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

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

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Editorial

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Awareness of Bangladeshi women about a preventable cancer

Sufi Hannan Zulfiqar Rahman[1]

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Citation: Rahman SHZ. Awareness of Bangladeshi women about a preventable cancer. Cancer J Bangladesh 2023;4(1):1-2.

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Cervical cancer is a public health problem throughout the world. According to GLOBOCAN estimates 2020, it is the fourth most common cancer in women globally. The problem is worse in developing countries. In some developing countries it is the most common cancer in women and its incidence rates are up to 10 times and mortality rates are up to 18 times higher than in developed countries. During the last few decades, significant advancement has been achieved in understanding of its pathogenesis by Human papillomavirus (HPV). It resulted in invention of HPV vaccine and high-performing screening tests that made this cancer preventable at primary and secondary level. As this cancer is preventable, in 2020 World Health Assembly, the decision-making body of World health Organization (WHO) adopted global strategy for cervical cancer elimination. Its goal is to fully vaccinate 90% of girls with HPV vaccine by the age of 15, screen 70% women using a high-performing screening test at least twice by the age 45 and treat and manage 90% of women with pre-invasive and invasive cervical cancer (90-70-90 targets) by the year 2030, to get on the path to eliminate cervical cancer within the next century.

Developed countries reduced both the incidence of and mortality from cervical cancer in last five to six decades by implementing effective prevention programmes initially by cervical cancer screening and more recently by screening and HPV vaccination. Success of these prevention programmes resulted from availability of facilities as well as knowledge, awareness and motivation of women. Because of the knowledge and awareness, self-sampling for cervical cancer screening was found effective in these countries which made screening easier and increased screening coverage. On the other hand, developing countries are lagging behind both in availability of preventive services and awareness of people about the disease and where to come to seek services.

Because only availability of services without awareness of people cannot bring success to any prevention programme, the month of January every year is observed as the cervical cancer awareness month by the WHO in its member countries. It is aimed to raise awareness about cervical cancer prevention. The theme of cervical cancer awareness month January 2023 is 'ending cervical cancer within a few generations by creating awareness about cervical cancer screening and HPV vaccination'.

Bangladesh is a developing country where cervical cancer is the second most common cancer in women. Epidemiological risk factors for cervical cancer prevailing in Bangladesh include early marriage and thereby early initiation of sexual activity, multiparity, sexually transmitted infections and low socioeconomic condition. The government of Bangladesh started to implement cervical cancer screening programme in 2004 to prevent cervical cancer. To further strengthen cervical cancer prevention programme, the government adopted 'National Strategy for Cervical Cancer Prevention and Control' in 2017. Spanning over five years from 2017 to

2022, the strategy is the first step to align agendas and activities among all stakeholders to ensure a coordinated approach in cervical cancer prevention. It includes making screening, HPV vaccination, treatment and palliative care services available and creating awareness and motivating people community based discussions involving women and men, educating girls, booklet distribution and publicity in print and electronic media. A study conducted in a district of Bangladesh which was published in 'PLOS Global Public Health' in January 2022 shows majority of the women included in the study never heard about cervical cancer and who have heard have poor knowledge about its risk factors, symptoms, screening and treatment. Rural and uneducated women were found less aware than urban and educated women. Though the study subjects may not represent whole female population of Bangladesh, it gives us a guide that we have to strengthen our awareness programme and we have to reach the rural uneducated people. Along with discussions in community and girls' schools publicity in electronic media should be strengthened because this can reach urban educated as well as rural uneducated people at the same time and create nationwide awareness.

Original Article

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Marrow Biopsies: A Histochemical Study on 36 Cases of Primary Myelofibrosis

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Abstract:

Background: *Bone marrow fibrosis (BMF) is associated with a variety of reactive as well as neoplastic conditions. Primary myelofibrosis (PMF) is a rare hematological malignancy with higher mortality and morbidity due to progression of BMF. The amount of bone marrow reticulin and collagen fibrosis is detected by reticulin and Masson's trichrome (MT) stains, respectively. The study aimed to explore the pattern and degree of BMF in PMF cases with above mentioned special stains along with conventional Hematoxylin & Eosin (H&E) stain.* ***Method:*** *Thirty-six histopathologically suggested or diagnosed cases of PMF were studied at the Department of Pathology, BSMMU. Paraffin blocks of trephine biopsy specimens of the selected cases were collected. H&E, reticulin and MT stains were applied on the re-cut sections. Extent of BMF was assessed by examining the sections using proposed semiquantitative grading systems. The cases were divided into two groups. Patients having bone marrow fibrosis (MF) grade MF-0 to MF-1 were considered absent pathological BMF, whereas those cases with MF-2 to MF-3 as present pathological BMF.* ***Results:*** *In this study, 19 (52.8%) PMF cases had pathological BMF diagnosed by only H&E. Moreover, thirty-four (94.4%) patients had pathological BMF corresponding to MF-2 to MF-3 detected by special stains.* ***Conclusion:*** *Significantly higher ($p<0.05$) detection of pathological BMF cases with use of additional special stains recommends that, both reticulin and MT stains can be used routinely to assess BMF properly according to special grading system. Stages of bone marrow fibrosis have different prognostic and therapeutic implications.*

Key words: Bone marrow fibrosis, Primary myelofibrosis, reticulin fibrosis, collagen fibrosis, reticulin stain, Masson's trichrome stain, Hematoxylin & Eosin, bone marrow fibrosis (MF) grade.

Introduction:

Primary myelofibrosis (PMF) is a rare hematological malignancy encountered under the myeloproliferative neoplasms (MPNs) category. It is a clonal myeloproliferative disease characterized by the proliferation of mainly megakaryocytic and granulocytic components in the bone marrow, associated with reactive deposition of bone marrow connective tissue and

extramedullary hematopoiesis. The condition is clinically manifested by anemia, progressive hepatosplenomegaly, and may even be asymptomatic at diagnosis (30%).[1] William Dameshek, an internationally renowned American hematologist, classified PMF in the "myeloproliferative diseases" group in 1951.[2] The disease was first included in the World Health Organization (WHO) classification of myeloid malignancies in 2001.[3] Due to the frequent association with poor cellularity of bone marrow aspirates in PMF patients, a trephine biopsy of the marrow is recommended for evaluation of the marrow cellularity, topography, stromal changes, and maturation pattern of the hematopoietic cells.[4]

There is a stepwise evolution from an initial pre-fibrotic to an overt fibrotic stage with marked reticulin or collagen fibrosis in the bone marrow, often with osteosclerosis. The marrow is hypercellular for age in the early or pre-fibrotic stage. There is an increase in abnormal megakaryocytes and granulocytes with reticulin fibrosis corresponding to normal bone marrow or not exceeding grade 1. Most cases of PMF are diagnosed initially in the overt fibrotic stage. The bone marrow is more often normocellular or hypocellular, with patches of active hematopoiesis alternating with hypocellular regions of loose connective tissue and/or fat. The bone marrow shows increased reticulin or collagen fibrosis (grade 2 or 3) in this stage. Very late in the course, the fibrotic marrow space may be converted into bone, a change called "osteosclerosis." [5-7] The revised criteria of the "WHO classification of myeloid neoplasms, 2016" outlined the diagnosis of PMF into pre-PMF and overt PMF, which included modified grading of reticulin and collagen bone marrow fibrosis.[8]

Pathogenesis of fibrogenesis: The proliferation of fibroblasts leads to an increase in reticulin fibers (reticulin fibrosis) and/or collagen fibers (collagen fibrosis). Reticulin fibrosis, often reversible after successful treatment, may exhibit a correlation to disease prognosis. Collagen fibrosis is prominently present in the later stage of the disease and is often associated with a poorer prognosis.[9-11] Bone marrow stromal fibrosis is a reactive process associated with abnormalities in the number and/or function of megakaryocytes and platelets. PDGF, TGF-α, epidermal growth factor, endothelial cell growth factor, TNF-α, IL-1, IL-6, etc., can be produced by the cellular components of clonal proliferation. These act on fibroblasts to produce extracellular matrix and are also involved in the expression of proteases that inhibit enzymes responsible for the extracellular matrix degradation. [9,10,12] Reticulin fibers are few and exist as a fine network of scattered fibers without intersection throughout the normal bone marrow. Bundles of reticulin fibers constitute collagen fibers, the latter of which are usually absent in the bone marrow interstitium.[9] Connective tissue components, especially reticulin fibers, are poorly visualized in H&E-stained sections. Silver impregnation techniques, such as Gordon & Sweet and Gomori's stains, are used to observe reticulin fibrosis, while Masson's trichrome stain identifies collagen fibrosis. [9,13]

The present study was designed to observe the histological pattern of reticulin and collagen fiber deposition in the bone marrow of 36 PMF cases and to evaluate the degree of fibrosis using the aforementioned special stains.

Materials and methods:

This cross-sectional study analyzed 36 consecutive samples of formalin-fixed paraffin-embedded trephine biopsies obtained from patients at the Department of Pathology, BSMMU between March 2020 and February 2022. The study received approval from the Institutional Review Board of the same institute. Included cases met the histopathological criteria for primary myelofibrosis as outlined by the 2016 revised WHO criteria for hematological malignancies. Clinical and laboratory data were collected at the time of diagnosis and systematically recorded using a prepared proforma. Patients with myelofibrosis secondary to other hematological malignancies (e.g., myelodysplastic syndromes, chronic myeloid leukemia, lymphoma, acute leukemia), tumor metastasis, non-neoplastic diseases, or myelofibrosis secondary to chemotherapy or radiotherapy, as well as those with bone marrow specimens showing extensive crush artifacts or inadequate sampling (e.g., <1 cm long), and patients unwilling to provide informed consent, were excluded from the study. All included patients' requisition forms and clinical records were collected and carefully re-evaluated. Recut sections, approximately 5 μm thick, were obtained from paraffin blocks for staining with H&E, reticulin (Gordon & Sweet's method), and Masson's trichrome stain using a standard protocol.

Re-evaluation of bone marrow sections:

Using Haematoxylin & Eosin stain (H&E): Architectural details were studied, including marrow cellularity, granulopoiesis, erythropoiesis, and megakaryopoiesis. The presence of fibroblastic proliferation with or without collagen deposition in the marrow, as demonstrated by the characteristic pink colour, either focally or diffusely, was considered as the presence of bone marrow fibrosis in H&E-stained sections. Reticulin fibres are not detected by this stain. The presence of osteosclerosis with a different pattern in the marrow was observed as a component of bone marrow fibrosis according to Kvasnicka et al.[14] The highest osteosclerosis grade occupied in at least 30% of the marrow area was determined as the dominant grade in heterogeneous cases.

Using special stains: Bone marrow fibrosis was evaluated using reticulin and MT stains for each case by three observers (SA, BPD, AKMNK).

Using reticulin stain only: The pattern of deposition of reticulin fibres was observed independently by one of the observers (SA) in reticulin-stained sections. Presence of admixed collagen fibres was estimated as bundles of thick fibres as reticulin stain with Gordon & Sweet's method cannot discriminate between reticulin and collagen fibres. A semiquantitative grading system was followed based on "European consensus on bone marrow fibrosis (MF) grading, 2005" as followed by Kvasnicka et al.[14]to determine the degree of myelofibrosis within a range of MF-0 to MF-3. In cases with heterogeneous pattern of fibrosis, final 'MF' score was determined by the highest grade present in at least 30% of the marrow area. Mean (±SD) value of bone marrow fibrosis (MF) grade was calculated with the reticulin stain.

Using MT stain only: The pattern of deposition of collagen fibres was observed independently by another observer one (BPD) in MT-stained sections. Assessment of above mentioned 'MF' scoring was done for MT-stained slides which involved observation of areas with collagen deposition as indicated by characteristic blue colour. Focally, MT positive area constituted MF-2 collagen fibrosis, whereas the MT-positive marrow area e"30% was regarded as MF-3. All the MT negative cases were MF-0. Mean (±SD) value of bone marrow fibrosis (MF) grade was calculated with the MT stain.

Degree of collagen fibrosis was also assessed following another semiquantitative grading of collagen deposition within proposed four-grade system.[14] In specimens with heterogeneous pattern of collagen deposition, the final score was determined by the highest pattern present in at least 30% of the bone marrow area.

Using reticulin and MT stains in combination: The final 'MF' grade was determined based on agreement among three observers (SA, BPD, AKMNK) according to examination of the staining pattern of same slides with both special stains under a multi-headed microscope. In the case of the same patient showing different findings in 'MF' grade in reticulin and MT-stained slides due to controversy in evaluating collagenized areas, the final grading was decided based on MT positivity as conclusive for collagen fibrosis. Ultimately, MF-2 and MF-3 cases were considered as having pathological marrow fibrosis corresponding to overt fibrotic stage of PMF. Those cases with degree of fibrosis MF-0 to MF-1 were identified as pre-fibrotic patients with absent pathological fibrosis. Mean (±SD) value of bone marrow fibrosis (MF) grade was calculated with these special stains.

Use of special stains[10,14]:

No.	Stain	Purpose	Colour	Internal control
1.	**Reticulin**	For demonstration of the presence of reticulin fibers, collagen type III.	Black (Gordon & Sweet's method) Yellowish or, brownish (Gomori's method)	Perivascular area
2.	**Masson's trichrome**	For demonstration of the presence of collagen fibers type I.	Blue	Perivascular area

Semiquantitative bone marrow fibrosis (MF) grading system based on "European consensus-2005" (Kvasnicka et al.[14]):

- **MF-0:** Scattered linear reticulin with no intersections corresponding to normal bone marrow.
- **MF-1:** Loose network of reticulin with many intersections, especially in perivascular areas.
- **MF-2:** Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of thick fibres mostly consistent with collagen and /or focal osteosclerosis.
- **MF-3:** Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of thick fibres mostly consistent with collagen usually associated with significant osteosclerosis.

Semiquantitative grading of collagen deposition (Kvasnicka et al.[14]):

- **Grade 0:** Perivascular collagen only (normal).
- **Grade 1:** Focal paratrabecular or/and central collagen deposition without connecting meshwork.
- **Grading 2:** Paratrabecular or/and central collagen deposition with focally connecting meshwork or generalized paratrabecular apposition of collagen.
- **Grading 3:** Diffuse (complete) connecting meshwork of collagen.

Semiquantitative grading of osteosclerosis (Kvasnicka et al. 14):

- **Grade 0**: Regular bone trabeculae (distinct paratrabecular borders).
- **Grade 1:** Focal budding, hooks, spikes or paratrabecular apposition of new bone.
- **Grade 2:** Diffuse paratrabecular new boone formation with thickening of trabeculae, occasionally with focal interconnection.
- **Grade 3:** Extensive interconnecting meshwork of new bone with overall effacement of marrow space.

Statistical analysis: All the recorded data were analyzed SPSS Windows (SPSS Inc., Chicago, Illinois, USA) version 24.0 software. Continuous variables were expressed as mean values (±SD), and categorical variables were expressed as absolute frequency and percentage, which were presented in tables. *P*-value £0.05 was considered statistically significant.

Results:

Among 36 PMF cases, 27 (75%) were male and 9 (25%) were female with mean age 51.4±15.5 years (Table I).

Table I: *Distribution of cases according to age (n=36)*

Age range (yrs.)	Frequency	Percentage
≤40	10	27.8
41-50	6	16.7
51-60	8	22.2
≥61	12	33.3
Total	36	100.0

In this study, 19 (52.8%) patients had detectable bone marrow fibrosis (BMF) as revealed by examination of only H&E-stained slides. When both the reticulin and Masson's trichrome stained slides were examined besides H&E, 34 (94.4%) patients had detectable pathological BMF corresponding to BMF grade MF-2 to MF-3. Presence of detectable pathological BMF is significantly higher ($p<0.05$) with additional use of special stains when compared with the use of H&E stain alone (Table II).

When slides were examined with only reticulin stain, 32 (88.9%) patients had found pathological BMF. Twenty-nine (80.6%) patients showed pathological BMF with use of only MT stain. Table III shows comparison of BMF detection with only reticulin and only MT with combined use of these special stains.

Among 36 cases, only 2 (5.6%) patients showed reticulin fibrosis grade MF1. Thirteen (36.1%) patients had bone marrow fibrosis MF2; 5 (13.9%) of them showed dense reticulin fibrosis without MT detected collagen fibrosis.

Table II: *Comparison of H&E stain with combined use of reticulin and MT for detection of BMF*

Stain	BMF present		BMF absent		*p*-value
	Frequency	Percentage	Frequency	Percentage	
H&E	19	52.8	17	47.2	<0.05
Special stains	34	94.4	2	5.6	

Table III: *Comparison of BMF detection with only reticulin, MT and in combination of the two*

BMF	Only reticulin n (%)	Only MT n (%)	Both reticulin and MT n (%)	*p*-value
Present	32 (88.9)	29 (80.6)		0.33 (NS)
Absent	4 (11.1)	7 (19.4)		
Present	32 (88.9)		34 (94.4)	0.39 (NS)
Absent	4 (11.1)		2 (5.6)	
Present		29 (80.6)	34 (94.4)	0.07 (NS)
Absent		7 (19.4)	2 (5.6)	

NS Not significant

Table IV: *Distribution of study subjects according to bone marrow fibrosis (MF) grades in pre-fibrotic cases*

Bone marrow fibrosis grade (MF)	Pre-fibrotic (MT negative) n (%)
0	0 (0.0)
1	2 (5.6)
Bone marrow fibrosis grade (MF) mean (± SD)	1.00 ± 0.0

SD- Standard deviation

Twenty-one (58.3%) patients had bone marrow fibrosis MF-3 with significant collagen fibrosis and osteosclerosis. All study subjects were divided into pre-fibrotic and overt fibrotic groups after evaluation of fibrosis comprising 2 (5.6%) and 34 (94.4%) patients respectively. Table IV and Table V show the distribution of study subjects according to bone marrow fibrosis (MF) grades. Mean MF grade values of 36 cases using only reticulin and only MT stain were found 2.25±0.7 and 2.19±1.2 respectively; whereas combined use of these special stains revealed 2.53±0.6. Mean MF grade was significantly higher (p-0.01) with using only reticulin than only MT (table-VI). Collagen fibrosis grade was assessed with findings of Masson's trichrome stain (table-VII). Only 5 (13.9%) overt fibrotic patients had absent collagen fibrosis (grade- 0). Among 34 overt fibrotic patients, 33 (97.1%) had presence of osteoscleosis (Table-VII).

Table V: *Distribution of study subjects according to bone marrow fibrosis (MF) grades in overt fibrotic cases*

Bone marrow fibrosis grade (MF)	Overt fibrotic n (%)		
	MT negative	MT positive without osteosclerosis	MT positive with osteosclerosis
2	5 (13.9)	1 (2.8)	7 (19.4)
3	0	0	21 (58.3)
Total	13 (36.1) (MF-2) + 21 (58.3) (MF-3) = 34 (94.4)		
Bone marrow fibrosis grade (MF) mean (± SD)	2.62 ± 0.49		

SD- Standard deviation

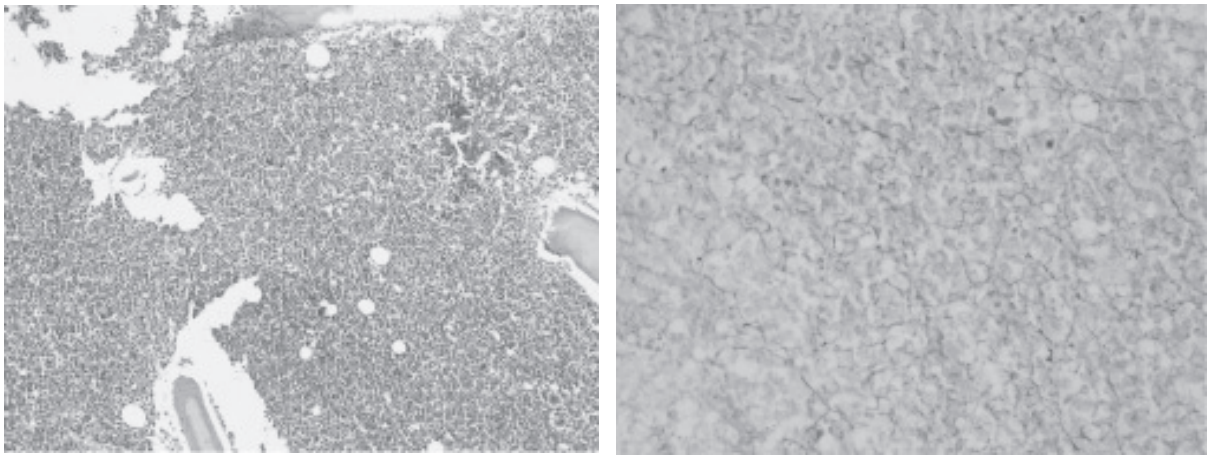
Table VI: *Comparison of mean MF grade values with only reticulin, MT and in combination of the two (n=36)*

Mean MF grade (± SD)	Only reticulin	Only MT	Both reticulin & MT	*p*-value
	2.25±0.73	2.19±1.17		0.01 (S)
	2.25±0.73		2.53±0.61	0.07 (NS)
		2.19±1.17	2.53±0.61	0.07 (NS)

SD- Standard deviation NS- Not significant, S- Significant.

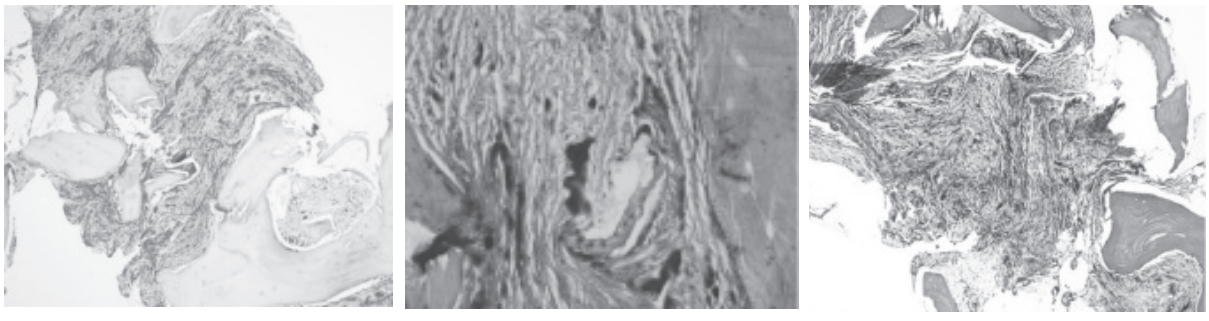
Table VII: *Distribution of total cases according to collagen fibrosis and osteosclerosis grade (n=36)*

Collagen fibrosis grade	Pre-fibrotic (n=2) n (%)	Overt fibrotic (n=34) n (%)
0	2 (5.6)	5 (13.9)
1	0	6 (16.7)
2	0	10 (27.8)
3	0	13 (36.1)
Osteosclerosis grade		
0	2 (5.6)	1 (2.8)
1	0	8 (22.2)
2	0	11 (30.6)
3	0	14 (38.9)



a) b)

Figure 1: *Photomicrograph showing a pre-fibrotic case of primary myelofibrosis, (a) H&E stain (100x) revealed, hypercellular marrow with predominance of granulocytic and megakaryocytic population, (b) MF-1 with reticulin stain (400x).*



a) b) c)

Figure 2: *Photomicrograph showing an advanced fibrotic case of primary myelofibrosis, (a) H&E stain (100x) revealed, severely hypocellular marrow with distorted architecture and osteosclerosis, (b) MF-3 with reticulin stain (400x), (c) diffuse meshwork of collagen fibrosis grade-3 with MT stain (100x).*

Discussion:

Bone marrow fibrosis means any increase of single reticulin fibre or bundles of fibres to form collagen. The term 'myelofibrosis' is frequently applied in relation to myeloproliferative neoplasms (MPNs), which is significantly associated with BMF.[15] According to morphometric assessment of bone marrow fibre content, myelofibrosis means accumulation of thickened argyrophilic fibres with length exceeding 25 µm, clustering in hematopoietic regions to alter the marrow architecture.[16] The study of bone marrow morphology in trephine biopsies is the basis of diagnosis and therapeutic efficacy of MPNs. Previously, different scoring systems were in practice to assess bone marrow fibrosis. Among them, Baumeister, Manoharan and Hannover[17] systems are noteworthy. A four scaled (MF 0-3) semiquantitative and qualitative scoring system is currently followed to differentiate among reticulin fibrosis, collagen fibrosis and osteosclerosis, based on "European Consensus System, 2005", which has been updated in WHO classification of myeloid neoplasms since 2008. This scoring system requires application of reticulin stain and has recommended additional MT stain in higher fibrotic grades (MF 2-3) for definite evaluation of collagen fibrosis. [4,6,14,18-20]

The term 'primary myelofibrosis' gained its popularity in 2008. Prior to that, the condition was designated as 'agnogenic myeloid metaplasia', 'myelofibrosis with myeloid metaplasia', 'chronic idiopathic myelofibrosis' (CIMF) etc.[21] The Cologne criteria was established by Thiele et al.[22] to define the pre-fibrotic stage of the disease with combined clinical and corresponding histomorphological features. Another set of diagnostic criteria was developed by the Italian Society of Hematology, which lacked to characterize the pre-fibrotic stage.[23-24] Hannover classification system has divided the fibrosis increase into three stages: early myelosclerosis, myelofibrosis, and advanced myelofibrosis.[17]A proposed set of European Clinical and Pathological criteria divided CIMF into four stages: pre-fibrotic (MF0), early CIMF (MF1), manifest CIMF (MF2), overt fibrotic CIMF (MF3). The latter may be complicated by osteosclerosis (MF>3; osteomyelosclerosis).[23-24] CIMF was divided into pre-fibrotic or cellular and fibrotic stage with different morphological features.[25] Finally, the disease was entitled to pre-fibrotic and overt fibrotic PMF based on MF score.[8]

The bone marrow is mainly composed of type I and type III collagen. Reticulin is composed of individual fibrils or small bunches of thin type III collagen fibrils surrounding a core of type I collagen fibrils. Type III collagen regulates the diameter and fibrillogenesis of more thick type I collagen fibrils. Reticulin fibres are few in number, and exists as a fine network of scattered fibres without intersection throughout the normal bone marrow, prominently around the blood vessels and endosteum. Bundles of reticulin fibres constitute collagen fibres, which are absent in the normal marrow interstitium. These are found usually around blood vessels and in the bone trabeculae. Reticulin fibrosis is often associated with collagen fibres of variable amount, which may not be detectable by MT stain unless there is a marked increase in reticulin fibres. Deposition of MT identifiable collagen fibres of any quantity, even intermingled with abundant reticulin fibres, constitutes "collagen fibrosis". The latter signifies more severe disease conditions of the marrow, and less likely to be reversible with treatment.[9-10,26] The study conducted by Shehata et al.[27]revealed predominantly grade 0 expression of anticollagen I and III in reactive marrow, whereas significantly higher percentage of grade 4 in MT detected fibrotic group.

In the present study, 55.6% of the patients were over 50 years old and 44.4% were d"50 years. Most of the participated patients were male. PMF is most commonly diagnosed in the 6^{th} – 7^{th} decades of life. Usually, men and women are nearly equally affected by PMF.[6] The significantly higher detection of pathological BMF cases with special stains and significant difference between reticulin and MT assessed mean MF grade can suggest to establish that, the routine use of both special stains is essential to evaluate the amount and nature of marrow fibrosis properly than performing either one of these stains or H&E alone. Those hypercellular fibrotic cases necessitate application of reticulin stain that resemble to prefibrotic stage of PMF with H&E stain.

Bone marrow fibrosis should be assessed in haematopoietic areas in thin tissue sections avoiding areas of fatty tissue, edema, hemorrhage and crush artifact. These areas produce overestimation of fibrous content, especially in reticulin stained sections. Gordon and Sweet technique of reticulin staining fails to discriminate between reticulin and collagen fibres. Reticulin fibres can be diffusely

increased without positive trichrome staining due to deposition of immature collagen. Reticulin stain revealed coarse bundles of thick black fibres are mostly consistent with collagen fibres.[14,28-29] In our study, five (13.9%) cases exhibited pathological BMF by reticulin stain. All of them were negative in MT stain. Their final fibrosis grade was determined as 'MF-2'. Three (8.3%) cases showed 'MF-3' fibrosis in reticulin stain. Ultimately, these cases revealed trichrome positive 'MF-2' for collagenized areas. Oppositely, reticulin fibrosis can be underscored in inadequately performed reticulin stain due to inappropriate fixation, embedding, shrinkage of tissue, etc.[14,30] Two (5.6%) cases in the present study were estimated as pre-fibrotic in reticulin stain. All of them demonstrate pathological BMF in MT stain. Eleven (30.6%) cases were MF-2 in reticulin stain. They were confirmed for 'MF-3' in MT stain. Al-Khafaji et al.[10]observed that, even H&E can detect a higher percentage of severe marrow fibrosis than the special stains, possibly due to presence of fibroblastic reaction without production of collagen fibres. Overt fibrotic patients often present with variable degree of osteosclerosis characterized by formation of focal budding, spikes and final interconnecting meshwork of new bone.[14,31] In current study, eight (22.2%), 11 (30.6%) and 14 (38.9%) patients presented with osteosclerosis grade 1, 2 and 3, respectively (table-VII). Osteosclerosis is usually associated with areas of collagenization. Our study showed that, five (13.9%) patients had demonstrable osteosclerosis inspite of being MT negative for collagen fibrosis. They were MF-2 for diffusely increased reticulin fibres. It possibly observed due to increased deposition of osteoid reflecting higher osteoblastic activity in PMF.[31] One 60 years old pre-fibrotic patient had seemingly grade-1 osteosclerosis with focal budding, which may be due to age related thickening of bone trabeculae.

Higher degree of bone marrow fibrosis predicts poor prognosis in terms of survival. Gianelli et al.[20] observed the relationship between the prognostic scores according to "International Prognostic Scoring System (IPSS)" and grades of fibrosis. In the study conducted by Guglielmelli et al.,[32] overt PMF was found to be enriched in patients with anaemia, thrombocytopenia, leucopenia, higher circulating blast count, constitutional symptoms, large splenomegaly and more unfavorable karyotype. Current two scoring system, MIPSS70 (Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis) and MIPSS70-plus version 2.0 is based on reticulin fibrosis grading. Presence of advanced reticulin fibrosis and the amount of collagen fibers demonstrate a strong correlation with abnormal blood count and severity of underlying disease, as shown in several studies.[33]Pre-fibrotic cases may be difficult to differentiate from masked polycythaemia vera or early phase of essential thrombocythaemia. Hence, they are diagnosed as "Myeloproliferative neoplasm, unclassifiable (MPN-U)". Identification of MPNs associated myelofibrosis (MPN-MF) cases has importance for management, even if they are unclassifiable. Several clinical trials including selective JAK1/JAK2 inhibitor therapy have been shown to rapid reduction, or reversal of myelofibrosis associated symptoms, and prolong overall survival in these cases.[18,24,34]

Conclusion:

Assessment of reticulin fibrosis, collagen fibrosis and osteosclerosis according to definite scoring system can discriminate all components of the complex bone marrow fibrous matrix. Reticulin fibres are not identifiable using H&E stain. For estimation of definite collagenized area, MT stain has no alternative, though it may fall short of detection of collagen fibres in a fibrotic case even if it contains diffusely increased reticulin fibres. For better prognostication of myelofibrotic patients, it is rational to use both special stains additionally to get a complete picture of the nature and amount of stromal fibres.

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Author contributions:

- Conception and design: SA
- Data acquisition, analysis, and interpretation: SA, BPD, RY, TI, AKMNK
- Manuscript drafting and revising it critically: SA, EK, SSUM, TI, USS
- Approval of the final version of manuscript: AKMNK

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Original Article

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Evaluation of Risk Factors in Recurrent Cervical Cancer after Primary Radiotherapy

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Abstract

Background: *It is generally recognized that early treatment provides the best chance of cure of cervical cancer. Delay in initiation of treatment is the main reason for recurrence and decrease survival rate.* ***Objective: To ev****aluate the risk factors in cervical cancer patients after primary radiotherapy.* ***Method:*** *This cross-sectional observational study was done from January 2021 to December 2021 in the Gynecological Oncology department of National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka. Total 127 histologically confirmed cervical cancer patients (50 recurrent & 77 non recurrent) were included in the study by purposive sampling technique.* ***Result:*** *Mean age of the patient was 46.50 (± 8.572) years in recurrent group and 49.450 (± 8.780) years in non-recurrent group of cervical cancer patient. Most of the patients were housewives (87.4%), multipara (71.6%), non-smoker (52.7%). Seventy (55.1%) patients had FIGO stage IIB at the time of diagnosis. About 95 percent of patient was taken CCRT plus ICRT as primary treatment. Overall recurrence rate is 39.4% among the study population. In most of the patients (82%), recurrence occurred within first 3 years of completion of treatment. Patients age <35 years, tumor size >4 cm, tumor appearance, histologic grade, FIGO stage and positive lymph node status were significantly associated with recurrence of cervical cancer ($p < 0.05$) but histologic cell types of tumors did not show significant result ($p > 0.05$).* ***Conclusion:*** *Overall recurrence rate is 39.4% in the study. Most of the patients recur within first three years. Patients age < 35 years, tumor size >4 cm, tumor appearance, histologic grade, FIGO stage and lymph node involvement were significantly associated with recurrence of cervical cancer (*$p < 0.05$*).*

Introduction

Cervical cancer is the fourth most common cancer in women with an estimated 604,127(6.5%) new cases and 341,831 (3.4%) deaths in 2020 globally. About 8,068 new cervical cancer cases are diagnosed annually in Bangladesh.[1]

The Primary treatment options of cervical cancer are radical surgery or radiotherapy (FIGO stage IB and IIA). Adjuvant radiotherapy is given on the basis of risk factors. Radical external beam radiation therapy is the gold standard for advanced disease. Failure is

anticipated in approximately 10 to 20% of the cases so treated. Radiotherapy can be given in all stages of cervical cancer. Though RT is the optimal therapy for cervical cancer with an appreciable outcome, treatment for a tumor relapse remains tough. Thus, it is essential to find out risk factors for recurrence which might benefit from additional or novel therapies, such as targeted agent, consolidation chemotherapy after RT.[2]. In contrast, patient with advanced stage disease (stage II-III) are at high risk (20-50%) of local relapse.[3]

The aim of the current study is to evaluate the risk factors in recurrent cervical cancer patients after primary radiotherapy.

MATERIALS AND METHODS

Thiscross-sectional analytical study was conducted on 127 patients from January 2021 to December 2021 at the department of Gynecological Oncology, National Institute of Cancer Research & Hospital, Dhaka. All consecutive patients with carcinoma cervix attending OPD for follow up, at least 6 months after completion of primary radiotherapy were the study population. All statistical analyses were performed using SPSS for Windows software (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, IBM Corp.). The association between recurrence and prognostic factors was analyzed by chi-squared test. Binary logistic regression was used to calculate the odds ratio for risk factors. The significance level was set at 5%. *p*-value < 0.05 was considered statistically significant

RESULTS

Mean age of the patient was 46.50 (± 8.572) years in recurrent group and 49.450 (± 8.780) years in non-recurrent group of cervical cancer patient. Other demographic and personal variables are shown in the Table I. One hundred six patients (83.5%) had FIGO advanced stage (IIB-IVA) disease at the time of diagnosis and only 21 patients had FIGO early-stage disease. Among advanced stage disease, 47 patients were in recurrent group and 59 in non-recurrent group while among 21 early-stage disease, 3 were in recurrent group and 18 were in non-recurrent group. Most of the patients (99, 77.9%) had their tumor appearance exophytic type, other types were ulcerative (4, 3.1%), endocervical (17, 13.4%) and erosive (7, 5.5%). Most of the patients (114, 89.8 %) had squamous cell carcinoma on histopathology. Thirteen patients (10.2%) had diagnosed as having non squamous cell carcinoma. Most of the patients (76, 59.8%) had Grade II cancer while 16 patients (12.6%) had Grade III tumor. Thirty-five patients (27.6%) were diagnosed as Grade I disease. In sixty-seven cases (52.8%), the tumor size was ≤4 cm. In 60 (47.2%) cases the size of the tumor was more than 4 cm (Table-II).

Table I: *Distribution of the patients by demographic variables (n=127)*

Demographic variables	Recurrent group Frequency (%)	Non-recurrent group Frequency (%)	*p*-value
Age in yrs. (mean ± SD)	46.50 ± 8.572	49.450 ± 8.780	
Monthly family income (BDT)			
≤1800 (n=67)	26(38.8)	41(61.2)	0.891
>1800 (n=60)	24(40)	36(60.0)	
Occupation			
Housewife (n=111)	43(38.7)	68(61.3)	0.701
Service (n=16)	07(43.8)	09(56.2)	
Parity			
Primiparous (n = 5)	02(40%)	03(60)	0.942
Multiparous (n= 91)	35(38.5)	56(61.5)	
Grand multiparous(n=31)	13(41.9)	18(58.1)	
Smoking habit			
Non-smoker (n=67)	26(38.8)	41(61.2)	0.881
Smoker(active/passive) (n=60)	24(40.0)	36(60.0)	
OCP intake			
No (n=60)	24(40.0)	36(60.0)	0.87
Yes (n=67)	26(38.8)	41(61.2)	

p-value obtained by Chi-square test.

Table II: *Distribution of tumor characteristics (n= 127)*

Characteristics	Total no of patient	Recurrent group Frequency (%)	Non-recurrent group Frequency (%)
FIGO stage			
Early stage (IB3-IIA)	21	03 (14.3)	18 (85.7)
Advanced stage (IIB-IVA)	106	47 (44.3)	59 (55.7)
Tumor appearance			
Ulcerative	4	02 (50)	02 (50)
Endocervical	17	15 (88.2)	02 (11.8)
Exophytic	99	31 (31.3)	68 (68.7)
Erosive	7	02 (28.5)	05 (71.5)
Histology			
Squamous cell carcinoma	114	46 (40.35)	68 (59.6)
Non squamous cell carcinoma	13	04 (30.76)	09 (69.24)
Histologic grade			
Grade I	35	08 (22.9)	27 (77.1)
Grade II	76	31 (40.8)	45 (59.2)
Grade III	16	11 (68.8)	05 (31.2)
Tumor size (cm)			
≤ 4	67	17 (25.37)	50 (74.63)
>4	60	33 (55.0)	27 (45.0)

Among 127 cervical cancer patients, fifty patients (39.4%) had recurrence in different sites. On univariate analysis it was demonstrated that patient's age, FIGO stage, tumor appearance, histologic grade and tumor size were significantly associated with recurrence and metastasis of the disease ($p< 0.05$) but tumor histology was not associated with recurrence and metastasis of the disease ($p> 0.05$) (Table IV).

Binary logistic regression analysis was performed to assess the impact of several independent variables (age of patient, parity, socioeconomic condition, occupation, smoking habit, OCP intake, tumor size, FIGO stage and histologic grade) on cervical cancer recurrence. This test shows that patients age < 35 years were 6.1 times more likely to develop recurrence than the patients with > 35 years old [OR- 6.104, 95% CI (1.213-30.711), p=0.014], patients with tumor size > 4 cm were 3.59 times more likely to develop recurrence of cervical cancer than the patients with tumor size < 4 cm [OR-3.59, 95% CI (1.699-7.605), p=0.001] and patient with grade III tumor were 4.06 time more likely to develop recurrence than the patient with grade I & II tumor [OR-4.061, 95% CI (1.316-12.531), patients with FIGO advanced stage were 4.779 times more chance to develop recurrence than the patients with early stage disease[OR – 4.779, 95% CI (1.32-17.21)] but other variables show no significant result (Table V).

Table-III: *Distribution of the patients by different treatment related variables*

Variables	Total no of patient	Recurrent group Frequency (%)	Non-recurrent group Frequency (%)	*p*-value
Treatment type				
EBRT	2	02 (100)	0 (0)	
EBRT + ICRT	5	05(100)	0(0)	0.003*
CCRT + ICRT	120	43(35.8)	77(64.2)	
Modalities used				
Cobalt 60	84	32(38.0)	52(62.0)	0.361
LINAC	43	18(41.9)	25(58.1)	
Planning with CT simulation				
Yes	44	10 (22.7)	34 (77.3)	
No	83	40(48.2)	43(51.8)	0.007
EBRT started within				
30-60 days	71	14 (19.7)	57 (80.3)	< 0.001
>60 days	56	36 (64.3)	20 (35.7)	
Duration of RT (wks.)	77	22 (28.6)	55 (71.4)	
≤15	40	21 (52.5)	19 (47.5)	0.005
16-18	10	07 (70.0)	03 (30.0)	
≥18				
Duration of brachy. (wks.)				
< 9	51	7 (13.7)	44(86.3)	
10-12	46	16(34.8)	30(65.2)	< 0.001
>12	28	25(89.3)	03(10.7)	

p-value obtained by Chi-square test or *Fisher's Exact test.

Table IV: *Univariate analysis of association of clinicopathological parameters with recurrent and metastatic cervical cancer (n = 127).*

Characteristics	No. of patient	Recurrent group Frequency (%)	Non-recurrent group Frequency (%)	*p*-value
Age (years)				
≤35	9	7 (77.7)	2 (22.3)	0.014
>35	118	43(36.4)	75(63.6)	
FIGO stage				
Early stage (IB3-IIA)	21	03 (14.3)	18 (85.7)	0.01
Advanced stage (IIB-IVA)	106	47 (44.3)	59 (55.7)	
Tumor appearance				
Ulcerative	4	02 (50)	02(50)	
Endocervical	17	15(88.2)	02(11.8)	0.001
Exophytic	99	31(31.3)	68(68.7)	
Erosive	7	02 (28.5)	05(71.5)	
Histology				
Squamous cell carcinoma	114	46 (40.35)	68(59.6)	0.503
Non squamous cell carcinoma	13	04 (30.76)	09(69.24)	
Histologic grade				
Grade I	35	08(22.9)	27(77.1)	
Grade II	76	31(40.8)	45(59.2)	0.007
Grade III	16	11(68.8)	05(31.2)	
Tumor size (cm)				
≤ 4	67	17 (25.37)	50(74.63)	0.001
>4	60	33(55.0)	27(45.0)	

p-value obtained by Chi-square test

Table V: *Binary logistic regression analysis of risk for cervical cancer recurrence*

Risk for cervical Cancer	*p*-value	OR	95% CI	
			Lower	Upper
Age of patient (<35 yrs.)	0.014	6.104	1.213	30.711
Tumor Size (>4 cm)	0.001	3.59	1.699	7.605
Histological grade (Grade III)	0.011	4.061	1.316	12.531
FIGO (advanced stage: IIB-IVA)	0.021	4.779	1.32	17.21

p-value & odds ratio (OR) obtained by binary logistic regression test.

DISCUSSION

In present study, the mean age of the patient was 46.50 (± 8.572) years in recurrent group and 49.450 (± 8.780) years in non-recurrent group of cervical cancer patient. Monthly family income was 16730.50 (±10580.31) BDT in recurrent group and 17345.4 (± 10130.30) BDT in non-recurrent group (Table I). Most of the patients (111, 87.4%) were housewives (43 in recurrent group and 68 in non-recurrent group) and 16 (12.6%) were service holders (7 in recurrent group and 9 in non-recurrent group). Most of the patients (91, 71.6%) were multipara and majority of the patients (67, 52.7%) were not smokers (26 in recurrent group & 41 in non-recurrent group). Sixty patients (47.3%) stated that they were subjected to passive or active smoking (24 in recurrent group & 36 in non-recurrent group). In our culture majority of the patients were subjected to passive smoking. Foreign studies identified, smoking even passive smoking increase risk to develop cervical cancer but not associated with risk of recurrence of cervical cancer.[4] Our study findings also show that smoking is not associated with the risk of recurrence of cervical cancer. A considerable number of patients (60, 47.2%) did not take OCP (24 in recurrent group & 36 in non-recurrent group) (table-II). Previous study shows that women who have used oral contraceptives increase risk to develop cervical cancer but not associated with recurrence of cervical cancer after treatment.[5,6]

In present study, one hundred six patients (83.5%) had FIGO advanced stage (IIB-IVA) disease at the time of diagnosis and only 21 patients had FIGO early-stage disease. This scenario of the current study is more consistent with the finding of a previous study where approximately more than 50% of the patients had stage over IIB.[7] Unfortunately, lack of diagnostic instruments, facilities of cancer treatment and cultural problem in the third world countries such as our region lead to delay in diagnosis of cervical cancer. In this study, most of the patients (99, 77.9%) had their tumor appearance exophytic type. This finding is more consistent with another previous study finding where predominant morphologically tumor type near about 80% was exophytic.[8] In the present study, most of the patients (112, 89.8 %) had squamous cell carcinoma on histopathology and thirteen patients (10.2%) had diagnosed as having non squamous cell carcinoma (table-II). Similar finding also found in a Bangladeshi study where predominant cell type of tumor was squamous cell carcinoma (91%).[9] In present study, leading number of patients (76, 59.8%) had Grade II cancer while 16 patients (12.6%) had Grade III tumor.

This is the general scenario of developing countries where cervical cancer screening is not well-established making identification of early cancer tough. In a study in Pakistan almost similar trend was reported,[10] where 20(35.71%), 22(39.28%) were in stages II and stage III respectively. In sixty-seven cases (52.8%), the tumor size was ≤4 cm. In 60 (47.2%) cases the size of the tumor was more than 4 cm. In this study a significant number of patients (60, 47.2%) had tumor size >4 cm which is vulnerable to develop recurrence of the tumor (table-II).

In this study, most of the cases (120, 94.5%) CCRT plus ICRT was employed due to the institutional protocol considering the above-mentioned ground. Recurrence is significantly high in patients receiving only EBRT and EBRT + ICRT than the patients receiving CCRT + ICRT (p-0.003). This study findings are more consistent with the findings of a recent meta-analysis by Chemoradiotherapy for Cervical Cancer Meta-Analysis

Collaboration where they showed that CCRT reduced local and distal cervical cancer recurrence and progression.[11]

In this study, in 84 patients (66.1%) Cobalt 60 machine was used to give external beam radiotherapy while 43 patients (33.9%) did receive their treatment by LINAC machine. Furthermore, chemotherapy enhances the radio sensitivity of tumor cells for better control and also controls potential distal tumor metastasis.[8] There was no significant difference in recurrence among the patients receiving Cobalt 16 and LINAC. This finding is more consistent with another study findings by K Holcomb et al., where rate of recurrence in patients treated with cobalt 60-unit vs Linear accelerator, rate of recurrence 65.6% vs 64.2% (no significant difference).[12] Forty-four patients received planning with CT simulation while 83 patients were not taken planning with CT simulation. Recurrence was significantly high in patients not receiving planning with CT simulation than the patients who were receiving planning with CT simulation (p= 0.007) (Table VI). In a study Beadle et al., it was found that that majority (66%) of pelvic nodal failure in conventional method. CT simulation provides more precise and individualized field delineation.[13] In the present study, most of the patients (71, 55.9%) started EBRT within 30-60 days and 56 patients started EBRT in > 60 days after confirming the diagnosis. Recurrence is significantly high in patients who received EBRT in > 60 days after confirming diagnosis than those who received EBRT within 30-60 days (p < 0.001) (table III).

In this study, in 77 patients (60.6%) the duration of the treatment was less than or equal to 15 weeks, in 40 cases (31.4%) the duration of treatment was 16 to18 weeks and in 10 cases (8.0%) the duration of treatment was >18 wks. The usual recommended duration of treatment is 55 days. In our setting due to scarcity of machine and manpower more time than expected is required which makes the patient vulnerable to treatment failure including recurrence. Recurrence was significantly high in patients where duration of treatment > 18 weeks than the patients who completed their treatment in d" 15 weeks and 16-18 weeks (p -0.005) (table VIII). The series by Teh et al. also found that treatment time of more than 8 weeks was significantly associated with poorer OS and DFS.[11] In this study, among 125 patients, 51 patients received brachytherapy in < 9 weeks, 46 patients within 10-12 weeks and 28 patients received in > 12 weeks. In patients who received brachytherapy in > 12 weeks, recurrence is significantly high than the patients who received in < 9 weeks and within 10-12 weeks (p-<0.001) (Table IX). A study by Teh et al. found that the patient who did not complete EBRT in time had treatment terminated early because of deteriorating performance status.[11]

The recurrence rate of cervical cancer ranges from-10% for FIGO stages Ib-IIa to -60% in locally advanced cases (stages IIb-IVa).[14] Recurrence rate ranging from 19% to 36% have been reported in various series following treatment of cervical cancer.[15-17] Overall recurrence rates of cervical cancer in this study is 39.4% and it is nearly similar with the above mention figures.

In most of the cases (112, 88.2%) lymph node was not involved but in fifteen patients (11.8%) lymph node was involved with the cancer. In contrast to this finding in a study by Liu et al. in 244 stage IIB patients, they found 25.8% patients had LNs metastasis, and 62.7% patients only had suspicious LNs.[7] Pre-treatment enlarged pelvic lymph nodes is also associated with recurrence of cervical cancer which is consistent with findings of a previous study by Sobhan et al.[9]

The present study identified tumor size > 4 cm, patient age < 35 years, tumor appearance, FIGO stage and histologic grade as an independent risk factor associated with recurrence of cervical cancer except tumor histologic type which is not associated with recurrence of cervical cancer (p < 0.05) (table-IV).Previous studies also identified several risk factors such as tumor size, lymph node metastasis, patient age, tumor appearance, tumor type, FIGO stage and histologic grade which are associated with the recurrence of cervical cancer.[8,9,18,19]Present findings of this study demonstrated that patient's age (< 35 years) was an independent risk factor for recurrence of cervical cancer (table-IV) which was consistent with the findings of previous studies.[8,18,19] The incidence of cervical cancer has increased among the young women over the last few years, with worse clinical outcome due to early recurrence. [1]Previous studies demonstrated that a cervical cancer lesion with a diameter > 4 cm is more difficult to control compared to smaller lesions[11] which is comparable to the present study findings (table-IV). The reason may be that large tumor lesions are more frequently associated with an earlier onset of distant tumor metastasis.[22, 23]

In the present study, tumor appearance specially ulcerative, endocervical and exophytic varieties are associated with recurrence of the cervical cancer which is compatible with a previous study finding (table-IV).[11] Large cervical cancer lesion with a cauliflower-like (Exophytic) and ulcerative tumor appearance often lack sufficient blood supply in their lesion center; thus, they subsequently recruit hypoxic cell and are more resistant to radiation therapy, may result in difficult control of these large, exophytic, ulcerated cervix cancers, subsequently causing recurrence or metastasis.[24-26] The present study suggest that histological grade III cervical cancer is highly associated with recurrence of cervical cancer (p- 0.011, OR-4.061, with 95% CI) [table-IV). This study findings contradict with previous studies [8, 21, 29] which show histological grade even high grades are not associated with recurrence of cervical cancer. FIGO stage of tumor has an impact on recurrence of cervical cancer shown in a previous study.[27] This finding is consistent with the finding of present study (table-IV). Some studies contradict with the present study finding regarding FIGO stage of cervical cancer.[3,9,28] In the present study binary logistic regression was performed to assess the impact of several factors on cervical cancer recurrence. In this present study, patient age < 35 years, tumor size >4 cm, tumor appearance, histological grade III, FIGO clinical stage except histologic cell types were identified as predictors of recurrence of cervical cancer. Thus, future large-scale studies are required in our setting to verify these findings prior to their application in clinical practice (Table V).

In conclusion, it may be stated that overall recurrence rate is 39.4% among the study population. In most of the patients (82%), recurrence occurred within first 3 years of completion of treatment. Patients age < 35 years, tumor size >4 cm, tumor appearance, histologic grade, FIGO stage and positive lymph node status were significantly associated with recurrence of cervical cancer ($p<0.05$) but histologic cell types of tumors did not show significant result ($p > 0.05$). Binary logistic regression analysis demonstrated that age of the patients < 35 years, tumor size > 4 cm, histological grade III tumor and FIGO advanced stage were independent risk factors for the recurrence of cervical cancer. About 83% of the patients of this study were FIGO stage IIB-IVA at the time of diagnosis. This scenario demand expansion of the screening programs at the community level of the country to identify the disease at early stage.

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Original Article

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Association of Obesity and Colorectal Cancer Among the Patients Attending at NICRH - A Case-Control Study

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Introduction:

Colorectal cancer is the third most commonly occurring cancer in men and second most commonly occurring cancer in women. There is a pronounced gradient in incidence rates between developing and developed countries with almost 60% of the cases occurring in developed regions. Based on American cancer society statistics 2020, the estimated number of new CRC cases and deaths in the United States are approximately 150,000 and 54,000 respectively.[1] Although the exact incidence of colorectal cancer in Bangladesh is not known, still then from Globocan prediction it is believed to be around 4.5%.[2] Over the past 27 years, the incidence cases of CRC have doubled worldwide, and have been increased three times in China. The unmet medical needs of CRC have been a growing public health issue.

The incidence of obesity is increasing worldwide and obesity associated diseases account for a large portion of public health challenges. Among obesity related disorders, a direct and independent relationship has been ascertained for colorectal cancer (CRC).[3] The prevalence of overweight (defined as a body mass index (BMI) between 25.0 and 29.9 kg/m^2) and obesity (BMI≥30 kg/m^2) has increased dramatically during the last decade.[4] In the EU, approximately 40-50% of men and 25-35% of women are overweight and an additional 15-25% of men and 15-25% of women are obese.[5] However the WHO Western Pacific Regional Office (WPRO) has proposed the definition of obesity in Asian populations with overweight defined as BMI 23.0-24.9 kg/m^2 and obesity defined as BMI≥25kg/m^2.[6]

According to Continuous Update Project Panel there was strong evidence that consuming processed meat, red meat and alcoholic drinks and greater body fatness increases the risk of colorectal cancer. There was also strong evidence that physical activity is protective against colon cancer specifically and the wholegrain, food containing dietary fibre, dairy products and calcium supplements decrease the risk of colorectal cancer.[7]

Several systematic reviews and meta-analyses summarized the evidenced that while the relative risk

associated with obesity was higher for colon cancer than for rectal cancer and it was higher in men than in women, abdominal obesity (as determined by waist circumference and waist to hip ratio) had a strong association with colon cancer in both sexes.[8-10]

Obesity, as a characteristic of metabolic syndrome, is related to chronic low-grade inflammation in obese subject. Several mechanisms linking adiposity to CRC risk have been proposed, among these, obesity related insulin resistance, hyperinsulinemia, sustained hyperglycaemia, oxidative stress,[11] adicytokine production[12] and hyperinsulinaemia related increase of insulin like growth factor-1(IGF-1)[13] all responsible for cancer promoting effect, favouring tumour growth, increasing cell migration and ultimately leading to metastasis. So chronic inflammation is a major link between obesity and tumour microenvironment in CRC.

In this respect, it is worth noting that obesity appears to be associated with worse cancer outcomes, both in terms of cancer recurrence and mortality.[14]

Materials and Methods:

It was a case control study. Data were collected from patients aged more than 18 years with histologically confirmed colorectal cancer within 6 months of diagnosis from February 2020 to January 2021 in a tertiary care hospital, NICRH. Controls were selected as healthy male and female subjects sharing identical socioeconomic status like patients, aged more than 18 years. Data were collected by interviewing patients using a structured and pretested questionnaire. The variables considered included age, socioeconomic status. personal habit, past medical history, height, weight, BMI, waist circumference, hip circumference, waist to hip ratio, histopathological type of cancer. The statistical analysis was carried out using SPSS software.

Result:

A total of 84 respondents were enrolled in each group of the study. The mean age of the control was 44.75 (±10.23) years and that of the case was 46.36 (±11.63) years.

Most of the respondents in both case and control group were male (70.2% and 61.9% respectively). Most of the female respondents in both groups were housewives (28.6% in case group and 34.5% in control). Regarding food consumption, no significant difference between cases and controls were found in rice/atta consumption pattern. But statistically significant differences were noted between two groups on meat, fatty food and vegetables consumptions ($p<0.05$).

Most of the case group were sedentary workers (84.5%), on the contrary more respondents in controls group used to do moderate (26.2%) and heavy workers (6%). Forty-one patients (48.8%) and 27 (32.1%) respondents in control group had history of smoking. More respondents in control group had positive family history of cancer (34.1%) while more respondents (11.1%) in case group gave history of alcohol consumption.

Table 1 : *Characteristics of respondents*

Variables	Case n (%)	Control n (%)
Gender		
Male	59 (70.2)	52 (61.9)
Female	25 (29.89)	32 (38.1)
Occupation		
Housewife	24 (28.6)	29 (34.5)
Day laborer	14 (16.7)	17 (20.2)
Agri worker	17 (20.2)	13 (15.5)
Service holder	6 (7.1)	06 (7.1)
Business	0 (0.0)	4 (4.8)
Others	23 (27.4)	15 (17.9)
Food consumption		
Rice/Atta		
<3times/day	13 (15.5)	09 (10.7)
>3times/day	71 (84.5)	75 (89.3)
Meat		
<once/week	49 (58.3)	63 (75.0)
>once/week	35 (41.7)	21 (25.0)
Fatty food		
<3times/week	58 (69.0)	73 (86.9)
>3times/week	26 (31.0)	11 (13.15)
Vegetables		
<4times/week	41 (48.8)	25 (29.8)
>4times/week	43 (51.2)	59 (70.2)
Physical activity		
Sedentary	71 (84.5)	57 (67.9)
Moderate	11 (13.1)	22 (26.2)
Heavy	2 (2.4)	5 (6.0)
Personal variables		
Smoking	41 (48.8)	27 (32.1)
Family h/o cancer	20 (23.8)	32 (38.1)
Alcohol consumption	10 (11.9)	07 (8.3)

Around 63% cases have WHR above 0.85 which indicates central obesity & this percentage was 33.1% in control group. More than 70% cases had WC above 80 cm while only 46.4% respondents in control group had WC >0.80 cm. Regarding BMI about three fourth of the case patients (73.8%) had BMI of 25 or more. All these differences were statistically significant (p<0.05).

Table II : *Distribution of respondents by body size*

Anthropometric variables	Case n (%)	Control n (%)
Waist to hip ratio		
>0.85	53 (63.1)	28 (33.3)
≥0.85	31 (36.9)	56 (66.5)
Waist circumference		
>80	59 (70.2)	39 (46.4)
≤80	25 (29.8)	45 (53.6)
BMI (kg/m^2)		
≥25	62 (73.8)	34 (40.5)
<25	22 (26.2)	50 (59.5)

Regarding diagnosis, leading number of patients were suffering from rectal cancer (44%). More than 40% of the patients had developed colon cancer. Only few patients were suffering from cancer of the ascending colon, descending colon, sigmoid colon or colorectal cancer (15.6%).

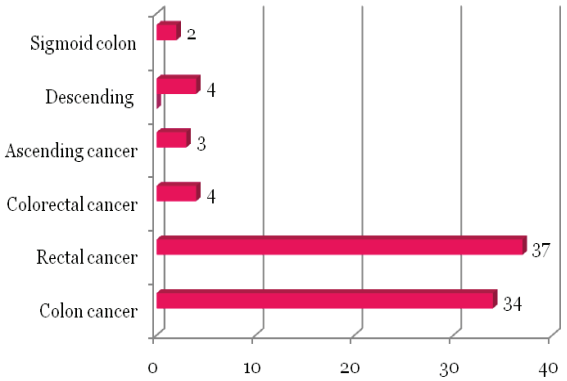

Fig.-1: *Distribution of the case patients by diagnosis*

In 26 (60.5%) colon cancer patients, WHR was above 0.85 while in 17 (39.5%) colon patients, the WHR was below 0.85, however this difference was not statistically significant (p>0.05). More than 70% colon cancer patients had WC over 80 cm while 10 (29.4%) had WC below 80 cm. Similar statistics were found regarding BMI. In 23 (62.2%) rectal cancer patients the WHR was above 0.85 and 26 (70.2%) had WC over 80 cm. 25 patients (67.6%) had BMI >25kg/m^2 and 12(32.4%) rectal cancer patients had BMI <25kg/m^2. These differences were statistically significant (P<0.05).

Table 3: *Distribution of colon and rectal cancer patients by anthropometric ariables*

Anthropometric variables	Colon cancer (n=43) n (%)	p-value	Rectal cancer (n=37) n (%)	p-value
WHR				
>0.85	26 (60.5)	0.17	23 (62.2)	1.139
≤0.85	17 (39.5)		14 (37.8)	
WC				
>80	24 (70.6)	0.016	26 (70.2)	0.014
d"80	10 (29.45)		11 (29.6)	
BMI				
≥25	24 (70.6)	0.016	25 (67.6)	0.033
<25	10 (29.4)		12 (32.4)	

Table IV: *Distribution of colon and rectal cancer patient by sex*

Parameter	n (%)
Colon Cancer	
Male	31 (72.1)
Female	12 (27.1)
Rectal Cancer	
Male	26 (70.3)
Female	11 (29.7)

In 43 colon cancer patient, 31 (72.1%) were male. In rectal cancer, most of patients were male (26, 70.3%) as well.

Table 5: *Binary logistic regression analysis of risk for colorectal cancer*

Risk for colorectal cancer	B	Wald	*p*-value	OR
Age	-0.007	0.119	0.731	0.993
Male sex	-0.378	0.574	0.449	0.257
Smoking	0.386	0.595	0.44	0.552
Rice/ Atta consumption	-1.026	3.138	0.076	0.115
Vegetable intake	-0.903	4.509	0.034	0.176
Meat consumption	0.912	3.28	0.07	0.928
Fatty food intake	1.414	6.911	0.009	1.433
Physical exercise	-1.666	7.431	0.006	0.057
BMI				
≥25 kg/m^2	1.422	18.211	0.001	2.157
WC				
≥80 cm	0.932	5.079	0.024	1.129
Waist hip ratio				
≥ 80.5	1.136	8.215	0.004	1.432

Binary logistic regression was performed to assess the impact of several factors on the likelihood that respondents would have developed colorectal cancer. The model contained 11 independent variables. The full model containing all predictors was statistically significant (p<0.001), indicating that the model was able to distinguish between respondents with or without colorectal cancer. Only six of the independent variables made a unique statistically significant contribution to the model (vegetables intake, fatty food intake, physical exercise, BMI, waist circumference, waist hip ratio).The strongest predictor of developing colorectal cancer was BMI>25 kg/m^2 recording an odds ratio of 4.14.This indicated that respondents who had BMI >25kg/m^2 were over 4 times more likely to develop colorectal cancer, controlling for all other factors in the model. The odds ratio of 0.189 for physical exercise was less than 1, indicating that moderate to heavy exercises were .189 times less likely to develop colon cancer than respondents with sedentary works, controlling for other factors in the model.

Discussion:

The current study was conducted at the National Institute of Cancer Research and Hospital to find out the relationship between colorectal cancer and obesity. Epidemiological data have reported a positive association between obesity (both general as assessed by BMI and abdominal as ascertained by waist circumference or waist to hip ratio) and colorectal cancer. In addition to its effects on colorectal cancer incidence, obesity may play a role in colorectal cancer recurrence, treatment outcomes and survival.[15]

The mean age of the case was 46.56(±11.63) years. Fifty-nine (70.2%) respondents in case group were male and rest were female. Similar findings (in male RR:1.40(1.33-1.47) and in female RR:1.07(0.97-1.18) were published in 8 case-control studies as reported by Moghaddam et al. in their review article.[3]

In the present study food consumption habits of the respondents were compared between two groups. Statistically significant differences were noted between cases and controls on meat, fatty food and vegetables consumption (p<0.05). In case group more patients used to take meat and fatty foods than control group while opposite trends was noted regarding vegetables consumption.

Most of the patients in case group were sedentary workers but the number of moderate workers was just double in control group. An umbrella review that included 19 reviews, 26 meta-analysis and 541 original articles reported "strong" evidence of the reactive physical activity on colon cancer.[16] Significantly more respondents (48.8%) in case group used to smoke than control group (32.1%).

Twenty-four colon cancer patients (70.6%) had waist circumference (WC) over 80 cm while 10 (29.4%) patients had WC below 80 cm. Similar statistics were found regarding BMI. These differences were statistically significant (p<0.05). Twenty six patients (70.2%) had waist circumference (WC) over 80 cm and 11(29.6%) rectal cancer patients had WC below 80 cm. Twenty-five patients (67.6%) had BMI >25kg/m^2 and 12 (34.4%) rectal cancer patients had BMI<25kg/m^2.In 2001, Bergstrom and colleagues were the first to quantitatively summarize the association between general obesity and risk of colon cancer from six studies and reported the risk of developing colon cancer to be 33% higher in obese people compared to people with normal weight.[17]

In a systematic review, the association between obesity and colorectal cancer was stronger for men than for women, for colon than for rectal cancer and for distal than for proximal colon.[18] Similar results were found in the present study.

On binary logistic regression a model was constructed which showed only six variables made a unique statistically significant contribution to the model. BMI ≥25kg/m^2 with an odds ratio (OR) of 4.14 was the strongest predictor of developing colorectal cancer. Almost similar OR was found for fatty food intake (4.11). The other risk factors were WHR>0.85(OR:3.11), WCe"80 cm (OR:2.54). The protective factors for colorectal cancer were physical exercise with odds ratio 0.189 and the other is vegetable consumption with odds ratio 0.405. An increase in colorectal cancer incidence in rapidly developing Asian countries such Japan, Singapore, China during the last 20-50 years points to an etiologic role of dietary lifestyle habits.[19]

Today there is convincing evidence that lifestyle associated risk factors such as abdominal and general obesity and nutritional factors red and processed meat and alcoholic beverages increase the risk of colorectal cancer, whereas physical activity and food rich in dietary fiber decrease the risk.[20]

Conclusion:

Like the existing literature the current study provides strong evidence that obesity is positively related to colorectal cancer. Both general and abdominal obesity are associated with an increased risk of colorectal cancer development. The strongest predictor of developing colorectal cancer was BMI>25 kg/m^2 (OR:4.14), fatty food intake (OR:4.11), WHR>0.85 (OR:3.11) and WC>80cm (OR:2.54). Physical exercise (OR:0.189) and vegetables consumption (OR:0.405) were found to be protective against development of colorectal cancer.

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Original Article

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Apheretic Platelet Transfusion during Covid-19 Pandemic: Experience from a Tertiary Care Cancer Hospital

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Abstract

Background: *Treatment related thrombocytopenia is a common and significant complication of cancer treatment. Thrombocytopenia is also a manifestation of haematological malignancy, solid tumors with bone marrow infiltration. It may lead to major haemorrhage like gastrointestinal, intracranial, intrapulmonary bleeding to hemorrhagic shock even death if left untreated. Chemotherapy induced thrombocytopenia may impact cancer treatmentin the form of chemotherapy delays and dose modifications. Platelet transfusions are used to treat thrombocytopenia for the last 30 years. During the COVID 19 pandemic period Transfusion Medicine Department of National Institute of Cancer Research & Hospital has to face uncertainties in distribution of platelets due to restrictions and lockdown. Despite challenges Transfusion Medicine Department have to continue uninterrupted platelet component support for cancer patients.* ***Methodology****: This observational study was conducted in the Department of Transfusion Medicine at National Institute of Cancer Research & Hospital over a 23 month period between March 2020 and June 2022. This study was done to analyze the situation during COVID19 period in a resource constrained country like Bangladesh despite shortages in donor & logistics. Data were collected from hospital records. Analysis was done by SPSS version 25.* ***Results****: Total 500 patients received apheretic platelet transfusion during the study period. Among them 288 (57.6%) were male and 212 (42.4%) were female. Majority129 (25.8%) were between the ages of 11 and 30 years than any other age group, according to age group analysisnext common age group was 21-30 years 108 (21.6%). Patients suffering from haematological malignancy 438 (87.6%) were the major recepients of apheretic platelet transfusion, followed by solid tumors 44 (8.8%) and other than malignancy 11(2.2%). Year wise distribution reflects majority 291(58.2%) of admitted patients*

received transfusion in the year 2021 followed by 150 (30%) in 2022 and 59 (11.8%) in 2020 respectively during COVID19 pandemic period. Year wise distribution reflects demand for platelet not decreased rather increased during pandemic in comparison to a prospective study done in NICRH in January 2018 to December 2019, included 210 platelet transfusion. Chemotherapy induced thrombocytopenia 464 (92.8%) patients were the largest group who needed platelet transfusion support. Patients with pre-transfusion platelet count between 10,000-30,000/ mm^3comprised the major group who received apheresis platelet transfusion. ***Conclusion:*** *Hematological malignancy and chemotherapy induced thrombocytopenia patients are the major receivers of apheretic latelet transfusion. Pre-transfusion platelet count between 10,000 - 30,000/mm^3comprised the major group needed platelet transfusion support while undergoing cancer treatment.*

Keywords: *Oncology patients, thrombocytopenia, apheretic platelet transfusion, COVID-19.*

Introduction:

Approximately 7000 units of platelets are transfused daily in the United States according to American Red Cross data estimation, the majority of these platelets are apheresis platelets.[1–3] Thrombocytopenia, an abnormally low blood platelet count, is a common side effect of myelosuppressive chemotherapy.[4–6] Different studies estimated that approximately 10% to 38% of patients with a solid tumor and 40% to 68% of patients with a hematologic malignancy patients experience thrombocytopenia.[6–10] The AABB recommends prophylactic platelet transfusion in hospitalized adult patientswith therapy-induced hypoproliferative thrombocytopenia who have a platelet count 10×109 cells/L or less to reduce the risk for spontaneous bleeding.[11] American Society of Clinical Oncology (ASCO) first published a guideline on platelet transfusion for cancer patients in 2001.[12] The guideline recognized the important role of platelet transfusion in the prevention and treatment of bleeding episodes in patients with treatment-related thrombocytopenia but also emphasized to avoid the overuse of platelet transfusions by carefully selecting patients who are likely to benefited most. Considering the cost of platelet transfusions, coupled with its potential adverse effects, like febrile and allergic reactions, transfusion related acute lung injury, and bacterial contamination,[13] ASCO panel emphasized on the importance of evidence-based transfusion practice. On March 11, 2020, the COVID-19 has been declared as the pandemic by the World Health Organization.[14] The coronavirus disease 2019 (COVID-19) pandemic disrupted the global blood supply. Low- and middle-income countries (LMICs) already experienced blood supply deficits that preceded the pandemic.[15] Using data from the records kept in transfusion medicine department we quantified and analyzed the pandemic's impact apheresis platelet collections and transfusions during the pandemic period.

Objective: To analyze the demographics of patients receiving platelet transfusion, year wise platelet transfusion requirement, different indications and current practices of platelet transfusion in NICRH,

Material & Methods:

This observational study was conducted among admitted patients who received platelet transfusion over a 23 months period between March 2020 and June 2022. National Institute of Cancer Research and Hospital is the only tertiary care cancer hospital in Bangladesh with 500 inpatient beds capacity. NICRH has one apheresis platelet collection machine which can supply up to six single donor unit platelets per day. Platelets were collected from donors by apheresis in outdoor settings in the Transfusion Medicine Department maintaining strict infection protection measures during COVID19 pandemic.

Platelet products, Apheresis

Platelet are prepared in two ways: concentrated and pooled from whole blood (WB) donations, or collected directly from donors via an automated apheresis

instrument.[16] Platelet concentrates (PCs) are also known as random donor platelets (RDP) or pooled platelets. The number of platelets in PC or RDP is variable, but 4 to 6 units of PCs need to be pooled to provide a therapeutic dose of at least 3 $x10^{11}$ platelets for adult patients. Apheresis platelets (APs) are also known as single-donor platelets (SDP). A typical apheresis procedure often can collect sufficient platelets to be split into 2 or even 3 doses of platelets, with each dose providing approximately the equivalent of 6 or more units of PCs (ie, 3–6 x 10^{11} platelets).[17]

Comparative studies have shown that the post-transfusion increments, hemostatic benefit, and adverse effects are similar with any of these platelet products. Thus, in routine circumstances, they can be used interchangeably.[18]

ASCO recommendation

Platelet can be transfused for both theraputic and prophylactic purposes,ASCO has published evidence based guidelineon indications of platelet transfusion for adults and children >4 months of age with hematologic malignancies, solid tumors or hypoproliferative thrombocytopenia.[18]

Platelet transfusion threshold in patients with hematologic malignancies

ASCO recommends a threshold platelet count <$10x10^9$/L for prophylactic platelet transfusion for patients receiving chemotherapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, or coagulation abnormalities (for example, acute promyelocytic leukemia) and in those undergoing invasive procedures or in circumstances in which platelet transfusions may not be readily available in case of emergencies, as might be the case in outpatients wholive at a distance from the treatment center.[18]

Platelet transfusion threshold for solid tumors

The risk of bleeding in patients with solid tumors who develop chemotherapy-induced thrombocytopenia is related to the depth and duration of the platelet nadir, although other factors also contribute. ASCO recommends threshold of <$10x10^9$/L for prophylactic platelet transfusion, which is based on extrapolation from studies in hematologic malignancies. Platelet transfusion at platelet count >$10x10^9$ is appropriate in patients with active localized bleeding, which can sometimes be found in patients with necrotic tumors.[18]

Dosage

The volume of doses of platelet is approximately 350-400 ml. One apheretic unit must contain a minimum of 3 x 10^{11}. Platelets. One apheresis unit should increase the adult patient's platelet count to20,000-60,000/iL. For paediatrics, the dose is 5-10 mL/kg. Apheretic platelets contain 200-400 mL of plasma when concentrated. The survival of transfused platelets averages 3 to 5 days but will decrease if the consumption process is present. One unit of apheretic platelets will be approximately 30,000/iL in an average sized adult.

Challenges in platelet inventory management

Platelets must be stored at room temperature and has a short shelf life of only 5 days because of the risk for bacterial growth during storage. Therefore, maintaining hospital platelet inventories is logistically difficult and highly resource-intensive.[19,20]

Due to short shelf life five days, platelets need to be collected as per the requirement and cannot be collected and stored similar to the Red Blood Cell units. NICRH is the only tertiary care cancer hospital in Bangladesh in public sector which has 23 departments including Transfusion Medicine Department. Everyday for managing cancer patients with thrombocytopenia transfusion medicine department have to maintain uninterrupted supply of platelet component therapy. At the time of lockdown, many patients were already admitted to hemato-oncology, medical oncology andonco-surgery and other departments. Many of these patients required platelet transfusions for prophylactic and therapeutic purpose,

Results

Total 500 patients received apheretic platelet transfusion (APT) during the study period. Among them 288 (57.6%) were male and 212 (42.4%) were female. Age group distribution showed about 129 (25.8%) patients are in the age group 10-20 years, next common age group is 21-30 years 108 (21.6%). Minimum age of the patient was 3 years maximum age was 70 years. Year wise distribution reflects majority 291(58.2%) of admitted patients received transfusion in the year 2021 followed by 150 (30%) in 2022 and 59 (11.8%) in 2021respectively. Patients suffering from haematological malignancy were

the largest group 438 (87.6%) who received platelet transfusion. 462 (92.8%) patients are needed platelet transfusion support while receiving chemotherapy. More than half of the patients have 279 (55.8%) pretransfusion platelet count between 10,000/mm^{3}and 30,000/mm^3. Acute leukaemia patients are the major recipients of apheretic platelet transfusion.

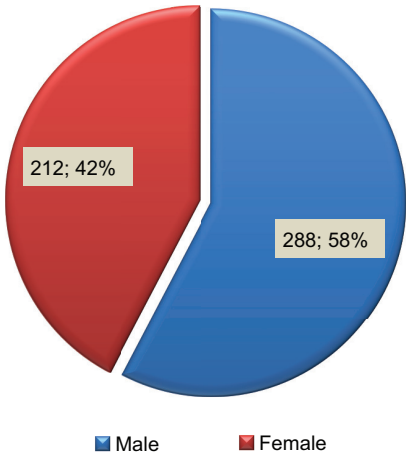

Figure 1: *Distribution of the patients by gender*

Table I : *Age group of the patients*

Age groups (yrs)	Number of patients	Percentage
3-10	63	12.6
11-20	129	25.8
21-30	108	21.6
31-40	82	16.4
41-50	56	11.2
51-60	56	11.2
61-70	6	1.2

Table II : *Year wise distribution of patients who received APT during the study period*

Year	Number of patients	Percentage
2020 (March to December)	59	11.8
2021 (January to December)	291	58.2
2022 (January to July)	150	30
APT Apheretic Platelet Transfusion		

Table III: *Distribution of patients by type of treatment received*

Treatment received	Frequency	Percentage
CT	464	92.8
RT+CT	4	0.8
Before treatment	32	6.4
Total	500	100

Table IV: *Distribution of patients by pre-transfusion platelet count*

Platelet Count/iL	Number of patients	Percentage
1,000 -10,000	112	22.4
10,000-30,000	279	55.8
30,000-50,000	90	18
50,000-80,000	19	3.8

Disease	Number	Percentage
Hematological malignancy (n=438)		
ALL	194	38.8
AML	205	41
CML	14	2.8
Lymphoma	12	2.4
Leukaemia	10	2
Multiple Myeloma	2	0.4
Myelodysplastic Syndrome	1	0.2
Solid tumours (n=44)		
Osteosarcoma	7	1.4
Ca-Breast	6	1.2
Ca-Lung	7	1.4
Ca-Pancreas	1	0.2
Ca-Urinary Bladder	2	0.4
Ca-Stomach	3	0.6
Ca-Liver	3	0.6
Ca-Cervix	3	0.6
Ca-Rectum	1	0.2
Ewing's Sarcoma	5	1
PNET	1	0.2
Neuroblastoma	4	0.8
Retroperitoneal Tumour	1	0.2
Other (n=18)		
Aplastic Anaemia	9	1.8
Dengue	1	0.2
Bleeding Disorder	1	0.2
Unknown Diagnosis	7	1.4

Several platelet transfusion guidelines have been developed by different societes[11,18,21] however, platelet transfusion practices are still heterogeneous because the available transfusion guidelines are not consistently followed and their implementation may be challenging in some clinical contexts.The COVID-19 pandemic has major implications for blood transfusion. There were unpredictable patterns of demand, and transfusion medicine departments need to plan for reductions in donations and loss of crucial staff due to sickness and public health restrictions.A reduction in donor numbers has largely been matched by reductions in demand for transfusion. Contingency planning includes prioritisation policies for patients in the event of predicted shortage. A range of strategies maintain ongoing equitable access to blood for transfusion during the pandemic.[22]

Blood transfusion is mandatory to support patients with hematological diseases, during surgery with high blood loss, or when acute bleeding occurs. However, during COVID-19 blood transfusion is limited by blood products availability depending on blood donation. Reduction in blood donation (due to lockdown and cancellation of mobile collection) and the deferral of donors suspected of being infected to prevent disease transmission could create a mismatch between demand and supply.

Before COVID-19 pandemic a prospective observational study was done in the Transfusion Medicine Department of NICRH from January 2018 to December 2019 which revealed annual apheresis platelet transfusion was 210 SDP units.[23] In the year 2022 during midst of COVID-19 pandemic Transfusion Medicine Department of NICRH have to supply 291 SDP units despite lockdown and potential shortages of donors which implies demand for platelets does not decreased rather increased during pandemic.

Conclusion

This study highlights that demand for constant and continuous platelet transfusion for oncology patients remains same during pandemic period. For sustainable platelet inventory management contingency planning is needed

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Original Article

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Impact of Different Mucin Stains in Diagnosing Variants of Cervical Adenocarcinoma

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Abstract

Background: *The incidence of cervical adenocarcinoma has been increasing worldwide despite the decreasing trend of squamous cell carcinoma. A similar increasing trend in the incidence of cervical carcinoma is obvious in Bangladesh due to the poor prognosis of cervical adenocarcinoma, Carcinomas that arise in the endocervix usually display variable morphology sometimes resulting in problems in diagnosis.*

Objective: *In this study, the potential role of four mucin stains, namely PAS, PAS-D, alcian blue (pH-2.5) and mucicarmine were investigated to categorize cervical adenocarcinoma variants.*

Methodology: *This observational study was carried out on the cases of diagnosed cervical adenocarcinoma from January 2014 to February 2017 at the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and a private histopathology diagnostic center in Dhaka city. Total 40 cases were included in this study. They were properly stained according to protocol with H&E stain, followed by some special stains for mucin.*

Results: *Our findings revealed that more than 90% cases of cervical adenocarcinoma belonged to 30-59 years age group of patients. To observe the morphological variants in endocervical adenocarcinoma, microscopic examination turned out that among the 40 histologically diagnosed cases, 18 cases were endocervical adenocarcinoma, usual type (45%), whereas 11 cases endometrioid carcinoma, 7 cases were villoglandular carcinoma, 2 cases for each of serous carcinoma and clear cell carcinoma. Serous carcinoma and clear cell carcinoma were the least common variants (each 5%) in this study. Both the cases of serous carcinoma were moderately differentiated and non-mucinous. Both clear cell carcinomas were poorly differentiated containing large pleomorphic cells with moderate amount of cytoplasm. One of these contained intracytoplasmic glycogen, which was PAS negative after diastase treatment. The other clear cell carcinoma contained PAS-positive intracytoplasmic mucin even after diastase treatment.*

Conclusion: *Epithelial mucins are secreted by epithelial cells for protection and lubrication. It may be produced in abundance (or focally) by some adenocarcinomas; thereby aiding in refining the histological diagnosis. However, in most cases, PAS stain alone would be sufficient to serve the purpose.*

Introduction

Cervical carcinoma ranked as the fourth most prevalent cancer in women and the fourth leading cause of cancer-related deaths worldwide in 2020.[1] However, it holds the position of the second most common cancer and the second highest cause of cancer-related deaths among Bangladeshi females.[2] Despite the steady decline in the incidence of cervical squamous cell carcinoma over the last four decades in many developed countries, primarily due to cytological screening programs such as the Papanicolaou test[3], recent studies have highlighted a rising trend in the incidence of cervical adenocarcinoma globally.[4]

Significantly, cervical adenocarcinoma currently accounts for 10-25% of total cervical carcinomas, compared to 5-10% three decades ago in developed countries.[5] Similarly, Bangladesh has observed a noticeable increase in cervical adenocarcinoma cases. Specifically, diagnosed cases of cervical adenocarcinoma comprised 7.1% of total cervical cancer cases in 2011, rising to about 8.6% in 2015 at the Department of Pathology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. However, the current crude rate of cervical cancer in Bangladesh stands at 9.8 (rate per 100,000 women per year) as of 2020.[6]

The clinical diagnosis of cervical adenocarcinoma is of paramount importance due to its poorer prognosis, attributed to its lower sensitivity to radiotherapy and chemotherapy compared to squamous cell carcinoma.[7,8] Carcinomas arising in the endocervix often exhibit variable morphology, leading to diagnostic challenges.[9] Furthermore, some of these morphologic variants are linked to distinctive biological behaviors.[10] Conversely, certain benign glandular proliferations of the cervix may be misdiagnosed as adenocarcinoma.[9]

Methodology

This observational study focused on cases of diagnosed cervical adenocarcinoma spanning from January 2014 to February 2017. The study was conducted at both the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU), and a private histopathology diagnostic center in Dhaka city. A total of 40 cases were included in the study. These cases underwent proper staining according to protocol, initially with H&E stain, followed by additional staining for mucin using special stains.

Role of mucin stains in diagnosing cervical adenocarcinoma

Mucins are secreted by epithelial cells for protection and lubrication. This type of mucin is known as epithelial mucin, and it may be produced in abundance (or focally) by some adenocarcinomas.

Epithelial mucins are of two varieties, acidic and neutral:

- Acidic mucins are Alcian Blue (AB)-positive (blue color). Most adenocarcinomas elaborate acid mucins.
- Neutral mucins are present in gastric foveolar cells, duodenal Brunner glands and prostate glands. They are PAS-positive (pink color). Unlike acid mucins, neutral mucins do not react with mucicarmine, AB or colloidal iron.[11]

Histochemically, Alcian blue and mucicarmine-positive materials are found intracellularly in nearly all cases of conventional cervical adenocarcinoma.[12] Usually, mucicarmine stain is more preferable due to greater specificity and intensity of staining in comparison to PAS stain. PAS also gives good result but the only drawback is that keratin also takes the same stain. So, the chances of false positivity increase. The study also shows that normal endocervical glands and inflammatory lesions of the cervix uteri contain mixture of all mucins with neutral mucin being predominant.[13]

Preeti et al.[14] stated that Mucin stains should be done routinely on moderately and poorly differentiated squamous cell carcinoma for evidence of mucin secretion which can be missed on H&E stain. Such carcinomas are known to have a more aggressive clinical course associated with a poorer survival when compared to non-mucin secreting squamous cell carcinoma.

Changsan et al. suggests that mucin histochemistry should be carried out routinely in all the cases of carcinoma cervix as Hematoxylin and Eosin staining is not sufficient.[15] These aids in the early detection of previously unrecognized mucin secreting adenocarcinoma and adenosquamous carcinoma, which pursue a more aggressive clinical course, and poorer prognosis than non mucin producing squamous cell carcinoma.

The study by Keshav et al.[16] suggests that PAS stains give positive reaction with glycogen or neutral polysaccharides but Alcian blue stain is more specific as it reflects the content of mucopolysachharides. So, these stains are useful in separation of adenocarcinomas into histological variants. This study also concluded

that, mucin staining should be done in all cases of carcinoma cervix in order to avoid errors in diagnosis and to detect poorly differentiated adenocarcinoma and mixed carcinomas.

The role of PAS, Alcian blue and mucicarmine to categorize different subtypes of cervical adenocarcinoma is questionable. The study conducted by Preeti et al.[14] showed that all adenocarcinoma cases are positive for both PAS and Alcian blue stain. The study conducted by Chaurasia et al.[13] also demonstrates that all adenocarcinoma cases are positive for both PAS and mucicarmine stain.

Results

Morphological variants of the cervical adenocarcinoma cases.

To observe the morphological variants in endocervical adenocarcinoma, a thorough microscopic examination was conducted among the 40 histologically diagnosed cases with H&E. Our findings revealed that among these cases, endocervical adenocarcinoma, usual type 18 (45%), endometrioid carcinoma 11 (27.5%), villoglandular carcinoma 7 (17.5%), serous carcinoma 2 (5%), and clear cell carcinoma 2 (5%) (Fig-1).

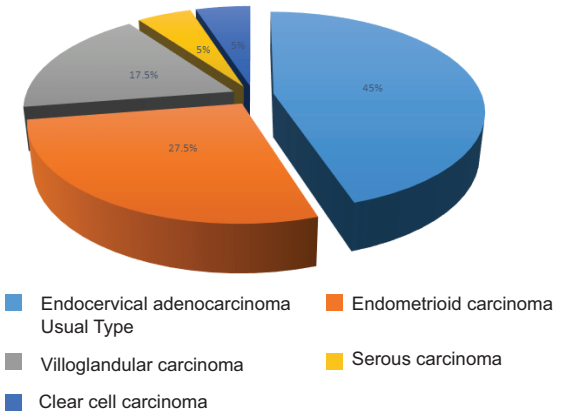

Figure 1. Distribution of morphological variants of cervical adenocarcinoma

Distribution pattern of mucin

Table 1 shows positivity of four special stains for mucin in different morphological categories of cervical adenocarcinoma in different locations of cells identified in this study except serous carcinoma, which was negative for all mucin stains.

Table 1. Mucin stains in different morphological variants of cervical adenocarcinoma

Special stains for mucin	Location of mucin		
	Cytoplasm	Only apical	Luminal secretion
Endocervical adenocarcinoma, usual type (N=18)			
PAS	18 (100.0)	0	13 (72.0)
PAS-D	18 (100.0)	0	13 (72.0)
Alcian blue (pH 2.5)	17 (94.0)	0	12 (66.7)
Mucicarmine	16 (89.0)	0	11 (61.0)
Endometrioid carcinoma (N=11)			
PAS	1 (9.0)	1 (9.0)	4 (36.0)
PAS-D	-	1 (9.0)	4 (36.0)
Alcian blue	-	1 (9.0)	4 (36.0)
Mucicarmine	-	1 (9.0)	3 (27.0)
Villoglandular carcinoma (N-7)			
PAS	5 (71.4)	0	3 (42.8)
PAS-D	5 (71.4)	0	2 (28.6)
Alcian blue	4 (57.0)	0	2 (28.6)
Mucicarmine	3 (42.8)	1 (14)	2 (28.6)
Clear cell carcinoma (N=2)			
PAS	2 (100.0)	0	2 (100.0)
PAS-D	1 (50.0)	0	2 (100.0)
Alcian blue	1 (50.0)	0	1 (50.0)
Mucicarmine	1 (50.0)	0	2 (100.0)

Percentages are shown in the parenthesis

All of the 18 cases of endocervical adenocarcinoma were positive for PAS and PAS-D, and mucin was mostly found both in cytoplasm and luminal secretion.

More than 50% (6/11) of cases of endometrioid carcinoma were negative for all four mucin stains. Only one case showed mild PAS positivity within the cytoplasm, two showed positivity within apical margin, and four cases showed positivity within the luminal secretion only.

In villoglandular carcinoma cases, around 70% cases (5/7) were PAS positive whereas mucicarmine was positive in 3 cases.

Both the cases of clear cell carcinoma were PAS positive whereas 1 case showed negativity for other three mucin stains.

Intensity of mucin stains in cervical adenocarcinoma cases

Intensity of PAS stain

Intensity of PAS stain in different variants of cervical adenocarcinoma cases were recorded in Table 2. Except serous carcinoma, all other variants were more or less PAS positive of different degrees. Most of the cases of endocervical, villoglandular, and both of the clear cell types were PAS positive. Both the cases of serous carcinoma were PAS negative. Figure 1 showing PAS positivity of endocervical adenocarcinoma.

Table 2: *PAS positivity in different types of cervical adenocarcinoma cases*

Types of cervical adenocarcinoma	PAS cases positivity			
	Strong	Moderate	Weak	Negative
Endocervical (n, %)	8(44.4)	8 (44.4)	2 (11.2)	0 (0.0)
Endometrioid (n, %)	0 (0.0)	0 (0.0)	5 (45.0)	6 (55.0)
Villoglandular (n, %)	1 (14.3)	3 (42.9)	1 (14.3)	2 (28.6)
Serous (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)
Clear cell type (n, %)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)

Intensity of PAS-D stain

Table 3 showed the positivity of PAS after diastase treatment in different variants of cervical adenocarcinoma. The PAS positive endocervical and villoglandular carcinoma were also PAS-D positive. One case of the clear cell carcinoma, which was moderately PAS positive, showed negativity after diastase treatment. Figure 2 reveals PAS positivity after diastase treatment.

Table 3: *PAS-D positivity in different types of cervical adenocarcinoma cases*

Types of cervical adenocarcinoma	PAS cases positivity			
	Strong	Moderate	Weak	Negative
Endocervical (n, %)	8 (44.4)	7 (38.9)	3 (16.7)	0 (0.0)
Endometrioid (n, %)	0 (0.0)	0 (0.0)	5 (45.5)	6 (54.5)
Villoglandular (n, %)	1 (14.3)	3 (42.9)	1 (14.3)	2 (28.6)
Serous (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)
Clear cell type (n, %)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)

Intensity of Alcian Blue stain

Alcian Blue positivity in different variants of cervical adenocarcinoma cases were shown in Table 4. Alcian blue was positive in most of the endocervical, villoglandular and one of the clear cell types. Both cases of serous type and most of the endometroid types were Alcian Blue negative. Endocervical type alone showed strong alcian blue staining. Figure 3 illustrates positivity of alcian blue stain.

Table 4: *Alcian Blue positivity in different types of cervical adenocarcinoma cases*

Types of cervical adenocarcinoma	Alcian Blue cases positivity			
	Strong	Moderate	Weak	Negative
Endocervical (n, %)	7 (38.9)	5 (27.8)	5 (27.8)	1 (5.6)
Endometrioid (n, %)	0 (0.0)	0 (0.0)	4 (36.4)	7 (63.6)
Villoglandular (n, %)	0 (0.0)	1 (14.2)	3 (42.9)	3 (42.9)
Serous (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)
Clear cell type (n, %)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)

Intensity of mucicarmine stain

Table 5 shows mucicarmine positivity in different types of cervical adenocarcinoma cases. Except serous type most cases were mucicarmine positive. Most of the endocervical and villoglandular types were mucicarmine positive. Both the serous cases and one of the clear cell types were mucicarmine negative. Most of the endometriod cases were mucicarmine negative. Figure 4 showing mucicarmine positive endocervical adenocarcinoma.

Table 5: *Mucicarmine positivity in different types of cervical adenocarcinoma cases*

Types of cervical adenocarcinoma	Mucicarmine positivity			
	Strong	Moderate	Weak	Negative
Endocervical (n, %)	5 (27.8)	2 (11.1)	9 (50.0)	2 (11.1)
Endometrioid (n, %)	0 (0.0)	0 (0.0)	3 (27.3)	8 (72.7)
Villoglandular (n, %)	0 (0.0)	1 (14.2)	3 (42.9)	3 (42.9)
Serous (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)
Clear cell type (n, %)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)

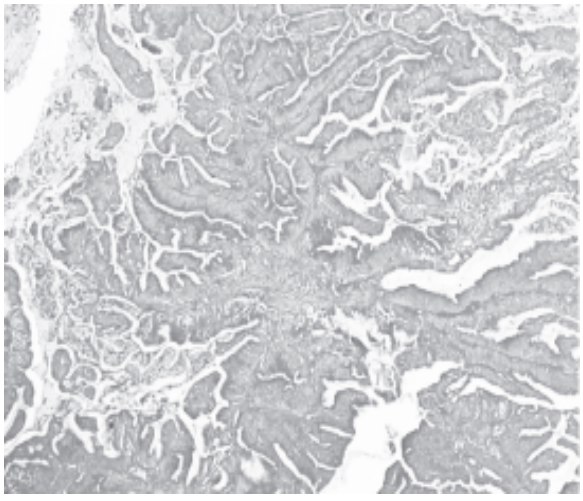

Figure 1: *Photomicrograph of endocervicaltype adenocarcinoma of cervix showing PAS positive material within the cytoplasm, x200 (Case no. 30, PAS, x200).*

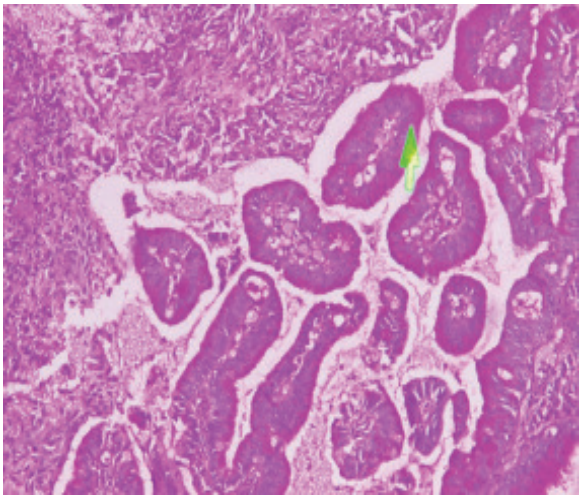

Figure 2: *Photomicrograph of a case of endocervical adenocarcinoma showing diastase resistance PAS positive material. (PAS-D 400x), (Case no. 30, PAS-Dx stain, x200).*

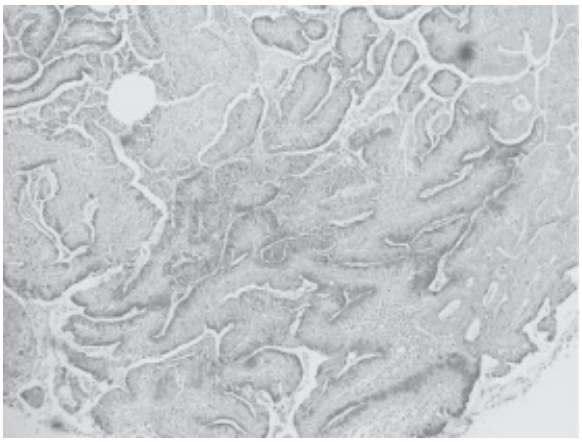

Figure 3: *Photomicrograph of endocervicaltype adenocarcinoma of cervix. Alcian blue positive areas are seen in the cytoplasm o the cells, x200(Case No. 05, Alcian blue stain).*

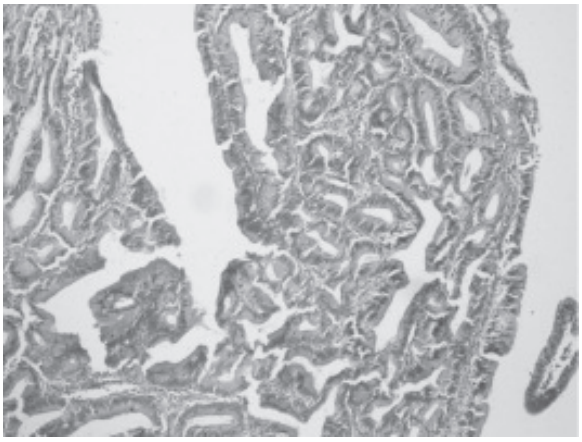

Figure 4: *Photomicrograph of endocervical type cervical adenocarcinoma showing mucicarmine positive cytoplasmic mucin, (Case no. 30, Mucicarnmine stain, x200)*

DISCUSSION

This retrospective study was done with the objective to examine thoroughly the morphological variants of cervical adenocarcinoma, their mucin content and distribution. A total of 40 cases of cervical adenocarcinoma were studied. Morphological variants that were identified with H&E stain and mucin stains are: Endocervical adenocarcinoma, usual type (45%); Endometrioid carcinoma (27.5%), villoglandular carcinoma (17.5%), serous carcinoma (5%), and clear cell carcinoma (5%).

Out of 40 study cases, endocervical adenocarcinoma, usual type, was the most common type, 18 cases (45%). Most of these tumors were well to moderately differentiated characterized by papillary and glandular structures along with mucin positivity both in cytoplasm and luminal secretions. Wilber et al.[5] stated that endocervical adenocarcinoma account for 90% of all adenocarcinoma of cervix, and they are mostly well to moderately differentiated having mucin poor eosinophilic cytoplasm. According to Kindelberger et al.[17] cytoplasm of the cells of cervical adenocarcinoma may be eosinophilic, mucinous appearing or a mixture of these. In this study, percentage of endocervical adenocarcinoma, usual type was less than expected, possibly because the sample size was small and not representative of the population.

In this study 11 cases (27.5%) of cervical adenocarcinoma were endometrioid carcinoma, representing a much greater percentage than those reported in literatures. According to Wilber et al.[5], endometrioid variants are rare accounting for not more than 5% of all cervical adenocarcinoma. However, the exact occurrence of endometrioid variant is not well established, because the morphological features sometimes overlap and subjective variation plays a significant role in making the histological diagnosis[17]. The endometrioid variants presented with more crowded and stratified cells resembling endometrial epithelium. These tumors were mucin poor.

Out of 40 cases, 7 (17.5%) were diagnosed as villoglandular carcinoma with villous-papillary architecture. Though this tumor has been reported as uncommon, in this study it is the third most common variant of cervical adenocarcinoma. Five of these seven villoglandular adenocarcinoma contain intracytoplasmic mucin.

Serous carcinoma and clear cell carcinoma were the least common variants (each 5%) in this study. Both the cases of serous carcinoma were moderately differentiated and non-mucinous. Both clear cell carcinomas were poorly differentiated containing large pleomorphic cells with moderate amount of cytoplasm. One of these contained intracytoplasmic glycogen**,** which was PAS negative after diastase treatment. The other clear cell carcinoma contained PAS-positive intracytoplasmic mucin even after diastase treatment.

Keshav et al.[16] and Chauasia et al.[13]have suggested to do mucin stain as a judicious adjunct for the diagnosis

of cervical adenocarcinoma. Special stains for mucin such as PAS, PAS-D, Alcian blue (pH-2.5) and mucicarmine stains are useful in diagnosing adenocarcinoma.

In this study, the potential role of four mucin stains, namely PAS, PAS-D, alcian blue (pH-2.5) and mucicarmine were investigated to categorize cervical adenocarcinoma variants. However, not much remarkable differences in staining pattern of these four mucin stains were noted in categorizing the variants. Most of the adenocarcinoma cases showed positive reaction for all four mucin stains, more consistently with PAS stain. Preeti et al.[14] showed in their study that all adenocarcinoma cases were positive for both PAS and alcian blue stains. The study conducted by Chaurasia, Sharma, and Gharde[13] also demonstrated that all adenocarcinoma cases were positive for both PAS and mucicarmine stain. However, during the present study it was found that PAS stain was more intense in all mucin-positive cases. On the other hand, mucicarmine stain was negative in 40% of the cases.

Keshav et al.[16] suggested that PAS stains give positive reaction with glycogen or neutral polysaccharides but alcian blue stain is more specific as it reflects the content of mucopolysaccharides. This study also correlated with this and mucin staining should be done in all cases of carcinoma cervix in order to avoid errors in diagnosis and to detect poorly differentiated mixed carcinomas, which may not be detected on H&E staining alone.

Conclusion:

In conclusion, morphological variations of cervical adenocarcinoma were quite evident in this study out of only 40 cases as follows: 45% endocervical adenocarcinoma, usual type; 27.5% endometrioid carcinoma; 17.5% villoglandular carcinoma; 5% serous carcinoma; and 5% clear cell carcinoma. Mucins stains as adjunct to routine H&E sections helped to identify distribution pattern of mucin within tumor cells, thereby aiding in refining the histological diagnosis. However, in most cases, PAS stain alone would be sufficient to serve the purpose.

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Original Article

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Asymptomatic COVID-19 in Cancer Patients of Bangladesh: A Hospital-Based Study

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Abstract:

Background: *In an attempt to provide insight on the issue of justification for screening cancer patients who are asymptomatic for COVID-19, this study was conducted aiming to see whether the rate of asymptomatic COVID-19 in cancer patients of Bangladesh is significantly high or low in any type of cancer, age group, gender or region of Bangladesh and to compare the epidemiological trend of asymptomatic COVID-19 in cancer patients with COVID-19 in the general population.* ***Methods:*** *It was a cross-sectional study based on data collected retrospectively from hospital records. Records of COVID-19 screening tests of cancer patients who did not have any COVID-19-like symptom but were screened for SARS-CoV-2 infection by Real-Time Reverse Transcription-Ploymerase Chain Reaction (rRT-PCR) before starting cancer treatment at the National Institute of Cancer Research and Hospital (NICRH) of Bangladesh during the 1st June 2021 to the 31st May 2022 were retrieved. COVID-19 positivity rate for this period, cancer types, age group, gender and regions of Bangladesh were calculated and analysed by two-sided Chi-square test to see the association of asymptomatic COVID-19 with these variables. National COVID-19 positivity data for this period was retrieved from the COVID-19 Dynamic Dash Board for Bangladesh to compare the epidemiological trend of asymptomatic COVID-19 in cancer patients with COVID-19 in the general population.* ***Results:*** *Asymptomatic COVID-19 was found in 6.37% of cancer patients of NICRH. The highest number of patients was with breast cancer and 7.71% of them were positive, the highest number of patients was from the age group 31-50 years and 6.74% of them were positive, female patients were more than males but the positivity rate was similar in both genders, the highest number of patients was from the Dhaka*

division and 6.29% of them were positive. Asymptomatic COVID-19 was not associated with any type of cancer, age group, gender or region of Bangladesh. Epidemiological trend of asymptomatic COVID-19 in cancer patients with time followed the COVID-19 trend in the general population. ***Conclusion:*** *Asymptomatic COVID-19 was not significantly high or low in any type of cancer, age group, gender or region of Bangladesh. The epidemiological trend of asymptomatic COVID-19 in cancer patients follows the trend of COVID-19 in the general population.*

Key words: *Asymptomatic COVID-19, COVID-19 in cancer patients, COVID-19 screening, COVID-19 epidemiological trend, SARS-CoV-2 infection*

Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection emerged in Bangladesh in March 2020 a few days before the World Health Organization (WHO) declared it a pandemic[1,2]. Cancer patients are usually immunosuppressed by the disease or by its treatment and are more prone to SARS-CoV-2 infection[3,4]. Complications and mortality are higher in SARS-CoV-2 infected cancer patients particularly those who are on anticancer treatments[5-7]. Though asymptomatic SARS-CoV-2 infections are lower in patients with comorbidities including those with cancers, these patients can be a potential source of infection to others[8,9].

In March 2020 the Government of Bangladesh adopted screening of symptomatic individuals for COVID-19[1]. But asymptomatic COVID-19 cases cannot be detected by symptom-based screening. NICRH, the only tertiary cancer care centre in the public sector in Bangladesh is providing treatment to cancer patients coming from different regions of the country. In the pandemic situation, it became essential for NICRH to find out asymptomatic COVID-19 cases with cancer because they may be the source of infection to other patients and health care providers. If uninfected cancer patients acquire COVID-19 in the centre from asymptomatic COVID-19 patients, it may result in severe disease and increased mortality in many of them[5-7]. Moreover, it became a critical question for the centre whether to continue or postpone anticancer treatment of SARS-CoV-2 infected cancer patients. In July 2020, the European Society of Medical Oncology (ESMO) published a guideline for managing cancer patients during the pandemic situation on the basis of an international expert panel consensus[10]. According to that guideline, NICRH started screening cancer patients for COVID-19 before hospital admission, chemotherapy, radiotherapy and surgery regardless of the presence or absence of COVID-19-like symptoms, and if found SARS-CoV-2 RNA positive, postpone treatment until they become negative. However, a systematic review of published literature and expert panel consensus guidelines concluded that they did not find strong evidence to support screening asymptomatic cancer patients before starting anticancer treatment even though it is suggested in the consensus guidelines. The same systematic review stated that there is a lack of studies that directly addressed COVID-19 screening of asymptomatic cancer patients before treatment[11]. This study was an attempt to address this gap and to contribute to providing insight on this issue.

Literature is available on asymptomatic COVID-19 in cancer patients in the USA and China[12-14]. We found literature on the prevalence of asymptomatic and symptomatic COVID-19 in the general population of Bangladesh[15]. We also found literature on clinical presentation and outcome of COVID-19 infected hospitalised cancer patients of Bangladesh[16]. To the best of our knowledge and search for literature, we did not find any publication on asymptomatic COVID-19 in cancer patients of Bangladesh. This study was aimed to find the rate of asymptomatic COVID-19 in cancer patients of Bangladesh and to see whether asymptomatic COVID-19 is significantly high or low in patients with any type of cancer, age group, gender or

region of Bangladesh. It also aimed to compare the epidemiological trend of asymptomatic COVID-19 in cancer patients with the trend in the general population.

Materials and Methods

This was a cross-sectional study based on data collected retrospectively from hospital records of COVID-19 screening test registrar of NICRH. It was conducted after approval of the protocol by the Institutional Review Board of NICRH (Approval No.: NICRH/IRB/2022/248, Date: 24/09/2022). One year COVID-19 screening test records of cancer patients of NICRH spanning from the 1st June 2021 to the 31st May 2022 were retrieved. This period was chosen because records of the test results in the PCR Lab registrar were available from the 1st June of 2021. Cancer patients who did not have any COVID-19-like symptom but screened by SARS-CoV-2 RNA test before treatment were included regardless of whether the test was positive or negative. COVID-19 screened cancer patients having fever, cough, running nose, breathing difficulty or any other COVID-19-like symptom were excluded. A total of 4,267 patients fulfilled these criteria and were included in the analysis.

Histologically diagnosed cancer patients coming to NICRH for various modalities of cancer treatment were screened. In the registrar, cancer diagnoses were recorded on the basis of the organ involved in most of the cases, and the histological type in others. To facilitate statistical analysis, cancer type data was then standardised by grouping the cancer types according to the International Statistical Classification of Diseases 10th Revision (ICD-10) codes[17]. In this study subjects, ICD-10 codes C1-C14 (oral cavity and pharyngeal cancers) included cancers of the tongue, gum, buccal mucosa, salivary glands, tonsils and pharynx, codes C15-C26 (digestive tract cancers) included cancers of the oesophagus, stomach, liver, gallbladder, pancreas, colon and rectum, codes C32-C34 (respiratory tract cancers) included cancers of the larynx and lung, codes C40-C41 (bone cancers) included osteosarcoma and Ewing's sarcoma, code C44 (skin cancers) included both melanoma and non-melanoma skin cancers, codes C51-C56 (female genital organ cancers) included cancers involving ovary, uterus, cervix, vagina and vulva, codes C61-C62 (male genital organ cancers) included cancers involving prostate, testis and penis, codes C64-C67 (urinary tract cancers) included cancers involving kidney, ureter and urinary bladder, codes C69-C71 (malignant tumours of eye and brain) included malignant tumours of the eyelid, retina, meninges and the brain.

All tests were done at the PCR Lab of the Department of Immunology and Molecular Biology of NICRH. All samples were nasal swabs collected at the COVID-19 sample collection booth of NICRH and transported to the laboratory in viral transport media on the same day. Tests were done either on the same day or preserved in the refrigerator at 2-8°C and tested on the next day. All samples were tested for SARS-CoV-2 RNA by rRT-PCR using Bio-Rad CFX 96 Real-Time PCR detection system (Bio-Rad Laboratories Inc., USA) and Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (Sansure Biotech Inc., China) according to manufacturer's instructions.

As an operational definition, the term 'asymptomatic COVID-19' was used for patients without any COVID-19-like symptom but positive for SARS-CoV-2 RNA by rRT-PCR test, the term 'asymptomatic cancer patients' was used for cancer patients not having COVID-19-like symptoms regardless of the presence or absence of symptoms due to cancer and the term 'region of Bangladesh' refers to the administrative division of Bangladesh.

COVID-19 positivity rate during this period, types of cancer, age group, gender and regions of Bangladesh were calculated and analysed by two-sided Chi-square test to see the association of asymptomatic COVID-19 with these variables using IBM SPSS Statistics 25.0 for Windows (IBM Corporation, USA). Probability (p) value <0.05 was considered statistically significant. The national daily COVID-19 positivity rate of the general population of Bangladesh for this period was retrieved in Microsoft Excel format from the COVID-19 Dynamic Dashboard for Bangladesh[18]. The national monthly positivity rate and positivity rate for this one year were calculated using Microsoft Excel. The monthly rate of asymptomatic COVID-19 in cancer patients of NICRH was plotted against national data to compare the epidemiological trends of these two with time.

Results

A total of 4,267 asymptomatic COVID-19 patients with various types of cancers were included in this study. The majority of these patients came as outpatients for various modalities of cancer treatment. Inpatients screened before surgery or chemotherapy was also included. The patients were aged between 1 to 120 years with a mean age of 44.85 years and a standard deviation of 17.01. The highest number of patients was from the age group 31-50 years followed by 51-70 years, females were more than males, the highest number of patients was from Dhaka division followed by Chattogram division and the majority of the patients were screened before chemotherapy (Table I).

Asymptomatic COVID-19 was found in 6.37% of cancer patients. The number of asymptomatic cancer patients screened for COVID-19 and positivity rate in various age groups is shown in Table 2. Positivity rate was highest in the age group >70 years and lowest in the 51-70 years age group. Asymptomatic COVID-19 positivity rate was not significantly high or low in asymptomatic cancer patients of any age group.

Table 1. *Characteristics of patients screened for asymptomatic COVID-19 (n = 4,267)*

Characteristics	Number	Percentage
Age group (years)		
≤18	402	9.42
19-30	444	10.41
31-50	1826	42.79
51-70	1471	34.47
>70	124	2.91
Gender		
Male	1798	42.14
Female	2469	57.86
Catchment region (Division)		
Barishal	546	12.80
Chattogram	803	18.82
Dhaka	1559	36.54
Khulna	473	11.08
Mymensingh	381	8.93
Rajshahi	241	5.64
Rangpur	206	4.83
Sylhet	58	1.36
Reason for screening		
Hospital admission	399	9.35
Chemotherapy	2355	55.19
Radiotherapy	319	7.48
Surgery	1194	27.98

Table 2. *COVID-19 positivity rates in asymptomatic cancer patients of various age groups*

Age group	No. Screened	No. Positive	Positivity rate (%)	*p*-value
≤18 years	402	25	6.22	0.67
19-30 years	444	32	7.21	
31-50 years	1826	123	6.74	
51-70 years	1471	83	5.64	
>70 years	124	9	7.26	
Total	4267	272	6.37	

Asymptomatic COVID-19 positivity rate was almost similar in males and females (Table 3).

Table 3. COVID-19 positivity rates in male and female asymptomatic cancer patients

Gender	No. Screened	No. Positive	Positivity rate (%)	*p*-value
Male	1798	114	6.34	0.93
Female	2469	158	6.40	
Total	4267	272	6.37	

Asymptomatic COVID-19 positivity rates in cancer patients from eight administrative divisions (regions) of Bangladesh are shown in Table 4. The rate was highest in patients from the Sylhet division and lowest in those from the Barishal division. It was not significantly high or low in asymptomatic cancer patients from any region of Bangladesh.

Table 4. *COVID-19 positivity rate in asymptomatic cancer patients from eight regions of Bangladesh*

Division	No. Screened	No. Positive	Positivity rate (%)	*p*-value
Barishal Division	546	30	5.49	0.62
Chattagram Division	803	46	5.73	
Dhaka Division	1559	98	6.29	
Khulna Division	473	30	6.34	
Mymensingh Division	381	29	7.61	
Rajshahi Division	241	20	8.30	
Rangpur Division	206	13	6.31	
Sylhet Division	58	6	10.34	
Total	4267	272	6.37	

Cancer types of patients grouped according to ICD-10 codes and asymptomatic COVID-19 positivity rate of each group are shown in Table V. The highest number of patients screened had breast cancers followed by female genital tract cancers. Female genital tract cancer patients included 489 cervical cancer, 216 ovarian cancer, 32 uterine cancer and 28 vulva and vaginal cancer patients. Respiratory organ cancer patients included 545 with lung cancer and 127 with larynx cancer. As a single-organ cancer, the number of patients with lung cancer was second to those with breast cancer. COVID-19 positivity rate was highest in patients with malignant tumours of eye and brain followed by in patients with urinary tract cancers but the number of patients with these cancers was small. COVID-19 positivity rate was zero in patients with skin cancers and male genital organ cancers and the number of patients with these cancers was also small. On statistical analysis, asymptomatic COVID-19 was not found significantly high or low in any type of cancer.

Table 5. *Cancer types of patients screened for asymptomatic COVID-19 and positivity rates*

ICD-10	Cancer	No. screened	No. positive	Positivity rate (%)	*p*-value
C1-C14	Oral cavity and pharynx cancers	251	13	5.18	
C15-C26	Digestive tract cancers	590	43	7.29	
C32-C34	Respiratory tract cancers	672	46	6.85	
C40-C41	Bone cancers	318	21	6.60	
C44	Skin cancers	22	0	0.00	
C50	Breast cancers	934	72	7.71	0.10
C51-C56	Female genital organ cancers	765	36	4.71	
C61-C62	Male genital organ cancers	40	0	0.00	
C64-C67	Urinary tract cancers	84	8	9.52	
C69-C71	Malignant tumours of eye and brain	12	2	16.67	
C73	Thyroid cancers	17	1	5.88	
C81-C96	Leukaemias and lymphomas	181	13	7.18	
C76-C80	Ill defined, secondary and unknown primary	381	17	4.46	
Total		**4267**	**272**	**6.37**	

The monthly COVID-19 positivity rate of asymptomatic cancer patients of NICRH and the national monthly COVID-19 positivity rate in the general population of Bangladesh are plotted in Figure 1. It shows COVID-19 positivity rate was higher from June 2021 to August 2021 and from January 2022 to February 2022 in both data. It also shows two peaks in both, one in July 2021 and the other in January 2022. Asymptomatic COVID-19 in cancer patients of NICRH was higher than COVID-19 in the general population only in June and July 2021 but lower in all other months. However, it shows the epidemiological upsurge and decline trend of asymptomatic COVID-19 in cancer patients with time, followed the trend of COVID-19 in the general population.

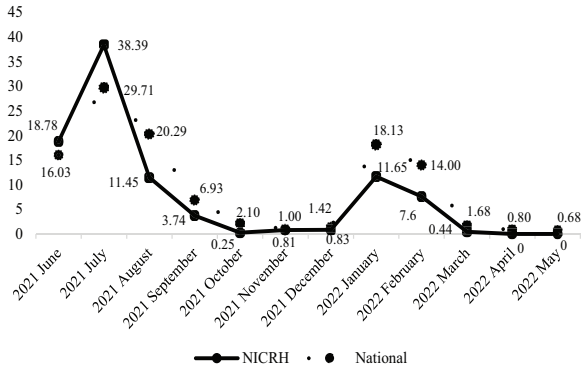

Figure 1. *Epidemiological trends of asymptomatic COVID-19 in cancer patients of NICRH and the national COVID-19 positivity in the general population of Bangladesh from June 2021 to May 2022*

As calculated from the daily positivity rate in the general population for this one year, the national COVID-19 positivity rate during this period was 9.39%[18]. Therefore, asymptomatic COVID-19 in cancer patients of NICRH (6.37%) during this period was lower than COVID-19 in the general population.

Discussion

This study was based on hospital records of NICRH of patients with various types of cancers who did not have symptoms suggestive of COVID-19 but were screened for SARS-CoV-2 infection by rRT-PCR test from the 1st June 2021 to the 31st May 2022. In our centre, we found asymptomatic COVID-19 in 6.37% of cancer patients for this period (Table 5). National data shows that COVID-19 in the general population was 9.39% for the same period[18]. Therefore, asymptomatic COVID-19 in cancer patients of NICRH was lower than COVID-19 in the general population of Bangladesh. This difference may be due to the difference in the presence or absence of symptoms in the individuals screened. National COVID-19 screening data included the results of symptomatic as well as asymptomatic individuals regardless of the presence or absence of cancer or any other comorbidity from whole Bangladesh whereas subjects included in this study were asymptomatic cancer patients seeking treatment at NICRH. A nationwide community-based cross-sectional study on 44,865 individuals during the period of April to October 2020 that included both symptomatic and asymptomatic individuals from 32 districts of Bangladesh found COVID-19 in 17.97% of symptomatic and 6.41% of asymptomatic individuals[15]. This indicates COVID-19 positivity rate in asymptomatic cancer patients is similar to asymptomatic individuals in the general population of Bangladesh.

Searching literature on the rate of asymptomatic COVID-19 in cancer patients, we noticed that different studies found different rates of asymptomatic COVID-19 in cancer patients. These studies were conducted in different places and at different periods of time during this pandemic. In addition, these studies had differences in sample size, inclusion criteria of study subjects and sampling technique. In Bangladesh, a hospital-based study on 43 COVID-19-positive cancer patients with and without COVID-19-like symptoms from August to October 2020 found asymptomatic COVID-19 in 23.30% of patients[16]. We found a much lower rate of asymptomatic COVID-19 in our cancer patients. Our study had a larger sample size, included only asymptomatic cancer patients, either positive or negative for SARS-CoV-2 RNA and it was conducted in a different time period. This may have contributed to the difference in positivity rate in the cancer patients of the same country. A study on 16 hospitalised cancer patients in Wuhan city of China from February to April 2020 found asymptomatic COVID-19 in 18.80% of patients whereas a hospital record-based study in the same city on 3,261 consecutive COVID-19-positive cancer patients from March to April 2020 found asymptomatic COVID-19 in 2.50% of patients[12,14]. A hospital-based cross-sectional study in New York City of the USA on 80 COVID-19-positive cancer patients from June to September 2020 found asymptomatic

COVID-19 in 3.75% patients whereas another hospital-based study in the same city of the USA on 537 cancer patients from April to June 2020 found asymptomatic COVID-19 in 0.64% of cancer patients[13,19]. A health system record-based study in Houston city of the USA from March to November 2020 that included 1,164 cancer patients of which 181 were COVID-19 positive, found asymptomatic COVID-19 in 13.00% of cancer patients[20]. In Europe, a hospital-based study on 260 consecutive cancer patients during the period of April to June 2020 in Piacenza, Italy found 3.85% asymptomatic COVID-19 in cancer patients and another study on 878 cancer patients from June to November 2020 in three regions of France found asymptomatic COVID-19 in 3.30% cancer patients[21,22].

As per our objective, we analysed whether asymptomatic COVID-19 is significantly high or low in any type of cancer, age group, gender and region of Bangladesh. We did not find a statistically significant association of asymptomatic COVID-19 with any of these variables. A healthcare record system-based study in Boston, USA on 22,914 COVID-19-screened cancer patients that included both COVID-19 positive and COVID-19 negative patients from various parts of the USA during the period of January to May 2020, found COVID-19 in 7.8% of cancer patients. They did not find an association of COVID-19 with age or gender but found significantly higher COVID-19 in haematological cancer in comparison with solid tumours. Among solid tumours they found it higher in prostate cancer patients and lower in patients with oesophageal cancers, hepatocellular carcinoma, squamous cell skin cancers, squamous cell head and neck cancers, urothelial cancer and bone cancer. They also found an association of COVID-19 with race and ethnicity[23]. Our study is also hospital record-based. COVID-19-screened cancer patients included in our study were only the asymptomatic ones, the system we used for classifying cancer was different and our sample size was smaller than that study. Moreover, in our study, the number of cancer patients in the groups with a high or zero positivity rates was very small (Table 5). These differences might be the reason for not finding an association with cancer types in our study. Our study subjects were from an ethnically homogeneous population. So we could not determine any association with race or ethnicity.

The strength of this study is its relatively large sample size and the fact that it was conducted over a one-year-period. Because of that, we could compare the upsurge and decline trend of asymptomatic COVID-19 in cancer patients of NICRH with COVID-19 trend in the general population of Bangladesh. This comparison shows that the epidemiological trend of asymptomatic COVID-19 in cancer patients follows the COVID-19 trend in the general population (Fig. 1).

This study has several limitations. As it was done on the basis of PCR Lab records, we did not find any record of the stage of cancer, performance status or comorbidities. We also did not have follow-up records. So we could not analyse and would not be able to provide any information on clinical course, outcome or how much time they required to get negative. A study on 201 cancer patients with COVID-19 shows that mortality is higher in patients with metastatic or relapsed cancers[24]. A study on 742 cancer patients with COVID-19 in Colombia found significantly higher asymptomatic COVID-19 in cancer patients if they were females, in the age group 18-30 years, had cancer in remission, ECOG (Eastern Cooperative Oncology Group) performance status grade 0 and no other morbidity[25]. A modeling study and some systematic reviews with meta-analysis show that asymptomatic COVID-19 patients can be a source of infection to others and may play a role in COVID-19 outbreaks[8,9,26]. As we did not have any record of contact tracing, we cannot determine whether asymptomatic COVID-19-positive cancer patients included in our study have transmitted the infection to others.

This study was intended to provide insight into the rationale for screening asymptomatic cancer patients for COVID-19 and delaying the treatment of positive patients. Some studies found that delaying cancer treatment due to COVID-19 may have adverse outcomes[27-29]. A systematic review designed to understand the impact of treatment delay due to COVID-19 analysed findings of 34 eligible published literature and concluded that even a four-week delay in cancer treatment may increase mortality[30]. Another systematic review that analysed 18 eligible published literature and four expert panel guidelines addressing the justification of treatment delay of asymptomatic COVID-19 patients did not find strong evidence to support screening asymptomatic cancer patients and delaying treatment if

they are SARS-CoV-2 RNA positive[11]. These findings are against screening asymptomatic cancer patients for COVID-19 and delaying the treatment of positive patients. On the contrary, a study states that treatment delays due to COVID-19 may not hinder outcome[31]. To address this debated issue, this study analysed COVID-19 screening test results of a relatively large number of asymptomatic cancer patients. Though this study's findings cannot directly answer to the question of whether screening and delaying treatment of asymptomatic COVID-19-positive cancer patients is justified or not, its data and findings may contribute to researchers interested in systematic review with meta-analysis to find the answer to the question.

In conclusion, asymptomatic COVID-19 was found in 6.37% of cancer patients in Bangladesh. It was not significantly high or low in any type of cancer, age group, gender or region of Bangladesh. The rate of asymptomatic COVID-19 in cancer patients of Bangladesh is similar to the rate of COVID-19 in asymptomatic individuals in the general population but lower than the national COVID-19 positivity rate. The epidemiological trend of asymptomatic COVID-19 in cancer patients follows the trend of COVID-19 in the general population. These findings and its data may contribute to systematic reviews with meta-analysis intended to verify the justification of screening and delaying treatment of asymptomatic COVID-19-positive cancer patients.

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Review Article

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Rehabilitation of Breast Cancer related Lymphedema - A Review

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Abstract:

Lymphedema is a problem that may occur after breast cancer surgery. It can occur months or years after treatment. Managing breast cancer-related lymphedema can be challenging, and rehabilitation approaches may be beneficial in individual cases. Rehabilitation treatment can be taken to reduce or relieve symptoms. If left untreated, lymphedema can get worse. Properly getting treatment can lower the risk of infections and complications. Pre-requisites for successful rehabilitation are the availability of physicians, nurses and therapists who are specially trained and experienced in each program.

Keywords: *Breast Cancer Related Lymphedema, Rehabilitation, Complex decongestive Therapy*

Introduction:

Breast cancer-related lymphedema results from obstruction or disruption of the lymphatic system associated with cancer treatment (removal of lymph nodes and radiotherapy); patient personal factors [obesity or higher body mass index (BMI)] can increase the risk of lymphedema; and infections or trauma can trigger lymphedema.[1] Accordingly, an in-depth understanding of breast cancer-related lymphedema (BCRL) and its treatments is necessary for all clinical providers. BCRL, a much-feared sequela of breast cancer treatment, results from disruption to the lymphatic system that prevents adequate drainage from lymphatic vessels causing protein-rich lymph fluid to accumulate in the interstitial space. This excess fluid can cause abnormal swelling in the breast, trunk or upper extremity on the side of treatment. Depending on the extent of oedema, symptoms of BCRL can include arm tightness,

heaviness/fullness, pain, and impaired limb function.[2] Health professionals commonly prescribe a range of conservative treatments to treat lymphedema, including complex physical therapy (CPT), manual lymphatic drainage (MLD), compression (bandages, garments and pumps), low-level laser therapy or exercises. Surgery may be considered when pitting lymphedema is present, characterised by increased interstitial fluid and low responsiveness when the tissue is compressed.[3]

The purpose of this study was to review BCRL management, focusing on evidence-based strategies and investigational approaches.

Methods: We conducted a comprehensive search of the online databases, especially of the last decades, to identify published studies describing the management of BCRL. References of relevant review articles were searched to identify studies missed by the database search. Information from retrospective and prospective randomized controlled trials and original articles concerning lymphedema were included in this study. Only articles in the English language were reviewed.

Incidence: In a recent meta-analysis, the overall estimated incidence of chronic arm oedema after breast cancer was found to be 21.4%, indicating that BCRL is a widespread problem affecting 1 in every 5 patients following breast cancer treatment. Due to the lack of diagnostic criteria for BCRL, the reported incidence varies from less than 5% to more than 50%.[2]

Risk factor: Lymphedema that develops after breast cancer treatment is thought to be related to the extent of axillary node involvement, type of breast surgery, and radiation therapy. These factors lead to decreased lymphatic drainage and stasis of fluids in the skin/tissue areas that generally drain to the axilla, including the ipsilateral breast, chest, lateral and posterior upper trunk, arm, and hand.[4] Emerging evidence indicates a lack of breast reconstruction as another treatment-related risk factor. Conversely, discord exists in the literature regarding the risk posed by taxane-based chemotherapy.[2]

Diagnosis and Assessment of Lymphedema: Lymphedema, principally, is classified as primary and secondary according to the aetiology. Lymphedema is called primary lymphedema when it progresses due to the congenital absence of lymphatic system components or their primary malformations. However, lymphedema depending on the factors such as radiotherapy, surgical intervention, trauma, inflammation, cancer invasion or mass compression, is classified as secondary lymphedema. Lymphedema is categorized as acute and chronic based on time intervals. Temporary lymphedema continuing shorter than 6 months and pitting when held down is acute. Nevertheless, lymphedema continuing longer and non-pitting with developing fibrosis is named chronic. There are two types of classification constituted by using the volume difference between a healthy arm and an arm with lymphedema to evaluate lymphedema more objectively. In the Tracey-volume categories, lymphedema is expressed 3 degrees. Mild: The volume difference between the two arms is about 150-400 ml. Moderate: The difference is about 400-700 ml. Severe: The difference is above 700 ml. In the Stillwell-percentage categories difference between the two extremities is shown as %. Mild: Volume difference between two arms is 11- 20 %. Moderate: The difference is 21-40 %. Evident: The difference is 41-80 %. Severe: The difference is more than 80 %.[5]

Treatment: Although post-mastectomy lymphedema has been known for decades, affecting thousands of women operated on for breast cancer who are often otherwise free of neoplastic disease, the treatment of this disorder has not yet been standardized. This results from a lack of effective therapies and well-conducted studies. Most patients are managed conservatively since no surgical procedure is entirely satisfactory. Recent reports have shown the effectiveness of different conservative treatments, often based on pneumatic compression of the affected limb or manual draining massage.[6] Surgical treatment for lymphedema includes microsurgical lymphovenous or lympholymphatic anastomoses, debulking, and liposuction.[1]

Rehabilitation: The rehabilitation program **starts** with a medical evaluation by the physiatrist, who clinically evaluates and identifies rehabilitation needs and sets goals to be met in the rehabilitation program. The patient is then directed to an educational group that gives information about the rehabilitation treatment.[7]

For the International Society of Lymphology, the main physical therapy treatment for lymphedema is complex physical therapy (CPT), a technique combining manual

lymphatic drainage (MLD), functional compression wrapping, therapeutic exercises, skin care, lymphatic self-massage, and use of elastic wrap. However, a total reduction of the lymphedema and maintenance of the result obtained from this treatment is still a great challenge.[8]

Conservative treatments have traditionally been the mainstay and are the initial treatment for all stages of lymphedema. The non-surgical treatment includes manual lymphatic drainage (MLD), complex decongestive therapy (CDT), and compressive garments. CDT is the hallmark of conservative lymphedema management. CDT is a non-invasive multimodality treatment that includes MLD, skin care, compression bandaging, and exercises. In breast cancer-related lymphedema, a physical therapist typically conducts the exercise component of CDT. It includes active and passive mobilization of all arm, wrist, and hand joints, ball-squeezing manoeuvres, and stretching of the pectoral and trapezius muscles. Another consideration of CDT is that the MLD component usually requires a skilled massage therapist. CDT is time-consuming, typically performed in 2 phases, with phase I involving weeks of intensive care with daily treatment sessions and phase II involving ongoing maintenance treatments less frequently. CDT often requires five sessions per week for 4 to 6 weeks and the concomitant use of continuous bandaging. While these treatments can effectively slow the progression of symptoms, they do not address the underlying pathology and are insufficient for many patients. Other modalities used have included topical laser therapy and pneumatic compression pumps.[9] Patient education focusing on risk reduction strategies is promising for lymphedema risk reduction. After controlling for confounding factors of treatment-related risk factors, patient education remains an important predictor of lymphedema outcome. While strict prevention measures may promote fears and frustration, one essential risk reduction behaviour under patient control is maintaining optimal body weight because excess weight is associated with decreased lymphatic function.[1]

Results: The standard of care for lymphedema is a multimodal decongestive therapy regimen that includes MLD, skin care, compression bandaging, and exercise. The CDT has been shown to improve extremity volume, pain, and quality of life in patients who develop lymphedema due to breast cancer. Kim et al. reported a reduction in lymphedema volume with CDT. Increased functionality may be an increase or a reduction in the oedema burden on the extremity.[10]

Compression bandaging and manual lymph drainage (MLD): One controlled study sought to ascertain whether four weeks of treatment with multi-layer compression bandaging alone was sufficient to reduce lymphedema or enhanced treatment outcomes could justify the additional cost of therapist-provided MLD. The study protocol did not include a post-intervention self-treatment or maintenance phase. Exercise is considered a standard part of CDT during the intensive therapist phase and the subsequent self-treatment maintenance phase.[11]

Due to these limitations, additional treatment strategies must be considered to optimize the treatment efficiency. In the present research, we found further effectiveness by combining CDT with ultrasound or faradic in treating symptoms related to the BCRL. The parameters used herein for faradic current can trigger muscle contraction, which could contribute to favourable clinical results. Electrical stimulation reduces oedema by increasing muscle contraction, which results in increased lymph flow and blood flow. Muscle contraction favours the removal of intercellular proteins; therefore, stimulating muscle contraction may be the most effective way to increase blood flow in muscles. Evidence shows blood flow can increase to 30 folds during rhythmic muscle contractions. In addition, muscle exercises improve revascularization in muscles.[12]

Another important issue in these patients is pain. A discomforting sense of pain that involves the extremities of patients with BCRL may be the early indicator of increased interstitial pressure associated with LE. This complication has been reported in 20 to 50% of BCRL patients. Patients often describe the pain as burning, aching, constriction, scar sensitivity, discomfort, or tenderness. Undoubtedly, pain limits daily activities to some degree. Some factors contributing to pain may be noted as mastectomy, axillary lymph node dissection, tissue trauma during the surgery, dissection of the intercostobrachial nerve, or intraoperative injury of axillary nerve branches.[13] Adding MLD to previously bandaged patients adds a positive effect, but the clinical impression is that bandaging is the most effective volume-reducing factor in combined treatment.[14]

Conclusion:

The primary adverse consequences after surgical treatment and, often after chemotherapy or radiotherapy, are pain (post-surgical treatment, post-chemotherapy, post-radiotherapy), upper limb impairment, postural imbalances, lymphedema, fatigue, and depression. Because of the increasing number of BC survivors, rehabilitation is becoming more important: rehabilitation goals are to encourage an appropriate recovery of activities of daily living (ADL), prevent and alleviate adverse treatment outcomes and promote quality of life (QoL).15 Most of the articles were published during the last decade, demonstrating that the investigated subject undergoes continual updating and elicits the interest of healthcare professionals.16 For Breast Cancer-related lymphedema, special Rehabilitation techniques can be undertaken to minimize the symptoms and complications. Some clinical trials are in progress. We expect diverse and potential measures to be applied to prevent Breast Cancer related lymphedema shortly.

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Case Report

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Rectal Cancer Metastatic to The Breast - A Rare Case Report

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Abstract

Breast tumors originating from non-breast tissues are infrequent, making up a small percentage of all breast tumors. While it is well-documented that various primary cancers, such as lymphoma, lung cancer, and melanoma, can metastasize to the breast, the occurrence of a breast mass originating from rectal cancer is exceptionally rare. Rectal cancer ranks as the third most common cancer globally, and around 20% of patients are diagnosed with distant metastases at their initial assessment. However, these metastases are usually observed in the lymph nodes, liver, or lungs. Given the distinct approaches to monitoring and managing these two conditions, a definitive diagnosis is pivotal in handling such exceedingly uncommon cases. Here we discuss a patient with a recurrent breast lump which was metastatic lesion from extramammary site malignancy.

INTRODUCTION

Metastasis to the breast from extramammary malignancy is rare. The incidence ranges from 0.5 to 1.3% in the clinical reports.[1] Lymphoma, melanoma, sarcoma, lung carcinoma and ovarian tumor are common extramammary primary malignancy metastasized to breast.[2]

CASE REPORT

Ms 'J' 19 years of age hailing from south Shahjahanpur Railway colony Narayanganj presented to us with the complaints of recurrence of right sided breast lump for 10 months, P/R bleeding for 4/5 months and abdominal distention for 15 days. According to the patient statement she was reasonably well 10 months back. Then she noticed a lump in her right breast which was rapidly increasing in size and not associated with any pain. She consulted with a local physician and underwent an unplanned lumpectomy. Histopathological examination revealed infiltrative lobular carcinoma and resected margin was involved by the tumor.

Then she was referred to Dhaka at a private hospital where H/P slide was reviewed and revealed mucinous carcinoma and immunohistochemistry (IHC) show TNBC In the meantime tumor again appeared within 1 month in the previous operation site. The patient again underwent WLE of the breast lump and histopathology revealed well differentiated infiltrating ductal carcinoma, mucinous type and all margin free of tumor. Then patient received 7 cycle adjuvant CT with ACT.

But during last part of chemotherapy patient again developed breast lump. At the same time, she noticed P/R bleeding both fresh and altered along with loose stool and mucus discharge. She also complained anorexia and significant weight loss for last 2 months. With these complaints she came to the GI OPD of NICRH On further query in GI 0PD she said that she had some form of alteration of bowel habit in the form of frequent diarrhea and mucus discharge for last 1 year After that she gradually developed abdominal distention along with scanty or no passage of stool with only blood and mucus discharge. She has no H/O cough, hemoptysis bone pain, jaundice, there is no significant past history. She is amenorrheic for last 6 months. She is fully immunized as per EPI schedule. She is from middle class family. Her father died due to throat cancer.

On general examination, the patient was anxious looking, irritated average body built, Nutritional status: Global PG-SGA category C, ECOG performance status 3, anemia present, jaundice absent, no accessible lymph nodes were palpable including left supraclavicular lymph node. The vitals were within normal limit. On local examination of the breast, there was a lump at the right breast, 4X3 cm in diameter involving upper outer and central quadrant with skin ulceration and fixation with pectoralis muscle. No axillary lymphadenopathy. Left breast appeared normal

On abdominal examination, abdomen was distended, flanks were full, umbilicus everted, mildly tender, no organomegaly, shifting dullness was positive. Bowel sound was exaggerated. On DRE, there was a circumferential ulcero-proliferative lesion, which was fixed and almost occluding the lumen of the rectum, about 4 cm from the anal verge. Other systemic examination reveals no abnormalities. Her blood parameters were CBC: HB% 13.6, TC 6.7x10^3 µL, PC 155 x10^3 µL, S. Albumin: 25.0g/L, CEA: 6.0 ng/ml, SGPT: 13.0U/L, S. Creatinine: 0.6 mg/dl. Plain X-ray of abdomen shows distended bowel loop suggestive of obstruction. MRI of pelvis revealed soft tissue mass of rectum and rectosigmoid junction with perilesional fat invasion, no enlarged lymph nodes. CT scan of the chest showed recurrence or residual of carcinoma right breast with no pulmonary metastasis.

CT scan of abdomen revealed carcinoma rectum causing invasion into posterior wall of the cervix and vagina involving both lateral pelvic side wall partially obscuring perivesical fatline posteriorly with no abdominal lymphadenopathy. Biopsy from breast lump showed ductal carcinoma recurrence. Proctoscopic biopsy from rectal growth revealed mucinous adenocarcinoma-primary/metastatic. Finally, immunohistochemistry from both breast and rectal tissue was done. Breast tissue: CK20 positive CDX2 positive, GATA3 negative, CK7 negative. Rectal tissue: CK20 positive, CDX2 positive, GATA3 negative, CK7 negative. Histopathological evaluation and immunohistochemical profiles were in support of rectal adenocarcinoma (primary) and the breast revealed metastatic adenocarcinoma of colorectal origin.

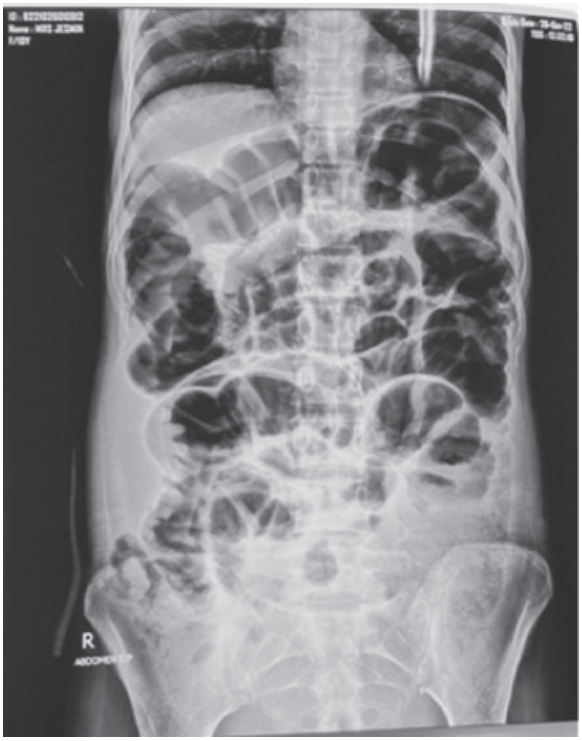

Fig.-1: *Plain X-ray of abdomen*

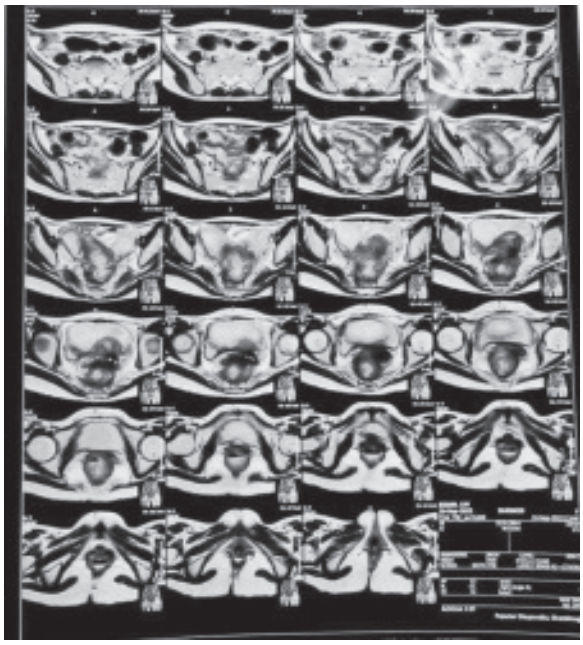

Fig:2.1 *MRI of the Pelvis*

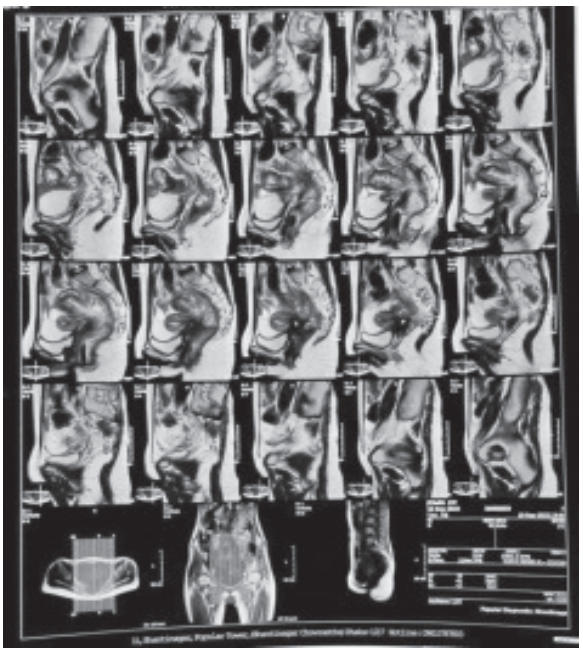

Fig:2.2 *MRI of the Pelvis*

Fig.-3.1 *CT scan of the chest*

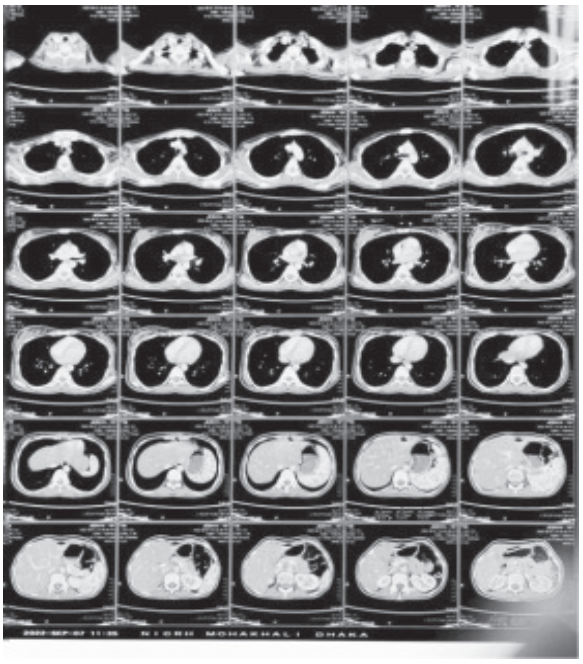

Fig:3. *CT scan of the chest*

DISCUSSION

Primary colorectal adenocarcinoma (CRC) metastatic to the breast is extremely rare, with the medical literature having only 19 recorded cases. So, our case may be the 20th of this type. Typically, CRC metastatic to the breast is indicative of widely disseminated disease and a poor prognosis.[3]

Metastases to the breast from extra-mammary malignancies are rare 0.43%. Lymphoma, melanoma, sarcoma, lung carcinoma and ovarian tumour are

common extra-mammary primary malignancies metastasizing to breast.[2] Metastases from colon to breast was first reported by McIntosh and from rectum by Lal in 1999.[4] These metastatic lesions must be differentiated from primary breast tumors on the basis of history, clinical, radiological features, morphology of tumor and immune-histochemistry.[4] Most metastases present as palpable breast masses, occasionally adherent to the skin with slight left predominance, most common being upper outer quadrant. Rarely are there multiple or bilateral lesions.[5] Schaekelford et al. reported 55% to the left, 30% to the right and only 3% with bilateral breast metastasis.[3] Toombs and Kalisher reported pain, tenderness or discharge is distinctly unusual. Nipple retraction has not been described, although adherence to the skin has been reported in 25%. Axillary node involvement was frequently encountered.[6] Our case presented in UOQ and central quadrant of Rt breast

Suganthi Krishnamurthy reported the youngest patient age 23 years old with rectal cancer metastasis to the breast,[7]our patient only 19 years. The time from initial diagnosis to metastasis to the breast varies between 1 month and 15 years, average between 1 and 5 years.[8]

Differentiating primary from metastatic breast neoplasms is not always easy. Mammograms help in settling doubts. The classic mammographic finding is a rounded, well-circumscribed mass no speculation, microcalcification or thickening of the skin.[5,9] Typical ultrasound (US) features of hematogenous metastases include single or multiple, round to oval shaped, well-circumscribed hypo-echoic masses without spiculations, calcifications, or architectural distortion located superficially in subcutaneous tissue or immediately adjacent to the breast parenchyma. Histologically, the metastatic tumors show the morphological characteristics of the primary tumors.[10] In our patient both rectal and breast malignancy revealed mucinous adenocarcinoma. In majority cases, immune-histochemistry can help to make an accurate diagnosis. Testing for expression of CK7 and CK20 is considered to be most beneficial. The great majority of primary breast cancers are CK7-positive and CK20-negative, while colorectal carcinomas are usually CK7-negative and CK20-positive. In our case both the rectal and breast tumor tissue revealed CK20 positive, CDX2 positive indicating colorectal origin breast metastasis. Mucinous differentiation of colorectal cancer is associated with poor outcome. In our patient, rectal tumor showed mucinous differentiation which explains the poor response to the neoadjuvant chemotherapy. Most patients succumb to the aggressive course of the disease within a year after the diagnosis of the primary tumor. Surgical treatment of secondary breast cancer is usually palliative. Mastectomy has no significant role; systemic chemotherapy is necessary in these patients. Mastectomy with effective systemic chemotherapy can prolong survival of these patients. However, its role is mostly palliative.[5,9] Metastasis to breast in rectal adenocarcinoma occurs via different pathways. Baum et al. hypothesized that tumor cells or fragments carrying the cellular genome may be released into the circulation and subsequently taken up by cells of the reticulo-endothelial system. Such genetic material may be passed to other cells of the reticulo-endothelial system and possibly to other normal cells via transfection. This could lead to expression of oncogenic sequences and development of cancer cell phenotypes in unexpected locations. The potential pathways into the circulation include: 1) metastasis through a lymph-vessel, the ductus thoracicus and body circulation to the breast; 2) metastasis through the communicating branches between the portal vein and venae intercostales to the breast; and 3) metastasis through the inferior hemorrhoidal veins, the venae hypogastrica and body circulation to the breast. We consider the second route may lead to breast metastasis in our patient.[1]

CONCLUSION

Ca rectum metastasised to the breast is a very rare entity and it indicates wide spread dissemination of disease and has a poor treatment response, and carries a poor prognosis. In case of metastatic breast lump radiological study of the breast may be misleading, mimicking a primary mammary carcinoma. Histopathologic clues of metastases include a lack of an in-situ component, prominent lymphovascular space invasion, and a “triple-negative” phenotype. However, when histology offers no definitive clues of a metastasis, proper diagnosis of this rare event requires an accurate clinical history, thorough physical examination, proper immunohistochemical workup and high level of suspicion. So multidisciplinary approach is crucial in avoiding unnecessary surgical procedures and pursuing proper subsequent patient management

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