RESEARCH ARTICLE

Commonest Cancers in Pakistan - Findings and Histopathological Perspective from a Premier Surgical Pathology Center in Pakistan

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Abstract

Context: There are no recent authoritative data about incidence and prevalence of various types of cancers in Pakistan. Aim: To determine the frequency of malignant tumors seen in our practice and provide a foundation for building a comprehensive cancer care strategy. Materials and Methods: 10,000 successive cases of solid malignant tumors reported in 2014 were included. All cases had formalin fixed, paraffin embedded specimens available and diagnosis was based on histological examination of H&E stained slides plus ancillary studies at the Section of Histopathology, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi. The latest WHO classifications were used along with the latest CAP protocols for reporting and the most updated TNM staging. Results: There were 9,492 (94.9%) primary tumors while 508 (5.1%) were metastatic. Some 5,153 (51.5%) were diagnosed in females and 4,847 (48.5%) in males. The commonest malignant tumors in females were breast (32%), esophagus (7%), lymphomas (6.8%), oral cavity (6.7%) and ovary (4.8%), while in males they were oral cavity (13.9%), lymphomas (12.8%), colorectum (7.9%), stomach (6.9%) and esophagus (6.6%). Malignant tumors were most common in the 5th, 6th and 7th decades. About 8% were seen under 20 years of age. Conclusions: Oral cavity and gastrointestinal cancers continue to be extremely common in both genders. Breast and esophageal cancers are prevalent in females. Lung and prostate cancer are less common than in the west. Ovarian cancer was very common but cervix cancer was less so.

Keywords: Cancer - carcinoma - lymphoma - sarcoma - decade-wise age data - histological types

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Introduction

We are the biggest center for Histopathology in Pakistan, a country of over 180 million people, and receive cases from all over the country. Last year, we reported over 57,000 surgical pathology and over 18,000 cytology specimens. We are a major referral center for difficult and challenging cases from all over the country and malignant tumors constitute a major chunk of our practice. Since we receive cases from all over Pakistan, frequencies of various malignant tumors in our practice are a fair indication of their frequency in Pakistan. Even today, there is no 'cancer registry' in Pakistan and there is no definite data regarding the incidence of various cancers. This state of affairs is very depressing since cancer takes a heavy toll of human life in this extremely populous country and incurs a huge cost in terms of morbidity and mortality. The majority of the people are poor, and have little access to even basic necessities of life. Not only are accurate figures regarding the incidence and prevalence of cancers unknown, the diagnosis and management of malignant tumors is extremely suboptimal (in terms of facilities, qualified physicians, therapeutic options etc.). The majority of patients cannot afford the cost of treatment. Cancer patients often die painful and miserable deaths. Little to no facilities are available in remote areas and people need to travel to larger cities in order to get treatment which is very expensive. Although the government and private sector have taken a number of initiatives to improve cancer care in the country, the overall situation remains bleak.

An important step in achieving better cancer care is to determine the incidence of various cancers in the country. A pathology department cannot accurately determine cancer incidence. However, being the busiest histopathology department in the country receiving cases

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from all over Pakistan, we can provide a fair assessment of the frequency of various cancers in Pakistan.

The aim of this study was to determine the frequency of various cancers in Pakistan based on our practice. This data will hopefully provide a foundation which can help in building an accurate cancer registry and developing a comprehensive cancer care strategy.

Materials and Methods

A total of 10,000 successive cases of malignant tumors reported in the Section of Histopathology, AKUH in the year 2014 were included in the study. Only solid tumors were included, leukemias were excluded. All cases included were formalin fixed, paraffin embedded specimens. Only tumors fulfilling well defined criteria for malignancy were included. Borderline tumors such as borderline ovarian neoplasms or borderline phylloides tumor of breast were not included. Giant cell tumor of the bone, borderline histiocytomas (dermatofibrosarcoma protuberans), and locally aggressive conditions such as fibromatosis were not included. Gastrointestinal (including pancreatobiliary) neuroendocrine tumors (NETs) were included. Low grade appendiceal mucinous neoplasms (LAMNs) and low grade pseudomyxoma peritonei were excluded. All grade II and higher Central Nervous System (CNS) neoplasms were included. However, grade I CNS tumors such as pilocytic astrocytoma, grade I meningioma, myxopapillary ependymoma etc were not included. In all cases, diagnosis was based on microscopic examination

Table 1. Malignant Tumors in Males and Females Combined (n=10,000)

S. No #	Organ and tumor Type	"Over all Total No."	Percentage (%)	Females Total No. (5153)	Percentage (%)	Males Total No. (4847)	Percentage (%)
1	Breast Cancer	1650	16.5%	1650	32.0%	-	-
2	Oral cavity Carcinoma*	1021	10.2%	345	6.7%	676	13.9%
3	Lymphoma	974	9.7%	352	6.8%	622	12.8%
	Non Hodgkin Lymphoma Nodal	(375)		(130)		(245)	
	Non Hodgkin Lymphoma Extranodal	(358)		(126)		(232)	
	Hodgkin Lymphoma	(241)		(96)		(145)	
4	Esophageal Carcinoma	680	6.8%	362	7.0%	318	6.6%
5	Colorectal Carcinoma	595	5.9%	211	4.1%	384	7.9%
6	Skin Carcinoma	489	4.9%	201	3.9%	288	5.9%
7	Gastric Carcinoma	475	4.7%	139	2.7%	336	6.9%
8	Lung Carcinoma	380	3.8%	77	1.5%	303	6.3%
9	CNS Malignant Tumor**	356	3.6%	117	2.3%	239	4.9%
10	Urinary bladder Carcinoma	325	3.2%	80	1.5%	245	5.1%
11	Larynx and vocal cord carcinoma	270	2.7%	105	2.0%	165	3.4%
12	Ovarian Carcinoma	248	2.5%	248	4.8%	-	-
13	Prostate Carcinoma	237	2.4%	-	-	237	4.8%
14	Endometrial Carcinoma	187	4.8%	187	3.6%	-	-
15	Cervix Carcinoma	140	1.4%	140	2.7%	-	-
16	Thyroid Carcinoma	137	1.4%	91	1.8%	46	0.9%
17	Renal carcinoma	123	1.2%	43	0.8%	80	1.6%
18	Ewing Sarcoma	119	1.2%	56	1.1%	64	1.3%
19	Gall bladder carcinoma	104	1.04%	75	1.4%	29	0.6%
20	Testicular malignant Tumors	102	1.02%	-	-	102	2.1%
21	Ampullary, Periamapullary, pancreatic, Small intestine Carcinoma	102	1.02%	38	0.7%	64	1.3%
22	Salivary gland malignancies	88	0.9%	33	0.6%	55	1.2%
23	Osteosarcoma	86	0.86%	34	0.6%	52	1.1%
24	Liver carcinoma	82	0.8%	35	0.7%	47	1.0%
25	Pleomorphic Sarcoma	61	0.6%	20	0.4%	41	0.8%
26	Leiomyosarcoma	57	0.57%	21	0.4%	36	0.7%
27	Synovial Sarcoma	53	0.5%	24	0.5%	29	0.6%
28	Plasma cell Neoplasm	43	0.4%	15	0.3%	28	0.6%
29	Nose, Paranasal sinuses, nasopharynx carcinoma	43	0.4%	20	0.4%	23	0.5%
30	Metastatic Tumors	508	5.1%	264	5.1%	244	5.0%
31	Miscellaneous malignant Tumor	264	2.6%	170	3.3%	94	1.9%

*Includes lip, tongue, floor of mouth, buccal mucosa, hard palate, upper and lower gingiva; **Central Nervous System (CNS)

of Hematoxylin and Eosin (H&E) stained slides. Special stains e.g. Periodic Acid Schiff Alcian Blue ± diastase, reticulin etc. were performed whenever required. A large panel of Immunohistochemical stains (IHC) was utilized whenever necessary to reach a conclusive diagnosis. IHC was used in all cases of Hodgkin and Non Hodgkin lymphomas. The latest WHO classifications were used. Resection specimens were reported in strict accordance with the latest College of American Pathologists (CAP) protocols(Washington, 2013) and staged according to the most updated TNM classifications.(Edge et al., 2010)

All relevant data was recorded and analysed using the SPSS 19.0 software package. p-values for different variables were calculated using the Chi Square and Fisher Axact tests. p-value equal to or less than 0.05 was considered significant.

Results

A total of 10,000 consecutive cases of malignant solid tumors diagnosed in the Section of Histopathology, AKUH in 2014 were included. Out of these, 9492 (94.9%) were primary tumors while 508 (5.1%) were metastatic tumors. Out of 10,000, 5153 (51.5%) tumors were diagnosed in females and 4847 (48.5%) in males. The overall breakup is shown in Table 1. The decade wise breakup of the commonest malignant tumors in females and males is shown in Tables 2 and 3 respectively. The decade wise breakup of all 10,000 malignant tumors is shown in Table 4.

Breast carcinoma was the commonest malignant tumor in females (32%). Out of 1650 cases, 685 (41.5%) involved the right breast, 787 (47.7%) involved the left and 26 (1.6%) were bilateral. In 152 cases (9.2%), the laterality was not known. The decade wise breakup is shown in Table 2, while frequency of various histologic types is shown in Table 5. Invasive Ductal Carcinoma, NOS was the commonest histologic type comprising 1427 cases (86.5%), this value was statistically significant (p-value: <0.0001).

Cancer of the oral cavity was overall the second commonest type of malignant tumor (Table 1). Out of a total of 1021 cases, 676 (66.2%) occurred in males while 345 (33.8%) occurred in females. M:F ratio was 1.95:1. The p-value (<0.0001) was statistically significant. Cancer of the oral cavity included cancer of the buccal (cheek) mucosa, floor of mouth, lip, tongue, hard palate and oropharynx (hypopharynx). All cases were histologically

Table 2. Decade-wise Age Distribution of Commonest Malignant Tumors in Females (n=5153)

Age Range in years	Breast (n=1650)	Oral (n=345)	NHL Nodal (n=130)	NHL Extranodal (n=126)	HL (n=96)	Esophagus (n=362)	Stomach (n=139)	Colorectum (n=211)	Skin (n=201)	Lung (n=77)	CNS (n=117)
0-10	-	-	3 (2.3%)	7 (5.5%)	8 (8.3%)	-	-	-	2 (1.0%)	-	12 (10.2%)
11-20	7 (0.4%)	3 (0.9%)	18 (13.8%)	11 (8.7%)	27 (28.1%)	10 (2.8%)	-	11 (5.2%)	2 (1.0%)	-	17 (14.5%)
21-30	148 (9.0%)	15 (4.3%)	14 (10.8%)	17 (13.5%)	17 (17.3%)	46 (12.7%)	13 (9.3%)	30 (14.2%)	8 (4.0%)	-	32 (27.4%)
31-40	359 (21.7%)	50 (14.5%)	14 (10.8%)	15 (11.9%)	15 (15.6%)	53 (14.6%)	19 (13.7%)	35 (16.6%)	20 (10%)	10 (13%)	19 (16.2%)
41-50	525 (31.8%)	99 (28.7%)	20 (15.4%)	29 (23%)	16 (16.7%)	104 (28.7%)	28 (20.1%)	47 (22.3%)	46 (23%)	15 (19.5%)	15 (12.8%)
51-60	345 (20.9%)	92 (26.7%)	34 (26.1%)	27 (21.4%)	6 (6.2%)	77 (21.3%)	36 (25.9%)	54 (25.6%)	49 (24%)	24 (31.2%)	11 (9.4%)
61-70	186 (11.3%)	53 (15.4%)	19 (14.6%)	20 (15.9%)	6 (6.2%)	57 (15.7%)	35 (25.2%)	25 (11.8%)	48 (24%)	20 (26%)	10 (8.5%)
>70	80 (4.8%)	33 (9.6%)	8 (6.1%)	-	1 (1.0%)	15 (4.1%)	8 (5.8%)	9 (4.3%)	26 (13%)	8 (10.4%)	1 (0.8%)

Age Range in years	U. Bladder (n=80)	Ovary (n=248)	Endometrium (n=187)	Thyroid (n=91)	Cervix (n=140)	Ewing Sarcoma (n=56)	G. Bladder (n=75)	Salivary Gland (n=33)	Osteosarcoma (n=34)	Kidney (n=43)	Liver (n=35)
0-10	-	6 (2.4%)	-	-	-	10 (17.8%)	-	-	6 (17.6%)	-	-
11-20	-	24 (9.7%)	-	11 (12.1%)	-	29 (51.8%)	-	2 (6.1%)	20 (58.8%)	-	-
21-30	2 (2.5%)	43 (17.3%)	12 (6.4%)	23 (25.3%)	8 (5.7%)	12 (21.4%)	4 (5.3%)	7 (21.2%)	4 (11.8%)	3 (7%)	-
31-40	8 (10%)	33 (13.3%)	11 (5.9%)	23 (25.3%)	40 (28.6%)	5 (8.9%)	5 (6.7%)	9 (27.3%)	2 (5.9%)	8 (18%)	2 (5.7%)
41-50	10 (12.5%)	62 (25%)	43 (23%)	14 (15.4%)	48 (34.3%)	-	16 (21.3%)	7 (21.2%)	1 (2.9%)	16 (37.2%)	6 (17.1%)
51-60	26 (32.5%)	38 (15.3%)	78 (41.7%)	11 (12.1%)	19 (13.6%)	-	28 (37.3%)	6 (18.2%)	1 (2.9%)	10 (23.2%)	14 (40%)
61-70	18 (22.5%)	36 (14.5%)	32 (17.1%)	6 (6.6%)	20 (14.3%)	-	18 (24%)	-	-	4 (9.3%)	10 (28.6%)
>70	16 (20%)	6 (2%)	11 (5.9%)	3 (3.2%)	5 (3.6%)	-	4 (5.3%)	2 (6.1%)	-	2 (4.6%)	3 (8.6%)

squamous cell carcinoma of various grades (with 25 cases or 2.4% showing histologic features consistent with sarcomatoid carcinoma- a histologic variant). The decade wise breakup is shown in Tables 2 and 3 while the site wise breakup is shown in Table 6. As shown in Table 6, oral mucosa was the commonest site for oral cancers comprising 56.3%. The p-value was statistically significant (<0.0001).

Lymphoma was the second commonest malignant tumor in males and the third commonest in females (Table 1). Out of a total of 974 cases, 622 (63.9%) were diagnosed in males and 352 (36.1%) in females. M:F ratio was 1.76:1. The p-value was statistically significant (<0.0001). Out of 974 cases, 733 (75.3%) were Non Hodgkin lymphomas (NHL) while 241 (24.7%) were Hodgkin Lymphomas. Of the 733 NHLs, 375 (51.2%) were nodal, while 358 (48.8%) were extranodal. The decade wise breakup in males and females is shown in Tables 2 and 3.

Of the 733 NHLs, 477 (65.1%) were diagnosed in males, while 256 (34.9%) were diagnosed in females (Table 1). The p-value was statistically significant (<0.0001). Of the 375 nodal NHLs, 245 (65.3%) were in males while 130 (34.7%) were in females. The p-value was statistically significant (<0.0001). Of the 358 extranodal NHLs, 232 (64.8%) were in males while 126 (35.2%) were diagnosed in females. The p-value was statistically significant (<0.0001). The sites of involvement of extranodal NHL and the histological types of nodal and extranodal NHLs are shown in Table 7. Almost 68% of all extranodal NHLs were Diffuse Large B Cell Lymphoma (DLBCL). The p-value was statistically significant (<0.0001).

Out of the 241 cases of Hodgkin lymphoma (HL), 145 (60.2%) were diagnosed in males while 96 (39.8%) were diagnosed in females. The M:F ratio was 1.51:1.0. The p-value was statistically significant (<0.0001). The decade wise breakup is shown in Tables 2 and 3. Mixed cellularity and nodular sclerosis were the commonest

Table 3. Decade-wise Age Distribution of Commonest Malignant Tumors in Males (n=4847)

Age Range in years	Oral (n=676)	NHL Nodal (n=245)	NHL Extranodal (n=232)	HL (n=145)	Esophagus (n=318)	Stomach (n=336)	Colorectum (n=384)	Skin (n=288)	Lung (n=303)	CNS (n=239)
0-10	-	9 (3.7%)	16 (6.9%)	34 (23.4%)	-	-	-	1 (0.3%)	-	22 (9.2%)
11-20	4 (0.6%)	22 (9.0%)	37 (15.9%)	40 (27.6%)	11 (3.5%)	5 (1.5%)	16 (4.2%)	4 (1.4%)	-	22 (9.2%)
21-30	72 (10.6%)	21 (8.6%)	31 (13.4%)	31 (21.4%)	23 (7.2%)	20 (6%)	40 (10.4%)	14 (4.9%)	3 (1%)	46 (19.2%)
31-40	119 (17.6%)	44 (18%)	36 (15.5%)	12 (8.3%)	40 (12.6%)	38 (11.3%)	77 (20.1%)	39 (13.5%)	13 (4.3%)	56 (23.4%)
41-50	183 (27.1%)	51 (20.8%)	31 (13.4%)	11 (7.6%)	62 (19.5%)	61 (18.1%)	76 (19.8%)	47 (16.3%)	59 (19.5%)	43 (18%)
51-60	166 (24.5%)	33 (13.5%)	31 (13.4%)	8 (5.5%)	95 (29.9%)	97 (28.9%)	82 (21.3%)	74 (25.7%)	85 (28.18%)	26 (10.9%)
61-70	84 (12.4%)	49 (20%)	40 (17.2%)	7 (4.8%)	55 (17.3%)	74 (22%)	65 (16.9%)	63 (21.9%)	100 (30%)	21 (8.8%)
>70	48 (7.1%)	16 (6.5%)	10 (4.3%)	2 (1.4%)	32 (10.1%)	41 (12.2%)	28 (7.3%)	46 (16%)	43 (14.2%)	3 (1.2%)
Age Range in years	U. Bladder (n=245)	Larynx (n=165)	Thyroid (n=46)	Kidney (n=80)	Testis (n=102)	Ewing Sarcoma (n=36)	G. Bladder (n=29)	Salivary Gland (n=55)	Osteosarcoma (n=52)	Liver (n=47)
0-10	-	-	-	-	9 (8.8%)	18 (28.6%)	-	1 (1.8%)	8 (15.4%)	-
11-20	2 (0.8%)	-	1 (2.2%)	-	15 (14.7%)	30 (47.6%)	-	2 (3.6%)	29 (55.8%)	1 (2.1%)
21-30	3 (1.2%)	-	9 (19.6%)	1 (1.2%)	36 (35.3%)	9 (14.3%)	1 (3.4%)	6 (10.9%)	8 (15.4%)	2 (4.2%)
31-40	14 (5.7%)	3 (1.8%)	7 (15.2%)	9 (11.2%)	27 (26.5%)	2 (3.2%)	2 (6.8%)	8 (14.5%)	3 (5.8%)	2 (4.2%)
41-50	40 (16.3%)	40 (24.2%)	7 (15.2%)	23 (28.7%)	8 (7.8%)	2 (3.2%)	10 (34.5%)	16 (29.1%)	3 (5.8%)	10 (21.3%)
51-60	72 (29.4%)	48 (29.1%)	14 (30.4%)	24 (30%)	4 (3.9%)	2 (3.2%)	5 (17.2%)	10 (18.2%)	1 (1.9%)	16 (34.1%)
61-70	62 (25.3%)	57 (34.5%)	6 (13%)	19 (23.7%)	3 (2.9%)	-	7 (24.1%)	10 (18.2%)	-	10 (21.3%)
>70	52 (21.2%)	17 (10.3%)	2 (4%)	5 (6.3%)	-	-	4 (13.8%)	2 (3.6%)	-	6 (12.8%)

histologic subtypes comprising 103 (42.7%) and 100 (41.5%) cases respectively. There were 5 cases (2.1%) of Nodular lymphocyte predominant HL, 4 cases (1.6%) of lymphocyte rich subtype and 1 case (0.4%) of syncytial variant. In 28 cases (11.6%), further histologic subtyping was not possible and a diagnosis of HL, NOS was rendered.

Esophageal carcinoma was the fourth commonest malignant tumor overall in both males and females, second in females and fifth in males. Out of a total of 680 cases, 362 (53.2%) were diagnosed in females and 318 (46.8%) in males. F:M ratio was 1.41:1.0. Of the 680 cases, 442 (65%) were located in the lower third of the esophagus (statistically significant, p-value: <0.0001), 92 (13.5%) in the middle third, and 28 (4.1%) in the upper third. In 118 cases (17.3%), exact location was not known. As many as 660 (97.1%) cases were conventional squamous cell carcinomas on histologic examination. This value was statistically significant (p-value: <0.0001). There were 16 (2.3%) adenocarcinomas and 4 (0.6%) cases of basaloid squamous cell carcinoma. Out of 680, 215 cases (31.6%) were received from Balochistan province bordering Iran and China. The decade wise breakup is shown in Tables

Table 4. Decade Wise Breakup of All Malignant Tumors (n=10,000)

Age range (in years)	Number	Percentage (%)
0-10	245	2.4%
20-Nov	523	5.2%
21-30	902	9.0%
31-40	1421	14.2%
41-50	2169	21.7%
51-60	2235	22.3%
61-70	1733	17.3%
>70	772	7.7%

Table 5. Frequency of Various Histologic Types Of Breast Carcinoma and Malignant Ovarian Tumors in Females

Histologic type	Total No.	Percentage (%)
Malignant ovarian tumors (n=248)		
Papillary serous carcinoma	74	29.8%
Endometrioid carcinoma	60	24.2%
Mucinous carcinoma	20	8.1%
Clear cell carcinoma	16	6.4%
Poorly differentiated carcinoma	7	2.8%
Dysgerminoma	11	4.4%
Granulosa cell tumor	20	8.1%
Yolk sac tumor	13	5.2%
Malignant mixed germ cell tumor	9	3.6%
Malignant Sertoli-Leydig cell tumor	4	1.6%
Juvenile granulosa cell tumor	3	1.2%
Immature teratoma	6	2.4%
Small cell carcinoma	2	0.8%
Squamous cell carcinoma arising in cystic teratoma	2	0.8%
Malignant mixed germ cell tumor	1	0.4%
Breast carcinomas (n=1650)		
Ductal, NOS	1427	86.5%
Lobular	108	6.5%
Metaplastic	51	3.1%
Mucinous	26	1.6%
Papillary	23	1.4%
Medullary	4	0.2%
Tubular	4	0.2%
Ductolobular	4	0.2%
Tubulolobular	1	0.06%
Adenoid cystic	1	0.06%
Cribriform	1	0.06%

Table 6. Site-wise Distribution of Oral Cavity Cancer in both Males and Females (n=1021)

Site	Number	Percentage (%)
Oral (buccal, cheek) mucosa	575	56.3%
Tongue	224	22%
Lip	59	5.8%
Floor of mouth	58	5.7%
Palate	49	4.8%
Oro/hypopharynx	30	2.9%
Gum	10	0.9%
Not known	16	1.5%

Table 7. Frequency of various Histologic Types of Nodal and Extranodal NHL; and Sites of Involvement of Extranodal NHLs

Sites of involvement of extranodal NHLs (n=358)		
Sites of involvement	Total No.	Percentage (%)
Stomach	39	10.90%
Colon	32	8.90%
Small intestine	30	8.40%
Bone (predominantly spine)	25	7.00%
Abdomen	19	5.30%
CNS	18	5.00%
Skin	17	4.70%
Tonsil	15	4.20%
Soft tissue	15	4.20%
Oral cavity	14	3.90%
mediastinum	12	3.40%
Nose and nasopharynx	10	2.80%
Face	10	2.80%
Liver	8	2.20%
Retro peritoneum	8	2.20%
Salivary gland	7	1.90%
Lung	6	1.70%
Testis	6	1.70%
Breast	5	1.40%
Female genital tract	5	1.40%
Eye	5	1.40%
Pharynx	5	1.40%
Thyroid	4	1.10%
Mesentery	4	1.10%
Others	16	4.50%
Not known	23	6.40%

2 and 3.

Colorectal carcinoma was the fifth most common malignant tumor overall in both males and females. It was the third most common in males and sixth in females. Out of a total of 595 cases, 384 (64.5%) were diagnosed in males and 211 (35.5%) in females. M:F ratio was 1.8:1.0. This value was statistically significant (p-value: <0.0001). Of the 595 cases, 448 (75.3%) were located in the left and 128 (21.5%) in the right colon. The p-value was statistically significant (<0.0001). In 19 (3.2%) cases, laterality was unknown. All 595 cases were adenocarcinomas. The large majority were conventional mucin secreting adenocarcinomas which comprised 566 (95.1%) cases, a value that was statistically significant (p-value: <0.0001). Of the remaining 29 cases, 15 (2.5%) showed neuroendocrine differentiation, 10 (1.7%) were mucinous carcinomas and 4 (0.7%) were signet ring adenocarcinomas. A total of 535 (89.9%) out of 595 cases were well to moderately differentiated. The decade wise breakup is shown in Tables 2 and 3.

Table 7 (continued). Frequency of Various Histologic Types of Nodal and Extranodal NHL; and Sites of Involvement of Extranodal NHLs

Histological type	Total No.	Percentage (%)
Nodal NHL (n=375)		
DLBCL*	182	48.50%
CLL /SLL**	51	13.60%
Follicular lymphoma	36	9.60%
Mantle cell lymphoma	19	5.10%
Precursor T cell NHL	18	4.80%
ALCL***	17	4.50%
Precursor B cell NHL	14	3.70%
Burkitt lymphoma	14	3.70%
PTCL****	13	3.50%
Marginal zone lymphoma	5	1.30%
Plasmablastic lymphoma	1	0.30%
NHL, NOS	5	1.30%
"*Diffuse large B cell lymphoma; **Chronic Lymphocytic Leukemia /Small Lymphocytic Lymphoma; ***Anaplastic Large Cell Lymphoma; ****Peripheral T Cell Lymphoma"		
Extranodal NHL (n=358)		
DLBCL*	243	67.90%
Burkitt lymphoma	29	8.10%
PTCL**	16	4.50%
ALCL***	12	3.40%
Pre T ALL****	12	3.40%
Follicular lymphoma	10	2.80%
Extranodal marginal zone lymphoma	9	2.50%
Pre B ALL	7	1.90%
Mantle cell lymphoma	7	1.90%
MALT lymphoma*****	4	1.10%
Mediastinal B cell lymphoma	2	0.60%
IPSID******	2	0.60%
Hairy cell leukemia	1	0.30%
Angioblastic T cell lymphoma	1	0.30%
Lymphoplasmacytic lymphoma	1	0.30%
Mycosis fungoides	1	0.30%
SLL /CLL*******	1	0.30%
"*Diffuse large B cell lymphoma; **Peripheral T Cell Lymphoma; ***Anaplastic Large Cell Lymphoma; ****Acute Lymphoblastic Lymphoma; *****Mucosa Associated Lymphoid Tissue; ******Immunoproliferative Small Intestinal Disease; *******Chronic Lymphocytic Leukemia /Small Lymphocytic Lymphoma"		

A total of 475 cases of gastric carcinoma were diagnosed during the study period. Out of these, 336 (70.7%) were in males and 139 (29.3%) in females. M:F ratio was 2.4:1.0. The value was statistically significant (p-value: <0.0001). Of the 475 cases, 113 cases (23.8%) were located in the proximal and 174 (36.6%) in the distal stomach. In 28 cases (5.9%), site of biopsy was given as 'body'. As many as 50 cases (10.5%) were located at the gastroesophageal junction (GEJ). In 110 cases, (23.1%) exact location of the tumor was not known. All 475 cases were adenocarcinomas. Of these 7 (1.5%) showed neuroendocrine differentiation, 2 (0.4%) corresponded histologically to mucinous carcinoma, while 1 case (0.2%) was diagnosed as hepatoid adenocarcinoma. Out of 475, 326 (68.6%) were poorly differentiated (signet ring adenocarcinoma or diffuse type) while 149 (31.4%) were well to moderately differentiated (intestinal type adenocarcinomas). The p-value was statistically significant (0.002). The decade wise breakup is shown in Tables 2 and 3.

A total of 489 cases of skin carcinoma were diagnosed. Of these, 288 (58.9%) were diagnosed in males and 201 (41.1%) in females. M:F ratio was 1.43:1.0. The histologic types included squamous cell carcinoma comprising 253 cases (51.7%), basal cell carcinoma comprising 152 cases (31.1%), malignant melanoma comprising 55 cases (11.2%) and cloacogenic carcinoma comprising 7 cases (1.4%). Other histologic types included adnexal carcinomas NOS comprising 9 cases (1.8%), sebaceous carcinoma comprising 6 cases (1.3%), 1 case each of trichilemmal carcinoma and kaposi sarcoma (0.2%) and 2 cases of merkel cell carcinoma (0.4%). In 4 cases (0.8%), exact histologic type or origin could not be determined. The decade wise breakup is shown in Tables 2 and 3.

A total of 380 cases of lung cancer were diagnosed. Of these, 303 (79.7%) were diagnosed in males and 77 (20.3%) in females. M:F ratio was 3.93:1.0. The p-value was statistically significant (<0.0001). Out of 380 cases, 198 (52.1%) involved the right lung and 130 (34.2%) involved in left lung. In 52 cases (13.7%), laterality was not known. The breakup of the histologic types is shown in Table 8.

A total of 356 malignant CNS neoplasms were diagnosed. Of these, 239 (67.1%) were diagnosed in males while 117 (32.9%) were diagnosed in females. M:F ratio was 2.04:1.0. The value was statistically significant (p-value: <0.0001). The breakup of the histologic types is shown in Table 9.

A total of 325 cases of urinary bladder carcinoma were diagnosed during the study period. Of these, 245 (75.4%) were diagnosed in males and 80 (24.6%) in females. M:F ratio was 3.06:1.0. This value was

Table 8. Frequency of Various Histologic Types of Lung Carcinoma, Malignant Salivary Gland Tumors and Thyroid Gland Tumors in Males and Females

Primary lung carcinoma in males and females (n=380)					Malignant salivary gland tumors (n=88)					Thyroid carcinoma (n=137)				
Histologic Type	Male (n=303)		Female (n=77)		Histologic type	Male (n=55)		Female (n=33)		Histologic type	Male (n=46)		Female (n=91)	
	Number	(%)	Number	(%)		Number	(%)	Number	(%)		Number	(%)	Number	(%)
Squamous cell carcinoma	124	40.90%	20	26%	Mucoepidermoid carcinoma	25	45.50%	14	42.40%	Papillary carcinoma	27	58.70%	52	57.10%
Adenocarcinoma	117	38.60%	42	54.50%	Adenoid cystic carcinoma	11	20.00%	10	30.30%	Papillary carcinoma, follicular variant	7	15.20%	10	11.00%
Small cell carcinoma	46	15.20%	9	11.70%	Polymorphous low grade carcinoma	6	10.90%	3	9.10%	Follicular carcinoma	6	13.00%	11	12.10%
Large cell neuroendocrine carcinoma	4	1.30%	1	1.30%	Carcinoma ex pleomorphic adenoma	5	9.10%	2	6.10%	Anaplastic carcinoma	3	6.50%	7	7.70%
Adenosquamous carcinoma	4	1.30%	2	2.60%	Acinic cell carcinoma	2	3.60%	1	3.00%	Medullary carcinoma	3	6.50%	6	6.60%
Sarcomatoid carcinoma	2	0.70%	1	1.30%	Myoepithelial carcinoma	2	3.60%	2	6.10%	Insular carcinoma	--	--	3	3.30%
Undifferentiated large cell carcinoma	1	0.30%	--	--	Malignant mixed tumor	1	1.80%	1	3.00%	Hurthle cell carcinoma	--	--	2	2.20%
Non-small cell carcinoma, NOS	4	1.30%	1	1. 3%	Poorly differentiated carcinoma	1	1.80%	--	--					
Bronchoalveolar carcinoma	1	0.30%	1	1. 3%	Carcinosarcoma	2	3.60%	--	--					

statistically significant (p-value: <0.0001). All 325 cases corresponded histologically to urothelial carcinomas. Of these, appreciable squamous differentiation was seen in 27 (8.3%) and glandular differentiation in 22 (6.8%) cases. Sarcomatoid areas were seen in 9 cases (2.8%). Out of 325, 218 (67.1%) were high grade urothelial carcinomas. The p-value was statistically significant (<0.0001). 90 (27.7%) were low grade, while 17 (5.2%) corresponded to papillary urothelial neoplasm of low malignant potential. Of the 218 high grade tumors, 142 (65.1%) were detrusor muscle invasive (statistically in significant, p-value: 0.2018), 30 (13.8%) were non muscle invasive while no detrusor muscle was present in the specimen to assess invasion in 46 cases (21.1%).

A total of 270 cases of carcinoma of larynx and vocal cord were diagnosed during the study period. Of these, 165 (61.1%) were diagnosed in males and 105 (38.9%) in females. M:F ratio was 1.57:1.0. The value was statistically not significant (p-value: 0.063). Of the 270 cases, 260 (96.3%) corresponded histologically to conventional squamous cell carcinoma, while 10 (3.7%) were reported as spindle cell carcinoma (sarcomatoid carcinoma). The p-value was statistically significant (<0.0001).

A total of 248 cases of malignant ovarian tumors were diagnosed during the study period. The right ovary was involved in 45 cases (18.1%) and the left ovary in 52 cases (21%). Bilateral involvement was seen in 59 cases (23.8%). Laterality was not known in 92 cases (37.1%). The decade wise breakup is shown in Table 2 while the breakup of histologic types is shown in Table 5. A total of 179 cases of endometrial carcinoma were diagnosed during the study period. Of these, 97 (54.2%) were well differentiated, 75 (41.9%) were moderately differentiated and 7 (3.9%) were poorly differentiated. Histologically, 3 out of 179 (1.7%) corresponded to papillary serous carcinoma and 1 (0.6%) to clear cell carcinoma. In addition to these 179, another 8 (4.3%) endometrial malignant tumors were diagnosed which included 3 cases of malignant mixed mullerian tumors, 3 cases of endometrial stromal sarcoma and 1 case each of adenosarcoma and leiomyosarcoma. A total of 140 cases of carcinoma cervix were diagnosed during the study period. The overwhelming majority 137 (97.8%) were histologically consistent with squamous cell carcinoma. The p-value was statistically significant (<0.0001). Remaining 3 cases (2.2%) were histologically consistent with cervical adenocarcinoma. The decade wise breakup of malignant endometrial and cervical tumors is given in Table 2.

Out of a total of 137 thyroid carcinomas diagnosed during the study period, 46 (33.6%) were diagnosed in males and 91 (66.4%) in females. This value was statistically not significant (p-value: 0.0722). F:M ratio was 1.97:1.0. The breakup of histologic types is shown in Table 8.

Out of a total of 123 renal cancers diagnosed during the study period, 80 (65%) were diagnosed in males and 43 (35%) in females. The value was statistically not significant (p-value: 0.1488). M:F ratio was 1.86:1.0. 56 (45.5%) were located in the right and 53 (43.9%) in the left kidney. In 2 cases (1.6%), the tumors involved both kidneys. In 12 cases (10%), laterality was not known. Histologically, 100 out of 123 cases (81.3%) were consistent with clear cell renal cell carcinoma. This value was statistically significant (p-value: <0.0001). Of the remaining 23 cases, 11 (8.9%) were consistent with sarcomatoid carcinoma, 8 (6.5%) with papillary carcinoma, while 2 cases each (1.6%) were consistent with chromophobe renal cell carcinoma and squamous cell carcinoma. The decade wise breakup is shown in Tables 2 and 3.

Out of 102 malignant testicular tumors, 48 (47.1%) were located in the right testis, 29 (28.4%) in the left while 1 case (1.0%) involved both. In 24 cases (23.5%), laterality

Table 9. Histologic Types of Malignant CNS Neoplasms in Both Males and Females (n=356)

Histologic type	Total No.	Percentage (%)
Diffuse Astrocytoma, Grade II	4	1.1%
Anaplastic Astrocytoma, Grade III	3	0.8%
Glioblastoma Multiforme, Grade IV	76	21.3%
Oligodendroglioma, Grade II	54	15.2%
Anaplastic oligodendroglioma, Grade III	72	20.2%
Ependymoma, Grade II	19	5.3%%
Anaplastic Ependymoma, Grade III	16	4.5%
Atypical Meningioma, Grade II	26	7.3%
Anaplastic Meningioma, Grade III	3	0.8%
Medulloblastoma, Grade IV	31	8.7%
CNS PNET, Grade IV *	5	1.4%
Gliosarcoma, Grade IV	6	1.7%
Glioblastoma with oligodendroglioma Component (GBMO), Grade IV	15	4.2%
Anaplastic Oligoastrocytoma, Grade III	8	2.2%
Oligoastrocytoma, Grade II	1	0.3%
Pleomorphic Xanthoastrocytoma, Grade II	6	1.7%
Central Neurocytoma, Grade II	3	0.8%
Atypical Choroid Plexus Papilloma, Grade II	1	0.3%
Pineocytoma, Grade II	1	0.3%
Ganglioglioma, Grade II	1	0.3%
AT/RT, Grade IV **	2	0.6%
Hemangioblastoma, Grade II	1	0.3%
Anaplastic Hemangiopericytoma, Grade III	2	0.6%

* Primitive Neuroectodermal Tumor; ** Atypical Teratoid and Rhabdoid Tumor

was not known. Seminoma and malignant mixed germ cell tumors were the commonest histologic types comprising 44 (43.1%) and 35 (34.3%) cases respectively. Other types including Yolk Sac tumor (14 cases, 13.7%), immature teratoma (6 cases, 5.9%), embryonal carcinoma (2 cases, 1.9%) and malignant sertoli cell tumor (1 case, 1%). The decade wise breakup is shown in Table 3.

A total of 237 cases of prostatic adenocarcinoma were diagnosed in the study period. Average Gleason grade (score) was 6 in 41% and 7 in 39%. Average tumor volume was 60 to 65%. Perineural invasion was present in 110 cases (46.4%). Out of 237 cases, 9 patients (3.8%) were under 50 years of age, 43 (18.2%) were between 51 and 60, 105 (44.3%) were between 61 and 70 and 80 (33.7%) were above 70 years of age.

Out of a total of 119 cases of Ewing sarcoma diagnosed, 63 (52.9%) were diagnosed in males and 56 (47.1%) in females. M:F ratio was 1.12:1.0. Of the 119 cases, 52 (43.7%) were bone based while 63 (52.9%) were soft tissue based. In 4 cases (3.4%) location was not known. The decade wise breakup is given in Tables 2 and 3.

As many as 75 (72.1%) out of 104 Gall bladder carcinomas were diagnosed in females while 29 (27.9%) were diagnosed in males. This value was statistically significant (p-value: <0.0001). In 101 cases (97.1%), the tumor invaded full thickness of the wall and invaded the peri-muscular connective tissue. This value was statistically significant (p-value: <0.0001). In 35 cases (33.6%), the tumor perforated the serosa (visceral peritoneum) and directly invaded the liver or another organ. Cystic duct resection margin was positive in 21 cases (20.2%). In 3 cases (2.9%), specimen was received in multiple pieces and it was not histologically possible to determine the extent of tumor invasion. The decade wise breakup is given in Tables 2 and 3.

A total of 88 malignant salivary gland tumors were diagnosed. Of these, 55 (62.5%) occurred in males and 33 (37.5%) in females. The p-value was statistically not significant (0.0838). The M:F ratio was 1.66:1.0. The decade wise breakup is given in Tables 2 and 3 while histologic types are shown in Table 8.

Of the 86 cases of osteosarcoma, 52 (60.5%) were diagnosed in males and 34 (39.5%) in females. M:F ratio was 1.53:1.0. Femur and tibia were the commonest sites comprising 25 (29.1%) and 24 (27.9%) cases respectively. Other bones involved were humerus (7 cases, 8.1%), radius (5 cases, 5.8%), ileum (4 cases, 4.6%), fibula (4 cases, 4.6%), rib (3 cases, 3.5%), jaw (2 cases, 2.3%), ulna (2 cases, 2.3%) and foot (2 cases, 2.3%). In 8 cases (9.3%), exact location was not known. The decade wise breakup is given in Tables 2 and 3.

Of the 82 cases of hepatocellular carcinoma seen during the study period, 47 (57.3%) were diagnosed in males and 35 (42.7%) in females. M:F ratio was 1.3:1.0. All cases were diagnosed on core biopsies. As many as 80 (97.6%) were histologically well differentiated. This value was statistically significant (p-value: <0.0001). The decade wise breakup is given in Tables 2 and 3.

Discussion

Carcinoma of the oral cavity, lymphoma (Non Hodgkin and Hodgkin combined) and esophageal carcinoma were among the top five malignancies in both males and females. Breast cancer was the commonest cancer in females (32% of all malignancies in females) and it was overall the single most common type of cancer reported. In males, colorectal and gastric carcinomas rounded off the top five. In females, ovarian carcinoma completed the top five while colorectal carcinoma, fifth overall in both sexes combined, was at number six. Lung cancer, among the top three cancers in most international studies was eighth overall in our series, sixth in males and fifteenth in females. The lower incidence in females can be attributed to smoking habits (women in Pakistan smoke much less compared to women in other parts of the world). Gastric carcinoma, fourth in males was at seventh place overall due to its lower (tenth) place in females. Skin cancer was

very common occupying sixth place overall and seventh place in both sexes. Malignant tumors of the CNS occupied ninth place overall in our series, and ninth and eleventh place in males and females respectively. Carcinoma of the urinary bladder was at tenth place overall, eighth in males and fourteenth in females. Carcinomas of endometrium and cervix occupied the eighth and ninth places in females. In males, prostatic carcinoma, among the top three malignancies in most series was at number ten. Cancer of larynx and vocal cord occupied eleventh place overall, eleventh in males and twelfth in females. A comparison with incidence rates of different cancers around the world is at this point warranted. Across Asia, the incidence rates vary greatly and there are significant (three fold) differences in both sexes.(Shin et al., 2010) In Thailand, lung cancer was the commonest cancer in both males and females but in a particular region of Thailand, liver cancer was the commonest. In females, breast and cervical cancer were the most common while oral and pharyngeal cancers were also extremely common in both sexes. This variability in the incidence of various types of cancers even within different regions of the same country results from different risk factors prevalent in different regions to which the populations of particular areas are exposed.(Sriplung et al., 2005) In Thailand, colorectal and breast cancers showed a statistically significant increasing trend in the 1990s while incidence rates of other cancers remained sTable.(Sriplung et al., 2005) In India, lung, esophagus, stomach, oral and pharyngeal cancers were the commonest cancer types in males while cancers of cervix and breast followed by oral cavity, stomach and esophagus were the predominant cancer types in females.(Murthy et al., 2008) A report using data from India's National Cancer Registry Program showed that the incidence of various types of cancers in India was increasing in both sexes and that increase in population size, increase in the number of elderly people, urbanization etc. were responsible for this increasing cancer burden. It noted that the existing diagnostic and treatment facilities were inadequate to tackle the present cancer load and recommended that these facilities be urgently strengthened and increased to handle the cancer load which is expected to increase consistently till 2026.(D'Souza et al., 2013) It is unfortunate that in Pakistan, there is not even a regional cancer registry, what to say of a national one. Our situation is identical to India in terms of rising cancer burden and grossly inadequate diagnostic /treatment facilities but tragically, we do not have the data to determine the exact magnitude of an undeniably grim situation. Past and recent attempts to develop regional cancer registries were not very successful.

Data from two population based registries in Ibadan and Abuja regions in Nigeria showed that breast and cervical cancers were the commonest cancers in females while carcinoma of the prostate was the commonest cancer in males. About 66% cancers were seen in females.(Jedy-Agba et al., 2012) In Malawi, almost 60% cancers were seen in females. Cancer of cervix was the commonest followed by kaposi sarcoma, cancers of esophagus, breast and non-Hodgkin lymphoma. In males, Kaposi sarcoma was the commonest followed by cancer of esophagus, non-Hodgkin lymphoma and cancers of prostate and urinary bladder. Cervical cancer accounted for over 45% of all cancers in females, while Kaposi sarcoma accounted for almost 51% of all cancers in males. Even in females, Kaposi sarcoma comprised over 21% of all malignancies. Surprisingly, the incidence of breast carcinoma was very low in Malawi (4.6%), a figure much lower than anywhere else in the world.(Msyamboza et al., 2012)

Unlike other studies from Asia and Africa, where carcinoma of cervix was among the top most malignancies, it was the ninth most common cancer in females in our series accounting for 2.7% of all cancers in females. This low incidence of carcinoma cervix may reflect low sexual promiscuity in Pakistani women.

In Europe, data from a population based cancer registry in Cyprus- a Mediterranean country with a unique cultural and environmental setting- prostate, lung, colorectal and bladder cancers were the commonest in males, while breast, colorectal, uterine and thyroid cancers were the commonest cancers in females. This study found that the overall cancer incidence in Cyprus was lower compared to the other countries in the region.(Cooter et al., 2015) A study by the Italian network of cancer registries showed that cancer incidence was increasing in both sexes. However, mortality from cancer was decreasing. Prostate and lung cancer were the commonest cancers in Italian males while breast cancer accounted for about one-fourth of all cancers in females.(AIRT Working Group, 2006)

In general, the incidence of cancers is increasing worldwide, although incidence of specific types has stabilized in the developed countries. Mortality from cancer is decreasing in the developed world. This is unlike the developing world where both cancer incidence and cancer mortality are increasing, while the infrastructure to fight cancer is grossly inadequate.

A recent study from Germany(Bahr et al., 2015) showed that the number of new cancer cases in Germany will go on increasing at least up to 2020 and that the number of hospital days and sickness costs will increase.

In North America, data from a study on epidemiology of cancer in United States(Cresanta, 1992) demonstrated that just four cancers (breast, lung, prostate and colorectal) accounted for 56% of all cancer related mortality. The study highlighted genetic and environmental factors important in specific types of cancer for example cigarette smoking and tobacco abuse (in cancer of lung, oral cavity, larynx, esophagus, pancreas, urinary bladder, kidney), young black women (breast), black men (lung & prostate), young whites with excessive sun exposure (malignant melanoma), and the elderly (colorectal cancer). US data focusing on cancer trends between 1975 and 2000 showed that incidence of all cancers in the US increased from the mid-seventies upto 1992, rates then decreased between 1992 and 1995 and finally stabilized between 1995 and 2000. Similarly, mortality rates from all cancer sites declined from 1994 to 1998 and then stabilized from 1998 through 2000.(Weir et al., 2003) Yearly US cancer statistics compiled by the American Cancer Society based on the most recent data on cancer incidence and mortality demonstrated that incidence and mortality rates from all cancer sites continued to decrease from 2000

onwards in males. However, incidence rates continued to increase by about 0.3% per year in females from 1995 through 2003. Mortality rates continued to decrease for the three commonest cancers in males (lung, colorectum and prostate) as well as for the commonest cancers in females (breast and colorectum). In 2004, cancer death rates in males and females fell by 18.4 % and 10.5% respectively compared to the nineties. Cancer incidence rates in females began to fall around 2000 by about 0.6% per year through 2005. Cancer mortality rates in males declined by 19.2% between 1990 and 2005 and about 80% of the decrease was due to decreased mortality from lung, prostate and colorectal cancers. Similarly, mortality rates in females declined by 11.4 % and about 60 % of the total decrease was due to decreased mortality from breast and colorectal cancers. The decline in cancer mortality rates in the United States over a 16 year period resulted in the avoidance of around 767,000 deaths. This figure emphasizes the importance of disseminating our current knowledge of cancer in all segments of population and the importance of supporting new advancements in cancer prevention techniques as well as early detection and treatment of cancer. (Jemal et al., 2004; Jemal et al., 2006; Jemal et al., 2007; Jemal et al., 2008; Jemal et al., 2009; Jemal et al., 2010)

As shown in Table 4, a total of 768 out of 10,000 malignant tumors (7.7%) were diagnosed in patients upto 20 years of age. The most frequent in this age group were Non-Hodgkin Lymphoma (123), Hodgkin Lymphoma (109), Ewing Sarcoma (87), malignant CNS tumors (73) and Osteosarcoma (63 cases). Other tumors diagnosed frequently in young patients included rhabdomyosarcoma (37 cases), ovarian malignant tumors (30), Synovial sarcoma (26), testicular malignant tumors (25), Wilm's tumor (22), neuroblastoma (20) and retinoblastoma (19 cases). It is important to remember that only solid tumors were included in our study and leukemias (extremely common in the young) were not included. In the US, solid tumors of the CNS were the commonest malignant tumors in children up to age of 14 years.(Cresanta, 1992) In Brazil, the commonest malignant tumors in children, based on fourteen population based cancer registries, were lymphomas and CNS tumors.(de Camargo et al., 2010) However, in both US and Brazil, leukemia was the commonest malignancy in children and adolescents. (Cresanta, 1992; de Camargo et al., 2010) In Shanghai, China, based on data from the population based Shanghai Cancer Registry, the five commonest solid malignant tumors in children up to the age of 14 years were malignant CNS tumors, lymphomas, malignant germ cell tumors, neuroblastoma and soft tissue sarcoma. The incidence rate for malignant tumors was the highest in the first five years of life.(Bao et al., 2013) In Italy, data AIRTUM showed that cancer incidence was greater in the 0-14 than in the 15-19 year age group. Leukemias were the commonest malignances. Among solid tumors, Non Hodgkin and Hodgkin lymphoma, malignant CNS tumors and neuroblastomas were the commonest. Cancer incidence rates were decreasing in the 0-14 year age group, while they were still increasing in the 15-19 year age group. However, cancer mortality showed a persistent decline in both age groups.(AIRTUM Working Group, 2013) These studies show that, similar to our study, malignant CNS tumors are common in children and adolescents. Data on childhood CNS tumors from 13 Eastern and Southern European Cancer registries showed that astrocytomas constituted the most common malignant CNS tumors in the age groups 0-14 years (30%) followed by embryonal tumors (26%).(Papathoma et al., 2015)

As seen in Table 4, malignant tumors were most common in the 31 to 70 year age group reaching a peak in the 41 to 60 year age group.

Breast cancer is the commonest type of cancer and the commonest cause of death from cancer in women worldwide. Its incidence is highest in North America and Europe and low in Asia and Africa.(Parkin et al., 2001) However, as seen in Tables 1 and 2, this is not the case in Pakistan. It was the most common cancer in women comprising 32% of all cancers diagnosed in women. It was slightly more common in the left breast i.e. 47.7% compared to 41.5% in the right breast. As shown in Table 5, over 72% cases were diagnosed in the age range 31 to 60 years. Invasive Ductal Carcinoma, NOS was the commonest histologic type comprising 86% of all cases (Table 5). This figure was higher than the figure of approximately 75% reported in some studies.(Berg and Hunter, 1995)

In the United States, the incidence and death rate from breast cancer are constantly declining.(Jemal et al., 2009; Jemal et al., 2010) In our neighboring India, breast cancer has replaced cancer of cervix as the commonest in females especially in urban areas where it comprises 30 to 40% of all cancers in women.(Nanda Kumar et al., 2010) This change from cervix to breast occurred in just over a decade (1990 to 2003). The incidence rate of cancer of cervix is decreasing while that of breast cancer is increasing.(Takiar and Srivastav, 2008)

The high incidence of oral cancer in both sexes is related to the widespread ingestion of paan (betal quid), chalia, naswaar; cigarette, cigar and hooka smoking; poor oral hygiene etc. As shown in Tables 2 and 3, oral cancer was commonest in the fifth and sixth decades of life. The inner cheek (buccal) mucosa was the commonest site in the oral cavity followed by the tongue. (Table 6). Mouth and tongue cancer is very common in the subcontinent, where many of the major risk factors such as cigarette or bidi smoking, betal quid chewing, tobacco chewing etc are rampant. It is no wonder that the highest incidence rates of oral cancer in females are found in the Indian subcontinent.(Snkaranarayanm et al., 1998) In India, studies have shown regional differences in the incidence rates of oral cancers in both males and females according to data from registries in different regions of the country.(Yeole, 2007) One study showed that buccal mucosa was the commonest site of oral squamous cell carcinoma comprising 63.7% followed by retro molar area comprising 15%. This study also concluded that the incidence rates of oral cancer vary widely according to geographic location. However, it emphasized that even within one location, other factors such as age, sex, site, habit etc cause further variation in incidence rates. (Sharma et al., 2010) The US National Cancer Institute's

SEER data showed that incidence rate as well as five year survival rate from oral cancer had remained constant inspite of advances in surgery and radiation. The study emphasized that early detection of localized lesions with appropriate treatment and aggressive counseling of the public to prevent use and give up smoking and alcohol were extremely important in decreasing the morality rates from oral cancer.(Silverman, 2001)

Israel is another country with very high incidence rates of oral cancer. Data from the Israel National Cancer Registry showed that squamous cell carcinoma in males was extremely common above age 55 years.(Zini et al., 2010) A large population of fair skinned people and high level of sun exposure have resulted in the lip being the commonest site for oral cancer comprising 36.8%. (Zini et al., 2010) In Israeli Arabs, most cases of oral cancer occurred in males (high level of smoking), mean age was 54.4 years, oropharynx was the commonest site (28.3%), while squamous cell carcinoma was the most common histologic type.(Zini et al., 2012) All the above studies on oral cancer from around the world demonstrate geographical and regional variations in incidence rates, and also show considerable variation in the commonest exact site depending on multiple factors including habit, tobacco and alcohol , exposure to sun etc.

Lymphomas were among the three commonest malignancies in both males and females. They were more common in males and over 75% were non Hodgkin lymphomas (NHL). Nodal were more common (51.2%) than extra nodal NHLs (48.8%). Nodal NHLs in both sexes were most common in the fourth to seventh decades, whereas extra nodal NHLs were more evenly distributed from the second to seventh decades of life. The gastrointestinal tract (stomach, small intestine, and colon) was the commonest site of extranodal NHLs followed by bone. Diffuse Large B Cell Lymphoma (DLBCL) was the commonest histologic type of NHL, comprising 48.5% of nodal and almost 68% of extra nodal NHLS.

Hodgkin lymphoma (HL) was most common in the first to third decades of life in males. However, it occurred at a somewhat older age in females with most cases in the second to fifth decades. Mixed Cellularity and Nodular Sclerosis histologic subtypes were almost equally common. Italian cancer figures reported that incidence of HL was increasing in women although mortality from HL decreased significantly in both males and females. (AIRT Working Group, 2006) In the United States, acute lymphoblastic leukemia was the commonest malignancy in children up to the age of 14 years.(Cresanta, 1992) In our study, precursor B and T lymphoblastic lymphomas / acute lymphoblastic leukemias accounted for almost 14 % of all NHLs (Table 7). A study from Jordan showed similar results with NHLs comprising over 78.4 % and extra nodal lymphomas 30.5% of all lymphomas.(Haddadin, 2005) In our series, NHL comprised over 75% and extranodal lymphomas 30.5% (identical to the figures from Jordan) of all lymphomas. There is a strikingly evident but unexplained male predominance in many lymphoma subtypes in all age groups and autoimmune diseases are associated with increased risk for development of lymphomas especially in females.(Roman and Smith, 2011) This marked propensity of NHLs for males in both children and adults was also noted in two recent studies from United Kingdom, which also demonstrated that males were usually diagnosed at younger ages compared to females. However, no survival difference was detected between males and females.(Smith et al., 2011; Smith et al., 2015)

Esophageal carcinoma was the second commonest malignancy in women. As many as 53.2% esophageal carcinomas in our series were diagnosed in women. In 65% cases, the tumor was located in the lower third of the esophagus. Over 97% were squamous cell carcinomas on histologic examination. Over 66% were diagnosed in the fifth, sixth and seventh decades of life (Tables 2 and 3). These findings were similar to our earlier findings. (Ahmad et al., 2013) Over 31% cases were received from Baluchistan province along Pakistan's borders with Iran, Afghanistan and China. The above mentioned geographic region has well documented high rates for esophageal cancers in both males and females.(Curado et al., 2013)

Colorectal carcinoma was much more common in males (64.5%). Over 75% were located in the left colon especially in the sigmoid and rectum. All cases corresponded histologically to adenocarcinomas. Colorectal carcinoma was most commonly diagnosed in the fourth to seventh decades of life. Our earlier study showed similar findings with almost 63% occurring in males and over 80% in the left colon.(Ahmad et al., 2013)

Gastric Carcinoma was also much more common in males. Almost 71% occurred in males. Almost 37% were located in the distal stomach. All cases were adenocarcinomas and almost 69% were poorly differentiated signet ring adenocarcinomas on histologic examination. In our earlier study, over 67% occurred in males, 62% were located in the distal stomach and over 74% were poorly differentiated signet ring carcinomas. (Ahmad et al., 2013) Helicobacter pylori infection is very common in Pakistan and it is among the high prevalence countries for H pylori infection.(Khan et al., 2013) This is probably an important etiologic factor contributing to the high incidence rates of gastric cancer in Pakistan.

Although we do not have exact figures, the incidence of cancers of esophagus, stomach and colon are increasing in Pakistan. Esophageal cancer is extremely common worldwide and has a high mortality rate.(Herszenyi and Tulassay, 2010) Incidence and mortality rates have recently shown a reducing trend in some parts of the world. (Xie et al., 2012) However, in Asia, the incidence and mortality rates remain high.(Lin et al., 2013; Bafandeh et al., 2006) The incidence and mortality rates associated with gastric cancer remain very high in developing countries.(Miwa et al., 2002) However, these rates have decreased significantly in many developed countries. (Crew and Neugut, 2006) Gastric cancer remains very common in East Asia, Eastern Europe and in Central and South America.(Herszenyi and Tulassay, 2010) In both United States and Italy, incidence and death rates for gastric and colorectal cancers have shown a significant decrease in both sexes.(AIRT Working Group, 2006; Jemal et al., 2010) However, colorectal cancer remains one of the commonest cancers worldwide with the highest

incidence rates in developed countries in North America, Europe, Australia and New Zeeland and remains a leading cause of death, with obesity and physical inactivity as important contributing factors. Although its incidence is considered to be low in Asia, Africa and South America (poor or developing countries),(center et al., 2009) this is not our experience. It exacts a heavy toll in both morbidity and mortality in Pakistan. Developed Asian countries like Hong Kong, continue to show increased incidence rates for colorectal cancer(Xie et al., 2012) and developing countries like Iran and Thailand also demonstrate increased incidence rates in both males and females.(Khuhaprema and Srivatanakul, 2008; Abdifard et al., 2013)

Skin cancer was common in both sexes. Almost 59% were diagnosed in males. The large majority were diagnosed from the fourth decade onwards (Tables 2 and 3). The three commonest histologic types were squamous cell carcinoma (51.7%), basal cell carcinoma (31.1%) and malignant melanoma (11.2%). This is in contrast to western data which indicate that BCC is the commonest histologic type (approximately 70%) followed by SCC.(52,53) In Pakistan, although there is severe sun exposure, the large majority of people are dark-skinned. The incidence of these cancers is directly related to the amount of sun exposure and the lack of melanin pigment in the skin.(Casson, 1980, Crowson, 2006) However, the low incidence of malignant melanoma, as compared to the west where it is among the ten commonest malignant tumors in both males and females(Jemal et al., 2010) is in accordance with the well-known fact that these tumors mainly occur with excessive sun exposure in fair skinned people who have very little melanin pigment in their skin. (Beral et al., 1983)

Lung cancer was at number six among males. However, it was much less frequent in females (Tables 2 and 3), most likely due to the fact that cigarette smoking is much less common in Pakistani women compared to the west. Pakistani women are more likely to smoke huqqa, a tobacco preparation. Huqqa smoking is more prevalent in women living in rural areas compared to those living in cities. Even among males, lung cancer was much less common compared to the West where it remains the commonest cancer in both sexes. In the US, at least among males, its incidence rate and mortality are decreasing.(Jemal et al., 2010) Italian figures also show a decrease in mortality rate from lung cancer in males. However in Italian women, the incidence of lung cancer is increasing.(AIRT Working Group) In US women, the mortality rates from lung cancer were increasing in those states where prevalence of smoking was higher.(Jemal et al., 2008) Lung cancer remains a deadly and devastating disease worldwide and five year survival rates remain under 20%.(Williams and Sandler, 2001) In our series, the majority of cases in both males and females occurred in the fifth, sixth and seventh decades of life (Tables 2 and 3). It was much more common in males (79.7%). The right lung was involved more commonly (51.2% cases). Among histologic types, squamous cell carcinoma and adenocarcinoma were almost equally represented, while small cell carcinoma comprised just over 15% (Table 8). A recent Study from Poland showed that lung cancer accounted for almost half of all cancer related deaths in people above 65 years of age.(Radziszewska et al., 2015) An interesting study from Guangzhou, China showed that apart from the major risk factors like smoking, air pollution and certain occupational hazards, other less well documented risk factors such as degree of indoor air pollution, general conditions in homes, cooking practices and cooking environment, size of the kitchen etc. were important especially in relation to the development of lung cancer in nonsmoking females. This study also made the interesting observation that consumption of fresh vegeTables was a protective factor for lung cancer in both genders.(Du et al., 1996)

Malignant tumors of larynx and vocal cord were also common. Cancer of larynx was much more common in males (61%). The large majority of cases in both sexes were diagnosed in the fifth, sixth and seventh decades of life (Tables 2 and 3). Over 96% corresponded histologically to squamous cell carcinoma. According to Western data, cancer of larynx accounts for 2.2% of all cancers in males and 0.4% in females, most cases are diagnosed in the fifth decade of life and beyond and almost 96% patients are males.(Rafferty et al., 2001) In our study, compared to western data, the tumor was more common in females accounting for 2.7% of all cancers in both genders, 3.4% of all cancers in males and just over 2% of all cancers in females (Tables 1 to 3). Cigarette smoking is a major risk factor for cancer of larynx.(Muscat and Wynder, 1992) However, tobacco abuse in other forms is also a major risk factor(Cresanta, 1992) and the smoking of huqqa (a form of tobacco) especially in rural areas probably accounts for increased incidence rate of laryngeal cancer in Pakistani women compared to the west.

Ovarian cancer was among the five commonest cancers in females. Papillary serous carcinoma and endometrioid carcinoma were the commonest histologic types. Ovarian malignant tumors were evenly distributed in the third to seventh decades of life with a peak in the fifth decade. Almost 12% occurred in patients 20 years or younger (Table 2). The incidence of ovarian carcinoma has remained relatively constant around the world. However, recent Italian figures showed a decrease in incidence. (AIRT Working Group, 2006) According to US Cancer Statistics, 2010,(Jemal et al., 2010) ovarian cancer was the ninth commonest cancer in women accounting for 3% of all cancers in women and was the fifth commonest cause for death from cancer in women accounting for 5% of all deaths. In our series, ovarian cancer accounted for 4.8% of all cancers in women (Table 2). Ovarian cancer is responsible for the greatest number of deaths resulting from malignant tumors of the female genital tract. (Cannistra, 2004) Since ovarian cancer has a high case-fatality ratio (due mostly to late diagnosis), recent studies have attempted to build risk prediction models which can help identify women at increased risk. Such women can benefit from targeted prevention measures such as screening or chemo preventive drugs.(Li et al., 2015)

Malignant CNS neoplasms were surprisingly common accounting for almost 5% of all malignant tumors in males (Table 3) and over 3.5% overall (Table 1). Over 67% were

diagnosed in males. Glioblastoma Multiforme (GBM) and grade II and III oligodendrogliomas were the commonest CNS malignancies comprising almost 57% of all cases. Medulloblastoma was the commonest malignant CNS neoplasm in children. The majority of malignant CNS tumors were diagnosed in the third to sixth decades of life in males and in the second to fifth decades in females. However, over 18% in males and almost 25% in females occurred in patients younger than 20 years of age (Tables 2 and 3). In the United States, diffuse astrocytomas were the most common primary intracranial tumors comprising almost 60% and approximately 8% of these were GBMs. Oligodendrogliomas, grades II and III accounted for only 4% of primary intracranial tumors.(CBTRUS, 2008) In our series, grade II and III oligodendrogliomas comprised over 35% of all primary brain tumors while grade II , III and IV astrocytomas comprised just over 23% of which the large majority were GBMs (Table 9). However, in a previous study performed in our department, the number of astrocytic and oligodendroglial neoplasms was almost equal.(Zubair et al., 2011)

Urinary bladder cancer was very common in males. It was the eighth commonest malignancy in males and fourteenth commonest in females. Over 75% cases were diagnosed in males. All cases were histologically consistent with urothelial carcinoma. Over 67% were high grade cancers of which over 65% of which were detrusor muscle invasive. This figure could be higher since in over 21% cases, no deep muscle was present in the biopsy to assess muscle invasion. International studies show that bladder cancer is the seventh commonest cancer worldwide accounting for about 3.2% of all cancers and is more than three times more common in males than females with a worldwide M:F ratio of 3.5:1.(Parkin et al., 1994; Ferlay et al., 2001) According to US Cancer Statistics 2010,(Jemal et al., 2010) bladder cancer was the fourth commonest cancer in males accounting for 7% of all cancers However, mortality wise it was ninth accounting for 3% for all cancer deaths in males. According to Italian Cancer Figures 2006,(AIRT Working Group, 2006) incidence and mortality rates of bladder cancer decreased in males. In both males and females, bladder cancer is most prevalent in North America, Western Europe and Australia.(Pisani et al., 2002; Parkin et al., 2003) Although considered to be much more common in developed compared to developing countries, it ranked among the commonest malignancies in males in our series (Table 3). Tobacco smoking is a major risk factor in the development of bladder cancer and the risk of developing bladder cancer is several times higher in smokers than in non-smokers. Like lung cancer, the risk is also proportionate with the number of cigarettes smoked and the duration of smoking. (Brennan et al., 2000; Negri and La Vecchia, 2001)

Prostate cancer was the tenth commonest cancer in males comprising 4.8% (Table 3). It is the sixth most common cancer worldwide(Parkin, 2001) comprising 9.7% of all cancers in males. It is more common in the developed countries comprising over 15% and less so in the developing countries comprising over 4% of all cancers in males. According to US cancer statistics, it was the commonest cancer in males comprising 28% and second commonest cause of death from cancer in males comprising 11% of all cancer deaths in males. However, both the incidence and death rates from prostate cancer have declined in the US.(Jemal et al., 2010) Italian cancer figures 2006 also demonstrated a decrease in mortality from prostate cancer.(AIRT Working Group) In India, prostate cancer ranked among the most common malignancies in males especially in the largest Indian cities like Mumbai, Delhi, Kolkata and Bangalore. Indian registries show a statistically significant increase in the incidence rate of prostate cancer.(Jain et al., 2014) It has a lower fatality rate compared to most other cancers and accounts for 5.6% of all cancer deaths in males. Survival rates in prostatic cancer are much higher in the developed countries.(Brawley, 1997) In our series, almost 78% patients were above 60 years of age. Worldwide, over 75% prostate cancers occur above 65 years of age.(Epstein et al., 2004)

The more common malignant tumors encountered in our practice have been discussed. It is hoped that this study will be an important step towards developing a comprehensive cancer registry in Pakistan.

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