12. Other and unspecified malignant neoplasms

CNS: central nervous system.

Methods

Childhood tumors, excluding epithelial tumors of the skin, leukemia, lymphoreticular system neoplasias, metastases, and hamartomas, were included in the study. A retrospective archive search covering the period of 2006-2010 was carried out in pathology laboratories of six reference centers in Ankara. Since participating centers in this study are among the biggest state pediatry and university hospitals which also usually receive referral cases from other parts of the country, the patient population used in this study might be considered at least representative for middle Anatolia region of Turkey. Patients were classified by parameters of age, sex, localization, histopathological diagnosis, and biological behavior. The age groups were as follows: 0-1, 2-4, 5-10, 11-14, and 15-18 years. Localization was categorized as the intraabdominal cavity, head and neck, intrathoracic cavity, pelvic region, genital region, central nervous system (CNS), extremities, breast, and paravertebral region. The ICCC-3 was used for the diagnosis of tumors (Table 1). Moreover, all patients were grouped into 4 categories as malignant, benign, borderline, and unknown according to their clinical behavior. The tumors were classified according to World Health Organization criteria (WHO Blue Book Series, Lyon). Renal and liver tumors were classified according to their localization. Rhabdomyosarcomas (RMSs) were classified as soft tissue sarcomas without consideration of their localization, while Ewing family tumors (Ewing sarcoma [ES]/peripheral primitive neuroectodermal tumor [PNET]) were categorized mainly according to their locations (CNS, bone tumors, etc). Data analysis was performed using SPSS for Windows, version 11.5.

Results

A total of 1362 solid tumors from 1358 patients were included in this study, comprising 646 (47.6%) males and 711 (52.4%) females. Four patients had double tumors and gender data were not available in one patient. The number of patients in the age groups 0-1 years, 2-4 years, 5-10 years,11-14 years, and 15-18 years was 201 (14.8%), 281 (20.7%), 352 (25.9%), 301 (22.2%), and 223 (16.4%), respectively.

Based on the tumor behavior, the 1362 tumors were classified as malignant (708), benign (645), borderline (2 serous ovarian tumors), unknown (2 hemangiopericytomas) tumors. In the remaining 5, the behavioral pattern of the tumor was non-informative [3 adrenocortical neoplasia and 2 gastrointestinal stromal tumors (GIST)]. We examined the tumor behavior according to sex and found that 349 of the 646 males

had malignant tumors (54.0%) and 291 (45.0%) had benign tumors. On the other hand, 357 (50.2%) of the 711 females had malignant tumors and 351 (49.4%) had benign tumors.

Age-specific incidence

Tumor behaviors were evaluated in the age groups. In the 0-1 year group (except 3 patients with adrenocortical neoplasia having no available information about tumor behavior), 133 patients (66.2%) had malignant tumors and 65 (32.3%) had benign tumors. In the 2-4 years group (except 1 patient having hemangiopericytoma and 1 patient having GIST with no information about tumor behavior), 186 patients (66.2%) had malignant tumors and 93 (33.1%) had benign tumors. In the 5-10 years group (except 1 patient with borderline serous ovary tumor), 174 patients (49.4%) had malignant tumors and 177 (50.3%) had benign tumors. In the 11-14 years group (except 1 patient having GIST without information about tumor behavior), 125 patients (41.5%) had malignant tumors and 175 (58.1%) had benign tumors. In the 15-18 years group (except 1 patient with borderline serous ovary tumor and 1 patient with hemangiopericytoma with unknown behavior), 90 patients (40.4%) had malignant tumors and 131 (58.7%) had benign tumors.

Site-specific incidence

Excluding 80 tumors without information about localization, 1282 of the 1362 tumors were classified according to their localizations. Among the 1282 tumors, 28.5% (365) were in the intraabdominal cavity, 17.6% (225) in the head and neck, 11.9% (152) in the extremities, 11.3% (145) in the CNS, 8.5% (109) in the genital region, 6.3% (81) in the pelvic region, 4.3% (55) in the intrathoracic cavity, 2.7% (35) in the breast, and 2.0% (25) in the paravertebral region.

Histopathology-specific incidence

Of the 708 malignant tumors, 679 were classified according to the ICCC. Among the malignant tumors, 19.2% (136) were sympathetic nervous system (SNS) tumors, 15.0% (106) renal tumors, 14.8% (105) soft tissue sarcomas, 10.9% (77) CNS tumors, 10.6% (75) adult type carcinomas, 8.9% (63) mixed germ cell tumors (GCTs), 5.9% (42) retinoblastomas (RB), 5.4% (38) bone tumors, and 5.2% (37) liver tumors. Twenty-nine (4.1%) of the malignant patients were not classified by the ICCC (desmoplastic small round cell tumors, small round cell tumors not specified, tymomas, extrarenal rhabdoid tumors, and some granulocytic sarcomas) (Fig. 1).

All the 645 benign tumors were classified histopathologically. Totally 52.2% (337) of the tumors were soft tissue tumors, 16.9% (109) embryonic tumors, 10.5% (68) CNS tumors (pilocytic astrocytomas), 7.8% (50) bone tumors, 5.4% (35) epithelial tumors, 4.7% (30) mixed epithelial mesenchymal tumors, and 1.6% (10) sex-cord stromal tumors (SCST). Additionally, this group included 4 benign pheochromocytomas and 2 paragangliomas (Fig. 2).

Malignant tumors were also evaluated according to the age groups and their histopathology.

In the 0-1 year group (133 tumors), 50 (37.6%) were SNS tumors, 23 (17.3%) renal tumors, 21 (15.8%) GCT, 16 (12.0%) soft tissue sarcomas, 15 (11.3%) hepatoblastoma (HB), 4 (3.0%) CNS tumors, and 4 other tumors.

In the 2-4 years group (186), 55 (29.6%) were SNS tumors, 40 (21.5%) renal tumors, 22 (11.8%) soft tissue sarcomas, 21 (11.3%) GCTs, 15 (8.1%) CNS tumors, 12 (6.5%) RB, 5 (2.7%) HB, and 16 other tumors.

In the 5-10 years group (174), 38 (21.8%) were renal tumors, 26 (14.9%) CNS tumors, 25 (14.4%) soft tissue sarcomas, 24 (13.8%) SNS tumors, 10 (5.7%) bone tumors, 8 (4.6%) GCTs, 7 (4.0%) RBs, 7 (4.0%)

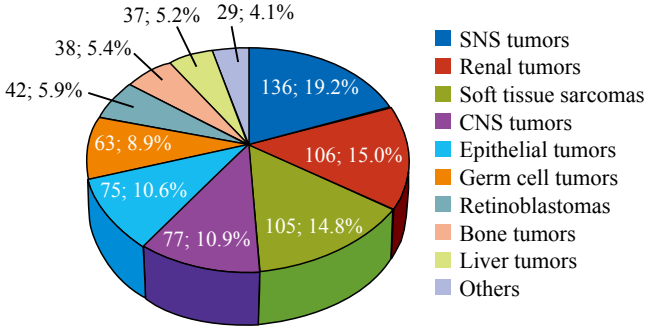

Fig. 1. Distribution of the malignant tumors according to their histopathology. SNS: sympathetic nervous system; CNS: central nervous system.

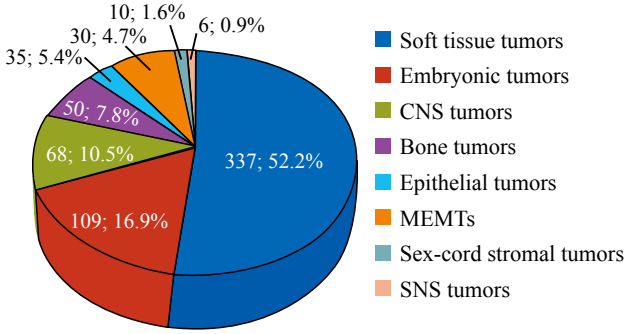

Fig. 2. Distribution of the benign tumors according to their histopathology. SNS: sympathetic nervous system; MEMT: mixed epithelial mesenchymal tumor; CNS: central nervous system.

Table 2. Histopathologic diagnosis of benign and malignant tumors

Benign tumors (*n*=645)	Histopathologic diagnosis (*n*)	Malignant tumors (*n*=708)	Histopathologic diagnosis (*n*)
Soft tissue tumors (337)	Hemangioma (127), Lymphangioma (51), Lipoma (40), Neurofibroma (23), Dermatofibroma (20), Fibromatosis (16), IMT (8), Schwannoma (7), Giant cell tumor of tendon sheath (5), Xanthogranuloma (5), Infantile fibrous hamartoma (5), Angiofibroma (5), Juvenile hemangioendothelioma (3), Neurothekeoma (3), Nodular fasciitis (3), Infantile myofibromatosis (2), Glomus tumor (2), Granular cell tumor (2), Leiomyoma (2), Lipoblastoma (2) (*)	SNS (136)	Neuroblastoma (114), Ganglioneuroblastoma (22)
Embryonic tumors (109)	Mature cystic teratoma (68), Ganglioneuroma (36), Dermoid cyst (5)	Renal tumors (106)	Wilm's tumor (81), Mesoblastic nephroma (8), Clear cell sarcoma (7), Renal cell carcinoma (6), Neuroblastoma (4)
CNS (68)	Pilocytic astrocytoma (35), Craniopharyngioma (17), Meningioma (7), CPP (3), DNET (2), Hypophysis adenoma (2), Schwannoma (1), Desmoplastic infantile astrocytoma (1)	Soft tissue tumors (105)	Rhabdomyosarcoma (56), Malignant mesenchymal tumor not further specified (14), MPNST (7), Fibromyxoid sarcoma (7), Leiomyosarcoma (6), DFSP (3), Epithelioid hemangioendothelioma (3), Synovial sarcoma (3), Granulocytic sarcoma (2) (*)
Bone tumors (50)	Osteochondroma (21), Enchondroma (10), Non-ossifying fibroma (6), Giant cell tumor (4), Fibrous dysplasia (4), Chondromyxoid tumor (3), Osteoblastoma (2)	CNS (77)	Medulloblastoma (20), Ependymoma (17), Astrocytoma (11), GBM (7), ES/PNET (6), Ganglioglioma (5), Pleomorphic xanthoastrocytoma (3), Oligodendroglioma (2), AT/RT (2) (*)
Epithelial tumors (35)	Follicular adenoma (5), Adrenocortical adenoma (4), Pleomorphic adenoma (4), Serous cystadenoma (4), Solid pseudopapillary tumor (4), Mucinous cystadenoma (3), Parathyroid adenoma (3), Encapsulated thymoma (2) (*)	Epithelial tumors (75)	Papillary carcinoma (28), Undifferentiated nasopharynx carcinoma (16), Well-differentiated endocrine tumor (11), Adenocarcinoma (6), Adrenocortical carcinoma (4), Follicular carcinoma (3), Thymoma (2) (*)
Mixed epithelial mesenchymal tumors (30)	Fibroadenoma (27), Tubular adenoma (2), Benign phyllodes tumor (1)	Germ cell tumors (63)	Yolk sac (31), Immature teratoma (18), Mixed germ cell tumor (11), Dysgerminoma (3)
Sex-cord stromal tumors (10)	Juvenile granulosa cell tumor (4), Leydig cell tumor (3), Sex-cord gonadal stromal tumor (1), Sertoliform cystadenoma (1), Sertoli cell tumor (1)	Bone tumors (38)	Osteosarcoma (26), Ewing family tumor (12)
		Liver (37)	Hepatoblastoma (27), HCC (5), Neuroblastoma (2), Undifferentiated embryonic sarcoma (1), leiomyosarcoma (1), Ganglioneuroblastoma (1)

(*): Single cases are not included. AT/RT: atypical teratoid rhabdoid tumor; CNS: central nervous system; CPP: choroid plexus papilloma; DFSP: dermatofibrosarcoma protuberans; DNET: dysembryoplastic neuroepithelial tumor; ES/PNET: Ewing sarcoma/primitive neuroectodermal tumor; GBM: glioblastoma multiforme; HCC: hepatocellular carcinoma; IMT: inflammatory myofibroblastic tumor; MPNST: malignant peripheral nerve sheath tumor; SNS: sympathetic nervous system.

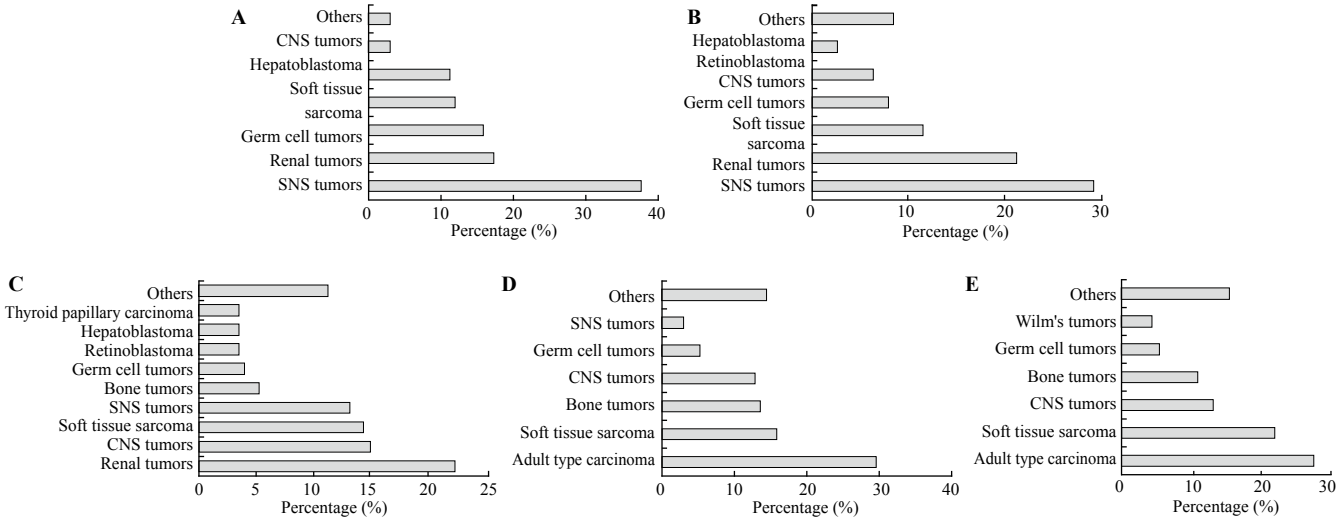

Fig. 3. Distribution of the malignant tumors according to age groups. **A:** 0-1 year (*n*=133); **B:** 2-4 years (*n*=186); **C:** 5-10 years (*n*=174); **D:** 11-14 years (*n*=125); **E:** 15-18 years (*n*=90). SNS: sympathetic nervous system; CNS: central nervous system.

HBs, 7 (4.0%) thyroid papillary carcinomas, and 22 other tumors.

In the 11-14 years group (125 tumors), 39 (31.2%) were adult type carcinomas, 21 (16.8%) soft tissue sarcomas, 18 (14.4%) bone tumors, 17 (13.6%) CNS tumors, 7 (5.6%) GCTs, 4 (3.2%) SNS tumors, and 19 other tumors.

In the 15-18 years group (90 tumors), 25 (27.8%) were adult type carcinomas, 20 (22.2%) soft tissue sarcomas, 12 (13.3%) CNS tumors, 10 (11.1%) bone tumors, 5 (5.6%) GCTs, 4 (4.4%) Wilm's tumors, and 14 other tumors (Fig. 3).

Table 3. Documentation solid tumors in the literature

Reference	Total number of tumors	Age	Most frequent malignant solid tumors
Acta Pediatrica 2011, Ljungman et al[19]	2487	<15 y	1. Nephroblastoma 2. Soft tissue tumors 3. Neuroblastoma 4. Germ cell tumors 5. Bone tumors 6. Retinoblastoma 7. Epithelial neoplasms and malignant melanomas 8. Liver tumors
Br J Cancer 2010, Baade et al[18]	13 925	<15 y	1. CNS tumors 2. Neuroblastoma 3. Retinoblastoma 4. Renal tumors 5. Liver tumors 6. Bone tumors 7. Soft tissue sarcomas 8. Germ cell and other gonadal tumors 9. Adult type carcinomas
Eur J Cancer Prev 2010, Lacour et al[4]	8473	<15 y	1. CNS tumors 2. Neuroblastoma
J Surg Res 2010, Vasudevan et al[5]	31 685	<20 y	1. CNS tumors 2. Soft tissue sarcomas 3. Retinoblastoma 4. Bone tumors
Pediatr Blood Cancer 2009, Bao et al[6]	609	<14 y	1. CNS tumors
Afr J Paediatr Surg 2009, Tanko et al[7]	87	NA	1. Rhabdomyosarcoma
Rev Med Inst Mex Seguro Soc 2008, Rendon-Macias et al[8]	61	<19 y	1. CNS tumors 2. Bone tumors
Pediatr Blood Cancer 2008, Michel et al[9]	1735	<15 y	1. CNS tumors 2. Neuroblastoma 3. Soft tissue sarcoma 4. Renal tumors 5. Bone tumors 6. Germ cell tumors 7. Retinoblastoma 8. Liver tumors
Cancer 2008, Linabery et al[10]	22 694	<19 y	1. CNS tumors 2. Germ cell tumor 3. Neuroblastoma 4. Wilms tumor 5. Non RMS STS 6. RMS 7. Osteosarcoma 8. Thyroid carcinoma 9. MM 10. RB 11. ES/PNET 12. Hepatoblastoma
Arch Pediatr 2006, de Bouyn-Icher et al[13]	71	neonates	1. Neuroblastoma 2. Soft tissue sarcomas 3. CNS tumors
Arch Pediatr 2005, Lacour et al[14]	1086	<14 y	1. CNS tumors 2. Sympathetic nervous system tumors 3. Soft tissue sarcomas 4. Renal tumors 5. Bone tumors
Pediatr Blood Cancer 2004, Desandes et al[15]	4234	<15 y	1. CNS tumors 2. Sympathetic nervous system tumors 3. Renal tumors
Pediatr Blood Cancer 2004, Desandes et al[16]	699	15-19 y	1. Adult type carcinomas 2. Germ cell tumors 3. CNS tumors 4. Bone tumors 5. Soft tissue sarcomas
US SEER NCI, p51-164[11] (2000-2004)	17 933	<20 y	1. CNS tumors 2. Carcinomas and other malignant epithelial neoplasms 3. Sympathetic nervous system tumors 4. Soft tissue sarcomas 5. Renal tumors 6. Bone tumors 7. Germ cell and other gonadal tumors 9. Retinoblastoma 10. Liver tumors
TUBA (Turkish Academy of Sciences)[12]	7673	<15 y	1. CNS tumors 2. Sympathetic nervous system tumors 3. Soft tissue sarcomas 4. Renal tumors 5. Bone tumors 6. Germ cell tumors and other gonadal tumors 7. Retinoblastoma 8. Adult type carcinomas 9. Liver tumors
Middle East Cancer Consortium Monograph (MECC)[17]	4611	<20 y	**Cyprus:** 1. CNS 2. NB 3. RT 4. Soft tissue sarcomas 5. Bone tumors **Israel (Jews):** 1. CNS 2. NB 3. Soft tissue sarcomas 4. Bone tumor 5. RT 6. Carcinoma 7. GCT 8. RB 9. Others 10. Hepatic tumor **Israel (Arabs):** 1. CNS 2. Soft tissue sarcomas 3. NB 4. RT 5. Carcinoma 6. GCT 7. Bone tumor 8. Hepatic tumor 9. Others 10. RB **Egypt:** 1. CNS 2. RB 3. Bone tumor 4. Soft tissue sarcomas 5. RT 6. Others 7. Carcinoma 8. GCT 9. Hepatic tumor **Jordan:** 1. CNS 2. Soft tissue sarcomas 3. NB 4. Bone tumor 5. RT 6. RB 7. Carcinoma 8. GCT 9. Hepatic tumor 10. Others **US seer:** 1. CNS 2. Carcinoma 3. SNS 4. Soft tissue sarcomas 5. RT 6. Bone tumor 7. GCT 8. RB 9. Hepatic tumor 10. Others
Present study	708	<18 y	1. Sympathetic nervous system tumors 2. Renal tumors 3. Soft tissue sarcomas 4. CNS tumors 5. Adult type carcinomas 6. Germ cell tumors 7. Retinoblastoma 8. Bone tumors 9. Liver tumors

CNS: central nervous system; RMS: rhabdomyosarcoma; MM: malignant melanoma; ES/PNET: Ewing sarcoma/primitive neuroectodermal tumor; STS: soft tissue sarcoma; RB: retinoblastoma; NB: neuroblastoma; RT: renal tumor; GCT: germ cell tumor; SNS: sympathetic nervous system; NA: not available.

Additionally, tumor incidence was determined in the newborn period. Malignant tumors were found in 27 newborns (immature teratomas in 10 newborns, neuroblastomas in 6, RMSs in 3, mesoblastic nephromas in 2, HBs in 2, Wilm's tumor in 1, ganglioneuroblastoma in 1, RB in 1, and yolk sac tumor in 1). Histopathologic diagnoses in the malignant and benign tumor groups are shown in Table 2.

Discussion

Tumor epidemiology studies originate basically from clinical series or from cancer databases. These studies concentrate mostly on malignant cases and usually lack histopathologic diagnostic details. The databases of benign tumors are usually not available in the cancer registry. Comparable studies conducted by histopathology units are limited and, to our knowledge, no pediatric solid tumor series are available to obtain detailed information about the distribution of benign solid tumors in this age group. The present study was designed to describe the spectrum of pediatric solid tumors in the Ankara region including 6 largest reference hospitals.

The incidences of tumors in this study were found to be compatible with those reported in the literature (Table 3).[4-19] However, the incidences of CNS tumors and bone tumors were usually lower when compared with the reported values, which might be due to the case profiles of the attending centers and frequent referral of pediatric CNS tumors and bone tumors to adult oncology institutions, thus not included in the present study.

Slight regional variations in tumor incidence rates were proposed by different studies.[5,7,17] Retinoblastoma was the second most frequent tumor of childhood after CNS tumors according to Egypt statistics of the Middle East Cancer Consortium (MECC).[17] The incidences of retinoblastoma in our study varied when compared with the published data. They were significantly lower than those of three reports,[5,17,18] and significantly higher than those reported elsewhere.[10,17] A histopathological study[7] found that soft tissue sarcoma (rhabdomyosarcoma) was the most prevalent solid tumor in African children. Our results were mostly compatible with those reported in the literature. However, a significant numerical superiority of carcinoma and renal tumor was observed in our study when compared to the reported data.[10,12,17,18]

In the present study, we observed a balanced distribution between malignant and benign tumors in children under 18 years although malignant cases were predominant slightly. Comparison between age groups revealed, however, malignant tumors far outnumbered benign tumors under 4 years, and balanced between 5-10 years. The number of benign tumors was increasing after 11 years of age. More than 50% of the malignant cases between 0-4 years had SNS tumor and renal tumor, whereas after 15 years adult type carcinoma and bone tumor were predominant. In our study, a vast majority of benign tumors were of soft tissue origin (52.2%), followed by benign embryonic tumors.

The present series is the largest histopathology based pediatric solid tumor series comprising both malignant and benign solid tumors of childhood which also provides detailed information on individual diagnostic groups.

In conclusion, the cancer patterns of children in the Ankara region mostly resemble with those of the western population. This study provides useful information on the diagnosis of solid tumors in children and highlights variations in cancer incidence in different age groups.

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