RESEARCH COMMUNICATION

Epidemiology of Soft Tissue Sarcomas in Karachi South, Pakistan (1995-7)

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Abstract

Introduction: The present study was conducted with the objective of examining epidemiological characteristics of soft tissue sarcomas (STSs) in Karachi. Patients and methods: Epidemiological data of 96 (63 male and 33 female) incident STS cases registered at Karachi Cancer Registry (KCR) for Karachi South (KS), from 1st January 1995 to 31st December 1997, were reviewed. Results: The age standardized rate (ASR) world per 100,000 were 3.3 (2.9%) and 2.1 (1.6%) in males and females, respectively, with mean ages of of 41.4 years (95% CI 35.77; 46.97) and 40.2 years (95% CI 31.27; 49.03). The age-specific curves showed a gradual increase in risk from the first until the eighth decade in both genders, with the highest peak at 75+ in females and 70-74 years in males. In males, 8 (12.7%) STS cases were diagnosed in the pediatric age group (0-14), 12 (19.1%) in adolescents and young adults (15-24 years), 19 (30.1%) in adults 25-49 years of age and 24 (38.1%) in the 50 years+ age group. In females the respective frequencies were 11%, 26%, 30% and 33%. The most common histological tumor was rhabdomyosarcoma, though the occurrence of the histological subtypes was age-dependent. Rhabdomyosarcomas and Ewing's sarcomas were more frequent in children and adolescents whereas fibrosarcomas, leiomyosarcomas, liposarcomas, malignant fibrous histiocytomas (MFHs) and schwannomas were encountered in the elderly. Conclusion: Karachi falls into a high risk region for STS, observed in a relatively younger population, with a male predominance, high frequency of rhabdomyosarcoma and advanced stage at diagnosis. Information on grading and staging remain incomplete for most cases, which negatively affect disease management and survival.

Key Words: Soft tissue sarcoma - epidemiology - South Karachi, Pakistan

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Introduction

Sarcomas are a heterogeneous group of rare tumors that arise predominantly from the embryonic mesoderm and are further categorized into bone and soft tissue sarcoma (Cormier and Pollack, 2004). In this article we focus on soft tissue sarcoma (STS) arising at all sites except the internal organs.

STS are a divergent group of neoplasms accounting for less than 1% of all cancers in adults and approximately 7% in children (Froehner and Wirth, 2001; Nijhuis et al., 1999). STS are grouped together because of common risk factors with similar clinical, biological, and pathologic features. Prognosis as defined by the staging system is determined by the anatomic location (depth), size and spread of the tumor. The route of metastases is hematogenous (Cormier and Pollack, 2004).

STS arise primarily from the body connective tissues (CT) viz. fibrous, adipose and muscle tissue. Approximately 8700 new cases of STS are diagnosed each year in the United States (US) and about 1500 in the United Kingdom (Clark et al., 2005). In the US, 850-900 children and adolescents younger than 20 years of age are diagnosed with STS each year, of which approximately 350 are rhabdomyosarcoma. Currently, more than 50 morphological types of STS have been identified (Fletcher et al., 2002). The most common adult STS are liposarcoma (21.4%), malignant fibrous histiocytoma (MFH) (20.2%), leiomyosarcoma (20.0%), fibrosarcoma (11%) and synovial sarcoma (9.6%). The most common sites of primary tumor were the extremity (51.1%), retroperitoneum/viscera (28.8%), trunk (15.9%), head and neck (3.7%) and breast (0.4%) (Torosion et al., 1988).

The etiology of STS is obscure. Most soft-tissue sarcomas are sporadic; few have an identifiable cause (Clark et al., 2005). Several risk factors have been identified including predisposition to genetic syndromes, ionizing radiation and exposure to certain chemicals such as vinyl chloride, phenoxyacetic acid herbicides, chlorphenols, dioxin and arsenic; medicinal measures such

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as Thorotrast exposure. There is a well investigated role of the human immunodeficiency virus 1 (HIV-1), and the human herpesvirus 8 (HHV-8) in the tumorigenesis of AIDS-related Kaposi's sarcoma and of Epstein–Barr virus in AIDS associated leiomyosarcoma (McClain et al., 1995). STS associated with a clinically identified genetic disease represents 2.8% of the cases; most of these cases are related to von Recklinghausen neurofibromatosis. Evidence supports a relationship between occupational and therapeutic irradiation. Radiation-induced STS represents 3.3% and may develop 3 to 15 years after therapeutic irradiation for lymphoma, cervical cancer, testicular tumor, or breast cancer (Brady et al., 1995). Chronic lymphedema-associated angiosarcoma (Stewart–Treves syndrome) usually occurs as a rare complication of treatment for breast cancer (Penel et al., 2001). Hormones and chronic repair processes are also associated causally with STS (Penel et al., 2008; Froehner and Wirth, 2001). Children with hereditary retinoblastoma (owing to a germ-line mutation in the RB1 tumor-suppressor gene) and patients with the Li–Fraumeni syndrome (germ-line mutation in p53 tumor-suppressor gene) are also at risk of developing STS (Wong et al., 1997; Strong et al., 1992).

The present study was conducted with the objective of examining descriptive epidemiological characteristics and pathology of STS in Karachi.

Patients and Methods

Epidemiological data of primary incident STS cases registered at Karachi Cancer Registry (KCR) for Karachi South (KS), during 1st January 1995 to 31st December 1997 were reviewed. Cancer registration started at KCR in 1995. The main sources for the KCR registry are pathology, oncology or treatment center data as well as hospital admission and discharge data. Specially trained KCR investigators register the data.

All cases of soft tissue sarcoma were included for the present study, with the exception of STS arising in internal organs, or bones. ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) categories included for topography were C490-499. ICD-O3 categories included for morphology were M8800-8933, 8963, 8990-8991, 9020-9044, 9120-9134, 9141-9340 and 9540-9581.

The surgical specimens were initially evaluated on hematoxylin and eosin (H&E) stained sections. Special stains and imunohistochemistry were selectively used. Monoclonal antibodies used were ASMA, cytokeratin MNF, cytokeratin AE1/AE3, cytokeratin CAM 5.2, desmin, EMA, LCA, NSE, S100, smooth muscle actin and vimentin. The reported epidemiological cancer data were rechecked, and residency status re-ascertained. People residing in the specified geographical regions for more than six months were considered residents. Cases were categorized by tumor site, age and sex of the patients. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grade and stage.

Data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) and computerized using a customized version of CANREG-4 software (WHO, 2002). Manual and computerized validity checks for the cancer data were performed as per recommendations of the International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR). This involved factors influencing comparability i.e. classification and coding (Parkin, 1994). Completeness of records, data consistency and the possibility of duplicate records are continuously and extensively checked.

Crude, age-adjusted, and age-specific incidence rates were calculated using the person years of population at risk by sex and 5-year age-groups. The estimated mid 1996 population of KS based on the 1998 census (copy obtained from the Sindh Bureau of Statistics) was used for the analyses (population of 893,684 males and 794, 920 females) assuming an annual growth rate of 1.94%. The growth rates were based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution (Segi M, 1960). 'The standardized rate is the incidence rate that, theoretically, would have been observed if the population had a standard age distribution. The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population averaged over the number of years for which data are presented'. Incidence tables were based on ICD-10. (WHO, 1992).

Tumors were staged according to UICC 'Tumour Node Metastasis Classification' (Hermanek P and Sobin LH, 1992). Where no TNM classification was available or TNM classification was incomplete, the extent of disease information was used. Data were analyzed using SPSS 16.0.

Results

A total of 96 STS were registered at KCR for KS, during a 3 year period, 1st January, 1995 to 31st December 1997. Of these STS, 63 (65.6%) were diagnosed in males and 33 (34.4%) in females. The male, female ratio was 2:1.

STS accounted for 2.9% and 1.6% of all cancers in males and females respectively. It did not rank amongst the ten most common malignancies in Karachi in either gender (Bhurgri et al., 2000; 2002). The age standardized rate (ASR) world per 100,000 and the crude incidence rate (CIR) were 3.3 and 2.3 in males and 2.1 and 1.4 in females respectively. Microscopic confirmation was 99%. The mean age of male patients was 41.4 years (95% CI 35.8; 47.0; SD ±21.11); the age range was 78 years (2 to 80 years). The mean age of the female patients was 40.15 years (95% CI 31.3; 49.03; SD ±22.4), age range was 72 years (8 to 80 years).

Age-specific curves showed a gradual increase in risk from the first until the eighth decade in both genders, with the highest peak at 75+ in females and 70-74 years in males. There was a tri-modal pattern to the ASIRs i.e. 3 peaks were observed. The first peak was at 20-25 years, the second at 40-45 and the third at 65-70 years in females

Table 1. Morphological Distribution of STS by Age and Gender (% data)

Age (years)	Relative Frequency	Ewing's sarcoma	Rhabdo-myosarcoma	Dermato-fibro	Synovial sarcoma	MFH	Fibro-sarcoma	Lipo-sarcoma	Leiomyo-sarcoma	Schwannoma	Others
Males											
0-14	12.3	25	62.5				12.5				
15-24	19.3		41.6		25	16.7			16.7		
25-49	29.8		10.5			10.5	26.3	15.8	5.3	15.8	15.8
50+	38.6		4.2	4.2		20.8	12.5	16.7	8.3	4.2	29.1
Females											
0-14	11.0	33	67								
15-25	26.0		14.3	14.3	42.8	14.3	14.3				
25-49	30.0				25	12.5		25			37.5
50+	33.0					11.1	33.3	11.1	22.2	11.1	11.1

Table 2. Morphological Distribution of STS by Gender (No and%)

ICD-03	Morphology of STS	Males		Females		Both genders	
8800	Soft tissue sarcoma NOS	5	8.0	2	6.1	7	7.3
8810	Fibrosarcoma	8	12.7	5	15.2	13	13.5
8830	Malignant Fibrous histiocytoma	10	15.9	4	12.1	14	14.6
8832	Dermatofibrosarcoma	1	1.6	1	3.0	2	2.1
8850	Liposarcoma	8	12.6	4	12.1	12	12.5
8890	Leiomyosarcoma	6	9.5	1	3	7	7.3
8900	Rhabdomyosarcoma	14	22.2	4	12.1	18	18.8
9040	Synovial sarcoma	4	6.3	6	18.1	10	10.5
9130	Hemangioendothelioma			1	3.0	1	1.0
9150	Hemangiopericytoma			2	6.1	2	2.1
9180	Osteogenic sarcoma	1	1.6			1	1.0
9251		1	1.6			1	1.0
9260	Ewings sarcoma	1	1.6	1	3.0	2	2.1
9364	Peripheral neuroectodermal tumour	2	3.2			2	2.1
9540		1	1.6			1	1.0
9560	Schwannoma	1	1.6	1	3.0	2	2.1
9581	Alveolar soft part sarcoma			1	3.0	1	1.0
	Total	63	100	33	100	96	100

and 70-75 years in males. Only 12% of the male and 18% of the female cases were older than 65 years in our study.

In males 8 (12.7%) STS cases were diagnosed in the pediatric age group (0-14), 12 (19.1%) cases in the adolescents and young adults (15-24 years), 19 (30.1%) cases in adults 25-49 years of age and 24 (38.1%) cases in the 50+ age group. In females the respective frequencies were 11%, 26%, 30% and 33%. The morphological distribution varied in these groups. Tables 1 and 2 show the histological subtypes of STS, stratified by gender and age group.

The most common histological tumor types in males were rhabdomyosarcomas (n=5, 62.5%), Ewing's (n=2, 25%) and fibrosarcomas (n=1, 12.5%) in children. The 15-24 year age group also showed a high rhabdomyosarcomas (n=5, 41.6%) followed by synovial sarcoma (n=3, 25%), leiomyosarcoma and malignant fibrous histiocytoma (n=2, 16.7%) each. The 25-49 year age group showed a high fibrosarcoma (n=5, 26.3%), synovial sarcoma and liposarcoma (n=3, 15.8%) cases each; malignant fibrous histiocytoma, rhabdomyosarcoma and undifferentiated sarcoma (n=2, 10.5%) cases each, leiomyosarcoma and peripheral neuro-ectodermal tumour (n=1, 5.3%) case each. The older age group (50-75 years) showed a high malignant fibrous histiocytoma (n=6, 25%) liposarcoma (n=4, 16.7%), fibrosarcoma (n=3, 12.5%), leiomyosarcoma and undifferentiated sarcoma (n=2, 8.3%) cases each.

Table 3. Distribution of STS by Anatomical Site and Gender

ICD-O3	Site	Males		Females	
490.00	Head & neck	9	14.3	1	3.03
491.00	Upper limb	11	17.5	10	30.3
492.00	Lower limb	21	33.3	5	15.2
493.00	Thorax	7	11.1	1	3.0
494.00	Abdomen	3	4.8	3	9.1
495.00	Pelvis/RP*	6	9.5	4	12.1
496.00	Trunk	-	-	1	3.0
499.00	Not specified	6	9.5	8	24.2
Total		63	100	33	100

*retroperitoneum

The most common histological tumor types in females were rhabdomyosarcomas (67%) and Ewings (33%) in children. The 15-24 year age group showed a high synovial sarcoma (42.8%), the 25-49 year age group also showed a high synovial sarcoma, along with liposarcoma and sarcomas of vascular origin (25.0% each). The older age group (50-75 years) showed a higher fibrosarcoma (33.0%) and leiomyosarcoma (22.2%).

STS were mostly situated in the extremities, 50.8% in males and 45.2% in females. The most common anatomical site involved was lower limb (33.3%) in males and upper limb (30.3%) in females (Table 3).

Table 4. Distribution of STS by Topography; Comparison with Other Published Data

Anatomical site		Current study	Penel et al 2008#	Toro et al 2006#	Clark et al 2005	Cormier Pollock 2004	Nijius et al 1999	Torosian et al 1988	Tsujimoto et al 1988
	n=	96	26,758	658			456	565	290
490	Head and neck	10.4	7.2	3.03	10.0	9.0	13	3.7	15.5
491	Upper limb	21.9	13.0	30.3	20.0		16		
492	Lower limb	27.1	34.2	15.2	40.0		29		
491-2	Extremities	49.0	47.2	45.5	60.0	59.0	45	51.1	43.0
493	Thorax	8.3	4.5	3.03			11	0.4	
494	Abdomen	6.3	6.0	9.1			12	28.8	14.3
495	Pelvis, inc. RP*	10.4	12.3	12.1	20.0	15.0	15		
496	Trunk	1.0	15.0	3.0	10.0	19.0	2	15.9	27.2
498	Overlapping sites	-	1.0	-	-	6.2	2	-	-
499	Not specified	14.6	6.8	24.2	-	-	-	-	-
Total		100	100	100	100	100	100	100	100

#Study based on adult sarcomas, *retroperitoneum,

Table 5. Distribution of STS by Morphology, Comparison with Other Published Data

ICD-03	Morphology	Current study	Penel et al 2008#	Toro et al 2006#	Cormier et al 2004	Tsujimoto et al 1988	Torosian et al 1988	Nijhuis et al 1999	Kransdorf 1995
	n=	96	26,758	658	-	290	565	456	38,484
8810	Fibrosarcoma	13.5	-	4.8	-	5.5	11.0	-	5
8830	MFH	14.6	17.1	12	28	34.8	20.2	18	24
8832	Dermatofibrosarcoma	2.1	10.5	-	-	-	-	14	6
8850	Liposarcoma	12.5	11.5	20	15	9.7	21.4	18	14
8890	Leiomyosarcoma	7.3	23.9	17	12	5.5	20.0	15	8
8900	Rhabdomyosarcoma	18.8	4.6	4.0	-	7.9	-	5	-
9040	Synovial sarcoma	10.5	-	6.5	10	8.3	9.6	4	5
9260	Ewings sarcoma	4.2	-		-	-	-	1	-
9560	Schwannoma; MPNST	2.1	-	3.6	6	6.9	-	4	6
	Others	14.4	32.4	32.1	29	21.4	17.8	21	32

#Study based on adult sarcomas, MPNST- Malignant peripheral nerve sheath tumor

Discussion

This is a population-based epidemiological study on STS. On the basis of the incidence (1995-7) reported in the present study (ASR 3.3/100.000 males; 2.1/100,000 in females) Karachi falls into a high risk region for STS, ranked 4th amongst the 230 contemporary registries listed in 'Cancer Incidence in the Five Continents' volume 8 (CIV 8) for males and 10th in females. Asian registries overall reported a lower incidence in CIV volume 8. The incidence of STS in KS was comparable to the incidence in contemporary United States (US) and European populations. Amongst Asian registries KS males had the highest incidence whereas the incidence of STS in females came in third following registries in Israel (Jews 2.5/ 100,000) and Manila (2.2/100,000) (Parkin et al., 2002). Overall the South Asian population has one of the lowest incidences of STS. The current study shows a higher male, female ratio, in comparison to the slight male predominance reported (Nijhuis et al., 1999) by most epidemiological studies.

Apart from the data of CIV8, there are few published epidemiological population-based studies on STS available for comparison, probably due to the rarity of the lesion. Also all available studies on STS are related to the North American or European populations with limitations to comparability. Above all most publications were centre-based; either gave tabulations of STS which were not morphology-specific or restricted to a single morphology, in the form of case series. Comparison was also restricted by the selection criteria of published studies as some included sarcomas arising in internal organs which overestimated the incidence rates of certain morphologies and in advanced cases may confuse the site of origin.

STS was seen in a relatively younger population in Karachi. The mean age of the cases (males - 41.4 years; females 40.2 years) in the present study is below the age cited in literature viz. 65 years (Fletcher et al., 2002), 64 years (Gustafson P, 1994) and 52 years (Penel et al., 2008) and 51 years (Tsujimoto et al., 1988). Only 12% of the male and 18% of the female cases were older than 65 years in our study. All other studies have reported that nearly half the patients are older than 65 years indicating that sarcomas are tumors of the elderly in most populations (Nijhuis et al., 1999), apparently not in ours.

In the current study most STS (49%) were located in the extremities, predominantly the lower extremity and hip region (27.1%). Similar findings have been published by almost all authors (Tsujimoto et al., 1988; Nijhuis et al., 1999; Cormier et al., 2004; Clark et al., 2005). A higher incidence in the upper limb however was reported by Toro in 2006. The distribution of STS varies with different studies as shown in table 4. The reported involvement of extremities was 43% by Tsujimoto et al, 45% by Nijhuis et al, 45.5% by Toro et al, 51.1% by Torosian et al, 59% by Cormier and Pollock, 59.9% by Lawrence et al and

60% by Clark et al. These variations could be due to a selection bias as the studies reporting a higher limb involvement were multicentre hospital-based studies not population-based. Such studies over-register the treatable cases at more obvious sites but may miss out advanced cases at obscure sites. The advantage of population-based studies is that they are free of selection bias. Fletcher et al (2002) had reported that three fourths of the STS are located in the extremities.

The most common histological types in our study were rhabdomyosarcoma, which is a finding contrary to all reported literature (see Table 5). Most studies report MFH and liposarcoma as the most common sarcomas (Gustafson, 1994; Nijhuis et al., 1999). Our finding needs further investigation. As immunochemistry was performed on all cases of rhabdomyosarcoma, the cause is not likely to be a misdiagnosis.

The occurrence of the histological subtypes was age-dependent. Rhabdomyosarcoma and Ewing's sarcoma were most frequently diagnosed in children and adolescents whereas leiomyosarcoma, liposarcoma, MFH and synovial sarcoma were not seen in the juvenile group but frequently encountered in the elderly. Rhabdomyosarcomas were not observed beyond the age of adolescence. The incidence of MFH, leiomyosarcoma and liposarcoma increased with age.

A three-step system was used for STS grading and extent of disease information used for staging as most cases had incomplete information. Large series confirm that grade and size are of similar prognostic importance in STS management. The incomplete information on these prognostic variables would negatively affect disease management and survival in Karachi. Internationally, a three-step grading system devised by the French Federation of Cancer Centers Sarcoma Group (Guillou et al., 1997) or a four-step grading systems (Greene et al., 2002) are widely used. The staging system largely used is devised by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (Greene et al., 2002; Ramanathan et al., 1999).

Karachi falls into a high risk region for STS, which was observed in a relatively younger population, with a male predominance and a high frequency of rhabdomyosarcoma. Information on grading and staging remained incomplete for most cases, which would negatively affect disease management.

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