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CONTENTS

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Cancer J Bangladesh. Vol. 2, No. 1, January 2021
www.nicrh.gov.bd

CONTENTS

Editorial

Cancer J Bangladesh 2021;2(1): 1-3
http://nicrh.gov.bd/publication

COVID-19 Pandemic: Global Consensus for the Management of Paediatric Cancer Patients

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COVID-19 pandemic is a serious challenge for delivering treatment to children with cancer all over the world. To solve this problem International Society for Pediatric Oncology (SIOP), Children's Oncology Group (COG), St Jude Global program and Childhood Cancer International (CCI) provided a framework for healthcare teams caring for children with cancer during the pandemic. They have brought together the relevant clinical leads from SIOP Europe, COG and SIOP-PODC (Pediatric Oncology in Developing Countries) to focus on the six most curable cancers that are part of the WHO Global Initiative for Childhood Cancer.

The WHO Global Initiative for Childhood Cancer (GICC) has set an ambitious goal of improving survival rates for the 90% of the world's children who live in low- and middle-income countries (LIMC) to 60% by 2030.[1, 2] The GICC has identified six common index cancers - Acute Lymphoblastic Leukemia (ALL), Burkitt lymphoma (BL), Hodgkin lymphoma (HL), Retinoblastoma, Wilms tumor, and low-Grade Gliomas (LGGs).

Global consensus is that wherever possible, children with a likely diagnosis of cancer during this pandemic should undergo a clinical assessment and proper investigations to establish a confirmed diagnosis and be offered effective therapy within the resources available while reducing the risk of COVID-19 exposure.[3]

General guidance for adapting cancer services and cancer treatment during the COVID-19 **pandemic:**[3]

Standards of care for the diagnosis, treatment and supportive care for children with cancer should not be compromised or electively modified during the pandemic, if at all possible. If treatment modification is mandatory, these should be done by a whole service approach rather than by individual clinical decision making. All cancer centers should make an anticipatory and planned process to adapt their service to potential resource limitations. It is necessary to limit patient visits to clinics and hospital admissions. Where possible, all elements of cancer treatment should continue without modification unless resources become overwhelmed. Maintaining lists of cases where care has been adapted and to develop a prioritized approach to review care when normal service capacity resumes.

Recommendations for adapting the diagnosis and treatment for the WHO index cancers

All children suspected of having cancer should be investigated without delay. Where a patient presents with advanced cancer and concurrent COVID-19, the essential investigations should be done to establish an accurate cancer diagnosis and interim therapy to control

disease may be a safe approach and permit recovery from COVID-19 before commencing disease-directed treatment.

In nonemergency presentations with concurrent COVID-19 such as an abdominal mass, intraocular retinoblastoma or low-stage Hodgkin lymphoma, it is reasonable and safe to defer diagnostic investigations until the child has recovered and proceed with resource-adapted investigations as best can be achieved. Multidisciplinary tumor board meetings should continue for decision-making, if necessary, through phone/ teleconferencing to ensure social distancing.

1. Acute Lymphoblastic Leukemia (ALL)

Children presenting with ALL should undergo full investigation to establish the diagnosis and risk stratification and commence treatment according to institutional standard of care (SOC), protocols or clinical trials. Children with concurrent COVID-19 and hyperleukocytosis should commence immediate treatment with supportive care and a steroid prophase and commence disease-directed therapy on recovery from COVID-19.[4]

If necessary, patients should initiate treatment based on bone marrow/blood cytomorphology, age and complete blood counts.[5]

2. Hodgkin Lymphoma

All children and adolescents presenting with progressive lymphadenopathy should undergo immediate clinical evaluation and the best available diagnostic imaging and biopsy. Outpatient-based therapy is recommended according to setting-appropriate SOC without protocol modification. If access to radiotherapy is very limited, a chemotherapy-only approach especially for low- and intermediate-risk disease is acceptable.

3. Retinoblastoma

Intraocular retinoblastoma requires access to an experienced ophthalmologist for an immediate examination under anesthesia (EUA) to determine the intraocular extent of disease and laterality, as this will determine treatment with either local therapy or local and systemic chemotherapy. In resource-limited settings, most patients with advanced intraocular disease and no salvageable vison will require immediate enucleation to control disease followed by systemic chemotherapy.[6, 7] Standard post-enucleation chemotherapy without dose modification as an outpatient is recommended.[8]

4. Wilms Tumor

All children presenting with an abdominal mass undergo an immediate clinical assessment and diagnostic imaging, the minimum being an abdominal US scan and chest X-ray and if available a CT scan of the chest and abdomen. For primary renal tumors in children (age > 6 months) during the pandemic, where the immediate nephrectomy (COG) approach is not possible, recommendation is proceeding to SIOP based preoperative chemotherapy, based on the best available disease staging but without biopsy in children aged < 7 years.[9]

5. Burkitt Lymphoma

At diagnosis in fully resourced and HIC settings with an emergency presentation, no pandemic modifications are recommended for the initial assessment and diagnosis, even if a child presents with concurrent COVID-19. In resource-limited settings, a simplified assessment based on the constellation of clinical features, a minimally invasive biopsy and diagnostic imaging with chest X-ray and ultrasound (US) is sufficient to establish a safe diagnosis and commence supportive care and therapy. Where disease is advanced with concurrent comorbidity, a treatment prophase with stepped dosing corticosteroids alone with supportive care, before commencing disease-directed chemotherapy, is a safe approach for achieving immediate disease control and may mitigate the severity of life-threatening tumor lysis syndrome.

6. Low-Grade Glioma (LGG)

For children with LGG receiving chemotherapy, the recommendation is to continue the planned treatment without modification.

Some special consideration:

Radiotherapy

Prioritization and triaging of cases for radiotherapy based on acuity, curability is essential. In case of delaying or deferring treatment, use of alternative modalities and condensed regimens may be possible.

Surgery

Surgery needed for childhood cancer to be tailored according to the COVID-19 prevalence and health system capacity. Some modifications in the timing and practice of surgery may be required to provide safe treatment without compromising oncological prognosis.

Blood product use and support

Centers should revise their use of blood products and transfusion policies for safe and adequate blood supplies. In asymptomatic children, the safe threshold for red cell transfusion is Hb > 7.0 g/dL. The threshold for prophylactic platelet transfusion in patients with no risk factors for bleeding is recommended as 10×10^9/L. For procedures, the platelet threshold for lumbar puncture (LP) for a new diagnosis of ALL is recommended at 50×10^9/L and 20×10^9/L for subsequent LPs; for bone marrow aspirate 10×10^9/L, and for bone marrow biopsy, it is 20×10^9/L.[10]

Procedural support

Centers using general anesthesia for painful procedures should continue to provide these. Where access is limited policies for safe and effective sedation with appropriate patient monitoring and post procedure supervision may be adopted.

Palliative care and support

Children with cancer those comes for palliative care are vulnerable population during this COVID 19 pandemic. Integration of palliative care into the ongoing care of children with cancer is essential during these difficult times.

For continuation of childhood cancer management every cancer center needs a planned process to adapt its service considering resource limitation in this pandemic time. So, families are able to take treatment for their children with cancer.

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Original Article

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Trends and Distributions of Cancer at NICRH: Extract from the Cancer Registry Data 2005-2014

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Abstract

Like other countries cancer is a burning health issue in Bangladesh. Unfortunately, we do not have proper data regarding its prevalence and trends. The aim of the current study was to determine the trends and distributions of cancers at National Institute of Cancer Research and Hospital (NICRH). Retrospective analysis was done on the cancer patients registered at NICRH during January, 2005 to December, 2014. Out of 79431 patients, 45924 (57.8%) were male and majorities were from 45-54 years age group. Most frequent cancers were respiratory system and intrathoracic organs (22.9%) followed by digestive organs (19.6%), breast (11.6%), and lip, oral cavity and pharynx (10.3%) and female genital organs (10.1%). Lung cancer was the leading cancer among male followed by oesophagus and stomach. Among female breast cancer topped the list followed by cervical cancer, and lung cancer. In conclusion, it can be said that an increasing trend of cancer was observed at NICRH over ten years from 2005 to 2014. Lung and breast cancer was the leading cancer in male and female respectively. Illiterate and middle-aged population suffered more from the disease. Strong emphasis should be given to increase awareness against cancers in Bangladesh.

Key Words: *Common cancers, distributions, cancer registry*

Introduction

According to the report of World Health Organization (WHO) in 2012, there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer worldwide. Fifty seven percent (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred in the less developed countries.[1]

Lung, liver, stomach, colorectal and breast cancers cause the most cancer deaths each year. The most frequent types of cancer differ between men and women. Tobacco use is the most important risk factor for cancer causing over 20% of global cancer deaths and about 70% of global lung cancer deaths. Cancer causing viral infections such as HBV/HCV and HPV are responsible for up to 20% of cancer deaths in low- and middle-income countries.[2] More than 60% of world's total new annual cases occur in Africa, Asia and Central and South America. These regions account for 70% of the world's cancer deaths.[2] It is expected that annual cancer cases will rise to 22 million within the next two decades.[2]

Cancer is one of the major causes of morbidity and mortality, and it is one of the leading causes of mortality in Bangladesh. Like other developing countries, cancer is expected to be double in our country in the next two decades.[3,] It is worth mentioning that at least 30% of these cancers are preventable.[4] Unfortunately, reliable statistical data about trends of cancer and its distributions in Bangladesh is scarce.

This study was planned to determine the trends of cancers in Bangladesh on the basis of data available in the 'Cancer Registry' at National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh.

Materials and methods

Data of 80120 cancer patients registered in the 'Cancer Registry' of NICRH, Dhaka during January 2005 to December 2014 were analyzed retrospectively in the current study. A checklist was used to extract relevant information from the cancer registry.

Flow of patients at NICRH

After initial registration, patient identification, socio-demographic characteristics and history of tobacco uses were noted at cancer register interview room. Method of diagnosis, clinical stages and details of treatment were collected from the diagnosed cases. After completing this session each patient was directed to the medical officers of respective departments. The medical officer then took a brief clinical history and conducted appropriate physical examination. Attending doctors reviewed all the relevant documents of the concern disease and used to give new investigations if needed. Patients along with all investigation reports were then sent to chief medical officer, who placed the patients before the Tumor Board. Tumor Board was consisted of experienced professors, associate and assistant professors of various sub-specialties. They then decided on the final diagnosis and treatment modalities. ICD-O (3rd edition) coding was used to code each and every cancer.[15] Data for this were extracted for all relevant records of the hospital like inpatient registry, Tumor Board Record, etc. In the registry form the most valid basis of diagnosis was recorded. Data management and other operational works were done by cancer epidemiology department of NICRH. During data analysis and reporting, a strict procedure was applied to maintain confidentiality of the information of the patients. A prior permission was obtained from the all patients during registration consenting for use of their information for subsequent analysis and use without recognizing their identity. Statistical analyses were per formed with the SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) software. Descriptive statistics were applied. Student's t test for continuous variables and the chi square test for categorical variables were used in the assessment of differences between the two groups when appropriate. All the statistical tests were two-tailed and p-values <0.05 were considered as statistically significant.

Results

There were 79431 confirmed cancer patients attending at NICRH during the year 2005 to 2014. Out of these total, 45924 (57.8%) were male and 33507 (42.2%) were female. Majority of the patients were married. Illiterate patients were suffering from cancer more than literate in both sexes (34.3% (n=15739) for male and 45.9% (n=15390) for female). In males farming was the leading profession while majorities of women were housewives (Table 1.1 & 1.2). Figure 1 describes age-wise distribution of cancers. More than one-fourth (n=19633, 25.7%) were at the age group 45-54 years. The two next leading age groups were 55-64 years (n=17709, 22.3%) and 35-44 years (n=13255, 16.7%). Table 2.1 & 2.2 showed different types of cancer based on ICD-O (3rd edition) coding. It was found that majority, 18117 (22.8%) of the cancer involving respiratory system and intra thoracic organs followed by digestive organs, 15583 (19.6%) and breast cancer, 9197 (11.6%). In fact, in most of the years breast cancer was almost steadily increasing. The frequency of breast cancer on ten years (2005-2014) were 491 (9.1%), 715 (11.0%), 867 (12.5%), 759 (10.2%), 1196 (12.4%), 758 (9.9), 823 (11.9), 933 (12.2), 1396 (12.6%) and 3910 (11.7%) respectively. Top 10 cancers at NICRH were shown in Table 3.1 & 3.2. Lung cancer topped the list in all ten years. In 2005 cervical cancer was the 2nd leading cancer but in the next successive nine years breast cancer occupied the 2nd position. Cancer of the oesophagus, stomach, liver, lymph nodes were the other leading cancer.

Table 1.1: Socio-demographic characteristics of the patients by Gender(2005-2010)

Demography	2005		2006		2007		2008		2009		2010	
	M(%)	F(%)	M(%)	F(%)	M(%)	F(%)	M(%)	F(%)	M(%)	F(%)	M(%)	F(%)
Religion												
Islam	2861(52.9)	2162(40.0)	3600(55.5)	2471(38.1)	3723(53.8)	2751(39.7)	3987(53.4)	2984(40.0)	5026(51.5)	4099(42.0)	5303(52.7)	4092(40.6)
Hinduism	205(3.8)	146(2.7)	206(3.2)	177(2.7)	206(3.0)	227(3.3)	262(3.5)	209(2.8)	324(3.3)	277(2.8)	376(3.7)	268(2.7)
Christianity	11(0.2)	13(0.2)	13(0.2)	19(0.3)	6(0.1)	6(0.1)	7(0.1)	9(0.1)	8(0.1)	19(0.2)	3(0.0)	20(0.2)
Buddhism	9(0.2)	4(0.1)	5(0.1)	1(0.0)	2(0.0)	5(0.1)	1(0.0)	2(0.0)	0(0.0)	3(0.0)	0(0.0)	2(0.0)
Marital status												
Never married	364(6.7)	143(2.6)	376(5.8)	190(2.9)	307(4.4)	141(2.0)	368(4.9)	167(2.2)	376(3.9)	225(2.3)	463(4.6)	265(2.6)
Married	2696(49.8)	1845(34.1)	3434(52.0)	2236(34.4)	3619(52.3)	2647(38.2)	3883(32.0)	2839(38.1)	4972(51.0)	4086(41.9)	5198(51.0)	4059(40.3)
Widow/Widower	15(0.3)	315(5.8)	11(0.2)	233(3.6)	7(0.1)	195(2.8)	4(0.1)	192(2.6)	7(0.1)	78(0.8)	16(0.16)	48(0.5)
Divorced	1(0.0)	21(0.4)	0(0.0)	9(0.1)	4(0.0)	6(0.1)	2(.0)	5(.0)	3(.0)	7(0.1)	8(.08)	10(0.1)
Education												
Not applicable	66(1.2)	25(0.5)	61(0.9)	34(0.5)	60(0.9)	35(0.5)	87(1.2)	36(0.5)	74(0.8)	47(0.5)	78(0.8)	57(0.6)
Illiterate	1137(21.0)	1127(20.8)	1406(21.7)	1284(19.8)	1749(25.3)	1465(21.2)	1760(23.6)	1568(21.0)	1479(15.2)	1566(16.1)	2357(23.4)	2049(20.4)
Primary	970(17.9)	676(12.5)	1321(20.3)	896(13.8)	1340(19.3)	1097(15.8)	1452(19.5)	1144(15.3)	1982(20.3)	1702(17.5)	1628(16.2)	1294(12.9)
Secondary	574(10.6)	331(6.1)	595(9.2)	301(4.6)	427(6.2)	220(3.2)	630(8.4)	328(4.4)	1163(11.9)	745(7.6)	1038(10.3)	702(7.0)
Higher secondary	164(3.0)	89(1.6)	213(3.3)	82(1.3)	219(3.2)	112(1.6)	167(2.2)	72(1.0)	394(4.0)	206(2.1)	299(3.80	141(1.4)
Graduate and above	175(3.2)	77(1.4)	228(3.5)	71(1.1)	142(2.1)	60(0.9)	158(2.1)	56(0.8)	263(2.7)	130(1.3)	285(2.8)	140(1.4)
Occupation												
Not applicable (up to 5 yrs)	70(1.3)	28(0.5)	61(0.9)	32(0.5)	17(0.2)	17(0.2)	87(1.2)	36(0.5)	74(0.8)	47(0.5)	78(0.8)	57(0.6)
Service	466(8.6)	119(2.2)	492(7.6)	102(1.6)	413(6.0)	78(1.1)	424(5.7)	58(0.8)	648(6.6)	170(0.8)	629(6.9)	128(1.3)
Business	460(8.5)	20(0.4)	503(7.7)	5(0.1)	459(6.6)	26(0.4)	512(6.9)	19(0.3)	603(6.2)	16(0.3)	692(6.9)	16(0.2)
Agriculture	876(16.2)	41(0.8)	1138(17.6)	20(0.3)	1472(21.3)	25(0.4)	1124(15.1)	29(0.4)	1621(16.6)	28(0.4)	2248(22.3)	20(0.2)
Day labourer	283(5.2)	17(0.3)	281(4.3)	24 90.4)	361(5.2)	21(0.3)	266(3.6)	4(0.1)	514(5.3)	21(0.1)	384(3.8)	18(0.2)
House wife	-	1949(36.0)	-	2280(35.2)	-	2654(38.3)	-	2755(36.9)	-	3571(36.8)	-	3590(35.7)
Retired/aged	661(12.2)	72(1.3)	1054(16.2)	73(1.1)	1035(14.9)	76(1.1)	1486(19.9)	191(2.6)	1447()	391(2.6)	1334(13.3)	364(3.6)
Industrial worker	69(2.2)	11(0.5)	75(1.2)	3(0.0)	39(.6)	2(0.0)	68(0.9)	17(0.2)	116(1.2)	65(0.7)	103(1.0)	17(0.2)
Student	191(3.5)	78(1.4)	214(3.3)	129(2.0)	141(2.0)	5(0.1)	271(3.7)	111(2.1)	245(2.5)	179(2.1)	217(2.2)	172(1.7)

Table 1.2: Socio-demographic characteristics of the patients by Gender (2011-2014)

Demography	2011		2012		2013		2014	
	M (%)	F (%)	M (%)	F (%)	M (%)	F (%)	M (%)	F (%)
Religion								
Islam	4344 (96.4)	3031 (96.5)	3982 (94.0)	2535 (93.6)	4601 (94.3)	2613 (95.3)	5767 (51.9)	4659 (41.9)
Hinduism	162 (3.6)	106 (3.4)	245 (5.8)	160 (5.9)	266 (5.4)	124 (4.5)	338 (3.0)	301 (2.7)
Christianity	1 (0.0)	3 (0.1)	5 (0.1)	11 (0.4)	12 (0.2)	6 (0.2)	15 (.1)	15(0.1)
Buddhism	0 (0.0)	1 (0.0)	2 (0.0)	3 (0.1)	2 (0.0)	0 (0.0)	5 (.0)	7 (0.1)
Marital status								
Never married	348 (7.7)	153 (4.9)	306 (7.2)	136 (5.0)	366 (7.5)	181 (6.6)	414 (3.7)	193 (1.7)
Married	4152 (92.1)	2947 (93.8)	3917 (92.5)	2235 (82.5)	4511 (92.4)	2156 (78.6)	5703 (51.3)	4136(37.2)
Widow/Widower	7 (0.2)	39 (1.2)	10 (0.2)	331 (12.2)	3 (0.1)	394 (14.4)	9 (0.1)	627 (5.6)
Divorced	0 (0.0)	2 (0.1)	1 (0.0)	7 (0.3)	1 (0.0)	12 (0.4)	0 (0.0)	26 (0.2)
Education								
Not applicable	117 (2.6)	61 (1.9)	94 (2.2)	49 (1.8)	88 (1.8)	58 (2.1)	99 (0.9)	50 (0.5)
Illiterate	1665 (36.9)	1413 (45.0)	1627 (38.4)	1261 (46.5)	1910 (39.1)	1305 (47.6)	2276 (20.5)	2352 (21.2)
Primary	1763 (39.1)	1224 (39.0)	1607 (38.0)	973 (35.9)	1848 (37.9)	940 (34.3)	2483 (22.4)	1813 (16.3)
Secondary	537 (11.9)	271 8.6 ()	450 (10.6)	214 (7.9)	530 (10.9)	248 (9.0)	608 (5.5)	394 (3.5)
Higher secondary	212 (4.7)	92 (2.9)	231 (5.5)	119 (4.4)	240 (4.9)	105 (3.8)	311 (2.8)	220 (2.0)
Graduate and above	214 (4.7)	79 (2.5)	225 (5.3)	93 (3.4)	265 (5.4)	87 (3.2)	349 (3.1)	153 (1.4)
Occupation								
Not applicable (up to 5 yrs)	54 (1.2)	33 (1.1)	75 (1.8)	47 (1.7)	88 (1.8)	54 (2.0)	92 (0.8)	43 (0.2)
Service	998 (22.1)	77 (2.5)	714 (16.9)	83 (3.1)	768 (15.7)	64 (2.3)	845 (7.6)	129 (1.2)
Business	777 (17.2)	11 (0.4)	746 (17.6)	3 (0.1)	780 (16.0)	1 (0.0)	943 (8.5)	12 (0.1)
Agriculture	2191 (48.6)	8 (0.3)	2079 (49.1)	12 (0.4)	2432 (49.8)	4 (0.1)	3291(26.6)	10 (0.1)
Day labourer	153 (3.4)	2 (0.1)	209 (4.9)	1 (0.0)	263 (5.4)	1 (0.0)	302(2.7)	5 (0.0)
House wife	-	2902 (92.4)	-	2463 (90.9)	-	2498 (91.1)	-	4650 (41.9)
Retired/aged	52 (1.2)	3 (0.1)	237 (5.6)	10 (0.4)	308(6.3)	6 (0.2)	294 (2.6)	15 (0.1)
Industrial worker	15 (0.3)	0 (0.0)	12 (0.3)	0 (0.0)	22 (0.5)	0 (0.0)	61(0.5)	0 (0.0)
Student	267 (5.9)	105 (3.3)	162 (3.8)	90 (3.3)	220 (4.5)	115 (4.2)	269 (2.5)	146 (1.4)

Table 2.1: *System wise distribution of the cancer patients by year (2005-2010)*

System wise distribution of cancers	Year						Total
	2005	2006	2007	2008	2009	2010	
Lip, oral cavity and pharynx (C00-C14)*	608 (11.2)	695 (10.7)	767 (11.1)	905 (12.1)	1114 (11.4)	882 (8.8)	4959 (10.8)
Digestive organ (C15-C26)	835 (15.4)	1083 (16.7)	1450 (20.9)	1344 (18.0)	1832 (18.8)	1932 (19.2)	8468 (18.4)
Respiratory system and intrathoracic organs (C30-C39)	1175 (21.7)	1436 (22.1)	1572 (22.7)	1765 (23.7)	2266 (23.2)	2421 (24.0)	10598 (23.0)
Bones, joints and articular cartilage (C40-C41)	172 (3.2)	170 (2.6)	72 (1.0)	148 (2.0)	55 (.6)	138 (1.4)	753 (1.6)
Haemopoietic and reticuloendothelial systems (C42)	46 (.9)	51 (.8)	34 (.5)	62 (.8)	40 (.4)	122 (1.2)	355 (0.8)
Skin (C44)	130 (2.4)	169 (2.6)	73 (1.1)	94 (1.3)	89 (.9)	87 (0.9)	641 (1.4)
Peripheral nerve and autonomic nervous system (C47)	3 (.1)	7 (.1)	2 (.0)	1 (.0)	4 (.0)	4 (0.0)	21 (0.0)
Retroperitoneum and peritoneum (C48)	0 (.0)	3 (.0)	13 (.2)	18 (.2)	30 (.3)	23 (0.2)	87 (0.2)
Connective, subcutaneous and other soft tissues (C49)	224 (4.1)	144 (2.2)	64 (.9)	153 (2.0)	319 (3.3)	222 (2.2)	1125 (2.4)
Breast (C50)	491 (9.1)	715 (11.0)	867 (12.5)	759 (10.2)	1196 (12.3)	1245 (12.4)	5287 (11.5)
Female genital organs (C51-C58)	692 (12.8)	733 (11.3)	789 (11.4)	95 (12.6)	1112 (11.4)	1294 (12.9)	5609 (12.2)
Male genital organs (C60-C63)	125 (2.3)	136 (2.1)	138 (2.0)	125 (1.7)	147 (1.5)	147 (1.5)	827 (1.8)
Urinary tract (C64-C68)	166 (3.1)	148 (2.3)	154 (2.2)	199 (2.7)	249 (2.6)	180 (1.8)	1095 (2.4)
Eye, brain and other parts of CNS (C69-C72)	137 (2.5)	160 (2.5)	145 (2.1)	194 (2.6)	178 (1.8)	190 (1.9)	1004 (2.2)
Thyroid and other endocrine glands (C73-C75)	62 (1.1)	53 (.8)	57 (.8)	77 (1.0)	104 (1.1)	93 (0.9)	446 (1.0)
Other ill defined sites (C76)	7 (.1)	12 (.2)	50 (.7)	56 (.8)	72 (.7)	69 (0.7)	273 (0.6)
Lymph nodes (C77)	184 (3.4)	370 (5.7)	581 (8.4)	520 (7.0)	773 (7.9)	820 (8.1)	3237 (7.0)
Unknown primary site (C80)	354 (6.5)	407 (6.3)	96 (1.4)	96 (1.3)	176 (1.8)	198 (2.0)	1325 (2.9)
Total	5411 (100.0)	6492 (100.0)	6924 (100.0)	7458 (100.0)	9756 (100.0)	10067 (100.0)	46110 (100.0)

* ICD-O (3rd edition) code

Table 2.2: *System wise distribution of the cancer patients by year (2011-2014)*

System wise distribution of cancers	Year				Total
	2011	2012	2013	2014	
Lip, oral cavity and pharynx (C00-C14) *	779 (10.2)	585 (8.4)	644 (8.4)	1238 ()	3246 (9.7)
Digestive organ (C15-C26)	1697 (22.2)	1471 (21.2)	1816 (23.8)	2131 ()	7115 (21.4)
Respiratory system and intrathoracic organs (C30-C39)	1746 (22.8)	1492 (21.5)	1845 (24.2)	2436 ()	7519 (22.6)
Bones, joints and articular cartilage (C40-C41)	95 (1.2)	185 (2.7)	148 (1.9)	220 ()	648 (1.9)
Haemopoietic and reticuloendothelial systems (C42)	164 (2.1)	112 (1.6)	205 (2.7)	224 ()	705 (2.1)
Skin (C44)	50 (0.7)	49 (0.7)	36 (0.5)	71 ()	206 (0.6)
Peripheral nerve and autonomic nervous system (C47)	3 (0.0)	3 (0.0)	5 (0.1)	4 ()	15 (0.0)
Retroperitoneum and peritoneum (C48)	22 (0.3)	9 (0.1)	18 (0.2)	18 ()	67 (0.2)
Connective, subcutaneous and other soft tissues (C49)	260 (3.4)	501 (7.2)	243 (3.2)	187 ()	1191 (3.6)
Breast (C50)	758 (9.9)	823 (11.9)	933 (12.2)	1396 ()	3910 (11.7)
Female genital organs (C51-C58)	723 (9.5)	441 (6.4)	152 (2.0)	1158 ()	2474 (7.4)
Male genital organs (C60-C63)	109 (1.4)	103 (1.5)	105 (1.4)	139 ()	456 (1.4)
Urinary tract (C64-C68)	179 (2.3)	159 (2.3)	162 (2.1)	241 ()	741 (2.2)
Eye, brain and other parts of CNS (C69-C72)	202 (2.6)	141 (2.0)	144 (1.9)	194 ()	681 ()2.0
Thyroid and other endocrine glands (C73-C75)	90 (1.2)	73 (1.1)	55 (0.7)	90 ()	308 (0.9)
Other ill-defined sites (C76)	67 (0.9)	109 (1.6)	54 (0.7)	51 ()	281 (0.8)
Lymph nodes (C77)	646 (8.4)	644 (9.3)	936 (12.3)	1160 ()	3386 (10.2)
Unknown primary site (C80)	58 (0.8)	43 (0.6)	123 (1.6)	150 ()	374 (1.1)
Total	7648 (100.0)	6943 (100.0)	7624 (100.0)	11108 ()	33323 (100.0)

Table 3.1: *Distribution of patients by top ten malignancies(2005-2010)*

Position	2005		2006		2007		2008		2009		2010	
	Cancer sites	n(%)	Cancer sites	n(%)	Cancer sites	n(%)	Cancer sites	n(%)	Cancer sites	n(%)	Cancer sites	n(%)
1	Lung	902 (16.7)	Lung	1076 (16.4)	Lung	1231 (17.3)	Lung	1299 (17.4)	Lung	1708 (17.5)	Lung	1934 (19.2)
2	Cervix	561 (10.4)	Breast	715 (11.0)	Breast	840 (12.3)	Breast	754 (10.1)	Breast	1189 (12.2)	Breast	1239 (12.3)
3	Breast	559 (10.3)	Cervix	583 (9.0)	Lymph nodes and lymphatics	581 (8.4)	Cervix	694 (9.3)	Cervix	849 (8.7)	Cervix	991 (9.8)
4	Lymph nodes and lymphatics	300 (5.5)	Lymph nodes and lymphatics	372 (5.7)	Cervix	574 (8.4)	Oesophagus	357 (4.8)	Oesophagus	448 (4.6)	Oesophagus	530 (5.3)
5	Larynx	268 (5.0)	Oesophagus	295 (4.5)	Oesophagus	404 (5.8)	Stomach	264 (3.5)	Stomach	380 (3.9)	Stomach	461 (4.6)
6	Oesophagus	215 (4.0)	Larynx	291 (4.5)	Stomach	330 (4.8)	Liver	215 (2.9)	Liver	298 (3.1)	Liver	353 (3.5)
7	Oral cavity	213 (3.9)	Stomach	269 (4.1)	Liver	229 (3.3)	Larynx	189 (2.5)	Rectum	206 (2.1)	Gall bladder	192 (1.9)
8	Bones and cartilage	177 (3.3)	Oral cavity	257 (4.0)	Tongue	215 (3.1)	Cheek /buccal mucosa	171	Gall bladder (2.3)	192 (2.0)	Rectum	149 (1.5)
9	Stomach	169 (3.1)	Bones and cartilage	165 (2.5)	Larynx	163 (2.4)	Gall bladder	152) (2.0	Larynx	186 (1.9)	Larynx	142 (1.4)
10	Unknown primary	337 (6.2)	Unknown primary	424 (6.5)	Gall bladder	139 (2.0)	Rectum	148(2.0)	Cheek /buccal mucosa	181 (1.9)	Ovary	142) (1.4

Table 3.2: *Distribution of patients by top ten malignancies (2011-2014)*

Position	2011		2012		2013		2014	
	Cancer sites	n (%)	Cancer sites	n (%)	Cancer sites	n (%)	Cancer sites	n (%)
1	Lung	1374(18.0)	Lung	1150(16.6)	Lung	1520(19.9)	Lung	1983(17.9)
2	Breast	747(9.8)	Breast	818(11.8)	Breast	932(12.2)	Breast	1386(12.5)
3	Cervix	539(7.0)	Oesophagus	378(5.4)	Lymph node	478(6.3)	Lymph node	1038(9.3)
4	Lymph node	384(5.0)	Cervix	320(4.6)	Oesophagus	400(5.2)	Cervix	894(8.0)
5	Oesophagus	373(4.9)	Stomach	305(4.4)	Stomach	391(5.1)	Oesophagus	456(4.1)
6	Stomach	365(4.8)	Lymphoma	281(4.0)	Liver	328(4.3)	Stomach	432(3.9)
7	Liver	297(3.9)	Liver	246(3.5)	Rectum	223(2.9)	Liver	390(3.5)
8	Gall bladder	177(2.3)	Rectum	152(2.2)	Gall bladder	175(2.3)	Rectum	290(2.6)
9	Rectum	159(2.1)	Gall bladder	150(2.2)	Blood	163(2.1)	Cheek /buccal mucosa	245(2.2)
10	Base of the tongue	153(2.0)	Supraglottis, Epiglottis	104(1.5)	Colon	104(1.4)	Gall bladder	236(2.1)

Table 4 : *Distribution of five leading cancers by sex (2005-2014)*

Sites	Male		Sites	Female	
	n	%		n	%
Lungs	12265	27.1	Breast	9000	26.9
Oesophagus	2837	6.3	Cervix	6794	20.3
Stomach	2378	5.2	Lung	1912	5.7
Liver	1895	4.2	Oesophagus	1174	3.5
Larynx	1798	4.0	Stomach	986	2.9

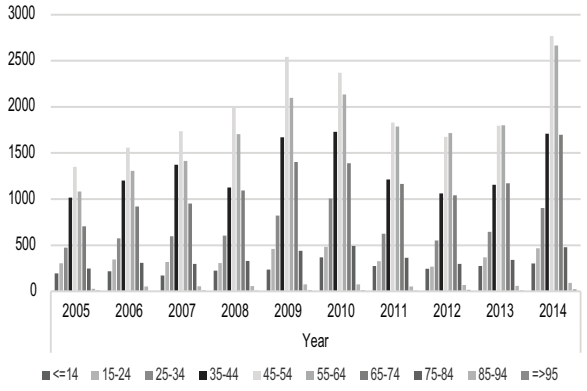

Fig-1: *Age group distribution of the cancer patients by year*

The leading cancer among male were lung cancer 12265 (27.1%), oesophageal cancer 2837 (6.3%) and stomach cancer 2378 (5.2%). The leading cancer among female were breast cancer 9000 (26.9%), cervical cancer 6794 (20.3%) and lung cancer 1912 (5.7%). Top five cancers based on gender shown in table 4.

Discussion

It is clear from the study findings that incidence rate of cancer is increasing at NICRH over years. Like one previous study published in an international journal lung and breast cancer topped the list among male and female, respectively.[6] Especially, illiterate and aged people were suffering more from cancers. It is understandable that people without education also lack awareness about

healthy life style.[7] These findings are in line with that of an international study.[7] Although the literacy rate in Bangladesh is increasing fast it is considered low in comparison to developed countries[8], and the rate of illiteracy is particularly high in the rural areas. At present in Bangladesh, we do not have any population-based cancer registry, so, the prevalence of cancer in rural Bangladesh is not known. Especially in rural setting underreporting of cancer cases is a major concern in Bangladesh due to lack of smooth access to health. Prevailing social practices also play important role in this regard. At the outset people with cancer usually seek treatment from the homeopathy, unani, ayurveda or from spiritual healers.[6] Most of these patients die before actual diagnosis of cancers. Irrespective of sexes the leading sites of cancers at NICRH were the lung, breast and uterine cervix. Similar results were found from previous report.[9] These findings oppose the study findings of two other studies where lung cancer was reported as 2nd leading cancer.[10, 11] Higher prevalence of smoking in Bangladesh than those studied countries might be the underlying cause for such discrepancy. Smoking is the single most preventable risk factor for lung cancer. During the study period about 45% Bangladeshi male used smoked tobacco; this percentage was negligible in female (1.5%). But prevalence of smokeless tobacco use among females (27.9%) was slightly higher than male (26.4%).[12, 13] The risk of developing lung cancer increases with age[12] which supports our findings that highest cancer was among 45–54-year age group. Patients usually visit a cancer specialist at the very advanced stage. The present study found breast cancer as the leading cause of cancer among female at NICRH which was consistent with previously published report.[10] Some studies conducted in South Asia and other developing countries confirmed the breast cancer as 2nd or 3rd cancer among female. [10, 11] The high rate of breast cancer in our country might be due to lack of awareness about the benefit of breast self-examination (BSE) and early reporting to the doctor, poor compliance with follow-up for women with positive results, lack of education, lack of trust in the existing healthcare system etc. Due to socio-cultural perspective female patients are uncomfortable to discuss issues involving the female organs with male physicians, their husbands or other women.[14] It was found that cervical cancer is the 2nd most prevalent cancer among female which was in line with some previously published studies.[9-10] Some studies[15] showed that 81% of cervical cancer cases occur in Latin America, Africa, Eastern/ Southern Europe, Pacific Island Nations and South-central Asia. Moreover, cervical cancer was the leading cause of cancer related death among women in developing countries.[15] The major risk factors for cervical cancer were identified as infection with Human papilloma virus (HPV), early and multiple sexual partners, lack of menstrual hygiene and unprotected sex.[16-18] Most of these risk factors also exist among Bangladeshi population. The strength of the study was huge number of cancer patients attending at NICRH. Although patients have to bear or share cost for some of the treatment modalities, the treatment is given free in general. Therefore, this hospital can attract patients from all strata of society for cancer related services. Still then, due to location proximity people from around Dhaka city was included more in the cancer registry which introduced bias. We could not consider patients who took treatment from the private hospitals or abroad or those who died before reporting to hospital.

Conclusion

It can be said that an increasing trend of cancer was observed at NICRH over ten years from 2005 to 2014. Lung and breast cancer was the leading cancer in male and female respectively. Illiterate and middle-aged population suffered more from the disease. Socio-cultural, lifestyle- and diet-related issues are important in the development of cancer. Proper emphasis should be given to increase awareness against cancers in Bangladesh.

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Original Article

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Pattern of Gynecological Malignancies in Bangladesh: Five Years' Experience at National Institute of Cancer Research & Hospital (NICRH)

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Abstract:

Gynecological malignancies contribute to the global burden of disease and are of public health interest. According to the International Agency for Research on Cancer indicate that gynecological cancers accounted for 20% of the 14.1 million estimated new cancer cases and 8.2 million cancer deaths among women in the world in 2012. Due to lack of cancer awareness and proper screening facilities in developing countries like Bangladesh, most women usually report at advanced stages, which adversely affect the prognosis and clinical outcomes. Pattern of gynecological malignancy varies between developed and developing countries. The estimation of cancer burden is necessary to set up priorities for disease control. ***Objective:*** *To identify the pattern of gynecological malignancies.* ***Methodology****: It was an observational study which was conducted in Gynecological Oncology department of national institute of cancer research & hospital (NICRH), Dhaka. Study period was five years starting from 2014.* ***Result:*** *Total number of gynecological malignancies was 17885 in that 5 yrs. In 2014 to 2018 the number was 3885, 3206, 2766, 3245 and 4783 respectively. Among them the most of the cases were cervical cancer, which was 45.5%. Next common was ovarian (11.8%), endometrial (2.9%) & vulva/vaginal (1.3%) malignancies.* ***Conclusion:*** *Trend of Gynecological malignancy has increased in our country. It is clear that cancer is an urgent global challenge. So, we should take measures to scale up prevention, early detection and diagnosis, treatment and quality care services.*

Key words**:** *Pattern, Gynecological Malignancies, Bangladesh*

Introduction:

Global cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths. In worldwide one-in-sex women will develop cancer over the course of their life time and one-in-eleven women will die from their disease. The burden of cancer is growing at an alarming rate and it is one of the leading causes of death worldwide.[1] According to Globocan 2018, gynecological malignancy stands the second position after the breast cancer in Bangladeshi female. A number of factors appear to be driving this increase, for example; a growing and aging global population, increases in

exposure to cancer risk factors and factors linked to social and economic development.[1]

Gynecological cancers are a group of different malignancies of the female reproductive system. The most common types of gynecological malignancies are cervical cancer, ovarian cancer and endometrial cancer. There are less common gynecological malignancies including cancer of the vagina, vulva, gestational trophoblastic tumors (GTN) and fallopian tube cancer.

According to CDC, all women are at risk for developing gynecological cancers and the probability increases with age. Geographical variation exists in the pattern of distribution of gynecological malignancies. In developed countries (USA data), among the gynecological cancer with the highest incidence is uterine cancer (24.8 per 100000); ovarian cancer is a second (11.4 per 100000) and cervical cancer is third (7.5 per 100000). But in developing countries incidence is reserve.[2]

Bangladesh has no running population-based-cancer registry and no data on cancer incidence are recorded at the national level. Information on and knowledge of the pattern of distribution of cancer is an important basis for health planning and prioritizing a cancer prevention program in any population. National institute of cancer research & hospital (NICRH) of Dhaka is a tertiary care level hospital of Bangladesh. This institute of Bangladesh has all facilities of cancer treatment. In gynecological oncology department of NICRH are a lot of patients of gynecological malignancies from whole Bangladesh. The aim of this study was to identify the pattern of gynecological malignancy in our institute.

Cervical cancer:

Cervical cancer is a preventable disease and regular pap's smear has been used in developed countries to screen for their low-incidence rates. Unfortunately, in developing counties such as in Bangladesh, due to lack of awareness programs, most women have presented in the advanced stages of cervical cancer. In national level, VIA (visual inspection with acetic acid) which can be done by primary health worker, is an accepted screening, although the incidence of cervical cancer has not been declining in the country. In Bangladesh, cervical cancer is the 2nd most common female cancer after breast cancer. According to Globocan 2018, total number of cervical cancers was 8068 case which occupied the 12% of total female cancer.[1] In our institute, cervical cancer is the most common gynecological malignancy.

Ovarian cancer:

Ovarian cancer has emerged as one of the most common malignancies affecting women in Bangladesh. As per Globocan 2018 data, ovarian cancer is the 2nd common gynecological malignancy. [1] Majority of ovarian cancers present at advanced stage due to vague sign & symptom of disease. In our institute, ovarian cancer is also 2nd common gynecological malignancy. But ovarian cancer is the most lethal gynecological malignancy. Unfortunately, most of them are known to relapse after primary treatment which includes cytoreductive surgery and chemotherapy.

Endometrial cancer:

Endometrial cancer is the most common gynecological malignancy in the western countries [2] but in Bangladesh, the incidence rates are low. Most of these cancers present at an early stage and are associated with a good prognosis. In NICRH, corpus uteri represent the 2% of gynecological malignancy and third common gynecological malignancy which is very similar to the Globocan 2018 findings.

Vulval cancer:

Vulvar cancer is accounting for less than 1% of malignancies in women and for 3-5% of malignancies of the female genital tract. With an estimated incidence is of 1-2 cases per 100,000 women/year worldwide.[3] In the early age patients, vulvar cancer is usually related to HPV infection (usual-type VIN – vulvar intraepithelial neoplasia). In the older patients, vulvar lesions develop from VIN exhibiting epithelial atypia and are not related to HPV infection. The most common histological types are squamous cell carcinomas (86%), melanomas (4.8%), sarcomas (2.2%), basal cell carcinoma (1.4%), and adenocarcinomas (1.2%).[4] Recently, vulvar cancer incidence has risen.

Vaginal cancer:

primary vaginal cancer is rare entity. most of cases lesions of vagina coming from another primary site. Although cancer of the vagina is disease of postmenopausal women, an increase in young women being diagnosed with primary vaginal cancer has been

reported, especially in countries with a high HIV prevalence. This will be associated with persistence of high-risk HPV infection. The attention should be on primary prevention with prophylactic HPV vaccination.[5] According to Globocan 2018, vaginal cancer ranked 33 (0.17%) of all cancer in that 5 years. [1]

Gastational trophoblastic neoplasia/ Gastational trophoblastic disease (GTN/ GTD):

Gestational trophoblastic disease (GTD) is a field of both benign and malignant gestational tumors, including hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. The last four entities are referred to as gestational trophoblastic neoplasia (GTN). GTN can result in significant morbidity and mortality if left untreated because of their aggressiveness and propensity to wide metastasize.[6]

Methodology:

It was an observational study where data were collected retrospectively from 1 January 2014 to 31 December, 2018. The data were extracted from cancer registry of gynecological oncological department of NICRH. Inclusion criteria was gynecological malignancy and exclusion criteria were non gynecological malignancies and benign gynecological conditions.

Result:

Total numbers of gynecological malignancy patients who attended the GOPD (Gynecological oncology outpatient department) of NICRH in that five years (2014-2018) were 17885. Fig. 1 shows the distribution of gynaecological cancer patients at NICRH during that five years. From 2014 to 2016 the number gradually reduced and in the next two years number increased. There were 8145 new and 5459 old cervical patients and 2104 new and 1358 old ovarian cancer patients during that period of time (Fig. 2). Trends of all gynecological malignancy from 2014 to 2018 is depicted in figure 3. In first three years the number cervical cancer did not change that much, slight fall is found in 2016 but in next two years the number gradually increased. Almost similar trend is observed in case ovarian cancer. Although the numbers of endometrial cancer and cancer of the vulva and vagina were small, they also shown an upward trend form 2016 onward.

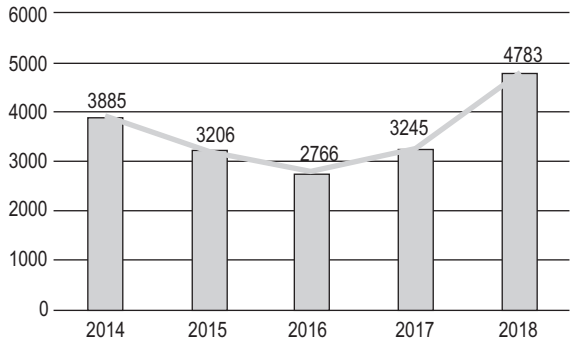

Fig. 1: *The distribution of gynaecological cancer patients at NICRH (2014-2018)*

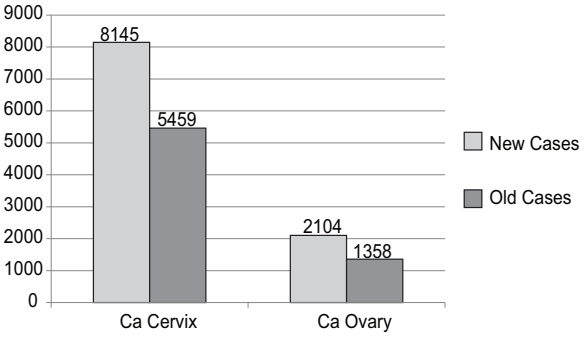

Fig. 2: *Bar chart showing old and new cases of two main gyanecological cancers*

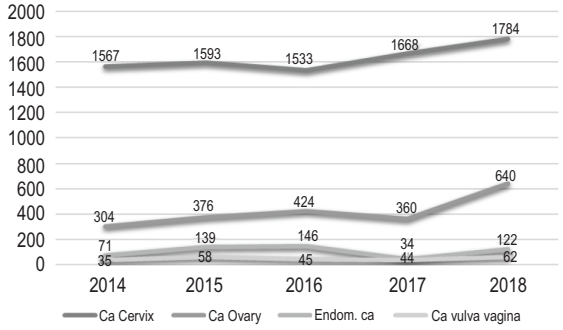

Fig. 3: *Trends of all gynecological malignancy from 2014 to 2018*

Discussion:

Till today there is no population-based cancer registry in our country. So, at present it is not possible to know the exact incidence rate of gynecological malignancies. Our hospital-based cancer registry shows that gynecological malignancies were increasing day by day. In this study, the common gynecological malignancy was cervical cancer (45.5%). This was comparable with

findings of other studies. [1, 4, 7, 8] Worldwide, cervical cancer accounts for 493000 new cancer cases, 273000 deaths and over 80% of cervical cancer cases occur in developing countries.[7] Ovarian cancer was the second common cancer in this study which was about 12%. Our finding is similar to several other finding. [8, 9] But Maheshwari et al. reported, ovarian cancer has emerged as one of the most common malignancies affecting women in India.[10] Endometrial cancer was the third common (2.9%) gynecological malignancy in this study. Several other studies have similar findings. This was in contrast to what was reported in western countries, where corpus uteri cancer was the most common gynecological cancer.[11] Vulval & vaginal cancer is the least common (1.3%) gynecological cancer in this series. These two conditions were generally rare and they occur in elderly women.

Conclusion:

Gynecological malignancy is of public health interest due to the dreaded nature of the disease and its contribution to the global burden. Cervical cancer remains the leading gynecological malignancy in this center, as in most developing countries, despite the fact that the preventive measures are known and achievable with good national control policies and political well.

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of paper.

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Original Article

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Knowledge, Attitude and Practice of Smoking in Male Patients with Lung Cancer: A single Center Study

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Abstract:

Introduction: *Tobacco in any form, is injurious to human body. It is estimated that about 40 percent of all cancers diagnosed in the United States are associated with smoking tobacco. In Bangladesh, according to WHO, 43.3% adults use tobacco products (men 58.0% women 28.7%), among them, 23.0% smoke tobacco (men 44.7%; women 1.5%). In addition, about one-fourth of the deaths in Bangladeshi men between 25-69 years are due to smoking related illness. In USA, approximately 1 in 3 patients smoke at or around the time of cancer diagnosis. Studies have shown that those who continue to smoke after diagnosis of lung cancer are at higher risk for poorer prognosis, as compared with cancer patients who quit. The risk can be minimized by educating the patients and caregivers regarding the benefit of cessation of smoking.* ***Methodology:*** *Hence, we conducted an descriptive, cross sectional study to assess the knowledge and practice towards smoking as a risk factor, among lung cancer patients in NICRH, by convenient sampling. N= 50.* ***Result:*** *Result revealed that, 13 (26%) of our respondants are current smoker and 37 (74%) are ex-smoker. Mean age was 58.86 (range 47-75) years. The mean duration of smoking was 23.04 (range 10-40) years. Thirty-one (62%) participants have been agreed that tobacco smoking causes cancer and only 8 (16%) of the respondents knew that smoking is the leading cause of lung cancer.* ***Conclusion:*** *Smokers underestimate their risk of lung cancer. They are very reluctant to quit smoking and few patients still smoke despite their grave diagnosis. It's very necessary to make a clear perception about smoking as a risk factor for lung malignancy.*

Keywords: *Smoking, Lung cancer, Knowledge, Attitude, Practice*

Introduction:

According to Globocan, 2018 lung cancer is the second most common cause of cancer death in Bangladesh. Cigarette smoking is the major risk factor of lung cancer. Approximately 1 in 3 patients smoke at or around the time of cancer diagnosis.[1] Studies have shown that those who continue to smoke after diagnosis are at higher risk for poorer prognosis, adverse treatmentrelated side effects, and deteriorating quality of life as compared with cancer patients who quit.[2] Reductionof treatment effectiveness, increase recurrence, or development of new primary tumors may be resulted from continuation

of smoking.[1-4] Number of cigarettes smoked, the patterns of smoking on individual cigarettes, and the number of years smoked are the factors that determine the level of tobacco exposure and also known as tobacco use behavior. Nicotine is the primary determinant of smoking behavior. It is the major addictive substance and factor which reinforces continued smoking.[5-6] Over time, smokers become habituated to an acceptable level of nicotine intake and tend to consume a relatively stable number of cigarettes per day and to smoke those cigarettes in a relatively consistent manner in order to maintain an acceptable level of nicotine in their system across the day.[7] In spite of having strong willingness, most smokers are unsuccessful in their attempts to quit smoking. Some of the smokers pose an unrealistic optimism that their risk is lower than other smokers who take more cigarettes in a day and they have perception of having few sticks per day is not harmful at all. Even some diagnosed patients also think that what will happen more by quitting smoking as they have already been diagnosed with cancer.[8-9] The aim of this study was to get an idea about the perceptions of lung cancer patients about smoking so that smoking prevention intervention can be done easily.

Materials and methods:

This study was a descriptive, cross-sectional study conducted at National Institute of Cancer Research and Hospital (NICRH) from September to October 2020 among the lung cancer patients admitted in NICRH. Convenaient sampling technique was used in this study with a sample size of 50. Histologically diagnosed case of lung cancer (small cell & Non-small cell lung cancer) patients admitted at NICRH who were former or current smoker and ECOG (Eastern Co-operative oncology Group) performance status 0 to 3 were included in this study and out-patient department (OPD) patients, patients with brain metastases, who were never smoker were excluded from this study. 'Current smoker' was someone who had smoked greater than 100 cigarettes (including hand rolled cigarettes, cigars, cigarillos etc) in their lifetime and has smoked in the last 28 days. 'Former smoker' was someone who had smoked greater than 100 cigarettes in their lifetime but had not smoked in the last 28 days. 'Never smoker' was someone who had never smoked or not smoked greater than 100 cigarettes in their lifetime.

Results:

Among the 50 respondents common age group was 51-60 years with a mean age of 58.86 years (range 47-75). None of them were illiterate but only four respondents were found to have studied above HSC level. Half of the respondents were found to have income between 10 to 30 thousands Bangladeshi taka per month. Most common histopathological variant were adeno-carcinoma followed by squamous cell carcinoma, small cell carcinoma and others. Table-1 is showing the disease and demographic characteristics of the respondents of this study.

Table-1: *Demographic characteristics of the patients & histopathological types of the cancer*

Traits	Range	Frequency
Age	41-50	4
	51-60	29
	61-70	14
	71-80	3
Education	Primary	18
	SSC	16
	HSC	12
	Above HSC	4
Economic status	Up to 10K	14
	>10K-30K	25
	>30K	11
Histopathology	Squamous	17
	Adeno	24
	Small cell	8
	Others	1

13 (26%) of our respondents are current smoker and 37 (74%) are former smoker (Figure: 1)

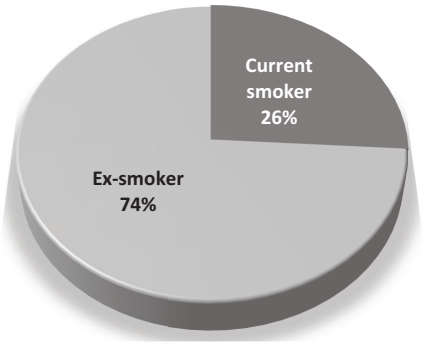


Fig.-1: *Smoking status of respondents*

Most of them (56%) smoked more than 40 years, 40% of the respondents have smoking history between 15-30 years and only 4% of the respondents smoked less than 15 years (Figure:2). Pack year calculation reveals most of the respondents have smoked between 10-30 pack year (20-30 pack year: 23 respondents; 10-20 pack year: 21 respondents) (Figure: 3).

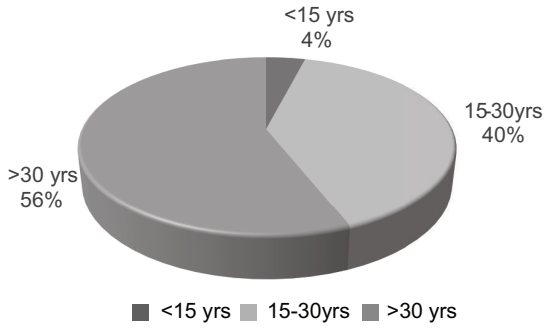
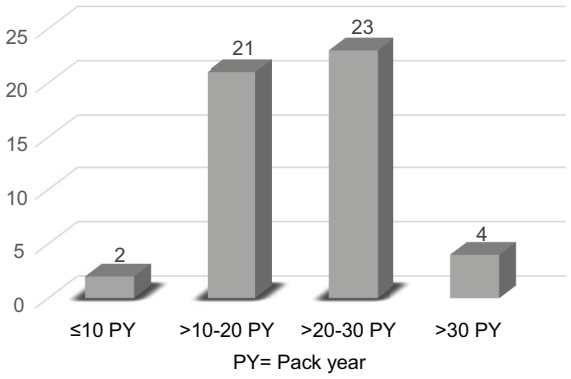


Fig.-2: *Smoking duration of respondents*



PY= Pack year

Fig.-3: *Calculated Pack year of respondents*

Table-II is showing the perception of the respondents about smoking which reflects their knowledge, attitude and practice regarding smoking.

Table-II: *Perception of respondents about smoking*

	Question	Yes	No
Knowledge	Smoking is injurious to health	43	7
	Smoking causes lung cancer	16	34
	Smoking is the leading cause of lung cancer	8	42
Attitude	Smoking cessation will improve health	24	26
	Passive smoking is harmful	17	33
Practice	Lung cancer depends more on anything else rather than smoking	38	12
	Exercise undoes most smoking effects	30	20
	Vitamins undoes most smoking effects	36	14
	No risk of cancer from smoking a few years	39	11

Discussion:

Smoking is the major risk factor for lung cancer. Many of the patients continue smoking even after diagnosis. Poor prognosis, increase treatment related side effects, early recurrence are resulted from continuation of smoking. Its necessary to understand the smoking related behavior of the lung cancer patients for smoking prevention intervention not only to reduce the incidence of lung cancer but also to prevent treatment related complication, recurrence, second primary cancer and increase treatment effectiveness.

In this study, 26% patients have been found to be current smoker. One third of smokers diagnosed with cancer continued smoking, have been found by Hall et al.[2] Most of the smokers have history of smoking for long duration. More than half of the respondents (56% to be precise) smoked more than 40 years, 40% of the respondents have smoking history between 15-30 years and only 4% of the respondents smoked less than 15 years. Pack year calculation reveals most of the respondents have smoked between 10-30 pack year (20-

30 pack year: 23 respondents; 10-20 pack year: 21 respondents) while Hall et al.[2] and Weinstein et al.[9] reported 17.5 and 14.08 cigarettes consumption per day respectively in their studies.

In the current study 43 respondents admitted that they knew smoking is injurious to health but only 16 respondents knew that smoking causes lung cancer and only 8 respondents have the idea of smoking is the leading cause of lung cancer. Twenty-four respondents aggreed about the fact that smoking cessation will improve their health but its a bit frustrating because only 17 respondents stated that they knew passive smoking is harmful**.** There are some myths which have been found through quiery. Common myths are lung cancer depends more on anything else rather than smoking (38 respondents), exercise undoes most smoking effects (30 resepondents), vitamins undo most smoking effects (36 respondents), no risk of cancer from smoking a few years (36 respondents). Weinstein et al.[9] had found, 51.7% current smokers and 35.6% former smokersstated that exercise undoes most smoking effects; 28% current smokers and 17.6% former smokers believed thatvitamins undo most smoking effects; 13.4% of current and former smokers thought that no risk of cancer from smoking a few years and Lung cancer depends more on genes than anything else belived by 35.8% current and 31.1% former smokers.

This study was designed to get an idea about the perceptions of the lung cancer patients about smoking. This study reflets that there is lack of knowledge about the harmful effects of smoking among the lung cancer patients and they have been adopted to believe in many myths. Although it was just an observational and descriptive type of study with a very few sample but still the informations we have got from this study cannot be ignored and will be helpful for further larger study and also in smoking prevention intervention.

Conclusion:

Smokers underestimate their risk of lung cancer. Smokers show optimism by claiming that they are less at risk. Cancer patients still smoke despite their grave diagnosis. It is very disappointing that, being aware about the risk, lung malignancy patient doesn't quit smoking or they are very reluctant to quit. It's very necessary to make a clear perception about smoking as a risk factor for lung malignancy.

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Original Article

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Bilateral Carcinoma Breast: NICRH Experience

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Abstract

Background: *The incidence of bilateral breast cancer (BBC) has risen recently throughout the globe. Women diagnosed with breast cancer of one breast are at a greater risk of developing contralateral breast tumor. The aim of current study was to access the type of bilateral affection in breast cancer and time of involvement after first operation.* ***Materials & methods:*** *This observational study was conducted on patients with breast carcinoma from 2015 January to 2018 December. Patients who were presented with bilateral breast cancer or contralateral breast cancer with systemic metastasis were included.* ***Results:*** *Mean age of the patients was 41.2 years with a range of 22 to 65 years. The leading age group was 31-40 years (34.6%). There was no cyto- or histological diagnosis in four percent cases. No first diagnosis was found in 44% cases. Locally advanced breast cancer was found in 43% cases. Forty-four (56.4%) patients had recurrence and/or metastasis, 25 (32.1%) had residual & metastasis, eight (10.3%) patients had developed same time lesion and one case had primary bilateral breast cancer. Synchronus and metachronus lesions were found in 56.4 % & 44.6 % cases respectively. After 5 years, bilateral involvement was found in 11.6% cases. There was strong relationship with type of recurrence in BBC with chemotherapy received while grade of the tumor was also correlated with type of recurrence.* ***Conclusion:*** *In our institution bilateral involvement was found to be associated with incomplete chemotherapy received or not receiving neoadjuvant chemotherapy where required by the patients. Follow up should be needed for determining the relationship of bilateral involvement with long survival. Emphasis should be given throughout the country about awareness of the patient about receiving CT/RT timely & completely.*

Key words: *bilateral breast cancer, recurrence, metastasis, Bangladesh*

Introduction

The incidence of bilateral breast cancer (BBC) has risen recently as a result of increase in life expectancy due to improvement in early diagnosis and therapy.[1] Women diagnosed with breast cancer of one breast are at two to six times greater risk of developing contralateral breast tumor, than developing a first breast cancer in general population.[1, 2] Risk factors for the development of BCB include family history of breast cancer, initial tumor diagnosed at an early age, lobular histology of the first tumor, treatment received for the first tumor, small size and early stage at diagnosis, receptor status and Her-2/

neu positive patients.[3] Risk factors for the development of BCB include f**amilial, hereditary and some multicentric factors.**[2, 3] Numerous studies have found that patients with BBC were significantly younger at the time of diagnosis of their initial cancer and considered age as the most important predictor for contralateral breast cancer.[3, 4] The earlier a woman develops a first breast cancer, the higher the risk of developing a contralateral tumor.[5, 6]

Contralateral breast cancer (CLBC) is either a metastatic lesion or the second primary cancer, and occurs either synchronously or metachronously.[7] In contrast to second primary breast cancer metastasis from the opposite breast is a sign of advanced disease. Clinical differentiation of a second primary carcinoma versus metastatic carcinoma is frequently uncertain. The spread of breast carcinoma to the second breast is usually across the sternum via the lymphatics, producing quite different mammographic findings.[8] CLBC is either a metastatic lesion or the second primary cancer. From biological and therapeutic viewpoints, it is important to differentiate metastatic lesions from second primary cancer in BBC.[4, 8] Though the distinction is not always easy.[9,10] proposed criteria for the diagnosis of second primary breast cancer in 1984 as follows: (i) there must be in situ change in the contralateral tumor, (ii) the tumor in the second breast is histologically different from the cancer in the first breast, (iii) the degree of histological differentiation of the tumor in the second breast is distinctly greater than that of the lesion in the first breast, (iv) there is no evidence of local, regional, or distant metastases from the cancer in the ipsilateral breast.

Synchronous carcinomas are defined as two or more tumors of different histological type where each are malignant and distinct from each other, and neither can arise due to metastasis from the other. Some consider tumors arising within 6 months to one year interval as synchronous and beyond that as metachronous.[9] BBC had a significantly higher distant metastasis rate than those with unilateral breast carcinoma[10] Improved life expectancy after breast cancer treatment and routine use of contra-lateral breast mammography has led to increased incidence of BBC.[11]

Materials & methods:

This observational study was conducted on patients with breast carcinoma from January 2015 to December 2018 in the department of Surgical Oncology of National Institute of Cancer Research and Hospital (NICRH). Patients who were presented with bilateral breast cancer or contralateral breast cancer with systemic metastasis were included.

Observation and results

Mean age of the patients was 41.2 years with a range of 22 to 65 years. The leading age group was 31-40 years (34.6%) followed by 41-50 years age group (33.3%) (Figure 1).

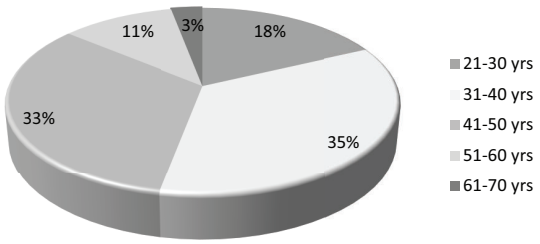

Fig. 1: *Age group in years (n=78)*

Seven (9%) patients were presented with early breast cancer, 33 (42.3%) patients with locally advanced cancer and four (5.1%) patients with metastasis. No first diagnosis was found in 34 (44%) cases. No first diagnosis includes TX, NX, lumpectomy/mastectomy, incomplete or lost previous document. (Table 1)

Table 1: *Clinico-histological characteristics**

Parameter	Number	Percentage
Staging		
Early	07	09.0
LABC	33	42.3
Metastasis	04	05.1
No first diagnosis	34	43.6
Histo/cyto diagnosis		
Duct cell carcinoma	71	91.0
Doubtful diagnosis	03	03.8
Pagets disease	01	01.3
No report	03	03.8
First HPR		
Well differentiated	03	03.8
Moderately differentiated	41	52.6
Poorly differentiated	17	21.8
Not mentioned	17	21.8

*Data of the first affected breast is considered here

Diagnosis either by FNAC, true-cut biopsy or open biopsy taken into consideration. In most of the cases duct cell carcinoma was diagnosis (71, 91%) of cases, in three (3.8%) cases diagnosis was doubtful while in same number of cases no cyto- or histological diagnosis was present (Table 1). Regarding HPR majority of the cases (41, 52.6%) had well differentiated lesion and 17 (21.8%) cases showed poor differentiation. In 17 patients HPR was not mentioned (Table 1).

In the study group right breast was affected first in 37.2% case and left side in 41.0% instances while at the same time both breasts were affected in 21.8% patients (Table II).

Table II: *Lesion related variables*

Parameter	Number	Percentage
Affected site		
Right	29	37.2
Left	32	41.0
Both	17	21.8
Type of the lesion		
Synchronus	44	56.4
Metacronous	34	44.6

Types of bilateral breast lesions were synchronus (56.4%) & metachronus (44.6 %). Bilateral breast cancer was defined as synchronous when contralateral cancer was identified within 6 months after the first breast cancer. Contralateral breast cancer, diagnosed with the interval of more than 6 months, was defined as metachronous bilateral breast cancer. (Table II).

Table III: *Chemotherapy related variables*

Parameter	Number	Percentage
Type of CT		
Neoadjuvant	18	23.1
Adjuvant	21	26.9
CT after lumpectomy/ mastectomy	30	38.5
None	09	11.5
Completion of CT		
Complete	36	46.2
Incomplete	33	42.3
None	09	11.5

Eighteen (23%) patients received neoadjuvant chemotherapy, 21 (26.9%) received adjuvant CT and 30 (38.5%) cases received CT after unplanned lumpectomy or incomplete mastectomy. In the current study 36 (46.2%) patients completed their CT, 33 (42.3%) had incomplete CT. Nine (11.5%) did not receive any CT (Table III).

Forty-four (56.4%) patients had presented at NICRH with recurrence & or metastasis, 25 (32.1%) patients had residual & metastasis, eight (10.3%) cases had bilateral breast involvement at same time and only one (1.3%) case had primary bilateral breast cancer. Here working definition of recurrence: 6 months after OT, residual: < 6 months after OT, metastatic: opposite breast/ axilla/ other sites, same time: both breast within 6 months from history or HPR, Primary: different grades at the same time (Table IV).

Table IV: *Distribution by presentation and recurrence of lesions*

Parameter	Number	Percentage
Type of presentation		
Recurrence and/or metastasis	44	56.4
Residual & metastasis	25	32.1
Same time	08	10.3
Primary bilateral Breast cancer	01	01.3
Time of recurrence		
Within 6 months	44	56.4
Within 24 months	20	25.6
Within 36 months	05	06.4
Within 60 months	07	09.0
Within 120 months	01	01.3
More than 120 months	01	01.3
Site of recurrence		
Multiple site	30	38.5
Single site	48	61.5

Majority of the patients (44, 56.4%) had developed recurrence within 6 months, 20 (25.6%) cases had recurrence with 24 months and five (6.4%), seven (9%) and one (1.3%) patients had recurrence within 36, 60 and 120 months respectively. One patient had developed recurrence after 120 months (Table 4). In the current study opposite breast/ opposite axilla involvement with metastasis to other site also taken. Here significant portion of patients had multiple site recurrence (30, 38.5%); but most of the patients had single site recurrence (48, 61.5%) (Table-IV).

Table V : *Relationship with chemotherapy received and mode of presentation in bilateral ca breast*

Type of CT received	Type of recurrence/mode of presentation			*p*-value*
	Recurrence and/ or metastasis	Residual and metastasis	Same time	
Neoadjuvant	09	04	05	0.009
Adjuvant	15	04	01	
None	07	01	01	
CT after unplanned lumpectomy/mastectomy	13	16	01	

*Chi square test

There was strong relationship with type of recurrence with chemotherapy received and type of recurrence in bilateral ca breast (*p*= .009) (Table 5).

Discussion

The leading age group was 31-40 years (34.6%) followed by 41-50 years age group (33.3%) with a median age 40.0. Similar median ages of the patients were reported by Khairy et al.[10] On the other hand Padmanabhan et al. [11] in their study found median age of 66 years which ruled out the hereditary cause of synchronous breast cancer in their patients.

In our group, three patients (3.8%) had positive family history that differed with the study of Padmanabhan et al.[11] (30% of BBC patients). The cause may be due to ignorance, not got the opportunity for the standard treatment causing bilateral involvement of the carcinoma breast in our patients.

The current study showed high percentage of infiltrating ductal carcinoma (91%) which is similar to other studies. The most common histopathological type was infiltrating ductal carcinoma reported by Khairy et al. (78%)[10] and Padmanabhan et al. (71.5%). [11]

Regarding HPR majority of the cases (41, 52.6%) had well differentiated lesion and 17 (21.8%) cases showed poor differentiation. In 17 patients HPR was not mentioned (Table 1). In contrast grade III breast carcinoma was revealed in 9 and grade I cancer in 3 specimens in Khairy et al. [10] study.

In our study patients were presented with locally advanced stage III in 42% which is much lower than reported by Khairy et al.[10] (85.7%). **Mutlak** et al.[12] in their study found significant associations between rate of recurrence and the latency period between first complaint and surgical treatment in months, size of primary tumor, number of lymph nodes involved, stage of primary tumor and histopathological degree of differentiation of carcinoma of breast grade. which is in line with the current study findings.

Bilateral breast lesion in our study was synchronous in 56.4 % & metachronous 44.6 % which is consistent with Vuoto et al.[3] study who detected BBC in 7.98% of breast cancer cases with a higher incidence of metachronous versus synchronous, 58.8% and 41.2% respectively.

In most of the studies of BBL majority are metachronous tumour. [1, 3, 11, 13] This was contradictory to our study where synchronous breast cancer was more than metachronous might be due to more unplanned operation and delay or not receiving adjuvant therapies properly by our patients.

Time of recurrence in our study is shown in Table 4. Though in our study survival was not calculated, it was found that most of the recurrence (82%) was found within 2 years.

In Ibrahim et al.[2] study, the disease-free survival for all patients showed drop at one year due to the metastatic and local recurrent cases, then showed a second drop at 2 years and then after 5 years. Cheang et al. showed that most of recurrences (38.5%) occurred between 12-15 months after treatment. [14] The risk of recurrence is highest in the first 2–3 years. So, it was the important of close follow up of our patients for the first two years after primary treatment. [12]

According to the study by Barbieri et al.[15] median interval between breast-conserving surgery and initiation of radiotherapy for patients not receiving chemotherapy

was 104 days (range, 43 to 461 days), 7/13 relapses (54%) occurred in the group of patients whose surgery-to-radiotherapy interval was 180 days. In our study there was strong relationship with chemotherapy received and type of recurrence in bilateral ca breast (p=0.009).

Conclusion:

Bilateral involvement was associated with incomplete chemotherapy received or not receiving neoadjuvant chemotherapy where required by the patients in our setting. closely follow up and early detection of contralateral breast cancer should be mandatory. Proper social and educational care is needed to these patients for early detection of a second malignancy. Further studies are needed to verify the aggressiveness of bilateral breast cancer and to identify the risk factors in our context.

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Case Report

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Palliative Stenting of the Obstructing GI Tract Malignancy: A Case Series at NICRH

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Abstract

Background: *Palliative stenting for relieving malignant obstruction of the gastrointestinal tract is routinely practiced in western world. Obstructing advanced GI malignancy requires bypass or exteriorization of proximal gut before NACT or as a bridge to definite surgery.* ***Objective:*** *The aim of the study was to review the experience at tertiary cancer hospital and short-term outcome with endoscopic stenting in lieu of palliative bypass surgery for advanced and obstructing GI malignancy.* ***Methods:*** *This observation study was carried out in the surgical out patient department of NICRH where all therapeutic endoscopic facilities were available. All patients treated with stenting in a 2 years period from 2018-2020 were studied.* ***Results:*** *Fifty-six patients received 60 stents. No case of perforation occurred. In fifteen cases (26.78%) clogging with food occurred; in 5 cases (8.92%) displacement occur. Tumour overgrowth was noted in 7 (12.66%) cases. Four patients (6.72%) received a second stent. Mean survival of patients with esophageal stent was 221 days. Four patients received 4 stents in their colon or rectum. The stents were placed in the sigmoid (n=2), the descending colon (n=1), and the transverse colon (n=1). Mean survival of colonic stent patients was 331 days. No perforation, no clogging by stool and no tumour ingrowth among patients with colonic stent but single cases (25%) had dislocation. Eighteen patients received a total of 18 stents because of obstructing stomach cancer. 12 (61.22%) patients at cardia. Mean survival after gastric stent placement was 176 days. There was no perforation, one case of clogging (8.33%), and two cases of tumour ingrowth (16.66%). 5 patients undergone duodenal stenting. Remaining one at Billroth II anastomotic site. Single patients (20%) required laparotomy and stent extraction due to duodenal stent migration. Mean survival after duodenal stent placement was 242 days. No perforation, no clogging and no tumour ingrowth.* ***Conclusions:*** *The present series shows that placement of expandable metallic stents in the obstructing GI tract malignancy as an alternative to bypass surgery is safe, cost effective, less complications, less hospital stay and provides good palliation and if adjunct chemo or radiotherapy given, lengthens life. Also recommended proper counseling of patients and proper therapeutic endoscopic training from surgeon's part before palliative stenting.*

Key Words: *Endoscopic stent placement, Micro-Tech endoscopy metallic stent, obstructing GI tract malignancy, palliation, endoscopy*

Introduction

Obstruction of the gastrointestinal tract malignancy are considered advance stage and require palliative bypass or proximal extoriarization of gut before definitive surgery.[1, 2] Tumours can impair bowel function in several ways: occlusion of the lumen, impairment of peristalsis due to tumour ingrowth, masses in the mesentery or omentum or adhesions creating an extra-luminal obstruction, and finally infiltration of the enteric nervous system causing dysmotility.[3] Obstruction due to intra- or extra-luminal obstruction can be treated by endoscopic placement of metallic self-expandable stents.

Oesophageal carcinoma mostly detected late with local and systemic metastases precluding resection. Most patients suffer from progressive dysphagia, and palliative care is the only option. Gastroesophageal and colorectal cancer are occurring increasingly.[4] Due to routine diagnostic endoscopy and colonoscopy in case of complaints and screening many patients can be cured by surgical resection. However, there are lots of patients presenting with metastases and incurable disease at the initial presentation. In these patients, palliative therapy is the only option before any definite surgery.[5] Sometimes it is impossible to do a surgical resection of the primary tumour, mostly due to co-morbidity and low body mass index. In cases of malignant bowel obstruction stent placing can be an alternative in lieu of stoma or act as bridge to definitive surgery.

Finally, patients with gastric cancer, duodenal cancer or ingrowing pancreatic cancer presenting with obstruction, who are unfit for surgery can be benefited by stenting. The aim of the present study was to review the experience in a tertiary cancer research hospital with endoscopic stenting of obstructing malignancies in the gastrointestinal tract.

Patients and methods

All patients treated with endoscopic stenting in a two years period at NICRH from 2018-2020 were studied. Self-expandable Micro-Tech endoscopy stents, USA from, Micro-Tech (Nanjing) co. ltd., made in china were used for all patients. In case of oesophageal stenting the partially Micro-Tech endoscopy partially covered stent with sutured loop ends was placed. This stent has a proximal flare of 23 mm to ensure fixation at the proximal edge of the tumour. The applied length varies according to the length of the obstruction (10-14 cm with a covered length of 8-10 cm). All patients received a stent with proximal release. For duodenal and gastric stenting Micro-Tech endoscopy uncovered stents, USA were used. These uncovered stents, have a body of 24mm and a length of 9-14cm, with a stent flare of 30 mm. These stents were placed through the working channel of the endoscope. In the case of colonic stenting Micro-Tech endoscopy intestinal stents, USA stents were applied. The specifications are: body diameter 22-25 mm, flare of 27-30 mm and a length of 90-120 mm. These stents have a distal release.

Endoscopy was performed with endoscopes (gastroscopes and colonoscopes) of Pantax medica, Japan (90k series). All procedures were done with conscious sedation with midazolam 5 mg, sometimes inj. Profopol by a trained nurse. All stents were applied via guide-wires through the endoscope (in case of stomach, duodenal, or colon obstruction) or via guide-wires placed besides the endoscope through the tumour stenosis (oesophagus and rectum). Placement of the stent was done under endoscopic control. In case of malignant stricture, prior pneumatic or bougie dilatation by Cook® Savary-Gilliard® dilator were done. The patient preparation for oesophageal stent placement was overnight fasting, gastric lavage for duodenal stent, 20% mannitol with enema simplex for colonic stent. Statistical analysis was done with chi-square test for contingency tables or t-test. A value below 0.05 was considered statistically significant.

Results

Each patient diagnosed as obstructing malignancies located in oesophagus, stomach, duodenum, or colon and rectum where open bypass was not possible due to distant metastasis or patient's poor general condition undergone a self-expandable metallic stent by therapeutic endoscopist at surgical outpatient department's endoscopy suit. Some patients undergone palliative therapy and some patients had neoadjuvant therapy in the form of chemotherapy or radiotherapy.

Fifty-six patients (42 male, 14 female, mean age 72 years, range, 42-81years) received 60 stents because of oesophageal cancer. Mean survival after esophageal stent placement was 221 days, range, 70-624 days. Out of 56, 54 patients undergone 1 year follow up to December, 2020. 11(19.64%) patients died due to their

disease progression, 4 (7.14%) patients died due to comorbidities. Rest of the patients 53.57% with chemo-radiation and or surgery are currently still alive. Two patient received 2nd covered stents which dislocated due to a very short stenotic tract and the effect of palliative chemotherapy with tumour necrosis. No post procedural perforation was seen. In fifteen cases (26.78%) (twice in three patients, thrice in single patient) clogging of the stent with food specially fibres and meat bolus occurred. These were easily removed by endoscopy without sedation. Tumour overgrowth was seen in four cases (7.14%). No additional treatment was initiated in two cases because no important obstruction was noted; two patients needed double stent (stent over stent).

Four patients (3 male, 1 female, mean age 68 years, range, 42-86 years) received 5 stents in their colon or rectum. One patient had a very long stenotic segment (due to lt colonic cancer) and received two stents placed longitudinally in one procedure. The stents were placed in the rectum (n=2), the sigmoid (n=2), and the transverse colon (n=1). All patients had a dominant stenosis with obstruction. Mean survival after colonic stent placement was 331 days (range, 65-610days). Perforation did not occur. No tumour in-growth. This patient was treated with a surgical stoma. Dislocation occurred in single cases (25%) 15 days after placement. The stent was repositioned in the next follow-up. There was no clogging.

Eighteen patients (10 men, 8 women, mean age 65 years, range, 42-76 years) received 18 stents because of obstructing stomach cancer. There were 5 distal gastric cancers and 12 cancer located in the cardia or at gastroesophageal junction. The latter received partially covered expandable stents with antireflux bulb, the remainder uncovered stents. Single stent was placed in at stoma site of Billroth II resection stomach. Mean survival after gastroeophageal junction stent placement was 176 days (range, 55-387 days). There was no perforation, no case of clogging, and tumour ingrowth were at two cases. Two patients got pneumatic dilatation each because of ingrowth. Two of them received no additional treatment.

Five patients (4 male, 1 female, mean age 63 years, range, 40-76 years) had stent placement in their distal stomach. This was because of ingrowing pancreatic cancer in single cases and obstructing antral cancer in four patients. Mean survival after duodenal stent placement was 242 days (range, 67-347 days). No perforation or clogging occurred. tumour ingrowth at two cases were seen. The tumour ingrowth did not lead to significant new obstruction. Single case (20%) required laparotomy and extraction of stent, resection and anastomosis due to stent migration at proximal jejunum.

Table I shows the complications. There was significant difference in occurrence of complication in different stents. Table II shows the survival of patients after stent placement. Patients with stenting because of colorectal cancer had a significantly longer survival ($p<0.02$). Table III shows 1 year follow-up status of patient getting stent for obstructing GIT malignancy.

Table 1: *Number of complications of stent placement in the different anatomic localizations*

Complications	Oesophageal (n=56)	Stomach (cardia) (n=12)	Distal stomach (n=5)	Colon/rectum (n=4)
Perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clogging	15 (26.8)	0 (0.0)	0 (0.0)	0 (0.0)
In (over) growth	7 (12.5)	2 (16.7)	0 (0.0)	1 (25.0)
Dislocation/Miration	5 (8.9)	0 (0.0)	1 (20.0)	1 (25.0)

Percentages are given in the parentheses

Table II: *Total survival in days after placement of the stent because of palliation*

Stent placement	Mean	SD	Median	Range
Oesophagus	221	151	121	70-624
Colon	331	396	194	65-616
Stomach (cardia)	176	135	108	55-387
Duodenum/distal stomach	242	113	98	67-347

Table II: *Status of patients 1 year follow-up after palliative stenting for obstructing GI malignancy*

Stent placement	Dead	Alive	Not documented
Oesophagus (n=56)	15(26.76)	39(69.64)	2(3.57)
Colon (n=4)	0(0.0)	4(100.0)	0(0.0)
Stomach (n=12)	2(16.57)	10(83.33)	0(0.0)
Duodenum/distal stomach (n=5)	2(40.0)	2(40.0)	1 (20.0)

Discussion

Placing a stent in the obstructing advanced GI tract malignancy can offer palliation in metastatic disease as well as symptom relief due to obstruction in locally advanced case unfit for surgery or before neoadjuvant therapy. The decision must be made by multidisciplinary tumour board which palliative option (bypass or stenting) will be appropriate for relieving obstruction before definitive treatment. Both covered and uncovered stents have different functional characteristics and the stent type must be selected on an individual basis.[4] In most cases technical and clinical success of oesophageal or gastroduodenal stenting is above 90%.[5, 6]

Recently, self-expandable metal stents placement become popular to relieve obstruction in lieu of bypass. The present series is the experience of stent placement as an alternative to bypass is routinely practice. By the placement of stents restoring passage of food or stool adequate symptoms relief was given and helped for neoadjuvant therapy before definite surgery.

Regarding cost benefit perspective stent placement should be considered if the life expectancy of the patient is at least two months. This is estimated by the range of survival after stent placement in the present group of patients. Some patients had to die within a very short time after stent placement. This was due to the course of their complicated underlying disease. However, survival was more than two months in the majority of patients.

Self-expanding metal stent for the treatment of dysphagia is accepted and evidence based.[7] In most of the cases partially covered stents were used in case of oesophageal or cardia cancer. Micro-Tech endoscopy stents are partially covered, including the proximal and distal flare and less dislocation was observed using the stents.[6, 8] Common complications after stent placement include chest pain and heartburn, nausea & reflux vomiting. Haematemesis is less but seen just after the procedure. Patient ability to swallow significantly increase during follow-up after six months. Stent migration less occurred with partially covered stents.[9] The self-expandable stents may take about four to five days to maximum fit at GIT lumen. Post stent pain was common. Pain was relieved with effective painkillers.

In one study 36 patients (43.4%) had recurrent dysphagia after stent placement, caused by tumour overgrowth in 32 cases.[10] In the present study, tumour overgrowth only occurred in 7(12.5%) of cases of oesophageal cancer. This low percentage may be due to adjuvant chemotherapy or radiotherapy as definitive treatment.

Lazaraki G et al.[10] in their study tried to evaluate predictive factors of food impaction or clogging in oesophageal stents. They reported food impaction in 41 out of 1360 patients (3.0%). Multivariate analysis showed that stent length was an independent predictor of food impaction.[10] Clogging occurred in 15(26.78%) cases in the present study, mostly in the initial period of the study. But this problem was solved easily by changing diet, specially avoid fibres, large meat piece, pureeing their food, also risotto rice. Food impaction was easily managed by endoscopic guided removal without sedation.

Placement of stents in the oesophagus is technically easy procedure. However, there are some differences in placement technique between the available stents. The endosurgeon should learn all pitfalls. In the present study only Micro-Tech endoscopy stents with a distal release system were placed. For this reason, during release of

the endoprosthesis the stent has to be pulled in order to prevent dislocation into the stomach. One major lesson learnt is that a partially covered Micro-Tech endoscopy stent is not the best option for placement over a short tight stenosis. Total 5 (9.82%) stent dislocated distally, one patient this stent dislocated two times. Whether this was due to tumour necrosis as a result of chemo-radiotherapy or because of the fact that the stent did not adhere tightly anymore to the oesophageal mucosa is unsure.

Mean survival in the literature after stent placement was 146.3±143.6 days (range, 13-680 days).[9] The mean survival in the presented patients, 221 days, is little difference with this report, probably due to use of stent not only for palliation but also for locally advanced cases which was cured by adjuvant chemoradiotherapy.

The aim in distal gastric or duodenal stenting with malignant gastric outlet obstruction is to re-establish an oral intake by restoring gastrointestinal continuity to improve the quality of life in the advanced stages of cancer. Endoscopic stenting is superior to operative gastrojejunostomy in terms of faster return to fluids and solids, and reduced morbidity for patients with a locally advanced cases, which can be cured by neoadjuvant chemotherapy followed by surgery. The main disadvantage to operative bypass is the high rate of delayed gastric emptying.[11] In the present study 18 patients received gastric or duodenal stents. For better adherence to the mucosa uncovered stents are preferred for use. Duodenal stent-related common complications are recurrence of symptoms due to stent clogging and stent migration. Stent dysfunction is reported in up to 25% of patients.[12] Complications are ingrowth or overgrowth of tumours in 12%, bleeding in 3%, stent migration in 1.5%, and perforation in 0.5%.[13] In the current study, tumour ingrowth and/or overgrowth was seen in 2 (16.67%) patients. These complications can be usually managed endoscopically, thereby restoring food passage.[14] But in this study, as patient got change chemotherapy schedule, tumor regression occur and no further obstruction occur.

Lee et al. in a paper reported that there was no difference in major complications between stent placement and surgery in cases of palliation for colon cancer. The patients treated with stenting had fewer early complications which is understandable since laparotomy is not required.[15] Stent placement in the colon has its complications; perforation, migration and occlusion found in 9%, 5% and 9% cases respectively.[16] Placement of a stent in the colon gives good and adequate palliation given the fact that all patients in the present study had passage for passing of stool and were treated effectively for the obstruction. No Clogging due to faecal impaction only occurred as gaining dietary experience from upper GIT stents and use of stool softeners and laxatives. No single case of perforation occurred. This is in contradiction with the literature. Especially in colon stent placement perforations are found.[17] Of course this complication is a worst-case scenario because the patient was already unfit for surgery. Happily, in our setting this never occurred. The probable explanation for the perforations mentioned in the literature are the fact that stent placement was used as a bridge to surgery in patients presenting with acute bowel obstruction with pre-stenotic dilatation.[18] In the present series all patient receiving a colon stent have sub-acute bowel obstruction. In addition, the majority also suffered from malignant ascites or distant metastasis.

Patients after stenting of the colon survive relatively long. This is probably the result of palliative treatment with chemotherapy in all cases. Chemotherapy significantly prolonged life in colorectal cancer with metastases. Placement of colon stents contributes to this survival. Stent placement is better than colostomy in terms of cost effectiveness and fewer complications.[19]

The present series shows that placement of expandable metallic stents in the obstructing GI tract malignancy as an alternative to bypass surgery is safe, cost effective, less complications, less hospital stay and provides good palliation and if adjunct chemo or radiotherapy given, lengthens life. Also, recommended proper counseling of patients and proper therapeutic endoscopic training from surgeon's part before palliative stenting.

Conclusions:

It has been demonstrated in the current series that placement of expandable metallic stents in the obstructing GI tract malignancy is safe and cost effective. Moreover, it has less complications, requires less hospital stay and provides good palliation. Most importantly, it lengthens life if adjunct chemo or radiotherapy given. It can be used as an alternative to bypass surgery but proper counseling of patients and

proper endoscopic training of the concerned surgeon are crucial.

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Case Report

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Bone Metastasis without Primary Tumor: A Well Differentiated Follicular Thyroid Carcinoma- A Case Report

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Abstract:

Metastatic tumors of the spine are accounted for 98% of all spine lesions. Without any thyroid enlargement spinal cord compression as the initial presentation of metastatic occult follicular carcinoma is unusual and relatively rare. A 48-years-old male patient presented with back pain which radiated to both-sided lower limbs for two months. He had no thyroid enlargement; no thyroid-related symptoms and his biochemical thyroid profile were normal. An oval (28 x 16 mm) intramedullary extradural heterogeneously enhancing lesion is seen in the spinal canal at the level of L2 vertebral body. The lesion causes thecal sac indentation and corresponding traversing nerve roots and cauda equine compression at the same level. The patient was treated by the surgery as the histopathology showed metastatic follicular thyroid carcinoma. This case highlights the importance of a thorough preoperative workup for metastatic spinal tumors. Evaluation of the thyroid consisting of thorough clinical history and examination should be done.

Keywords: *Occult follicular thyroid carcinoma, spinal cord compression, spinal metastasis, total thyroidectomy.*

Introduction:

The most common sites of metastases from follicular thyroid carcinoma are the lungs and bone. In a small number of patients, bone metastases may be the first sign of disease.[1] Metastatic spinal tumors are the most common tumors of the spine, accounting for 98% of all spine lesions. Malignancies that metastasize to the spine are breast (21%), lung (14%), prostate (7.5%), renal (5%), gastrointestinal (5%), and thyroid (2.5%).[2] Follicular thyroid carcinoma represents less than 10%, among the thyroid malignancies. This tumor is usually well encapsulated and often demonstrates vascular invasion and spread via vascular channel.[3] Bone is the second most common site of metastasis resulting from thyroid cancer, after the lung.[4] Follicular thyroid carcinoma is the most common histological origin of bone metastasis with an incidence ranging from 7% to 28%.[5, 6] Due to

metastatic follicular thyroid cancer spinal cord compression is uncommon and occurs mainly in the later stage of the disease.[3] Spinal cord compression as the initial presentation of follicular thyroid cancer, without there being any other symptoms of malignancy is rare.[4] Metastasis to the bone, specifically to the vertebral column, may present as bone pain, pathological fracture, or cord compression and is frequently a surgical issue.[7] However, spinal cord compression, as a complication of thyroid carcinoma, is uncommon. The literature review showed most of the metastatic follicular carcinoma had obvious thyroid swelling and had previous thyroid surgery. But, spinal metastasis of occult follicular carcinoma without any thyroid enlargement or any thyroid-related symptoms is unusual and relatively rare and because of this rarity of the disease, this case was reported. Every new patient with the onset of spinal cord compression should be considered in the differential diagnosis of metastatic thyroid carcinoma. We state that appropriate evaluation of thyroid for a diagnosed case of spinal metastases of unknown origin.

Case Report:

A 48-years-old male patient presented with complaints pain on the lower part of his back for 3 months. Initially, the pain was exacerbated by standing or walking and subsided by rest but later, the patient took some medications to get relief from the pain. His medical history was otherwise unremarkable. The patient had no history of hypertension, diabetes mellitus, bronchial asthma, tuberculosis, jaundice, or any neck swelling. The patient had no history of smoking, betel nut chewing, or alcohol intake. Magnetic resonance imaging (MRI) of the spine showed (28x16 mm) intramedullary extradural heterogeneously enhancing lesion is seen in the spinal canal at the level of L2 vertebral body. The lesion causes thecal sac indentation and corresponding traversing nerve roots and cauda equine compression at the same level is seen (Fig-1).

Decompression of spinal cord by laminectomy of L2 with excision of tumor from both intra-spinal and para-spinal region was done. The tissue was sent for histopathological examination.

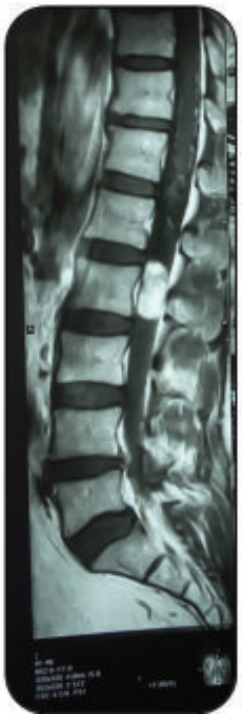

Fig. 1: *Magnetic resonance imaging (MRI) of the spine*

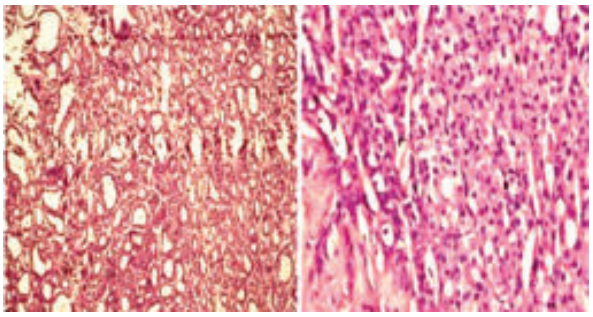

Fig. 2: *Metastatic follicular thyroid carcinoma*

Then again, the clinical examination of the thyroid gland was done which was found not enlarged and biochemical thyroid profile (T3, T4, and TSH) was found normal. But, ultrasonography (USG) of the thyroid gland shows multinodular goiter. Fine needle aspiration cytology (FNAC) of thyroid gland suggested in favor of nodular goiter. The patient then underwent a total thyroidectomy with central compartment dissection, but macroscopically no tumor was found in the extirpated issue. The histopathological examination of the tissue also revealed in favor of a multinodular goiter (Fig 3).

No of Slide
Four H&E stained slides are prepared from the submitted paraffin block.
Identification of Slide/block
NICRH-H-
Microscopic Description
Sections show thyroid tissue. The thyroid follicles are of different sizes. Majority or the follicles are dilated and contain colloid lined by atrophic follicular cells. Large areas of fibrosis are seen. Haemosiderin laden macrophages are seen in some areas. No malignancy is seen.
Dx
Paraffin blocks from thyroid gland smaller lobe & isthmus (review; biopsy): Multinodular goiter.
Remark
Extensive sampling is recommended.

Fig. 3: *Blocks from thyroid gland shows multinodular goiter*

Discussion:

Follicular thyroid carcinoma usually metastasizes through the hematogenous route to the bone, lung, and central nervous system.[8] Follicular thyroid carcinomas produce distant metastases without symptoms from a primary thyroid lesion.[9] Metastatic tumors of spine are a common and leading problem throughout the world. Between 5% and 10% of all cancer patients develop spinal metastases during their disease.[10] The commonest malignancies that metastasize to the spine include breast (21%), lung (14%), prostate (7.5%), renal (5%), gastrointestinal (5%), and thyroid (2.5%).[2] Among the thyroid cancer, only 5% of patients have metastases beyond the cervical or mediastinal area on initial presentation and a spinal metastasis as the presenting feature of thyroid cancer is unusual.[11, 12] However, Initial manifestation of spinal cord compression as newly diagnosed thyroid carcinoma is a rare event. Available data indicate that only a few sporadic cases of spinal cord compression presenting as the initial manifestation of occult thyroid carcinoma have been reported by Hsiao et al.[13] Shaha et al.[14] reported that only 4% of patients with thyroid cancer presented initially with distant metastasis. Of all thyroid cancer subtypes, follicular carcinoma is the most likely to present with distant metastasis[14] or to do so as a late event in long-standing disease.[15] Fornasier and Horne[16] reviewed a series of autopsy and found, out of 374 specimens from patients with malignancies, 140 of whom had metastatic spread to the vertebral bodies. They identified only one thyroid carcinoma metastasized to a vertebral body. Barron et al.[17] reviewed 127 autopsies of patients with spinal cord compression resulting from metastatic neoplasms and found only three of the tumors were of thyroid origin. Haghpanah et al.[18] reported a case of follicular thyroid carcinoma who presented with paraplegia and urinary incontinence also commented that follicular thyroid carcinoma with metastasis rarely presents with the clinical picture of spinal cord compression. The most common presenting symptom of patients with symptomatic spinal metastases is pain, which occurs in 83-95% of patients, and may precede the development of other neurological symptoms by weeks or months.[19] Motor dysfunction is the next most common symptom of patients with metastatic disease of the spine. Weakness in one or more muscle groups is found in 60-85% of patients with metastatic spinal cord compression.[20, 21]

Because of this rare clinical presentation, it may be a diagnostic challenge to clinicians as well as radiologists.[22] Physical examination and laboratory findings for spinal metastatic disease of an unknown origin are unlikely to raise suspicion for occult thyroid cancer. Therefore, routine workup of the thyroid with CT or MR imaging in metastatic spinal tumors is not usually recommended. The evaluation of a patient presenting with a spinal mass of an unknown origin, careful history taking, and a thorough physical examination after a clinical suspicion for thyroid cancer is mandatory. If a mass is palpated within the thyroid, fine needle aspiration is indicated to arrive at the diagnosis. The difficulty is evident from our cases as their initial presentation was due to the metastatic disease. MRI spine as the initial investigation of choice.

For detecting spinal metastases, a bone scan (99mTc-MDP) is more sensitive than plain radiographs. Until MRI became widely available myelogram and CT scan were the best diagnostic modalities for assessing acute spinal cord compression. Imaging spinal metastases MRI is the most sensitive and specific modality. (FDG) Fluorine-18 fludeoxyglucose (PET) positron emission tomography is a well-established method to differentiate

malignant from benign lesions in the spine or to demonstrate the viability of previously treated spinal tumor metastasis. In thyroid cancer, PET is useful in patients with metastatic poorly differentiated tumors with high thyroglobulin (Tg) levels and negative 131I whole-body scan results.[23, 24]

Early recognition of the primary source of the metastatic spinal disease is important because the functional outcome depends on the neurologic condition at the time of presentation. Therapeutic intervention should be done as early as possible after diagnosis for improve quality of life to alleviate pain, preserve or improve neurologic function, achieve mechanical stability, optimize primary and metastatic site tumor control. There are no definitive guidelines for the management of spinal metastases in well-differentiated thyroid cancer as much of the literature on spinal metastasis in thyroid cancer due to small case series. Surgical intervention at the metastatic site is indicated for patients with intractable pain, cord compression, neurological deficit, or cervical instability.[25]

Surgical treatment and/or external irradiation for the relief of symptoms, an appropriate and intensive treatment for some patients of both the metastatic and primary thyroid tumors is required to achieve long-term survival and good quality of life for the patients. Prevention for further neurological deficits, it is usually advisable to initially and promptly stabilize the spine, especially in the context of potential long-term survival. Traditionally, corticosteroids, local radiation treatment, and surgery to the vertebrae were all thought to be important for most patients with spinal cord compression.[26] Stojadinovic et al.[27] recommended surgery as the preferred method for resectable, locoregional recurrence, followed by radioactive iodine (RAI) therapy for iodide-avid thyroid cancer, or external-beam radiation for tumors that lack RAI avidity. Investigators also found that complete palliative debulking of the localized metastatic lesions of follicular thyroid carcinoma may be associated with an improvement in the patient's survival and quality of life.

Surgery as the preferred method for resectable, locoregional recurrence, followed by radioactive iodine (RAI) therapy for iodide-concentrating thyroid cancer, or external-beam radiation for tumors that lack RAI avidity.[28] Patients who underwent complete metastasectomy had significantly improved survival than those having palliative resection (5-year DSS, 70% vs. 30%, P-value = 0.004).[28] Proye et al. demonstrated that differentiated thyroid cancer is usually less life-threatening and that early diagnosis and appropriate treatment for distant metastases can significantly prolong the life span and improve quality of life.[29] It is important to treat the metastatic disease completely for better survival as indicated by the above-mentioned studies. However, this may not always be possible as complete resection cannot be achieved without high morbidity. Shaha et al. also reported that total thyroidectomy followed by RAI therapy and thyroxine suppressive treatment extended long-term survival (10-15 years) in 44% of patients with metastatic follicular thyroid carcinoma.[14]

Solitary distant metastases of follicular thyroid carcinoma are very rarely amenable to complete resection and thus some local procedures to delay tumor progression and for a symptom, palliation is used, such as embolization, radiofrequency, or cement injection and treatment with bisphosphonates.[30] The locoregional recurrence rate and the mortality rate both were reduced to about 25% in patients treated with RAI.[31] A recent review of the literature indicated that although external radiotherapy in association with RAI therapy affects cancer recurrence, pain relief, and the recalcification of osteolytic lesions, external radiotherapy *per se* cannot improve the survival rate.[32] Instead, complete removal of any tumoral bone tissue in patients less than 45 years of age and a cumulative dose of RAI therapy appeared to improved survival in patients with bone metastases originating from follicular thyroid carcinoma.[33]

The prognosis of occult thyroid carcinoma with distant metastasis also remains a source of debate. Proye et al.[29] demonstrated that follicular carcinoma is usually less life-threatening and that early diagnosis and appropriate treatment for distant metastases can significantly prolong the life span and improve life quality. Shaha et al.[4] also reported that total thyroidectomy followed by RAI therapy and thyroxine suppressive treatment extended long-term survival (10-15 years) in 44% of patients with metastatic follicular thyroid carcinoma. However, Pittas et al.[34] reported that the 10-year survival of patients diagnosed with bone metastasis was only 13%. The patient's refusal of further treatment and the significant co-morbidities probably have a major adverse effect on survival.

Conclusions:

In conclusion, aggressive treatment is indicated to control primary and metastatic disease. Surgery and radioiodine treatment is the best-combined modality for initial management. Radiotherapy, bisphosphonates, and small molecule inhibitors may be used for symptomatic relief and palliation.

Conflict of interest:

No financial disclosure.

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Review Article

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Prophylactic Granulocyte Colony Stimulating Factors in Paediatric Oncology

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Abstract:

Use of Granulocyte Colony Stimulating Factors (GCSF) in paediatric oncology is increasing. Randomized trials in paediatric patients are scarce. Using GCSF as primary prophylaxis is directed in the specific protocols. Secondary prophylaxis and therapeutic uses are under physician's discretion. GCSF is a costly drug. Finding the right clinical context is sometimes challenging after considering the risk benefit and cost consideration especially in developing country like Bangladesh. Though scheduled chemotherapy could be administered on time by using GCSF, it does not impact overall survival. In addition, documented infection and frequency of severe neutropenia could not be always avoided by GCSF treatment. This review focuses on GCSF use in paediatric oncology patients in the context of different strategy, disease pattern and chemotherapy intensity. It also highlights about cost consideration which adds financial burden on the patient. To find out the guidelines for rational and optimal use of GCSF in appropriate clinical context needs further randomized trials in the field of paediatric oncology.

Key words: *Granulocyte Colony Stimulating Factors, paediatric malignancy*

Introduction:

Chemotherapy induced haematological toxicity is the most common dose-limiting complication of cancer treatment, it occurs due to nonspecific killing of rapidly dividing cells in the bone marrow. Among the haematological toxicities neutropenia is most difficult to manage.[1] Chemotherapy regimens for paediatric malignancies is generally more intensive than adult regimens, so the haematological adverse effects may be more frequent and severe.[2] Subsequently it may lead to severe to very severe neutropenia and increase the risk of serious and life-threatening infection. It also delays timely initiation & continuation of cancer treatment. Thus, increases the chance of relapse.

Febrile neutropenia is a medical emergency that needs urgent hospitalization and antibiotic administration. It can lead to septic shock and even death if not addressed in a timely manner. It also increases the cost of care indirectly. For successful treatment of febrile neutropenia, neutrophil recovery is very important. The

use of G-CSF after myelosuppressive chemotherapy accelerates neutrophil recovery time. Both according to the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guideline recommend primary prophylaxis i.e., before onset of neutropenia or febrile neutropenia with G-CSF when the risk of FN associated with chemotherapy regimen is greater than 20%.[3, 4] Role of CSFs have received less attention in paediatric patients than adults, therefore, their effect in pediatric cancer is less clearly defined.[5]

G-CSF

GCSF a hematopoietic glycoprotein, discovered in the mid-1960s that regulates cell cycle activation, proliferation, terminal maturation, and survival of the myeloid lineage in the bone marrow producing mature neutrophils.

The first murine and human recombinant G-CSF was available in the late 1980s. Over the last twenty years, recombinant G-CSF has become one of the most commonly used supportive care drugs in pediatric and adult cancer patients receiving myelosupressive chemotherapy.

Filgrastim is nonglycosylated bacterially derived form of GCSF and lenograstim, is glycosylated form derived from engineered Chinese hamster ovary cells.[6] Filgrastim is the only formulation of GCSF approved by the US FDA and used in most paediatric studies. G-CSF shortens the time to post chemotherapy neutrophil recovery time by stimulating the proliferation and maturation of bone marrow committed myeloid progenitor cells.[7] The maturation time is shortened from 5 days to as little as 1 day.[8]

Polyethylene glycol (PEG)-filgrastim is a pegylated GCSF. PEG-filgrastim has long half-life, 46–62 hour and is used as a single dose unlike daily dose of GCSF. One molecule of PEG binds to N-terminal of filgrastim and gets converted to PEG-filgrastim that provides low antigenicity, minimal toxicity, and appropriate excretion.[9, 10]

Treatment Strategies

There are 3 basic strategies for GCSF use in patients getting chemotherapy. (i) Primary prophylaxis: is used for patients receiving intensive regimens having high risk of developing febrile neutropenia. (ii) Secondary prophylaxis is used only for patients who had experienced febrile neutropenia during previous courses of chemotherapy. (iii) Therapeutic use administers GCSFs only after the occurrence of neutropenia or infectious complications. Unnecessary use of GCSF can be avoided by following later two strategies in patients getting little or no benefit from GCSF.

Primary Prophylaxis in Solid Tumor

US Food and Drug Administration (FDA) approved GCSF first time based on its efficacy as primary prophylaxis in a phase III trial in adults patients receiving as many as 6 courses of the myelosuppressive regimen of cyclophosphamide, doxorubicin and etoposide (CAE) for small cell lung cancer.[11]

Fifty-nine children with metastatic neuroblastoma were studied in a non blind trial to either receive or not receive G-CSF after multi-agent chemotherapy.[12] Study result showed significant benefit in the duration of neutropenia (9 *vs* 26 days, $p < 0.001$) and the avoidance of treatment delays ($p < 0.05$), as well as in the duration of antibiotic use (12 *vs* 20 days, $p < 0.04$). Several important trends were also noted although they did not reach statistical significance: (i) the incidence of febrile neutropenia was 15 to 20% lower for each of the 4 chemotherapy cycles; (ii) the duration of hospitalization was shortened (20 *vs* 28 days, $p = 0.16$); and (iii) event-free survival periods were improved (2.4 *vs* 1.3 years, $p = 0.07$).

G-CSF has also been used to reduce chemotherapy interval to allow dose-intensification for paediatric patients with solid tumours. In a feasibility study of GCSF use by Womer et al.[13] included 73 children receiving chemotherapy for Ewings or soft tissue sarcoma. Therapy was given every 14 days, or when blood counts allowed (ANC >1 $\times 10^9$/L, platelets >75 $\times 10^9$/L), as opposed to the standard schedule of every 21 days. The result showed the median chemotherapy cycle interval was reduced to 16 days during induction.

Event-free survival estimates were comparable to, or superior to, those reported by other contemporary studies. G-CSF has also been used to significantly increase dose-intensity in more standard chemotherapy regimens using docetaxel.[14] and topotecan.[15] Because of the steep dose-response curves of some agents used to treat paediatric solid tumours, the approach described above is appealing.

Primary prophylaxis: Haematological Malignancy

Comparison of the studies that used GCSF as primary prophylaxis in childhood leukaemia is difficult because schedules and intensity of treatment regimens and timing of administration are not same. Acute lymphoblastic leukaemia (ALL) treatment regimens are divided into more intensive remission induction therapy, consolidation block and then less intense maintenance chemotherapy. A single-centre, double blind, randomised, placebo-controlled trial of GCSF by Pui et al.[16] included 148 children who were given GCSF or placebo 24 hours after the completion of induction therapy for ALL. In the GCSF group number of days of severe neutropenia (5.3 *vs* 12.7 days, $p = 0.007$) and subsequent delays in chemotherapy administration ($p < 0.001$) was reduced. Also, the patients receiving G-CSF had significantly shorter hospital stays (6 *vs* 10 days) and fewer documented infections. However, no significant difference was observed in the frequency of hospitalization or in the number of severe infections. In both groups the median costs of supportive care were similar ($US8678 for the patients receiving G-CSF; $US8616 for those receiving placebo). This finding underscores the expense of colony-stimulating factor (CSF) administration.

In a much smaller study of to either receive or not receive G-CSF during the latter part of ALL induction therapy, Dibenedetto et al.[17] randomly assigned 32 children with ALL in later part of induction of remission and treated them with or without GCSF observed no improvement in the duration of severe neutropenia, the number of episodes of febrile neutropenia, the number of days of hospitalization or the number of documented infections. Laver et al.[18] randomized 88 children with paediatric T-cell ALL or lymphoblastic lymphoma during induction of remission therapy and after 2 consecutive cycles of maintenance therapy to receive, or not receive G-CSF starting 24 hours after chemotherapy. Study found only during maintenance therapy was the duration of neutropenia was decreased for patients receiving G-CSF than for control group (6 *vs* 11 days, $p = 0.017$). There was no significant difference between two groups regarding duration of hospitalization or delays of subsequent chemotherapy.

Even though HGFs do not showed much advantages during, or immediately after, induction therapy for childhood ALL in the aforementioned studies, few studies have shown beneficial effects when GCSF are used after cycles of post induction intensification therapy.

A prospective study on 34 children with high risk ALL conducted by Welte et al.[19] showed incidence of febrile neutropenia (17 *vs* 40%, $p = 0.007$) and the median total days of intravenous antibiotic administration were reduced (18.2 *vs* 32.2 days, $p = 0.02$) for patients receiving G-CSF. There were also fewer delays in chemotherapy delivery, with a median difference of 10 days/patient ($p = 0.007$), although again there was no improvement in event free survival estimates. Clarke et al.[20] also randomly assigned 17 children with ALL or T-cell non-Hodgkin's lymphoma to either receive or not receive G-CSF after 1 of 2 post induction intensification blocks. Treated patients experienced a significant reduction in hospital days (5.5 *vs* 9 days, $p = 0.01$) and fewer delays in chemotherapy ($p = 0.05$).

Results of studies use of GCSF in AML are conflicting. One study showed significant decreases in length of hospitalization (20 *vs* 25 days, $p = 0.001$) and in days of antibacterial use (15 *vs* 18.5 days, $p = 0.0001$).[21] Although another study with a similar design showed no reduction in the frequency of serious infection.[22]

US FDA has approved GCSF and GM-CSF for use as primary prophylaxis after AML induction therapy in adults, but their benefits inconsistently seen, large randomised paediatric studies for GCSF recommendations use are lacking.

Some leukaemic cells in both ALL and AML express receptors for G-CSF and GM-CSF, HGFs may theoretically induce proliferation of the malignant clone.[23, 24]

Timing of Primary Prophylaxis

The standard clinical practice is to start G-CSF 24 hours after the last chemotherapy dose.[25,26] Usually, the nadir of the neutrophil count is expected to occur between 7 and 10 days after the completion of intensive chemotherapy. Some investigators speculated that delaying the start of HGF therapy to a time closer to nadir might reduce costs and still provide clinical benefit.[27] Rahiala J et al.[28] conducted a small study on 18 children with different types of malignancies receiving intensive chemotherapy for a variety of paediatric malignancies. Children were randomly

assigned to receive G-CSF at two different time points either on day 1 or day 5 after chemotherapy. For the second cycle, each child was treated at the alternative starting time. Although the group starting G-CSF treatment on day 5 received fewer days of G-CSF therapy (8.6 *vs* 5.4 days, $p < 0.001$), the duration of severe neutropenia and the incidence of febrile neutropenia were same for both groups (18 cycles in each arm). If fewer doses of HGF can achieve the same results, significant cost reduction could be obtained; however, these findings must be confirmed by larger trials.

It is noteworthy that HGFs are not used concurrently with chemotherapy or radiation therapy as rapid proliferation of stem cells could increase their sensitivity to myelotoxic treatments and could worsen neutropenia.[29-31]

Meropol et al.[31] showed that the incidence of severe neutropenia was much higher among adults receiving concurrent fluorouracil, leucovorin and G-CSF than among control individuals receiving an identical chemotherapy regimen without G-CSF. A washout period of at least 24 hours is usually observed before the next chemotherapy cycle is begun to allow discontinuation of stem cell stimulation.[32]

Secondary Prophylaxis

Although few prospective, randomised trials involving children have studied secondary prophylaxis with HGFs,[33] intuition suggests that these agents would benefit patients who have previously had febrile neutropenia. Adult patients in whom febrile neutropenia develops after the first chemotherapy cycle are at higher risk of subsequent episodes of febrile neutropenia than are patients in whom febrile neutropenia did not develop initially.[25]

This directed use of HGFs targets the patients who are likely to receive the most benefit. However, because many paediatric patients receiving intensive chemotherapy are already being given HGFs as primary prophylaxis, secondary prophylaxis is seldom employed. Nevertheless, secondary prophylaxis with HGFs remains an attractive alternative to reducing chemotherapy doses for the patient who is not receiving primary prophylaxis.

Therapeutic Use

Another therapeutic strategy has been to treat patients with HGFs only when neutropenia develops after chemotherapy. This strategy has been tried for patients either with [34, 35] or without [36, 37] fever. Although no randomised studies of G-CSF [36] have shown benefit for adult patients with neutropenia but no fever, there may be some benefit for certain patients with febrile neutropenia. In a randomised double-blind placebo-controlled trial, Mitchell et al.[34] studied a heterogeneous group of 112 children with different types of cancers admitted for 186 episodes of febrile neutropenia after receiving intensive chemotherapy. GCSF treated group had shortened period of neutropenia, fewer days of antibiotic administration and, most importantly, reduced hospital stays (5 days *vs* 7 days, $p = 0.04$).

A retrospective subgroup analysis showed, most benefited patients were those in whom febrile neutropenia developed less than 10 days after the completion of chemotherapy ($p = 0.01$). Usually, intensive chemotherapy regimens used in children dictate the use of HGFs for primary prophylaxis. Both the ASCO and European paediatric guidelines recommend the use of HGFs in children if they experience febrile neutropenia complicated by certain high-risk features such as pneumonia, multi-organ dysfunction or fungal infections if they already didn't get it. [29, 38]

Toxicity Spectrum of G-CSF

GCSFs are usually safe and well tolerated, adverse effects occur due to expansion of marrow precursors or release of cytokines. Toxicity profiles are mostly extrapolated from adult studies. One small study suggests that paediatric patients experience comparatively fewer adverse reactions.[39] The most frequently reported acute adverse effects of G-CSF are listed in listing I. Medullary bone pain is the most common acute adverse reaction, occurs in 15 to 39% of treated patients, compared with 0 to 21% of control individuals. [25, 26, 40]

The pain appears to be dose-related,[41] begins shortly after starting treatment and may occur again just before neutrophil recovery.[42] The pain is often mild and is usually relieved with paracetamol (acetaminophen). There appears to be no dose limiting toxicity because doses as high as 100 µg/kg have been well tolerated.[40]

However, daily doses of >10 µg/kg may not provide any further efficacy when used as primary prophylaxis.[29] Both G-CSF and GM-CSF cause temporary increases in serum levels of lactate dehydrogenase, uric acid and alkaline phosphatase, presumably because of increased cell turnover.[40]

Listing I: Frequently reported toxicities of granulocyte colony-stimulating factor

Bone pain
Injection site reactions
Rashes
Acute febrile neutrophilic dermatosis
Allergic reactions
Worsening of inflammatory conditions
Splenomegaly

Administration of G-CSF

For primary prophylaxis the standard dose of G-CSF is 5 µg/kg in adults [29, 40] and this dose is also commonly used in paediatric studies. [30, 38]

GCSF can be administered both subcutaneous and intravenous route; subcutaneous administration of G-CSF is the preferred route.[40] GCSFs are given daily until an adequate neutrophil count has recovered after the usual neutrophil nadir at 7 to 10 days. When HGF administration is stopped the ANC may decrease, possibly because of remargination or redistribution of cells.[43]

Although the filgrastim package insert recommends continuing GCSF administration until the postnadir ANC has reached 10 $\times 10^9$/L to avoid chemotherapy delays or the risk of infection, a lower ANC of 5 $\times 10^9$/L.[44] or even 1 $\times 10^9$/ [28, 45] may be adequate and may avoid unnecessary administration of HGF. Nearly half of paediatric oncologists polled in a recent survey used an ANC of 1 to 5 $\times 10^9$/L as a discontinuation criterion.[46] The recommended dose of PEG-filgrastim is 6 mg in adults and 100 µg/kg in children (maximum 6 mg) that is given to patients 24 h after chemotherapy.[47, 48]

Cost-benefit analysis of colony-stimulating factor use

As use of GCSF in oncology practice is widespread, their cost becomes a substantial concern. Cost benefit analysis studies in paediatric oncology patients are scarce & recommendations for paediatric patients are extrapolated from adult data. One study by Lyman and Balducci[49] calculated that when the estimated risk of febrile neutropenia was 40% or higher, the added cost of HGF was offset by the reduction of hospitalization expenses for febrile neutropenia. Pui et al. [16] showed children with ALL who were given G-CSF as primary prophylaxis after induction therapy had lower median hospital stays (6 *vs* 10 days) and fewer documented infections, however the median total costs of supportive care were similar in both groups. Bennett et al.[50] performed a retrospective cost analysis of G-CSF treatment for the paediatric patients with ALL after induction therapy and 2 cycles of maintenance chemotherapy and found no significant differences in the total median costs for treated and untreated patients over the entire study period. In another cost-analysis study, Riikonen et al.[35] found that using G-CSF as primary prophylaxis for 16 children with ALL or solid tumours resulted in a mean cost savings of $US1033 (1993 values) per chemotherapy course when compared with identical chemotherapy courses for the same patients without G-CSF. This nonblind study included a very heterogeneous group of patients and therapies, and the small numbers make drawing firm conclusions difficult. In a larger study, Mitchell et al.[34] reported that the hospital stay was 2 days shorter and the median bed costs were 29% lower per patient ($p = 0.04$) for 112 patients with febrile neutropenia who were given G-CSF therapeutically together with antibacterial than for patients receiving antibacterial alone. Unfortunately, nearly half of these heterogeneous groups of patients were enrolled in the trial more than once and the study was based on patient episodes of febrile neutropenia rather than on individual patients. Finally, Rubino et al.[51] randomly assigned 148 children with non-Hodgkin's lymphoma to either receive or not receive G-CSF starting 24 hours after the completion of each of the first 2 courses of COPADM therapy. The incidence of febrile neutropenia was no less for the patients receiving G-CSF than for the other group, but the median duration of febrile illnesses was 2 days shorter ($p < 0.01$). The total mean cost of induction therapy was not significantly different ($US29 765 for the G-CSF group and $US30 774 for control individuals1996 values). The authors concluded that GCSF administration in this context conferred no financial benefit. Though most of the studies showed

total cost of treatment with or without GCSF prophylaxis was similar, however one important issue is noteworthy that is GCSF prophylaxis received group benefited from fewer infections and shortened hospital stays, which indirectly improves quality of life.

Conclusion:

It is clear from this review that GCSF use is widespread and increasing in the field of paediatric oncology. Use of GCSF as primary prophylaxis in certain solid tumors and lymphoma is directed in the protocols. However, its use is not always helpful in reducing febrile neutropenia. It is also noteworthy that though by GCSF treatment chemotherapy delay could be avoided, it does not impact overall survival. Secondary prophylaxis and therapeutic uses are guided by physician's discretion and there is no optimal guideline available for paediatric oncologists. GCSF is a costly drug and it adds financial burden on the receiver, indiscriminate use should be avoided. Though sometimes challenging, it should be used rationally, it the right clinical context after judging the risk benefit ratio and cost consideration. Further randomized studies are needed in the field of paediatric oncology to find out the optimal use of GCSF.

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