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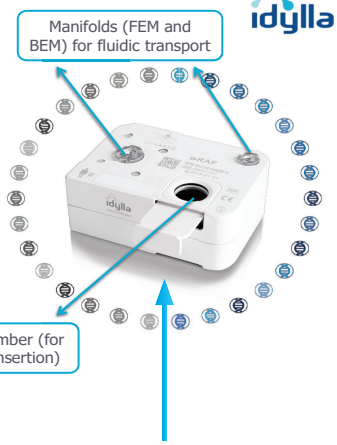

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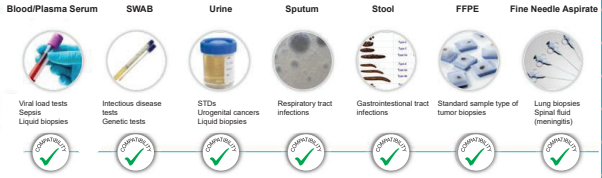

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The 'Cancer Journal of Bangladesh' is a peer reviewed medical journal published by the National Institute of Cancer Research & Hospital, Dhaka, Bangladesh. It is published twice a year, January and July. It accepts original articles, review articles and case reports and short communications of scientific merits related to cancer.

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The typing of the manuscript should be in English language (British style) on one side of A4 size paper with portrait orientation. The font should be Times New Roman with Font size 12, and the line spacing should be double space with 2.5 cm margin at both left and right-hand side, 5 cm header and 2.5 cm of the sheet. Submission of an electronic copy of the manuscript in a single Microsoft Word file is strongly recommended.

The title page, summary/abstract, text, acknowledgement, references, tables & legends, and disclosure of the conflict of interest each should begin on a separate page.

Standard abbreviation may be used. However, the full phrase for which the abbreviation stands for should precede its first use in the text unless it is a standard unit of measurements. Use of abbreviation in the title and abstract should be avoided.

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Editorial

Cancer J Bangladesh 2023;4(2): 58-59
http://nicrh.gov.bd/publication

The Role of Cancer Registry in Cancer Management: A Crucial Step for Bangladesh

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Abstract:

Cancer registries are vital for effective cancer management, offering insights into cancer incidence and trends. In Bangladesh, the Hospital-Based Cancer Registry (HBCR) at NICRH, established in 2005, has provided valuable data on cancer cases within hospital settings. Recent reports show that from 2018 to 2020, 42.6% of patients at NICRH had a cancer diagnosis. However, Bangladesh currently lacks a comprehensive National Population-Based Cancer Registry (PBCR). A pilot PBCR project launched in Hossainpur Upazila, Kishoregonj district, from July 2023 to June 2024, recruited 116,475 participants, revealing a cancer prevalence rate of 114 per 100,000. Establishing a national PBCR is crucial for obtaining a complete picture of cancer incidence across the country. It would improve data accuracy, inform policymaking, enhance research, and ultimately lead to better patient outcomes. Support from government, healthcare institutions, and international partners is essential to advance this initiative.

***Key words**:* HBCR, PBCR, incidence, NICRH

Cancer is a pressing public health issue worldwide, and its management depends on the availability of accurate and comprehensive data. In Bangladesh, the establishment of an effective cancer registry is critical for improving cancer care and developing targeted strategies for prevention and treatment. The Cancer Epidemiology department of the National Institute of Cancer Research and Hospital (NICRH) plays a pivotal role in this endeavor, highlighting the need for a robust national cancer registry to address the growing cancer burden.

Types of Cancer Registries

Cancer registries are instrumental in cancer management, providing essential data for public health planning and resource allocation. They generally fall into two categories:

1. Hospital-Based Cancer Registries (HBCRs): These registries collect data from hospitals and are valuable for understanding the cancer burden within specific healthcare settings.
2. Population-Based Cancer Registries (PBCRs): These registries gather data from populations, offering a broader perspective on cancer incidence and trends across regions.

The Evolution of Cancer Registry in Bangladesh

In Bangladesh, the journey towards organized cancer registration began in 2005 with the establishment of a systematic Hospital-Based Cancer Registry (HBCR) at NICRH. Since then, significant progress has been made. The first annual report for 2005 was published in 2006. Subsequent reports for the years 2005-2007, 2008-2010,

2011-2013, and 2014 were published between 2009 and 2015. A combined report for 2015-2017 was published in 2020. The most recent report, covering 2018-2020, shows that out of 83,795 new patients who attended the NICRH outpatient department, 35,733 (42.6%) had a confirmed or provisional diagnosis of cancer.

This consistent effort in maintaining and publishing HBCR data has been instrumental in understanding cancer trends within hospital settings. However, the scope of HBCRs is limited to the patient population of specific institutions and does not capture the broader epidemiological landscape.

The Need for a National Population-Based Cancer Registry

Currently, Bangladesh lacks a comprehensive National Population-Based Cancer Registry (PBCR). To address this gap, the Public Health and Informatics Department of BSMMU, supported by the National Cancer Control Program (NCDC) of DGHS, launched a pilot PBCR project called "PIONEER" in Hossainpur Upazila, Kishoregonj district in July 2023. This pilot registry has already recruited 116,475 participants, with a cancer prevalence rate of 114 per 100,000.

While this pilot project marks a significant step forward, a national PBCR is essential for several reasons:

1. Comprehensive data collection: A national PBCR would provide a more accurate and comprehensive picture of cancer incidence and prevalence across the country. This data is crucial for understanding cancer patterns and identifying high-risk areas.
2. Informed policy making: Reliable data from a national PBCR would enable policymakers to develop targeted cancer prevention and control strategies, allocate resources more effectively, and evaluate the impact of public health interventions.
3. Enhanced research opportunities: A national PBCR would facilitate cancer research by providing a rich data source for studies on cancer etiology, treatment outcomes, and survival rates.
4. Improved patient outcomes: By understanding the cancer burden at the population level, healthcare providers can better plan and implement interventions, leading to improved patient care and outcomes.

Call to Action

The establishment of a National Cancer Registry spearheaded by the Cancer Epidemiology Department of NICRH is a crucial step towards enhancing cancer management in Bangladesh. It is imperative that stakeholders, including the government, healthcare institutions, and international partners, support this initiative to build a comprehensive national registry. Such a registry will not only improve cancer surveillance and research but also ultimately lead to better prevention, treatment, and outcomes for cancer patients across the country.

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1. National Institute of Cancer Research and Hospital (NICRH). Annual Reports of the Hospital-Based Cancer Registry (HBCR) [2005-2020].
2. Public Health and Informatics Department, BSMMU. Pilot Population-Based Cancer Registry Report, Hossainpur Upazila, Kishoregonj District, July 2023-June 2024.
3. National Cancer Control Program (NCDC), DGHS. Support for the Pilot PBCR Project.

By advancing cancer registries, Bangladesh can take significant strides in addressing the cancer burden and improving the overall health of its population.

[**Notice:** The article "Marrow Biopsies: A Histochemical Study on 36 Cases of Primary Myelofibrosis" by Afroz et al., published in Volume 4, Issue 1, was inadvertently included in the journal. We are withdrawing it from that issue. We apologize for any inconvenience caused and appreciate your understanding. EE, Cancer J Bangladesh]

Original Article

Cancer J Bangladesh 2023;4(2): 60-64
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Early Outcome of D2 Gastrectomy - Our experience at Dedicated GI Onco-surgery Unit of NICRH

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Abstract

The most important prognostic factors of carcinoma stomach is lymph node metastasis. Adequate D2 lymphadenectomy enables-I. Accurate staging II. Reduces the incidence of recurrences III. Improve overall survival. In our study 50 cases of carcinoma stomach were considered where D2 gastrectomy performed and followed up. Our study period was 6 month (March 1,2022 to October 31,2022) and mean follow up period was 4 months. In our study, median operative time was 190 minutes, median number of retrieved LNs were 18. In this study, the morbidity rate was 16%, which is within the range reported previously. In our study, the rate of anastomotic leakage was 4% and duodenal stump leakage was also 4%. The postoperative SSI rate in this study was 12%. In our study, there were 3 mortalities (6%), which is slightly higher than that in previous studies.

Introduction

D2 lymphadenectomy is a matter of intense surgical research. Advantage of D2 dissection includes-I. Achieving an accurate staging II. Reducing the risk of locoregional recurrence III. Dutch trial confirmed that significantly more patients in D1 arm had local recurrences compared with those of D2. IV. A radical lymphadenectomy with a median LN yield of 24 reduce locoregional recurrence. V. Improve survival (disease-specific & overall). VI. Lymphadenectomy that included >16 LNs resulted in a better disease-specific survival across stages IA through to IIIA.VII. For every 10 extra LN dissected, the calculated overall survival improved by 7.6% VIII.D2 lymphadenectomy reduces the need for adjuvant radiotherapy. As radiotherapy facility is very limited throughout the country. Outcomes following D2 gastrectomy are- I. An extensive lymphadenectomy can improve disease-specific survival in resectable gastric cancer suggesting a benefit of D2 as compared with D1. II.D2 with spleen and pancreas preservation offers the most survival benefit. III. Safety of D2 has now been confirmed even in the context of NACT. D2 would be unnecessary for EGC without LN metastasis. Performance of a D2 provides the maximal

benefit in gastric cancer for stages e"IB. Our study was designed to test the feasibility and safeness of the extensive procedure if performed without distal pancreatectomy and splenectomy.

Anatomical consideration- D1, D2, D3 corresponds to removal of the first, second and third echelons of LN surrounding the stomach. Median numbers of LNs in each echelon were 17, 27 and 43, respectively. This roughly corroborates with the LN yield following a D1, D2 and D3 lymphadenectomy. To accurately stage gastric cancer (16 nodes), reduce the risk of locoregional recurrence (24 nodes) and to improve survival (up to 40 nodes. For TRG the LNs stations to be dissected. D1: 1 to 7 stations, D1+: D1 + 8a, 9, and 11p stations, D2: D1 + 8a, 9, 10, 11p, 11d, and 12a stations. For tumours invading the esophagus- D1+ includes 110 no.

D2 includes 19,20,110 and 111 no.

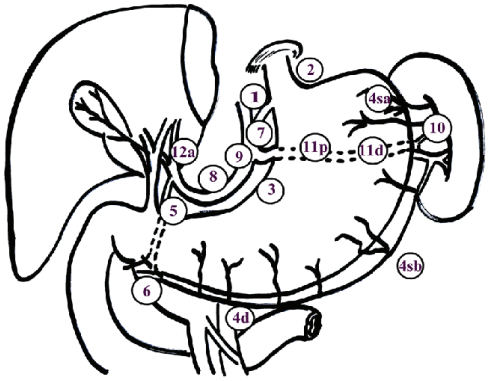

Fig 1: *Nodal stations of Stomach*

Methodology

Inclusion criteria: who have proven adenocarcinoma of the stomach (potentially curable).

Exclusion criteria: a. Who required emergency procedures**, b.** had a coexisting cancer**, c.** severe cardiorespiratory dysfunctions and d. where curative surgery could not be possible after laparotomy.

Assessment of Cancer Curability- I. Preoperative staging II. At laparotomy, no evidence of peritoneal and/or liver metastasis (P0, HO);

Study duration- From March 1,2022 to October 31, 2022.

Follow up: 2 to 7 months after operation (mean- 4 months).

Sample size: In this study sample size was 64 (10 cases were non operable and palliative surgery was done).4 cases were missed in the follow up. 50 cases were considered for this study where D2 gastrectomy were performed and followed up. Informed consent was obtained from the patients.Data on recruitment, surgical procedures, histopathologic findings, postoperative course, and patient follow-up evaluation were collected by a surgeon of the GI Oncosurgery unit, NICRH.

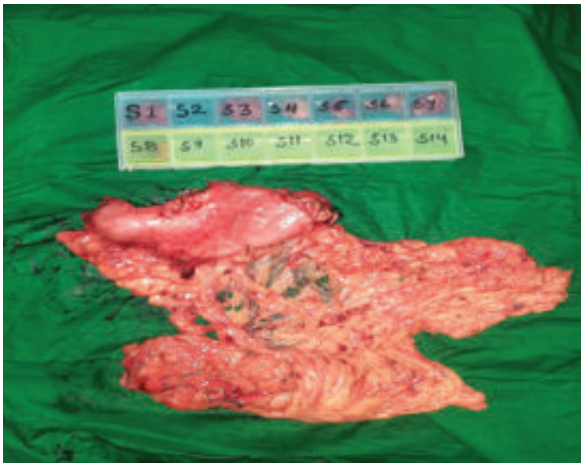

Fig.-1: *D2 gasrectomy specimen with lumph node station*

Table 1 : *Patient characteristics Values (n=50)*

Variables	Category	n (%)
Age (years)	<50	18 (36)
	>50	32 (64)
	mean ± SD	49.8 ± 10.7
Sex	Male	36 (72)
	Female	14 (28)
Comorbidities		18 (36)
	DM	8 (16)
	IHD	4 (8)
	HTN	6 (12)
Neoadjuvant therapy		16 (32)
Type of gastrectomy	Proximal gastrectomy	3 (6)
	Total gastrectomy	14 (28)
	Distal gastrectomy	33 (66)
Number of retrieved LN (range)		18 (5–35)
Adequacy of LN yield	>15	30 (60)
	< 15	20 (40)
Positive proximal surgical margin		
	0	0 (0)
Positive distal surgical margin		
	0	0 (0)
Grade	Grade 2	36 (72)
	Grade 3	**14 (28)**

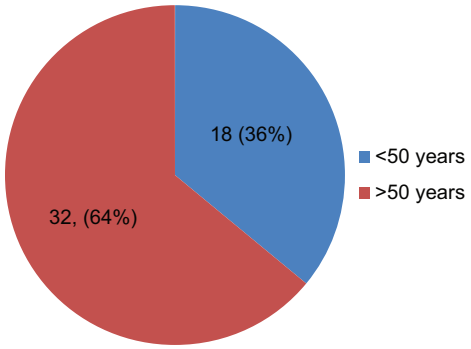

Fig.-2: *Age Distribution*

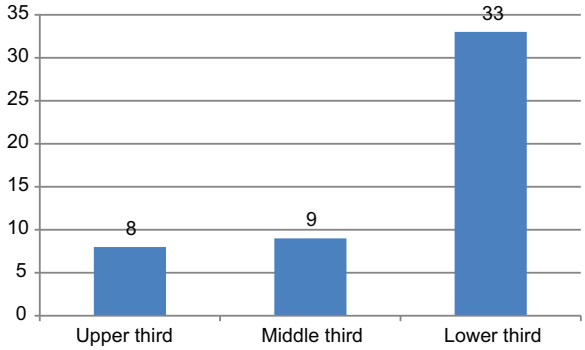

Fig.-3: *Location of tumor*

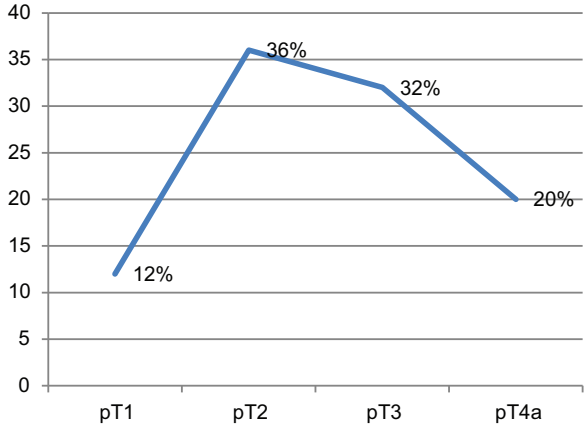

Fig.-4: *Pathological T stage*

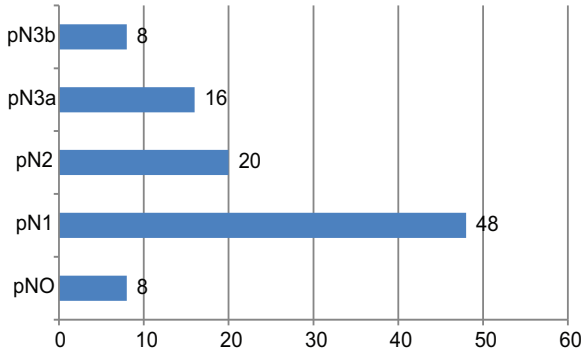

Fig.-5: *Pathological N stage*

Table II: *Operative Variables*

Per operative variables	I. Operative time (range)	190 min (150-240)
	II. Blood loss (ml) (range)	250 ml (200-300)
	III. Adhesions between the stomach and colon [n (%)]	2 (4)
	IV.Visceral organ injury [n (%)]	2(4)
	V. Mass was adherent to the pancreatic head [n (%)]	2(4)
	VI. Failure to fire the stapler [n (%)]	1(2)
Reconstruction	I. Esophagogastrostomy [n (%)]	3(6)
	II. Roux-en-Y [n (%)]	47(94)
Post operative variables-	Post operative Hospital stay (days) [median (range)]	9 days (8-30)
	Start oral fluids (days) [median (range)]	5 days (4-15)
Post operative complications	Anastomotic leakage [n (%)]	1 (2)
	Duodenal Stump Leak [n (%)]	1 (2)
	SSI [n (%)]	6 (12)
Redo laparotomy – 2 cases.	Anastomotic leakage following TRG	2
	Duodenal stump blow out following LRG	0
Follow up after 30 days	I. Incomplete adjuvant therapy	10 (20)
	II. Dumping syndrome	4 (8)
	III. Death	1(2)
	IV. Recurrence	0 (0)

Discussion:

In our study, median operative time: 190 min (150-240) (shorter than that of the study by Lee and colleagues in Korea (210 min).[1] This time is longer than that of the study conducted in China (185 min).2

The study showed median estimated blood loss was 250 ml, (like some studies).[3, 4–7] It is considered significantly higher than the blood loss in other studies conducted in Korea, China and Japan.[8, 1, 2]

In this study, median number of retrieved LNs were 18, which was the same as that in the study conducted by Brenkman et al.[11] in the Netherlands. In the CLASS-01 trial conducted in China[2], the mean number of retrieved LNs were 36.1, while in the JCOG0912 trial performed in Japan, the median number of LNs were 39.[8] In our study, 16 patients (32%) had received NACT, which may have influenced the number of harvested LNs. A study in China concluded that NACT resulted in a reduced LN count.[12] D2 gastrectomy is associated with slightly higher morbidity rates than D1 gastrectomy. In the KLASS-02 trial, the overall complication rates of D2 and D1 gastrectomy were 24.1% and 16.6%, respectively.[1] The difference was mainly due to decrease in local complications, not by systemic complications; in particular, the incidence of fluid collection and intra-abdominal bleeding. Bleeding was slightly higher with D2 gastrectomy than with D1. The postoperative morbidity rates of D2 gastrectomy range from 6.4 % to 24.2 %.[1,2,9] In our study, the morbidity rate was 16%, which is within the range reported previously.

Anastomotic leakage rates from previous studies range from 0.2% to 14%.[1,2,8,9] In our study, it occurred in one case (4%) of TRG, which is within the range of other studies. Duodenal stump leakage is one of the most severe complications with rates ranging from 0.4% to 2.4% in previous studies.[3,9] In the present study, it was detected in one patient (4%) with a rate that was 1% higher than previously reported results. Here the patient developed sepsis and redo laparotomy was performed. But unfortunately, the patient died. The postoperative SSI rate in our study was 12%, which is higher than other studies.[7,8]

Redo laparotomy was indicated in two patients (4%). One of whom underwent LRG and then developed duodenal stump leakage. Other patient underwent TRG and developed leakage from the anastomotic site. The redo laparotomy rate in our study was higher than that in studies conducted in Japan, Korea and China.[8,9,13]

According to the literature, mortality rates range from 0% to 5%.[1,9] In our study, there were 3 mortalities (6%), which is slightly higher than that in previous studies. Two of these three mortalities were due to a nonsurgical cause (AMI). So, the actual surgical mortality would be only one patient (2%) and would be within the range of the previous studies. This patient underwent LRG, developed duodenal stump leakage and died from severe sepsis.

In the present study, patients started oral fluids after a median period of 5 days, which is considered longer than the study performed in Korea, (3.7 days).[1] Patients in our study had a median post operative hospital stay of 9 days. It is longer than the studies conducted in Japan and Korea (7.5 and 8.1 days).[1,9] Patients mainly complained regarding dumping syndrome eg- vomiting, dyspepsia (8%). The rate is almost equal to other studies. There was a death and the cause could not be evaluated due to lack of information or documents.

Conclusion

D2 gastrectomy, in our surgical settings and facilities in Bangladesh, is a good option for gastric cancer surgery with oncological benefit. But more expertise and training are still needed to reduce morbidity and mortality associated with it.

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Original Article

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Clinical Response of Conventional Hypo-Fractionated Radiotherapy on Secondary Brain Tumors from Multiple Primaries: Validation in Low Resource Setting

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Abstract:

Background: *Parenchymal Brain metastases are a common manifestation of systemic cancer and exceed primary brain tumor in number and are a significant cause of neurologic problems. They can occur in 10-30% of all cancer patients. Radiotherapy has a major role to play in the management of brain metastases.* ***Objective:*** *The aim of the study was to estimate clinical response of whole brain radiotherapy in brain metastases in terms of improvement of their performance status and objective response.* ***Materials and Methods:*** *This quasi-experimental study was conducted from January 2006 to December 2008. A total of 50 cases were selected purposively for the study after fulfilling inclusion and exclusion criteria. Data were collected in a face-to-face interview in a semi-structured questionnaire. Diagnosis of brain secondaries was done with computed tomography and magnetic resonance imaging where primary malignancies were initially confirmed by histopathology or cytology reports. Improvement of presenting symptoms as well as performance status were assessed by using the Karnofsky Performance Status scale. All patients were treated with whole brain radiotherapy (WBRT) to a dose of 30 Gy in 10 fractions over two weeks on Cobalt^{60} machine through parallel opposed portals. Objective response was assessed by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0.* ***Results:*** *The study included 50 patients aged between 13 and 69 years. The mean ± SD was 49 ± 6.755 with male to female ratio 1.5: 1. Female were affected more 6th decades and male in 7th decades. Among 50 cases, primary was detected in 44 cases in which lung was the most common primary (38%) followed by breast (16%). The overall response rate was 70% (complete 12% and partial 58%). In the remaining 30%, stable disease was 16% and progressive decease 14%. Karnofsky Performance Status (KPS) score was improved or stable in most of the cases (82%) but the difference was statistically significant (*p*<0.05) in KPS 100 and KPS 70 group. Most patients achieved symptomatic improvement (mean 54.31%) and* p*-value was highly significant (<0.0001) or significant (<0.05) in vomiting, headache altered mental status and focal weakness group respectively. Early toxicities occurred during or shortly after whole brain radiotherapy were within manageable limit.* ***Conclusion:*** *The development of brain metastasis is often viewed as the end stage of the disease course and usually not curable. Immediate whole brain radiotherapy (30 Gy in 10 fractions in two weeks) is effective in both symptom palliation and improving performance status of life.*

Keywords: *Hypo-fractionated whole brain radiotherapy, symptoms palliation, quality of life.*

Introduction:

Secondary brain metastases are common manifestations of systemic cancer and are a significant cause of neurological problem[1]. The development of brain metastasis is an unfortunate and common complication in oncology and can occur in 10-30% of cancer patients[2]. Whenever the brain is metastasized by cancer cells from anywhere in the body, life expectancy becomes pathetically shortened usually below 9 months[3]. The incidence is thought to be increasing because of improved imaging and more frequent studies in cancer patients. Current outcome information for different treatment modalities indicates that local control and good neurological quality of life are commonly achieved by radiotherapy[3].

Median survival time for symptomatic brain metastases is approximately 1 to 2 months without therapy, 2 to 3 months with corticosteroid therapy and 3 to 6 months with whole brain radiotherapy (WBRT)[1]. The major result of WBRT is an improvement of neurological symptoms such as headache, vomiting, seizure, motor loss, mental impairment. The overall response rate ranges from 70% to 90%. But, unfortunately in most cases, symptomatic relief is not permanent, and symptoms recur with intracranial tumor progression. Re-treatment with a second course of WBRT can provide further palliation for patients with progressive brain metastases (who have at least a 6 months or longer remission of symptoms)[3].

Whole brain radiotherapy has been the standard treatment for brain metastases for several decades and remains an important treatment option, especially for patients with multiple brain metastasis[4]. However, recent advances have made computer assisted surgery and/or focused radiation (stereotactic radiosurgery) safe and effective treatment options for some patients with brain metastases[5]. Kondziolka et al.[6] performed the first randomized trial of WBRT with or without radiosurgery boost. Although, radiosurgery arm was found to have significantly improved time to local failure (median 36 vs. 6 months; $p = 0.0005$), survival was not found to differ significantly in the two arms (median 7.5 months for WBRT vs. 11 months for WBRT plus radiosurgery; $p = 0.22$). In a recent prospective study, Patchell et al.[7] compared the results of surgery alone to surgery plus whole brain irradiation. The intracranial relapse rate was 18% in the irradiated group and 70% in the non-irradiated group. There was no significant difference in survival or functional independence between the groups[7].

Numerous WBRT randomized trials were performed by Radiation Therapy Oncology Group (RTOG) and explored a wide range of radiation fractionation schemes for brain metastasis[8]. Studies of ultra-rapid fractionate WBRT (10 Gy in single fraction, 12 Gy in 2 fractions, 15 Gy in 2 fractions over 3 days) showed a possible increased risk of herniation and death within a few days of treatment and are not recommended [9]. Similarly, no advantage was observed in giving either 50 Gy in 20 fractions or 54.4 Gy 17 fractions over the more commonly prescribed 30 Gy in 10 fractions [9,10]. As a result, the common fractionation schemes include 30 Gy in 10 fractions and 40 Gy in 20 fractions. Due to huge patient load, 30 Gy in 10 fractionation scheme was taken as standard dose for WBRT for this study population (n= 50).

An exact data regarding socio-demographic pattern and management of patients with brain metastases are not available in Bangladesh. No significant studies have been performed to observe overall response of whole brain irradiation for patients with metastatic brain tumors. However, most studies have been retrospective reviews of various treatment paradigms. Without prospective controlled studies, no realistic comparisons of treatment can be made. Considering all these factors, the present study included 50 cases of secondary brain tumors from different primaries and was conducted prospectively from January 2006 to December 2008 at Radiotherapy department, Dhaka Medical College hospital. The clinical outcome treatment by standard hypo-fractionated WBRT (30 Gy in 10 fractions) for metastatic brain tumor patients along with socio-demographic characterization will be discussed scientifically.

Material and Methods:

The present study included 50 cases of secondary brain tumors referred from various hospitals and clinics to Radiotherapy department, Dhaka Medical College hospital and was conducted prospectively from January 2006 to December 2008. Informed consent was taken from each patient/attendant before enrolling in the study. Ethical permission was taken from the Ethical Review Board of Dhaka Medical College Hospital. The type of the study was quasi-experimental as 50 samples were taken purposively among total 176 cases of brain metastases attending within that period based on

inclusion and exclusion criteria. Inclusion criteria were: (a) Patients with Kernofsky Performance Status score (KPS) > 50 (b) Age >10 and < 70 years (c) CT or MRI evidence of multiple brain metastases with biopsy/ FNAC proven primaries or unknown primary malignancies. Exclusion criteria included: (a) Patients having prior radiotherapy to whole brain (b) Patients having primary brain tumors (c) Primary or unknown primary not confirmed by histopathology or cytology with brain metastasis (d) Patients with severe co-morbidities. Minimum laboratory criteria required to include: (a) Hb% > 10 gm/dl (b) WBC>4000/cmm (c) Platelet count > 100,000 / cmm (d) Bilirubin level < 1.0 mg/dl (e) Serum ALT < 40 ID (f) Serum creatinine < 1.5 mg/dl.

All patients were treated with whole brain radiotherapy (WBRT) to a dose of 30 Gy in 10 fractions over two weeks on Cobalt^{60} machine through parallel opposed portals. During radiotherapy, every patient was followed up every two-weekly interval for assessment of acute toxicities. Then Follow-up was advised monthly up to six months and once in three months later. At one month after completion of radiotherapy, response to treatment was initially assessed in terms of symptomatic improvement as well as performance status score (KPS). Radiological assessment by CT scan or MRI was performed 3 months later from last day of WBRT according to Response Evaluation Criteria In Solid Tumor (RECIST version 1.0). Data collecting instruments were a) Semi-structured Questionnaire b) Face to face interview c) Clinical and radiological findings d) Follow up chart. After collection, data were checked thoroughly for consistency and completeness. Then data were edited manually. SPSS for Windows version 20 for windows was used to analyze the data. Z test of proportion was carried out to assess the significant (p <0.05) association between pre and post-test variables respectively.

Results:

The current study reveals that lung cancer is the most common primary site, affecting 38% of patients, followed by breast cancer at 16% and unknown primary cancers at 12%. Kidney cancer, colorectal cancer, and malignant melanoma each make up smaller proportions, while stomach cancer, Ewing's sarcoma, and osteosarcoma are the least common, each representing only 2% of cases (Table I). It was found that most patients have a Karnofsky Performance Status (KPS) of 70 (30%), with fewer in the KPS80 (22%), KPS60 (18%), KPS90 (16%), and KPS50 (14%) categories (Figure 1). Adenocarcinomas and squamous cell carcinomas have high partial response rates (72.22% and 70%, respectively), with small cell carcinomas also showing a high partial response (80%). Seminomas and choriocarcinomas achieved complete responses, whereas melanomas, clear cell carcinomas, and osteosarcomas primarily showed progressive disease (Table II). It was found that adenocarcinomas and small cell carcinomas have highly significant response rates (p<0.0001), while other histologies show less effectiveness or variability (Table III). In the current study significant improvements in performance status for KPS scores of 100 and 70 after whole-brain radiotherapy (WBRT) were found, but not for lower scores (Table IV). It was demonstrated that WBRT significantly alleviates headaches, altered mental status, vomiting, and focal weakness, though it has less impact on seizures, altered sensation, ataxia, and visual changes (Table V).

Table- I : *Distribution of patients according to primary sites of lesions*

Primary sites	No. of patients	Percentage
Lung cancer	19	38
Breast cancer	08	16
Unknown primary cancer	06	12
Kidney cancer	02	4
Colorectal cancer	03	6
Stomach cancer	01	2
Malignant melanoma (lower extremity)	02	4
Gem cell tumor (testis, gestational tissue)	03	6
Head-neck cancer	02	4
Lymphoma (NHL)	02	4
Ewing's sarcoma (Rt. Femur)	01	2
Osteosarcoma (Lt tibia)	01	2

Table- II : *Overall response according to histology (n=50)*

Histology	Total	CR n (%)	PR n (%)	SD n (%)	PD n (%)
Adenocarcinoma (Breast, Lung)	18	1(5.55)	13(72.22)	4(22.22)	0 (0.0)
Sq. cell carcinoma (Lung, head neck)	10	0 (0.0)	7(70)	3(30)	0 (0.0)
Small cell carcinoma (Lung)	5	1 (20)	4(80)	0 (0.0)	0 (0.0)
Seminoma (Testis)	2	2(100)	0 (0.0)	0 (0.0)	0 (0.0)
Choriocarcinoma (Gestational tissue)	1	1(100)	0 (0.0)	0 (0.0)	0 (0.0)
Melanoma (Lower extremity)	2	0 (0.0)	0 (0.0)	0 (0.0)	2(100)
Clear cell carcinoma (Kidney)	2	0 (0.0)	0 (0.0)	0 (0.0)	2(100)
Lymphoma (NHL)	2	1(50)	1(50)	0 (0.0)	0 (0.0)
Osteosarcoma (Lt tibia)	1	0 (0.0)	0 (0.0)	0 (0.0)	1(100)
Ewing's sarcoma (Rt femur)	1	0 (0.0)	1(100)	0 (0.0)	0 (0.0)
Unknown primary malignancies	6	0 (0.0)	3(50)	1(16.67)	2(33.33)
Total	50	06	29	08	07

CR - Complete Response, PR - Partial Response SD - Stable Disease, PD - Progressive Disease Sq. cell carcinoma - Squamous cell carcinoma

Table - III: *Statistical analysis of objective response*

Histology	Total	Response occurred	Non Response	Z test of proportion	*p*-value	Significance
Adenocarcinoma (lung, breast)	18	14	4	3.65	<0.0001	HS
Small cell carcinoma (lung)	5	5	0	4.08	<0.0001	HS
Sq. cell carcinoma (lung, head neck)	10	7	3	1.34	>0.05	NS
Germ cell tumor (testis, gest. tissue)	3	3	0	3.36	< 0.001	S
Melanoma (lower extremity)	2	0	2	1.44	>0.05	NS
Clear cell carcinoma (kidney)	2	0	2	1.44	>0.05	NS
Lymphoma (NHL)	2	2	0	1.44	>0.05	NS
Osteosarcoma (Lt tibia)	1	0	1	1.01	>0.05	NS
Ewing's sarcoma (Rt femur)	1	1	0	1.01	>0.05	NS
Unknown primary malignancies	6	3	3	0	No Value	

S - Significant, NS - Not significant

Table- IV: *Statistical analysis of performance status before and after radiotherapy*

Performance Status	Before WBRT	After WBRT	Z Test of proportion	*p*-value	Significance
KPS 100	0	4	2.08	<0.05	S
KPS 90	8	10	0.52	>0.50	NS
KPS 80	11	14	0.69	>0.40	NS
KPS 70	15	8	2.20	<0.05	S
KPS 60	9	5	1.16	>0.50	NS
KPS 50	7	9	0.54	>0.50	NS

KPS - Kernofsky Performance status, S - Significant, NS - Not significant

Table- V: *Response analysis in terms of symptomatic improvement*

Symptoms signs	No of pts Before WBRT n (%)	No of pts After WBRT n (%)	Improvement in percentage n (%)	Z test of proportion	*p*-value	Significance
Headache	34(38)	8(16)	76.47	4.29	<0.0001	HS
Altered mental status	27(54)	12(24)	55.56	3.23	<0.005	S
Vomiting	30(60)	10(20)	66.67	4.47	<0.0001	HS
Seizure	17(34)	8(10)	52.94	1.07	>0.05	NS
Altered sensation	21(42)	14(28)	33.33	1.64	>0.05	NS
Ataxia	15(30)	9(18)	40.00	1.42	>0.05	NS
Focal weakness	18(36)	6(12)	66.67	2.93	<O.005	S
Visual change	7(14)	4(8)	42.86	1.069	>0.05	NS

HS - Highly Significant, S - Significant, NS - Not Significant

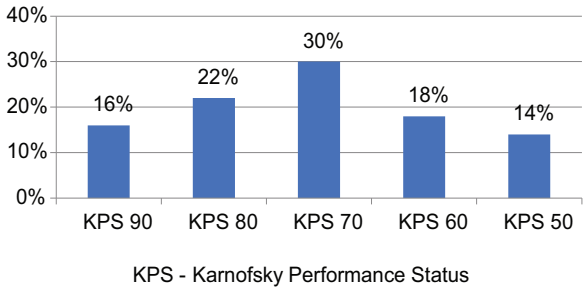

Figure 1: *Distribution of patients according to performance status*

Discussion:

This study evaluated the efficacy of conventional hypo-fractionated radiotherapy (WBRT) for secondary brain tumours from multiple primary cancers in a low-resource setting. The study involved 50 patients and was conducted at Dhaka Medical College Hospital from January 2006 to December 2008. The primary treatment modality was whole-brain radiotherapy (WBRT) delivered via a Cobalt-^{60} machine, with doses of 30 Gy in 10 fractions.

The patient cohort was predominantly affected by lung cancer (38%), with other cancers such as breast (16%) and unknown primary (12%) being less common. This distribution is consistent with the literature, which suggests that lung cancer is the leading cause of brain metastases[1, 3]. The performance status of patients, as measured by the Karnofsky Performance Status (KPS) scale, indicated a predominance of patients in the KPS70 category (30%), reflecting a moderate level of functional impairment.

The clinical response to WBRT was assessed through symptomatic improvement and performance status changes. Significant symptomatic relief was observed for headaches, altered mental status, and vomiting, with improvements ranging from 55.56% to 76.47% ($p < 0.005$). This finding aligns with previous studies demonstrating that WBRT can effectively alleviate these symptoms in patients with brain metastases [2, 6]. However, the response for other symptoms such as seizures and altered sensation was less significant, highlighting variability in symptom management.

Performance status improvements were notable in patients with initial KPS scores of 100 and 70, indicating meaningful enhancement in functional status. This result suggests that WBRT can be beneficial in improving the quality of life for some patients, particularly those with higher initial performance scores[8]. The statistical analysis revealed highly significant responses for adenocarcinomas and small cell carcinomas, with *p*-values <0.0001, underscoring the effectiveness of WBRT for these histologies[11,12]. Conversely, other cancer types such as melanomas and clear cell carcinomas showed less favorable outcomes, emphasizing the need for tailored treatment approaches[13, 14].

Overall, this study confirms that conventional WBRT is a valuable treatment modality for managing secondary brain tumors, particularly in settings with limited

resources. However, variability in treatment response underscores the necessity for individualized treatment strategies and ongoing research to optimize outcomes for all patients with brain metastases[15, 16].

Conclusion:

This study demonstrates that whole brain radiotherapy (WBRT) is effective in providing symptomatic relief and improving performance status in patients with secondary brain tumors, especially those with higher Karnofsky Performance Status (KPS) scores. Significant improvements were observed in headaches, altered mental status, and vomiting. However, response rates varied by tumor histology, with adenocarcinomas and small cell carcinomas showing the most significant benefits.

It is recommended to consider combined or alternative therapies alongside WBRT to address less responsive symptoms and improve outcomes for patients with lower Karnofsky Performance Status scores. Additionally, future research should focus on tailoring treatment approaches based on tumor histology to optimize efficacy.

Authors Contribution:

Conceptualization, conduction of the study for dissertation and writing of original manuscript, MKR; overall supervision and guidance, MMU; review and editing, RUA, SA; data summarization and technical assistance, JMS, MAW.

Conflict of interests:

The authors declared none.

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Original Article

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Pain Management of Pediatric Cancer Patients at BSMMU and Utilization of WHO Analgesic Ladder

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Abstract:

Background: *Addressing pain in pediatric cancer patients is a crucial component of their treatment, given its significant impact on their quality of life. The 2012 WHO guidelines now advocate for a two-step approach in managing pain in pediatric cancer cases.* ***Objective:*** *This study sought to identify the various types of cancer-related pain and to apply the WHO Analgesic Ladder in alleviating pain in pediatric cancer patients.* ***Method:*** *Conducted between June 2021 to December 2022, the study involved 120 pediatric cancer patients aged 4-18 years who were experiencing cancer-related pain. Pain severity was evaluated using the Faces Pain Scale and Numerical Rating Scale, and pain management was administered employing the two-step WHO Analgesic Ladder for cancer pain. Treatment included the use of medications such as paracetamol, morphine, gabapentin, and adjuvants. Patients were monitored for two weeks to assess their response to pain relief approaches.* ***Results:*** *Out of the 120 pediatric cancer patients, 56 (46.66%) experienced nociceptive pain, 10 (8.33%) experienced neuropathic pain, and 54 (45%) experienced mixed pain. Based on the evaluation, 48 (40%) reported mild pain, while 72 (60%) experienced moderate to severe pain. Among them, 50 (41.66%) were treated with acetaminophen alone, 12 (10%) received acetaminophen and gabapentin, 60 (50%) needed morphine only, and 13 (10.83%) required a combination of morphine and gabapentin. Furthermore, 7 (5.83%) underwent adjuvant therapy. Additionally, 10 (8.33%) patients developed mild itching, and 12 (10%) experienced morphine-induced constipation.* ***Conclusion:*** *The study demonstrates that cancer pain in pediatric patients can be effectively assessed by pain scale and managed following the WHO Analgesic Ladder, with no significant adverse effects. Hence, implementing the WHO Analgesic Ladder is crucial for the effective management of cancer-related pain in children.*

Keyword: *Pediatric cancer, nociceptive pain, neuropathic pain, morphine, Faces Pain Scale.*

Introduction

Pain is a common symptom throughout the disease process of childhood cancer with prevalence rates varying between 40 and 78%[1]. Cancer pain is a complex pain and pain relief in children has always been neglected due to the fact that children's pain is often not recognized and it is difficult to assess. Self-reporting or behavioral observational scales are commonly used

methods for pain assessment. In current practice, the two-step approach is considered an effective strategy for the pharmacological treatment of pain in children with cancer[2].

The WHO introduced the WHO analgesic ladder in 1986 to ensure adequate pain relief for cancer patients[3]. Originally featuring three steps, the ladder was later adapted to a two-step approach for children[3,4].

Effective management of pain in children with cancer is a crucial component of comprehensive care, especially at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Bangladesh, where efforts are focused on providing pediatric cancer patients with appropriate pain relief following the WHO ladder. The integration of the WHO Analgesic Ladder is pivotal in directing cancer pain management and enhancing the quality of life for pediatric patients at BSMMU. Cancer is a significant cause of persistent pain in children. Currently, the two-step approach is considered an effective strategy for the pharmacological management of pain in children with cancer[1]. Around 70% of children with cancer experience severe pain during their illness[5].

Pain in pediatric cancer patients can originate not only from the disease itself but also from the treatments and procedures involved[6]. More than half of young cancer outpatients experience insufficiently treated pain, impacting their emotional, psychological, and social well-being[6,7]. The WHO analgesic ladder, introduced in 1986, has since spurred ongoing efforts to enhance cancer pain management through diverse guidelines and recommendations. A ten-year validation study of the WHO analgesic ladder indicated that proper pharmacological interventions can effectively alleviate cancer pain for the majority of patients, with a failure rate of 12%[8,9].

The WHO principles of pain management[10,11] have recently been superseded by the 2012 "WHO Guidelines on the pharmacological treatment of persistent pain in children with medical illness[12]." The key pharmacological principles for achieving effective pain relief in cancer include following a two-step analgesic ladder, adhering to scheduled dosing, administering by the appropriate route, and customizing treatment for each individual[13]. Our study is focused on outlining the various types of cancer pain, incorporating the WHO Analgesic Ladder in pediatric cancer pain management, evaluating the response of the WHO analgesic ladder in these young cancer patients, and addressing potential side effects associated with morphine therapy.

Material and Method

This prospective study, carried out between June 2021 to December 2022 on pediatric cancer patients receiving inpatient care at the Pediatric Hematology & Oncology department at BSMMU. This study focused on patients experiencing pain who met all the specified inclusion criteria. Inclusion criteria encompassed new cases of pediatric cancer patients ranging from 4 to 18 years old, with diagnoses of hematological malignancies or solid tumors from the start of treatment until completion, and those enduring persistent pain due to the disease, inflammation, or anticancer therapy. Patients with procedural or post-operative pain were excluded from participation in the study. Pain severity was evaluated using the Faces Pain Scale and Numerical Rating Scale. For children aged 4 to 8 years, we selected the Wong-Baker FACES pain scale (Figure1) and for children older than 8 years, we used the 0-10 Numerical rating scale (Figure 2). Pain intensity measured by pain score value (Table I).

Table I

Assessment of Intensity of pain according to Score value

Intensity of pain	Score value
No pain	0
Mild pain	1-3
Moderate pain	4-6
Severe pain	7-9
Worst pain	10

Faces Pain Scale

Initial Instructions: Explain to the child that each face represents a person who is feeling happy because they are not in pain (injury) or sad because they are in some or a lot of pain. Face 0 is happy because it doesn't hurt him or her at all. Face 2 just hurts a little. Face 4 hurts a little more. Face 6 hurts even more. Face 8 hurts a lot. Face 10 hurts as much as you can imagine, although you don't have to cry to feel that bad. Ask children to choose the face that best describes how they are feeling (Figure 1).

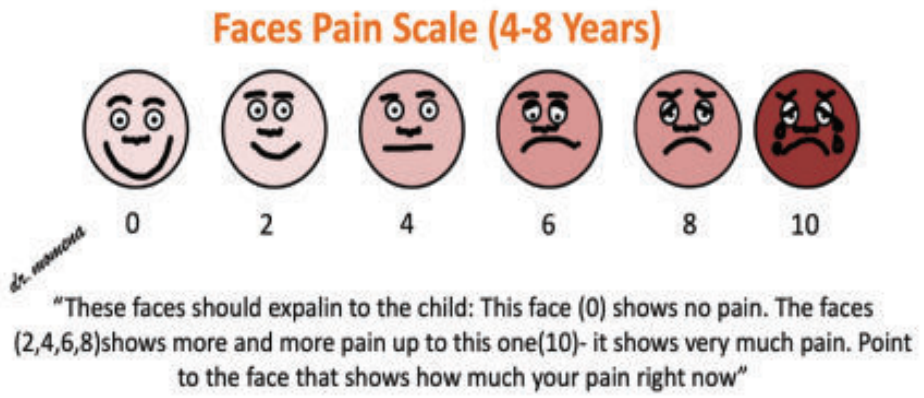

Figure 1: *Wong-Baker FACES pain scale*

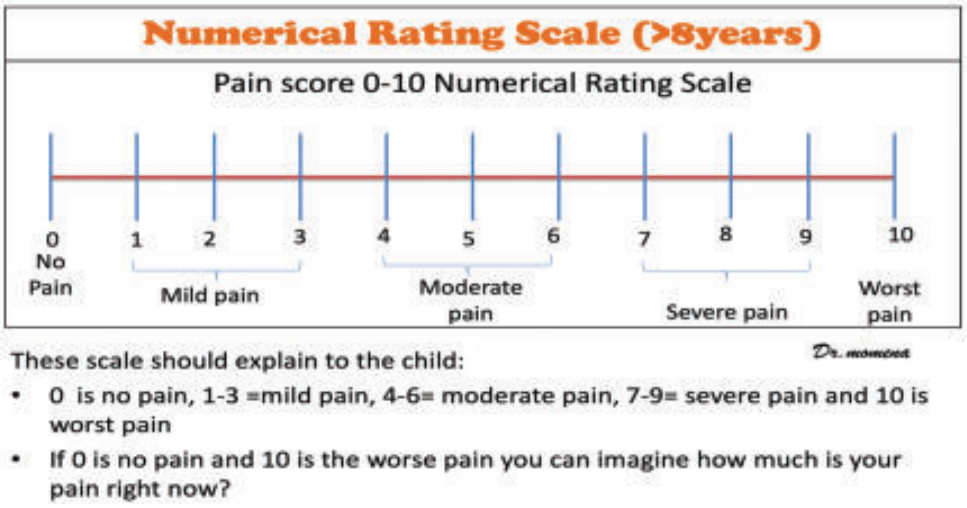

Figure 2: *Numerical rating scale*

Pain management is achieved using the WHO two-step analgesic ladder for cancer pain. Medications used included paracetamol, morphine, gabapentin and adjuvant (NSAIDs, Dexamethasone). Patients were followed for two weeks for their response to the analgesics and any side effects. WHO step 1 for mild pain (paracetamol) and WHO step 2 (morphine) for moderate to severe pain and gabapentin for neuropathic pain. All patients were followed for two weeks for their response to the analgesics by pain scale and any side effects. Patient bedside visits were conducted at least twice daily and medication adjustments and controls were made through proper assessment using a pain scale. All statistical analyzes were performed using SPSS (Statistical Package for Social Sciences) version 20 for Windows.

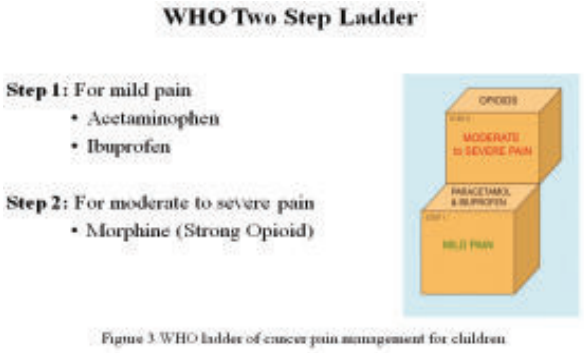

Figure 3. *WHO 2 step ladder for pain management in children*

Results

This study included one hundred and twenty patients. Their mean age was (5.60 ± SD 3.32) and their median

age was 7 years (range: 4–18 years). Eighty patients (66.66%) were male, and forty patients (33.33%) were female. Among the 120 patients, 85 (70.83%) were diagnosed with hematologic malignancy and 35 patients (29.17%) were diagnosed with solid tumor. Of the 120 pediatric cancer patients, 56 (46.66%) suffered from nociceptive pain, 10 (8.33%) from neuropathic pain, and 54 (45%) from mixed pain (Figure 4).

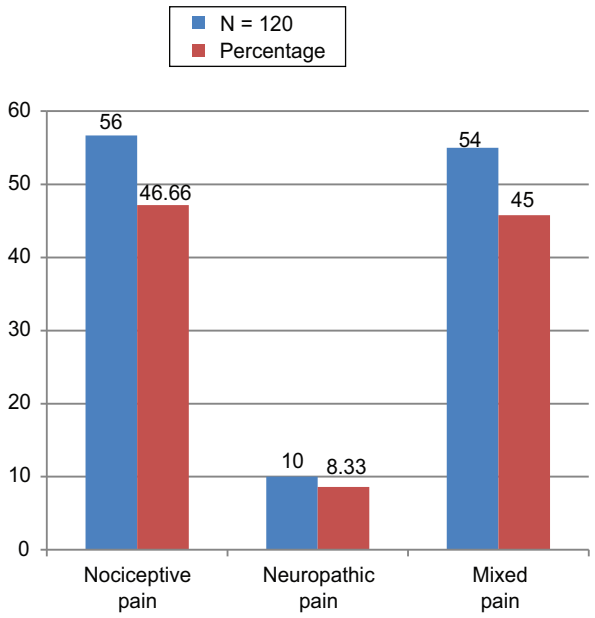

Figure 4. *Frequency of type of pain*

According to the grading scale, most patients had moderate to severe pain and 60 (50%) of patients received morphine. 50 (41.66%) children took paracetamol and other patients received combinations of paracetamol and gabapentin and a combination of morphine and gabapentin, while 7 (5.83%) received adjuvant treatment. The follow-up period of the patients was 14 days. After use of analgesic according to WHO- ladder all patients became pain free within two weeks (Table III). Over the entire treatment period, side effects were reported in 22 (18.33%) of patients. Of the 22 patients, 10 (8.33%) developed mild pruritus and 12 (10%) developed morphine-induced constipation. (Table II.)

Table 2. *Frequency distribution of intensity of pain, treatment and side effect (n=120)*

Variables	Number (n)	Percentage (%)
Intensity of pain		
Mild pain	48	40.0
Moderate to severe pain	72	60.0
Treatment		
Paracetamol	50	41.7
Paracetamol + Gabapentin	12	10.0
Morphine	60	50.0
Morphine + Gabapentin	13	10.8
Adjuvants	07	05.8
Morphine induced side effect		
Constipation	12	10.0
Itching	10	08.3

This table shows most of the children suffering from moderate to severe pain and mostly received medicine was morphine.

Table 3. *Assessment of pain after use of WHO-analgesic Ladder*

	Pain score with analgesics			
Pain intensity	0 hour	72 hours	Day 7	Day14
Mild (48)	20(1/10)	0/10	0/10	0/10
	18(2/10)	0/10		
	10(3/10)	0/10		
Moderate (42)	20(4/10)	2/10	0/10	0/10
	12(5/10)	3/10		
	10(6/10)	3/10		
Severe (30)	15(7/10)	3/10	05(2/10)	0/10
	10(8/10)	5/10		
	05(9/10)	6/10		

0- no pain, 1-3 mild pain, 4-6 moderate pain, 7-9 severe pain. After 72 hours all mild resolved, moderate pain became mild and most of the severe pain persisted as moderate pain. At day 7 only 5 patients suffered from mild pain who were initially achieving severe pain.

Discussion

The WHO three-step approach to pain control is used previously for both in children and adults. However, WHO recommends 2-steps analgesic ladder for children. Salah Abdel-Hadi et al., 2014 found the 2012 WHO guidelines recently recommended the 2 – step strategy in managing pediatric cancer pain[10]. Pain is a common and distressing symptom of childhood cancer, specially in hematological malignancy like leukemia[14,15]. In our study 70.83% was hematological malignancy that was also found in Flaminia Coluzzi et al., 2020. Hematological malignancy forms the majority of patients taking treatment in BSMMU. Pain in children with cancer was not only caused by the cancer itself, but also caused by some procedures like venipunctures, lumbar punctures, bone marrow aspiration, biopsies and other examinations[16-18]. The pain intensity of children assessed by some assessment tool in other study in this pain intensity also assessed by Faces pain scale and numerical rating scale. The level of pain intensity varied in children with cancer, most of them reported moderate pain (65%) while the others tended to experience severe (20%) or mild pain (15%).[16-18] In our study most of the children (60%) suffering from moderate to severe pain.

Usually the majority of cancer-related pain is acute pain. Acute pain usually occurs when normal nerves send messages from the injured or affected body tissues to the brain by a receptor called nociceptors. These cells are located in the body tissues and send pain signal when organs and tissues receive painful stimulation.

Seema Mishra., et al 2009 found 26(31%) pain was nociceptive in 26 (31%), neuropathic in 12 (14.3%) and mixed in 46 (54.8%) [18]. In our study we observed 56 (46.66%) suffered from nociceptive pain, 10 (8.33%) neuropathic pain, and 54 (45%) mixed pain. It is useful to point out that 41.66% of the patients received paracetamol (step-1) and 50% treated with strong analgesics (step-2) that also found in other study[18-21]. Effective management of some difficult but common pain syndromes such as neuropathic pain, requires extra management "beyond the ladder" such as amitriptyline and gabapentin and some adjuvant like dexamethasone, NSAIDs[22]. Most common morphine induced side effect observed were constipation, itching. No extreme CNS or respiratory depression was observed in any of our patients. Itching was found in 10 (8.33%) patients and total of 12 (10%) had constipation similar findings observed by Seema Mishra., et al 2009. In this study we observed, WHO analgesic ladder is useful for pain management in children without any severe complications.

Conclusion

Cancer pain in pediatric cancer patients can be well managed without any significant side effects. Therefore, the successful implementation of the WHO Analgesic Ladder is essential in managing pain in children with cancer. Further study is needed for more evaluation of neuropathic pain, side effects and development of tolerance of morphine and other adjuvants.

Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

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Original Article

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Epidemiology of Triple Negative Breast Cancer in Bangladesh: a Hospital Based Study

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Abstract

Background: *Triple negative breast cancer (TNBC) is a biologically aggressive type of breast cancer with younger age of onset. A substantial portion of breast cancer in Bangladesh is TNBC.* ***Methods:*** *This cross-sectional descriptive study was conducted to determine the demographic and reproductive characteristics of TNBC patients in Bangladesh. Eighty TNBC patients were studied in this research. Patients' demographic and reproductive history was collected through interview and information related to tumor was obtained from hospital and medical records.* ***Results:*** *The mean age and BMI of TNBC patients were 43.8(± 9.0) years and 24.54 (± 4.53) kg/m^2 respectively. The most of them (95%) were housewives and about 41% had secondary level of education. The median age of menarche and the age of menopause were 13 and 47 years respectively. All patients were married and 66.25% were multiparous. About 89% of the patients had breastfed their children. Contraceptive was used in 56.2% cases; about 46.6% of them took hormonal contraceptives. Family history of breast cancer was reported in 31.25% cases. Most of the cancers were invasive ductal carcinoma (95%) and 70% had grade II tumor. Lymph node and distant metastases were found in 73.75% and 20% of patients respectively. About 48% of patients had co-morbidities. All except one were unilateral and left sided cancer was found in 51.2% cases. About 76% patients had gone through surgery and 85% had received chemotherapy. Seven patients died within the 15 months.* ***Conclusion:*** *The TNBCs were young with normal nutrition, multiparous having breastfeeding history and about half of them did not take hormonal contraceptives.*

Key words: *Triple Negative Breast Cancer, socio-demographic characteristics, reproductive characteristics, cancer-related characteristics.*

Introduction

Breast cancer is the most common cancer in women and is the leading cause of cancer-related death in female worldwide. About 2.3 million people in the world are newly diagnosed with breast cancer in 2020[1]. In Bangladesh, it occupied the first position among the cancers occurring in females with a 5-year prevalence of 38.35 per 100,000 population of all ages[2].Triple negative breast cancer (TNBC) is a subtype of breast cancer and accounts for 10-15% of all breast cancers[3]. It is negative for both estrogen and progesterone receptors and also fails to over-express the human epidermal growth receptor type-2 (HER-2). TNBC typically presents at a younger age and does not

respond to endocrine therapy or HER-2 targeted therapies. It is biologically more aggressive and is associated with a high recurrence rate[4,5]. About 60% of the breast cancer patients attending to a specialized cancer hospital in Bangladesh were TNBC[6]. Though a large proportion of breast cancer is TNBC in Bangladesh, there is scarcity of epidemiological data of these patients. This study aimed to determine the epidemiological characteristics of TNBC patients attending a specialized cancer hospital in Dhaka, Bangladesh. The epidemiological data on TNBC will help identify the target group for timely screening programs, early diagnosis, and treatment to prevent or reduce cancer-related deaths in Bangladesh.

Objective

This study aims to assess the epidemiological characteristics of TNBC patients in Bangladesh.

Methods

This research was a cross-sectional descriptive study. Immunohistochemically (IHC) diagnosed TNBC patients from January 2021 to March 2022 were participated in this research. After getting approval from the Institutional Review Board (IRB) of BSMMU and ethical clearance from NICRH, 90 TNBC patients were invited over telephone to participate in this research. Verbal consent of the participants was taken over telephone because of the COVID-19 pandemic. Eighty TNBC patients who gave their consent were included in this study.

The demographic and reproductive information of the participants were collected over telephone or through face to face interview when they came for follow up or receiving chemotherapies. Tumor related information was collected from hospital records, histopathological and IHC reports and other investigation reports were collected from them via WhatsApp. The participants were made anonymous with a code. Frequency distribution and central tendency of data were statistically analyzed by IBM SPSS software, version 20.

Results

Nearly half of the patients (48.8%) were diagnosed between 36 to 45 years of age and the mean age at diagnosis (± SD) was 43.8 (±9.0) years. About 47% of patients were in normal nutritional status, 35.6% were overweight and the median BMI was 24.54 ± 4.53 kg/m^2. More than 22% of TNBC patients were illiterate, about 41% had secondary level of education and the most of them (95%) were housewives.

We could collect the reproductive history of 73 alive-patients. Majority of the TNBC patients had their menarche between the ages 13 to 14 years; the median age at menarche was 13 years. In this study 20 patients were postmenopausal; the median age of menopause was 47 years. All patients were married and 66.25% were multiparous. About 97% of patient had breastfed their children and 56.2% of patients had history of use of contraceptives mainly, hormonal contraception was reported in 46.6% of patients. The socio-demographic and reproductive characteristics are shown in Table I.

Table I

Socio-demographic and reproductive characteristics of the TNBC patients (n = 80)

Variables	Number (Percentage)	Mean ± SD* /median (range)
Mean age at diagnosis (years)		43.8 ± 9.0
Median BMI (kg/m^2), (n = 73)**		24.54 ± 4.53
Educational status		
No formal education	18 (22.5)	
Primary	25 (31.3)	
Secondary	33 (41.3)	
Tertiary	4 (5)	
Occupation		
Housewife	76 (95.0)	
Teachers and others	4 (5.0)	
Age at menarche (years), (n = 73)**		
10-12	22 (30.1)	
13-14	47 (64.4)	13 (10-16 years)
15-16	4 (5.5)	
Age of menopause (years) (n = 20)		
41 - 45	4 (20.0)	
46 - 50	9 (45.0)	47 (41-55)
51 - 55	7 (35.5)	
Number of children (n=80)		
1-2	27 (33.75)	
≥3	53 (66.25)	3 (1-10)
Breastfeeding status (n = 73) **		
No	2 (2.7)	
Yes	71 (97.3)	
History of contraceptive use (n = 73) **		
No	32 (43.8)	
Yes	41 (56.2)	
Hormonal	34 (46.6)	
Non-hormonal	7 (9.6)	

*SD, standard deviation, **Seven patients died before data collection

Table -II : *Cancer-related characteristics of the patients (n = 80)*

Cancer related characteristics	Number (Percentage)
Family history of breast cancer	
Negative	55 (68.75)
Positive	25 (31.25)
Lymph node metastasis	
No	21 (26.3)
Yes	59 (73.8)
Distant metastasis	
No	64 (80)
Yes	16 (20)
Co-morbidity	
Absent	42 (52.5)
Present	38 (47.5)
Histological type	
Invasive ductal carcinoma	76 (95.0)
Other*	4 (5.0)
Histological grade	
I	5 (6.3)
II	56 (70.0)
III	15 (18.8)
Not applicable	4 (5.0)
Laterality of the TNBC	
Right	38 (47.5)
Left	41 (51.2)
Bilateral	1 (1.3)
Treatment	
Surgery	61 (76.3)
Chemotherapy	68 (85.0)
Radiotherapy	15 (18.8)

* Other histological types were invasive lobular carcinoma 1, intra-cystic papillary carcinoma 1, medullary carcinoma 1 and metaplastic carcinoma 1

We found 31.25% of patients had a positive family history of breast cancer. Three patients had family history of other cancers- two ovarian and one esophageal cancer. Lymph node metastases were found in 73.8% and distant metastases in 20% of patients. About 48% of patients had co-morbidities. Reported co-morbidities were hypertension, diabetes mellitus, stroke and others. Most of the patients were diagnosed with invasive ductal carcinoma (95%) and 70% of TNBC patients had grade II cancer. Unilateral left-sided (51.2%) breast cancer patients were more than the right-sided (47.5%) cancer. Among the patients 76.3% had gone through surgery, 85% had experienced chemotherapy and only 18.8% treated with radiotherapy. Deaths were reported in seven cases from listing to data collection period.

Discussion

TNBC patients are usually younger than the patients with other types of breast cancer. The age of the TNBC patients varies according to geographic location and population. The median age of TNBC patients was reported as 58.8 years in an Italian study[7]. The Nurses' Health Study observed mean ages of TNBC patients to be 60 years for African American nurses and 58.9 years for White American nurses in research involving 2,653 breast cancer patients[8]. The median age of the Arab TNBC patients was reported 52 years and the mean age of the Chinese patients was 52.8 year[9,10]. An Indian study reported the mean age of TNBC patients was 47 years[11]. Our TNBC patients were the youngest (mean age 43.79 years) than the patients participated in those studies. The mean age of our study is also the lowest than the studies on Bangladeshi population conducted by Amee et al., Khan et al., Chowdhury et al. and Nishat et al. where the mean ages were reported as about 45 to 49 years[6,12-14].

In our study about 41% patients had secondary level and 5% had tertiary level of education and 22.5% had no formal education. Similar picture has been depicted in a study conducted by Bhattacharjee et al. on Bangladeshi breast cancer patients[15]. The number of patients without formal education is more in our study than that of Iqbal et al.[16]. This difference of educational level may be due site from where data were collected. In NICRH usually low to middle income patients come from the rural communities throughout Bangladesh, as it is a relatively low cost government specialized hospital. A study conducted on Pakistani breast cancer patients found about 32% were not educated but 21.7% had higher education [17]. This result also reflects the literacy among the breast cancer patients and that may be the cause of low level of health consciousness which hinders early diagnosis of cancer.

Research on Bangladeshi breast cancer patients have found the average age for menarche were from 11 to 13 years and our result is consistent with this finding[13,14]. The menopausal age of the breast cancer patients was reported between 40 to 42 years in 63% of the respondents in a study conducted in Bangladesh[18].The age of menopause in our study is relatable with this.

Multiparity is considered as a protective factor in breast cancer. But we found most of the TNBC patients were multiparous which is also consistent with another Bangladeshi study where 90% of breast cancer patients were multiparous[13]. Use of hormonal contraceptives is a risk factor of breast cancer. A study conducted by Bellah et al. on Bangladeshi population found 89.4% participants used hormonal contraceptives; on the other hand, about half of our patients used hormonal contraceptives[18].

A study reported in the U.S.A in 2018 that about 21.9% of TNBC patients had positive history of first- or second-degree relatives with breast cancer, which is a little less than the present study[19]. Familial or hereditary breast cancer is repeated more in TNBC than the other types of breast cancer[20]. About 42% had family history of breast cancer was reported in a study on Bangladeshi breast cancer patients [15].

Lymph nodes involvement has a prognostic value in breast cancer patients, especially axillary lymph nodes. In the current study, presence of lymph node metastasis has been found in 75.75% patients. Shetty and Rao (analyzed that in TNBC patients with one to three lymph nodes involvement was found in 35.4% and more than three lymph nodes involvement in 22.6%[11]. In Malaysian population TNBC showed lymph node infiltration absent in 59.5% patients[21]. Pan et al. found 42.3% TNBC patients had lymph node involvement[22]. Lymph node metastasis had seen in 31.3% of TNBC patients in turkey[23]. Our study found lymph node involvement more than those studies though two-thirds of the patients had TNBC of grade II.

Distal metastasis was found in only 8% of patients in the present study. Pan et al. (2017) showed 2.6% TNBC patients had developed distal metastasis[22]. Nakagawa et al. found distal metastasis in 21.6% of TNBC patients[23]. But Chen et al. found, 33.5% of all the cases had multiple organs metastases[24]. We found less involvement of distant organs by TNBC than these studies except Pan et al (2017) may be due to predominantly grade II tumor[22].

In a Bangladeshi study found 28.94% cases of TNBC manifested in histopathological grade III status[15]. An observational study in India had confirmed 85.1% TNBC patients had histologically ductal cell carcinoma and 74.4% of patients reached grade III[11]. Both these study support the finding of our finding.

In this study hypertension, diabetes mellitus, stroke and other co-morbidities were observed. Anothaisintawee et al. had suggested that diabetes mellitus significantly increased the risk of breast cancer in both Caucasian and Asian women[25]. We found diabetes mellitus in 8.8% of TNBC patients.

An observation regarding sidedness of breast cancer where 64.49% had left-sided breast cancer in Bangladeshi patients, this is in alignment with our present study findings[15].

Among invasive TNBC patients in China 71.89% had mastectomy, 85.22% had adjuvant chemotherapy and 39.22% had adjuvant radiotherapy[26]. The percentage of mastectomy is quite similar to the present study.

Conclusion

In Bangladesh, TNBC occurs in relatively young age group, with normal nutrition, multiparous, half of them took contraceptives and experienced chemotherapy. More than seven percent patients died within one and half a year which reflects its aggressiveness. Breast cancer awareness program, routine breast ultrasonography and female education is more important in early detection of TNBC.

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Conflict of interest

None

Ethical approval

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Review Article

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Pathogenesis of Cervical Cancer: Link with Life Cycle of Human Papillomavirus

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Abstract

Cervical cancer is almost always caused by persistent infection with high-risk type Human papillomavirus (HPV). HPV infects cervical transformation zone (TZ) and ectocervix to maintain productive life cycle by utilizing and manipulating the properties and machineries of the stratified squamous epithelial cells in a highly regulated manner. Regulated expression of E6 and E7 oncoproteins of HPV allows the infected cells to differentiate and the virus to complete its lifecycle. Persistent HPV infection may cause HPV genome integration with host cell DNA or epigenetic changes in the regulatory region of HPV genome. These may result in loss of regulation of HPV E6 and E7 oncoprotein expression. Therefore, these oncoproteins can continually degrade p53 and inhibit pRB tumour suppressor proteins of infected cells. This results in loss of cell differentiation, and loss of apoptosis of cells. Therefore, cells with exogenous or endogenous DNA damages can continue proliferation. As a result, the infected cells are gradually transformed to malignant cells. These transformed cells are initially present as cervical precancerous lesions which gradually progress to cervical cancer over decades. Better understanding of HPV genome, regulated gene expression during its productive life cycle and link of unregulated HPV gene expression during pathogenesis of cervical cancer resulted in significant advancements in approaches to primary and secondary prevention of cervical cancer over the past few decades.

Introduction

Cervical cancer is a significant cause of cancer morbidity and mortality in women worldwide. Its incidence and mortality rates are higher in low- and middle-income countries. In these countries women frequently present late with advanced stage. Treatment is almost ineffective in advanced cervical cancer[1,2]. Therefore, enormous efforts have been made by the researchers to find effective preventive and treatment measures for this cancer[3–5]. Finding the aetiological association between HPV and cervical cancer by HPV DNA testing during 1980s was a significant breakthrough in cervical cancer research[6,7]. Further studies provided insights into the understanding of HPV genome, virus-host cell interaction and molecular events in pathogenesis of cervical cancer[8–10]. Clinical application of these research findings resulted in a substantial advancement in approaches to its primary and secondary prevention[11–

[13]. This narrative review is aimed to discuss the existing knowledge on HPV genome and molecular events in its life cycle and malignant transformation of cervical epithelial cells by this virus to facilitate understanding of the pathophysiological basis of cervical cancer prevention.

Cervical Cancer

Aetiology

More than 95% of cervical cancers are HPV DNA positive regardless of their histological types[14]. Approximately 82% of cervical cancers are squamous cell carcinomas[15]. HPV DNA is found in 99.7% cervical squamous cell carcinomas. The magnitude of association between HPV infection and cervical squamous cell carcinoma is higher than that for association between smoking and lung cancer[16]. About 5% of cervical cancers are HPV DNA independent which are biologically and histologically separate entities[17,18].

Site of Origin

Cervical cancers almost invariably originate in the cervical TZ in women of reproductive age group[19–21]. Cervical TZ is a narrow region of metaplastic stratified squamous epithelium between the native columnar epithelium of endocervix and native stratified squamous epithelium of ectocervix. It is formed due to ectropion under the influence of oestrogen[22].

Stratified squamous epithelium of ectocervix and TZ consists of multiple layers of cells. These are called basal, parabasal, intermediate and superficial from below upwards. The basal layer cells have stem cell like property. They can divide to form more basal cells as well as differentiate and move up to form parabasal cells. Parabasal cells undergo maturation and differentiation to form intermediate cells. Intermediate cells undergo another round of maturation and differentiation to form superficial cells. Superficial cells are fully differentiated, mature and non-dividing. Mature intermediate and superficial cells contain glycogen. After their life span superficial cells die and desquamate. New cells are formed from the stem cells of basal layer to replace them[23].

In teen age girls and young women, particularly in women with multiple child births due to ectropion under the influence of oestrogen the TZ is more exposed to vagina whereas in older women it is less exposed due to entropion as a result of oestrogen withdrawal[22,24]. This exposure of cervical TZ to vagina in women of reproductive age group may make them more prone to HPV infection and cervical cancer[23,25]. In addition, existence of metaplastic epithelium makes TZ cells more prone to malignant transformation[26].

Natural History

Genital HPV infections are common in sexually active women. Most of the infections are transient and cleared spontaneously without producing any disease or symptom[27,28]. Transient HPV infections usually do not induce any morphological change in cervical epithelial cells. In some cases, they may induce mild morphological changes. These changes appear as Low-grade Squamous Intraepithelial Lesion (LSIL) in cytological smears and Cervical Intraepithelial Neoplasia 1 (CIN1) in histological sections. These morphological changes revert to normal when the infection is cleared[29,30]. In 15-20% of women infections with certain HPV types called high-risk HPV types become persistent. Most of the persistent HPV infections are cleared spontaneously. About 10-20% of persistent high-risk HPV infection may progress to cervical precancerous lesions within five years. Cervical precancerous lesions appear as High-grade Squamous Intraepithelial Lesions (HSIL) in cytological smears and as CIN2/CIN3 in histological sections. About 60-70% of CIN2/CIN3 lesions regress to normal and the rest 30-40% may progress to cervical cancer in 1-20 years. Once the precancerous lesion progresses to cancer, it does not regress naturally. Approximately 1% of all HPV infected women progress to develop invasive cervical cancer[31–35]. Thus, the natural history of cervical cancer implies involvement of both viral and host factors in persistence of HPV infection and progression to precancerous lesions and cervical cancer.

Human papillomavirus

Genome

HPVs are small (50-60 nm in diameter), non-enveloped virus with a double-stranded circular 8000 base-pair long DNA genome and icosahedral capsid. The HPV genome has an upstream regulatory region (URR) or long control region (LCR), six early (E1, E2, E4, E5, E6 and E7) genes and two late (L1 and L2) genes. The early genes encode proteins involved in viral genome replication and the late genes encode capsid proteins. HPV E1 protein is involved in early viral DNA replication. Its E2 protein is involved in viral DNA replication, E6 and E7 oncogene transcription regulation and late gene activation. HPV

E4 protein is involved in the release of progeny virus particles from host cells. Its E5 protein is involved in viral DNA replication, delaying host cell differentiation, apoptosis inhibition and host immune response evasion. HPV E6 is an oncoprotein that binds and degrades host cell p53 tumour suppressor protein and thereby delays differentiation and inhibits apoptosis of infected host cells. Its E7 is another oncoprotein which binds and inactivates host cell pRB tumour suppressor protein and thereby induces infected differentiated cells to reenter S phase of cell cycle so that viral DNA replication can go on. It also helps the virus to evade host immune response by inactivating interferon (IFN) gene. HPV early genes can be expressed in undifferentiated as well as differentiated cells but late genes can be expressed only in differentiated cells because factors needed to activate late gene are present only in differentiated cells[36]. Among the early genes, sequences of E1 and E2 are well-conserved while the sequences of E4, E5, E6 and E7 are diverse. The sequence of both late genes L1 and L2 are well-conserved and L1 is the most conserved or least variable gene. Based on sequence variation of L1 gene HPVs are classified into various genotypes or types. Each HPV genotype is at least 10% dissimilar in the sequence of its L1 gene with other genotypes. Currently more than 200 HPV genotypes have been identified which infect humans[37–40].

Transmission

HPVs are transmitted by skin-to-skin or sexual contact. They infect epithelium of skin or mucosa because their life cycle is dependent on properties and machineries of cells of various layers of stratified squamous epithelium[38,41]. Based on tissue tropism, they are categorised as cutaneous and mucosal types. Mucosal types infect epithelium of mouth, throat, respiratory tract and anogenital region. More than 40 HPV genotypes are known to infect mucosa of which 30 genotypes infect anogenital region including the uterine cervix[16,42].

High-Risk and Low-Risk HPV Types

Based on potential of causing cervical precancerous lesions and cancers, the International Agency for Research on Cancer (IARC) Multicenter Cervical Cancer Study Group classified HPV genotypes which infect cervical mucosa as 'high-risk', 'probable high-risk' and 'low-risk' types. Fifteen genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) were classified as high-risk HPV types, 3 genotypes (26, 53, and 66) as probable high-risk HPV types, and 12 genotypes (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108) as low-risk HPV types[43]. The study group conducted 11 case-control studies in nine countries and classified HPV types which are associated as single infections with an odds ratio for cervical cancer of at least 5.0 as high-risk HPV types, and at least 1.0 as low risk HPV types. In 2005, a panel of scientists at the IARC reassessed carcinogenicity of HPV and concluded that 13 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66) are carcinogenic to humans[44]. Among the high-risk HPV types, HPV 16 and HPV 18 together account for approximately 51% of cervical precancerous lesions and 70% of invasive cervical cancers. Rest of the HPV-induced cervical precancerous lesions and cancers are caused by other high-risk HPV types[45]. Low-risk HPV types are very rarely found in cervical cancers[46].

Life Cycle

HPVs infect cervical epithelia primarily by sexual route. Released HPVs from desquamated cells of male partner reach the basal cells through micro-trauma in the superficial layers where they can attach to their receptors and initiate infection. Common site of initiation of infection is the cervical TZ near the external os which is the most vulnerable part for micro-trauma during sexual intercourse[38,47–49].

After entering into the basal cells, the released viral DNA is transported to the nucleus and remains in circular extra-chromosomal or episomal form. In early infection, E1 and E2 genes start to express. Low concentration E1 and E2 cause a transient round of episomal HPV DNA replication resulting in 50-100 copies of episomes per cell[38,50,51]. These proteins cause further viral DNA replication with replication cycle of basal cells using DNA replication machinery of these cells. Replicated viral DNA segregate into daughter cells to maintain a stable copy number of episomal DNA[52,53]. As late genes cannot be expressed in undifferentiated cells, HPV cannot synthesize capsid or complete life cycle in basal cells[36,54,55].

To accomplish both DNA replication and capsid synthesis, HPVs utilize and manipulate machinery of differentiated superficial cells. They keep superficial cells in S phase of cell cycle for a longer period to

replicate DNA as well as allow them to differentiate to synthesize capsid[41,56–58]. When HPV infected basal cells differentiate and move to intermediate or superficial layers, HPVs express E6 and E7 genes. HPV E6 protein causes delay in differentiation and cessation of apoptosis of HPV infected superficial cells by degrading host cell p53 protein. HPV E7 protein causes the infected cells to reenter S phase of cell cycle by inactivating host cell pRB protein[37–39,51]. In S phase of intermediate and superficial cells, HPV genome can replicate to thousands of copies per cell utilizing the host cell DNA replication machinery[55–59]. After DNA amplification, when E2 protein concentration becomes high it inhibits E6 and E7 and activates L1 and L2 gene expression. Inhibition of E6 and E7 results in cessation of S phase and allows the cells to differentiate. In differentiated cells expression of L1 and L2 genes results in capsid synthesis, virion assembly and completion of life cycle. Progeny virions are shed from the desquamated superficial cells without causing cell lysis[36,38,57,60]. Therefore, HPVs replicate and maintain life cycle by manipulating squamous epithelial cells in a well-regulated manner. HPV E2 gene plays a very important role in maintenance life cycle of HPV as well as differentiation and maturation of cervical epithelial cells.

Pathogenesis of Cervical cancer

Manipulation of cervical stratified squamous epithelial cells by HPV genes is strictly regulated. Loss of this regulation may result in unfortunate consequences for the virus and the infected cell. The most important event in pathogenesis of cervical cancer is persistent high-risk HPV infection which may lead to loss of this regulation and development of cervical cancer[36,61].

Persistent HPV Infection

HPV infections are usually cleared spontaneously, 70% within one year and 90% within 2 years. In the rest HPV may cause persistent infection[27,28]. There is no uniform agreement regarding the definition of persistent HPV infection. Some studies defined it as detection of same HPV type in two follow up visits and others in three or more follow up visits. The interval between follow up visits varied between the studies[33]. However, if we consider the interval between follow up visits one year and same HPV type detection in three or more visits, we can define persistent HPV infection as 'when the same HPV type is detected for more than two years'.

The exact cause of HPV persistence is not known. Both viral and host factors are found to be involved. Among viral factors, infection by high-risk HPVs and simultaneous multiple HPV infections may have role in persistence[62–64]. Some studies found association of HPV viral load with persistence but other studies did not find enough evidence to support this observation[64–67]. Among host factors, presence of certain HLA alleles, smoking habit, having multiple sexual partners, prolonged use of oral contraceptives, alteration of vaginal microbial flora, immunodeficiency and simultaneous presence of other sexually transmitted infections (STI) are found important contributors[68–70].

Persistent high-risk HPV infection is associated with HPV genome integration into host cell DNA and epigenetic changes in LCR of HPV genome, loss of regulation of HPV gene expression and progression to cervical cancer[32–34,36].

HPV Genome Integration

HPV genome is frequently found to be integrated into host cell DNA in persistent HPV infection. Integration may arise because of persistent HPV infection and when integration occurs HPV infection becomes persistent. When integrated into the host cell DNA, HPV genome becomes linear from its circular episomal form. Integration may take the form of single genome integration into the host cell DNA or a multiple tandem repeat of HPV genome integration with intervening cellular DNA sequences at a single locus. In both types of integration, usually E2 gene is disrupted while E6 and E7 oncogenes genes are retained. It results in loss of activation of L1 and L2 genes as well as loss of inhibition of E6 and E7 gene. Thus genome integration is the dead end of HPV life cycle and initiator of malignant transformation of infected cells[71–74].

Epigenetic Changes

HPV persistence may cause epigenetic changes in its LCR and host cell genome. It may result in increased E6 and E7 expression, inhibition of host cell tunour suppressor gene expression and activation of oncogene expression. In this way epigenetic changes may contribute to malignant transformation of HPV infected cells[75–77].

Malignant Transformation

Disruption of E2 gene by integration or epigenetic change in LCR results in unregulated increased

expression of E6 and E7 mRNA and therefore E6 and E7 oncoproteins. These oncoproteins can now persistently exert their effect on p53 and pRB tumour suppressor proteins of host cells. HPV E6 protein degrades p53 and HPV E7 protein inactivates pRB[78–80].

Host cell p53 detects exogenous or endogenous DNA damages or mutations and halts the cells with damaged DNA at G1 and G2 checkpoints to allow damage repair. If the DNA damage or mutations cannot be repaired, it induces apoptosis of cells so that damaged DNA or DNA mutations cannot pass to daughter cells. It also plays role in cell differentiation[81–83]. Host cell pRB inhibits cells to enter S phase when growth inhibitors or DNA damages are present[84,85].Therefore, degradation of p53 by HPV E6 and inactivation of pRB by HPV E7 protein result in sustained proliferation, loss of differentiation and maturation and thereby malignant transformation of cells[9,14,16,37,72,79]. In addition, accumulation of DNA damage in daughter cells results in genomic instability, aneuploidy and telomerase activation. HPV E6 protein may also activate vascular endothelial growth factor (VEGF) gene. In addition, HPV E5 protein is also involved in malignant transformation by inhibiting apoptosis and activating c-MET gene[42,86]. All these genetic changes enhance malignant transformation of HPV infected cells[87–92]. To inhibit sustained cell proliferation, HPV infected cells increase p16 protein expression. But it cannot stop cell division because pRB is inactivated by HPV E7 protein not by Cyclin D-CDK4/6 molecules[93].Thus malignant transformation and cell proliferation can proceed in presence of p16. The E6 and E7 proteins of high-risk HPVs have high affinity for host cell p53 and pRB while those of low-risk HPVs have low affinity for these tumour suppressor proteins. Moreover, E7 protein of high-risk HPVs can inhibit IFN gene and allow the virus to escape immune response and cause persistent infection. Therefore, high-risk HPVs can manipulate cell cycle of host cells longer while low-risk HPVs cannot[16,37]. These may be the reason why high-risk HPVs are found associated with cervical cancer while low-risk HPVs are not.

Morphological and Physiological Changes in Cells

Malignant transformation by HPV brings morphological, physiological and metabolic changes in cervical epithelial cells. To support cell division there is increased DNA synthesis, increased nuclear size, cell size and altered morphology of cells. Along with increased DNA synthesis there is increased nuclear protein synthesis in cells. HPV itself and malignant transformation alter cellular metabolism that cause depletion of glycogen content in malignant cells[30,89,94–98].

Pathophysiological Basis of Cervical Cancer Prevention

Cervical cancer is preventable at primary and secondary level[11].

Primary prevention

Cervical cancer is caused by persistent infection with high-risk type HPVs. So prevention of high-risk HPV infection by HPV vaccination can prevent development of cervical cancer. Bivalent (HPV 16/18), quadrivalent (HPV 6/11/16/18) and nonavalent (HPV 6/11/16/18/31/33/45/52/58) vaccines are available and are being used to vaccinate girls to prevent cervical cancer. Vaccination by bivalent or quadrivalent vaccines can prevent 70% and nonavalent vaccine can prevent more than 95% of HPV infections and thereby development of cervical cancer[99–101].

Secondary prevention

Cervical cancer has a long precancerous stage at which treatment is very effective. So it can be prevented by screening and treatment at precancerous stage. Screening for cervical cancer is done by cytological, visual and HPV tests. Cytological tests like Papanicolaou smear (Pap smear) is being used since 1940s. A more advanced liquid based cytology (LBC) is being used currently. Cytology detects cellular morphological changes due to malignant transformation[3,30]. Visual inspection with acetic acid (VIA) and Visual inspection with Lugol's iodine (VILI) are being used in resource limited countries. VIA is based on detection of increased nuclear proteins and VILI detects glycogen depletion due to malignant transformation[95,96,102,103]. High-risk HPV DNA tests detect presence of HPV infection which may be transient, persistent or integrated[104]. HPV E6 and E7 mRNA test detects increased E6 and E7 expression and thus indicates HPV has been integrated and the cervical cells are in process of malignant transformation[105].

Conclusion and Future Direction

Understanding the HPV genome, regulated gene expression during productive life cycle and link of unregulated HPV gene expression during pathogenesis

of cervical cancer resulted in significant advancements in primary and secondary prevention of cervical cancer[11–13]. Treatment of advanced cervical cancer remains a challenge. This understanding guided the researchers to explore the possibility of targeting HPV E6 and E7 oncogenes and oncoproteins for cervical cancer treatment. Research on viral vector based therapeutic cancer vaccines targeting HPV E6 and E7 oncoproteins, CRISPR based and RNA interference (RNAi) based targeted therapy against HPV E6 and E7 oncogenes are advancing[2]. In near future these can be good treatment options for advanced cervical cancer with increased expression of HPV E6 and E7 mRNA.

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Case Report

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An Uncommon Presentation of a Rare Childhood Cancer: Primary Cutaneous Anaplastic Large Cell Lymphoma with Central Nervous System (CNS) Involvement

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Abstract:

Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is a CD30-positive lymphoproliferative disorder primarily seen in elderly individuals, with rare occurrences in children. PC-ALCL is clinically characterized by autoregressive, often recurrent multifocal or single nodules that can ulcerate.

In the pediatric population, there are currently no consensus guidelines for the treatment of cutaneous lymphoma. However, isolated forms of PC-ALCL in children are typically managed through various approaches, such as surgical excision or external beam radiation therapy.

We present the case of a 12-year-old boy with PC-ALCL involving the central nervous system (CNS), who initially responded well to the APO regimen for ALCL. However, the patient experienced a relapse before completing the treatment, indicating that the APO regimen may no longer be considered an effective treatment for pediatric cutaneous anaplastic large cell lymphoma. It is anticipated that the development of next-generation CNS-penetrating ALK inhibitors will offer potential benefits for patients in similar situations.

Introduction:

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL) that primarily affects the null-cell or T-cell lineage. The tumor is characterized by the presence of large lymphoid cells with abundant cytoplasm and consistent, strong expression of Ki-1 antigen (CD30). The condition was first described by Stein[1] in 1985. In Canada ALCL is a childhood tumor, accounting for 15% of all pediatric NHL with a yearly incidence ranging from 1.2 per million in children under 15 years.[2]

Studies indicate that the incidence of NHL in Southeast Asian pediatric populations is similar to that in Europe

and North America.[3] However, certain studies conducted in North America focusing on children of Asian ethnic origin have shown a higher incidence rate of ALCL compared to other types of NHL.

ALCL are subdivided into two subgroups on the basis of ALK (Anaplastic lymphoma kinase) protein expression i.e., ALK-positive ALCL and ALK-negative ALCL.[4] However, in 2008, the World Health Organization (WHO) introduced a classification system that categorized ALCL into three distinct biological types. These include:(a) Primary systemic ALK-negative ALCL, (b) Primary systemic ALK-positive ALCL (ALK-positive ALCL), and (c) Primary cutaneous ALCL (PC-ALCL). [5,6]

Primary cutaneous anaplastic large cell lymphoma (**PC-ALCL)** is usually seen in adult patients.[4,7] Childhood PC-ALCL is a rare occurrence, but it can manifest during the first decade of life. Among peripheral T cell non-Hodgkin lymphomas (NHL) in children, the incidence of PC-ALCL is approximately 1.7%. Typically, PC-ALCL presents as solitary localized nodules, although multiple lesions can be observed in up to 20% of pediatric patients. Ulceration, while uncommon in pediatric cases, may sometimes be present.

The lesions of PC-ALCL primarily appear on the face, extremities, trunk, and buttocks. In rare cases, spontaneous resolution of the lesions has been reported in pediatric patients. However, it is important to note that PC-ALCL can extend beyond the skin, spreading to lymph nodes or other organs. When this occurs, the management of the lymphoma shifts to that of systemic ALCL**[8]**, which involves a broader treatment approach targeting the affected lymph nodes or organs. In ALCL, CNS involvement is very rare but specially PC-ALCL with CNS involvement has not reported.

Establishing a proper diagnosis of PC-ALCL can be challenging due to its histological morphology, which bears similarities to other diseases like lymphomatoid papulosis. Histologically, PC-ALCL is characterized by irregular polygonal large cells arranged in sheets that extend throughout the dermis and, in some cases, the subcutis. While the presence of abundant eosinophilic or amphophilic cytoplasm and horseshoe-shaped nuclei is typical of PC-ALCL, these characteristic cells may not always be observed.

In diagnosing PC-ALCL, the expression of CD30+ antigen in more than 75% of anaplastic cells is indicative of the condition. However, it is important to note that the absence of this characteristic cell or lower CD30 expression should not rule out the possibility of PC-ALCL. Additional diagnostic techniques, such as immunohistochemistry and molecular studies, may be necessary to confirm the diagnosis and differentiate PC-ALCL from other similar lymphoproliferative disorders. Early era of PC-ALCL discover it is generally considered to be ALK-negative.[9] But recently, ALK-positive PC-ALCL has been reported in both children and adults.[10,11] Due to the overlapping features with other diseases and the potential variations in histological presentation, a comprehensive evaluation by experienced pathologists is essential for an accurate diagnosis of PC-ALCL.

There are no consensus guidelines for the treatment of PC-ALCL in the pediatric population, the isolated form of diseases is typically managed by surgical excision or external beam radiation therapy.[12] The most recently a trail has completed by COG, titled ANHL0131, where APO chemotherapy (vincristine, Adriamycin, and prednisone),which includes induction therapy followed by 15 cycles of maintenance therapy but we treated two cases of PC-ALCL by APO chemotherapy and both of them developed relapse.

PC-ALCL patients who develop CNS metastasis are often treated with cranial radiation. However, cranial radiation carries the risk of both short-term and long-term side effects, particularly in children. To address this concern, pharmaceutical companies have developed next-generation ALK inhibitors that can penetrate the blood-brain barrier. These new ALK inhibitors hold promise for future treatment approaches, as they offer the potential to avoid or reduce the need for radiation therapy in PC-ALCL patients with CNS metastasis. By targeting the cancer cells within the central nervous system, these drugs may provide effective control of the disease while minimizing the potential risks associated with radiation therapy.

Case:

In this report, we describe an unusual case involving a 12-year-old boy who presented with a history of multiple skin lesions distributed across his body for a duration of 3 months. Additionally, the boy experienced headaches persisting for 2 months, as well as generalized body aches lasting for 1 month. The patient also reported occasional episodes of vomiting over the course of one week. Notably, there was no prior history of fever, weight loss, night sweats, bleeding manifestations, cough, respiratory distress, joint pain, convulsions, or loss of consciousness. The recorded fever was intermittent, with the highest recorded temperature reaching 101°F. Headache was mild, generalized, lasted for minutes to hour, no aggravating or relieving factors.

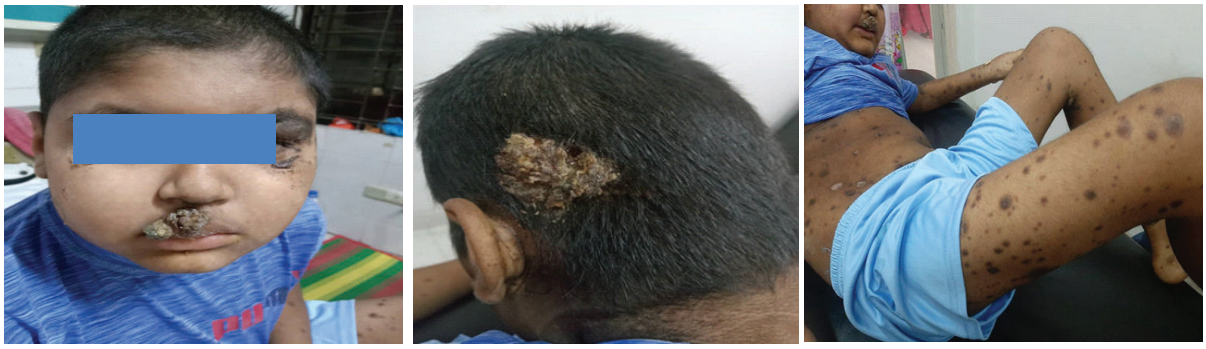

Fig-1. *Ulcerative plaques present on face, head, legs and body*

For the aforementioned complaints, the patient was initially treated with antibiotics; however, there was no improvement in the condition, and the lesions continued to increase. As a result, the doctor recommended a biopsy of the scalp lesion and subsequently referred the patient to the National Institute of Cancer Research and Hospital for further management.

The lesions initially appeared on the lower limbs and gradually spread to involve the entire body, including the upper limbs, face, perioral and periorbital areas, scalp, and genitalia. Eventually, they disseminated throughout the entire body. The lesions exhibited a range of characteristics, such as being brown to blackish in color, varying in size and shape. The largest lesion, measuring approximately 5X3 cm, was located on the scalp. The lesions presented as different types, including macular, papular nodular, fungating, crust, plaque-like, and only the scalp lesion exhibited discharge. The patient experienced tenderness throughout the body. No palpable lymph nodes were detected.

The fine-needle aspiration cytology (FNAC) was performed on the scalp lesion, and the results indicated the presence of a monomorphic population of large, immature cells with lymphoid origin. These cells were observed in a diffuse pattern, accompanied by a background of inflammatory cells mixed with blood. These findings are highly suggestive of a malignant lymphoma, specifically non-Hodgkin lymphoma (NHL).

The biopsy and histopathology examination of the scalp lesion revealed a proliferation of large histiocytic cells characterized by vesicular nuclei, prominent nucleoli, and occasional grooves, along with eosinophilic cytoplasm. These cells were found intermingled with scattered eosinophils and a few lymphocytes. These histopathological features are consistent with **Langerhans Cell Histiocytosis** (fig-2).

Immunohistochemistry (IHC) staining results indicate that the tumor cells are positive for CD3, CD30, and ALK-1, which is compatible with anaplastic Large Cell Lymphoma. The Ki-67 proliferation index is approximately 50%, indicating a moderate level of cell proliferation. CD20 staining shows a normal distribution of cells. However, CD68, CD-1a, and S-100 markers are negative, suggesting the absence of expression for these markers in the tumor cells. (Fig-3)

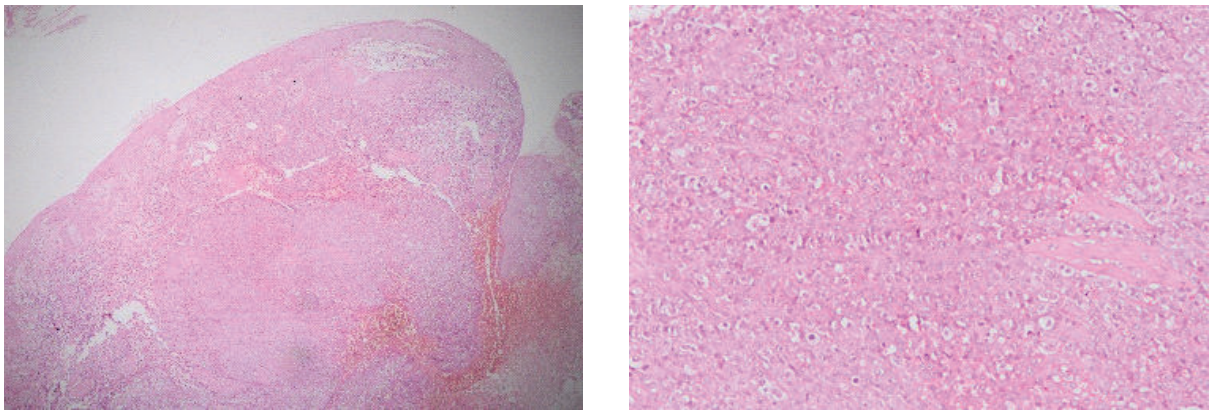

Fig.-2: *Depicts characteristic features of Langerhans Cell Histiocytosis*

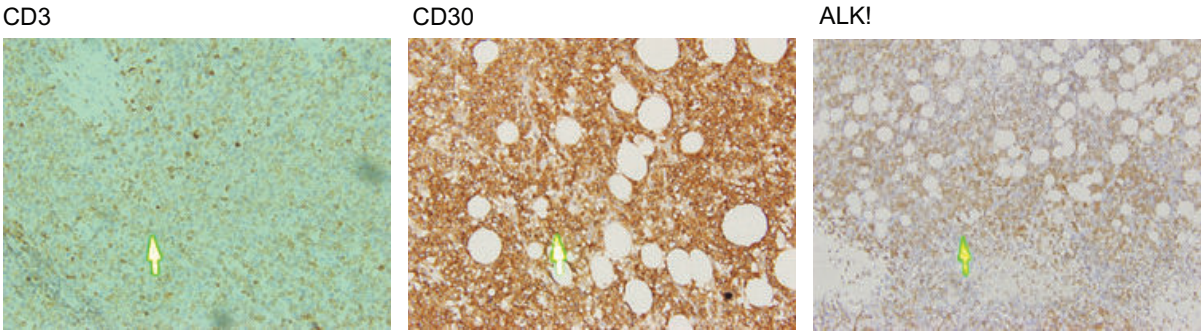

Figure 3: *Immunohistochemistry showing CD 30 positivity with positive CD3 and, ALK-1.*

CSF study for Malignant cell: CNS - 3

Bone Marrow study- Normal Active marrow.

Final Diagnosis- Anaplastic Large Cell Lymphoma with CNS involvement (Stage IV).

Studies for chromosomal abnormality or epithelial membrane antigen (EMA) expression were not possible to performed as they were unavailable/unaffordable.

Discussion

Anaplastic lymphoma kinase (ALK) was discovered in 1994, and initially, its positive expression detected by immunohistochemistry (IHC) was considered strong evidence of systemic ALCL (S-ALCL) and deemed less likely for the diagnosis of PC-ALCL. However, subsequent studies by multiple authors have reported ALK-positive cases of PC-ALCL, which tend to occur more frequently in children. It is worth noting that ALK positivity has also been observed in various pediatric cancers, including neuroblastoma and non-small cell lung cancer, as well as in other human tumors.

In the past, PC-ALCL was classified as a high-grade NHL, which was responsible for approximately 10% of childhood NHL. Primary cutaneous ALCL without nodal or visceral involvement at presentation is uncommon before 20 years of age.[13] Other features of PC-ALCL include low recurrence rates after therapy, favorable prognosis, and spontaneous remissions in 25% of cases, along with infrequent extra-cutaneous dissemination.[14]

We know PC-ALCL may follow the classic systemic form, start de-novo or arise from anaplastic transformation of other lymphomas such as Sézary syndrome (CD3+, CD4+, CD7", CD8") or Hodgkin's lymphoma and mycosis fungoides (CD8+, CD20+ with loss of CD2, CD3, CD5). Typically, Primary Cutaneous ALCL usually confined to the skin and progression to extracutaneous sites is rare but has been reported in about 10% of the cases.[15]

In our case, there were no signs of regional lymph node enlargement, liver involvement, or spleen involvement detected at the time of diagnosis. Additionally, the patient did not exhibit B symptoms such as fever, night sweats, or weight loss, which are often associated with systemic lymphoma. However, it is important to note that leg involvement was present in our case, which has been reported as an adverse prognostic indicator.[16]

The diagnosis of primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is typically established through a combination of clinical findings, histopathological examination, immunophenotypical analysis, and imaging methods. In histopathological examination, the presence of CD4+ T lymphocytes exhibiting anaplastic morphology and CD30 expression is observed as a non-epidermotropic diffuse infiltrate within the dermis. The mitotic rate is often high in PC-ALCL. In some cases, ulcerated lesions may be accompanied by inflammatory infiltrates comprising reactive lymphocytes, histiocytes, eosinophils, and neutrophils.

PC-ALCL exhibits a broad range of cytomorphologic variations and diverse histopathologic presentations. It is crucial to recognize these variants as they significantly differ from the typical morphological appearance of PC-ALCL. Failure to identify these variants may lead to misdiagnosis and inappropriate treatment of patients. Even different lesions from a single patient may show variable histopathologic patterns and cell morphologies.[17]

In our case, the initial biopsy report led us to believe that the histopathological findings were indicative of Langerhans Cell Histiocytosis (LCH). The examination of the soft tissue mass from the patient's scalp revealed a proliferation of large histiocytic cells with vesicular nuclei, prominent nucleoli, occasional grooves, and eosinophilic cytoplasm. These cells were observed alongside scattered eosinophils and a few lymphocytes, which suggested a diagnosis of Langerhans Cell Histiocytosis.

However, upon further investigations and considering the clinical context, it became apparent that the initial interpretation of the biopsy report was misleading. Subsequent evaluations and additional diagnostic tests revealed that the correct diagnosis was primary cutaneous anaplastic large cell lymphoma (PC-ALCL). Lymphoid cells in conventional cases of PC-ALCL express CD30 (more than 75% of cells) and variable degree of CD2, CD3, CD4, and CD5, and are usually negative for CD8, CD20, CD56, HSV, Epstein-Barr virus (EBV) and cytotoxic proteins.[18]

In our case, the IHC analysis revealed positive staining for CD3, CD30, and ALK-1, which is compatible with anaplastic Large Cell Lymphoma (ALCL). The Ki-67 index of approximately 50% indicates an active cell proliferation rate. CD20 showed a normal distribution, as it is a general B-cell marker and not typically expressed in ALCL. However, CD68, CD-1a, and S-100 markers were negative, which suggests the absence of Langerhans cells in the specimen. These immunohistochemical findings further support the diagnosis of anaplastic Large Cell Lymphoma.

CNS involvement in children with ALCL is also extremely rare [19] and CNS involvement in PC-ALCL is not mentioned in English literature. But CSF study of our patient revealed malignant cell (CSF-3).

Currently, there is a lack of consensus and specific guidelines for the treatment of primary cutaneous anaplastic large cell lymphoma (PC-ALCL) in the pediatric population. However, in cases of isolated PC-ALCL, the typical management approaches involve surgical excision or external beam radiation therapy. [12] In the most recently completed Children's Oncology Group (COG) trial, known as ANHL0131, the APO chemotherapy regimen (vincristine, adriamycin, and prednisone) was utilized as the backbone of the treatment approach. This trial included induction therapy followed by 15 cycles of maintenance therapy.

In our case, we initiated the APO regimen with CNS-directed therapy for induction, consisting of vincristine, doxorubicin, prednisolone, and intrathecal methotrexate (MTX), which was administered over a period of 4 weeks. After just 15 days of therapy, the boy showed significant improvement and experienced a resolution of all cutaneous manifestations. Following the induction phase, maintenance therapy was commenced and continued for a total of 15 cycles. However, despite the initial positive response to treatment, the patient unfortunately experienced a recurrence of the disease. Tragically, the recurrence was accompanied by severe septicemia, ultimately leading to the patient's demise.

We present this case to highlight the significance of recognizing the uncommon presentation of anaplastic large cell lymphoma (ALCL), as it can sometimes be confused with other diseases such as Langerhans cell histiocytosis (LCH) both clinically and histologically. In our case, the initial tissue biopsy revealed findings consistent with LCH, leading to diagnostic confusion.

Although it is generally believed that primary cutaneous ALCL (PC-ALCL) has a more indolent course compared to systemic ALCL, our patient experienced remission initially but unfortunately relapsed later. This serves as a reminder that while PC-ALCL may have a favorable prognosis overall, individual cases can exhibit varying outcomes, and relapse is a possibility.

Conclusion:

The spectrum of clinical, histological, and molecular features associated with primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is continuously expanding. These characteristics often overlap with other conditions that may exhibit either an indolent disease course or a more aggressive nature, such as peripheral T-cell lymphoma (TCL). In recognition of this complexity, the World Health Organization (WHO) has categorized these diseases under the umbrella term "Primary cutaneous CD30-positive T cell lympho-proliferative disorder" in 2022.

Ongoing research and advancements in the field will continue to shape our understanding of PC-ALCL and improve diagnostic accuracy and treatment outcomes. It is important for healthcare professionals to stay updated with the evolving knowledge and guidelines

related to PC-ALCL to provide optimal care for affected individuals.

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Declarations
Ethics approval

Conflict of interest
The authors declare no conflict of interest.

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Letter to the editor

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Ethical and Legal Challenges in Disclosing Genetic Information: A Multifaceted Perspective

Muhammad Rafiqul Islam

Dear Editor

I hope this letter finds you well. I am writing to share insights on the ethical and legal challenges associated with the rapid integration of genetic testing in healthcare, specifically focusing on the disclosure of genetic information to at-risk relatives. Is there a legal obligation for health professionals to disclose genetic information to a patient's relatives when a specific individual (relative) is at significant risk of harm, and such harm could be mitigated through the act of disclosure?

The rapid integration of genetic testing in healthcare has given rise to an array of intricate ethical and legal challenges. It is a contentious issue whether health professionals are obligated to disclose patients' genetic information to their relatives at serious risk of harm, and whether this potentially life-saving harm can be mitigated by disclosure. While patient confidentiality remains a pillar of medical ethics, the possibility of avoiding harm to identifiable individuals through the revelation of genetic data creates a compelling ethical dilemma. Striking a balance between upholding patient autonomy and safeguarding the well-being of family members susceptible to hereditary diseases underpins this multifaceted discourse. Several inherited conditions, such as hereditary breast cancer, ovarian cancer, and Lynch syndrome, can be prevented through effective preventive measures for patients and their relatives.[1] Genetic information plays an important role here, revealing inherited disease predispositions and determining the health trajectory of a patient's relatives. Therefore, it is imperative to manage this intricate terrain with a comprehensive framework that respects individual privacy rights, while recognizing the potential advantages of preventive measures for at-risk relatives. This necessitates exploring the legal and ethical dimensions of genetic information disclosure to develop a nuanced and responsible approach to advanced genetic testing in healthcare.

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Current Practice and Challenges:

In high-risk families, the effectiveness of cancer prevention depends in part on involving at-risk relatives in surveillance programs. In several studies, less than half of eligible at-risk relatives are being tested for hereditary cancer syndrome (from 15% to 94% in different studies.[2,3] Information dissemination about genetic test results often relies on family-mediated communication, a common practice in many countries. While patients generally acknowledge their responsibility to share information with their relatives, several factors hinder effective communication.[4] These include guilt, lost contact, and concerns about how the relatives might react. Studies have highlighted that information relayed through families is prone to misunderstanding or distortion.[5] For instance, research by Jacobs et al. revealed that relatives informed by patients tend to recall less accurate information than those reported directly by genetic health professionals.[6]

Healthcare professionals (HCPs) often need more inclination to acknowledge their responsibility to inform at-risk relatives, possibly due to unclear legal situations in many countries. The conflict between traditional patient confidentiality and the looser obligation to tell relatives at risk of a severe medical condition poses challenges for HCPs and exposes them to potential legal sanctions. Despite the legal requirement in France for patients to either inform at-risk relatives themselves or request their physician to do so, challenges persist in implementing this practice.[7] A recent report highlighted that the French legal framework doesn't necessarily eliminate the resistance from HCPs to inform patients' relatives directly. The report states that efforts are made to discourage patients from choosing this option.[8]

However, the research suggests that the approach of healthcare-mediated information delivery to at-risk relatives by HCPs could be significantly more effective in increasing the uptake of genetic testing compared to family-mediated information.[9] Big challenges in ethical responsibilities of a physician come from various social structures in sequence. The diagram below shows the multidimensional challenges:

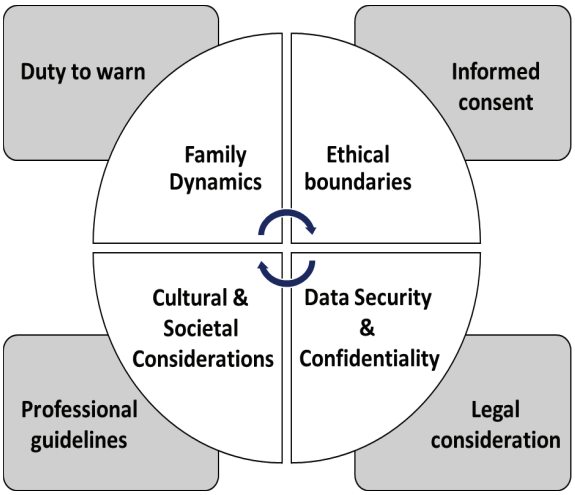

Figure 1: The challenges faced by physicians, when deciding to disseminate genetic data to their patients' at-risk relatives, are multifaceted and complex.

Duties and Boundaries:

Healthcare providers have a duty to warn individuals who are at risk of hereditary health issues when disclosing genetic information. This is guided by the principle of beneficence. Although there are some legal precedents that offer guidance, the exact legal implications and boundaries of this duty remain uncertain. Regulations such as the Health Insurance Portability and Accountability Act (HIPAA) emphasize the importance of providing clear and understandable information to patients, which promotes transparency, patient autonomy, and respect for patients' rights within the healthcare system. Professional guidelines from associations such as ASHG, ESHG, and WHO provide essential insights for physicians who disclose genetic information. They stress the importance of informed consent, counseling, and ethical frameworks to uphold patient confidentiality while prioritizing the well-being of everyone involved.

When disclosing genetic information, healthcare providers must adhere to guidelines set by esteemed institutions such as the General Medical Council (GMC) and legislation like the Genetic Information Nondiscrimination Act (GINA). The GMC emphasizes maintaining a delicate equilibrium while safeguarding at-risk relatives and patient confidentiality. Conversely, GINA prohibits genetic-based discrimination and underscores the necessity of strict privacy protocols. HIPAA regulates the secure handling of health information, including genetic data, mainly focusing on patient privacy and data protection.

When managing familial dynamics, healthcare providers need to consider the potential psychological, social, and familial implications of sharing genetic information. This requires a nuanced approach, considering the sensitive nature of familial relationships and the potential for discord or distress within families. Additionally, accommodating cultural beliefs, societal norms, and individual values within the legal and ethical frameworks is crucial to ensure culturally sensitive and equitable healthcare practices concerning the disclosure of genetic information.

Navigating the safety

Figure 2: *strategies of safe exit for physicians and patients*

Sharing genetic information within families is essential to prevent hereditary health risks, and a public engagement initiative can play a significant role in raising community awareness about its importance. By including workshops, community outreach, and online materials, the initiative can encourage responsible information sharing and foster open discussions. A comprehensive review of legal policies related to the disclosure of genetic information to at-risk relatives is critical. Collaborative ethical frameworks can guide healthcare practices towards equitable and responsible

dissemination of genetic information, promoting an inclusive approach that emphasizes transparent communication and cultural sensitivity. Investing in research and support services for both patients and at-risk relatives is essential. These advancements will facilitate the development of personalized interventions and support services, catering to the unique requirements of at-risk relatives and enabling them to make well-informed decisions about their health and well-being with confidence.

Conclusion

Healthcare providers have a moral obligation to share crucial information about hereditary conditions with those at risk, a careful balanced with other moral obligations and resources. Patients may also feel responsible to inform their loved ones, and healthcare providers can encourage collaborative efforts to ensure everyone who needs to know has access to important information. Health care providers and patients can benefit their families who may be at risk by fostering a culture of responsible information sharing.

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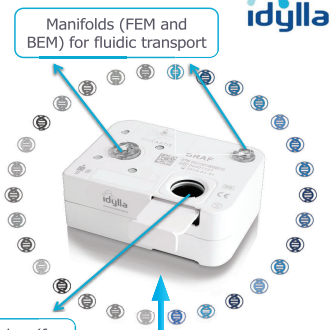

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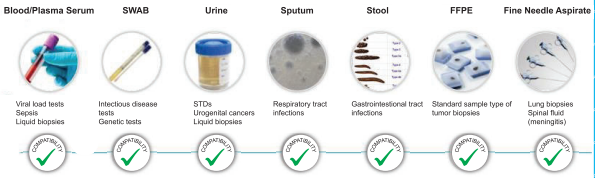

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#of Mutations	7	21	23		7	51 (49)	-
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