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Editorial

Cancer J Bangladesh 2022;3(2): 41-42
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Genetic Testing in Cancer Management

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Citation: Haque MN. Genetic Testing in Cancer Management. Cancer J Bangladesh 2022;3(2): 41-42.

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Abstract

Cancer is a genetic disease that is characterized by uncontrolled cell growth. Several genetic activities play roles in cancer development, such as the activation of oncogenes, the inactivation of tumor-suppressing genes, mutagenesis provoked by external factors, and epigenetic modifications. Surgery, chemotherapy, and radiotherapy have remained the standard treatment approach for several decades. Major challenges remain the recurrence and death due to disease progression.

However, over the last two decays, extensive research has been done on cell DNA sequencing and characterization, which led the world to find mutant genes causing cancer. This molecular profile has become increasingly important in cancer screening, treatment, prognostication, and therapy response prediction. The efficacy of various target therapies showed promising results. Developed countries use molecular biomarkers to treat various individualized, molecular-targeted therapies in routine clinical practice. The importance of molecular profiling and personalized medicine in managing cancer is also recognized in Bangladesh. Yet, genetic testing and targeted therapies must be more available at low cost and within reach of the vast majority of our population.

Introduction

A cell with normal DNA develops into a cancerous cell through the accumulation of genetic changes. Some of these alterations are acquired sporadically, and others are inherited in the form of cancer predisposition genes characterized by uncontrolled cell growth resulting in tumor spread locally or to another organ distally. For cancer development, several genetic activities play roles, such as the activation of oncogenes, the inactivation of tumor-suppressing genes, mutagenesis provoked by external factors, and epigenetic modifications1. For the last several decays, Surgery, chemotherapy, and radiotherapy remain the standard treatment approach for these patients depending on the tumor tissue, site of origin, or stage of the disease. These treatment modalities succeed in reducing cancer mortality rate, disease-free survival, and overall survival. Major challenges remain the recurrence and death due to disease progression.

However, cancer treatment is evolving and experiencing a period of change. Extensive research with the help of advanced technology and modern diagnostic facilities led the world to molecular testing that helps to find mutant genes causing cancerous tumors. It gradually becomes clearer that many common cancers have distinct molecular sub-types and, accordingly, different therapeutic approaches are required for each sub-type.[3,4]

Nowadays, the clinical utility has become important as the number of molecular diagnostic tests has grown substantially over the last decade. These include tests that specifically measure genetic variability (DNA), gene expression profiles (RNA), or protein expression of biological targets, including assays to identify signaling pathways that contribute to the regulation of cell proliferation and apoptosis in cancer. For example, the Tufts Evidence-based Practice Center reported that 50

new genetic assays for cancer-related conditions were introduced into clinical use between 2006 and 2011 for breast, colorectal, lung, prostate, and other cancers, resulting in a total of 112 gene-based tests for solid and hematologic tumors.[2]

Molecular biomarker also becomes increasingly important in risk assessment, disease stage, prognostication, and therapy response prediction, which essentially improves the prognosis and quality of life and reduces the unnecessary toxicities of treatment.5 Developed countries use molecular profiles to treat various individualized, molecular-targeted therapies in routine clinical practice. And the efficacy of various target therapies showed promising results, suggesting that we are approaching an era in which treatment decisions will be based on tumour molecular abnormality profile rather than tumour tissue type or anatomical site of origin.[5-7]

But there are still some challenges. Personalized treatment is not available for all types and subtypes of cancer; some personalized treatments are only available in clinical trials. Genetic testing can be expensive. Also, testing the genes in the tumor takes time-this can mean a long waiting time to get the personalized treatment. Some personalized treatments, such as targeted treatments, can be expensive, and at some point, targeted therapies stop working.[8, 9]

In Bangladesh, the importance of personalized medicine in managing cancer is also recognized. Unfortunately, very limited diagnostic and treatment facilities are available here. The cost still needs to be addressed so those patients can reach the modern standard treatment facilities in the ere of equity.

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Original Article

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Comparative Study Between Short Course of Palliative Radiotherapy and Short Course of Palliative Concurrent Chemo- Radiotherapy in the Treatment of Locally Advanced and Unresectable Head and Neck Cancer

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Abstract

Background: *Palliative radiotherapy provides effective palliation and improves quality of life in advanced incurable head & neck malignancies. It is believed that adding chemotherapy concomitantly with Radiotherapy improves survival and loco-regional tumor control over Radiotherapy alone.* ***Objectives:*** *To compare the tumor response and symptomatic improvement obtained either by short course palliative Radiotherapy or short course of palliative concurrent chemo- Radiotherapy in advanced and unresectable head & neck cancer.* ***Methods:*** *A Quasi-Experimental study was conducted in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka. A total of 60 patients were enrolled according to selection criteria and allocated into two groups- A & B. Arm A (30 patients) was treated with radiotherapy 20 Gy/5# with 4 Gy/ day over 5 consecutive days, and Arm B (30 patient) received 20 Gy/5# with concurrent injection Cisplatin at the dose of 6 mg/m^2/day as I/V bolus. The patients in both arms were assessed at 4 weeks after completion of treatment, followed by every six weekly up to 6 months. Tumor response was observed by RECIST (response evaluation criteria in solid tumor), and toxicities assess by RTOG acute radiation morbidity criteria.* ***Result:*** *Before starting treatment, all symptoms were similar in both groups. Then gradually improvement occurred in both groups. At the 2nd and 3rd follow-up, all symptoms subsided in both groups but were comparatively higher in group-B. At the 4th follow-up, most of the patients in both arms reported symptom improvement. Pain in the throat and/or oral cavity was present in a patient (arm A 16.7% vs. arm B 6.6%), difficulty in deglutition was noticed in 26.7% of patients in group-A, and 13.3% in group B, difficulty in taking food was noticed in 46.7% patients in group-A and 30.0% in group -B. The difference was statistically significant that indicates symptomatic improvement was better in treatment group B.* ***Conclusions:*** *Short course palliative radiotherapy plus chemotherapy results in better symptomatic control over short course palliative radiotherapy alone in locally advanced & unresectable head & neck cancer without any added toxicity.*

Keywords: Locally advanced unresectable head & neck cancer, palliative radiotherapy, palliative concurrent chemo- radiotherapy

Introduction

Head and neck cancers are common in developing countries, especially Southeast Asia.[1] Many patients with Head and Neck squamous cell carcinoma (HNSCC) present with advanced-stage disease. It is, therefore, essential to follow current treatment guidelines for patients with advanced or unresectable diseases to optimize patient outcomes.[2,3] The recommendations for patients with KPS 60 or more include concurrent chemoradiotherapy (cisplatin is preferred) or induction chemotherapy followed by either radiotherapy (RT) alone or concurrent (CCRT). However, if the patient has KPS 3 or more, he/she is not considered for combined modality therapy, and treatment is then individualized. HNSCCs in the developing world differ from those in the Western world in terms of age, site of disease, aetiology, and molecular biology.[4] Loco-regionally advanced unresectable HNSCC carries an unfavourable prognosis; multimodality treatment is required for managing these diseases, and effective treatment options often carry high toxicity and morbidity. It is widely recognized that palliative radiotherapy provides effective palliation and improved quality of life in advanced incurable malignancies, and it also reduces the many organic symptoms. Adding chemotherapy concomitant with radiotherapy is believed to improve survival and locoregional tumour control over radiotherapy alone.[5] It was evident that concurrent chemoradiotherapy improves the symptomatic outcome and survival rate of locally advanced cancer.[3] Therefore, this study aimed to evaluate the tumour response obtained by palliative or concurrent chemoradiotherapy radiotherapy in advanced, unresectable head and neck cancer in our setting.

Material and methods:

A Quasi-Experimental study was conducted in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka. The sample was selected by purposive sampling technique. Newly diagnosed cases of locally advanced head and neck squamous cell cancer who were inoperable (stage- IVA, IVB) with adequate organ functions (bone marrow, kidney, liver) and having Karnofsky performance status d”60 were included in this study. The patients with Nasopharyngeal carcinoma or having multiple synchronous malignancies were excluded from the study. Sixty patients were enrolled according to selection criteria and allocated into two groups- A & B. Arm A (30 patients) was treated with radiotherapy 20 Gy/5# with 4 Gy/day over five consecutive days. Arm B (30 patients) received 20 Gy/5# with the concurrent injection of Cisplatin at 6 mg/m2/day as an I/V bolus for 5 days.

Treatment plan:

All patients were treated with three-dimensional conformal radiotherapy planning, and contouring was done by RTOG guidelines. The position was supine, with a comfortably extended neck and arms by the side of the chest. The Head was customized headrest and immobilized by a thermoplastic mask. The dose of critical structures, especially the spinal cord, thyroid gland, and parotid gland, was kept within the tolerance limit. Dose distribution was verified accordingly. The daily dose of radiotherapy was calculated. During treatment, the total dose to the target area, the total number of fractions, dose per fraction, overall treatment time, and the number of fractions were monitored. Verification of fields and dose distribution were monitored properly before the execution of treatment.

Patient Assessment:

The patients were followed up at 4 weeks after completion of therapy, followed by 6 weekly, up to 6 months. Patients were assessed by history, physical examination and relevant examination. The response rate was assessed according to RECIST criteria. Symptomatic relief was assessed according to the presence or absence of symptoms. Radiotherapy toxicities were assessed according to RTOG guidelines.

Results:

This study showed the maximum incidence in the fifth decade (43.3% In Arm-A and 36.6% In Arm-B). The mean age at diagnosis was 52.57, (SD±6.962) range (40-60) years. In our study, 78.3% were male, and 21.6% were female; the ratio was 3.6:1. In this study, the oral cavity and larynx were the most common sites, where buccal mucosa and supraglottic larynx were the major sub-sites of the disease.

Table-I: *Distribution of patients according to age, KPS, TNM and clinical stage, histo pathological variety and sub-site of disease (n=60)*

Variables	Arm A (n = 30) No. (%)	Arm B (n = 30) No. (%)	*p*-value
Mean age	52.3±11.5	51.7±6.2	
KPS			0.275^{ns}
KPS60	0	0	
KPS50	7 (23.3)	6 (20)	
KPS40	15 (50)	17 (56.7)	
KPS30	8 (26.7)	7 (23.3)	
Site of primary tumors			0.567^{ns}
Oral cavity	10(33.3)	12(40.0)	
Oro-pharynx	6(20.0)	8(26.7)	
Hypo-pharynx	3(10.0)	2(6.7)	
Larynx	11(36.7)	8(26.7)	
Tumor category			0.971 ^{ns}
T1	0	0	
T2	9 (30.0)	7 (23.3)	
T3	16 (53.3)	17 (56.7)	
T4	5 (16.7)	6 (20.0)	
Node category			0.861 ^{ns}
N0	5(16.7)	4(13.3)	
N1	13(43.3)	10(33.3)	
N2	10(33.3)	13(43.3)	
N3	2(6.7)	3(10.0)	
Disease stage			0.502 ^{ns}
Stage IVA	18 (60.0)	16 (53.3)	
Stage IVB	12 (40.0)	14 (46.7)	
Histological differentiations			0.759 ^{ns}
Well	9 (30.0)	10 (33.3)	
Moderate	14 (46.7)	15 (50.0)	
Poor	7 (23.3)	5 (16.7)	

Before starting treatment, all symptoms were almost similar in both groups. Then gradual improvement occurred in both groups; most patients in both arms reported symptom improvement at the fourth follow-up. Pain in the throat and oral cavity was present in a minimal number of patients (Arm A 16.7% vs Arm B 6.6%), difficulty in deglutition was noticed in 26.7% of patients group-A, and 13.3% in group B, difficulty in taking food was noticed in 46.7% patients in group-A and 30.0% in group-B. The difference was statistically significant, which means major symptomatic improvement was better in treatment group B. None of the patients in any group experienced a complete response, and there was no significant difference in treatment response between the two groups in any follow-up. At the second follow-up, the highest number of patients showed partial response (63.3% in Arm A and 73.3% in Arm B). In subsequent follow-ups, the progressive disease gradually increased in both Arms. Although patients of Arm B had experienced slightly higher toxicities than Arm A, there was no statistical significance.

At first follow-up, pain in the throat and oral cavity was subsided in both groups but comparatively better in group B (Arm A 36.7% vs Arm B 26.7%). Difficulty in deglutition, difficulty in taking food and hoarseness of voice were the successive complaints and symptoms relief better in group B, but the difference was statistically non-significant. At the second follow-up, pain in the throat and oral cavity was noticed in 33.0% of patients in group-A and 16.7% in group B. Difficulty in deglutition was noticed in 40.0% of patients in group-A and 26.7% in group B. Difficulty in taking food was noticed in 56.7% of patients in group-A and 43.3% in group B, and hoarseness of voice was in 60.0% of patients in group-A and 46.7% in group B. The difference was statistically significant, with mean major symptomatic improvement associated with treatment group B. At the third follow-up, all symptoms subsided in both groups but were comparatively higher in group B. The difference was statistically significant except for the complaints of difficulty taking food. At the fourth and fifth follow-ups, most of the patients in both Arms reported symptoms of improvement. Pain in the throat and oral cavity was present in a minimal number of patients (Arm A 16.7% vs Arm B 6.6%), difficulty in deglutition was noticed in 26.7% of patients group-A, and 13.3% in group B, Difficulty in taking food was noticed in 46.7% patients in group-A and 30.0% in group-B. The difference in symptomatic improvement was statistically significant ($p<0.05$).

Table-3: *Assessment of major symptomatic improvement/ deterioration at different follow-up time (n=60)*

	Clinical symptoms	Arm A(n = 30)		Arm B(n=30)		*p*-value
		No.	*%*	*No.*	*%*	
Baseline.	Pain in throat and/or oralcavity	13	43.3	12	40.0	0.861ns
	Difficulty in deglutition	18	60.0	15	50.0	0.502ns
	Difficulty in taking food	22	73.3	24	80.0	0.567ns
	Hoarseness of voice	24	80.0	24	80.0	1.000ns
	Pain in throat and/or oralcavity	11	36.7	8	26.7	0.045s
	Difficulty in deglutition	15	50.0	14	46.7	0.952ns
At 1stfollow-up	Difficulty in taking food	20	66.7	20	66.7	1.000ns
	Hoarseness of voice	21	70.0	20	66.7	0.905ns
	Pain in throat and/or oralcavity	10	33.0	5	16.7	0.029s
	Difficulty in deglutition	12	40.0	8	26.7	0.037s
At 2ndfollow-up	Difficulty in taking food	17	56.7	13	43.3	0.025s
	Hoarseness of voice	18	60.0	14	46.7	0.028s
	Pain in throat and/or oralcavity	8	26.7	3	10.0	0.009s
At 3rdfollow-up	Difficulty in deglutition	10	33.3	5	16.7	0.029s
	Difficulty in taking food	15	50.0	13	43.3	0.062ns
	Hoarseness of voice	15	50.0	10	33.3	0.018s
	Pain in throat and/or oralcavity	5	16.7	2	6.6	0.048s
At 4thfollow-up	Difficulty in deglutition	8	26.7	4	13.3	0.013s
	Difficulty in taking food	14	46.7	9	30.0	0.002s
	Hoarseness of voice	7	23.3	5	16.7	0.083ns
	Pain in throat and/or oralcavity	5	16.7	2	6.6	0.048s
At 5thfollow-up	Difficulty in deglutition	8	26.7	4	13.3	0.013s
	Difficulty in taking food	14	46.7	9	30.0	0.002s
	Hoarseness of voice	7	23.3	5	16.7	0.083ns

Table-IV: *Clinical responses of treatment at different follow up for patients both Arm A and Arm B (n=60)*

Follow up(FU)	Response	Arm A (n=30)	Arm B(n=30)	*p*-value
		No. (%)	No. (%)	
1st FU	Partial response (PR)	12 (40.0)	13 (43.3)	0.320ns
	Stable disease	14 (46.7)	14 (46.7)	0.489ns
	Progressive disease (PD)	4 (13.3)	3 (10.0)	0.692ns
2nd FU	Partial response (PR)	19 (63.3)	22 (73.3)	0.409ns
	Stable disease	6 (20.0)	4 (13.3)	0.489ns
	Progressive disease (PD)	5 (16.7)	4 (13.3)	0.714ns
3rd FU	Partial response (PR)	18 (60.0)	21 (70.0)	0.420ns
	Stable disease	6 (20.0)	4 (13.3)	0.489ns
	Progressive disease (PD)	6 (20.0)	5 (16.7)	0.743ns
4th FU	Partial response (PR)	18 (60.0)	21 (70.0)	0.420ns
	Stable disease	6 (20.0)	4 (13.3)	0.489ns
	Progressive disease (PD)	6 (20.0)	5 (16.7)	0.743ns
5th FU	Partial response (PR)	13 (43.3)	19 (63.3)	0.187ns
	Stable disease	6 (20.0)	4 (13.3)	0.524ns
	Progressive disease (PD)	8 (26.7)	7 (23.3)	0.505ns

Table- V: *Assessment of Toxicities (n=60)*

Toxicity	Grade	Arm A (n = 30) No. (%)		Arm B (n=30) No. (%)		Chi- square value	*p*-value
		No.	%	No.	%		
Mucositis	Grade I	5	16.7	6	20.0	2.04	0.360
	Grade II	8	26.7	14	46.7		
	Grade III	2	5.7	8	26.7		
Nausea &	Grade I	13	43.3	15	50	0.07	0.788
vomiting	Grade II	9	30.0	9	30.0		
	Grade III	0	0	0	0		
Skin reaction	Grade I	10	33.3	11	36.7	0.98	0.611
	Grade II	13	45.0	15	50.0		
	Grade III	6	20.0	5	16.7		
Anaemia	Grade I	8	26.7	9	30.0	0.05	0.826
	Grade II	3	10.0	4	13.4		
Neutropenia	Grade I	5	16.7	5	16.7	1.75	0.417
	Grade II	9	30.0	11	36.7		
	Grade III	2	5.7	3	10.0		
Headache		5	16.7	6	20.0		
Loss of taste		11	36.7	14	46.7		
Xerostomia		10	33.3	12	40.0		

Discussion:

HNSCCs in the developing world differ from those in the Western world in terms of age, site of disease, aetiology, and molecular biology.[4] Poverty, illiteracy, lack of access to health care, and poor treatment infrastructure pose a major challenge in managing these cancers as most patients have advanced disease at presentation and are mostly incurable[6]. This study was carried out to evaluate the outcome of palliative radiotherapy and low-dose concurrent chemotherapy, as the literature showed a good quality of life with palliative radiotherapy in advanced head and neck cancer. This study evaluated the response to treatment and symptomatic improvement at different follow-up times. Before starting treatment, all symptoms were almost similar in both groups. Then gradually, improvement happened. Although symptomatic improvement was remarkable in both groups, it was significantly higher in Arm B, irrespective of all the symptoms at different follow-ups. There was no complete response in both arm; the partial response was excellent but non-significant between the two groups, although disease progression was higher in the fourth and fifth follow-ups. The findings of this study were consistent with the results of other studies.

A previous study reported that palliative chemo-radiotherapy improves the symptomatic outcome and survival rate. A Palliative course of treatment generally entails giving a moderate dose of radiotherapy over a short time. Thus providing a relatively high chance of shrinking the tumour and lessening symptoms[7]. Another study in Bangladesh demons-trated that a short-course palliative radiotherapy regimen is an effective treatment modality for sustained symptom relief with a reasonable response rate and acceptable toxicities in locally advanced head-neck cancer[8]. The optimal treatment of LAHNC requires personalized consideration of individual patient factors and multidisciplinary assessment. Palliative therapy is vital to improve the quality of life and reduce the many organic symptoms.

It is believed that IC (Intravenous chemotherapy) as part of ST (Systemic therapy) remains an appropriate therapeutic option for selected patients, including those with significant local symptoms. Adding chemotherapy concomitant with radiotherapy improves survival and locoregional control over radiotherapy alone[9]. Primary combined chemotherapy with cisplatin and radiotherapy is also the standard for patients with locally advanced, unresectable tumours. Adding cisplatin to radiotherapy improves disease control and overall survival in this setting. A meta-analysis including 50 studies showed an absolute benefit of 6.5% overall survival with an HR of 0.81 and p-value p<0.0001 for patients who received combined chemoradiotherapy10. In this study, the efficacy of concurrent cisplatin had also proven beneficial in the palliative setting, which is consistent with Kumar et al.[11].

HNSCCs in the developing world differ from those in the Western world in terms of age, site of disease, aetiology, and molecular biology.[4] Poverty, illiteracy, lack of access to health care, and poor treatment infrastructure pose a major challenge in managing these cancers as most patients have advanced disease at presentation and are mostly incurable.[6] This study was carried out to evaluate the outcome of palliative radiotherapy and low-dose concurrent chemotherapy, as literature showed a good quality of life with palliative radiotherapy in advanced head and neck cancer. This study evaluated the response to treatment and symptomatic improvement at different follow-up times. Before starting treatment, all symptoms were almost similar in both groups. Then gradually, improvement happened. Although symptomatic improvement was remarkable in both groups, it was significantly higher in Arm B, irrespective of all the symptoms at different follow-ups. There was no complete response in both arms; the partial response was good but non-significant between the two groups, although disease progression was higher in the 4th and 5th follow-up. The findings of this study were consistent with the results of other studies.

A previous study reported that palliative chemoradiotherapy improves the symptomatic outcome and survival rate. A Palliative course of treatment generally entails giving a moderate dose of radiotherapy over a short time. Thus providing a relatively high chance of shrinking the tumour and lessening symptoms.[7] Another study in Bangladesh demonstrated that a short-course palliative radiotherapy regimen is an effective treatment modality for sustained symptom relief with a good response rate and acceptable toxicities in locally advanced head-neck cancer.[8] The optimal treatment of LAHNC requires personalized consideration of individual patient factors and multidisciplinary assessment. Palliative therapy is important to improve the quality of life and reduce the many organic symptoms. It is believed that IC (Intravenous chemotherapy) as part of ST (Systemic therapy) remains an appropriate therapeutic option for selected patients, including those with significant local symptoms. The addition of chemotherapy concomitant with radiotherapy improves survival and locoregional control over radiotherapy alone.[9] Primary combined chemotherapy with cisplatin and radiotherapy is also the standard for patients with locally advanced, unresectable tumors. Adding cisplatin to radiotherapy improves disease control and overall survival in this setting. A meta-analysis including 50 studies showed an absolute benefit of 6.5% in overall survival with an HR of 0.81 and p value p<0.0001, for patients who received combined chemoradiotherapy.[10] In this study, the efficacy of concurrent cisplatin had also proven beneficial in the palliative setting, which is consistent with Kumar et al.[11]

In this study, few treatment-related early grade-3 toxicities were observed in both arms, including mucositis, skin reaction and neutropenia. Although those were slightly higher in Arm B, the difference was insignificant. The study of Kumar et al. had a higher incidence of toxicities in the combined modality treatment group[11]. A higher rate of acute toxicity was evident in RTOG 9501 and EORTC trials in patients who got chemoradiotherapy. The only difference was treatment intent, as in those trials, enrollment was done in radical intent.[12, 13]

This was a hospital-based study conducted in the Department of Radiotherapy Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, over a period of

12 month. Some important methodological issues might be raised, including patient selection, follow-up, sample size and the prospective identification of the effectiveness of therapy, all of which may exert a powerful influence on the results. Another major -

radiotherapy plus chemotherapy is better palliative treatment option for palliation of symptoms like pain, dysphagia, stridor, dyspnea without any detrimental effects and may also have slightly better loco-regional tumor control in advanced squamous cell carcinoma of head and neck.

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Original Article

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Risk Factors Association Among the Breast Cancer Patients of Bangladesh

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Abstract

Background*: Breast cancer is currently the most common cancer in women of Bangladesh, and its incidence is on the rise.* ***Aim****: This study aimed to find out the association of various risk factors among breast cancer patients in Bangladesh.* ***Methods and Materials:*** *An observational study was conducted among 433 diagnosed breast cancer patients who attended the National Institute of Cancer Research & Hospital for treatment and follow-up from January 2020- December 2021. The patients were interviewed using a pretested questionnaire regarding various risk factors which are considered to be associated with increased breast cancer risk.* ***Results:*** *The mean age at diagnosis was 43.90 (SD ±10.285) and the range was 22-70 years, 68% of patients were less than 50. The mean body weight was 60.5 Kg (SD ±9.53), and 16% of patients were more than 70 Kg. Patients premenopausal at diagnosis were 62.8%. The mean age of menarche was 12.4 years. The mean age at menopause was 45.25 years. Nulliparous patients were 3%, 48% had 2 or fewer children, and 49% had three or more children. The mean age at first delivery was 21.7 years. History of taking oral contraceptives was present in 74% of patients, Hormone replacement therapy in five patients, and infertility treatment by six patients. 94% patients gave a history of breastfeeding. A family history of breast cancer was present in 11% of patients. Family history of other cancer was present in 9%. Co-morbidities like Diabetic, Hypertension was present in 34.6%.* ***Conclusion:*** *Breast cancer patients in Bangladesh present at a younger age, and obesity is associated with breast cancer. Most women who developed breast cancer had no identifiable risk factor.*

Keywords: *Risk factors, breast cancer, Bangladesh*

Introduction:

Breast cancer is a major public health problem for women throughout the world. Although breast cancer has traditionally been less common in non-industrialized nations, its incidence in this area is increasing.1 Breast cancer has overtaken cervical cancer and is currently the most common cancer in women of Bangladesh. As per Globocan 2020, Breast cancer is the most common malignancy among women, with 19% prevalence in Bangladesh.[2]

As per the hospital-based cancer registry report published by the National Institute of Cancer Research & Hospital, in 2005, Cervical cancer was the top most malignancy in women accounting for 24.1%, followed by breast cancer (24%), whereas in 2015, breast cancer ranked the top most malignancy in women (29.5 %) and cervical cancer became the second (17.4%). [3,4]

The cancer registries of different countries also suggest that age-standardized incidence rates are rising even more rapidly in low-incidence regions such as Africa and Asia. Probably the socio-economic and lifestyle changes (e.g., late child-bearing and dietary changes) and associated changes in menstrual patterns are responsible for the rise in developing countries. At the same time, improved life expectancy will increase the burden of breast cancer in developing countries as more older women are likely to develop breast cancer than younger women.[5,6]

Multiple factors are associated with an increased risk of developing breast cancer. But the majority of these factors convey a small to moderate increase in risk for any individual woman. At least half of the women who develop breast cancer have no identifiable risk factor beyond increasing age and female sex.[7] Age is the strongest risk factor. Other factors are largely grouped into genetic, hormonal and reproductive, dietary, lifestyle and environmental factors. Among these, the high-risk factors are: (1) Early menarche (2) Late menopause (3) Late first full-term pregnancy (4) Nulliparity (5) No breast feeding (6) Family history of breast cancer in two or more first-degree relatives (7) Hereditary breast cancer. The minor risk factors are: (1) Obesity in postmenopausal women (2) Hormone Replacement Therapy (3) Smoking (4) Exposure to low-dose radiation (5) Excessive alcohol intake.[5,6,8]

The present study attempts to find out some of the risk factors of breast cancer among patients attending NICRH.

Materials and Methods

This observational study was conducted at NICRH from January 2019 to December 2021. A total of 433 diagnosed cases of breast cancer patients attending the Tumor board & Radiation Oncology department for treatment and follow-up during this period were included.

Patients with cancer other than breast cancer were excluded from the study.

Data was collected by interviewing the patients using a predesigned and pretested questionnaire, which included preliminary data, reproductive history, family history of breast and other cancer, parity, age at first full-term pregnancy, breastfeeding, menarche, menopause, use of oral contraceptive pills, hormone replacement therapy, infertility treatment. The data were analyzed using SPSS software.

Results

The Mean age at diagnosis of breast cancer was 43.90 (SD 10.285), the median age was 45 years, and age of the patients ranged from 22 to 70 years. 68 % of patients were in the age group <50 years and 33% were <40 years. Patients premenopausal at diagnosis were 62.8 % and 37.2% were post menopausal.

The mean age of menarche was 12.4 years. The mean age at menopause was 45.25 years. In the present study, 28% of patients had attained menopause before the age of 45 years.

The mean age at first delivery was 21.7 years. Nulliparous patients were 3%, 48% of patients had two or fewer children, and 49% had three or more children. Seventy-four percent of patients gave a history of using hormonal contraceptives in either oral or injectable. Five patients took hormone replacement therapy and infertility treatment six patients. History of breastfeeding was given by 94% of patients.

The mean body weight was 60.5 Kg (SD 9.53), and the range was 36-105 Kg. 41% of patients were > 60 Kg, and 16% of patients were >70 Kg weight. Hypertension was found in 10 % of patients and Diabetes Mellitus was present in 13% of patients, 8 % of patients had both hypertension & DM. Patients with no comorbidities were 65.38%.

Eleven percent of patients had family history of breast cancer and 9 % had family history of other cancer like ovary, endometrium, colorectal, prostate.

Table 1: *Distribution of risk factors among patients*

Risk factors	Case (n=433)	
	Number	Percent
Body weight (kg)		
<60	186	43
≥60	247	57
Menarche age (years)		
Don't remember	130	30
≤13	160	37
>13	143	33
Age of Menopause (years) (n=160)		
<45	78	49
≥45	82	51
Parity		
Nulliparous	13	3
<3 Children	209	48
≥3 Children	211	49
Age at first Delivery (years)		
≤21	268	62
>21	165	38
OCP used		
Yes	320	74
No	113	26
History of breast feeding		
Yes	407	94
No	26	6
Family history of cancer		
Family history of breast cancer	48	11
Family history of other cancer	39	9
No family history of cancer	346	80
Comorbidities		
Yes	152	35
No	281	65

Discussion

Multiple factors are associated with an increased risk of developing breast cancer. But the majority of these factors convey a small to moderate increase in risk for any individual women.

In our study, mean age at diagnosis was 43.90 years. 68% of patients were <50 years of age. Other studies reported 33% of women with breast cancer were less than age 50 years at the time of diagnosis.[9,10] Women between the ages of 20 years and 29 years accounted only 0.3% of breast cancer patients.[11]

The mean age of menarche was 12.4 years and the mean age at menopause was 45.25 years. In the present study 28% of patients had attained menopause before the age of 45 years. Studies reported that women who began menstruating at an early age (before age 12) and those who reach menopause after age 55 years had an increased risk of breast cancer.[12,13] In comparison with women who had menarche before the age of 12 years, later age at menarche (at least 14 years) was associated with an approximately 40% reduced risk of breast cancer.[14] The variations observed in different studies could be due to the difference in the socio-demographic, geographical, and lifestyle factors. In a study, 50% subjects had the age at menarche >13 years.[15] Early age at menarche is associated with increased risk of breast cancer and there appears to be a 20% decrease in breast cancer risk for each year if menarche is delayed.[16] A study reported that the risk of cancer did not differ with regard to menopausal status, age at menopause, and ever-use of hormone replacement therapy.[17]

The mean age at first delivery was 21.7 year. Nulliparous patients were 3.3%, 48% patients had 2 or less child and 48% had 3 or more children. Seventy four percent patients gave history of using hormonal contraceptive in the form of either oral or injectable. Hormone replacement therapy was taken by 5 patients and infertility treatment by 6 patients. History of breast feeding was given by 94% of patients.

In the present study, age at first child birth, parity, oral contraceptive uses, hormone replacement therapy and breast feeding did not show any significant association with breast cancer. Many studies have not confirmed an overall excess risk associated with use of oral contraceptives, but a number of studies have suggested that long-term use of oral contraceptives is associated with a higher risk for early onset of cancers, usually those occurring before age 45 years.[18] Gajalakshmi et al. showed duration of breast-feeding was negatively associated with breast cancer risk .[13] There is a decrease of 4.3% in risk for every 12 months of breast-feeding, so

that the protective effect becomes clearly evident only after many years of breast-feeding.[19] Studies reported that the mean age at first delivery was 21 years.[20,21] Women who had their first child after age 30 years or who never had a child were at a slightly higher risk for developing breast cancer. In contrast, there are consistent results that early age at first full-term pregnancy is not a strong protective factor in young women.[22] The result of this study is consistent with the results of many other studies.

Body size influences breast cancer risk differently in premenopausal and postmenopausal women; higher weight is associated with a lower risk of premenopausal breast cancer, whereas risk is reported to increase with BMI in postmenopausal white women. Weight control may reduce the risk among postmenopausal women.[23]

Eleven percent of patients had family history of breast cancer and 9 % had family history of other cancer like ovary, endometrium, colorectal, prostate. A family history of breast cancer has long been recognized as a risk factor for the disease, but only 5% to 10% of women who develop breast cancer have a true hereditary predisposition. Overall, the risk of developing breast cancer is increased 1.5 to 3-fold if a woman has a mother or sister with breast cancer. Family history however, is a heterogeneous risk factor with different implications.[7] Several major studies have conducted more detailed analyses and agreed that about 6% of breast cancer before the age of 55 years is linked to a family history of breast cancer in first-degree relatives.[18,2] We did not find an association of breast cancer with family history. This could be due to a smaller number of patients in our study, and maybe because of increased incidence of this disease in recent years.

Conclusions

The current data support that breast cancer patients of Bangladesh present at a younger age and obesity was associated with breast cancer. Age at menarche and menopause, age at first child birth, parity, breast feeding, oral contraceptive, family history of breast cancer did not show any significant association with breast cancer.

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Original Article

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Expression of *BRCA1* mRNA in FFPE tissue of Bangladeshi Breast Cancer Patients

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Abstract

Background: *In Bangladesh, about one-third (30.4%) of all cancers in females is the breast cancer and it occupies the second position irrespective of gender.* BRCA1 *is one of the most important tumor suppressor genes linked to breast cancer. BRCA1 protein is required for the maintenance of genomic integrity. The aim of this study was to measure the expression of* BRCA1 *mRNA in breast cancer tissue of adult Bangladeshi women.* ***Methods:*** *Total RNA was extracted from the histopathologically diagnosed formalin fixed paraffin embedded (FFPE) breast cancer tissues of 50 adult female patients. Total mRNA was amplified by Real-Time RT-PCR. Cancer related characteristics of the patients were recorded and analyzed using IBM SPSS version 23. The level of* BRCA1 *gene expression was calculated from the quantitative cycle threshold (Ct) value using* $2^{-\Delta\Delta Ct}$ *formula.* GAPDH *was used as a reference gene.* ***Results:*** *RNA extraction was possible from 29 FFPE tissue samples and 17 samples exhibited* GAPDH *gene expression.* BRCA1 *gene was silent or not expressed in 82.35% (14 samples), reduced in two samples and over-expressed in one sample. The mean age (± SD) of the patients was 45.16 (± 9.88) years; the mean BMI (± SD) was 22.90 (± 4.30) kg/m^2. About 46% of the patients were postmenopausal, the mean ages (± SD) of menarche and menopause were 12.96 (± 0.83) and 47.00 (± 5.04) years respectively. All the patients were diagnosed with invasive ductal carcinoma of grade II. About 66% of the breast cancers were immunohistochemically categorized as basal type or triple-negative breast cancer.* ***Conclusion:*** BRCA1 *gene did not express in the most of the invasive ductal breast carcinoma of grade II and in a few cases the gene was expressed in a reduced amount. The overall results indicate poor prognosis of the patients.*

Keywords: Ct value, BRCA1mRNA, formalin fixed paraffin embedded (FFPE) breast cancer tissue

Introduction

BRCA1 is one of the most important tumor suppressor genes linked to breast cancer. BRCA1 protein is required for the maintenance of genomic integrity. It regulates transcription by interacting with several transcription factors, controlling DNA repair, and participating in several signaling pathways involved in transcription and checkpoint control.[1] It is found on the long arm of chromosome 17 (17q21.31), starting at base pair 43,044,295 and ending at base pair 43,125,364.[2] *BRCA1* gene was identified in 1994 by positional cloning; it has 24 exons, 22 of which encode a protein of 220 kDa consisting of 1,863 amino acids.[3] Messenger RNA (mRNA) of this gene expresses at the late G1 or early S phase of the cell cycle before DNA synthesis, and the expression of the BRCA1 protein closely follows that of its mRNA. Deficiency in this gene produces a low expression of *BRCA1* mRNA.

Mutations in *BRCA1* gene are found to be associated with breast cancer and the frequency of these genetic mutations varies among ethnic groups and countries.[4] Methylation in *BRCA1* promoter region, low expression, and copy number deletions also cause a deficiency in BRCA1protein and produce similar phenotypic features of tumors due to *BRCA1* mutations.[5] *BRCA1* mRNA expression level emerged as the strongest predictor of survival and the expression of *BRCA1* genes could contribute to the tumor pathogenesis and therapeutic responses.[6] Research findings revealed that low expression of *BRCA1* is observed in high-risk women with a positive family history of breast cancer.[7] An inverse relationship is present between *BRCA1* DNA-methylation-status and *BRCA1* mRNA-expression.[6] Both in sporadic and hereditary breast cancers, decreased *BRCA1* mRNA expression have been observed.[8] *BRCA1* mRNA is reduced in sporadic breast cancer cells despite a lack of mutations.[9] Epigenetic silencing or genetic alterations/ mutations could be responsible for the low expression of *BRCA1* gene in sporadic breast cancer.[10] Recent studies have shown that *BRCA1*-related breast cancers have clinicopathological features that are usually associated with a poor prognosis, such as high-grade estrogen receptor (ER)-negative and progesterone receptor (PR)-negative status, and over expression of the receptor Her-2/Neu.[3] No significant relationship exists between *BRCA1* mRNA expression and cancer histological type but a significant link is present between *BRCA1* mRNA expression and cancer histological grade of the tumor.[11] According to Ali et al.[10] the rate at which *BRCA1* expression declines is determined by the tumor's grade as they found that the majority of individuals with *BRCA1* mutations (29.28%) had histological grade III. Higher histological grades, larger mitotic counts, poor differentiation, and a high frequency of necrotic regions and pleomorphism are all common features of tumors with *BRCA1* mutations. These features are frequently linked to a poor prognosis.[10] Another reason of poor prognosis is due to the greater occurrence of triple-negative cases among *BRCA1* mutated patients.[12] Studies also found that the expression of *BRCA1* mRNA influences the effectiveness of chemotherapy and helps in the prediction of survival of the patients.[13] Study on *BRCA1* mRNA expression in breast cancer would help researchers in making assumptions on responses to chemotherapeutics and prognosis of the disease. However, people having positive family history of breast cancer can be made alerted earlier in light of these two important issues. Since there remains scarcity of data regarding evaluation of *BRCA1* gene expression with its mRNA, this particular study was carried out to measure the expression of *BRCA1* mRNA in FFPE breast cancer tissue of Bangladeshi female patients with breast cancer.

Materials and Methods

The cross-sectional descriptive study was carried out in the Department of Anatomy, Bangabandhu Sheikh Mujib Medical University (BSMMU) with the collaboration of the Department of Histopathology and the Department of Immunology and Molecular Biology of National Institute of Cancer Research and Hospital (NICRH), Dhaka from March 2021 to February2022. Fifty histopathologically diagnosed FFPE breast cancer tissues were collected from NICRH. The cancer related histories of the patients were recorded using a structured questionnaire.

Isolation of RNA

Total RNA was extracted from four (10-ìm thick) sequential sections of histopathologically diagnosed FFPE breast cancer tissue using commercial RNA extraction kit (QIAGEN, USA). Paraffin from the tissue sections was removed by xylene and ethanol was used to remove xylene. The ethanol free tissue was lysed under denaturing conditions with proteinase K. The lysate was incubated at 56°C for 15 min, then at 80°C for 15 min. The RNA was extracted from the lysate using standard operation procedure (SOP) of the commercial kit. The extracted RNA samples were purified by RNeasy MinElute spin column (QIAGEN, USA). The RNA samples were quantified by a NanoDrop Microvolume Spectrophotometer.

Expression of BRCA1and reference gene (GAPDH) mRNA

Complementary DNA (cDNA) synthesis was done by ProtoScript II cDNA Synthesis kit (New England BioLabs,

USA) following manufacturer's instructions. Random primer was used for cDNA synthesis. Primers and probes for *BRCA1* and *GAPDH* genes were adopted from Egawa et al.[14] The forward primer of *BRCA1* is 5'-ACAGCTGTGTGGTGCTTCTGTG-3', and the reverse primer of *BRCA1* is 5'-CATTGTCCTCTGTCCAGGCATC-3'. *BRCA1* probe labeled with FAM (5' -CATCATTCACCCTTGGCACAGGTGT-3') were used to amplify and detect*BRCA1* mRNA. *GAPDH* primers (forward 5'-TCATTGACCTCAACTACATGGTTT-3', reverse 5'-GAAGATGGTGATGGGATTTC-3') and *GAPDH* probes labeled with VIC [TaqMan] (VIC-CAAGCTTCCCGTTCTCAGCC-TAMRA) were used as internal control for RT-PCR. Template cDNA was amplified using Bio-Rad CFX96 Touch Real-Time PCR (Bio-Rad, USA). Reaction mixture was prepared by adding Hot StarTaq Master Mix (Qiagen, USA), forward primers and reverse primers, probes and nuclease-free water for each *BRCA1* and *GAPDH*. Then cDNA was added to the reaction mixture. After that, amplification was performed in a 96-well optical plate at 95ÚC for 15 min, followed by 45 cycles at 94ÚC for 30 sec, 60ÚC for 30 sec and 72 ÚC for 1 min.

Data analysis

Statistical analysis was done by SPSS, IBM SPSS Statistics, version 23, 2015. In this study, when data was normally distributed mean value was used but when data was not normally distributed median value was used. Differences in cancer-related parameters according to *BRCA1* mRNA expression were evaluated using the Fisher Exact Test for categorical variables and Mann-Whitney U test for numerical variables.

Ethical issues

The research was conducted with the approval from the Institutional Review Board of BSMMU and ethical committee of NICRH. A memorandum of understanding (MOU) was also signed by the concerned persons of the above-mentioned institutions. After receiving informed consent from each patient, clinical information was recorded and FFPE breast cancer tissue was collected from the Department of Histopathology, NICRH. Each participating individual was given a special code number for maintaining confidentiality and protecting anonymity. Participating in this research was entirely voluntary and each of the participants had the right to withdraw their participation at any stage of the research.

Results

Result of expression of BRCA1 mRNA

Among the 29 samples of cDNA, 17 samples exhibited *GAPDH* gene expression. In these 17 samples, *BRCA1* gene was not expressed in 14 samples (82.35%), reduced in two samples but increased in one sample (Ct value 34.73 and $2^{-ÄÄct}$value was 13.102). The expression of *BRCA1* is presented in Table 1 and Figure 1.

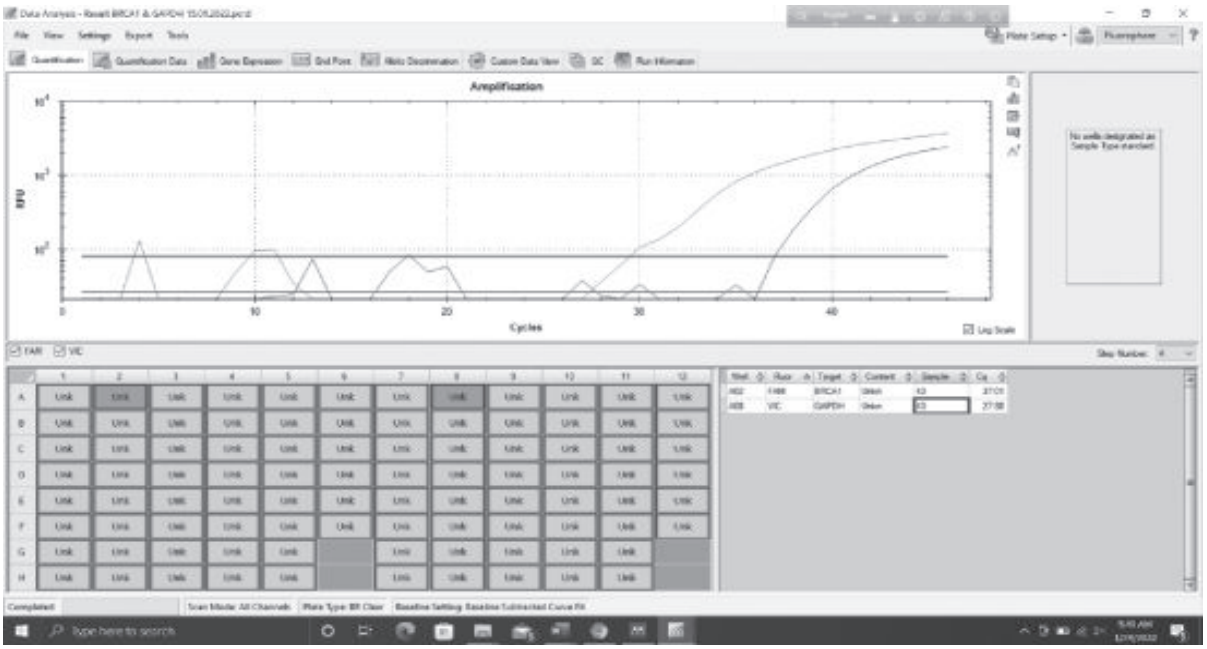

Fig.-1: *Amplification curve of BRCA1 (blue) and GAPDH (green) in log scale.*

Reproductive and cancer related characteristics of the patients

One-fourth of the total participant (breast cancer patients) in this research were 36 to 40 years old. Four patients (8%) aged thirty years or younger and four patients (8%) of above sixty years old. The mean age (± SD) of the breast cancer patients in this study was about 45 (± 9.88) years. Most of the patients (76%) in this study were in normal weight having the BMI in the range of 18.5-25 (kg/m^2). The mean BMI (± SD) was 22.90 (± 4.30) kg/m^2. About 46% of the patients were postmenopausal, the mean ages (± SD) of menarche and menopause were 12.96 (± 0.83) and 47.00 (± 5.04) years, respectively. In our study, 66% of the breast cancers were immunohistochemically categorized as basal type or triple-negative breast cancer (TNBC). About one quarter was Her-2 predominant. Luminal A and luminal B types were reported as six and four percent respectively (Figure2). In this study, all patients were histologically diagnosed with invasive ductal carcinoma and all were in grade II. Lymph node metastasis was found in all the patients but other organ metastasis was present in four (8%) breast cancer patients (Table 2).

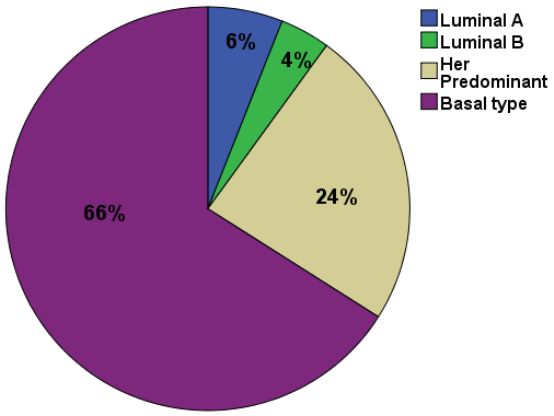

Fig.-2: *Immunohistochemical subtypes of breast cancer.*

Relation of BRCA1 mRNA expression with the cancer related characteristics of the patients

We did not find any statistically significant correlation between hormone receptor sensitivity and *BRCA1* expression (Table 3). No correlation was done with *BRCA1* expression and histological type, grade and lymph node metastasis, since all the breast cancers were histopathologically diagnosed as invasive ductal carcinoma in Grade- II stage and all had metastasis to lymph nodes.

Table 1 *BRCA1* expression status in FFPE breast cancer tissue

Total No of patient(n = 17)	Ct value of *BRCA1*	$2^{-\Delta\Delta Ct}$ value of *BRCA1*
Not expressed (n = 14)	–	–
Expressed (n = 03)		
ID No. 2	42.81	1.285
ID No. 15	40.71	0.059
ID No. 43	34.73	13.102

Table II *Cancer related characteristics of the patients (n = 50)*

Cancer-related characteristic	n (%)
Histopathological type- ductal carcinoma	50 (100)
Histological grade- II	50 (100)
Lymph node metastasis- present	50 (100)
Other organ metastasis	
Present	4 (8)
Absent	46 (92)

n, number; %, percentage

Table 3 *Correlation of BRCA1 expression status with selected reproductive characteristics*

Characteristic	*BRCA1* not expressed (n = 14)	*BRCA1* expressed (n = 3)	P value
Age; median (IQR)	40 (35,45)	35 (30, 55)	0.450 (NS*)
BMI; median (IQR)	23.5 (22.6, 27.1)	24.2 (18.7, 25.0)	0.753 (NS*)
Menopausal Status; n (%)			
Premenopausal	10 (71.4)	2 (66.7)	1.000 (NS*)
Postmenopausal	4 (28.6)	1 (33.3)	
Her-2/Neu; n (%)			
Positive	4 (28.6)	1 (33.3)	1.000 (NS*)
Negative	10 (71.4)	2 (66.7)	
Estrogen receptor; n (%)			
Positive	2 (14.3)	0 (0.0)	1.000 (NS*)
Negative	12 (85.7)	3 (100.0)	
Progesterone receptor; n (%)			
Positive	2 (14.3)	0 (0.0)	1.000 (NS*)
Negative	12 (85.7)	3 (100.0)	

*NS, Nonsignificant

Note: P value d" 0.05 indicates significant, > 0.05 indicates non-significant

P values are measured using Fisher Exact Test for categorical variables or Mann–Whitney U test for median.

Discussion

In this study *BRCA1* gene was silent or not expressed in 14 samples and exhibited reduced expression in two samples. Absent or reduced expression of *BRCA1* in sporadic breast cancer was associated with high grade of tumor, advanced lymph nodes metastasis, larger tumor, vascular invasion by the tumor cells, hormone receptors negative and triple negative status and poor prognosis.[5,15-17] In our study all tumors were in grade II and all patients had lymph nodes metastasis and the most of the cancers were ER- (90%) and PR (92%) negative and 66% were TNBC. These facts may be the cause of absent or not expressed status of *BRCA1* gene in the breast cancer patients of our study. In our research, 17.64% samples expressed *BRCA1* mRNA and in 82.35% samples, the mRNA was absent or not expressed. Finding of *BRCA1* expression status of our study is consistent with the findings of Al-Mulla et al.[18] and Kamal et al.[7] that demonstrated expression of *BRCA1* gene only in six out of 29 (20.69%) and six out of 30 (20%) breast cancer FFPE tissue samples respectively and approximately 80% cases were absent or not expressed *BRCA1* mRNA in those studies.

In our study, all the patients have been diagnosed as cases of invasive ductal carcinoma (IDC) and of grade II. Axillary lymph node metastasis was found in all patients. Axillary lymph nodes involvement has a prognostic value in breast cancer patients. It might be due to all tumors in our study were in advanced stage (IDC, grade II). An Indian study conducted by Chakraborty et al. also found significant association between tumor histology and grade with nodal status.[19] We observed metastasis in other organs in eight percent of patients.

The presence or absence of hormone receptor proteins such as estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (Her-2/Neu) in breast cancer cells plays an important role in breast cancer treatment like hormone therapy and Her-2/Neu targeted therapy as well as prognosis. In our study, the percentage of ER, PR andHer-2/Neu positive patients have been found lower (ER- 10%, PR- 8% andHer-2/Neu- 28%) than the ER, PR andHer-2/Neu negative patients (ER- 90%, PR- 92%, andHer-2/Neu-72%). Jung et al.[20] found Her-2/Neu negative patients more than the Her-2/Neu positive patients that supports

the findings of our study. Soni et al.[21] observed 40.20% ER positive, 40.40% PR positive and 21.80% Her-2/Neu over expression in breast cancers in India, our finding is not consistent with the finding of these researches. We did not find any statistically significant association between cancer-related characteristics with ER and PR status.

In our study, 66% of the breast cancers were categorized as basal type or triple-negative breast cancer (TNBC) on immunohistochemical basis. Carey et al. [22] observed 32% basal type breast cancer patients tested immunohistochemically for hormone receptors. Iqbal and Buch[23] found about 10-20% of breast cancers were TNBC. We found more TNBC patients than the findings of these studies. TNBC is a subtype of epithelial breast tumors that lacks over expression of Her-2/Neu and is immunohistochemically negative for the estrogen receptor and the progesterone receptor.[23,24] TNBC is an aggressive group of breast cancer subtypes despite having a good initial response to chemotherapy. Chemotherapy is the widely used strategic approach for both early-stage as well as advanced-stage of disease in treating TNBC patients.[25]

BRCA1 mRNA expression were correlated with cancer-related characteristics. We did not find any statistically significant association between *BRCA1* mRNA expression and hormone receptor sensitivity might be due to small sample size whereas in XU et al.[13] found low expression of *BRCA1* in ER and PR negative and HER2-positive patients in a prospective cohort study for eight years with large sample size (674 patients).

During FFPE tissue block preparation, the tissue is treated with formalin, xylene, paraffin and different concentrations of alcohol. It is also exposed to heat (~56ÚC melted paraffin). This process can cause fragmentation of RNA and deteriorate the quality of RNA. Another very crucial factor is time for maintenance of quality of RNA. When tissue is left in formalin in room temperature for several days the quality of RNA may be deteriorated. In our study, retrospective FFPE breast cancer tissue was used for assessing the expression of *BRCA1* in the cancer tissue. These tissues were exposed to the above-mentioned factors. For this reason, extraction of good quality RNA was not possible for evaluation of *BRCA1* expression in the later period. However, FFPE tissue is a good source for observation of nuclear and cellular events of the cancer cells. This picture cannot be seen from blood. Good quantity (concentration) and quality (purity) of extracted RNA are prerequisites for ensuring optimum reaction conditions for Real Time RT-PCR. For reliable results concentration has been expected to be 10 ng /µl (QIAGEN 2013). In our study, variation in RNA concentration was evident in different samples. We found less amount of RNA in many samples due to the selection of core biopsy FFPE tissue block, as the samples were collected before chemotherapy or radiotherapy. Mastectomy or lumpectomy is usually done after histopathological diagnosis of type, grade, hormone receptor sensitivity and neoadjuvant chemo or radiotherapy. In core biopsy, the amount of breast tissue is minimum. For that reason, collection of required quantity of RNA was not possible from 20 samples. Many of the researchers working with FFPE tissue had the similar experience; Al-Mulla *et al.*[18] analyzed 29 samples out of 48 that had yielded optimum quantity of tissue for successful RNA extraction and Real Time RT-PCR amplification. Kamal et al.[7] could collect only 30 tissue samples among 60 samples of breast cancer tissue. Margeli et al.[26] got 41 samples out of 80 tissue blocks appropriate for *BRCA1* assessment. Our finding is consistent with the findings of these researches.

Conclusions: Expression of *BRCA1* mRNA varies among ethnic groups and countries. Its expression depends on histological types, grades and hormone receptors sensitivity status of breast cancer. *BRCA1*mRNA expression level also predicts patient's survival. Most of the Bangladeshi breast cancer patients did not express *BRCA1* gene in the cancer tissue and in the few cases the gene was expressed in reduced amount. All cancers were invasive ductal carcinoma of grade II and majority of them were triple-negative breast cancer. The overall results indicate poor prognosis of the patients.

Statement conflict of Interest: The authors declare no conflict of interest

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Original Article

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Childhood Malignancy in Bangladesh: Twelve Years Journey of a Tertiary Care Specialized Cancer Hospital

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Abstract:

Background: *Childhood cancer is a major concern for the affected families throughout the world. Many times, at national and international level such cancer remained neglected. Burden of childhood cancer in low- and middle-income countries (LMICs) including Bangladesh is largely known. This observational study was done to assess the burden and pattern of childhood cancer at Paediatric Haematology and Oncology (PHO) department of National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh from January 2008 to December 2019.* ***Methods:*** *Retrospective review of medical records was done. The study period was divided into two parts: first six years (2008 - 2013) and second six years (2014 - 2019). Cancer cases were classified into 12 major groups according to International Classification of Childhood Cancer (ICCC-3) and a proportion of cases without any specific diagnoses were included into other 3 groups.* ***Results:*** *A total of 4458 paediatric cancer patients who attended the outpatient department of PHO were included in the study. Numbers of cases were much higher in second part of the study period than first part (3108 vs.1350). Mean age were 8.24 years (SD ±5.05 yrs.). Most of the children were from <6 years age group (38%). Male children were predominant (62.5%). Top seven malignancies were: malignant bone tumours (20.6%), retinoblastoma (14.5%), lymphomas and reticuloendothelial neoplasms (12.2%), CNS and miscellaneous intracranial and intraspinal neoplasms (9.4%), soft tissue and other extraosseous sarcomas (9.0%), renal tumours (6.0%) and leukaemia, myeloproliferative diseases, and myelodysplastic disease (5.9%)* ***Conclusion:*** *Considering the esteemed prevalence of childhood malignancy among Bangladeshi children it is clear that a remarkable portion of cases remain unnoticed and undiagnosed in the country though hospital attendance is increasing day by day.*

Key Word*: Childhood malignancy, Retinoblastoma, Malignant Bone Tumour, Bangladesh*

Introduction:

Majority of the childhood cancers are curable. However, the childhood cancer burden in low-and middle-income countries (LMICs), including Bangladesh, is poorly known, where a population-based cancer registry is almost non-existent. It is estimated worldwide, per year, there are at least 2,15,000 new childhood cancer cases occur in children aged 0–14 years and 85,000 cases in the age range 15–19 years.[1] Another study showed the calculated overall incidence rates for the age group 0–14 years were 140·6/million person-years, 155·8/million person-years in the 0–19 years age group, and 185·3/million person-years in the 15–19 years age group.[2] These figures may be an underrepresentation of the real burden of childhood cancer because of a paucity of reliable cancer registries in many LMICs. In LMICs, childhood cancer cases many times remain neglected.[3]

The National Institute of Cancer Research and Hospital (NICRH) is the only specialized cancer hospital in the government sector in Bangladesh. It has 23 departments, including Paediatric Haematology and Oncology (PHO). PHO started its journey as an individual department in 2008. Suspected or confirmed cases of malignancies of all ages are referred here from every part of the country. At first, patients attend the outpatient department, where diagnosis is confirmed by physical examination and essential investigation then multidisciplinary tumour board decides the management.

Childhood cancer represents a small proportion of all cancers. For this reason, data on childhood cancer incidence, even in the presence of population-based cancer registries, is often neglected. So, a hospital-based cancer registry can provide some idea about the burden of childhood cancer in many countries.

Treatment modalities and intensity vary according to the type of malignancy. Compilation of data on patient demographics and malignancy patterns helps to know which types of cancer are more common in an individual centre. Without evaluating the malignancy pattern in the centre dealing with, appropriate infrastructure development is difficult. Which malignancies should be treated in a particular centre mainly depends on the available standard and affordable treatment modalities and the possible supportive care in that centre. Many childhood cancers are curable if proper infrastructure and a trained workforce are available. Actual data about the burden and pattern of cancer attending a particular hospital is essential to develop cancer care facilities. The current study aimed to extract such data from childhood cancer patients who attended the PHO department of NICRH.

Material and Methods:

This was an observational study. A retrospective review of medical records of childhood cancer patients who attended the PHO department of NICRH was done. The study period was from January 2008 to December 2019, which was divided into two parts: the first six years (from 2008 to 2013) and the second six years (from 2014 to 2019). Cancer cases were classified into 12 major groups (I-Leukaemia, myeloproliferative diseases, and myelodysplastic diseases, II-Lymphomas and reticuloendothelial neoplasms, III-CNS and miscellaneous intracranial and intraspinal neoplasms, IV-Neuroblastoma and other peripheral nervous cell tumours, V-Retinoblastoma, VI-Renal tumours, VII-Hepatic tumours, VIII-Malignant bone tumours, IX-Soft tissue, and other extraosseous sarcomas, X-Germ cell tumours, trophoblastic tumours, and neoplasms of gonads, XI- Other malignant epithelial neoplasms and malignant melanoma, XII- Other and unspecified malignant neoplasms) according to International Classification of Childhood Cancer (ICCC-3)4 and a proportion of the cases that had no specific diagnoses, were included into other three groups: 1-small round cell tumour, 2-other than malignancy and 3-not confirmed cases.

Children under 18 years of age and both genders were included in the study. All patients were divided into three groups according to age. Group one is less than six years of age, group two is 6-12, and group three is more than 12. This protocol was approved by the ethical review committee (ERC) of NICRH. As this study was based on medical records, the informed consent issue was waived by the ERC of NICRH. Data were processed and analysed by SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) software.

Result:

A total of 4458 paediatric patients attended the outpatient department of PHO and were included in the study. Mean age were 8.24 (SD ±5.05) years. Most of the children were in age group less than six years 38% (n=1693), followed by 35.5% (n=1584) in >6-12 years age group and 26.5% (n=1181) in >12-18 years age group.

There was male predominance with 62.5% representation (n=2787). The top seven malignancies were: malignant bone tumours (MBT) (ICCC VIII) 20.6% (n=918), retinoblastoma (RB) (ICCC V) 14.5% (648/4458), lymphomas and reticuloendothelial neoplasms (ICCC II) 12.2% (n=544), CNS and miscellaneous intracranial and intraspinal neoplasms (ICCC III) 9.4% (n=421), soft tissue and other extraosseous sarcomas (ICCC IX) 402 (9.0%), renal tumours (ICCC VI) 6.0% (n=266) and leukaemia, myeloproliferative diseases, and myelodysplastic diseases (ICCC I) 5.9% (n=261) (Table I) .

Other malignancies included epithelial neoplasms and malignant melanomas (ICCC XI) (246, 5.5%), germ cell tumours, trophoblastic tumours, and neoplasms of gonads (ICCC X) (243, 5.5%), neuroblastoma and other peripheral nerve cell tumours (ICCC IV) (131, 2.9%), hepatic tumours (ICCC VII) (50, 1.1%), other and unspecified malignant neoplasms (ICCC XII) (20, 0.4%). The number of 'not confirmed' cases was 168 (3.8%), 'small round cell tumour' was 75 (1.7%) and 'other than malignancy' cases was 65 (1.5%) (Table I).

Just over 30% (n=1350) of the total patients reported during first part of the study period (2008-2013) whereas, a dramatic increase was observed during second part of the study period which is around 70% (n=3108) (Table I).

During first half of the study period common seven malignancies were: MBT 22.89% (n=309), RB 22.6% (n=306), lymphomas and reticuloendothelial neoplasms 13.19% (n=178), soft tissue and other extraosseous sarcomas 9.93% (n=134), renal tumours 5.48% (n=74), germ cell tumour 4.96% (n=67) and CNS tumour 4.67% (n=63) (Table II).

Table I: D*istribution of paediatric patients by types of malignancy*

Type of Malignancy	Male n (%)	Female n (%)	Total n (%)
Malignant bone tumours (ICCC VIII)	555 (19.9)	363 (21.7)	918 (20.6)
Retinoblastoma (ICCC V)	395 (14.2)	253 (15.1)	648 (14.5)
Lymphomas and reticuloendothelial neoplasms (ICCC II)	409 (14.7)	135 (8.1)	544 (12.2)
CNS and miscellaneous intracranial and intraspinal neoplasms (ICCC III).	278 (10.0)	143 (8.6)	421 (9.4)
Soft tissue and other extraosseous sarcomas (ICCC IX.)	241 (8.6)	161 (9.6)	402 (9.0)
Renal tumours (ICCC VI.)	159 (5.7)	107 (6.4)	266 (6.0)
Leukaemia, myeloproliferative diseases, and myelodysplastic diseases (ICCC I)	174 (6.2)	87 (5.2)	261 (5.9)
Other malignant epithelial neoplasms and malignant melanomas (ICCC XI.)	172 (6.2)	74 (4.4)	246 (5.5)
Germ cell tumours, trophoblastic tumours, and neoplasms of gonads (ICCC X)	99 (3.6)	144 (8.6)	243 (5.5)
Not confirm	100 (3.6)	68 (4.1)	168 (3.8)
Neuroblastoma and other peripheral nervous cell tumours (ICCC IV)	72 (2.6)	59 (3.5)	131 (2.9)
Small Round Cell tumour	40 (1.4)	35 (2.1)	75 (1.7)
Other than malignancy	42 (1.5)	23 (1.4)	65 (1.5)
Hepatic tumours (ICCC VII)	39 (1.4)	11 (0.7)	50 (1.1)
Other and unspecified malignant neoplasms (ICCC XI1)	12 (0.4)	08 (0.5)	20 (0.4)
Total	2787 (100.0)	1671 (100.0)	4458(100)

Table II: *Distribution of paediatric patients by years span*

	Year: 2008-2013				Year: 2014-2019		
Type of malignancy	Male n (%)	Female n (%)	Total n (%)	Type of malignancy	Male n (%)	Female n (%)	Total n (%)
MBT (ICCC VIII)	183 (21.1)	126 (25.9)	309 (22.8)	MBT	372 (19.3)	237 (19.9)	609 (19.6)
RB (ICCC V)	190 (21.9)	116 (23.9)	306 (22.6)	Lymphoma group	269 (13.9)	97 (8.1)	366 (11.8)
Lymphomas group (ICCC II)	140 (16.1)	38 (7.8)	178 (13.1)	CCNST	237 (12.3)	121 (10.2)	358 (11.5)
STS (ICCC IX)	84 (9.7)	50(10.3)	134 (9.9)	RB	205 (10.6)	137 (11.5)	342 (11.0)
Renal tumours. (ICCC VI)	53 (6.1)	21 (4.3)	74 (5.4)	STS	157 (8.1)	111 (9.3)	268 (8.6)
GCT (ICCC X)	29 (3.3)	38 (7.8)	67 (4.9)	Leukaemia group	163 (8.4)	82 (6.9)	245 (7.9)
CCNST (ICCC III).	41 (4.7)	22(4.5)	63 (4.6)	Renal Tumour	106 (5.5)	86 (7.2)	192 (6.1)
Other malignant epithelial neoplasms and malignant melanomas. (ICCC XI)	53 (6.1)	15 (3.0)	68 (5.0)	Other malignant epithelial neoplasms and malignant melanomas. (ICCC XI)	119 (6.1)	59 (4.9)	178 (5.7)
Neuroblastoma and other peripheral nervous cell tumours (ICCC VII)	22 (2.5)	17 (3.5)	39 (2.8)	GCT	70 (3.6)	106 (8.9)	176 (5.6)
Not confirmed	24 (2.7)	19 (3.9)	43 (3.1)	Not confirmed	76 (3.9)	49 (4.1)	125 (4.0)
Hepatic tumours (ICCC VII)	13 (1.5)	4(.8)	17 (1.2)	Neuroblastoma group	50 (2.6)	42 (3.5)	92 (3.0)
Leukaemia group (ICCC I)	11 (1.2)	5 (1.0)	16 (1.1)	Small Round Cell tumour	31 (1.6)	30 (2.5)	61 (1.9)
Small Round Cell tumour	9 (1.0)	5 (1.0)	14 (1.0)	Other than malignancy	35 (1.8)	17 (1.4)	52 (1.6)
Other than malignancy	7 (.8)	6 (1.2)	13 (.9)	Hepatic tumours	26 (1.3)	7 (0.6)	33 (1.0)
Other and unspecified malignant neoplasm (ICCC XI1)	6 (0.6)	3(.6)	9 (0.6)	Other and unspecified malignant neoplasm	6 (0.3)	5 (0.4)	11 (0.6)
Total	865(100)	485(100)	1385(100)	Total	1922 (100)	1186(100)	3108(100)

During second half of the study period (2014-2019) common seven malignancies were: MBT 19.59% (n=609), lymphomas and reticuloendothelial neoplasms 11.78% (n=366), CNS and miscellaneous intracranial and intraspinal neoplasms 11.52% (n=358), RB 11.00% (n=342), soft tissue and other extraosseous sarcomas 8.62% (n=268), leukaemia, myeloproliferative diseases, and myelodysplastic diseases 7.88% (n=245) and renal tumour 6.18% (n=192). (Table II).

In case of MBT the most common was Ewing sarcoma (ES) (n=402) and most common age group was >6-12 years of age. Second most common MBT was osteosarcoma (OS) (n=400) and most common age group in OS was above 12 years. Analysis of RB cases showed majority were unilateral (n=544) and most of the patients were from below 6 years of age group (n=582). In CNS and miscellaneous intracranial and intraspinal neoplasms group, the common sub-types were astrocytoma (n=95),

medulloblastoma (n=93), ependymoma (n=92) and brain stem glioma (n=30). Most common age group in CNS tumour was >6 - 12 years of age (Table III). In case of renal tumour, the most common tumour was nephroblastoma (n=252) and most common age group was less than 6 years of age. Non-Hodgkin Lymphoma (NHL) (n=294) was more common than Hodgkin Lymphoma (HL) (n=204). Most common age group in lymphoma patients was >6-12 years of age (Table III). In leukaemia, myeloproliferative diseases, and myelodysplastic diseases group the most common was Acute lymphocytic leukaemia (ALL) (n=221) (Table III).

In less than 6 years of age group the top seven malignancies according to frequency were RB (n=582), renal tumour (n=196), soft tissue sarcoma (n=160), lymphoma group (n=129), leukaemia group (n=115), MBT (n=99) and CNS tumour (n=98) respectively. In >6 to 12 years of age group the top seven malignancies according to frequency were MBT (n=360), lymphoma group (n=277), CNS tumour (n=219), soft tissue sarcoma (n=127), leukaemia group (n=108), RB (n=61), renal tumour (n=58). In above 12 years of age group the top seven malignancies according to frequency were: MBT (n=459), lymphoma group (n=138), soft tissue sarcoma (n=115), CNS tumour (n=104), leukaemia group (n=38), renal tumour (n=12), RB (n=5) (Table III).

Table III : *Distribution of Top seven malignant tumours (2008-2019)*

Malignancy		Age groups			Total
		<6 yrs. n (%)	6-12 yrs n (%)	>12yrs n (%)	
MBT (ICCC VIII)	ES	58(58.59)	186(51.67)	158(34.42)	402(43.79)
	OS	15(15.15)	139(38.61)	246(53.59)	400(43.57)
	PNET	23(23.23)	27(7.50)	37(8.06)	87(9.48)
	Others	3(3.03)	8(2.22)	18(3.92)	29(3.16)
	Total	*99(100.00)*	*360(100.00)*	*459(100.00)*	*918(100.00)*
RB (ICCC V)	Unilateral	486(83.51)	55(90.16)	4(80.00)	545(84.10)
	Bilateral	96(16.49)	6(9.87)	1(20.00)	103(15.90)
	Total	582(100.00)	61(100.00)	5(100.00)	648(100.00)
Lymphomas group	NHL	68(52.71)	144(51.99)	82(59.42)	294(54.04)
(ICCC II)	HL	33(25.58)	118(42.60)	53((38.41)	204(37.50)
	Others	28(21.71)	15(5.42)	3(2.17)	46(8.46)
	Total	*129(100.00)*	*277(100.00)*	*138(100.00)*	*544(100.00)*
CCNST (ICCC III)	Astrocytoma	14(14.29)	51(23.29)	30(28.85)	95(22.85)
	Medulloblastoma	31(31.63)	52(23.74)	10(9.62)	93(22.09)
	Ependymoma	23(23.47)	48(21.92)	21(20.19)	92(21.85)
	Brain stem glioma	9(9.18)	17(7.76)	4(3.85)	30(7.13)
	Others	21(21.43)	51(23.29)	39(37.50)	111(26.37)
	Total	*98(100.00)*	*219(100.00)*	*104(100.00)*	*421(100.00)*
STS (ICCC IX)	RMS	127(79.38)	74(58.27)	33(28.70)	234(58.21)
	Fibrosarcoma	11(6.88)	16(12.60)	11(9.57)	38(9.45)
	Synovial sarcoma	4(2.50)	15(11.81)	32(27.83)	51(12.69)
	Others	18(11.25)	22(17.32)	39(33.91)	79(19.65)
	Total	*160(100.00)*	*127(100.00)*	*115(100.00)*	*402(100.00)*
Renal tumours(ICCC VI)	Nephroblastoma	192(97.96)	54(93.10)	9(75.00)	255(95.86)
	Renal Ca.	1(.51)	3(5.17)	3(25.00)	7(2.63)
	Others	3(1.53)	1(1.72)	0	4(1.50)
	Total	*196(100.00)*	*58(100.00)*	*12(100.00)*	*266(100.00)*
Leukaemia group (ICCC I)	ALL	102(88.70)	89(82.41)	30(78.95)	221(84.67)
	AML	12(10.43)	12(11.11)	4(10.37)	28(10.73)
	Others	1(.87)	7(6.48)	4(10.51)	12(4.60)
	Total	*115(100.00)*	*108(100.00)*	*38(100.00)*	*261(100.00)*

Discussion:

The cure rate of childhood cancer in high-income countries (HICs) is above 80%, but the rates in LMICs remain remarkably lower.5 More than 80% of young people live in LMICs, but the survival rate of children with cancer is not yet significant.6 To improve survival rates for the children who live in LMICs to 60% by 2030, World Health Organization (WHO) has set a goal and announced a new effort – the WHO Global Initiative for Childhood Cancer (GICC) in September 2018.7 The GICC has identified six common index cancers—acute lymphoblastic leukaemia (ALL), Burkitt lymphoma (BL), Hodgkin lymphoma (HL), Retinoblastoma (RB) and Wilms tumour. ALL is the most common childhood malignancy, followed by Childhood Central Nervous System tumours (CCNST) and Lymphoma. However, in the case of hospital-based data, this pattern is not observed most of the time.

Childhood cancer is broadly divided into two categories haematological malignancies and solid tumours. Radiotherapy and Onco-surgery play an important role in solid tumour management. As NICRH is equipped with surgical oncology and radiotherapy facilities, paediatric solid tumour comprises the main bulk of childhood cancer here.

In our study MBT was 20.6% of total malignancy and ES and OS were most common. In case of ES common age group was 6-12 years and in case of OS it was above 12 years of age. MBT comprises 3-5% of total childhood malignancies.[8] In United States MBT constitutes approximately 6% of all new childhood malignancies and the male to female ratio was not much differ among younger children, but males had higher during adolescence period.[9] In our study ES and OS constituted 43.8% and 43.6% respectively. Studies showed OS were more than ES like OS (51%), ES (41%)[10] and OS (54.1%) and ES (30.8%).[11]

RB originating from retinal cells is the commonest intraocular malignancy in children. In the US 6.1% of paediatric malignancies was RB in children under the age of 5 years of age.[12] RB is around 4% of all childhood cancer[13] and worldwide yearly around 8,000 children develop RB.[14] Occurrence of RB is 1/16,000–18,000 live births in global population.[15] Depending on this incidence rate it can be estimated that every year around 450-500 new cases of RB occur in Bangladesh. But during the twelve years study period we found that only 648 cases of RB attended in NICRH which is one of the important tertiary care cancer hospital. So, we can understand a remarkable portion of RB patients remain undiagnosed and under-reported in the country. In our study RB comprises 14.5% of total malignancy which is second most common solid malignancy. RB is second most common childhood solid tumour after brain/ nervous system tumour in United Kingdom.[16] Yearly 250 to 300 cases of RB are diagnosed in USA.[13]

We found unilateral RB cases 83.95% (544/648) and bilateral RB 16.05% (104/648). A study in South Africa showed 82% unilateral RB and 18% bilateral RB.[17] Another study at the University of the Philippines–Philippine General Hospital (UP-PGH) showed 62.5% unilateral and 37.5% bilateral cases.[18] Another finding in that study was that among the bilateral cases, 56.1% consulted for unilateral signs/symptoms but on examination finding were bilateral disease. One patient was initially diagnosed to have unilateral disease but developed tumour in the opposite eye after 4 months of monitoring.[18] Our study showed male predominance. The USA study had found a mild female predominance but difference was not significant.[13] Mild male predominance was found in the study in Mexico.[19] Study in China showed the mean age of RB patients was 2.8±1.8 years.[20] In our study most of the patients of RB were in below 6 years of age group, even one case was 45 days old.

According to ICCC3 Lymphoma and reticuloendothelial neoplasms category of childhood malignancy include Hodgkin lymphomas II (a), Non Hodgkin lymphomas (except Burkitt lymphoma) II (b), Burkitt lymphoma II (c), miscellaneous lymphoreticular neoplasms II (d) and unspecified lymphomas II (e).

Lymphomas are third most common childhood malignancy after acute leukaemia and CNS tumour, and constitute about 12% of all malignancies in paediatric patients.[21] In our study lymphoma was the third most common malignancy and 12.2% of total childhood malignancies. Most common lymphoma was NHL (except Burkitt lymphoma) 54.04% and then HL 37.50% In one study among all cases of lymphoma 58% were NHL and 42% were HL.[22] NHL accounts for approximately 7% of cancers in children and adolescents in USA.[23] In our study NHL was 6.59% of total malignancies and around half (144/294) were among 6-

12 years age group. HL accounts for 5-6% of childhood cancers.[24] In NICRH during the study period HL was 4.58% of total malignancies.

One study of BFM group reported a male to female ratio of NHL was 2.7:1[25] and other study showed 2.4:1[26]; that are similar to the value in our study 2.5:1 (male-71.77%, female -28.23%). In our study in case of HL 82.35% males and 17.65 % females with male to female ratio of 4.5:1. Study in Egypt showed male to female ratio in HL was 1.7:1 which included 62.71% males and 37.29% females.[24]

Childhood Central Nervous System Tumours (CCNST) includes several histological subtypes. It is around 25% of childhood tumours in children between 0–14 years of age group and 9% in15–24 years of age group.[27] It is the most common solid tumour in children and 2nd most common childhood malignancy.[28] In our study CCNST is the 4th most common tumour and 9.4% of total malignancy. Study in Canada showed males predominance which was 56.8% and the main histological types were low-grade (I/II) astrocytoma's (26.4%), medulloblastoma (10.6%), anaplastic astrocytoma/glioblastoma multiforme (7.1%) and ependymoma (7.0%).[29] In NICRH during the study period 71% patients of CCNST were male and main sub types were astrocytoma (22.57%), medulloblastoma (22.09%), ependymoma (21.85%) and brain stem glioma 7.1%. Prevalence of CCNST increased in our institute during the last six years; 63/421 cases during 2008-2013 and 358/421 cases during 2014-2019. This sharp rise might be attributable to the communication factor with the paediatric neurosurgeons. But if we consider the worldwide incidence rate of CCNST yet we found many CCNST were unnoticed in our country.

Soft tissue sarcomas (STS) form a set of heterogeneous neoplasms originating from mesenchymal cells. They comprising 5.8% of childhood cancers.[30] Rhabdomyosarcoma (RMS) is the most common STS in children, accounting for more than 50% of cases.[31] In NICRH during the study period STS were 9% of total malignancy and most common were RMS 55.97%.

Malignant renal tumour comprises 7% of childhood cancer.[32] In case of renal tumour 95% are nephroblastoma.[33] In our study renal tumours were 6% of total malignancies and the most common type was nephroblastoma (94.74%) and around 72% occurred in less than 6 years age group.

Worldwide, leukaemia is the most common childhood malignancy, and it is about 30% of total childhood cancer[34], but in our study, it was only 5.9% of total malignancies. The reason is that in our country, childhood haematological malignancies, mainly leukaemia are treated at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Among leukaemia, the most common were ALL (84.67%), and then AML (10.73%), and the common age group in the case of leukaemia were less than six years of age, followed by 6-12 years of age.

Malignant germ cell tumours (GCTs) are a rare and heterogeneous group of tumours that account for 3% of paediatric cancers.[35] In a study female was predominate with a male: female ratio of 0.8:1.[35] In NICRH GCT were 5.5% of total malignancies with female predominance (59.26%). The most common GCTs at NICRH during the study period were yolk sac tumour 1.5% dysgerminoma 1.1% and immature teratoma 7%. Among GCT, 0.3% cases were diagnosed as intracranial and intraspinal germ cell tumours in our study.

Neuroblastic tumours arise from cells of the peripheral sympathetic nervous system and show a varied biological and clinical behaviour ranging from spontaneous regression to progression, and they may either respond to treatment or become resistant to it. Neuroblastoma accounts for 8–10% of childhood cancer.[36] But, in our study, it was only 2.9%.

Olfactory neuroblastoma (ONB), originating from olfactory neuroepithelium of the sinonasal region and it is a rare and aggressive tumour. In our institute during the study period 12 cases of ONB were attended the OPD.

Hepatic malignancy comprises approximately 1% of all childhood malignancies.[37] Hepatoblastoma (HB) is the most common hepatic malignancy in paediatric age. In the United States, 80% of children had HB who were registered with malignant liver tumours in 2000.[38] In our study, hepatic malignancy was 1.1% of total malignancies, and the most common was hepatoblastoma (86%). Colorectal Carcinoma (CRC) is rare in children and comprises approximately 1% of childhood malignancies.[39] During the study period in our institute, CRCs were 1.4% of total malignancies. Another uncommon childhood malignancy is nasopharyngeal carcinoma (NPC). In our study, it was

77, 1.7% of total malignancies. Some rare childhood malignancies cases were also attended OPD of PHO of NICRH.

Conclusion:

This hospital-based study provides a picture of the increasing burden of childhood cancer at NICRH, which warrants the development of infrastructure & ensuring logistical support so that services can be catered according to the main bulk of malignancy profile. Considering the prevalence of childhood malignancy among our paediatric population, it is clear that a remarkable portion of cases remains undiagnosed and unnoticed. Awareness development among health professionals and general people about childhood cancer is essential to improving the situation.

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Original Article

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Diagnosis of Epithelial Ovarian Carcinoma Prior to Neoadjuvant Chemotherapy: The Role of Cytology

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Abstract

Preoperative histologic diagnosis of pelvic mass is mandatory for proper management of patients who are selected for neoadjuvant chemotherapy (NACT) and interval debulking surgery. The aim of this study was to evaluate diagnostic accuracy of image guided fine needle aspiration cytology (FNAC) in the pretreatment diagnosis of the ovarian cancer. This cross-sectional observational study was conducted from August 2020 to July 2021 on 34 ovarian cancer patients at department of Gynaecological Oncology of National Institute of Cancer Research and Hospital (NICRH), Dhaka. The mean age of the respondents was 46.92 (±10.92) years. Most of the participants were married (95.7%), literate (86.9%) and housewives (80%). Majority of the them were from rural areas (58%) and belonged to lower middle-class family (73.9%). Sample adequacy of FNAC was 94.1%. The sensitivity, the specificity, the positive predictive value, the negative predictive value and the diagnostic accuracy of FNAC were 89.7%, 50%, 96.3%, 25%, 87.1% respectively. Image guided cytology can be a safe and cheap alternative to the more expensive and time consuming procedures like core biopsy and minimal invasive procedure in pretreatment diagnosis of ovarian cancer.

Key words: *FNAC, neoadjuvant chemotherapy, epithelial ovarian cancer*

Introduction

Ovarian cancer is the seventh most common cancer in women and worldwide ovarian cancer affects 313,959 women per year.[1] It accounts for 4% of all female cancers[2] and about 70% of epithelial ovarian cancers (EOC), the most common form of ovarian cancers, are not diagnosed until the disease has involved the upper abdomen or spread beyond the abdominal cavity.[3]

The standard treatment for ovarian cancer is primary debulking surgery followed by adjuvant chemotherapy (CT), but recently neoadjuvant CT (NACT) and interval cytoreduction has been performed in selected patients staged IIIC-IV.[4] Vergote et al.[5] observed that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option

for patients with bulky stage IIIC or IV ovarian carcinoma. After these studies, minimally invasive procedures became more important as first steps for treating patients with many comorbidities and candidates for suboptimal cytoreduction without changing the main goal of leaving no residual tumor after the interval debulking surgery.[6] Prior to commencing chemotherapy, optimal management should include a firm histologic diagnosis to confirm the clinical, radiologic, and biochemical diagnoses of ovarian cancer.[7]

In these advanced cases, neoadjuvant chemotherapy followed by interval debulking can improve the cytoreduction and reduce surgery-related morbidity[8]. For diagnosis of epithelial ovarian tumors prior to neoadjuvant chemotherapy histology and/or cytology are considered superior to clinical factors (CA125 and radiology).[3]

Yet, histopathology remains the gold standard, ultrasound and CT guided fine needle aspiration cytology (FNAC) can be an optimum modality for the diagnosis of primary and metastatic ovarian neoplasms and evaluation of recurrent malignant tumors, which might influence patient management consequently.[4] FNAC is a cheap, rapid and sensitive method that provides a cytological sample for diagnosis of pelvic tumors. It can be done as an outpatient procedure without complications. The aim of this study was to evaluate diagnostic accuracy of image guided fine needle aspiration cytology (FNAC) in the pretreatment diagnosis of the ovarian cancer prior to NACT.

Materials and Methods

This cross-sectional observational study was conducted from August 2020 to July 2021 on 34 ovarian cancer patients at department of Gynaecological Oncology of National Institute of Cancer Research and Hospital (NICRH), Dhaka. Advanced stage epithelial ovarian cancer (according to clinical and/or radiological criteria) and patients who were selected for NACT included in this study. Exclusion criteria were patients with coagulation disorders and ovarian cancer other than EOC.

Study population were evaluated by proper history taking, clinical examination and investigations. Informed consent is the prerequisite for data collection. After clinical workup, the patients were subjected to abdominal/ pelvic USG-or CT-guided FNAC. The mass was localized and aspiration performed using a 22-to 23-gauge needle attached to a 10 mL syringe. For deep-seated lesions, a lumbar puncture needle was used.

Prior to the commencement of the study, the protocol was approved by the Ethics Committee of NICRH. Data were collected, coded, revised and entered into statistical software. The qualitative data was presented as number and percentages while the quantitative data was presented as mean, standard deviation and ranges. Fisher's exact tests was used for comparison of agreement rates. Statistical analysis for sensitivity, specificity, positive predictive value, negative predictive value and overall diagnostic accuracy of FNAC was done by 2x2 contingency table by comparing the test diagnosis with the gold standard histopathological diagnosis. The significance level was set at 5%. All statistical analyses were performed using SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, IBM Corp.) software.

Results

This study includes 34 ovarian cancer patients with mean ± SD age of 46.92 ±10.916 years. Most of the patients were married (95.7%) and housewives (79.7%). About 58% of participants were residing in rural areas. Majority of the participants were literate (86.9%) in different categories. Most of them (73.9%) were belong to lower middle-class families. There were two inadequate sample, one chemotherapy response score (CRS) 3 and one benign case. So, these four cases were excluded from initial analysis. Due to these two inadequate samples, FNAC adequacy revealed about 93.75%. 31 cases were included in analysis of diagnostic accuracy, where one case was false positive and one case was true negative.

CT scan was done in 15 cases (44.11%). Six patients (17.64%) underwent USG test and about 38.25% of patients had both CT scan and USG tests. The median CA-125 level was 1200.0 with ±SD 3476.2 U/ml. Percentage of USG guided FNAC (63.3%) was much higher than that of CT guided FNAC (36.7%). In about 87% cases FNAC gave positive impression for

malignancy while in three instances (10.0%) negative impression was given. In one case (3.3%) the result was stated as suspicious. Out of 30 cases, adenocarcinoma was the leading diagnosis (13, 43.3%). Papillary serous cystadenocarcinoma and serous cystadenocarcinoma were the other two diagnoses (13.3% and 10% respectively). However, in 10 cases (33.3%) the diagnosis was not mentioned. All of the 10 not-mentioned entity in FNAC were diagnosed to have papillary serous cyst adenocarcinoma. Out of 13 patients of adenocarcinoma by FNAC, 11 retained the diagnosis (93.3%). The diagnosis of papillary serous cyst adenocarcinoma by FNAC was 75% correct. However, these differences were statistically not significant (p>0.05).

The effectiveness of FNAC of ovarian mass was assessed against the gold standard of histopathology. It was found that sensitivity and specificity of FNAC were 89.7% and 50% respectively. The positive predictive value, the negative predictive value and diagnostic accuracy of FNAC were found to be as 96.3%, 25% and 87.1% accordingly.

Table I: Distribution of the participants by adequacy of sample (n=34)

Characteristics	Frequency	Percent
Adequate	32	94.1
Inadequate	2	5.9

Out of 34 participants, about 94% adequacy is obtained.

Table II : *Suggestive Histological Subtype in FNAC (n=30)*

Suggestive histological subtype	Frequency	Percent
Not mentioned	10	33.3
Adenocarcinoma	13	43.3
Papillary serous cystadenocarcinoma	4	13.3
Serous cystadenocarcinoma	3	10.0
Total	30	100.0

Table III: *Concordance between FNAC impressions and final histopathological types (n=30)*

Suggestive histological subtype of FNAC impressions	Final histopathology types				Fisher's Exact test	p-value
	Papillary serous cyst adenocarcinoma	Granulosa cell tumour	Endometroid carcinoma of uterus	Benign		
Not mentioned (n=10)	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	9.861	0.564
Adenocarcinoma (n=13)	11 (93.3)	1 (3.3)	0 (0.0)	1 (3.3)		
Serous cystadenocarcinoma (n=3)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Papillary serous cystadenocarcinoma (n=4)	3 (75.0)	0 (0.0)	1 (25.0)	0 (0.0)		
Total	27 (90.0)	1 (3.3)	1 (3.3)	1 (3.3)		

Table IV: *Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of FNAC compared to histopathology for ovarian cancer (n=31)*

FNAC	Histopathology		Sn[a] (%)	Sp[b] (%)	PPV[c] (%)	NPV[d] (%)	DA[e] (%)
	Malignant	Benign					
Malignant	26	01	89.7	50	96.3	25	87.1
Benign	03	01					

Discussion

The clinicopathological evaluation of ovarian masses is a challenging field. Difficulty in gaining access to the tumor site is itself a major obstacle and the wide spectrum of lesions presents a disconcerting picture to the pathologist. Prior to NACT, preoperative tissue diagnosis of ovarian tumour is essential for proper tailoring of the treatment plan.

Concerning adequacy rate for FNAC, it was 94.1% in our study . This finding of FNAC adequacy is similar to that reported by Fischerova et al.[9] that was 93.02% and Singh et al.[10] that was 91.2%.

Regarding histological subtype by FNAC, adenocarcinoma was the leading diagnosis (43.3%). Papillary serous cystadenocarcinoma and serous cystadenocarcinoma were the other two diagnoses (13.3% and 10% respectively). In 10 cases (33.3%) the diagnosis was not mentioned at all which was a major drawback of such investigation. By FNAC, about 66.7% histologic subtype was identified preoperatively. In a similar study done in Canada showed the accuracy of FNAC for tumour subtyping (55% of cytological diagnosis) which was near to similar to our result. [11]

Concordance between pre- and post-chemotherapy histologic subtypes were seen in 85% patients in a study of Freedman et al.[11] and 80.9% in a study of Mehedi et al.[12] About 10% could not be accurately classified on cytology.[13] Our observation (75%) was near to consistent with these studies.

The effectiveness of FNAC of ovarian mass was assessed against the gold standard of histopathology. It was found that FNAC was 89.7% sensitive to diagnose the ovarian mass correctly while it showed 50% specificity to rule out the condition. The positive predictive value, the negative predictive value and diagnostic accuracy of FNAC were found to be as 96.3%, 25% and 87.1% respectively. Most of the studies like Mehedi et al.[12]; Stewart et al.[14]; Khan et al.[15] and Zulfu et al.[16] discussed about the accuracy of aspiration cytology diagnosis in patients with ovarian cancer that were 88.2%, 89%, 89,7% and 86.5% respectively and that are comparable to the current study. On the other hand, this finding is not consistent with the result of Bandhapaday et al.[4] and Freedman et al.[11] which were 97.6% and 96.2% respectively. This discrepancy may be due to presence of false positive case in our study. In the current study there was only one false positive case regarding malignancy.

Khan et al.[15] studied 120 patients with ovarian masses and performed USG guided FNAC in 28 clinically suspected malignant cases. The overall sensitivity, specificity and diagnostic accuracy of FNAC in diagnosis of various ovarian masses were 79.2%, 90.6% and 89.9%, respectively. In study of Singh et al.[10], the sensitivity, specificity and diagnostic accuracy of FNAC were 82.3%, 92.3% and 84.2% respectively. The positive predictive value (PPV) and negative predictive value (NPV) were addressed by a previous study done in Egypt that were 100% and 71.4% respectively.[17] In our result, the specificity and the NPV were 50% and 25% respectively which were not consistent with the findings of others. This disagreement probably due to presence of both true negative and false negative cases in FNAC group of this present study.

The study had some limitations that must be acknowledged. The study was conducted in a single center which may not be representative for the whole population and small sample size of this study limits the generalization

Conclusion

Though FNAC cannot preserve the tissue architecture, it can be a safe and cheap alternative to the more expensive and time consuming procedures like core biopsy and minimal invasive procedure in pretreatment diagnosis of ovarian cancer.

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Case Report

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Mucormycosis Induced Liver Abscess in A Child with Acute Lymphoblastic Leukemia: A Rare Case Report

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Abstract

Mucormycosis is a life-threatening condition in immunocompromised patients. A 10 years old boy with Acute Lymphoblastic Leukemia (ALL) with Mucormycosis leading to a burst hepatic abscess subsequently developed empyema thoracis and hydropneumothorax Patient was successfully treated with Amphotericin B, and treatment of leukemia was continued. This case highlights that mucormycosis should be considered in differential diagnosis in immunocompromised patient with hepatic abscess or empyema thoracis on typical clinical and radiological findings. The high degree of suspicion with the rapid start of empirical antifungal therapy and drainage of pus is essential for a better outcome.

Keywords: *Mucormycosis, ALL, Liver abscess.*

Introduction

Immunocompromised patients are more susceptible to develop invasive fungal infections. The most common fungi are Candida and Aspergillus. Rarely, fungal infections are also caused by Mucor and Entomophthorales spp. Fusarium spp. and Scedosporium spp. Mucormycosis is an opportunistic fungal infection; can produce life-threatening events in immunocompromised conditions like leukemia, organ transplantation, uncontrolled diabetes mellitus and immunosuppressive chemotherapy.[1-6] We report a case of ALL with hyperglycemia who developed mucormycosis leading to a liver abscess that burst to form empyema thoracis and was successfully treated with antifungal agents.

Case

A 10 years old boy diagnosed with Acute Lymphoblastic Leukemia, was admitted with high-grade continued fever

associated with chills and rigor. The boy also had pain at the right hypochondrium and lower right side of the lower chest wall. The patient subsequently developed hemoptysis and acute watery diarrhea. The patient was on induction of remission chemotherapy according to UKALL 2003 Regimen B and also developed steroid-induced hyperglycemia.

On examination, he was ill-looking, mildly pale, and febrile (100°F); other vital signs were within normal limits. Anthropometrically he thrived well. Chest movement was asymmetrical and diminished on the right side. Chest expansibility was diminished & percussion note was dull on the same side. Breath sound was vesicular and diminished on the right side & crepitation was present on both sides. On abdominal examination, tenderness was present in right lower zone and there was no organomegaly. Other systemic examinations revealed no abnormality. Chest X-Ray P/A view revealed right-sided pleural effusion and HRCT of the chest revealed a ruptured liver abscess with extension into the chest.

Hemoglobin: 7.0 gm/dl, TC of WBC: 760/cmm, Neutrophil 25%, Lymphocyte 46.1%, Monocyte 28.9 %, SGPT: 208 U/L, S. Albumin 3.2g/dl. Urine R/E: normal finding, urine, and blood C/S revealed no growth of organism. We treated the patient at first with Inj. Cefepime, then we added Inj. Vancomycin, along with Inj. Metronidazole & Tab. Voriconazole, but the patient did not respond rather developed hydropneumothorax. So, emergency chest drain tube was inserted and R/M/E and C/S of pus was sent for fungus. C/S revealed no growth but R/M/E for fungus showed fungal hyphae suggestive of Mucormycosis. Then Inj. Amphotericin (5mg/kg) was added along with previous medications. But after seven days patient developed a bronchopleural fistula and drain tube in the chest was kept until spontaneous resolution occurred. Patient's condition significantly improved day by day & after four days, we restarted the chemotherapy, and subsequently, patient was discharged to home with advice.

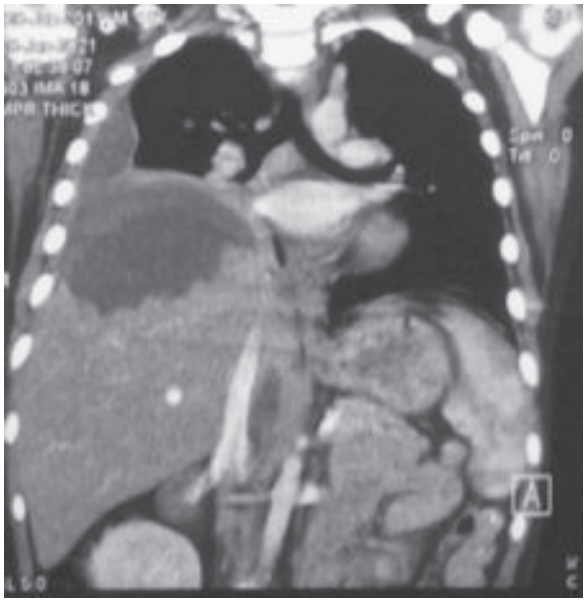

Figure 1: *Ruptured hepatic abscess*

Discussion

Mucormycosis is a rare disease caused by fungi of the order Mucorales. The organisms of mucormycosis are molds usually found in soil and decaying organic matter. Usually, its entry route is by airborne spores, but others include the cutaneous route with traumatic disruption or direct injection or catheters.[12] In a susceptible person, spores germinate into hyphae. Then invade surrounding tissue, including blood vessels, causing ischemia, necrosis, infarction, and black pus formation. The mortality rate of mucormycosis is 44-80%.[7-9] Mucormycosis mainly affects rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, renal, and central nervous systems. Hepatic involvement generally occurs as a disseminated disease with gastrointestinal or pulmonary involvement.[11] Elitzur et al.[14] stated that Ninety-two percent of mucormycosis cases occurred in patients with acute leukemias. Sixty-five percent are during the induction phase of treatment.

We present here an extremely devastating mucormycosis infection in a patient of ALL on induction chemotherapy that causes at first liver abscess which bursts to form empyema thoracis, subsequently pneumothorax and subcutaneous emphysema. This type of case is rarely encountered in a Pediatric Hematology and Oncology department. The diagnosis of mucormycosis is difficult. Up to suspicion, treatment should be started as soon as possible to decrease mortality and morbidity. Our patient has multiple risk factors for developing mucormycosis, such as hematological malignancy, steroid therapy, hyperglycemia, and induction chemotherapy.

The European Conference on Infections in Leukemia (ECIL 3) recommends Liposomal Amphotericin B or

Amphotericin B lipid complex as first-line therapy for treating mucormycosis. Duration should be at least 6-8 weeks. Not only the duration of therapy but prompt initiation of the antifungal agent is crucial for survival.[10] Surgical intervention should be done if there is no radiological improvement after 4-5 weeks of antifungal therapy. Otherwise, there is more risk of death.[13] The liver abscess can be due to bacterial, amoebic, fungal, and parasitic causes. Pyogenic liver abscess is the most common. It occurs by direct, hematogenous dissemination from the biliary tree infection, peritonitis and bowel leakage. The fungal abscess is the second most common after bacterial cause. It does not form pus in the liver but invades to blood vessels causing tissue necrosis.[15] In our case, we did not find pus in the liver because of the necrotic tissue that had formed without liquefaction. Pak et al.[17] stated that pneumonia is a common initial site of infection, and usually, it is the source of disseminated mucormycosis. Our patient presents with pneumonia as well as liver abscess concomitantly. So, the lung may be a source of primary infection.

Conclusion

In conclusion, hepatic mucormycosis is rare and typically seen in disseminated disease in immunocompromised individuals. Management involves appropriate surgical intervention and medical treatment with Amphotericin B. Earlier diagnosis may prevent unwanted sequelae.

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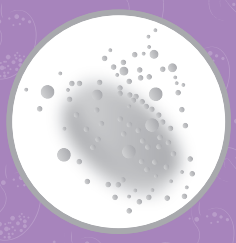

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