ISSN: 2789-4622 (print)
ISSN: 2789-4630 (online)

CANCER JOURNAL OF BANGLADESH

Cancer J Bangladesh. Vol. 5, No. 2: July 2024
www.nicrh.gov.bd

CONTENTS

AN OFFICIAL JOURNAL OF TEACHERS' ASSOCIATION OF
NATIONAL INSTITUTE OF CANCER RESEARCH & HOSPITAL (NICRH)

Oncology & Biotech

Ziska Pharmaceuticals Ltd. is one of the leading pharmaceutical companies in Bangladesh, serving the nation for more than 35 years. Ziska is always striving to fulfill the unmet need of the patients by launching new molecules to the market through continuous efforts in research and development.

Keeping the legacy of bringing new hope to lives, Ziska Pharma has started a new venture in the specialized field of oncology and biotech.

"A step into innovation" **with this slogan Ziska Oncology & Biotech proudly introduces**

- CRIZONA — Crizotinib 250 mg cap.
- Osikin — Osimertinib INN 80 mg
- Gefikin — Gefitinib BP 250 mg
- Abiron — Abiraterone acetate USP 250 mg
- Lenvakin — Lenvatinib INN 4 mg & 10 mg
- Tukanic — Tucatinib INN 150 mg
- Neupomax — Filgrastim BP 30 MU/0.5 ml
- Imakin — Imatinib BP
- Olakin — Olaparib INN 150 mg
- Paribac — Niraparib INN 100 mg
- Palbokin — Palbociclib INN 125 mg
- Trombola — Eltrombopag INN
- Nivamo — 40 mg/4 ml, 100 mg/10 ml — Nivolumab INN
- PEMOMAB — Pembrolizumab INN 100 mg/ 4 ml

ZISKA PHARMA
Ziska Pharmaceuticals Ltd.
Green City Edge (3rd floor), 89 Kakrail C/A, Dhaka-1000
Web: www.ziskapharma.com

CANCER JOURNAL OF BANGLADESH

Vol. 5, No. 2: July 2024

The Official Journal of the Teacher's Association of
National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh
www.nicrh.gov.bd

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

While every efforts being made by the members of the editorial board to avoid inaccurate, misleading and duplicate imformation within the individual article, it is the sole responsibility of the author(s) for such act. The members of the editorial board accept no liability whatsoever for the consequences of any such inaccurate, misleading and duplicate information. It is not the task of the editors to investigate scientific fraud paper.

The editor reserve the rights to change the writing into customary style and if necessary shortens the material accepted for publication and to determine the priority and time of publication.

Published by

Prof (Dr.) Md. Jahangir Kabir on behalf of the Teacher's Association of NICRH

Printed at:

Asian Colour Printing
130, DIT Extension Road, Dhaka, Bangladesh
Phone: 49357726, 58313186
E-mail: asianclr@gmail.com

Subscritption

Tk 200 or $ 30 per copy

Address of Correspondence

Dr. Md. Johirul Islam, Executive Editor, Cancer Journal of Bangladesh, Department of Cancer Epidemiology, Block B (3rd floor), National Institute of Cancer Research and Hospital, Mohakhali, Dhaka-1212
E-mail: dr.johir@gmail.com

INFORMATION FOR THE CONTRIBUTORS

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

Requirements for manuscript submission: Based on the 'Uniform Requirements for Manuscript Submission to Biomedical Journals' recommended by the International Committee of Medical Journal Editors (ICMJE), the followings are the minimum requirements for the manuscripts submitted for publications:

The authors should submit two copies of manuscripts giving their full name with initial, highest academic degrees, designations and institutional affiliation at the time of the scientific work, with name and contact address (including cell phone number and email address) of the author responsible for correspondence in the title page. The manuscript must be accompanied by a forwarding letter to the publisher, signed by all authors, containing the statements that the article has neither been published before nor it has been under consideration for publication in any other journal.

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

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

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

The references must be in the Vancouver style and they should be numbered consecutively in the order in which they are first mentioned in the text.

Ethical aspect: All manuscripts of the original articles or case report must have ethical clearance from the Institutional Review Board (IRB) as appropriate for the scientific work.

Other information: All measurements/ values should be expressed in SI unit. For online submission, all the word files should be sent as .zip or .rar files. All submitted manuscripts will be peer reviewed. After peer review the manuscripts will be placed before the editorial board for final approval before publication. The editorial board reserves the right, if necessary, to change the style of the writing, to shorten the material accepted for publication, and to determine the priority and time of publication.

Address for Submission of Manuscript

The Executive Editor
Cancer Journal of Bangladesh
Department of Cancer Epidemiology (3rd floor, Block B)
National Institute of Cancer Research & Hospital
TB Gate, Mohakhali, Dhaka-1212, Bangladesh
E-mail: dr.johir@gmail.com

ISSN: 2789-4622 (print)
ISSN: 2789-4630 (online)

CANCER JOURNAL OF BANGLADESH

Cancer J Bangladesh. Vol. 5, No. 2: July 2024
www.nicrh.gov.bd
A BMDC recognized journal (sl. 157)

CONTENTS

Editorial

Cancer J Bangladesh 2024;5(2): 41-42
http://nicrh.gov.bd/publication

Cancer Immunotherapy with mRNA Vaccine

Sufi Hannan Zulfiqur Rahman[1]

[1] Associate Professor & Head, Immunology & Molecular Biology, National Institute of Cancer Research and Hospital, Dhaka

Citation: Rahman SHZ. Cancer Immunotherapy with mRNA Vaccine. Cancer J Bangladesh 2024;5(2):41-42.

Correspondence: Dr. Sufi Hannan Zulfiqur Rahman, Associate Professor & Head, Department of Immunology & Molecular Biology, National Institute of Cancer Research and Hospital, Dhaka. E-mail: sufihannan@yahoo.com

Immunotherapy is considered an auspicious approach to cancer treatment because of its efficacy, safety, and potential to treat almost all cancers. Since 2011 several immune checkpoint inhibitors that boost the immune response against cancers have been approved by the United States Food and Drug Administration (US FDA) for cancer treatment.[1] Cytokines that modulate the immune response and monoclonal antibodies that bind to cell surface receptors expressed by some cancer cells and kill them are also used.[2,3] An evolving and promising cancer immunotherapy option is therapeutic cancer vaccines. Various vaccine platforms have been explored by scientists globally to treat cancers. These include live attenuated, killed, or genetically modified whole-organism vaccines, subunit vaccines, DNA vaccines, messenger RNA (mRNA) vaccines, and cell-based vaccines. Currently, US FDA-approved therapeutic cancer vaccines are BCG (Bacillus Calmette-Guerin, a live attenuated *Mycobacterium bovis*) for urinary bladder cancer, T-VEC (Talimogene laherparepvec, a genetically modified Herpes simplex virus 1) for metastatic melanoma, and Sipuleucel-T (a dendritic cell vaccine containing prostatic acid phosphatase antigen) for castration-resistant prostate cancer.[4] A relatively new and innovative vaccination platform is mRNA vaccines. Identifying the gene sequence of optimal tumour-specific antigen, and finding a suitable delivery platform is of significant value for designing an mRNA vaccine. Advancements in gene sequencing and bioinformatics analysis tools have eased the technique for identification of the DNA sequence of optimal tumour-specific neoantigens, and the development of lipid nanoparticle delivery vehicles improved the mRNA vaccine delivery to the tissues.[5] After the discovery of nucleoside-modified mRNA vaccine by Katalin Kariko and Drew Weissman and its successful application in combating the COVID-19 pandemic, scientists and pharmaceutical companies are optimistic about its successful application for cancer immunotherapy.[6,7] An mRNA cancer vaccine may be prepared with shared or personalised neoantigens. When injected into muscles or subcutaneous tissue, they are taken up by the resident dendritic cells and macrophages. The mRNA produces the encoded protein antigen in the cytoplasm of the cells which is expressed on the cell surfaces with MHC molecules. When the dendritic cells or macrophages migrate to the regional lymph nodes, T lymphocytes recognise the antigen and get activated. Activated T lymphocytes differentiate into cytotoxic T lymphocytes, migrate to the tumour microenvironment and kill the tumour cells expressing the same antigen. Even though no mRNA vaccine has passed Phase III clinical trial and none got US FDA approval for clinical use until now, this vaccine platform seems to have huge prospects in cancer immunotherapy. This is because these vaccines are non-infectious, non-mutagenic, degrade naturally, activate both humoral and cell-mediated immune systems, more than one antigen sequence can be included in one vaccine, and can be produced rapidly in scalable amounts *in vitro*. In

addition, its production cost is relatively lower than other vaccines. Many clinical trials have been conducted to treat various cancers with therapeutic mRNA vaccines. These include non-small cell lung cancer, colorectal cancer, gastric cancer, oesophageal cancer, triple-negative breast cancer, urinary bladder cancer, pancreatic cancer and hepatocellular carcinoma. Most of these clinical trials are either in Phase I or Phase II. In some rials, mRNA vaccines were applied alone, and in others in combination with immune checkpoint inhibitors. Both approaches have shown good safety and efficacy in the trials. However, significant challenges remain to the clinical application of mRNA vaccines in cancer immunotherapy. These include the complexity and difference of tumour microenvironment across the cancers, and instability of mRNA molecules both *in vitro* and *in vivo*.[8] A better understanding of the tumour microenvironment and anti-tumour immune response is required to be innovative in designing better mRNA vaccines to overcome these challenges and their successful application in cancer treatment. Considering safety, efficacy, scalable production, and low production cost, continued research and investment in mRNA cancer vaccines appear to have a tremendous opportunity in cancer immunotherapy, and these vaccines are expected to change the landscape of cancer treatment in the near future.

References

1. Vaddepally RK, Kharel P, Pandey R, Garje R, Chandra AB. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. Cancers (Basel). 2020;12(3):738. doi: 10.3390/cancers12030738.
2. Weiner LM, Dhodapkar M V., Ferrone S. Monoclonal antibodies for cancer immunotherapy. Lancet. 2009; 373 (9668):1033-40. doi: 10.1016/S0140-6736(09) 60251-8.
3. Berraondo P, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez-Gracia JL, et al. Cytokines in clinical cancer immunotherapy. Br J Cancer. 2019 Jan;120(1):6-15. doi: 10.1038/s41416-018-0328-y.
4. Sarangi R, Mahapatra S, Bahinipati J, Jhajharia S, Pradhan T. Therapeutic cancer vaccines: Where do we stand? J Integr Med Res. 2023;1(4):158-163. doi: 10.4103/jimr.jimr_28_23.
5. Fan T, Zhang M, Yang J, Zhu Z, Cao W, Dong C. Therapeutic cancer vaccines: advancements, challenges, and prospects. Signal Transduct Target Ther. 2023;8(1):450. doi: 10.1038/s41392-023-01674-3.
6. Krause W. mRNA—From COVID-19 Treatment to Cancer Immunotherapy. Biomedicines. 2023;11(2):308. doi: 10.3390/biomedicines11020308.
7. Bansal A. From rejection to the Nobel Prize: Karikó and Weissman's pioneering work on mRNA vaccines, and the need for diversity and inclusion in translational immunology. Front Immunol. 2023;14:1306025. doi: 10.3389/fimmu.2023.1306025.
8. Wang B, Pei J, Xu S, Liu J, Yu J. Recent advances in mRNA cancer vaccines: meeting challenges and embracing opportunities. Front Immunol. 2023;14:1246682. doi: 10.3389/fimmu.2023.1246682.

Original Article

Cancer J Bangladesh 2024;5(2): 43-48
http://nicrh.gov.bd/publication

A Comparative Study between Weekly Versus Three Weekly Concurrent Chemoradiation in Locally Advanced Laryngeal Cancer

Rezwanul Quader[1], Mohammed Mehbub Ahsan Rony[2], Tanzina Meher Shathi[3], Afroja Begum Tania[4], Marwa Mobarak[5]

[1]Assistant Registrar, Radiation Oncology Department, National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka

[2]Assistant Professor, Radiation Oncology Department, NICRH, Mohakhali, Dhaka

[3]Medical Officer, Mugda Medical College & Hospital, Mugda, Dhaka

[4]Assistant Professor, Oncology Department, Enam Medical College & Hospital, Savar Dhaka

[5]MPH (Resident), National Institute of Preventive & Social Medicine (NIPSOM), Dhaka

Citation: Quader R, Rony MMA, Shathi TM, Tania AB, Mobarak M. A comparative study between weekly versus three weekly concurrent chemoradiation in locally advanced laryngeal cancer. Cancer J Bangladesh 2024;5(2): 43-48.

Correspondence: Dr. Rezwanul Quader, Assistant Registrar, Radiation Oncology Department, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka. Email: rezwanbmc@gmail.com

Received : 09 November 2024
Accepted : 11 December 2024
Published : 15 March 2025

ABSTRACT:

Background: *Laryngeal cancer, especially in locally advanced stages, is commonly treated with concurrent chemoradiation. Cisplatin is frequently used in combination with radiation, but the optimal dosing schedule—weekly versus three-weekly—remains unclear.* ***Objective:*** *The purpose of this study was to compare the response of cisplatin weekly and three weekly concurrently with radiation therapy in patients with locally advanced laryngeal cancer.* ***Materials and methods:*** *This was a quasi-experimental study where 66 patients with locally advanced laryngeal cancer of stage III-IVA were enrolled in the Department of Radiation Oncology of the National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, between July 2017 and June 2018. Among them, 33 patients in each arm received concurrent chemoradiation; the study arm (arm B) received three weekly cisplatin of 75 mg/m² while the control arm (arm A) received weekly cisplatin of 40 mg/m². The external beam radiation therapy dose was 66 Gy in 33 daily fractions in six weeks.* ***Results:*** *The median age was 55.06 (SD ± 6.833; range:38-66) years in Arm-A and 54.48 (SD±5.789; range:38-65) years in Arm-B. Most patients presented with sore throat (88%) and hoarseness of voice (90%). According to the site, 63.6% were supra-glottic, and 36.4% were in the glottic region in both arms. Among them, 42 patients presented with stage III and 24 with stage IVA; most were moderately differentiated (41). Follow-up at 12 weeks after completion of chemoradiation, complete response was found in 22(66.6%) and 26 (78.8%) patients; meanwhile, partial response was observed in 5 (15.2%) and 3 (9.1%) patients in Arm A and Arm B respectively. Stable disease was found in 6 (18.2%) and 4 (12.1%) patients in arms A and B, respectively. (P value 0.539). In grades 2 and 3, mucositis, xerostomia, and dermatitis were more common in arm A than in arm B grades 2 and 3, dysphagia is more prevalent in arm B than in arm A (6.1% vs 12.1% and 12.1% vs 24.2% in grades 2 and 3, respectively). Nausea, vomiting and nephrotoxicity are more common in arm B than in arm A. All patients of both arms suffered from mild to moderate haematological toxicities.* ***Conclusion:*** *Concurrent chemoradiation with three weekly cisplatin is comparable to weekly cisplatin. However, further large, randomized, multiple centres study should be conducted to reach any conclusion.*

Keywords: Locally advanced laryngeal cancer, concurrent chemoradiation, cisplatin.

Introduction:

Laryngeal cancer is the most common cancer of the upper aerodigestive tract.[1] It is the ninth most common cancer in Asia[2] and one of the ten leading cancers in the Indian subcontinent.[3] Laryngeal cancer is far more common in males than females, with approximately 3-6% of all cancers in males and only about 0.2-1% in females.[4] Of all laryngeal cancers, approximately 29% of cases presented as locally advanced at diagnosis.[5] Early laryngeal cancer comprises stages I and II, whereas advanced laryngeal cancer comprises stages III to IVB according to TNM staging.[6,7] Concurrent chemoradiation therapy is the current standard of care for patients with locally advanced laryngeal cancer.[8] Over the past 40 years, the management of locally advanced laryngeal cancer has evolved from an initial approach with primary surgery and/or radiotherapy to modern multi-modality approaches using definitive concurrent chemoradiation.[9] For patients with locally advanced lesions not amenable to voice-sparing surgery, total laryngectomy followed by adjuvant radiotherapy became the preferred treatment of choice compared to radiotherapy alone regarding local control and survival.[10] However, to achieve this goal at the price of significant functional morbidity from total laryngectomy as well as the sequelae of which include loss of natural voice, permanent tracheostomy and alteration in swallowing function that often result in social stigmatization and psychological disturbances.[11] So, nowadays, concurrent chemoradiation is the treatment of choice for locally advanced laryngeal cancer. According to RTOG 91–11,[12,13] concurrent chemo-RT improved 5-year larynx preservation (84%) vs. induction chemo (71%) and RT alone (66%), and LRC for CCRT (69%) vs. induction chemo (55%) and RT alone (51%). Chemo reduced the rate of DM (13% concurrent vs. 14% induction chemo vs. 22% RT alone) and improved DFS (39% with chemo vs. 27% with RT alone). There are several chemotherapy agents used in combination with radiation, including single-agent cisplatin weekly or three weekly; cisplatin in combination with paclitaxel or 5-FU; 5-FU in combination with hydroxyurea; carboplatin in combination with paclitaxel or 5-FU and single-agent cetuximab.[6,12,14-20] Thus, the most appropriate chemotherapy given concurrently with radiation therapy for locally advanced laryngeal cancer requires further clarification. Some studies suggested that concurrent chemoradiation with three weekly cisplatin resulted in better overall survival (OS) and progression-free survival (PFS) compared to weekly cisplatin,[21,22] but other studies showed no difference.[23,24] Considering the available data from the literature, it becomes evident that more studies comparing three weekly 75 mg/m² of cisplatin to weekly administration of 40 mg/m² of cisplatin are required, particularly in patients receiving definitive chemoradiation for laryngeal cancer.

Methods:

This quasi-experimental study was conducted from July 2017 to June 2018 in the Department of Radiation Oncology of the National Institute of Cancer Research and Hospital, Mohakhali, Dhaka.

Eligibility criteria:

Newly diagnosed 66 patients with histopathologically confirmed SCC of locally advanced laryngeal cancer of stage III-IVA and no evidence of distant metastasis were enrolled. ECOG's performance status was up to 2 and between 18 and 70 years. Patients were excluded if there was evidence of uncontrolled infection, such as patients with double primary. Written informed consent was obtained from the patients prior to participation in the study, and the IRB of NICRH gave ethical clearance.

Radiotherapy:

All patients received a total dose of 66 Gy in 33 fractions over 6 weeks, using a telecobalt-60 machine in lateral parallel opposed fields (2D). If required, a low anterior neck field was used. The off-cord was done at 44Gy. For positive nodes, an electron boost was given after 44 Gy. The upper border was 2 cm above the angle of the mandible, and the lower border was at the root of the neck.

Chemotherapy:

The control arm (arm A) received weekly cisplatin of 40 mg/m² in combination with radiotherapy, while the study arm (arm B) received three weekly cisplatin of 75 mg/m² on days 1, 22, and 43 along with radiotherapy. A dose-adequate hydration policy was maintained, and proper pre-medication was given.

Patients' assessment:

During concurrent chemoradiation therapy, patients were assessed every week during therapy. Symptomatic

response and acute toxicities were in every week with physical examination. Tumor response was evaluated according to RECIST criteria. Toxicity was observed according to the cooperative group of common toxicity criteria and common terminology criteria for adverse effects (CTCAE) version 5.0 (2018). After treatment, patients were carefully supervised to attain the first follow-up at 6 weeks and the second follow-up at 12 weeks. Follow-up examination includes history taking, physical examination, and radiological and laboratory tests as needed.

Statistical analysis:

Data analysis was done according to the study's objectives using the SPSS for Windows version 20.0. Differences between the two means were assessed by *t*-test to compare the patient's characteristics. All outcomes were compared by Chi-square test. Fisher's Exact test was done when more than 20% of cells in the cross table had an expected frequency <5. A *p*-value of <0.05 in the tailed test was considered statistically significant.

Results:

The median age was 55.06 (SD ± 6.833; range:38-66) years in Arm-A and 54.48 (SD±5.789; range:38-65) years in Arm-B. Details of the patient's characteristics are shown in Table I. Fifty-eight patients (87.9%) were male, eight (12.1%) were female, and 57.6% belonged to the lower class. Fifty-eight patients were smokers; among them, 45.5% had a history of more than 20 packs per year in both arms. Most of the patients complained of sore throat (88%) and hoarseness of voice (90%) (Fig. 1). According to the site, 63.6% were supra-glottic, and 36.4% were in the glottic region in both arms. Among them, 42 patients presented with stage III and 24 with stage IVA; most were moderately differentiated (41 patients). Forty-seven patients (71%) presented with N1 disease, and six (9%) had N2 disease.

At follow-up 12 weeks after completion of chemoradiation, complete response was found in 22(66.6%) and 26 (78.8%) patients. Meanwhile, partial response was observed in 5 (15.2%) and 3 (9.1%) patients in Arm A and B, respectively. Stable disease was found

Table 1 : *Baseline characteristics of patients*

Baseline characteristics		Arm A n (%)	Arm B n (%)
Age	Mean ± SD	55.06±6.83	54.48±5.79
Sex	Male	30(90.9)	28(84.9)
	Female	3(9.1)	5(12.1)
Economic status	Lower class	18(54.5)	20(60.6)
	Middle class	10(30.3)	10(30.3)
	Upper class	5(15.2)	3(9.1)
ECOG performance status	PS=0, 1	26(78.8)	28(84.8)
	PS=2	7(21.1)	5(15.2)
Histology grading	Well differentiated	5(15.2)	6(18.2)
	Moderately differentiated	19(57.6)	22(66.7)
	Poorly differentiated	9(27.3)	5(15.2)
Stage	Stage III	20(60.6)	22(66.7)
	Stage IVA	13(39.4)	11(33.3)
Site	Glottic (24)	13(39.4)	11(33.3)
	Supra-glottic (42)	20(60.6)	22(66.7)

Arm A=weekly cisplatin; Arm B=Three weekly cisplatin

Table 2 : *Acute toxicities of concurrent chemoradiation*

Toxicity	Arm A (weekly cisplatin)			Arm B (Three weekly cisplatin)		
	G-I (%)	**G-II** (%)	**G-III** (%)	G-I (%)	**G-II** (%)	**G-III** (%)
Haematological toxicity						
Anaemia	72.7	24.2	3.1	54.5	42.4	3.1
Neutropenia	18.2	3.1	0	12.1	3.1	0
Non-haematological toxicity						
Oral mucositis	30.3	39.3	30.3	45.5	33.3	21.2
Xerostomia	18.1	81.8	0	33.3	66.7	0
Dysphagia	81.8	6.1	12.1	63.6	12.1	24.2
Dermatitis	45.5	24.2	30.3	39.4	36.4	24.2
Nausea Vomiting	27.2	15.2	15.2	33.3	24.2	15.2
Nephropathy	3.1	0	0	12.1	0	0

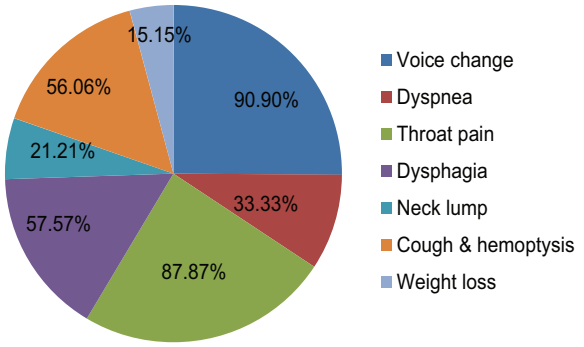

Figure 1: *Distribution of patients by presenting symptoms*

in 6 (18.2%) and 4 (12.1%) patients in Arm A and Arm B, respectively (*p*-value 0.539). The treatment response is shown in Fig. 2.

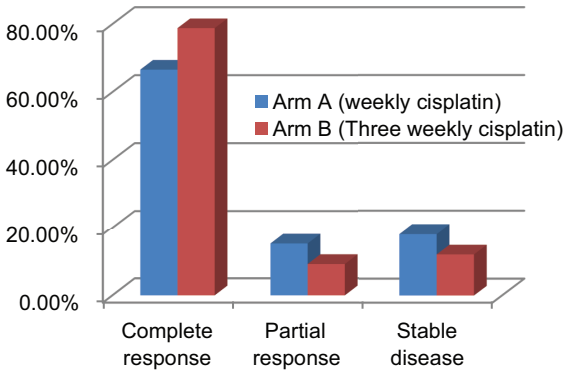

Figure 2: *Distribution of the patients by treatment responses*

Acute toxicities were noted in Table II. Grade 1 oral mucositis was more common in arm B compared to arm A (30.3% vs 45.4%), whereas grade 2 and 3 toxicity was more common in arm A compared to arm B(39.3% vs 33.3% and 30.3% vs 21.2% in grade 2 & 3 respectively). Grade 2 xerostomia is more observed in arm A compared to arm B (81.8% vs 66.6%). In grades 2 and 3, dysphagia is more prevalent in arm B than in arm A (6.1% vs 12.1% and 12.1% vs 24.2% in grades 2 and 3, respectively). Dermatitis is more common in arm A than in arm B (45.4% vs 39.3%). All patients of both arms suffered from mild to moderate anaemia, while grade 2 anaemia was more observed in arm B than in arm A (24.2% vs 42.4%). Nausea and vomiting were more observed in arm B in comparison to arm A (33.3% vs 27.2 and 15.2% vs 24.2% with grade 1 & 2 toxicity, respectively). The nephropathy is more seen in arm B than in arm A (12.1% vs 3.1%). However, all findings were statistically insignificant.

Discussion:

Laryngeal cancer is one of the most common head-neck malignancies worldwide, accounting for 20% of all cases. It is the ninth most common cancer in males in Asia. About 40% of patients are present with advanced-stage laryngeal cancer, and most of the tumours are squamous cell carcinomas. For the management of advanced laryngeal cancer, ideal strategies include radiotherapy alone or with chemotherapy.[1,2] Definitive chemoradiation is one of the most common treatment approaches for locally advanced squamous cell

carcinoma of the larynx, as it preserves larynx function and disease control and improves survival.[3] This study was conducted from March 2017 to March 2019 with the aim of comparing the treatment outcomes of weekly concurrent chemoradiation and three concurrent chemoradiation therapies in locally advanced squamous cell carcinoma of the larynx. A total of 66 patients with locally advanced carcinoma of the larynx were assessed for eligibility, and ultimately, 66 patients were included in the study after giving informed written consent. In the present study, arm A patients were treated with weekly cisplatin 40 mg/m² and radiation, while arm B patients were treated with cisplatin 75 mg/m² for three weeks concurrently with radiation. Both arms received conventional radiotherapy of 66 Gy in 33 fractions (200 cGy) for 6 ½ weeks. The mean age was 55.06 (SD ± 6.833) years (range: 38-66 years) in Arm-A and 54.48 (SD ± 5.789) years (range: 38-65 years) in Arm-B, and most of the patients were between 40-60 years of age group (69.60% in Arm-A, 84.90% in Arm-B). These results correspond with the previous findings[2]. It is less common in people under 40; in this study, only 4 out of 66 patients were below this age. In this study, male preponderance (87.9%) was also observed compared with female (12.1%), which aligns with other research.[4,5] In the current study, 87.8% of patients had smoking habits, and 45.4% of patients were heavy smokers. Many case-control and cohort studies have demonstrated that tobacco significantly increases the risk of laryngeal cancer.[2] According to ECOG performance status, only 12 patients (18.2%) had PS 2. All patients in the study presented with multiple symptoms; the most common clinical presentations were sore throat (90.8%), throat pain (87.8%), cough (18.2%), and dysphagia (57.5%). The distribution of laryngeal carcinoma by site showed that supraglottic carcinoma (63.63%) was more common than glottis carcinoma (36.4%), consistent with previous studies.[3,5] Among the study participants, 63% had stage III disease, while 37% were in stage IVa, aligning with previous reports.[3] Histological grading showed 15.1% well-differentiated, 57.5% moderately differentiated, and 27.2% poorly differentiated tumours. During radiotherapy, patients were assessed weekly for response and toxicity. The most prevalent acute toxicities were oral mucositis, skin toxicity, and dysphagia. Other toxicities included haematological toxicities (anaemia, neutropenia), nausea-vomiting, and nephropathy. Grade 2 and 3 oral mucositis was more common in the weekly CCRT group (39.3% vs. 33.3% and 30.3% vs. 21.2%, respectively). Dysphagia was observed in 81.8% of patients in arm A and 63.6% in arm B, with higher grades in arm B. These findings are consistent with previous studies on definitive chemoradiation in head-neck cancer.[6,7] Skin toxicities increased with the duration of therapy. Grade 2 toxicity was more prevalent in the three-weekly CCRT arm, while grade 3 toxicity was more frequent in the weekly CCRT arm, although the difference was not statistically significant. This observation aligns with previous research.[8] Xerostomia was found in all patients in both arms, with grades 1 and 2 in 18.1% vs. 33.3% and 81.8% vs. 66.6%, respectively. No patients developed grade 3 xerostomia during radiotherapy, which is consistent with prior studies[3]. In terms of local control, a complete response was found in 66.7% of arm A patients and 78.7% of arm B patients. Partial response was observed in 15.1% and 9.1% of patients in arm A and arm B, respectively. Stable disease without local or distant relapse was observed in 18.1% of patients in arm A and 12.1% in arm B. There were no treatment-related deaths. A prior study reported a two-year locoregional control rate of 88% with concurrent cisplatin-based chemoradiotherapy.[3] Though this study assessed short-term outcomes, the findings are in agreement with previous research. Other studies have shown an 88.5% complete response rate with 11.5% residual disease after treatment completion.[4] In contrast, one study reported an overall response rate of 92.3% in the three-weekly group, slightly higher than 91.0% in the weekly group.[9] Concurrent chemoradiation with three-weekly cisplatin resulted in better locoregional control and overall response than weekly cisplatin. Thus, three-weekly cisplatin appears preferable for stage III and IVa locally advanced laryngeal carcinoma. However, the regimen including 75 mg/m² of cisplatin every 3 weeks is associated with significant acute toxicity, including nephrotoxicity, nausea, vomiting, anaemia, and neutropenia. Patients receiving this regimen require close monitoring and timely supportive care.

References

1. Karatzanis AD, Psychogios G, Waldfahrer F, et al. Management of early glottic cancer: outcome and study of recurrence patterns. Head Neck. 2014;36(7):989-94.
2. Bobdey S, Jain A, Balasubramaniam G. Epidemiological review of laryngeal cancer: An Indian perspective. Indian J Med Paediatr Oncol. 2013;34(3):154-8.

3. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349(22):2091-8.

4. Franchin G, Minatel E, Gobitti C, et al. Radiotherapy with or without chemotherapy in locally advanced squamous cell carcinoma of the head and neck. Tumori. 2014;100(5):488-95.

5. Aboziada MA, El-Hossieny HA, Nabil Y, et al. A randomized phase II study comparing weekly versus every three weeks cisplatin concurrently with radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. Gulf J Oncolog. 2017;1(23):29-36.

6. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity-modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomized controlled trial. Lancet Oncol. 2011;12(2):127-36.

7. Gupta T, Agarwal JP, Ghosh-Laskar S, et al. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single-institution experience. Head Neck Oncol. 2012;4:34.

8. Espeli V, Casiraghi O, Desandes E, et al. Quality of life and functional outcomes after chemoradiotherapy versus total laryngectomy in patients with advanced laryngeal cancer. Radiother Oncol. 2012;104(2):239-45.

9. Lee CC, Ho HC, Su YC, et al. Comparison of weekly versus three-weekly cisplatin regimen for patients with advanced head and neck cancer receiving concurrent chemoradiotherapy. Medicine (Baltimore). 2018;97(36):e12133.

10. American Joint Committee on Cancer (AJCC). Cancer Staging Manual. 8th ed. Springer; 2017.

11. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: A period analysis. Oncologist. 2010;15(9):994-1001.

12. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003;21(1):92-8.

13. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24-35.

14. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC and RTOG. Head Neck. 2005;27(10):843-50.

15. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol. 2004;22(1):69-76.

16. Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients. Radiother Oncol. 2011;100(1):4-14.

17. Pignon JP, le Maître A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update incorporating 93 trials and 17,346 patients. Radiother Oncol. 2009;92(1):4-14.

18. Curran D, Giralt J, Harari PM, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol. 2007;25(16):2191-7.

19. Bourhis J, Le Maître A, Baujat B, et al. Individual patients' data meta-analysis in head and neck cancer: The MACH-NC project. Radiother Oncol. 2010;96(1):29-36.

20. Ghi MG, Paccagnella A, Ferrari D, et al. Induction TPF followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer: A randomized phase II feasibility trial. Ann Oncol. 2017;28(9):2206-12.

21. Rischin D, Peters LJ, O'Sullivan B, et al. Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): A phase III randomized trial. Lancet Oncol. 2010;11(4):279-86.

22. Budach W, Bölke E, Kammers K, et al. Induction chemotherapy followed by concurrent radiochemotherapy versus concurrent radiochemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck: A meta-analysis. Strahlenther Onkol. 2016;192(8):535-44.

23. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: An RTOG analysis. J Clin Oncol. 2008;26(21):3582-9.

24. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. J Clin Oncol. 1998;16(4):1310-7.

Original Article

Cancer J Bangladesh 2024;5(2): 49-54
http://nicrh.gov.bd/publication

Comparison Between Two Palliative Radiotherapy Schedules of 16 Gy in 2 Fractions Versus 20 Gy In 5 Fractions to See Short Term Response in Locally Advanced Stage IIIB and Advanced Stage IV NSCLC

Samia Wahid Muna[1], Rowshan Ara Begum[2], Lubna Mariam[3], Quazi Shihab Uddin Ibrahim[4], Kamran Nahar Liza[5]

[1]Specialist, Radiation Oncology, United Hospital Ltd, Gulshan, Dhaka
[2]Professor, Radiation Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka
[3]Associate Professor, National Institute of ENT, Dhaka
[4]Assistant Professor, OSD, DGHS
[5]Resident, NICRH

Citation: Muna SW, Begum RA, Mariam L, Ibrahim QSU, Liza KN. Comparison between two palliative radiotherapy schedules of 16 Gy in 2 fractions versus 20 Gy in 5 fractions to see short term response in locally advanced stage IIIB and advanced stage IV NSCLC. Cancer J Bangladesh 2024;5(2): 49-54.

Correspondence: Dr. Samia Wahid Muna, Specialist, Radiation Oncology, United Hospital Ltd, Gulshan, Dhaka. Email: samiawahidmuna @gmail.com

Received : 02 November 2024
Accepted : 07 December 2024
Published : 15 March 2025

Abstract

***Background**: Lung cancer is the most common malignancy worldwide. Most patients are present with inoperable tumor and the majority of disease symptoms are related to its local progression. Between two types of lung cancer, non-small cell lung cancer (NSCLC) comprised the maximum cancer incidence. **Objectives**: To compare the short-term clinical response of two palliative radiotherapy schedule of 16 Gy in two fractions versus 20 Gy in five fractions to reduce intrathoracic symptoms. **Method**: This Quasi-Experimental study was conducted in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, from November 2020 to November 2021. A total of 60 patients with histopathologically proven non-small cell carcinoma with locally advanced, unresectable stage (IIIB-IV) NSCLC attended in Radiation Oncology Department of NICRH were enrolled in this study as per selection criteria. They were selected by purposive sampling technique and were allocated into two Arms: Arm-A and Arm-B. In Arm-A, 30 patients received 16 Gray (Gy) radiotherapy in 2 fractions, in a week apart whereas in Arm-B, 30 patients received 20 Gray in 5 fraction, single daily fractionation, 1 week duration. Then symptoms and response were assessed 4-6 weeks after radiotherapy according to RECIST criteria (Response Evaluation Criteria in Solid Tumor) and toxicities were assessed by RTOG (radiation Therapy Oncology Group) criteria. Data were collected, processed and analyzed with the help of computer program SPSS 22.0 Software. **Result**: In arm-A, mean age of the patient was 51.3±10.2 years and maximum incidence was seen in the 5th decade 33.3%. In Arm-B, mean age of the patient was 48.6±11.5 years and maximum study subjects (43.3%) were found in the age group of 40-49 years. Male to female ratio was 3.6:1. Majority of patients in both arm was presented with cough (Arm-A 43.3% and Arm-B 40.0%), hemoptysis (Arm-A 60.0% and Arm-B 50.0%), Chest pain (Arm-A 73.3% and Arm-B 80.0%) and dyspnea (Arm-A 80.0% and Arm-B 80.0%). In this study most of the patients [Arm A 17(56.6%) and Arm B 20(66.6%)] were in stage IIIB (p>0.05). At first follow up, cough subsided in both groups but comparatively better in Arm-B, hemoptysis, chest pain, dyspnea were next successive complaints were better improved in group B but the difference was statistically non-significant. **Conclusions**: Present study concluded that palliative radiotherapy schedules of 16 Gy in 2 fractions is equally effective to 20 Gy in 5 fractions in the treatment of locally advanced NSCLC with locoregional control, symptom relief with lesser toxicities.*

Introduction

Lung cancer is the most prevalent cause of cancer death and disability-adjusted life years (DALYs) in men, and the second greatest cause of cancer death and DALYs in women, accounting for 1.9 million fatalities and 40.9 million DALYs in both sexes.[1] Lung cancer, including trachea and bronchus cancer, is commonly viewed as a hazard to world health, imposing a tremendous cost on individuals and families while also having substantial economic and resource implications. Lung cancer control should be a key objective to improve global health, especially to accomplish the reduction of one-third premature mortality from non-communicable diseases (NCDs) by 2030, one of the United Nations (UN) Sustainable Development Goals (SDGs).[2] In 2020, an estimated 19.3 million new cancer cases (18.1 million excluding non-melanoma skin cancer) and over 10.0 million cancer deaths (9.9 million excluding non-melanoma skin cancer) were reported globally. From 2007 to 2017, the incidence of lung cancer climbed by 37 percent. Overall, lung cancer was the second most frequent malignancy, following non-melanoma skin cancer, with 2.2 million new cases.[1]

Currently, the majority of lung cancer cases are detected in symptomatic patients, with the most prevalent symptoms being cough, fatigue, dyspnea, chest discomfort, weight loss, and hemoptysis. Hemoptysis has the best positive predictive value (2.4%-7.5%), however it occurs in only one-fifth of lung cancers.[3] Survival is determined by disease burden and stage at the time of presentation. Early intervention and treatment planning based on clinical, pathological, and radiological exams are critical. The lung cancer stage classification was developed by the International Association for the Study of Lung Cancer (IASLC) using statistical analysis of a 100,000-patient international database. The 8th edition of this staging system has been updated to provide more exact categorization based on prognostic analysis of each tumor-node-metastasis (TNM).[4]

The last decade has seen a revolution in the care of non-small cell lung cancer (NSCLC), with significant breakthroughs in screening, diagnosis, and treatment. Depending on the stage, tumor location, histology, genetic mutations, and patient's condition, NSCLC treatment options often include surgery, radiation, chemotherapy, immunotherapy, and molecularly targeted therapy, either alone or in combination.[5] The treatment options for non-small cell lung cancer (NSCLC) are mostly determined by the cancer's stage (extent), but other criteria such as a person's performance status and lung function, as well as specific cancer characteristics and logistical assistance, are also significant.

A randomized MRC trial[6] provides solid evidence for a modest improvement in survival (5% at one year and 3% at two years) in patients with improved PS who were treated with 12-13 fractions of 3 Gray. Other research has also favored longer RT regimens. However, the most recent randomized study (with 421 patients) from Norway[7] found that delayed palliative RT of 42 Gray in 15 fractions or 20 Gray in 5 fractions did not outperform the 17 Gray in 2 fractions regimen in terms of symptom management and mortality. Toy et al. concluded in an intriguing literature analysis that symptomatic NSCLC patients can be treated safely and successfully with one or two fractional RT regimens. However, selected patients with adequate performance status (PS) may be evaluated for higher-dose regimens if the prospect of a small increase in survival and palliation is deemed worthwhile despite the added inconvenience and toxicity.[8]

Methods:

This quasi-experimental nonrandomized prospective study was conducted in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka from November 2020 to October 2021 over a period of one year. A total of 60 patients with histopathologically proven non-small cell carcinoma with locally advanced, unresectable and advanced/metastatic stage (IIIB-IV) attended in Radiation Oncology Department of NICRH were included as per selection criteria. Patients were allocated two groups- arm A and arm B, each arm contained 30 cases. Arm - A received 16 Gray radiotherapy in 2 fractions, in a week apart (with conventional radiotherapy) whereas Arm - B received 20 Gray in 5 fractions, single daily fractionation, 1-week duration (with conventional radiotherapy).

Subjects were instructed on the study's objectives, risks and benefits, freedom to participate, and anonymity. Informed written consent was acquired accordingly. Pre-treatment evaluations included a full history and

physical examination, complete hemogram, blood sugar, serum urea and creatinine, liver function tests, serum electrolytes, chest X-ray (CXR), ultrasonography (USG), CT scan and/or MRI, and cardiological evaluation if needed. Data were collected on a data collection sheet. Symptoms and responses will be evaluated on the 6th, 12th, and 18th weeks, in accordance with RTOG guidelines. Following the gathering of all information, data were examined, validated for consistency, and adjusted to produce the final output. Following editing and coding, the coded data was entered straight into the computer using SPSS version 12. The results were presented in tables. A *p*-value <0.5 is considered statistically significant.

Results:

Table- 1 : *Demographic characteristics of the Arm-A and Arm-B patients*

	Arm A n (%)	Arm B n (%)
Age (years)		
30-39	2 (6.6)	1 (3.3)
40-49	10 (33.3)	13 (43.3)
50-59	8 (26.6)	9 (30.0)
60-69	9 (30.0)	7 (23.3)
70	1 (3.3)	0 (0)
Mean ± SD	51.3±10.2	48.6±11.5
Range	32-70	30-64
Gender		
Male	25 (83.3)	23 (76.7)
Female	5 (16.7)	7 (23.3)
Risk factors		
Smoking	20 (66.7)	21 (70.0)
Betel leaf	16 (53.3)	15 (50.0)
Smoking and betel leaf	12 (40.0)	11 (36.7)

In both arms, the highest incidence occurred in the fourth decade (33.3%). The patient's mean age was 51.3 ± 10.2 years. In arm B, the highest percentage (43.3%) was recorded in the 40-49 age range. The average age of the patient was 48.6±11.5 years. Male to female ratio was 3.6:1. The majority of the patients were smokers in both arms. Many patients smoked and chewed betel leaf.

Table-2: *Distribution of the patients by Karnofsky performance score (KPS) status (n=60)*

Karnofsky performance score	Arm A n (%)	Arm B n (%)	*p*-value
KPS 70	7 (23.3)	6 (20.0)	0.275
KPS 60	15 (50.0)	17 (56.7)	
KPS 50	8 (26.7)	7 (23.3)	

The table shows that at the start of therapy, the majority of patients in both arms had a KPS score of 60 (50.0% and 56.6% in Arm-A and Arm-B, respectively). Thirteen patients (21.6%) had a KPS score of 70, fifteen (25.0%) had a KPS score of 50, and none had a KPS score of 80.

Table-3: *Pretreatment clinical stage of the patients in both arms (n-60)*

Stages of the disease	Arm A n (%)	Arm B n (%)	*p*-value
Stage IIIB	17 (56.7)	20 (66.7)	0.824
Stage IVA	13 (43.3)	10 (33.3)	

It was noted that most of the patients [Arm A (56.6%) and Arm B (66.6%)] were in stage IIIB. However, no statistical significance was observed between arms in respect to stage (p>0.05).

Table- 4: *Clinical responses of treatment at different follow up of patients in both Arm A and Arm B (n=60)*

Response	Arm A n (%)	Arm B n (%)	*p*-value
1st follow up			
Complete response (CR)	0	0	-
Partial response (PR)	12 (40.0%)	13 (42%)	0.320
Stable disease	14 (46.0%)	14 (46%)	0.489
Progressive disease	4 (13.3%)	3 (12.0%)	0.692
2nd follow up			
Complete response (CR)	0	0	-
Partial response (PR)	19(63.3)	22(73.3)	0.409
Stable disease	6(20.0)	4(13.3)	0.489
Progressive disease	5(16.7)	4(13.3)	0.714
3rd follow up			
Complete response (CR)	0	0	-
Partial response (PR)	18(60.0)	21(70.0)	0.420
Stable disease	6(20.0)	4(13.3)	0.489
Progressive disease	6(20.0)	5(16.7)	0.743ns

The study found that 40% of patients had a partial response in Arm A, compared to 42% in Arm B (p>0.05). 46% of patients from both arms have stable illnesses. During treatment, 4 (13.3%) patients in arm A exhibited disease progression, whereas 3 (12.0%) patients in arm B had progressive disease (p>0.05). At the second follow-up following treatment completion, PR was 63.3% in arm A and 73.3% in arm B (p>0.001). At the third follow-up following treatment completion, PR was 60.0% in arm A and 70.0% in arm B (p>0.05).

At the first follow-up, cough improved in both groups, but Arm-B had a higher rate of improvement (arm A 36.7% vs Arm-B 26.7%). Hemoptysis, chest pain, and dyspnea were the following complaints, and Arm-B had a higher rate of symptom relief, although the difference was not statistically significant. At the second follow-up, cough was observed in 33.0% of patients in Arm-A and 16.7% in Arm-B, hemoptysis in 40.0% of patients in Arm-A and 26.7% in Arm-B, chest discomfort in 56.7% of patients in Arm-A and 43.3% in Arm-B, and dyspnea in 60.0% of patients in Arm-A and 46.7% in Arm-B. At the third follow-up, all symptoms were reduced in both arms, however Arm-B had a higher prevalence. The difference in symptomatic improvement was not statistically significant (p<0.05).

Table- 5: *Assessment of major symptomatic improvement/ deterioration at different follow-up time (n=60)*

	Clinical symptoms	Arm An (%)	Arm Bn (%)	*p*-value
	Cough	13 (43.3)	12 (40.0)	0.861
Baseline	Hemoptysis	18 (60.0)	15 (50.0)	0.502
	Chest pain	22 (73.3)	24 (80.0)	0.567
	Dyspnea	24 (80.0)	24 (80.0)	1.000
At 1st follow-up(6 weeks aftertreatment)	Cough	11 (36.7)	8 (26.7)	0.577
	Hemoptysis	15 (50.0)	14 (46.7)	0.952
	Chest pain	20 (66.7)	20 (66.7)	1.000
	Dyspnea	21 (70.0)	20 (66.7)	0.905
At 2nd follow-up(12 weeks aftertreatment)	Cough	10 (33.3)	5 (16.7)	0.233
	Hemoptysis	12 (40.0)	8 (26.7)	0.409
	Chest pain	17 (56.7)	13 (43.3)	0.438
	Dyspnea	18 (60.0)	14 (46.7)	0.438
At 3rd follow-up (18 weeks after treatment)	Cough	8 (26.7)	3 (10.0)	0.182
	Hemoptysis	10 (33.3)	5 (16.7)	0.233
	Chest pain	15 (50.0)	13 (43.3)	0.791
	Dyspnea	15 (50.0)	10 (33.3)	0.294

At baseline, all symptoms were nearly identical in both groups. Then, progressively improved.

Table- 6: *Assessment of Toxicities (n=60)*

Toxicity	Grade	Arm A	Arm B	*p*-value
Radiationpneumonitis	Grade I	5 (16.7)	3 (10.0)	0.330
	Grade II	3 (10.0)	2 (6.7)	
	Grade III	1 (3.3)	1 (3.3)	
Fatigue	Grade 0	12 (40.0)	13 (43.3)	0.842
	Grade I	9 (30.0)	7 (23.3)	
	Grade II	8 (26.7)	6 (20.0)	
Esophagitis(Dysphagia)	Grade I	9 (30.0)	8 (26.7)	0.092
	Grade II	2 (6.7)	0 (0.0)	
	Grade III	0 (0.0)	0 (0.0)	
Skin reaction	Grade I	8 (26.7)	9 (30.0)	0.826
	Grade II	3 (10.0)	4 (13.3)	
Anemia	Grade I	5 (16.7)	5 (16.7)	0.417
	Grade II	9 (30.0)	11 (36.7)	
	Grade III	2 (6.7)	3 (10.0)	

Toxicities were equivalent between the two arms, but Esophagitis, particularly grade I and II, was more prevalent in arm A. Skin reactions were more prevalent in arm B. Radiation pneumonitis was higher in arm A, although the difference was not statistically significant.

Discussion:

In arm-A, the highest incidence was observed in the fourth decade at 33.3%. The patient's mean age was 51.3 ± 10.2 years. The highest proportion (43.3%) of Arm-B participants were between the ages of 40 and 49. The average age of the patient was 48.6±11.5 years. The age distribution resembles a normal distribution, with a significant proportion of middle-aged patients compared to extreme age groups. Approximately 66.7% of patients were aged 40 to 60 years. In this study, the male to female ratio was 3.6:1.

Consequently, the median age at which lung cancer is diagnosed is 70 years for both males and women. Individuals aged 55 to 74 account for approximately 53% of cases, while 37% of instances occur in those aged 75 and older. The incidence of lung cancer is highest in men aged 85–89, with a rate of 585.9 per 100,000. In women aged 75–79, the rate is 365.8 per 100,000. In men over the age of 40 and women over the age of 59, lung cancer is the most common cause of mortality.[9]

The male-to-female ratio was 6.15:1 in a study conducted in Bangladesh. The age range was 25 years to 95 years, with a mean age of 62 years. Over 85% of the patients were aged 50 years or older.[10] Another study conducted at a tertiary level hospital in Bangladesh demonstrated that lung carcinoma was the most prevalent form of cancer among the patients. During the three-year period, a total of 3,209 patients with lung cancer were treated, with 86% of them being male. Approximately 29% of them were in the 55-64 age category, while approximately 23% were in both the 45-54 and 65-74 age groups. A smoking history was reported by approximately 52% of the participants.[11]

In this study, the majority of patients in both Arms reported cough (Arm-A 43.3% and Arm-B 40.0%), hemoptysis (Arm-A 60.0% and Arm-B 50.0%), chest pain (Arm-A 73.3% and Arm-B 80.0%), and dyspnea (Arm-A 80.0% and Arm-B 80.0%). A few patients reported experiencing a loss of appetite, fever, and weight loss. A similar study indicated that the most prevalent symptoms were wheezing, fatigue, dyspnea, chest pain, weight loss, and hemoptysis. Hemoptysis is present in only one-fifth of lung cancers, despite having the greatest positive predictive value of 2.4%–7.5%.[3]

The effectiveness of palliative radiotherapy is contingent upon the category of predominant symptoms. Hemoptysis and chest pain are the most effective symptoms for palliation, as demonstrated by numerous investigations, including the present one.[6,7] In certain investigations, irradiation also led to effective relief of cough, which was the least effectively palliated in our series and the recently reported study. [7]

The majority of patients in this study were in stage IIIB, with Arm A comprising 17 (56.6%) and Arm B comprising 20 (66.6%). Nevertheless, there was no statistically significant difference between the Arms in terms of stage. The results of the current study indicate that arm A (palliative radiotherapy schedules of 16 Gray in 2 fractions) is equally efficacious as arm B (20 Gray in 5 fractions) in the treatment of locally advanced NSCLC. At the initial follow-up, both groups experienced a resolution of their coughs; however, Arm-B demonstrated a statistically non-significant advantage (arm A 36.7% vs arm B 26.7%). Subsequently, hemoptysis, dyspnea, and chest pain were reported, with Arm-B experiencing a more favorable response to these symptoms. PR was 60% in arm A and 70% in arm B at the final follow-up, which occurred 18 weeks after the cessation of treatment (p>0.05). The discrepancy was not statistically significant.

In patients with improved PS, a randomized MRC trial[6] demonstrated a modest increase in survival (5% at 1 year and 3% at 2 years) when they were treated with 12-13 fractions of 3 Gray. Other studies have also advocated for more extended RT schedules. Nevertheless, the most recent randomized study from Norway[10] demonstrated that the 17 Gray in 2 fractions regimen was not preferable to the protracted palliative RT of 42 Gray in 15 fractions or 20 Gray in 5 fractions in terms of symptom control and survival. In a comprehensive literature review, Toy et al. have determined that RT regimens of one or two fractions can be used to safely and effectively treat symptomatic patients with NSCLC. However, if the modest improvement in survival and palliation is deemed to be worth the additional inconvenience and toxicity, certain patients with adequate PS may be considered for higher dose regimens.[8]

A prospective randomized study was conducted to compare two palliative radiotherapy schedules for inoperable symptomatic non-small-cell lung cancer (NSCLC). The two groups exhibited comparable main clinical characteristics, as well as the incidence and severity of the initial disease-related symptoms. Treatment tolerance was satisfactory and did not vary between the study arms. The degree of relief of all analyzed symptoms did not exhibit any significant differences between the study arms. The 2-fraction schedule's potential for routine management of symptomatic inoperable NSCLC is indicated by its enhanced overall survival and treatment convenience.[12]

Conclusions:

The results of this study indicate that the palliative lung cancer radiotherapy schedules of 16 Gray in 2 fractions, administered one week apart, and 20 Gray in 5 fractions, administered once daily, with a 1-week duration, were equivalent in terms of treatment tolerance and palliative effect. Both groups experienced substantial improvements in their symptoms.

References:

1. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol, 2019;5:1749-68
2. United Nations (UN). Sustainable Development Goals (SDGs). Available online: https://www.un.org/ sustainable development/health/ (accessed on 21 Oct 2021).
3. Shim J, Brindle L, Simon M, George S. A systematic review of symptomatic diagnosis of lung cancer. Fam Pract, 2014; 31(2):137–148.
4. Brierley JGM, Wittekind C. TNM classification of malignant tumor, 2017; 8th edn. Wiley, NJ.
5. Alexander M, Kim S, Cheng H. Update 2020: Management of Non-Small Cell Lung Cancer. Lung, 2020; 1-11.
6. Macbeth FR, Bolger JJ, Hopwood P, Bleehen NM, Cartmell J, Girling DJ, et al., for the Medical Research Council Lung Cancer Working Party. Randomized trial of palliative two-fraction versus more intensive 13-frac-tion radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Clin Oncol, 1996;8:167–75
7. Sundstrom S, Bremnes R, Aasebo U, Aamdal S, Hatlevoll R, Brunsvig P et al. Hypo-fractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. J Clin Oncol, 2004; 22: 801– 10.
8. Toy E, Macbeth F, Coles B, Melville A, Eastwood A. Palliative thoracic radiotherapy for non-small-cell lung cancer. Am J Clin Oncol, 2003; 26: 112-20
9. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Transl Lung Cancer Res, 2018;7(3):220-233
10. Akhtar P, Masud Z, Alam M, Begum M. Profile of Lung Cancer: A One-Year Report. J Medicine, 2011; 12(2): 115-119
11. Zaman M. Cancer Registry Report of the NICRH, 2005-2007. National Institute of Cancer Research and Hospital, 2009:1-33
12. Senkus-Konefka E, Dziadziuszko R, Bednaruk-M³yñski E, Pliszka A, Kubrak J, Lewandowska A, et al. A prospective, randomized study to compare two palliative radiotherapy schedules for non-small-cell lung cancer (NSCLC). British journal of cancer. 2005;92(6):1038-45.

Original Article

Cancer J Bangladesh 2024;5(2): 55-61
http://nicrh.gov.bd/publication

Evaluation of Short-Term Outcomes of Surgery for Colorectal Cancer

Ahmed Mizanur Rahman[1], Md. Jahangir Kabir[2], Noor-E-Fatema[3]

[1]Associate Professor, Department of Surgical Oncology, National Institute of Cancer Research & Hospital(NICRH), Dhaka.

[2]Associate Professor, Department of Surgical Oncology, NICRH

[3]Junior Consultant, Department of Gynaecological Oncology, NICRH

Citation: Rahman AM, Kabir MJ, Fatema NE. Evaluation of Short-Term Outcomes of Surgery for Colorectal Cancer. Cancer J Bangladesh 2024;5(2): 55-61.

Correspondence: Dr. Ahmed Mizanur Rahman, Associate Professor, Department of Surgical Oncology, NICRH, Mohakhali, Dhaka. E-mail: anindomonsur@yahoo.com

Received : 24 October 2024
Accepted : 29 November 2024
Published : 15 March 2025

Abstract

*Surgical resection is the principal treatment for colorectal cancer, but it carries significant morbidity and mortality. This cross-sectional study was carried out from January 2017 to August,2018. Total fifty-nine (59) patients with colorectal adenocarcinoma with defined inclusion and exclusion criteria were evaluated. Most of the complications occurred in male group (33.9%) and in the >50 years age group (17%). Forty four percent (44%) cases were in the pathological stage pT2NOMX (Stage I). The most common complication (56%) was wound infection. Postoperative complications were more in the rectal cancer patients than colonic cancer cases. Hypoalbuminaemia and cardiac disease had significant association in the patients with complication (*p*<0.05). Per-operative blood loss >300 ml was associated with higher complication rate (*p*<0.05).* ***Conclusion:*** *Hypoalbuminaemia, cardiac disease, per-operative blood loss> 300 ml, stage of disease and laparoscopic approach influence the postoperative outcomes following colorectal cancer surgery.*

Key word: *Colorectal cancer, complication, short term outcomes*

Introduction

Colorectal cancer (CRC) is the third most common malignancy and the fourth leading cause of cancer-related deaths worldwide.[1] Its prevalence in Bangladesh is 6.5% in males and 2.7 % in females.[2] The curative treatment of CRC is surgery. Even surgical resection of metastatic disease is considered whenever possible. Short term outcome of CRC is important in the sense that it reflects not only the immediate effect of surgery but also affect the long-term outcomes. Patients who experience complications in the early postoperative period demonstrate poorer long-term functional results, increased local recurrence rate, and reduced 5-year cancer survival[3]. The complication rate is more in the advanced stage of the tumor.4 Surgical institutions often use operative mortality, complications rate, length of stay, readmission rate, patients's satisfaction, functional health status, and other measures of health-related quality of life. Measurement and comparison of postoperative outcomes may result in improvement in perioperative care and may help surgeons improve their practice. Several studies measured short-term outcomes in terms of postoperative complications, duration of operation, intraoperative blood loss, postoperative pain, recovery of intestinal function, length of hospital stay, mortality, and quality of life. Oncological outcomes described in the literature as short-term outcomes are the extent of resection, number of lymph nodes (LNs) harvested, local recurrence, survival, etc.[5,6]

Patients and Method

This cross-sectional study was carried out from March 2023 to September 2023 in the Department of Surgical

Oncology, NICRH, Dhaka. A total of fifty-nine postoperative patients with histologically proven primary colorectal adenocarcinoma comprising new cases of colon cancers and rectal cancers (Including cases who received total neoadjuvant therapy) were included. Patients with residual cancer, recurrent CRC, who underwent palliative surgery were excluded from the study. Institutional ethical clearance was obtained and informed written consent was obtained from patients. CRCs were grouped into colon and rectal cancers. Colon cancers were considered from caecal cancer up to sigmoid cancers. Rectosigmoid junction cancers were included in the rectal cancer group. All patients were followed up in the postoperative period during the hospital stay and inquired about any morbidity or mortality within 30 days following surgery. Patients who had uneventful recovery were compared to those who had eventful recovery. The outcomes were measured in terms of complication rate, total time needed for operation, per-operative blood loss, time to pass first flatus, time to tolerate regular diet, time to become ambulant, mortality, postoperative hospital stay, pathological status, and margin status. Quantitative data were expressed as mean and standard deviation. Qualitative data was expressed as frequency and percentage, and comparison was carried out by Chi-square (χ^2) test. A probability value (p) of less than 0.05 was considered to indicate statistical significance.

Result

Among 59 patients, 38 (64%) were male, and the rest were female (Fig. 1). Twenty-one male patients (55%) and eleven (52%) of 21 females developed postoperative surgical complications. Thirty-six cases (61%) were rectal cancer, and 23 (39%) were colonic cancers. Postoperative complications developed in 12 (52%) of 23 colon cancer cases and in 20 (55%) of 36 rectal cancer cases. Hypoalbuminemia was present in 25 patients, but 18 of them developed complications ($\chi 2=5.51$, p-value <0.05). Cardiac diseases were present in 5 cases, and all of them developed complications. Haemoglobin level below 10 gm/dL at presentation was present in 29 cases, but complications developed in 17 cases even after correction. Renal disease (CKD), COPD, and liver diseases were present in lower frequency. Complications developed in 10(71.4%) out of 14 patients with diabetes mellitus. Forty-two patients had no co-morbidity, but 17 (29%) of them developed complications (Table 1). Forty-six (78%) patients underwent open surgery, and 11 (19%) underwent laparoscopic surgery (Fig. 1). Two laparoscopic cases were converted to open surgery (Conversion rate 3.4%).

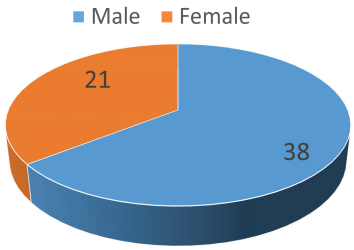

Table 1: *Preoperative comorbidities & complication rates*

Comorbidity	With complications n (%)	Without complications n (%)
Diabetes	10(17)	04(7)
Cardiac disease	05(8)	—
Liver disease	01(2)	—
Chronic Obstructive pulmonary disorder	01 (2)	—
Chronic kidney disease	01(2)	—
Anaemia (Hb<10 gm/dL)	17(29)	12(20)
Hypoalbuminemia (S.Albumin <3.5gm/dl)	18(31)	07(12)

The most performed operation was open abdomino-perineal resection of the rectum (19 cases, 32%). Out of 11 laparoscopic cases, five were laparoscopic right hemicolectomy, four were laparoscopic abdomino-perineal resection, one was laparoscopy-assisted left hemicolectomy, and one was laparoscopy-assisted anterior resection (Table II).

Table 2: *Frequency of different types of colorectal cancer operations*

Name of the operations	Frequency	Relative frequency
Right hemicolectomy	10	16.9
Open Anterior resection (AR)	12	20.3
Open Abdominoperineal resection (APR)	19	32.5
Extended Right Hemicolectomy (RH)	05	8.5
Sigmoid colectomy	01	1.7
Total colectomy	01	1.7
Laparoscopic AR	01	1.7
Laparoscopic APR	04	6.8
Laparoscopic RH	05	8.5
Laparoscopic left hemicolectomy	01	1.7
Total	59	100.0

Less than 300 mL per-operative blood loss occurred in 44 patients, and complications developed in 20 (45%) patients. Whereas 12 (80%) patients developed

complications among 15 patients with more than 300 mL per-operative blood loss. (Table III).

Table 3: *Per-operative blood loss, total operation time*

Variables	Complications n (%)	No complications n (%)
Per-operative blood loss		
< 300 ml	20(34)	24(41)
>300 ml	12(20)	3(5)
Total operation time (Min)		
<120	2(3)	4(7)
120-180	13(22)	14(24)
>180	17(29)	9(15)

Among 32 patients with complications, the most frequent was surgical site infection, accounting for 30.50% of 59 cases. The next common complication was anastomotic leak, 4 cases (6.77%), which was more frequent in open surgeries (Table 4). Surgical site infection was more common in patients operated on by open approach.

Table 4: *Frequency of different postoperative complications following open and laparoscopic operation*

Postoperative complications	Open Surgery approach (OS) n (%)	Laparoscopic Surgery Approach (LS) n (%)
Seroma	1(3)	-
Surgical site infection	15(48)	2(6)
Anastomotic leak	4(13)	-
Intra abdominal abscess	1(3)	-
Intestinal obstruction	1(3)	-
Ileostomy/colostomy complications	1(3)	-
Burst abdomen	1(3)	-
wound Perineal dehiscence	2(6)	-
Acute renal failure	1(3)	-
Postoperative bleeding	1(3)	1(3)
Urethral injury	1(3)	-
Total	29(91)	3(9)

Most of the patients were in the pathological stage I (PT2N0) group (26 cases). Out of them, 17(28.81%) patients developed complications. Four of nine patients in the stage II group developed complications.

Twenty-one patients were in stage III, and among them, 11 patients developed complications. In three patients accurate histopathological staging could not be done (pT2NX, pT3NX) (χ^2=5.26, *p*-value <0.05, Table 5). A total of 11 (19%) patients were operated laparoscopically. Their outcomes were compared to 48 (81%) patients of the open surgery group in terms of operating time, per-operative blood loss, time to pass first flatus, time to tolerate regular diet, time to ambulation, postoperative complication rate, mortality, length of postoperative hospital stay, number of lymph node harvested.

Table 5: *Tumour variables and complication*

Variables	Patients with complication n (%)	Patients without complication n (%)
Pathological stage		
Stage I	17(29)	09(15)
Stage II	04(07)	05(8)
Stage III	11(19)	10(17)
Stage not known	—	03(5)
Tumour grade		
Well diff	7(12)	2(3)
Moderately diff	19(32)	14(24)
Poorly diff	6(10)	11(19)
DRM		
Positive	01(2)	—
Negative	31(52)	27(46)
Number of (LN) retrieved		
<12	17(29)	20(34)
>12	15(25)	07(12)

DRM: Distal Resection Margin, Diff: Differentiated

The laparoscopy group was found to have less per-operative bleeding, less mortality, less postoperative hospital stays and earlier functional recovery. (*p*-value <0.05). However, time to ambulation following surgery was similar in both groups. More than 12 lymph nodes retrieved in 64% of open approaches and 54% of laparoscopic approach. However, the difference was not statistically significant, with a *p*-value of >0.05 (Table 6).

Table 6. *Short term outcomes in open and laparoscopic approach*

Outcome		Open n Approach (%)	Laparoscopic Approach n (%)	*p*-value
Operating time	<180 min	28 (47	5 (8)	>0.05
	>180 min	20 (34)	6 (10)	
Per-operative blood loss	>300 ml	36 (61)	10 (17)	<0.05
	<300 ml	12 (20)	1 (2)	
Time to pass first flatus		4.16±2.07	2.18±0.40	—
Time to tolerate normal diet		6.91±3.88	3.36±1.50	—
Time to ambulation		4.87±3.58	4.00±1.89	—
Postoperative complications	No	20 (34)	7 (12)	<0.05
	Yes	28 (47)	4 (7)	
Mortality	No	46 (78)	11 (19)	-
	Yes	2 (3)	—	
Length of postoperative hospital stay (Days)				
	<10	19(32)	8(14)	<0.05
	>10	29(49)	3(5)	
Surgical Margin				
	Negative	47(80)	11(19)	
	Positive	1(2)	—	-
Number of lymph nodes retrieved				
	<12	17(29)	5(8)	>0.05
	>12	31(53)	6(10)	

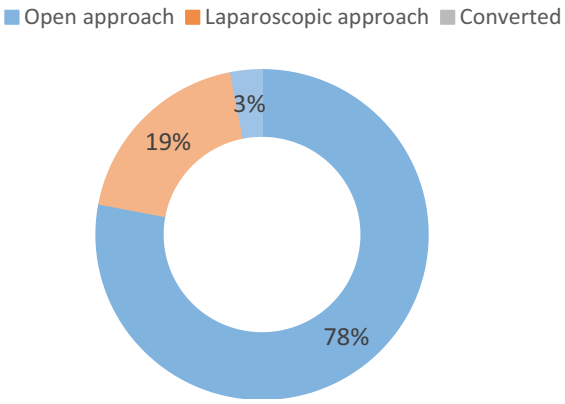

Figure 2: *Percentage of patients operated by laparoscopic and open surgery and the conversion rate.*

Discussion

This study reveals that male patients developed more postoperative surgical complications than females (55% vs 52%), but the difference was not statistically significant (χ^2=0.013, *p*-value >0.05). A study by Khan et al. shows that the proportion of male patients with complications was as high as 70% compared to female patients.7 The observed difference in postoperative complication rate in the colon cancer group (12 out of 23 cases, 52%) and rectal cancer group (20 out of 36 cases, 55%) was not statistically significant (χ^2=0.064, *p*-value> 0.05). Nineteen (30.5%) out of 33 patients who received CCRT developed complications, and one of 3 patients who did not receive CCRT developed complications (χ^2=0.652, *p*-value >0.05), which is not significant, indicating no association of the complication rate due to CCRT. However, in a study by Milgrom et al., neoadjuvant CCRT was not associated with 30-day postoperative morbidity and mortality[8], supporting our findings.

The observed difference in complications among 10 diabetic and four non-diabetic patients was not significant (χ^2 =2.2 *p*-value >0.05) (Table 3). In a study by Yap et al., surgical complications developed in 21.6% of diabetics compared to 16.1% of non-diabetics.[9] This may be due to the result of preoperative proper glycaemic control in our patients. A study by Anand et al. shows

that patients with diabetes have a 23% lower risk of mortality and morbidity following colorectal resection.[10] Cardiac disease was present in 5 cases, and all of them developed complications, and the finding was statistically significant (p-value <0.05).

Complications developed in 18(72%) of 25 patients with hypoalbuminemia. The observed difference in complication in the presence of hypoalbuminemia was statistically significant ($\chi 2$ =5.51, p-value <0.05) (Table 1). A study by Loshiriwat shows that 29% of the hypoalbuminemia had complications, whereas none of the patients with normal albumin levels developed complications.[11] Serum albumin level of 3.1 gm/dL is the limit to occur an adverse event in colorectal cancer patients.[12]

Postoperative complications were significantly associated with per-operative blood loss, but total operation time had no association with the complication rate. Complications occurred in 20 out of 44 patients with <300 ml per-operative blood loss and in 12 of 15 patients with blood loss >300 ml. The observed difference was statistically significant, indicating a strong association between per-operative blood loss and complication rate (χ^2 =5.37 p-value <0.05) (Table 3). A study by Okamura shows that morbidity was 46% among patients with preoperative blood loss > 200 ml, compared to 30% among those with blood loss <200 ml.[13]

Surgical site infection was the most frequent surgical complication, occurring in 30.5% of cases. It was more common following rectal cancer operation than colon cancer operations (23.7% vs 6.8% cases) (χ^2 =3.06, p-value >0.05) (Table 4) and in open surgery than laparoscopic surgery (33.3% vs 18.2%) (χ^2 =3.63, p-value >0.05). A study by Murray et al. Shows an overall surgical site infection rate of 12.3%.[14] Rectal resection is associated with overall surgical site infection in comparison with left- or right-sided colonic resections.[14] A study by Rahman et al. found surgical site infection in 52% of open surgery cases, but no infection was found in the laparoscopic group.[15]

The 30-day mortality rate was 3.4%. In literature, postoperative mortality of 2% to 6% following colorectal cancer resection has been described.16 In a study by Sjo et al. The mortality rate was 3.5% in elective cases and 10% in emergency patients, and the overall complication rates were 24% and 38%, respectively,[17] whereas Nickelsen et al., recorded 3.9% 30-day mortality.18 The high incidence of postoperative overall complication rate in this study may be due to the high rate of surgical site infection (56% of 32 cases of complications).

Out of 26 patients with stage I disease, 17 (29%) patients developed complications, but 11 of 20 patients with stage III disease developed complications ($\chi 2$ =5.26 p-value <0.05), which was statistically significant for the higher rate of complications among the stage-I colon cancer (Table 5). This higher rate of complications in stage-I disease may be due to the increased number of patients receiving CCRT before surgery, thereby downstaging the tumour but increasing the rate of complications. The observed difference in complication rates in patients who had retrieved LNs number less than 12 (47% of 37 patients) and who had retrieved LNs more than 12 (68% of 22 patients) was not statistically significant (χ^2 =1.14 p-value >0.05) (Table 6). A study by Duares shows that the postoperative complication rate is not associated with the pathologic stage (Duares et al., 2018). The observed differences in complications rate in tumours of different differentiation was not statistically significant (χ^2 =4.60 p-value >0.05) (Table 5). Complications developed in 57% of moderately differentiated compared to 35% of poorly differentiated tumours.

Short-term outcome differences between laparoscopic and open surgery were observed. Regarding operating time, 58.3% (28 cases) of open surgery cases had an operating time of less than 180 minutes, and six (54.5%) of LS cases took more than 180 minutes. The difference was not statistically significant (χ^2 =0.60 p-value >0.05). This may be due to extensive adhesion following CCRT and surgeons' expertise in the early stage of the learning curve of LS, which is a reason for the increased time of operation. These findings are same as the finding of study by Tominaga where the LS group had longer operating time.[19] The observed difference in postoperative complications rate in the OS group and LS group was not statistically significant ((χ^2 =1.73, p-value >0.05). A recent study shows that the OS group had a higher incidence of overall postoperative complications than the LS group, 25.1% vs 35.2%; 6 whereas another study found no statistically significant difference in postoperative complications observed between LS and OS groups of rectal cancer.[20]

The length of postoperative hospital stays (prolonged when >14 days) significantly differed between 29 (76%) out of 38 patients of OS and in 3 (27%) out of 11 cases of LS (χ^2 =3.96 *p*-value <0.05) (Table 6), indicating that the LS group had a lower length of postoperative hospital stay. This is in contrast to a study by Ding et al., which shows no differences in terms of length of hospital stay between LS and OS group.[20] whereas Chen et al. found that the LS group was associated with shorter postoperative hospital stays than the OS group (11.12 days vs 12.47 days, respectively).[21]

The number of LNs retrieved >12 following OS was observed in 28(62%) cases and 54% of the LS group. This observed value was not statistically significant (χ^2 =1.02 *p*-value >0.05), signifying that the LS approach of CRC achieved LN retrieval like that achieved by the OS approach. The mean time to pass flatus after surgery (was 4.16±2.07 days in the OS group vs. 2.18±0.40 days in the LS group, and the mean time to start oral feeding was shorter in the LS group (6.91±3.88 days in open surgery vs. 3.36±1.50 days in LS group). However, time ambulation following surgery was almost identical in both groups.

Conclusion:

This study reveals that hypoalbuminaemia, cardiac disease, stage of disease and laparoscopic approach of surgery influenced the postoperative outcomes following colorectal cancer (CRC) surgery. Laparoscopic approach of surgery resulted in less per-operative blood loss; shorter length of postoperative hospital stays. The number of lymph nodes retrieved is not affected by approach of surgery. Preoperative optimization, treatment of comorbidity and adopting laparoscopic approach may result in improved postoperative outcome.

References:

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jema A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2016;65(4):681-9.
2. Hussain SA, Sullivan R. Cancer control in Bangladesh. *Jpn J Clin Oncol.* 2013;43(11):1159-69.
3. Angelucci GP, Sinibaldi G, Orsaria P, Arcudi C, Colizza S. Morbidity and mortality after colorectal surgery for cancer. *Surg Sci.* 2013;4(12):520-4.
4. Jiang J, Huang JH, Lin C, Lin HH, Lan YT, Chang S. Impact of postoperative complications on the long-term outcomes of colorectal cancer patients who underwent curative resection. *Clin Surg.* 2020;3:1-3.
5. Morneau M, Boulanger J, Charlebois P, Latulippe J, Lougnarath R, Thibault C, et al. Laparoscopic versus open surgery for the treatment of cancer: a literature review and recommendations from the Comité de l'évolution des pratiques en oncologie. *Can J Surg.* 2013;56(6): 297-310.
6. Chiu H, Wang J, Chen C, Lin Y, Tsai H, Huang C, et al. Short- and long-term outcomes of laparoscopic-assisted surgery, mini-laparotomy, and conventional laparotomy in patients with stage I-III colorectal cancer. *J Minim Access Surg.* 2018;14(4):321-7.
7. Khan MR, Bari H, Raza SA. Early postoperative outcomes after curative colorectal cancer surgery. *Singapore Med J.* 2013;52(3):200-5.
8. Milgrom A, Goodman KA, Garrett MN, Philip BP, Gillem JG, Larissa KT, et al. Neoadjuvant radiation therapy prior to mesorectal excision for rectal cancer is not associated with postoperative complications using current techniques. *Ann Surg Oncol.* 2014;21(7):2295-302.
9. Yap R, Wilkins S, Staples M, Oliva K, McMurrick PJ. The effect of diabetes on the perioperative outcomes of colorectal cancer surgery patients. *PLoS One.* 2016;11(6):e0158129.
10. Anand S, Chong C, Chong RY, Nguyen GC. Impact of diabetes on postoperative outcomes following colon cancer surgery. *J Gen Intern Med.* 2010;25(8):809-13.
11. Lohsiriwat V, Chinswangwatanakul V, Lohsiriwat S, Akaraviputh T, Boonnuch W, Methasade A, et al. Hypoalbuminemia is a predictor of delayed postoperative bowel function and poor surgical outcomes in right-sided colon cancer patients. *Asia Pac J Clin Nutr.* 2007;16(2):213-7.
12. Haskins IN, Baginsky M, Amdur RL, Agarwal S. Preoperative hypoalbuminemia is associated with worse outcomes in colon cancer patients. *Clin Nutr.* 2017;36(5):1333-8.
13. Okamura R, Hida K, Hasegawa S, Sakai Y, Hamada M, Yasui M, et al. Impact of intraoperative blood loss on morbidity and survival after radical surgery for colorectal cancer patients aged 80 years or older. *Int J Colorectal Dis.* 2016;31(2):327-34. doi: 10.1007/s00384-015-2405-5.
14. Murray A, Adelaide C, Ravi P, David E, Ravi K. Diseases of the colon & rectum. *Dis Colon Rectum.* 2016;59(6):493-500.
15. Rahman R, Sheikh SH, Islam R, Lima IJ, et al. Early outcome of laparoscopic abdomino-perineal resection (APR) in low rectal and anal cancer. *Gastroenterol Hepatol Open Access.* 2015;2(5):00056. doi: 10.15406/ghoa.2015.02.00056.

16. Clarke C, Nancy YY, Feig BW. Cancer of the colon, rectum, and anus. In: Feig BW, Denise CC, editors. *The MD Anderson Surgical Oncology Handbook.* 6th ed. Philadelphia: Wolters Kluwer; 2018. p. 519-33.

17. Sjo O, Larsen S, Lunde O, Nesbakken A. Short-term outcome after emergency and elective surgery for colon cancer. *Colorectal Dis.* 2009;11(7):733-9.

18. Nickelsen TN, Jørgensen T, Kronborg O. Lifestyle and 30-day complications to surgery for colorectal cancer. *Acta Oncol.* 2018;44(3):218-23.

19. Tominaga T, Takeshita H, Arai J, Takagi K, Kunizaki M, To K, et al. Short-term outcomes of laparoscopic surgery for colorectal cancer in oldest-old patients. *Dig Surg.* 2015;32(1):32-8.

20. Ding Z, Wang Z, Huang S, Zhong S, Lin J. Comparison of laparoscopic vs. open surgery for rectal cancer. *Mol Clin Oncol.* 2017;6(2):170-6.

21. Chen CF, Lin Y, Tsai H, Huang CW, Yeh YS, Ma CJ. Short-term and long-term outcomes of laparoscopic-assisted surgery, mini-laparotomy, and conventional laparotomy in patients with stage I-III colorectal cancer. *J Minim Access Surg.* 2018;12(4):321-34.

Original Article

Cancer J Bangladesh 2024;5(2): 62-68
http://nicrh.gov.bd/publication

The Impact of Oral Hygiene Practice on the Severity of Oral Mucositis in Children with Acute Lymphoblastic Leukemia Receiving Induction Chemotherapy

Renesha Islam, Chowdhury Yakub Jamal [2], Wahida Nargis [3], Tandra Chakma [4], Farzana Islam [5], Momtahina Mou [6], Minha Islam [7]

[1]Resident Physician (Pediatrics), 250 Bedded General Hospital, Gopalganj.
[2]Ex-Professor, Department of Pediatric Hematology and Oncology, BSMMU, Dhaka.
[3]Assistant Registrar, Department of Pediatric Hematology and Oncology, Sir Salimullah Medical College Mitford Hospital, Dhaka
[4]Medical Officer, Department of Pediatric Hematology and Oncology, BSMMU, Dhaka.
[5]Assistant Professor, Department of Pediatric Hematology and Oncology, BSMMU, Dhaka.
[6]Indoor Medical Officer, Department of Pediatric Hematology and Oncology, Dhaka Medical College Hospital, Dhaka.
[7]CAD Designer, Nikken International Asia Co. Ltd, Dhaka.

Citation: Islam R, Jamal CY, Nargis W, Chakma T, Islam F, Mou M, Islam M. The Impact of Oral Hygiene Practice on the Severity of Oral Mucositis in Children with Acute Lymphoblastic Leukemia Receiving Induction Chemotherapy. Cancer J Bangladesh 2024;5(2): 62-68.

Correspondence: Dr. Renesha Islam, Resident Physician (Pediatrics), 250 bedded general hospital, Gopalganj. E-mail: reneshaislam@yahoo.com

Received : 14 December 2024
Accepted : 04 March 2024
Published : 15 March 2025

Abstract

Background: *In pediatric acute lymphoblastic leukemia (ALL), oral mucositis (OM) is the most frequent and excruciating side effect of chemotherapy. This study aimed to evaluate the role of proper oral hygiene maintenance on the reduction of incidence and severity of OM in children with ALL undergoing the induction phase of chemotherapy.* ***Method:*** *Following ethical approval, this prospective observational study was carried out for 1 year in the Department of Pediatric Hematology and Oncology (PHO), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. A total of 40 children (5–18 years old) with ALL, 20 in the control group and another 20 in the intervention group receiving the induction phase of chemotherapy, were included in the study. In accordance with the PHO BSMMU procedure, chemotherapeutic medications, and supportive measures were applied to all patients. Only the intervention group strictly adhered to oral hygiene practices during the 35 days of the induction period.* ***Result:*** *Of the 40 children with ALL, the mean age of the patients was 8.5±3.2 years, with male predominance (77.5%), whereas the common variety (95% and 90% were in the control and intervention groups, respectively) was ALL (B cell). The demographic characteristics of both groups were statistically similar. Prior to beginning chemotherapy, about 75.5% of patients knew about standard oral hygiene practices but did not actively follow them, and 55% of patients brushed their teeth twice a day without adhering to other oral care techniques. Overall, 37.5% of patients experienced OM throughout the 35 days of induction chemotherapy: of these. 13.3% were in the intervention group, and 26.7% were in the control group. Similarly, days of OM development were delayed in the intervention group compared to the control group. However, no significant difference was found between both groups.* ***Conclusion:*** *The application of proper oral hygiene techniques can decrease the incidence and occurrence of OM in pediatric ALL undertaking induction chemotherapy.*

Keywords: *Oral hygiene, Oral Mucositis, Acute Lymphoblastic Leukemia, Children*

Introduction

In Bangladesh, with an approximate annual number of 13,000 new cases, Acute lymphoblastic leukemia (ALL) is considered the most prominent type of childhood leukemia, accounting for 75–80% of the total instances.[1] By using intensive chemotherapeutic regimens, the cumulative overall survival rate for pediatric patients has increased from 70 to 97% in recent years.[2, 3]

However, chemotherapy causes damage to the mucosal barrier even while it stops the growth and development of cancer cells. As a result, oral mucositis (OM) is one of the major adverse effects of chemotherapy and the most frequent oral complication found in pediatric acute lymphoblastic leukemia (ALL) patients following the initial period of chemotherapy.[4-6]

The term "oral mucositis" (OM) describes inflammation of the oral mucosa, which generally displays as erythematous change, swelling, atrophy, and, at last, ulceration. It affects 20% to 80% of children who take chemotherapy exclusively. If left with insufficient prevention and lack of control, OM can significantly impair a patient's quality of life, reduce the efficacy of treatment, which hinders patients' chances of survival, recovery, and remission.[3,5,7-9]

According to guidelines from the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology and (MASCC/ISOO), oral health care practices are the primary element of measures used to lessen the severity of OM. Pediatric oral hygiene is crucial for both resilient, healthy tooth development as well as lowering the risk of infection. Moreover, one of the patient groups most in need of oral care is children. So, in order to minimize OM brought on by chemotherapy, strict maintenance of oral hygiene should be a common procedure, particularly in pediatric hematology and oncology unit.[4,6,7,10]

Methods

This prospective comparative study was conducted in the Department of Pediatric Hematology and Oncology (PHO), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka followed by ethical approval. The aim of the study was to find out the possible effects of maintaining proper oral hygiene in reducing the occurrence and severity of OM in pediatric patients with ALL undergoing induction chemotherapy.

A total of 40 children aged 5 to 18 years of both genders, who were newly diagnosed with ALL and admitted from January 2022 to December 2022 for 35 days of induction chemotherapy with the capability of brushing, flossing and mouth rinsing individually or with the help of the parents as judged by the principal investigator, were included in this study. Children with OM or any oral lesion at initial assessment, neurodevelopmental delays, mental retardation, or patients who had previously undergone oncological treatment or on palliative therapy were excluded. After acquiring informed written consent from patients or guardians, a pre-designed data collection sheet was used to gather the data. Induction chemotherapy was given to all patients as per the modified UK-ALL 2011 protocol of PHO, BSMMU (Regimen-A for standard risk patients and regimen-B for high-risk patients), with supportive treatment. Stratified randomization was used to ensure the recruitment of 20 patients of regimen-A and 20 patients of regimen-B (total 40 patients; 10 regimen-A and 10 regimen-B in both Control and intervention group respectively) for uniform distribution. Then only patients and parents of the intervention group received audiovisual oral care program that included instructions and information about the oral care with a pamphlet detailing the oral hygiene practices (Table-1) before starting chemotherapy. Prior to receiving induction chemotherapy, initial assessment was done followed by 12 evaluations that were then conducted in both groups of patients every three days until the 35 days of induction chemotherapy were over. The degree of OM was assessed under artificial lighting while all physical barriers were in place. The OM was assessed and scored by the World Health Organization (WHO) mucositis scoring system (Table-2). To verify response and adherence to treatment, oral hygiene status was strictly monitored. After collection, all the required were checked, verified for consistency and tabulated using the SPSS for Windows version 24 software.

Result:

Among 40 children with ALL, 20 only received chemotherapeutic drugs with supportive care (Control group), and the other 20 child patients received the above-mentioned treatment with proper knowledge about oral care and strictly adhered to maintaining oral hygiene practice (Intervention Group). Description of the oral hygiene practice10-11 in intervention group is

presented in Table I while in Table II the World Health Organization (WHO) mucositis scoring system to assess severity of OM is shown. Table III shows, mean age of the study patients was 8.5±3.2 years with 77.5% were male. Among all, 92.5% was Muslim and 47.5% was residing in urban area. Demographic characteristics of both groups were statistically similar (Table-III).

Amongst the study patients, 95% and 90% were diagnosed as ALL (B cell) in the control and intervention groups, respectively (Figure 1). Table IV demonstrates before starting chemotherapy, 55% brushed their teeth twice a day without adhering to further oral care methods, and approximately 75.5% knew about proper oral hygiene practices but did not particularly apply them. Oral care practice and previous knowledge of both groups were statistically similar.

During the follow-up period, overall, 37.5% of patients had developed OM; among them, 26.7% were in the control group and 13.3% were in the intervention group.

Table-I: *Description of the oral hygiene practice[10-11] in intervention group (n=20)*

Dental treatment before or at the beginning of treatment, if necessary.

After waking up and before bedtime: Gentle dental brushing with soft bristle toothbrush and toothpaste using Bass Sulcular technique for 90 seconds. Then gently clean the gums, tongue and soft tissue with the toothbrush. Rinsing mouth with Chlorhexidine Gluconate mouthwash (~30 seconds). Swish thoroughly and spit out. Do not swallow. Do not eat or drink anything including water after using the mouthwash.

Within 30 minutes after each meal: Rinsing mouth with Chlorhexidine Gluconate mouthwash twice daily (~30 seconds).

Table- II: *World Health Organization (WHO) mucositis scoring system to assess the severity of Oral Mucositis (OM) [12]*

Grade	Severity	Mucosal change & functional outcome
0	None	No symptoms
1	Mild	Soreness, slight erythema, no ulceration
2	Moderate	Soreness, erythema, ulcers, patients can eat and drink
3	Severe	Erythema, painful ulcers, patients cannot tolerate solid food but can swallow liquids
4	Urgent	Severe pain, patients cannot swallow solid or liquid food.

Table- III: Demographic characteristics of the study patients (n=40)

Demographic characteristics	Control group(n=20) n (%)	Intervention group(n=20) n (%)	Both groups(n=40) n (%)	*p*-value
Age (years)				
<10	13 (65)	12 (60)	25 (62.5)	0.743
≥10	7 (35)	8 (40)	15 (37.5)	
Mean ± SD	8.5±3.2	8.5±3.2	8.5±3.2	1.00
Gender				
Male	15 (75)	16 (80)	31 (77.5)	0.704
Female	5 (25)	4 (20)	9 (22.5)	
Religion				
Muslim	19 (95)	18 (90)	37 (92.5)	0.548
Hindu	1 (5)	2 (10)	3 (7.5)	
Persisting Family history of malignancy	2 (10)	3 (15)	5 (12.5)	0.500
Residence				
Urban	9 (45)	10 (50)	19 (47.5)	0.751
Rural	11 (55)	10 (50)	21 (52.5)	

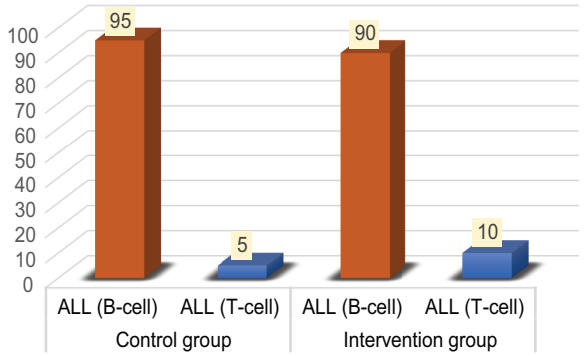

Fig.-1: *Diagnosis of patients in both groups (n=40)*

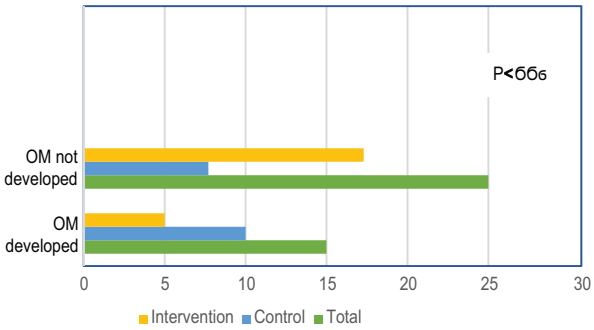

Fig. 2: *Development of Oral Mucositis (OM) among the study patients during follow up (n=40)*

Development of OM was significantly lower among the intervention group. (Figure 2).

Table V shows the severity of OM was significantly higher in control group in comparison to intervention group during the follow up day 9, day 12, day 15, day 18 and day 21.

Table 4 demonstrates that days of OM development were delayed in intervention group than control group. But no significant difference is found between both groups.

Table-4: *Oral mucositis severity detection by using WHO grading system in both the groups during follow up period (n=40)*

Grading of OM severity during follow up		Control group (n=20) n (%)	Intervention group (n=20) n (%)	Both groups (n=40) n (%)	*p*-value
Day 3	Grade 1	1 (5)	0 (0)	1 (2.5)	1.00 (NS)
Day 6	Grade 1	2 (10)	0 (0)	2 (5)	0.410 (NS)
	Grade 2	2 (10)	1 (5)	3 (7.5)	
Day 9	Grade 1	3 (15)	0 (0)	3 (7.5)	0.021 (S)
	Grade 2	3 (15)	0 (0)	3 (7.5)	
Day 12	Grade 1	3 (15)	2 (10)	5 (12.5)	0.015 (S)
	Grade 2	6 (30)	0 (0)	6 (15)	
Day 15	Grade 1	3 (15)	0 (0)	3 (7.5)	0.009 (S)
	Grade 2	4 (20)	0 (0)	4 (10)	
Day 18	Grade 1	4 (20)	1 (5)	5 (12.5)	0.003 (S)
	Grade 2	6 (30)	0 (0)	6 (15)	
Day 21	Grade 1	2 (10)	1 (5)	3 (7.5)	0.012 (S)
	Grade 2	6 (30)	0 (0)	6 (15)	
Day 24	Grade 1	1 (5)	1 (5)	2 (5)	0.738 (NS)
	Grade 2	2 (10)	0 (0)	2 (5)	
Day 27	Grade 1	2 (10)	1 (5)	3 (7.5)	1.00 (NS)

Table 5: *Oral mucositis severity detection by using WHO grading system in both the groups during follow up period (n=40)*

Grading of OM severity during follow up		Control group (n=20) n (%)	Intervention group (n=20) n (%)	Both groups (n=40) n (%)	*p*-value
Day 3	Grade 1	1 (5)	0 (0)	1 (2.5)	1.00
Day 6	Grade 1	2 (10)	0 (0)	2 (5)	0.410
	Grade 2	2 (10)	1 (5)	3 (7.5)	
Day 9	Grade 1	3 (15)	0 (0)	3 (7.5)	0.021(S)
	Grade 2	3 (15)	0 (0)	3 (7.5)	
Day 12	Grade 1	3 (15)	2 (10)	5 (12.5)	0.015(S)
	Grade 2	6 (30)	0 (0)	6 (15)	
Day 15	Grade 1	3 (15)	0 (0)	3 (7.5)	0.009(S)
	Grade 2	4 (20)	0 (0)	4 (10)	
Day 18	Grade 1	4 (20)	1 (5)	5 (12.5)	0.003(S)
	Grade 2	6 (30)	0 (0)	6 (15)	
Day 21	Grade 1	2 (10)	1 (5)	3 (7.5)	0.012(S)
	Grade 2	6 (30)	0 (0)	6 (15)	
Day 24	Grade 1	1 (5)	1 (5)	2 (5)	0.738
	Grade 2	2 (10)	0 (0)	2 (5)	
Day 27	Grade 1	2 (10)	1 (5)	3 (7.5)	1.00

S= Significant

Table 5: *Days of Oral mucositis development in both groups of patients during follow-up in induction period (n=15)*

Days	Controlgroup(n=10) Mean ± SD (range)	Intervention group(n=5) Mean ± SD (range)	Both groups(n=15) Mean ± SD (range)	*p*-value
Oral mucositis development duringInduction period	12.6±5.4(3-18)	13.6±7.6(3-21)	12.8±5.8(3-21)	0.756

Discussion:

While multimodal chemotherapeutic protocols for childhood ALL have greatly increased overall survival rates in recent years, they have also increased the occurrence of side effects, such as OM. However, research on the negative effects of OM on treatment compliance and the outcome of pediatric ALL is very sparse, particularly in developing countries such as Bangladesh.[1,7,8]. The goal of the current study was to further enhance patient outcomes by investigating how adequate oral hygiene practice can help in preventing OM in pediatric ALL patients throughout the induction phase of chemotherapy.

According to our study, the mean age of the patients with ALL was 8.5±3.2 years, 77.5% were male, and the most prevalent type in both groups was ALL (B cell), 95% and 90% in the control and intervention groups, respectively. Our results were in line with earlier research conducted in Bangladesh, where ALL (B cell) was the most usual form particularly common in the 5–9 years age group (41%), with a predominant gender being males (58%) [1].

Both groups' demographic traits were statistically similar. None of the patient's characteristics, including age, gender, religion, residential location, were shown to be significantly correlated with the beginning of OM. These findings are consistent with the previously reported studies.[1,7-9,14-16]

This study showed around 55% brushed their teeth twice a day without adhering to further oral care methods and 75.5% knew about proper oral hygiene practices but did not particularly practice them. previous knowledge and oral hygiene practice of both groups were statistically similar. which were also found in Cheng et al., 2001 and Gutiérrez-Vargas et al.2020[10,11]

Overall, 37.5% of patients experienced the development of OM throughout the follow-up period; of these, 13.3% were in the intervention group and 26.7% were in the control group. The control group experienced significantly higher OM development (p<0.001). In the same way, Özalp Gerçeker et al., 2024, found that 27.7% of patients overall developed mucositis, compared to 18.2% (n=4) of patients in the control group and 9.5% (n=2) of patients in the study group.[10] Additionally, the control group's development of OM was significantly higher (p <0.001) than that of the study group that adhered to the oral care protocol observed in Kostak et al., 2020.[4]

In this study, the severity of OM was significantly higher in control group in comparison to intervention group during the follow up Day 9, Day 12, day 15, day 18 and day 21. Similarly, days of OM development was delayed in intervention group than control group. But no significant difference is found between both groups. These results align with the earlier studies published.[4,9-11]

Because 100% of the intervention population in this study strictly followed the oral hygiene procedure, the prevalence rate of OM was 26.7%, which is significantly lower than rates previously reported in literature[14]. Therefore, the results of our study may help to further improve the outcomes for pediatric ALL by educating children and their parents about oral care techniques for the prevention of OM from the initiation of treatment. As stated by Qutob et al., (2013), practicing adequate oral hygiene and understanding its significance can help steer clear of the OM development.[13] Even though it cannot stop from developing in the first place, the use of precautionary oral hygiene techniques in combination with continuing medical interventions has been crucial in reducing the severity and duration of OM.[17-19]

Conclusion

Proper oral hygiene significantly reduces the occurence and severity of oral mucositis in pediatric ALL patients. While awareness is high, adherence remains low, highlighting the need for better education. Integrating oral care into treatment plans can improve patient outcomes and quality of life.

References

1. Nahar K, Ferdousi, SA, Hasan, AR, Islam A, Islam, A. Incidence and Outcome of Childhood Acute Leukemia in A Tertiary Care Hospital of Bangladesh Armed Forces. Dhaka Shishu (Children) Hospital Journal. 2023; 38(1), 17–26.
2. Santiago R, Vairy S, Sinnett D, Krajinovic M, Bittencourt H. Novel therapy for childhood acute lymphoblastic leukemia. Expert Opinion on Pharmacotherapy. 2017; 18(11), 1081–1099.
3. Curra M, Gabriel AF, Ferreira MBC, Martins MAT, Brunetto AT, Gregianin LJ, Martins MD. Incidence and risk factors for oral mucositis in pediatric patients receiving chemotherapy. Supportive Care in Cancer. 2021.
4. Kostak MA, Semerci R, Eren T, Kocaaslan EN, Yildiz F. Effects of oral Health Care Education on the Severity of Oral Mucositis in Pediatric Oncology Patients. Turkish Journal of Oncology. 2020;35(4):422–29.
5. Mendonça RMH de, Araújo M de, Levy CE, Morari J, Silva RA, Yunes JA, Brandalise SR. Oral Mucositis in Pediatric Acute Lymphoblastic Leukemia Patients: Evaluation of Microbiological and Hematological Factors. Pediatric Hematology and Oncology. 2015; 32(5), 322–330.
6. Gutiérrez-Vargas R, Villasis-Keever MÁ, Portilla-Robertson J, Ascencio-Montiel IDJ, Zapata-Tarrés M. Effect of zinc on oropharyngeal mucositis in children with acute leukemia undergoing chemotherapy. Medicina Oral Patologia Oral y Cirugia Bucal. 2020; 25 (6), e791-8.
7. Attinà G, Romano A, Maurizi P, D'Amuri S, Mastrangelo S, Capozza MA, Triarico S, Ruggiero A. Management of Oral Mucositis in Children with Malignant Solid Tumors. Frontiers in Oncology. 2021; 11:599243.
8. Badr M, Hassan T, Sakr H, Karam N, Rahman DA, Shahbah D, Fehr S. Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences. Molecular and Clinical Oncology. 2016; 5(3), 300–306.

9. Figliolia S., Oliveira D, Pereira M, Lauris J, Maurício A, Oliveira D, Mello de Andrea M. Oral mucositis in acute lymphoblastic leukaemia: analysis of 169 paediatric patients. Oral Diseases. 2008; 14(8), 761–766.

10. Özalp Gerçeker G, Yýldýrým BG, Önal A, Bektaþ M, Leblebici A, Ören H, Olgun N. The Effect of Oral Care Protocols on Mucositis in Pediatric Cancer Patients: A Randomized Controlled Trial. J Contemp Med. July 2024;14(4):180-188.

11. Cheng KKF, Molassiotis A, Chang AM, Wai WC, Cheung SS. Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. European Journal of Cancer. 2001; 37:2056-2063.

12. Lalla, R.V., Bowen, J., Barasch, A., Elting, L., Epstein, J., Keefe, D.M., et al., 2014. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer, 120(10), 1453–1461.

13. Qutob AF, Gue S, Rvesz T, Logan RM, Keefe D. Prevention of oral mucositis in children receiving cancer therapy: a systematic review and evidenced based analysis. Oral Oncology. 2013; 49:102–7.

14. Attinà G, Ruggiero A, Maurizi P, Arlotta A, Chiaretti A, Riccardi R. Transdermal buprenorphine in children with cancer related pain. Pediatric Blood and Cancer. 2009; 52:125–27.

15. Farias Gabriel A, et al. Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta analysis. Oral Diseases. 2021; 00, 1-17.

16. Cheng KKF, Goggins WB, Lee VWS, Thompson DR. Risk factors for oral mucositis in children undergoing chemotherapy: a matched case–control study. Oral Oncology. 2008; 44: 1019–1025.

17. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004; 100:1995–2025.

18. Allen G, Logan R, Revesz T, Keefe D, Gue S. The Prevalence and Investigation of Risk Factors of Oral Mucositis in a Pediatric Oncology Inpatient Population; A Prospective Study. Journal of Pediatric Hematology/ Oncology. 2018; 40(1), 15–21.

19. Cheng KK, Molassiotis A, Chang AM, Wal WC, Cheunq SS. Evaluation of an oral care protocol intervention in the prevention of chemotherapy induced oral mucositis in paediatric cancer patients. The European Journal of Cancer 2001; 37: 2056–2063.

Original Article

Cancer J Bangladesh 2024;5(2): 69-74
http://nicrh.gov.bd/publication

Clinico-pathological profile and Treatment Outcome of Paediatric Hodgkin Lymphoma in Bangladesh: A Single Centre Experience

Eshita Reza Khan[1], Ferdousi Begum[2], Sabina Karim[3], Mehnaz Akter[3], Farida Yasmin[1], Shahinoor Akter Soma[1], Ismot Ara Zannat[4], Arafatara Khatun[5], Syeda Sharmin Ara[5]

[1]Assistant professor, Department of Paediatric Haematology and Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka

[2]Associate professor and Head, Department of Paediatric Haematology and Oncology, NICRH, Dhaka

[3]Associate professor, Department of Paediatric Haematology and Oncology, NICRH, Dhaka

[4]Registrar, Department of Paediatric Haematology and Oncology, NICRH, Dhaka

[5]Medical Officer, Department of Paediatric Haematology and Oncology, NICRH, Dhaka

Citation: Khan ER, Begum F, Karim S, Akter M, Yasmin F, Soma SA, Zannat IA, Khatun A, Ara SS. Clinico-pathological profile and Treatment Outcome of Paediatric Hodgkin Lymphoma in Bangladesh: A Single Centre Experience. Cancer J Bangladesh 2024;5(2): 69-74.

Correspondence: Dr. Eshita Reza Khan, Assistant Professor, Department of Paediatric Haematology and Oncology, National Institute of Cancer Research & Hospital. E-mail: dr.eshita.k@gmail.com

Received : 21 November 2024
Accepted : 03 December 2024
Published : 15 March 2025

Abstract:

Background: *Hodgkin lymphoma is a common and highly curable malignancy in children and adolescents. Due to low-resource settings, there are many clinical and pathological variations and alterations of treatment modalities in low-middle-income countries. This study aims to explore the clinicopathological profile of paediatric Hodgkin lymphoma and its outcome at the National Institute of Cancer Research and Hospital (NICRH) in Bangladesh.* ***Methods:*** *This observational study included paediatric Hodgkin lymphoma patients from the registry of the paediatric haematology and oncology department of NICRH from 2020 to 2022. All clinical, pathological, and treatment data, including outcomes and complications, were documented in a preformed data collection sheet after obtaining informed written consent.* ***Results:*** *The study included 104 paediatric Hodgkin lymphoma patients. The mean age is 9.9 years (range: 4-18 years), and 84.6% of patients are boys. Cervical lymphadenopathy is the most common clinical feature. Mixed cellularity histologic subtype is found in 68% of cases. The 2-year overall survival rate of paediatric Hodgkin lymphoma is 92.3%, and the relapse rate is 19.2%. The most common cause of mortality is chemotherapy-induced toxic death.* ***Conclusion:*** *The treatment outcome of paediatric Hodgkin lymphoma in Bangladesh is excellent. However, there is scope for improvement in reducing relapse rates and toxic deaths.*

Key words: *Paediatric, Hodgkin, Lymphoma, outcome, Bangladesh*

Introduction:

Hodgkin lymphoma (HL) is a common malignancy in children and adolescents. It accounts for 6.5% of all childhood cancers in the United States[1]. In developing countries, the incidence of HL is higher in children.[2] It is also one of the most curable subtypes of paediatric cancer. In Europe, the USA, and Canada, 5-year overall survival of paediatric HL is 93%, 96%, and 99%, respectively.[3,4]

The current recommendation is the risk-adapted multimodal therapy, such as cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (COPP-ABV) or doxorubicin, bleomycin, vincristine, etoposide, prednisone, and

cyclophosphamide (ABVE-PC); or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) with involved-field radiotherapy (IFRT). Risk-adapted therapy for paediatric HL has resulted in a significant reduction in serious long-term outcomes.[5,6]

Around the world, childhood HL displays different epidemiological, clinical, and pathological features according to various geographic locations. In low— and middle-income countries (LMIC), a high male-to-female ratio, younger age at presentation, high proportion of advanced stages and presence of constitutional symptoms, and predominance of mixed cellularity type of HL are usually observed.[7]

In LMICs, treatment strategies aim to balance between curative goals, toxicities, and local resources. The socio-economic situation leads to multiple problems that significantly impact paediatric HL treatment and outcomes. These issues include delays in referring patients to hospitals, high rates of abandonment, inadequate initial staging workup and response assessment due to financial constraints, lack of availability of radiotherapy, and a variety of other challenges.[8]

In resource-constrained settings like India, Iraq, and Egypt, the most used multi-agent chemotherapy is ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine); it is economical, can be administered on a daycare basis, and does not require frequent monitoring of blood counts.[8-13]

Information regarding the clinicopathological features and outcomes of paediatric Hodgkin Lymphoma in LMICs is still limited due to the lack of proper country registries, the paucity of updated follow-up data, and the lack of large studies that reflect the real-life situation of LMICs. To date, there has been no published research on paediatric HL in Bangladesh.

The National Institute of Cancer Research and Hospital (NICRH) in Bangladesh is a nationwide referral centre for cancer patients. The Department of Paediatric Haematology and Oncology has a high burden of HL patients. Therefore, a study in this department of NICRH would reflect the real-world scenario of paediatric HL in Bangladesh. The study also provides essential background data to identify the challenges in the management of childhood HL and to provide new insight to improve its outcome in the future.

Methodology:

Study design: It was an observational study. The parents/ guardians of all paediatric Hodgkin lymphoma patients from the registry of paediatric haematology and oncology department of NICRH from 2020 to 2022 were contacted for consent. Those who gave verbal consent were requested to come to the hospital for follow-up. During follow-up, all clinical, pathological, and treatment data with outcomes and complications were documented in a preformed data collection sheet after obtaining informed written consent.

Data analysis: Qualitative data were presented as percentages; quantitative data were presented as mean with standard deviation; Fisher's Exact test was used to detect associations.

Results:

Study population: There were 120 patients of Hodgkin lymphoma in the departmental registry notebook of the year 2020-2022. All entries were called over phone as per the phone number documented in the notebook. Among them. 16 entries could not be contacted. The rest 104 patients' parents or guardians gave informed consent for providing information over phone and during follow up visits (Fig. 1).

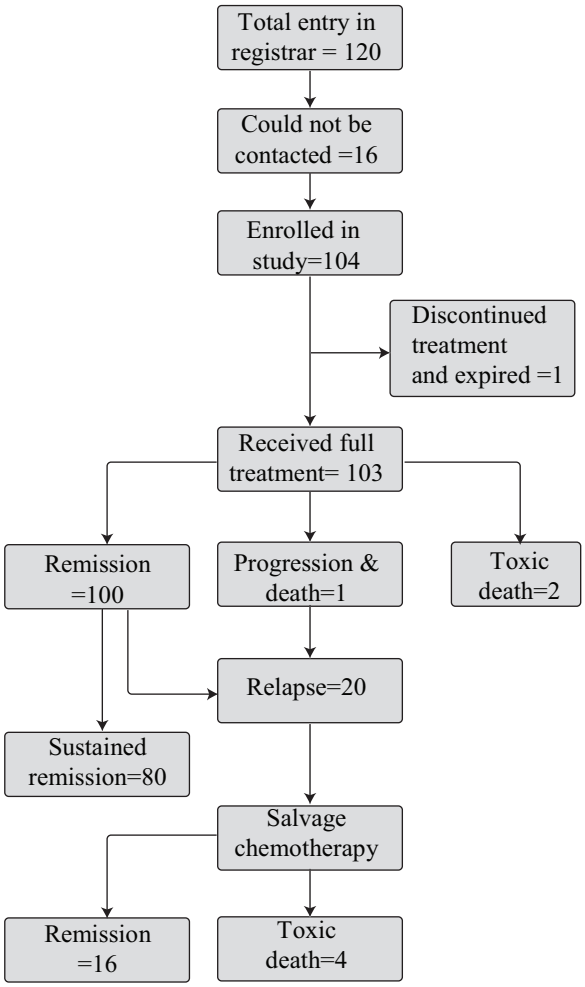

Fig.-1: *Study population*

Clinical features: The total number of patients was 104. Among them, 84% were male. The median age was 9.9 ±7.9 years. The most common clinical feature was cervical lymphadenopathy (96%). The liver was the most common site of extra-lymphatic involvement. Advanced staged diseases (stage III and IV) were found in 32.7% of cases. B symptoms and bulky diseases were observed in 59.6% and 21.1% of cases respectively (Table-I).

Table 1: *Clinical Features and stages of Paediatric Hodgkin Lymphoma*

Clinical features	Findings
Age in years, mean ±SD (range)	9.9 ±7.9 (4-17)
Age ≤5 years, number (%)	16 (15.3)
Sex, male, number (%)	88 (84.6)
Lymphatic sites involved, number (%)	
Cervical	96 (92)
Supraclavicular	6 (5.7)
Axillary	20 (19.2)
Mediastinal//hilar/paratracheal	18 (17.3)
Pelvic/retroperitoneal/mesenteric	16 (15.3)
Inguinal	12 (11)
Spleen	14 (13.4)
Extra-lymphatic sites involved, number (%)	
Liver	13 (12.5)
Pulmonary lesion/effusion	3 (2.8)
Bone	1 (0.9)
Bone marrow	2 (1.9)
Stages, number (%)	
Stage 1	5/104 (4.8)
Stage 2	65/104 (62.5)
Stage 3	18/104 (17.3)
Stage 4	16/104 (15.4)
Advanced stages (3 & 4)	34 (32.7)
B symptoms present, number (%)	62/104 (59.6)
Bulky disease present, number (%)	22 (21.1)

The most common histopathologic subtype was Mixed cellularity which was observed in 68.2% cases. In 12.5% cases, histopathological subtypes were not mentioned (Table 2).

This study followed patients for 24-54 months (mean 39.6 months). 2-year overall survival was 92.3%, with a relapse rate of 19.2%. Toxic death was the most common cause of mortality. Common complications include immune hemolytic anemia and post-therapy reactive lymphadenitis (Table 3).

Table 2: *Histopathology of Paediatric Hodgkin Lymphoma*

Histopathology	Number (%)
Mixed cellularity	71 (68.2)
Nodular sclerosis	12 (11.5)
Lymphocyte rich	7 (6.7)
Lymphocyte depleted	1 (0.9)
Not specified	13 (12.5)

Table 3: *Outcome and complications of Paediatric Hodgkin Lymphoma*

Outcome and complications	Number (%), range
2-year overall survival	96/104 (92.3)
2-year event-free survival	80/104 (76.9)
Relapse	20/104 (19.2)
Mean follow up period in months	39.6 ± 10.2, 24-54
Death, total	8 (7.7)
Toxic death after primary chemotherapy	2 (1.9)
Toxic death after salvage chemotherapy	4 (3.8)
Progressive disease	1 (0.96)
Abandonment	1 (0.96)
Immune hemolytic anemia (Coomb negative, steroid responsive)	3 (2.9)
Post-therapy reactive lymphadenitis (biopsy proven)	3 (2.9)
Post-therapy lymph node calcification (biopsy proven)	1 (0.96)
Post-radiotherapy hypothyroidism	2 (1.9)

ABVD was the most used chemotherapy protocol. There were no mortalities in patients with stage I or II diseases. However, in advanced-stage diseases (stage III and IV), there were two toxic deaths from primary chemotherapy and four toxic deaths from salvage chemotherapy. Progressive disease and abandonment were the cause of death in one patient each (Table 4).

There were 20 cases of relapses after primary chemotherapy. The relapse rate was 10-26% in various chemotherapy protocols, among which the lowest relapse rate was observed with the ABVE-PC protocol. Radiotherapy was given in 24 (23%) patients. The patients who received radiotherapy had a much lower rate of relapse, but it was not found to be significant in statistical analysis (Table 5).

Table 4: *Different chemotherapy protocols used with outcomes*

Stage	Protocol	Cases	Relapse	Death
I & II	ABVD	54	9	0
	COPP-ABV	10	3	0
	ABVE-PC	4	0	0
	BEACOPP	1	0	0
III & IV	ABVD	18	5	Discontinued treatment=1Toxic death after salvage BEACOPP=3
	COPP-ABV	5	1	0
	ABVE-PC	6	1	Toxic death after salvage BEACOPP=1
	BEACOPP	6	1	Toxic death on primary chemo=2Progressive disease= 1
Total		104	20	8

Table 5: Therapy modalities and relapse risk in Paediatric Hodgkin Lymphoma

Therapy modalities	Number of patients	Relapse	Relapse risk (%)	*p*-value*	
Chemotherapy protocols	ABVD	72	14	19.4	
	COPP-ABV	15	4	26	
	ABVE-PC	10	1	10	0.0736
	BEACOPP	7	1	14.2	
Radiotherapy	Radiotherapy used	24	1	4.1	
(Involved site)	No radiotherapy	80	19	23.7	

*Fisher's Exac

Discussion:

In this study, children aged ≤5 years of age constituted 15% of all patients, which contrasts with the developed world, where it is rare for under 5 years of age, but similar to the proportions (15-22%) observed in various studies in India and Egypt.[10,13-15]

In this study, 85% of patients were male. In developing countries, there is a male predominance in paediatric Hodgkin lymphoma.[10,13,14] The reasons for this gender distribution are not fully understood. Increased male susceptibility to infection, as well as social-cultural factors leading to reduced attention to female children, have been suggested.[16]

In this study, the most common histologic subtype was mixed cellularity. Unlike high-income countries, mixed cellularity is the predominant histologic subtype in low-middle-income countries. In two large studies in India involving 939 and 206 paediatric Hodgkin lymphoma cases, mixed cellularity histology was observed in 60.6% and 69.6% of cases, respectively.[10,17]

In this study, the treatment outcome was good, as 2-year overall survival was 92.3%, comparable with various studies in different parts of the world. However, the relapse rate was 19.2%. In an extensive study of paediatric Hodgkin lymphoma, the relapse rate was 15.9%.[18] According to EuroNet Paediatric Hodgkin Lymphoma Group, relapse/refractory disease may occur in approximately 10% in low stage and 15-20% in advanced paediatric Hodgkin lymphoma.[19]

In this study, the most used chemotherapy protocol was ABVD, as it is more economical and might be administered on a day-care basis. Radiotherapy was administered in 24/104 (23%) patients. In different extensive studies of paediatric Hodgkin lymphoma in India and Canada, 5-year overall survival with ABVD protocol is 95-97%.[11,20]

Previously, ABVD and ABVE-PC chemotherapy protocols were compared in a retrospective cohort of 224 paediatric Hodgkin lymphoma patients in the USA.

In two clinically comparable groups, event-free survival and overall survival were found to be similar, with similar dosages of anthracycline and use of radiotherapy.[21]

In this study, the patients who received radiotherapy were less likely to develop relapse, although the difference was not found to be statistically significant due to the low sample size. However, in a multicenter prospective study in India involving 262 paediatric and adolescent patients, radiotherapy was the only statistically significant predictor of event-free survival.[22]

Conclusion:

The treatment outcome of paediatric Hodgkin lymphoma in Bangladesh is excellent (2-year overall survival 92%). However, there is scope for improvement regarding reducing relapse rates, and more emphasis should be given to the improvement of supportive care to reduce toxic deaths.

Limitations:

Longer follow-up time would be helpful in exploring long-term complications.

References:

1. National Cancer Institute. NCCR*Explorer: An interactive website for NCCR cancer statistics [Internet]. Bethesda, MD: National Cancer Institute; [cited 2025 Feb 25]. Available from: https://nccrexplorer.cancer.gov
2. Macfarlane GJ, Evstifeeva T, Boyle P, Grufferman S. International patterns in the occurrence of Hodgkin's disease in children and young adult males. Int J Cancer. 1995 Apr 10;61(2):165-9.
3. Clavel J, Steliarova-Foucher E, Berger C, Danon S, Valerianova Z. Hodgkin's disease incidence and survival in European children and adolescents (1978-1997): report from the Automated Cancer Information System project. Eur J Cancer. 2006 Sep;42(13):2037-49.
4. Kahn JM, Pei Q, Friedman DL, Kaplan J, Keller FG, Hodgson D, et al. Survival by age in paediatric and adolescent patients with Hodgkin lymphoma: a retrospective pooled analysis of children's oncology group trials. Lancet Haematol. 2022 Jan;9(1):e49-e57.
5. Oeffinger KC, Stratton KL, Hudson MM, Leisenring WM, Henderson TO, Howell RM, et al. Impact of risk-adapted therapy for paediatric Hodgkin lymphoma on risk of long-term morbidity: A report from the Childhood Cancer Survivor Study. J Clin Oncol. 2021 Jul 10;39(20):2266-75.
6. Lo AC, Dieckmann K, Pelz T, Gallop-Evans E, Engenhart-Cabillic R, Vordermark D, et al. Paediatric classical Hodgkin lymphoma. Pediatr Blood Cancer. 2021 May;68 Suppl 2:e28562.
7. Dinand V, Arya LS. Epidemiology of childhood Hodgkin's disease: is it different in developing countries? Indian Pediatr. 2006 Feb;43(2):141-7.
8. Moleti ML, Testi AM, Al-Hadad S, Al-Jadiry MF, Foà R. Paediatric Hodgkin lymphoma in low-and middle-income countries (LMICs): A narrative review. Mediterr J Hematol Infect Dis. 2024;16(1):e2024078.
9. Hazarika M, Sutnga C, Raj N, Roy PS, Sarangi SS, et al. Paediatric Hodgkin's lymphoma: experience from a tertiary cancer center in North East India. Int J Contemp Pediatr. 2023 Feb;10(2):204-10.
10. Trehan A, Singla S, Marwaha RK, Bansal D, Srinivasan R. Hodgkin lymphoma in children: Experience in a tertiary care centre in India. J Pediatr Hematol Oncol. 2013 Apr;35(3):174-9.
11. Jain S, Kapoor G, Bajpai R. ABVD-based therapy for Hodgkin lymphoma in children and adolescents: Lessons learnt in a tertiary care oncology center in a developing country. Pediatr Blood Cancer. 2016 Jun;63(6):1024-30.
12. Al-Jumaily U, Rjeib HDH, Al-Mosawy S, Faraj S, Metzger M. Response-based approach for paediatric Hodgkin lymphoma in nations with restricted resources. Int J Hematol Oncol Stem Cell Res. 2024 Jul 1;18(3):285-96.
13. Ali N, Mansour M, Khalil E, Ebeid E. Outcome and prognostic factors of paediatric patients with Hodgkin lymphoma: A single-center experience. J Egypt Natl Canc Inst. 2023 Sep 11;35(1):29.
14. Radhakrishnan V, Dhanushkodi M, Ganesan TS, Ganesan P, Sundersingh S, Selvaluxmy G, et al. Paediatric Hodgkin lymphoma treated at Cancer Institute, Chennai, India: Long-term outcome. J Glob Oncol. 2016 Nov 9;3(5):545-54.
15. Sherief LM, Elsafy UR, Abdelkhalek ER, Kamal NM, Elbehedy R, Hassan TH, et al. Hodgkin lymphoma in childhood: Clinicopathological features and therapy outcome at two centers from a developing country. Medicine (Baltimore). 2015 Apr;94(15):e670.
16. Nandakumar A, Anantha N, Appaji L, Swamy K, Mukherjee G, Venugopal T, et al. Descriptive epidemiology of childhood cancers in Bangalore, India. Cancer Causes Control. 1996;7(4):405-10.
17. Bhurani D, Nair R, Rajappa S, Rao SA, Sridharan N, Boya RR, et al. Real-world outcomes of Hodgkin lymphoma: A multi-centric registry from India. Front Oncol. 2022 Feb 11;11:799948.
18. Friedmann AM, Wolfson JA, Hudson MM, Weinstein HJ, Link MP, Billett A, et al. Relapse after treatment of paediatric Hodgkin lymphoma: Outcome and role of surveillance after end of therapy. Pediatr Blood Cancer. 2013 Sep;60(9):1458-63.

19. Daw S, Hasenclever D, Mascarin M, Fernández-Teijeiro A, Balwierz W, Beishuizen A, et al. Risk and response adapted treatment guidelines for managing first relapsed and refractory classical Hodgkin lymphoma in children and young people: Recommendations from the EuroNet Paediatric Hodgkin Lymphoma Group. Hemasphere. 2020 Jan 10;4(1):e329.

20. Marr KC, Connors JM, Savage KJ, Goddard KJ, Deyell RJ. ABVD chemotherapy with reduced radiation therapy rates in children, adolescents, and young adults with all stages of Hodgkin lymphoma. Ann Oncol. 2017 Apr 1;28(4):849-54.

21. de Armas S, Huertas-Ayala C, Chan RY, Chi YY, Huh WW, Termuhlen A, et al. Survival of paediatric Hodgkin lymphoma patients treated with doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) at a single institution. Pediatr Blood Cancer. 2022 May;69(5):e29601.

22. Jain S, Bakhshi S, Seth R, Verma N, Singh M, Mahajan A, et al. Risk-based and response-adapted radiation therapy for children and adolescents with newly diagnosed advanced-stage Hodgkin lymphoma treated with ABVD chemotherapy: A report from the Indian Paediatric Oncology Group study InPOG-HL-15-01. Leuk Lymphoma. 2022 May;63(5):1111-8.

Original Article

Cancer J Bangladesh 2024;5(2): 75-78
http://nicrh.gov.bd/publication

Pattern of Recurrence in Rectal Cancer after Surgery

Md. Nurujjaman Sarker[1], Marzia Mehbin[2], Ahmed Mizanur Rahman[3], Md. Washif Shakir[4], Shahanara Yeasmin[5], AFM. Anwar Hossain[6]

[1]Junior Consultant, Department of Surgical Oncology, National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka, Bangladesh

[2]Medical officer, Department of Gynaecology & Obstetrics, Dhaka Medical College, Dhaka, Bangladesh.

[3]Assistant Professor, Department of Surgical Oncology, NICRH

[4] Registrar, Department of Surgical Oncology, NICRH

[5]Professor, Department of Physiology, Dhaka Medical College, Dhaka

[6]Professor & Ex-Head, Department of Surgical Oncology, NICRH

Citation: Sarkar MN, Mehbin M, Rahman AM, Shakir MW, Yeasmin S, Hossain AFMA. Pattern of Recurrence in Rectal Cancer after Surgery. Cancer J Bangladesh 2024;5(2): 75-78.

Correspondence: Dr. Md. Nurujjaman Sarker, Junior Consultant, Department of Surgical Oncology, National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka. Email: samiawahidmuna@gmail.com

Received : 24 October 2024
Accepted : 29 November 2024
Published : 15 March 2025

Abstract

Background: *Locoregional recurrence (LR) of rectal cancer continues to pose a significant clinical challenge, leading to considerable morbidity, low success rates for salvage treatments, and ultimately resulting in death for most patients. The aim of our study was to identify patterns of recurrence and to identify factors that were associated with recurrence.* ***Methods:*** *This was a cross-sectional hospital-based study done in NICRH, Bangladesh. All diagnosed cases of recurrent carcinoma rectum were retrieved, reviewed and collated from January 2017 to August 2018.* ***Results:*** *We had 31 cases with an age range between 26-66 years. The mean age of the patients was 43.8 years. Sixteen (51.61%) patients had local recurrence, 7 (22.58%) patients had only distant metastasis, the liver was the most common site (9.67%) and 08 (25.80%) patients had both local recurrence and distant metastasis. Twenty-three (74.20%) patients had an early recurrence, and 8 had a late recurrence (25.80%), which is more than 2 years after surgery.* ***Conclusions:*** *Most of the recurrences were local (perianastomotic), followed by both local and distant metastasis. The liver was the most common site for distant metastasis. The majority of the recurrences were related to the advanced nature of the diseases at the time of primary surgery, were moderate to poorly differentiated tumours, advanced T stage, and lymphovascular invasion by tumour.*

Keywords: *Recurrent rectal carcinoma; Pattern of recurrence; Time to recurrence*

Introduction:

Rectal carcinoma is responsible for 30–57% of all colorectal cancers.[1] Mortality rate is estimated at up to 50% per year, and 5-year survival rate for all stages is about 70%.[2]

Over the past two decades, there have been improvements in the management of rectal cancer in terms of postoperative death (falling from 10% to 2%), locoregional failure (dropping from 30%-40% to less than 15%), conservative surgery rates (increasing from 20% to 60%) and survival, with advances made in the understanding of the biology of this type of tumour as well as staging and the use of combined therapies.[3]

Nevertheless, Locoregional Recurrence (LR) of rectal cancer remains a significant clinical problem, associated with severe morbidity, low rates of success of salvage procedures, and eventual death in many patients.[4]

A majority of Locally Recurrent Rectal Cancers (LRRCs) occur within two years after treatment for primary Rectal Cancer (RC), and more than 90% are diagnosed within five years.[5] About 20-40% of patients with LRRC have distant metastases already at the time of diagnosis.[6]

Knowledge of the pattern and natural history of recurrence, the associated risk factors for their development and the mechanism by which they occur may serve as the foundation for efforts to improve the results of multidisciplinary care.

The aim of our study was to identify patterns of recurrence and to identify factors that were associated with the recurrence of rectal cancer.

Methods:

This cross-sectional study was conducted at the National Institute of Cancer Research and Hospital (NICRH), Bangladesh, from January 2017 to August 2018. Diagnosed cases of recurrent rectal cancer patients were taken to obtain their particulars and detailed clinical history and perform a physical examination to evaluate the clinical presentation. These findings, including previous operation details and past and present laboratory and imaging reports, were also recorded.

Results:

Sixteen patients (52%) were male and 15(48%) were female. The mean age was 43.8 years, and the age range was 26-66 years. The highest co-morbidity were cardiovascular and DM, with 6.45% in both. Fifteen (48%) patients were present with poor general condition, 9(29%) patients were present with pain, and 6 (6.45%) patients had per-rectal bleeding and lower abdominal mass.

Most of the tumours at the time of primary diagnosis were in the middle of the rectum in a position. That was 17 (54.84%) cases, distal 11 (35.48%) followed by proximal 3 (9.68%) cases. No neo-adjuvant treatments were given in 24 cases (77.42%), and only 7 cases (22.58%) of CCRT were given. In 21 cases, AR was done, and APR was done in 10 (32.26%) cases. Most of the tumours, 28 cases (90.32%), were at the T3 stage, 17 cases (54.84%) were at N1, the majority of them, 21 (67.75%), were moderately differentiated, 8 patients had poorly differentiated tumours, and 3 patients had well-differentiated tumour. Lymphatic invasion was present in 21 (67.74%) cases. Sixteen (52%) had local recurrence, 7(22%) patients had only distant metastasis, and both local recurrences and metastasis were in 8 (26%) cases. 23(74%) patients had an early recurrence, and 8(26%) patients had late recurrence.

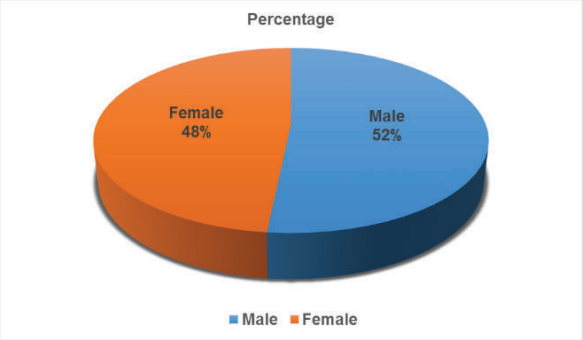

Figure-1: *Distribution of patients by sex*

Table 1. *Distribution of patients according to site of Recurrent Diseases (N=31)*

Presentation	Number	(%)
Local recurrence	16	51.61
Distant Metastasis	07	22.58
Liver	04	12.90
Lungs	01	3.22
Peritoneal	01	3.22
Paraaortic and Preaortic LNs	01	3.22
Both local recurrences & metastasis	08	25.80
Total	31	100

Table 2: *Primary tumour characteristics of all patients (N=31)*

Characteristics	Number (%)
Site of cancer	
Lower (3-5 cm)	11 (35.48)
Middle (>5 -10cm)	17 (54.84)
Upper(>10-15cm)	3 (9.68)
pT-stage	
T2	3 (9.68)
T3	28 (90.32)
Regional LN	
No	9 (29.03)
N1	17 (54.84)
N2	5 (16.13)
Grade of tumour	
Well diff	2 (6.45)
Moderate diff	21 (67.75)
Poorly diff	8 (25.80
Lymphatic invasion	
Negative	10 (32.25)
Positive	21 (67.75)

Discussion:

Recurrence after curative surgery in patients with rectal cancer remains a significant clinical problem. In this series, 31 patients were identified as having a case of recurrent disease (RD). Among 31 patients, 16 (51.61%) were male, and 15 (48.38%) were female. Males were more prevalent, and this data showed the same as the literature.[7] The age range was between 26 and 66 years, and the median was 43.8 years, which coincided with other series.[7] Majority of surgeries for rectal cancer treatment were anterior resection 21 (67.74%) and abdominoperineal resection (APR) 10 (32.26%), which has become decreased over the years. New surgical concepts, techniques, equipment, and neo-adjuvant therapy have made it an exception, not only in this series but also in all literature.[8]

Twenty-six (83.87%) patients were symptomatic at the time of diagnosis as a case of RD, and 5 (16.12%) patients were asymptomatic and diagnosed during routine follow-up. Most of the patients, 15 (48.38%) had poor general condition, 9 (29.03%) patients had pain in the lower abdomen, 6 (19.35%) patients had changes of bowel habit, 6(19.35%) cases per rectal bleeding, 5 (16.13%) patients had palpable abdominal mass, and 3 (9.67%) patients had urogenital symptoms. Which also correlates with another study.[9]

In the initial T stage, T3 was found in 28 (90.32%) of all recurrences, which is well justified, as deep tumours are more aggressive.[8] We found 29.03% of surgical specimens were N0, while in other series, N1 or N2 staging responded for up to 70.95% of all the recurrences. This finding is quite annoying, and it may be telling our group to look harder for cancer in lymphatic tissue in the mesorectum and mesocolon.

In our study, most of the patients, 21 (67.75%), had moderately differentiated adenocarcinoma, 8 (25.80%) patients had poorly differentiated carcinoma, and 2 (6.45%) patients had well-differentiated adenocarcinoma which correlates with other series.[1, 10]

Lymphatic invasion is also a significant prognostic indicator in rectal cancer. Positive lymph node patients share a 3 times greater risk of disease-related death.10 A Korean study some years ago showed that even in T1 and T2 tumours, N-positive staging is a predictor of diminished disease-free survival.[7] Most of the patients in this series were with lymphatic invasion (67.74%). It was also correlated with other studies [1, 10]

More than half of patients with RD had a Carcinoembryonic antigen (CEA), and CA19-9 level increased, which corresponded with Grossmann's study, which found a rise in postoperative CEA and CA19-9 levels in 41% and 45% cases, respectively, of patients with RD.[1]

Recurrences were categorized as local if they were perianastomotic and as distant if they involved the liver, lung, or other organs (e.g. para-aortic lymph nodes, peritoneum). Regional nodal recurrence and lateral pelvic lymph node recurrence of rectal cancer were included in the definition of local recurrence. Sixteen patients (51.61%) had local recurrence alone, 7 patients (22.58%) had distant metastasis alone, and 8 patients (4.5%) had both local recurrence and distant metastasis. The most common site of distant metastasis was the liver (n = 4, 12.90%), followed by the lung (n = 1, 3.22%), peritoneum (n = 1, 6.45%), and other organs (n = 1, 3.22%). These findings can be explained by the fact that most of the tumours in this series are in the Portal vein drainage territory, leading to more liver rather than lung metastasis.

In the early recurrence group, tumours most frequently recurred in the liver. The sites at which tumours recurred differed between the early recurrence and late recurrence groups, with late recurrences developing more frequently in lung 1 (12.50%) or locally 5 (62.50%). In the late recurrence group, 1 patient had a recurrence in the lung more than 7 years after curative surgery.

Several studies reported the different distribution of recurrent organs according to the time of recurrence.[11] A retrospective study of postoperative patients with colon and rectal cancer showed that the liver was the most common site of early recurrence and that local recurrence was more common in patients with rectal cancer than in those with colon cancer.[12] Liver metastases occurred more frequently in patients with early recurrence, whereas lung metastases occurred more frequently in cases of late recurrence.[7] Similarly, another study also reported that the liver was the main site of early recurrence, although the late recurrence group more frequently had a recurrence in the bone and peritoneum.[13] In our study, the pattern of recurrence also differed between the early and late recurrence groups, with liver 4 (17.39%) being the most common site of early recurrence, whereas tumours that recurred late were more common in lung 1(12.50%). Taken

together, these findings indicate that patients should be monitored carefully for lung metastases during the late period of postoperative surveillance.

In this study, recurrence occurred from 5 to 84 months, and the average disease-free survival in these 31 patients is 23.9 months, which is shorter than other series, describing up to 31 months.[14] We had one recurrence diagnosis within 5 months that could be seen as a residual disease rather than local recurrence. In another study, the majority of LRRCs occur within two years after treatment for primary RC, and more than 90% are diagnosed within five years.[5] So, it correlates with this study.

In conclusion, most of the recurrences were local (perianastomotic), followed by both local and distant metastasis. The liver was the most common site for distant metastasis. The majority of the recurrences were related to the advanced nature of the diseases at the time of primary surgery, were moderate to the poorly differentiated tumours, advanced T stage, and lymphovascular invasion by tumour,

Conflict of interest: There was no conflict of interest.

Acknowledgement: We gratefully acknowledge the contributions of the patients.

References

1. Seva-Pereira, G. Cypreste, R.N. et al. Recurrence pattern of rectal cancer after surgical treatment. Analysis of 122 patients in a tertiary care center. Journal of Coloproctology. 2018; 38(1):018-023.
2. Rezende Junior HC, Palma RT, Toloi GC, Martinez CAR, Waisberg J. Carcinoembryonic antigen levels in the peripheral and mesenteric venous blood of patients with rectal carcinoma. Arq Gastroenterol. 2013;50: 264–273.
3. Ortholan C, Francois E, Thomas O, Benchimol D, Baulieux J, Bosset JF, Gerard JP. Role of radiotherapy with surgery for T3 and resectable T4 rectal cancer: evidence from randomized trials. Dis Colon Rectum 2006; 49: 302-310
4. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993; 341: 457-460
5. Merkel S, Meyer T, Göhl J, Hohenberger W. Late locoregional recurrence in rectal carcinoma. Eur J Surg Oncol 2002;28(7):716—22.
6. Yun JA, Kim HC, Kim SH, et al: Prognostic significance of perineural invasion in stage IIA colon cancer. ANZ J Surg. 2016;86:1007-1013.
7. Chok KS, Law WL. Prognostic factors affecting survival and recurrence of patients with pT1 and pT2 colorectal cancer. World J Surg. 2007;31:1485–1490.
8. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345:638–646.
9. Westberg K, Palmer G, Johansson H, et al. Time to local recurrence as a prognostic factor in patients with rectal cancer. Eur J Surg Oncol. 2015;41:659–666.
10. Müssnich HG, Moreira LF, Gus P, Pimentel M, Simon T, Santos MB. Prognostic factors and survival in primary rectal adenocarcinoma. Rev Bras Coloproct. 2008;28: 62–71.
11. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471-1474.
12. Tsai H.-L., Chu K.-S., Huang Y.-H., Su Y.-C., Wu J.-Y., Kuo C.-H. Predictive factors of early relapse in UICC stage I-III colorectal cancer patients after curative resection. J Surg Oncol. 2009 Dec 15;100(8):736–743
13. Aghili M, Izadi S, Madani H, et al. Clinical and pathological evaluation of patients with early and late recurrence of colorectal cancer. Asian Pac J Clin Onco. 2010;l(6): 35-41.
14. Boyle KM, Sagar PM, Chalmers AG, Sebag-Montefiore D, Cairns A, Eardley I. Surgery for locally recurrent rectal cancer. Dis Colon carcinoembryonic antigen testing, chest x-ray, and colonoscopy. Ann Surg 1998;228:59-63.

Original Article

Cancer J Bangladesh 2024;5(2): 79-87
http://nicrh.gov.bd/publication

Expression of *BARD1* mRNA in Cancerous and Non-cancerous Breast Tissue of Bangladeshi Females Attending a Tertiary Care Cancer Hospital

Lutfun Nahar[1], Latifa Nishat[2], Sufi Hannan Zulfiqar Rahman[3], Farida Arjuman[4], Farzana Afroze[5], Samira Sultana Amee[6], Umma Habiba Laboni[7]

[1]Resident, Department of Anatomy, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka (Current Position: Assistant Professor, Department of Anatomy, Marks Medical College Hospital and Dental Unit, Dhaka)

[2]Associate Professor, Department of Anatomy, BSMMU

[3]Associate Professor and Head, Department of Immunology and Molecular Biology, National Institute of Cancer Research and Hospital (NICRH), Dhaka

[4]Associate Professor and Head, Department of Histopathology, NICRH, Dhaka

[5]Resident, Department of Anatomy, BSMMU (Current Position: Assistant Professor, Department of Anatomy, Enam Medical College, Savar)

[6]Assistant Professor, Department of Anatomy, Shaheed Syed Nazrul Islam Medical College, Kishoregonj

[7]Curator, Department of Anatomy, Nilphamari Medical College, Nilphamari

Citation: Nahar N, Nishat L, Rahman SHZ, Arjuman F, Afroze F, Amee SS, Laboni UH. Expression of BARD1 mRNA in Cancerous and Non-cancerous Breast Tissue of Bangladeshi Females Attending a Tertiary Care Cancer Hospital. Cancer J Bangladesh 2024;5(2): 79-87.

Correspondence: Dr. Latifa Nishat, Associate Professor, Department of Anatomy

Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. *Email*: latifanishat@gmail.com, dr.latifanishat@bsmmu.edu.bd

Received : 17 February 2025
Accepted : 03 March 2025
Published : 15 March 2025

Abstract

Background: BARD1 *is an important gene for DNA repair, gene transcription and apoptosis. Expression of* BARD1*in breast cancer patients varies in different populations.* ***Objective:*** *This study aimed to compare the expression of* BARD1 *mRNA in cancerous and non-cancerous breast tissue.* ***Methods:*** *Total RNA was extracted from 30 histologically diagnosed FFPE (Formalin Fixed Paraffin Embedded) breast cancer tissue and 19 non-cancerous FFPE breast tissue samples. Two-step real-time RT-PCR was done to amplify mRNA of* BARD1 *and* GAPDH *(as endogenous control) and the cycle thresholds (Ct) of each amplification curve were determined.* The BARD1 *expression level was obtained from its* $2^{-\Delta\Delta Ct}$ *value.*BARD1 *expression in cancer tissue was compared with that in non-cancerous tissue and was correlated with reproductive and cancer-related characteristics of breast cancer patients.* ***Results:*** BARD1 *mRNA expression was reduced or absent in the cancerous and non-cancerous breast tissue. The median (IQR) of expression in cancerous and non-cancerous breast tissue was 0.0036 (5.62) and 0.83 (13.67) respectively. Statistically significant difference in* BARD1 *expression was not found in cancerous and non-cancerous breast tissue.* BARD1*mRNA expression status was not associated with reproductive or cancer-related characteristics of the patients.* ***Conclusion:*** BARD1 *gene expression was similar in cancerous and non-cancerous breast tissue. Further research on a larger sample size is required to evaluate* BARD1 *mRNA expression and molecular behaviour of breast cancer in the Bangladeshi population.*

Keywords: BARD1 *mRNA, Breast cancer, FFPE breast tissue, Real-Time RT-PCR*

Introduction

The human *BARD1* (BRCA1-associated ring finger domain 1) acts as a tumour suppressor gene, located on the long arm of chromosome 2 (2q35) .[1,2] BARD1 was discovered in 1996. Since then, various mutations of this gene have been studied.[3] The gene consists of 11 exons that encode 777 amino acids with a molecular weight of 87 kDa.[4] BARD1partners with BRCA1 to form a heterodimer critical for DNA double-strand break repair via homologous recombination (HR), ubiquitination, and transcriptional regulation. The BRCA1-BARD1 complex mediates tumour suppression by maintaining genomic integrity.[5-9] *BARD1* gene expression is regulated in various ways. Its transcription is mediated by DNA damage response induced by cellular stressors such as ionizing radiation via transcription factors like p53.[10,11] Its expression is influenced by some hormones such as potential oestrogen receptor (ER) binding to promoter regions, suggesting regulation in hormone-responsive tissues (e.g., breast, ovary).[12] Alternative splicing generates isoforms with distinct functions (e.g., full-length BARD1 promotes HR, while some truncated isoforms may act as dominant-negative or pro-apoptotic)[13]. MicroRNAs (e.g., miR-203) may destabilize mRNA or inhibit translation.[14] Promoter hypermethylation can silence BARD1, observed in some cancers.[13] Its expression peaks during S/G2 phases, aligning with DNA replication and repair. BARD1also plays a vital role in the induction of apoptosis by stabilization of p53 protein.[10]

Germline mutations of BARD1 are associated with breast, ovarian, and other cancers. Loss of function of this gene causes impaired HR and increased genomic instability.[1] Low expression of its mRNA/ protein correlates with poor prognosis whereas over-expression of certain isoform may drive oncogenesis.[15] Studies have found that *BARD1* can be a potential target for breast cancer treatment[16]. Inhibitors of the enzyme poly ADP ribose polymerase (PARPi) have recently been approved by the FDA for the treatment of various neoplasms, including breast cancer with *BRCA* mutations.[17] During the treatment of ovarian and breast cancer patients having *BRCA1* mutations initially respond to the platinum and PARPi therapy but subsequently develop resistance to both PARPi and platinum compounds.[18] Tumours with BARD1/BRCA1 deficiency may exhibit synthetic lethality with PARP inhibitors.[19] BARD1 can acts as a biomarker, its expression level or isoform ratio could predict therapy response.[15] In bioinformatics analysis, Chen et al. found that *BARD1* expression was negatively correlated with distant metastasis-free survival (DMFS), disease-specific survival (DSS) and disease-free survival (DFS) but positively correlated with overall survival (OS) in univariate analysis. *BARD1* mRNA level influences breast cancer pathogenesis, hormone receptor sensitivity status, prognosis and overall survival of the patients[20]. *BARD1* expression status makes the oncologist aware of drug resistance, especially platinum resistance in *BRCA* mutant patients. Breast cancer is the leading cancer in females of Bangladesh.[21] We did not find enough data on *BARD1* expression status in Bangladeshi breast cancer patients. This research was carried out to measure and compare the expression of *BARD1* mRNA in cancerous and non-cancerous breast tissue and to find any association of *BARD1* expression with the reproductive and cancer-related characteristics of Bangladeshi breast cancer patients.

Materials and Methods

This cross-sectional analytical study was carried out in the Department of Anatomy, Bangabandhu Sheikh Mujib Medical University (BSMMU) with the collaboration of the Department of Histopathology and the Department of Immunology and Molecular Biology, National Institute of Cancer Research and Hospital (NICRH), Dhaka from March 2022 to February 2023.

Selection of patients

Histologically diagnosed 42 breast cancer patients and 30 females with non-cancerous breast disorders were selected from the registrar book of the Department of Histopathology of NICRH. From these patients, recently prepared 30 cancerous and 19 non-cancerous FFPE breast tissue (consists of 10 fibroadenoma, four fibrocystic diseases with ductal hyperplasia, two fibrocystic diseases, one ductal hyperplasia and two normal breast tissue) samples were chosen based on the availability of sufficient tissue in the blocks and the willingness of the patients to participate in the research. The reproductive and cancer-related characteristics of the patients were recorded using a structured questionnaire from interviewing the patients, hospital records, and histopathology reports. Molecular work was done in the Department of Immunology and

Molecular Biology of NICRH. Total RNA was extracted, and two-step real-time RT-PCR were done to amplify *BARD1* (target gene) and house-keeping gene (reference gene) *GAPDH* (Glyceraldehyde-3-phosphate dehydrogenase) sequence of each sample.

Extraction of RNA

Total RNA was extracted from four (10 μm thick) sequential sections of histologically diagnosed cancerous and non-cancerous FFPE breast tissue using PureLink^{TM} FFPE Total RNA extraction kit (Invitrogen by Thermo Fisher Scientific, USA) according to the instructions of the manufacturer of the kit. The extracted RNA samples were made free from any DNA contamination by DNase I digestion. The quality and quantity of the extracted RNA were measured by Eppendorf Biophotometer D30 (Eppendorf AG, Germany). Concentration of RNA from all samples were >20 ng/μL. Samples with RNA concentration >50 ng/μL were diluted to make their concentration <50 ng/ μL. Extracted RNA samples were stored at -80^{0}C until reverse transcription was performed.

Reverse transcription of extracted mRNA

The first-strand complementary DNA (cDNA) template was synthesized by reverse transcription of total mRNA in a thermal cycler (ProFlex, Thermo Fisher Scientific, USA) using a Viva cDNA synthesis kit (Vivantis Technologies Sdn Bhd, Malaysia) according to the manufacturer's instructions. Random hexamer primer was used for cDNA synthesis. The newly synthesized cDNA was stored at -80^{0}C until PCR amplification of *BARD1* (target gene) and *GAPDH* (endogenous control gene) was done.

Amplification of cDNA by real-time PCR

A multiplex PCR reaction mixture was prepared by adding 10 μL HotStarTaq Master Mix (Qiagen, USA), 1 μL forward primers, 1 μL reverse primers, 1 mL of probes for each *BARD1* and *GAPDH*. Then 16 μL of PCR reaction mixture and 4 μL of cDNA template were added to each well of the 96-well optical plate. After sealing with an optical sealer and centrifugation by a PCR plate centrifuge the cDNA was amplified using the Bio-Rad CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories Inc, USA). PCR cycles were: 1 cycle of 95^{0}C for 15 min for enzyme activation, followed by 45 cycles of 94^{0}C for 30 sec for denaturation, 60^{0}C for 30 sec for primer annealing and probe hybridization and 72^{0}C for 1 min for extension. Detection of fluorescence was done at 60^{0}C. Cycle threshold (Ct) values of FAM and VIC fluorescence were noted from the PCR amplification curves of *BARD1* and *GAPDH*.

Calculation of BARD1 mRNA expression

The expression of *the BARD1* gene was calculated from the Ct values of *BARD1* (target gene) and *GAPDH* (reference gene) of each sample. The difference in Ct value of *BRAD1* and *GAPDH* (ΔCt) was calculated by the formula: ΔCt = Ct of *BARD1* - Ct of *GAPDH*. The ΔΔCt of *BARD1* of each sample was calculated using the formula: ΔΔCt of *BARD1*= ΔCt of *BARD1* of selected sample – average ΔCt of *BARD1* of the non-cancerous tissue (as control). Gene expression level in a given sample was represented as $2^{-\Delta\Delta Ct}$.

Data analysis

Statistical analysis was done by IBM SPSS Statistics 25.0 (IBM Corporation, USA). Expression levels of *BARD1* mRNA in cancerous and non-cancerous breast tissue

Selection of PCR primers and probes

Primers and probes for *BARD1* and *GAPDH* genes were adopted from Reinholz et al. and Al-Mulla et al. respectively.[7,23]

Primers for *BARD1*

Forward primer: 5′- GCCTGTCGATTATACAGATGATGAAA- 3′

Reverse primers: 5′- CGCTGCCCAGTGTTCATTACT- 3′

Primers for *GAPDH*

Forward primer 5′- TCATTGACCTCAACTACATGGTTT- 3′

Reverse primer, 5′- GAAGATGGTGATGGGATTTC- 3′

BARD1 probe: FAM-AGAAGAATGAATCATCCTCAGCTAGCCACTGCT-TAMRA

GAPDH probe: VIC- CAAGCTTCCCGTTCTCAGCC- TAMRA

were compared using the Mann-Whitney U test. The association of *BARD1* mRNA expression status with reproductive and cancer-related characteristics was done using Fisher's Exact test. Reproductive characteristics of breast cancer patients and non-breast cancer females were compared using the unpaired t-test for quantitative variables and the Chi-square (χ^2) test for the categorical variables. All statistical tests were two-tailed and a *p*-value < 0.05 was considered statistically significant.

Ethical issue

All selected participants were informed that their breast tissue samples would be used for research purposes. They were also informed that they had the right to withdraw their participation from this study at any time. The study was approved by the Institutional Review Board of BSMMU (No.: BSMMU/2022/6960, Date: 18.07.2022) and NICRH (No.: NICRH/Permission/2022/216/1). A memorandum of understanding (MOU) was also signed by the Department of Anatomy, BSMMU and Department of Histopathology and Department of Immunology and Molecular Biology of NICRH.

Results

About 83% of cancers were sporadic breast cancer. All cancers were diagnosed as invasive ductal carcinoma and were of histological grade II. Most of the patients were oestrogen receptors (ER), progesterone receptor (PR), and Her-2/Neu negative (82.76%, 86.20% and 72.41% respectively). Lymph node metastasis was found in almost all (93.33%) of breast cancer patients, but other organ (distant) metastasis was found in only 10% of patients.

Reproductive characteristics of the breast cancer patients were similar to those of the females with non-cancerous breast disorders except for age and total duration of breastfeeding time. The females with non-cancerous breast disorders were younger than the breast cancer patients (mean age ± SD was 33.47 ± 10 and 43.77 ± 9.80 years respectively, *p*-value = 0.001). The breast cancer patients breastfed their babies for longer time than that of the non-cancerous females (mean total breastfeeding duration ± SD was 4.46 ± 1.79 and 3.42 ± 1.40 years respectively, *p*-value = 0.03). Reproductive characteristics of the participants are presented in Table I.

Table 1 *Reproductive characteristics of the breast cancer patients (n = 30) and females without breast cancer (n = 19)*

Reproductive characteristic	Breast cancer patient	Female without breast cancer	*P* value
Mean age ± SD (year)	43.77 ± 9.80	33.47 ± 10	**0.001**
Mean BMI ± SD (kg/m^2)	24.15 ± 3.31	24.17 ± 2.99	0.98
Mean age ± SD at menarche (year)	12.83 ± 0.79	12.79 ± 0.71	0.84
Menstrual cycle, n (%)[a]			
Regular	22 (73.33)	14 (73.68)	1.00
Irregular	8 (26.66)	5 (26.31)	
Menopausal status,n (%)[b]			
Menstruating	17 (56.66)	16 (84.21)	0.14
Postmenopausal	13 (43.33)	3 (15.79)	
Mean age at menopause ± SD (year)	45.08 ± 5.2	43.33 ± 5.6	0.85
Consanguinity of marriage, n (%)[b]			
Present	2 (6.66)	1 (5.26)	1.00
Absent	28 (93.34)	18 (94.74)	
Parity, n (%)[a]			
Uniparous	6 (20)	6 (31.58)	0.50
Multiparous	24 (80)	13 (68.42)	
Mean duration ± SD of breast feeding (year)	4.46 ± 1.79	3.42 ± 1.40	**0.03**
Contraceptive use, n (%)[b]			
Never used	4 (13.33)	4 (21.05)	0.69
Used	26 (86.73)	15 (78.95)	
Mean duration ± SD of contraceptive use (year)	6.55 ± 5.88	6.46 ± 4.15	0.55

p value < 0.05 indicates significant. [a]Chi-square (χ^2) was done, [b]Fisher Exact test was done
Unpaired t test was done to compare the means

GAPDH mRNA was amplified in all tissue samples. *BARD1* mRNA was not amplified in most of the cancerous (25 out of 30 samples) and non-cancerous (14 out of 19 samples) breast tissue (Figure 1a). Samples in which *BARD1* mRNA were amplified the Ct value of *BARD1* amplification curve was higher than that of the *GAPDH*, which indicates the reduced expression of *BARD1* compared to expression of house-keeping gene *GAPDH* (Figure 1b). The median (IQR) of expression of *BARD1*mRNA in cancerous and non-cancerous breast tissue was 0.0036 (5.62) and 0.83 (13.67) respectively. There was no statistically significant difference in *BARD1 mRNA* expression in cancerous and non-cancerous breast tissue (Figure 2). We did not find any association between *BARD1*mRNA expression and reproductive or cancer-related characteristics of the breast cancer patients (Table II).

Table 2: *Association of BARD1 expression status with reproductive and cancer related characteristics (n = 30)*

Characteristic		Number of patients n (%)	Expression status of *BARD1* Expressed (n = 5)	Not expressed (n = 25)	*P*-value
Reproductive characteristics					
Age (year)	28-45	16 (53.3)	1	15	0.16
	46-69	14 (46.7)	4	10	
BMI(kg/m^2)	18.5-24.9	22 (73.4)	5	17	0.34
	≥25	8 (26.6)	0	8	
Age at menarche, (year)	12-13	25 (83.3)	3	22	0.10
	≥14	5 (16.7)	2	3	
Menopausal status	Menstruating	17 (56.7)	2	15	0.63
	Postmenopausal	13 (43.3)	3	10	
Parity	1-3	29 (96.7)	4	25	0.17
	>3	1 (3.3)	1	0	
Duration of breastfeeding (year)	1-2	5 (16.7)	0	5	0.56
	>2	25 (83.3)	5	20	
Duration of contraceptives use (year)	Never used	4 (13.3)	0	4	0.90
	1-5	15 (50.0)	3	12	
	≥6	11 (36.7)	2	9	
Cancer related characteristics					
Age at diagnosis (year)	28-45	16 (53.3)	1	15	0.16
	46-69	14 (46.7)	4	10	
Family history of cancer	Present	5 (16.7)	1	4	1.00
	Absent	25 (83.3)	4	21	
Lymph node metastasis	Present	28 (93.3)	5	23	1.00
	Absent	2 (6.7)	0	2	
Distant metastasis	Present	3 (10.0)	0	3	1.00
	Absent	27 (90.0)	5	22	
Oestrogen receptor*	Positive	5 (16.7)	0	5	0.47
	Negative	24 (80.0)	5	19	
Progesterone receptor*	Positive	4 (13.3)	0	4	0.55
	Negative	25 (83.3)	5	20	
Her-2/Neu receptor*	Positive	8 (26.7)	1	7	0.83
	Negative	21 (70.0)	4	17	

*Hormone receptor was tested in 29 patients

P value <0.05 indicates significant; Fisher's Exact Test was done

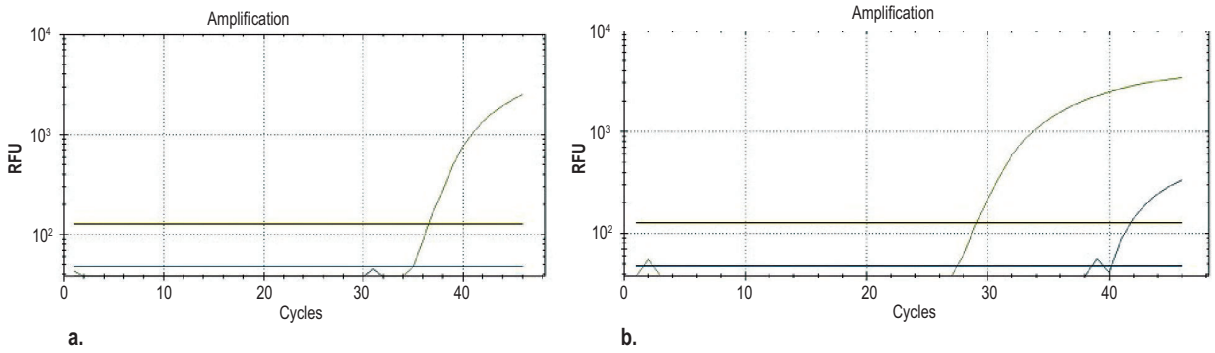

Figure 1. *BARD1 and GAPDH mRNA amplification curve (in log scale) in multiplex real-time RT-PCR. a. GAPDH mRNA (green curve) was amplified but BARD1 mRNA was not. b. Both BARD1 (blue curve) and GAPDH (green curve) mRNA were amplified. RFU: Relative fluorescence units.*

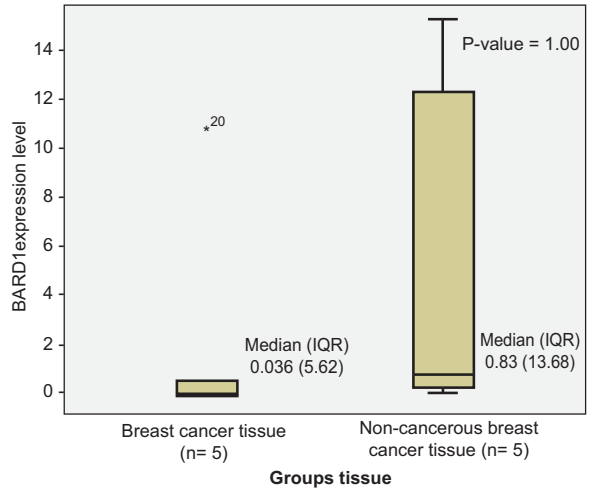

Figure 2. *Expression of BARD1 mRNA in cancerous and non-cancerous breast tissue.*

Discussion

BARD1 gene expression varies greatly in breast cancer tissue of different populations. A study conducted by Chen et al. found significantly higher *BARD1* gene expression in invasive ductal carcinoma than in normal breast tissue[20]. On the other hand, Reinholz et al. found lower expression of *BARD1* in invasive breast cancer than in normal breast tissue[7]. In our study, *BARD1* gene was not amplified in most of the cancerous and non-cancerous breast tissues, may indicate non-expression of *BARD1*. We found reduced expression of *BARD1* in rest of the samples and did not find any difference in the expression of this gene in cancerous and non-cancerous tissue with benign breast disorders. Reduced expression in cancer tissue is supported by Reinholz et al. findings. A recently conducted study on the same population found reduced or non-expression of *BRCA1* in both cancerous and non-cancerous breast tissue.[35] As *BARD1-BRCA1* complex maintains genomic integrity and tumour suppression, deficiency of this complex might be responsible for progression of cancer or such benign disorders.

The reproductive characteristics of our breast cancer patients are consistent with other Bangladeshi studies conducted on breast cancer patients.[24-27] However, our finding regarding nutritional status is different from that of a study that reported 45.50% of Bangladeshi breast cancer patients were undernourished.[28] Our finding is also different from a Turkish study that found the risk of breast cancer increased in females with high BMI.[29] The risk of breast cancer increases with the early age of menarche and the late age of menopause due to the longer period of exposure to ovarian hormones.[30] The age at menarche of our patients is consistent with a study on Japanese population (12.9 years).[31] The menopausal age of our patients is consistent with a study on the Indian population.[32] Studies found the lifetime duration of breastfeeding among women of reproductive age was inversely proportionate with the risk of breast cancer patients[33]. Other studies found a decreasing trend in breast cancer risk with an increasing total duration of breastfeeding among women of reproductive age[34]. However, our observation does not coincide with any of those findings, as all of our breast cancer patients breastfed their babies for a significantly longer duration than that of the non-cancerous patients.

The mean age at diagnosis of breast cancer was 42.70 years in our study, which is the youngest among the other Bangladeshi studies.[24-27] In the present study, all of the breast cancers were diagnosed as invasive ductal carcinoma (IDC) and of grade II. This finding is similar to the finding of other studies on Bangladeshi breast cancer patients by Amee et al., Nishat et al. and Yazdani-Charati et al.[26,35,36] Our findings are also consistent with an Indian study conducted by Soni et al[37]. Axillary lymph node involvement is important for evaluating the prognosis and guiding the treatment of breast cancer patients[38]. We observed almost all patients have lymph node metastasis but distant metastasis was found in about 10% of patients. This finding is also consistent with other Bangladeshi studies on breast cancer patients.[24-27] The majority of the breast cancer patients in our study were ER, PR and Her-2/Neu negative. This finding is also similar to Amee et al. but it is different from Soni et al. where about 40% of patients were ER+ve, 40.4% were PR+ve.[24,37]

We measured *BARD1*mRNA expression in 30 FFPE breast cancer tissue blocks and 19 FFPE non-cancerous breast tissue blocks from females with heterogenous noncancerous breast lesions which is a limitation of our research. It would be better if we could include normal breast tissue from a normal healthy female. But, it could not be ethically possible. However, the analysis would be better if the research could be done with a larger sample size.

Conclusion

BARD1 mRNA expression is similar in cancerous and non-cancerous breast tissue and the expression is not associated with reproductive and cancer-related characteristics of the breast cancer patients of Bangladesh. The result of this research may indicate the necessities of a follow up study involving larger number of breast cancer patients as well as females with non-cancerous breast disorders to evaluate the prognosis of these patients.

Acknowledgements

We express our gratitude to the patients who participated in this research. We would like to acknowledge the authority of BSMMU for funding support for conducting this study. We also express our gratitude to the faculties and all other staff of the Department of Anatomy of BSMMU, Department of Histopathology and Department of Immunology and Molecular Biology of NICRH, Bangladesh for providing the research facilities.

Funding

The study was funded by the Research Grant of BSMMU, Dhaka, Bangladesh

Conflict of interest

The author declaims no conflict of interest

References

1. Russi M, Marson D, Fermeglia A, Aulic S, Fermeglia M, Laurini E, Pricl S. The fellowship of the RING: BRCA1, its partner BARD1 and their liaison in DNA repair and cancer. PharmacolTher 2022;232:108009. doi: 10.1016/j.pharmthera.2021.108009.
2. Ratajska M, Matusiak M, Kuzniacka A, Wasag B, Brozek I, Biernat W, Koczkowska M, Debniak J, Sniadecki M, Kozlowski P, Klonowska K, Pilyugin M, Wydra D, Laurent G, Limon J, Irminger-Finger I. Cancer predisposing BARD1 mutations affect exon skipping and are associated with overexpression of specific BARD1 isoforms. Oncol Rep 2015;34(5):2609-2617. doi: 10.3892/or.2015.4235.
3. Œniadecki M, Brzeziñski M, Darecka K, Klasa-Mazurkiewicz D, Poniewierza P, Krzeszowiec M, Kmieæ N, Wydra D. BARD1 and Breast Cancer: The Possibility of Creating Screening Tests and New Preventive and Therapeutic Pathways for Predisposed Women. Genes (Basel) 2020;11(11):1251. doi: 10.3390/genes11111251.
4. Fox D 3rd, Le Trong I, Rajagopal P, Brzovic PS, Stenkamp RE, Klevit RE. Crystal structure of the BARD1 ankyrin repeat domain and its functional consequences. J BiolChem 2008;283(30):21179-86. doi: 10.1074/jbc.M802333200.
5. Jin Y, Xu XL, Yang MC, Wei F, Ayi TC, Bowcock AM, Baer R. Cell cycle-dependent colocalization of BARD1 and BRCA1 proteins in discrete nuclear domains. Proc Natl Acad Sci USA 1997;94(22):12075-80. doi: 10.1073/pnas.94.22.12075.
6. Scully R, Chen J, Ochs RL, Keegan K, Hoekstra M, Feunteun J, Livingston DM. Dynamic changes of BRCA1 subnuclear location and phosphorylation state are initiated by DNA damage. Cell 1997;90(3):425-35. doi: 10.1016/s0092-8674(00)80503-6.
7. Reinholz MM, An MW, Johnsen SA, Subramaniam M, Suman VJ, Ingle JN, Roche PC, Spelsberg TC. Differential gene expression of TGF beta inducible early gene (TIEG), Smad7, Smad2 and Bard1 in normal and malignant breast tissue.Breast Cancer Res Treat 2004;86(1):75-88. doi: 10.1023/B:BREA.0000032926.74216.7d.
8. Kleiman FE, Wu-Baer F, Fonseca D, Kaneko S, Baer R, Manley JL. BRCA1/BARD1 inhibition of mRNA 3' processing involves targeted degradation of RNA

polymerase II. Genes Dev 2005;19(10):1227-37. doi: 10.1101/gad.1309505.

9. Brzovic PS, Rajagopal P, Hoyt DW, King MC, Klevit RE. Structure of a BRCA1-BARD1 heterodimeric RING-RING complex. Nat StructBiol 2001;8(10):833-7. doi: 10.1038/nsb1001-833.

10. Feki A, Jefford CE, Berardi P, Wu JY, Cartier L, Krause KH, Irminger-Finger I. BARD1 induces apoptosis by catalysing phosphorylation of p53 by DNA-damage response kinase. Oncogene 2005;24(23):3726-36. doi: 10.1038/sj.onc.1208491.

11. Fabbro M, Savage K, Hobson K, Deans AJ, Powell SN, McArthur GA, Khanna KK. BRCA1-BARD1 complexes are required for p53Ser-15 phosphorylation and a G1/S arrest following ionizing radiation-induced DNA damage. J Biol Chem 2004;279(30):31251-8. doi: 10.1074/jbc.M405372200.

12. Creekmore AL, Ziegler YS, Bonéy JL, Nardulli AM. Estrogen receptor alpha regulates expression of the breast cancer 1 associated ring domain 1 (BARD1) gene through intronic DNA sequence. Mol Cell Endocrinol 2007;267(1-2):106-15. doi: 10.1016/j.mce.2007.01.001.

13. Irminger-Finger I, Ratajska M, Pilyugin M. New concepts on BARD1: Regulator of BRCA pathways and beyond. Int J Biochem Cell Biol 2016;72:1-17. doi: 10.1016/j.biocel.2015.12.008.

14. Pilyugin M, Irminger-Finger I. Long non-coding RNA and microRNAs might act in regulating the expression of BARD1 mRNAs. Int J Biochem Cell Biol 2014;54:356-67. doi: 10.1016/j.biocel.2014.06.018.

15. HawsawiYM, Shams A, Theyab A, Abdali WA, Hussien NA, Alatwi HE, Alzahrani OR, Oyouni AAA, Babalghith AO, Alreshidi M. BARD1 mystery: tumor suppressors are cancer susceptibility genes. BMC Cancer 2022;22(1):599. doi: 10.1186/s12885-022-09567-4.

16. Li L, Cohen M, Wu J, Sow MH, Nikolic B, Bischof P, Irminger-Finger I. Identification of BARD1 splice-isoforms involved in human trophoblast invasion. Int J Biochem Cell Biol 2007;39(9):1659-72. doi: 10.1016/j.biocel.2007.04.018.

17. Zhu Y, Liu Y, Zhang C, Chu J, Wu Y, Li Y, Liu J, Li Q, Li S, Shi Q, Jin L, Zhao J, Yin D, Efroni S, Su F, Yao H, Song E, Liu Q. Tamoxifen-resistant breast cancer cells are resistant to DNA-damaging chemotherapy because of upregulated BARD1 and BRCA1. Nat Commun 2018;9(1):1595. doi: 10.1038/s41467-018-03951-0.

18. Lord CJ, Ashworth A. Mechanisms of resistance to therapies targeting BRCA-mutant cancers. Nat Med2013;19(11):1381-8. doi: 10.1038/nm.3369.

19. Keung MY, Wu Y, Badar F, Vadgama JV. Response of Breast Cancer Cells to PARP Inhibitors Is Independent of BRCA Status. J Clin Med 2020;9(4):940. doi: 10.3390/jcm9040940.

20. Chen YZ, Zuo D, Ren HL, Fan SJ, Ying G. Bioinformatics Analysis of Expression and Alterations of BARD1 in Breast Cancer. Technol Cancer Res Treat 2019;18 :15330338 19892260. doi: 10.1177/1533033819892260.

21. Hospital Cancer Registry Report (2018-2020). National Institute of Cancer Research and Hospital, Dhaka. 2022. Accessed on: 14 November 2024. Available from: https://nicrh.gov.bd/reports

22. Wang Y, Krais JJ, Bernhardy AJ, Nicolas E, Cai KQ, Harrell MI, Kim HH, George E, Swisher EM, Simpkins F, Johnson N. RING domain-deficient BRCA1 promotes PARP inhibitor and platinum resistance. J Clin Invest 2016;126(8):3145-57. doi: 10.1172/JCI87033.

23. Al-Mulla F, Abdulrahman M, Varadharaj G, Akhter N, Anim JT. BRCA1 gene expression in breast cancer: a correlative study between real-time RT-PCR and immunohistochemistry. J HistochemCytochem 2005; 53(5): 621-9. doi: 10.1369/jhc.4A6544.2005.

24. Amee SS. Nishat L, Rahman SHZ, Farida A, Yesmin ZA, Laboni UH, Tanjin R, Akther Z. Expression of BRCA1 mRNA in FFPE tissue of Bangladeshi Breast Cancer Patients. Cancer J Bangladesh 2022;3(2):55-62.

25. Bhattacharjee A, Hossain AA, Yeasmin S, Akter T. Incidence, Epidemiology and Clinico-Pathological Status of Different Molecular Subtypes of Breast Cancer in NICRH, Dhaka. Delta Med Coll J2018;6(1):9–17.

26. Nishat L, Yesmin ZA, Arjuman F, Rahman SHZ, Banu LA. Identification of Mutation in Exon11 of BRCA1 Gene in Bangladeshi Patients with Breast Cancer. Asian Pac J Cancer Prev 2019;20(11):3515-3519. doi: 10.31557/APJCP.2019.20.11.3515.

27. Kabir E, Sadia M, Sathi A, Ahmad T, Moni MR, Rana S. Assessment of Nutritional Status of Cancer Patients in National Institute of Cancer Research Hospital (Nicrh), Dhaka , Bangladesh. IOSR J Nursing Health Sci 2018;7(6):34-43. doi: 10.9790/1959-0706023443.

28. Ozmen V, Ozcinar B, Karanlik H, Cabioglu N, Tukenmez M, Disci R, Ozmen T, Igci A, Muslumanoglu M, Kecer M, Soran A. Breast cancer risk factors in Turkish women—a University Hospital based nested case control study. World J Surg Oncol 2009;7:37. doi: 10.1186/1477-7819-7-37.

29. Sisti JS, Collins LC, Beck AH, Tamimi RM, Rosner BA, Eliassen AH. Reproductive risk factors in relation to molecular subtypes of breast cancer: Results from the nurses' health studies. *Int J Cancer.* 2016 May 15;138(10):2346-56. doi: 10.1002/ijc.29968. Epub 2016 Feb 8. PMID: 26684063; PMCID: PMC5245093.

30. Iwasaki M, Tsugane S. Risk factors for breast cancer: epidemiological evidence from Japanese studies. Cancer Sci 2011;102(9):1607-14. doi: 10.1111/j.1349-7006.2011.01996.x.

31. Ahuja M. Age of menopause and determinants of menopause age: A PAN India survey by IMS. J Midlife Health 2016;7(3):126-131. doi: 10.4103/0976-7800.191012.

32. Bellah SF, Salam MA, Karim MR, Hossain MJ, Ashrafudoulla M. Epidemiology of breast cancer among the female patients in Bangladesh. Orient Pharm Exp Med 2016;16(2):85–95.

33. Sofi NY, Jain M, Kapil U, Yadav CP. Epidemiological characteristics of breast cancer patients attending a tertiary health-care institute in the National Capital Territory of India. J Cancer Res Ther 2019;15(5):1087-1091. doi: 10.4103/jcrt.JCRT_868_16.

34. Lipworth L, Bailey LR, Trichopoulos D. History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature.J Natl Cancer Inst 2000;92 (4):302-12. doi: 10.1093/jnci/92.4.302.

35. Nishat L, Rahman SHZ, Arjuman F, Yesmin ZA, Nahar L, Laboni UH, Amee SS, Afroze F. Expression of BRCA1 mRNA in cancerous and non-cancerous breast tissue of Bangladeshi females attending a tertiary care hospital. Bangabandhu Sheikh Mujib Medical University Journal 2025;*18*(1), e76754. https://doi.org/10.3329/bsmmuj.v18i1.76754

36. Yazdani-Charati R, Hajian-Tilaki K, Sharbatdaran M. Comparison of pathologic characteristics of breast cancer in younger and older women. Caspian J Intern Med 2019;10(1):42-47. doi: 10.22088/cjim.10.1.42.

37. Soni S, Sethi N, Gupta A, Srivastava AS. Breast carcinoma histopathological correlation with molecular classification: A comparative study. Indian J Pathol Oncol 2020;7(4):613–9.https://doi.org/10.18231/j.ijpo.2020.121

38. Xu F, Zhu C, Tang W, Wang Y, Zhang Y, Li J, Jiang H, Shi Z, Liu J, Jin M. Predicting Axillary Lymph Node Metastasis in Early Breast Cancer Using Deep Learning on Primary Tumor Biopsy Slides. Front Oncol 2021;11:759007. doi: 10.3389/fonc.2021.759007.

Case Report

Cancer J Bangladesh 2024;5(2): 88-90
http://nicrh.gov.bd/publication

Isolated Internal Mammary Lymph Node Recurrence Treated with Radiotherapy Alone in Early Breast Cancer

Afsana Sharmin Anika[1], Md. Abdul Bari[2], Sarwar Alam[3], Qazi Mushtaq Hussain[4], Md Nazir Uddin Mollah[5], Sadia Sharmin[6], Janak Raman Parajuli[7]

[1]Ex-Resident, Department of Clinical Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka

[2]Professor, Department of Clinical Oncology, BSMMU, Shahbag, Dhaka

[3]Professor, Department of Clinical Oncology, BSMMU, Shahbag, Dhaka

[4]Senior Consultant, Clinical Oncology, Labaid Cancer Hospital and Super Specialty Center, Dhaka.

[5]Professor & Chairman, Department of Clinical Oncology, BSMMU, Shahbag, Dhaka

[6]Associate Professor, Department of Clinical Oncology, BSMMU, Shahbag, Dhaka

[7]Ex- Resident, Department of Clinical Oncology, BSMMU, Shahbag, Dhaka

Citation: Anika AS, Bari MA, Alam S, Hussain QM, Mollah MNU, Sharmin S, Parajuli JR. Isolated internal mammary lymph node recurrence treated with radiotherapy alone in early breast cancer. Cancer J Bangladesh 2024;5(2): 88-90.

Correspondence: Dr. Afsana Sharmin Anika, Department of Clinical Oncology, BSMMU, Dhaka. Email: afsananika.15@gmail.com

Received : 09 November 2024
Accepted : 11 December 2024
Published : 15 March 2025

Abstract:

Post-mastectomy radiotherapy plays a significant role in the multidisciplinary treatment of breast cancer. However, there is ongoing debate about whether internal mammary node irradiation (IMNI) is essential. IMNI is typically recommended for patients with tumours located in the central or medial areas of the breast.

A 55-year-old female patient, diagnosed with T1N0M0 invasive ductal carcinoma (IDC) in the upper and outer quadrant of the right breast, underwent simple mastectomy with adequate axillary clearance but did not receive adjuvant loco-regional radiotherapy. She now presents with an isolated recurrence in the internal mammary lymph node and was treated with internal mammary node irradiation alone.

Keywords: *Breast cancer; internal mammary node irradiation (IMNI); invasive ductal carcinoma*

Introduction:

Internal mammary node (IMN) involvement is a known poor prognostic factor for survival in patients with breast cancer.[1] Pathologic IMN involvement was found in 28-52% of patients with axillary lymph node (ALN) metastasis while 5-17% of those without ALN metastasis.[2] Regarding the location of tumors, it is reported that 54% of central and inner quadrant tumors and 18% of lateral quadrant tumors were associated with positive internal mammary lymph node (IMLN).[3] We treated a case of isolated internal mammary lymph node recurrence, despite negative axillary lymph node and tumour being located in lateral quadrant of breast. She was treated with regional internal mammary nodal irradiation.

Case Report

A 59-year-old woman underwent right mastectomy with axillary clearance for a T1 grade-1 invasive ductal carcinoma in 2020. None of the 10 dissected lymph nodes were involved by the tumor. The tumor was in the upper and outer quadrant of the breast. Her Estrogen and Progesterone receptors were positive, and HER-2 was negative. The patient did not receive radiotherapy post-operatively. She subsequently received adjuvant chemotherapy with CMF (Cyclophosphamide 600mg/m², Methotrexate 40mg/m² and 5-FU 600 mg/m²) regimen. Then, she was on endocrine therapy. After 6 months, she presented with pain in the central part of chest and follow up Contrast Enhanced Computed Tomography (CECT) of chest showed an enlarged right internal mammary lymph node (Figure 1).

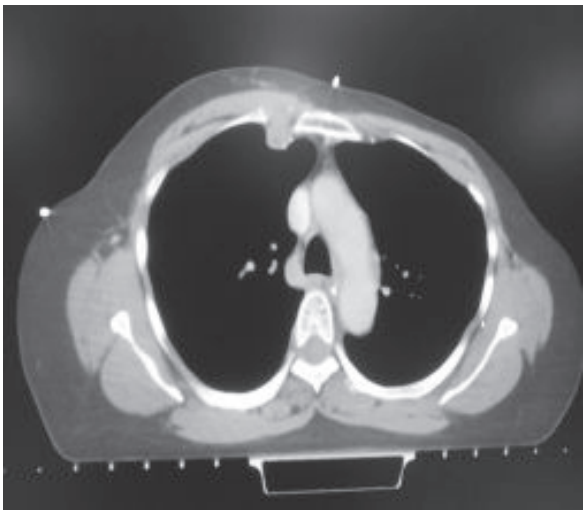

Figure 1: *CECT of chest image showing enlargement of right sided internal mammary lymph node at a level of the second right anterior intercostal space.*

CT guided core biopsy of the lymph node followed by histopathology revealed metastatic ductal carcinoma. On re-staging evaluation, no distant metastasis was found. This isolated internal mammary nodal (IMN) recurrence was treated with radiation by a total dose of 50 gray in 25 daily fractions. The radiation was delivered by Intensity Modulated Radiation Therapy Technique (IMRT) with 6 MV photon beam to reduce cardiac and lung doses (Figure 2).

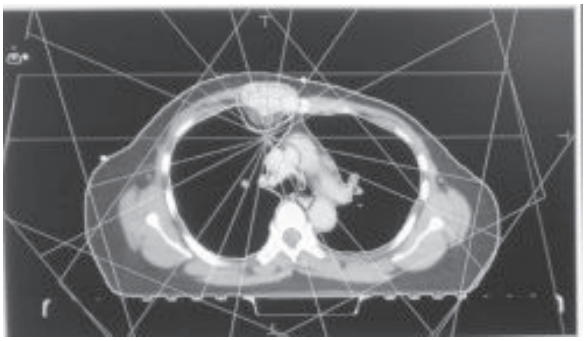

Figure 2: *Internal mammary lymph node irradiation by Intensity Modulated Radiation Therapy Technique (IMRT).*

No significant cardiac and/or pulmonary acute toxicities were developed during radiotherapy. The doses of organs at risk were within tolerance limit. Left lung and right lung received doses of V12<25% and V16<25% respectively as well as cardiac dose V21<25%. Response evaluation was done during radiotherapy on the 3rd week by CT image which showed partial response (Figure 3). Now, the patient is asymptomaticc

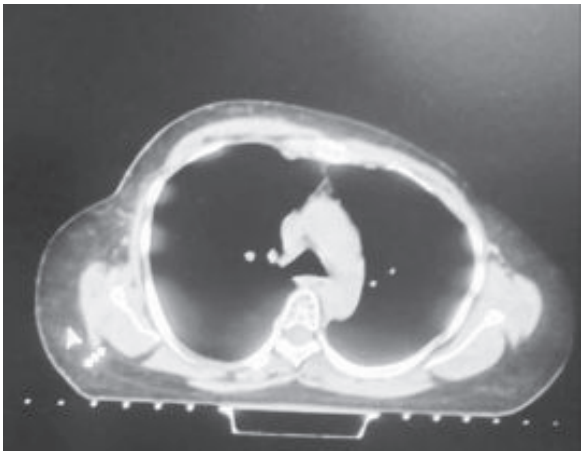

Figure 3: *CECT of chest image showing partial response during radiotherapy on 3rd week at a level of the second right anterior intercostal space.*

Discussion:

In the parasternal region, the IMN chain is a regional nodal drainage basin. Those nodes are situated along the internal mammary vessels in upper 3 intercostal spaces. Positive IM nodes having twice the chance of recurrence or death at 10 years.[4] The diagnosis of IMLN recurrence was based on clinical presentation and chest CT-scan.[5] Common presentations are parasternal

swelling with concomitant pain or skin involvement. While some patients might incidentally be diagnosed with IMLN recurrence during routine follow-up by chest CT-scan. A local lump and sternal erosion on the side of the treated breast was the typical CT-scan presentation. About half of the IMLN recurrences were found to be at multiple levels and were most seen in the second or third intercostal spaces. Isolated IMLN recurrence is rare, and its risk factors have not yet been clarified. Location of the tumour and positive ALN have been reported as high-risk factors of IMLN involvement.[6] Rarely axillary lymph node negative patient with lateral location of tumor may recur in IMLN. Post-mastectomy radiation delivered to IMLN demonstrated significant risk reduction in terms of loco-regional recurrence in such high risk tumours.[7] In regards to these studies, recurrence in internal mammary lymph node in our patient is quite less expected and contradicts those findings. This is a rare presentation.

Conclusion:

A Negative axillary lymph node does not always infer negative internal mammary lymph nodes and same goes for positive axillary lymph nodes. Inaccurate prediction of internal mammary lymph nodes metastasis might lead to over- or under-treatment. To overcome this, we need better imaging modality PET-CT scan which will help in proper evaluation of the metastatic status in these nodes and thus guide us for individualized internal mammary lymph nodes irradiation. The risk of metastasis in internal mammary lymph nodes, based on the status of axillary lymph nodes metastasis, is not always reliable.

References:

1. Sugg SL, Ferguson DJ, Posner MC, Heimann R. Should internal mammary nodes be sampled in the sentinel lymph node era? Ann Surg Oncol. 2000;7(3):188-92.
2. Cong BB, Cao XS, Cao L, Zhu H, Yu YS, Yu JM, et al. Internal mammary lymph nodes radiotherapy of breast cancer in the era of individualized medicine. Oncotarget. 2017;8(8):1583-90.
3. Handley RS, Thackray AC. Invasion of internal mammary lymph nodes in carcinoma of the breast. Br Med J. 1994;1(6860):61-3.
4. Cody HS, Urban JA. Internal mammary node status: a major prognosticator in axillary node-negative breast cancer. Ann Surg Oncol. 1995;2(1):32-7.
5. Scott WW, Fishman EK. Detection of internal mammary lymph node enlargement: comparison of CT scans and conventional roentgenograms. Clin Imaging. 1991; 15(5):268-72.
6. Huang O, Wang L, Shen K, Lin H, Hu Z, Liu G, et al. Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis: analysis of 2,269 Chinese breast cancer patients treated with extended radical mastectomy. Breast Cancer Res Treat. 2008; 107(3):379-87.
7. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med. 1997;337(14):956-62.

Case Report

Cancer J Bangladesh 2024;5(2): 91-93
http://nicrh.gov.bd/publication

Carcinoma En Cuirasse: A Rare Cutaneous Metastasis of Breast Carcinoma

Rehnuma Nasim[1], Nazma Azim[2], Nousheen Laila[3], Sirajum Monira[4]

[1] Junior Consultant, Skin & VD, National Institute of Cancer Research & Hospital (NICRH), Dhaka

[2] Programmer, Management information System, NICRH, Dhaka

[3] Research Assistant, Department of Cancer Epidemiology, NICRH, Dhaka

[4] Medical Officer, Department of Cancer Epidemiology, NICRH, Dhaka

Citation: Nasim R, Azim N, Laila N, Monira S. Carcinoma En Cuirasse: A Rare Cutaneous Metastasis of Breast Carcinoma. Cancer J Bangladesh 2024;5(2): 91-93.

Correspondence: Dr. Rehnuma Nasim, Junior Consultant (Skin & VD), NICRH, Dhaka. Email: rehnuma2009@gmail.com

Received : 19 July 2024
Accepted : 17 November 2024
Published : 15 March 2025

Abstract:

Carcinoma en cuirasse (CeC) is an uncommon form of cutaneous metastasis of breast cancer, characterized by diffuse sclerodermoid induration of the skin, with the skin of the chest wall being studded with carcinomatous indurated plaques. CeC can mimic postirradiation morphea, inflammatory breast cancer, radiation dermatitis, herpes zoster, and other cutaneous metastases.

We report the case of a 28-year-old female with a prior history of right breast invasive ductal carcinoma diagnosed 2 years earlier. Initially, she was diagnosed with invasive ductal carcinoma (T2, N2, M0) that was HER2, ER, and PR negative, and underwent a modified radical mastectomy followed by chemotherapy and radiotherapy. Histopathology of the lesional skin biopsy from the plaque was consistent with invasive ductal carcinoma. The patient also had a metastatic lesion in the left axillary lymph nodes at the time and was referred to the medical oncology department, where she was treated with gemcitabine and cisplatin. Any unexplained skin changes in breast cancer patients should be considered as carcinoma en cuirasse. Many advanced therapeutic options are available for metastatic breast cancer, and based on this case, patients with this condition may experience better outcomes.

Keywords: *Carcinoma en cuirasse, Cutaneous metastasis, Breast cancer, Invasive ductal carcinoma*

Introduction:

Carcinoma en cuirasse (CeC), also known as scirrhous carcinoma, is a rare form of cutaneous metastasis of breast cancer.[1] This type of cutaneous metastasis causes lymphatic blockage and eventual thickening of the chest wall skin, along with dermal and subcutaneous tissue fibrosis, resulting in an armor-like encasement of the trunk.[2] Among breast cancer patients, this phenomenon is typically observed months to years after mastectomy.[3] A retrospective study found that CeC was the first sign of cancer in 59 out of 7,316 breast cancer patients, emphasizing that unexplained skin involvement should not be overlooked.[4]

Case Report:

A 28-year-old female presented in April 2022 with an enlarging mass in the right breast. She was multiparous and had been taking oral contraceptive pills for the last 10 years. Fine-needle aspiration and excisional biopsy of the lump were consistent with grade II infiltrating ductal carcinoma. HER2, ER, and PR receptor status were negative. She received several cycles of chemotherapy and radiotherapy, followed by a right modified radical mastectomy.

In April 2024, she was referred to the Dermatology OPD with painful lesions on the right chest wall for 7 days.

The lesions were severely painful, and she had also developed swelling in the left axillary lymph nodes. On examination, a well-circumscribed, erythematous, tender, sclerosed plaque was observed, studded with papules and a few vesicles. Some ruptured vesicles showed signs of ulceration (Fig. 1). Initially, the lesions appeared to resemble herpes zoster, and she was treated accordingly. However, a week later, the patient returned for follow-up, and her symptoms had worsened.

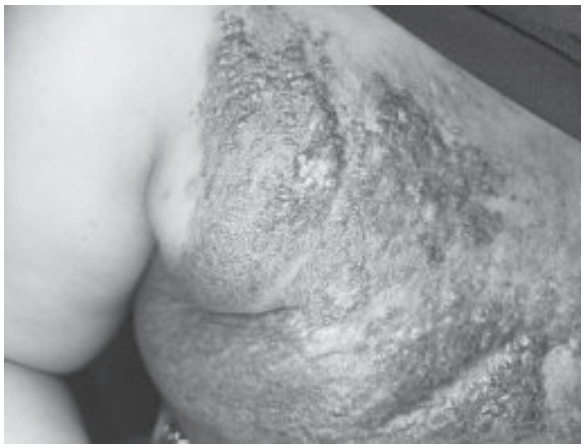

Figure 1: *Erythematous indurated plaque studded with papules and vesicles.*

A skin biopsy of the lesion was performed, which revealed invasive ductal carcinoma. The tumor cells were moderately differentiated (Fig. 2). Immunohistochemistry was not conducted due to financial constraints. Histopathology of the left axillary lymph node showed metastasis of invasive ductal carcinoma. Routine investigations were normal, and a chest X-ray and abdominal ultrasound were also unremarkable.

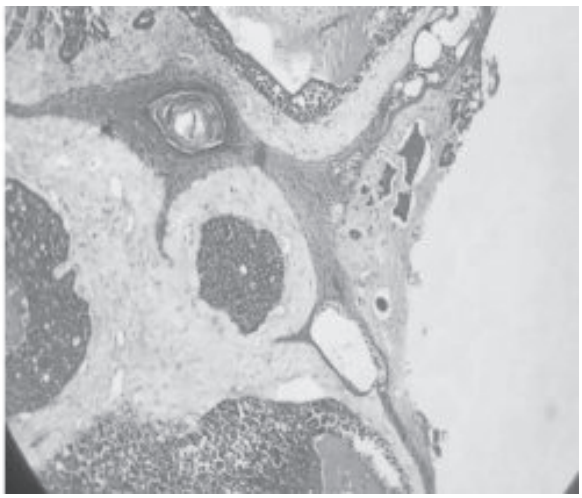

Figure 2: *Histopathology of lesional skin revealed moderately differentiated invasive ductal carcinoma*

The patient was referred to the medical oncology department for further management. Palliative chemotherapy was initiated, with gemcitabine and cisplatin, during the preparation of this report.

Discussion:

Breast cancer is the most frequently diagnosed malignancy in women worldwide.[5] Cutaneous metastasis of breast cancer is associated with advanced stages of the disease and a poorer prognosis.[6] The median survival of breast cancer patients with cutaneous metastases is 13.8 months, with a 3.1% 10-year survival rate.[7] Carcinoma en cuirasse is a special fibrotic form of cutaneous metastasis, spreading rapidly and enveloping the trunk like leather armor.[8] The duration from cancer diagnosis to cutaneous metastasis may vary; however, it is generally observed within 3 years of diagnosis.[9]

The clinical presentation of CeC includes two stages. Initially, it manifests as scattered, flesh-colored nodules on an erythematous skin surface and eventually coalesces into a sclerodermoid plaque, as seen in our patient.[10] Mahore et al. reported a case of a 50-year-old female who presented with nodular skin lesions, accompanied by indurated skin resembling a keloid.[3] Similarly, Salemnis et al. described a 60-year-old woman who developed a painful erythematous lesion that later became indurated and was studded with papules and vesicles.[11] These features are also similar to our case.

The specific clinical manifestations of CeC may lead to confusion with several other skin diseases, including postirradiation morphea, inflammatory breast cancer, radiation dermatitis, and other cutaneous metastases. Postirradiation morphea is an uncommon complication following radiation therapy, typically presenting as an erythematous indurated plaque, which may be mistaken for metastatic carcinoma.[12] However, histopathology can distinguish these conditions.

Prajapati et al. reported the case of a 22-year-old woman who had previously undergone a right modified radical mastectomy for infiltrating ductal carcinoma (IDC) Not Otherwise Specified (NOS) grade II with triple-negative receptor status. One year later, she presented with a

lump in the left breast and multiple cutaneous lesions on the right chest wall and left breast, which had been present for 5 months. Cutaneous metastasis or carcinoma en cuirasse developed on the right side after mastectomy, while the lesions on the left side were part of the initial presenting symptoms.[13] Our patient did not develop a contralateral breast lump; however, cancer had metastasized to the contralateral lymph nodes.

There is no established treatment consensus for CeC due to the rarity of this malignancy. However, reports indicate that chemotherapy, local irradiation, skin grafts, hormonal antagonists, and non-steroidal anti-inflammatory drugs have shown some success.[6,14,15]

A case of CeC presenting as invasive ductal breast cancer is reported here to highlight the phenomenon of cutaneous metastasis. The diagnosis of CeC relies on clinical and histopathologic features, which distinguish it from other entities described herein. Despite its rarity, early diagnosis and intervention of CeC are critical for dermatologists.

Conclusion:

Carcinoma en cuirasse is rare; however, any unusual skin findings, particularly in patients with a history of or active breast cancer, should raise suspicion for this condition to ensure appropriate staging and treatment.

References:

1. Kurashige Y, Kurashige K, Nagatani T, Hayashi M. Primary breast carcinoma en cuirasse derived from invasive lobular carcinoma: the first case report. *J Dermatol*. 2014 Dec;41(12):1122-3.
2. Varghese A, Singh A, Ambujam S. Carcinoma en cuirasse: a cutaneous clue for systemic malignancy. *Int J Prev Med*. 2013 Jan 20;4(1):122-3.
3. Mahore SD, Bothale KA, Patrikar AD, Joshi AM. Carcinoma en cuirasse: a rare presentation of breast cancer. *Indian J Pathol Microbiol*. 2010;53:351-8.
4. Shafiuddin M, Ravikiran HR, Hubli P. Review of a case of multiple distant cutaneous metastases from carcinoma breast. *J Evol Med Dent Sci*. 2014 Dec 11;3(69):14835-40.
5. Ullah MF. Breast cancer: current perspectives on the disease status. *Breast Cancer Metastasis and Drug Resistance: Challenges and Progress*. 2019:51-64.
6. Reich A, Samotij D, Szczêch J, WoŸniak Z, Szepietowski J. Carcinoma en cuirasse as an initial manifestation of inflammatory breast cancer. *Adv Dermatol Allergol*. 2016 Apr 2;33(2):142-5.
7. Schoenlaub P, Sarraux A, Grosshans E, Heid E, Cribier B. Survival after cutaneous metastasis: a study of 200 cases. *Ann Dermatol Venereol*. 2001 Dec;128(12):1310-5.
8. Vano-Galvan S, Moreno-Martin P, Salguero I, Jaen P. Cutaneous metastases of breast carcinoma: a case report. *Cases J*. 2009 Dec;2:1-2.
9. Johnson WC. Metastatic carcinoma of the skin. In: Lever's *Histopathology of the Skin*. 1997.
10. Xu P, Tan C. Primäres Mammakarzinom mit Ausbreitung auf die Brustwand–Carcinoma en cuirasse. *J Dtsch Dermatol Ges*. 2016 Jun;14(6):614-6.
11. Salemis NS, Christofyllakis C, Spiliopoulos K. Primary breast carcinoma en cuirasse: a rare presentation of an aggressive malignancy and review of the literature. *Breast Dis*. 2021 Jan 6;39(3-4):155-9.
12. Morganroth PA, Dehoratius D, Curry H, Elenitsas R. Postirradiation morphea: a case report with a review of the literature and summary of the clinicopathologic differential diagnosis. *Am J Dermatopathol*. 2013 Oct 4.
13. Prajapati S, Vats M, Goel A, Jain A. Carcinoma en cuirasse in a young female. *Case Rep*. 2017 Nov 14;2017:bcr-2017.
14. Lauren CT, Antonov NK, McGee JS, de Vinck DC, Hibshoosh H, Grossman ME. Carcinoma en cuirasse caused by pleomorphic lobular carcinoma of the breast in a man. *JAAD Case Rep*. 2016 Jul 1;2(4):317-9.
15. Group IC, Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, van Putten WL, van Rhoon GC, van Dijk JD, González DG. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. *Int J Radiat Oncol Biol Phys*. 1996 Jul 1;35(4):731-44.

Review Article

Cancer J Bangladesh 2024;5(2): 94-102
http://nicrh.gov.bd/publication

Advanced Intraocular Retinoblastoma: A Review of Current Management Practices in Developing Countries

Sabina Karim[1], Md. Hasnuzzaman[2], Rifat Moin Joya[3], Afiqul Islam[4]

[1]Associate Professor, Paediatric Haematology & Oncology, National Institute of Cancer Research & Hospital

[2]Associate Professor, Department of Oculoplasty, National Institute of Ophthalmology & Hospital (NIOH)

[3]Senior Consultant, Department of Oculoplasty, NIOH

[4]Professor & Ex Chairman, Paediatric Haematology & Oncology, BSMMU

Citation: Karim S, Hasanuzzaman M, Joya RM, Islam A. Advanced Intraocular Retinoblastoma: A Review of Current Management Practices in Developing Countries. Cancer J Bangladesh 2024;5(2): 94-102.

Correspondence: Dr. Sabina Karim, Associate Professor, Paediatric Haematology & Oncology, National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka. Email: sabinabd72 @yahoo.com

Received : 17 November 2024
Accepted : 03 February 2025
Published : 15 March 2025

Abstract:

Retinoblastoma, the most common primary intraocular malignancy in children, presents significant challenges in developing countries due to high prevalence rates, delayed diagnosis, and limited access to healthcare resources. The management of advanced intraocular retinoblastoma is highly complex, requiring personalized approaches tailored to the disease stage (as per the International Classification of Retinoblastoma, ICRB), genetic predisposition, psychosocial dynamics, cultural beliefs, and available institutional resources. Enucleation remains the first-line therapy for advanced cases, particularly in unilateral disease, offering an affordable, effective, and life-saving intervention when performed promptly. Delayed enucleation—beyond three months from diagnosis—is associated with increased mortality due to the risk of metastasis. Enucleation also provides critical diagnostic and prognostic value through histopathological evaluation and genetic testing, guiding subsequent treatment decisions. Pre-enucleation chemotherapy, often used in attempts to salvage the eye, can obscure high-risk pathological features, reduce surveillance accuracy, and inadvertently increase the risk of metastatic death in advanced cases. The 8th edition of the American Joint Committee on Cancer (AJCC) staging system offers an evidence-based framework for precise cancer staging, enabling physicians to assess the risk of metastatic death and recommend safe, appropriate treatment options. Risk-stratified adjuvant chemotherapy based on histopathological findings significantly improves survival outcomes in high-risk cases. Implementing a risk-based, resource-adapted treatment strategy in resource-limited settings is essential to optimize outcomes. Strengthening healthcare systems, improving early detection, ensuring timely access to affordable treatments, and fostering international collaborations are crucial steps toward addressing disparities in retinoblastoma care. By prioritizing early enucleation, accurate histopathology, and timely adjuvant therapy, we can enhance survival rates and improve the quality of life for children with advanced intraocular retinoblastoma in low-resource environments.

Keywords: *Advanced Intraocular Retinoblastoma, enucleation, resource-limited settings, AJCC staging, WHO Global Initiative for Childhood Cancer, adjuvant chemotherapy*

Introduction:

First described 200 years ago by James Wardrop[1], retinoblastoma (RB) is most common primary intraocular malignancy in children. Globally, it occurs in approximately 1 in 15,000–20,000 live births, resulting in around 9,000 new cases annually.[2] Although RB does not exhibit specific geographic or population hotspots, its highest burden is observed in regions with large populations and high birth rates, particularly in Asia and Africa.[2] Tragically, regions with the highest prevalence also experience the highest mortality rates, with 40–70% of diagnosed children dying from the disease, compared to only 3–5% in developed regions such as Europe, Canada, and the USA.[3]

Over the past century, significant advancements in diagnosis and treatment have revolutionized RB management in high-income countries, reducing mortality from over 95% to achieving survival rates exceeding 95%.[4] This remarkable progress has made RB a standout success story in paediatric oncology, with a 5-year survival rate of 99% in high-income settings, offering the best prognosis among paediatric cancers. In high-income countries (HIC), treatment priorities have evolved from ensuring survival to preserving the eye (globe) and maintaining useful vision. Conversely, in low- and middle-income countries (LMICs), delayed diagnosis and advanced disease presentation remain major challenges, with the primary focus still being the prevention of death.[4]

The striking disparity in outcomes highlights the pressing need to address technological and socioeconomic barriers in underprivileged regions. As one of the six priority paediatric cancers under the World Health Organization's Global Initiative for Childhood Cancer (GICC), RB offers a unique opportunity for intervention due to its recognizable clinical signs. Awareness campaigns can play a critical role in reducing diagnostic delays and preventing advanced presentations.[5] The GICC aims to increase childhood cancer survival rates in LMICs from the current 20–30% to 60% by 2030, potentially saving one million additional lives. Achieving this target requires strengthening healthcare infrastructure, improving access to affordable treatments, and fostering international collaboration to ensure equitable care for all children affected by RB.

Methodology:

This review aims to provide a comprehensive overview of the current state of retinoblastoma management, with a particular focus on advanced intraocular cases in developing countries. It aims to highlight the challenges faced in resource-limited settings, including delayed diagnosis, limited access to modern treatment modalities, and socioeconomic barriers contributing to poor outcomes. Additionally, the review emphasizes evidence-based strategies for improving survival rates, such as early enucleation, accurate histopathological evaluation, and timely adjuvant chemotherapy. A comprehensive search was performed using electronic databases such as PubMed and Google Scholar. Keywords included "retinoblastoma," "advanced intraocular retinoblastoma," "management in developing countries," "enucleation," "histopathology," "adjuvant chemotherapy," and "global disparities." Articles were selected based on their relevance to the epidemiology, diagnosis, and treatment of retinoblastoma, explicitly focusing on low- and middle-income countries (LMICs). Priority was given to studies discussing advanced disease management, enucleation outcomes, histopathological findings, and adjuvant therapies.

Epidemiology:

Retinoblastoma serves as a classic example of developmental tumours, accounting for 17% of neonatal cancers, 13% of infantile cancers, 6% of all paediatric cancers in children under five, and 3% of cancers in children under 15.[5] About 80% of retinoblastoma cases are typically diagnosed before age three. The incidence of this disease varies across countries, with middle-income nations contributing approximately 69% of cases, low-income countries 20%, and high-income countries 11%. Around 70–75% of retinoblastoma cases are unilateral and sporadic, while the remaining 25% are bilateral and inherited, usually presenting at a younger age.[6] Globally, the incidence of retinoblastoma is estimated at 1 in 16,000 to 18,000 live births, with most of the burden concentrated in India, China, Indonesia, Pakistan, Bangladesh, and the Philippines.[7]

In Bangladesh, where no nation-wide population-based cancer registry exists, a hospital-based study conducted at the National Institute of Cancer Research and Hospital revealed that among 4,458 childhood cancer patients treated at the Paediatric Haematology & Oncology

Department from 2008 to 2019, 648 (14.5%) were diagnosed with retinoblastoma. This included 306 cases (22.6%) from 2008–2013 and 366 cases (11.8%) from 2014–2019.[8]

India carries the highest burden of retinoblastoma globally, particularly within the Asia-Pacific region, with approximately 1,500 new cases diagnosed annually.[4] Following India, China reports the second-highest number of new retinoblastoma cases.[9]

Clinical Features:

Retinoblastoma (RB) is typically diagnosed around 18 months of age, with 95% of cases identified by the age of 5 years. The most common presenting symptoms include leukocoria (white pupillary reflex), strabismus (squint), a painful red eye, and poor vision. In addition to these typical features, RB can present with atypical manifestations such as pseudohypopyon, vitreous haemorrhage, or proptosis, which may pose diagnostic challenges. The presence of multiple primary tumours within the eye or bilateral retinoblastoma strongly suggests an inherited form of the disease associated with germline mutations in the RB1 gene. It often results in earlier onset and bilateral involvement.[10]

Early recognition of both typical and atypical features is critical for timely diagnosis and appropriate management, particularly in regions where delayed presentation and limited healthcare access are prevalent. Prompt identification of symptoms can significantly improve outcomes and reduce mortality in affected children.

Diagnosis:

The diagnosis of retinoblastoma is primarily clinical, with biopsy being contraindicated due to the risk of tumour dissemination. A detailed ocular examination under general anaesthesia (EUA) is essential for diagnosis and staging.[11] A B-scan ultrasound (USG) typically shows a rounded or irregular mass within the eye, marked by high internal reflectivity. This characteristic corresponds to the presence of intralesional calcifications, which are a hallmark feature of retinoblastoma.[10] Magnetic resonance imaging (MRI) is highly effective in identifying calcifications within the tumour, playing a crucial role in diagnosis, significantly when the fundus view is obstructed. Calcifications can be detected with significant sensitivity and specificity on T2-weighted images, often eliminating the need for CT scans.[12] MRI is also vital for staging, assessing whether the tumour has extended beyond the eye. It enables precise detection of extraocular invasion at critical sites such as the optic nerve, choroid, and sclera. Additionally, MRI is used to screen for trilateral retinoblastoma. In this condition, an intracranial tumour (commonly in the pineal or suprasellar region) occurs alongside retinal tumours, necessitating comprehensive imaging of the brain.[5]

Grouping and stating of advanced intraocular retinoblastoma:

The 8th edition AJCC RB staging system uniquely stratifies clinical high-risk retinoblastoma (RB) features within the cT2 and, especially, the cT3 categories. In contrast, previous classification systems grouped the clinical features outlined in cT3 into a single cluster, termed "group E." Past definitions for group E were never standardized, leading to significant confusion. For example, the International Classification for Retinoblastoma (ICRB), also known as the Wills Eye Hospital (WEH) group E, includes any tumour more significant than 50% of the globe's volume. On the other hand, the International Intraocular Retinoblastoma Classification (IIRC), or Children's Hospital of Los Angeles (CHLA) group E, includes diffuse infiltrating RB without specific size criteria. The AJCC 7th edition RB staging assigned high risk to tumours greater than 2/3 of the eye's volume. This lack of harmonization created confusion, hindered research meta-analyses, and posed risks for suboptimal treatment protocols in patient management.[13]

Advanced intraocular RB is defined by the 8th edition American Joint Committee on Cancer (AJCC) categories cT2 and cT3.[13] The AJCC clinical stage is also an independent predictor of globe survival; however, this staging system is not widely used for reporting clinical outcomes in published studies. A meta-analysis revealed that all included studies reported outcomes using some form of the A-E grouping system.[14] Various classification systems for RB have been developed to predict vision salvage, globe salvage, and survival.

In a global study of retinoblastoma, advanced intraocular retinoblastoma (group E) was identified as the most frequent state of RB at presentation.[15] Importantly, metastatic RB occurs exclusively in patients with advanced intraocular RB (group D or E eyes).[16] The

AJCC pTNM staging system is critical in evaluating the risk of tumour dissemination and guiding subsequent treatment decisions after enucleation.[9] This highlights the importance of adopting standardized and globally recognized staging systems to improve diagnosis, treatment planning, and outcomes for children with retinoblastoma.

IIRC	Group D	Group E
ICRB	Group D	Group E

Fig. 1 *Showing classification boundaries of advanced intraocular RB (Group D & E) by the International Intraocular Retinoblastoma classification & the International Classification of Retinoblastoma system (Modified from Sedaghat et al. Canadian Journal of Ophthalmology 2024;59(5):e635-e641)*

Management:

Managing retinoblastoma requires carefully integrating multidisciplinary care involving a team of paediatric oncologists, ophthalmologists, radiologists, radiation oncologists, child psychologists, social workers, nurses, and genetic counsellors.[10] Genetic testing, counselling, and screening of at-risk family members are essential to this management strategy.[11] In cases of advanced intraocular retinoblastoma, attempting globe salvage with systemic chemotherapy instead of opting for primary enucleation increases the risk of death due to metastasis. Delayed enucleation in advanced intraocular retinoblastoma further elevates this risk. Specifically, the risk is increased 3.3-fold when systemic chemotherapy is followed by secondary enucleation and 4.9-fold when chemotherapy is combined with eye salvage efforts. Therefore, primary treatment for advanced retinoblastoma must be carefully considered.[13] Best practices as defined by ophthalmologists sometimes differ from those proposed by paediatric oncologists. The trend of favouring systemic chemotherapy over primary enucleation has resulted in an increased risk of metastasis-related mortality. In resource-limited settings, reliable clinical stratification of high-risk features is the most valuable tool to guide clinicians in decision-making regarding adjuvant therapies.[13]

Clinical High-Risk Features:

A thorough primary ophthalmic evaluation is crucial for guiding the management of retinoblastoma (RB) patients. Various studies have analysed clinical features that may predict high-risk pathology and, consequently, the risk of systemic metastasis. Glaucoma or buphthalmos was found to be associated with high-risk pathology in a study of 182 consecutive patients with unilateral RB treated with primary enucleation. In contrast, conditions such as hyphema, orbital cellulitis, and diffuse infiltrative RB, collectively called "inflammatory eye," were not linked to high-risk pathology, and mortality was not analysed in this context.[17] A large study involving 326 primarily enucleated eyes concluded that vitreous haemorrhage, hyphema, staphyloma, and orbital cellulitis were predictors of high-risk pathology.[18]

Despite extensive literature identifying clinical high-risk features, only the AJCC staging system currently provides a prognosis-based risk stratification framework to support safe clinical decision-making.[19,20] Tomar et al. conducted a large multicenter data-sharing study, which provided statistically significant evidence demonstrating that neovascular glaucoma or buphthalmos, intraocular haemorrhage, and aseptic cellulitis are associated with an increased risk of metastatic death. Further analysis, stratified by treatment modality, revealed that the subcategories cT3c (glaucoma) and cT3e (orbital cellulitis) carry a significantly different risk of metastasis-related death depending on whether the patient undergoes primary enucleation or attempts eye salvage with systemic chemotherapy. This difference may be explained by intraocular pressure-related scleral thinning or inflammation-induced breaches in the sclera. In contrast, no significant difference in survival was observed across the three treatment arms for the subcategory cT3d (intraocular haemorrhage). A possible explanation is that bleeding may obscure the true extent of the tumour. Lastly, the authors found no significant association between anterior segment involvement and metastatic death. However, this finding should be interpreted with caution, as the registry's clinical data did not account for the specific involvement of the ciliary body and pars plana, which may have resulted in the downstaging of eyes that could otherwise have been classified under the cT3b subcategory.[13]

Advanced age at presentation was found to confer a worse prognosis, a finding supported by evidence from a recent study conducted by Aschero et al. in which

increasing age was correlated with high-risk genomic features.[21]

Histopathological High-Risk Features for adjuvant Chemotherapy: Metastasis represents the most critical poor prognostic factor in retinoblastoma (RB). While clinical findings may not reliably predict metastasis risk, histopathological data can provide a more reasonable estimate. Patients presenting with glaucoma and/or buphthalmos are significantly more likely to exhibit histopathologic high-risk features (HRFs).[18]

Gupta et al. reported that HRFs were present in 20.4% of children in developed countries, compared to 54.2% in developing countries.[22] The increased risk of metastasis observed in developing countries may be attributed to delays in diagnosis and treatment. However, the possibility of differing biological behaviour of tumours could also be a contributing factor.

Table I: *Histopathological risk features based on tumour invasion of ocular structures*[10]

Site	Type of involvement	Risk of metastatic disease
Choroid	Focal invasion <3 mm	Not increased
	Massive invasion ≥3 mm	Increased
Optic nerve	Prelaminar	Not increased
	Lamina cribrosa	Not increased
	Postlaminar	Increased
	At surgical margin	Increased
	Subarachnoid	Increased
Others	Anterior segment invasion	Increased
	Neovascularization with iris with glaucoma	Increased
	Extensively necrotic retinoblastoma	Increased
	Buphthalmus	Increased

Optic nerve invasion:

The prognosis of retinoblastoma is significantly influenced by the degree of optic nerve invasion. As shown in Table 8, there is a direct association between the extent of optic nerve invasion and mortality.[10] Specifically, an optic nerve stump measuring less than 5 mm attached to the enucleated eye is associated with a worse prognosis compared to stumps exceeding 5 mm.[18] In histopathology reports, it is crucial to document the precise level of tumourinvasion along the optic nerve, including classifications such as prelaminar, laminar, postlaminar, involvement at the surgical cut margin, and/or extension into the subarachnoid space.[10]

Table 2: *The association of extent of optic nerve invasion and mortality rate*[10]

Extent of optic nerve invasion	Mortality rate (%)
Optic nerve not involved	10
Superficial invasion	10
Presence of tumour up to the lamina cribrosa	29
Invasion of the tumour posterior to the lamina cribrosa	42
The presence of tumour at the transected surgical margin	80

Genetics of RB:

The discovery of the RB1 gene at chromosome 13q14 in the 1980s confirmed that RB1 was the first tumour-suppressor gene.[3] In both heritable and non-heritable retinoblastoma, biallelic mutations of the RB1 tumour-suppressor gene initiate tumour growth. Inheritable retinoblastoma, the first RB1 mutation (M1), is constitutional, predisposing the child to retinal tumours. Somatic mutations (M2) in one or more retinal cells trigger tumour growth. Very rarely, primitive neuroectodermal tumours arise in the pineal or suprasellar region, resulting in trilateral retinoblastoma. Germline testing to identify specific mutations is essential for effectively counselling families. Genetic testing for RB1 is now considered the standard of care in Canada and other developed countries[23], but it remains unavailable in many developing countries.[10]

Treatment of Retinoblastoma:

The optimal treatment approach for retinoblastoma is determined by several key factors, including the tumour stage as defined by the International Classification of Retinoblastoma (ICRB), whether cancer has spread beyond the eye (extraocular involvement), results from genetic (germline) testing, the family's social and psychological circumstances, and the medical resources

available at the treating institution.[24] In advanced cases, treatment often involves a multimodality approach, which may include enucleation, intravenous chemotherapy (IVC), and, in certain situations, external beam radiotherapy (EBRT). In low- and middle-income countries, advanced technologies such as intraarterial chemotherapy (IAC) and intravitreal chemotherapy (IVtrC) are typically not available, limiting treatment options.

Enucleation:

Enucleation is a surgical procedure used in managing retinoblastoma (RB), involving the removal of the affected eyeball while preserving the surrounding muscles. During the procedure, the optic nerve is severed, and an artificial implant is inserted to maintain the volume of the globe. Although enucleation results in the loss of the eye, it achieves a 99% cure rate for RB in that eye.[25] Most Group E eyes are best managed with enucleation, as the chances of vision salvage are poor, and there is a high risk of metastasis. Additionally, enucleation allows for identifying high-risk features (HRFs) in the eye, which may necessitate more aggressive treatment.[26]

When deciding between enucleation and globe salvage for advanced intraocular retinoblastoma, carefully evaluating the risk-benefit ratio is critical, as these eyes may harbour high-risk RB, posing a potentially life-threatening risk. A comparative analysis of 524 RB patients from India and the U.S. found that Asian Indian patients faced a fivefold higher likelihood of optic nerve invasion and a threefold increased risk of massive choroidal invasion compared to American patients.[27] The incidence of high-risk RB ranges from 15–17% in Group D eyes and 24–50% in Group E eyes. For eyes exhibiting clinical features predictive of high-risk RB, enucleation is recommended over globe salvage strategies to avoid fatal outcomes. Furthermore, globe salvage treatments for advanced RB require significantly more examinations under anaesthesia (EUAs)—averaging 16 versus 7 for primary enucleation—a disparity that may adversely affect neurological and cognitive development in children.[27]

On the other hand, there is no international consensus on a threshold retinoblastoma stage above which primary enucleation is required. However, it is widely accepted that advanced Group D tumours (IRC classification) / advanced cT2b (TNMH classification) occupying two-thirds or more of the vitreous cavity, or with massive vitreal and/or subretinal seeding, and advanced Group E tumours / advanced cT3a-e tumours usually require primary enucleation. Recent advancements and improvements in selective ocular administration routes, such as ophthalmic artery catheterization[29,30] or intravitreal injections,[31] have expanded the indications for conservative management. Exceptionally, Group E / cT3b eyes with limited anterior segment invasion may be eligible for conservative management, relying on the availability of intravitreal or intracameral chemotherapy.[32,33] Zhao et al.'s study concludes that chemotherapy before enucleation in group E eyes with advanced retinoblastoma downstage pathological evidence of extraocular extension and delaying enucleation beyond 3 months after diagnosis increases the risk of metastatic death due to reduced surveillance and suboptimal management of high-risk disease.[9]

Intravenous Chemotherapy (IVC):

Intravenous chemotherapy (IVC) remains the most widely used treatment approach for retinoblastoma (RB). It is used for chemoreduction prior to enucleation and in the adjuvant setting after enucleation. In most European countries, chemotherapy regimens typically combine vincristine (88.5%), etoposide (96.2%), and carboplatin (100%). In certain treatment centers, additional medications such as cyclophosphamide (26.9%), ifosfamide (7.7%), or topotecan (7.7%) are also utilized.[34]

Chemoreduction:

While IVC demonstrates effective tumour control in early-stage disease, its efficacy in advanced Group D and E RB is suboptimal when using standard triple-drug (vincristine, etoposide, carboplatin) chemo-reduction regimens. Carboplatin-based protocols are recommended as first-line therapy; however, if unavailable, an alternative regimen combining cyclophosphamide, vincristine, and doxorubicin may be considered. Although chemoreduction has shown promise in managing Group E eyes, enucleation is still preferred for unilateral Group E cases, as preoperative chemotherapy can downstage the tumour, mask risks of tumour extension, and increase the risk of metastatic death.[9] The role of high-dose carboplatin in improving

globe salvage in intraocular retinoblastoma was recently evaluated in a randomized controlled trial, which found no significant improvement in the proportion of globe salvage with the use of higher doses of carboplatin.[35]

Adjuvant Chemotherapy (Chemo-prophylaxis): Adjuvant chemotherapy is administered when high-risk histopathological features (HRFs) are present in the enucleated specimen. The doses are similar to those employed in chemoreduction, and four to six cycles of adjuvant chemotherapy are recommended. In a study by Honavar et al., among 80 patients with HRFs, only 4% developed metastasis after receiving adjuvant chemotherapy, compared to 24% of those who did not receive it.[26]

The benefits of adjuvant therapy must be carefully balanced against its potential side effects. Short-term side effects may include temporary bone marrow suppression and an increased risk of febrile neutropenia. In Central America, the AHOPCA group reported a treatment-related mortality rate of 4% following VEC chemotherapy (vincristine, etoposide, carboplatin). In contrast, in Europe and North America, treatment-related mortality after standard chemotherapy for retinoblastoma is nearly 0%. Ototoxicity remains a possible concern, although it appears uncommon in most patient groups; regular monitoring is nonetheless recommended. There is evidence that chemotherapy using alkylating agents or topoisomerase inhibitors may increase the risk of secondary cancers, particularly in individuals with hereditary retinoblastoma. Nevertheless, the incidence of second malignancies following adjuvant therapy alone remains low. While, the side effects of adjuvant therapy are generally manageable, they cannot be overlooked. Therefore, adjuvant treatment should only be offered to patients who face a significant risk of metastatic disease.[34]

External Beam Radiotherapy:

External-beam radiotherapy (EBRT) was first used to treat retinoblastoma in the early 1950s. However, it took nearly four decades to fully recognize that radiation significantly increases the lifelong risk of developing secondary cancers in children with a constitutional RB1 mutation.[3] Before the advent of intravenous chemotherapy (IVC), EBRT was commonly utilized as a means of globe salvage. Today, in most developed nations, EBRT is primarily regarded as a treatment of historical significance due to its various side effects and the higher success rates achieved with modern chemotherapy regimens for retinoblastoma. Nevertheless, EBRT is still used in specific indications, such as cases involving extraocular extension, recurrence in the orbit, or involvement of the optic nerve margin after enucleation.[24] The standard dose is 40–50 Gy administered over 3–4 weeks.[36] The most serious side effect of EBRT is the subsequent development of second primary neoplasms within the radiation field, particularly in patients with germline retinoblastoma. This risk has been reported to be as high as 53% by the age of 50, making individuals with a germline mutation more likely to die from these secondary cancers than from retinoblastoma itself. The most common second primary tumour is osteosarcoma, followed by other bone tumours, soft tissue sarcomas, melanoma, and epithelial tumours (including those of the bladder, breast, colorectum, kidney, lung, nasal cavity, prostate, retroperitoneum, thyroid, tongue, and uterus). Considering these risks, it is recommended to avoid EBRT whenever alternative effective treatment options are available.[24]

Conclusions:

The management of advanced intraocular retinoblastoma demands a meticulous, multidisciplinary approach tailored to each unique case. In developing countries, where resources and expertise vary, treatment decisions are often complicated by delays and limited access to modern therapies like intra-arterial chemotherapy (IAC) or intravitreal chemotherapy (IVtrC). Evidence strongly supports primary enucleation for advanced cases, especially in unilateral retinoblastoma, combined with risk-stratified adjuvant therapy guided by histopathology. The AJCC 8th edition staging system provides critical tools to predict metastasis risk and improve outcomes. For optimal results, early enucleation, accurate histopathology, and timely adjuvant chemotherapy must remain the cornerstone of care in resource-limited settings. Pre-enucleation chemotherapy, while sometimes pursued to preserve the eye or vision, can obscure high-risk pathological features, delay proper treatment, and increase mortality risks

References

1. Kivelä T. 200 years of success initiated by James Wardrop's 1809 monograph on retinoblastoma. Acta Ophthalmol. 2009;87(8):810-2. doi:10.1111/j.1755-3768.2009.01807.x.

2. Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol. 2009;93(9):1129-31.

3. Dimaras H, Kimani K, Dimba EA, Gronsdahl P, White A, Chan HS, Gallie BL. Retinoblastoma. Lancet. 2012 Apr 14;379(9824):1436-46. doi:10.1016/S0140-6736(11)61137-9.

4. Jain M, Rojanaporn D, Chawla B, Sundar G, Gopal L, Khetan V. Retinoblastoma in Asia. Eye (Lond). 2019 Jan;33(1):87-96. doi:10.1038/s41433-018-0244-7.

5. Munier FL, Beck-Popovic M, Chantada GL, Cobrinik D, Kivelä TT, Lohmann DR, et al. Conservative management of retinoblastoma: Challenging orthodoxy without compromising the state of metastatic grace. "Alive, with good vision and no comorbidity." Prog Retin Eye Res. 2019;73:100764.

6. Zhou M, Tang J, Fan J, Wen X, Shen J, Jia R, et al. Recent progress in retinoblastoma: Pathogenesis, presentation, diagnosis and management. Asia Pac J Ophthalmol (Phila). 2024;13(2):[Epub ahead of print].

7. Kaliki S, Vempuluru VS, Mohamed A, Al-Jadiry MF, Bowman R, Chawla B, et al.; Global Retinoblastoma Study Group. Retinoblastoma in Asia: Clinical presentation and treatment outcomes in 2112 patients from 33 countries. Ophthalmology. 2024 Apr;131(4):468-77. doi:10.1016/j.ophtha.2023.10.015.

8. Begum M, Islam MJ, Karim S, Khan ZJ, Kabir SMRZ, Begum F, et al. Childhood malignancy in Bangladesh: Twelve years journey of a tertiary care specialized cancer hospital. Cancer J Bangladesh. 2022;3(2):63-71.

9. Zhao J, Dimaras H, Massey C, et al. Pre-enucleation chemotherapy for eyes severely affected by retinoblastoma masks risk of tumour extension and increases death from metastasis. J Clin Oncol. 2011;29(7):845-51.

10. Gupta A, Meena J. A narrative review of retinoblastoma and recent advances in its management. Pediatr Med. 2020;3:79. doi:10.21037/pm-20-79.

11. Nag A, Khetan V. Retinoblastoma - A comprehensive review, update and recent advances. Indian J Ophthalmol. 2024 Jun 1;72(6):778-88. doi:10.4103/IJO.IJO_2414_23.

12. Rodjan F, de Graaf P, Brisse HJ, Goricke S, Maeder P, Galluzzi P, et al. Trilateral retinoblastoma: neuroimaging characteristics and value of routine brain screening on admission. J Neurooncol. 2012;109(3):535-44.

13. Tomar AS, Finger PT, Gallie B, Kivelä TT, Mallipatna A, Zhang C, et al.; American Joint Committee on Cancer Ophthalmic Oncology Task Force. Metastatic death based on presenting features and treatment for advanced intraocular retinoblastoma: A multicenter registry-based study. Ophthalmology. 2022 Aug;129(8):933-45. doi:10.1016/j.ophtha.2022.04.022.

14. Ravindran K, Dalvin LA, Pulido JS, Brinjikji W. Intra-arterial chemotherapy for retinoblastoma: an updated systematic review and meta-analysis. J Neurointerv Surg. 2019;11(12):1266-72.

15. Global Retinoblastoma Study Group, Fabian ID, Abdallah E, Abdullahi SU, et al. Global retinoblastoma presentation and analysis by national income level. JAMA Oncol. 2020;6(5):685-95.

16. Lu JE, Francis JH, Dunkel IJ, et al. Metastases and death rates after primary enucleation of unilateral retinoblastoma in the USA 2007-2017. Br J Ophthalmol. 2019;103(9):1272-7.

17. Chantada GL, Gonzalez A, Fandino A, de Davila MT, Demirdjian G, Scopinaro M, et al. Some clinical findings at presentation can predict high-risk pathology features in unilateral retinoblastoma. J PediatrHematol Oncol. 2009 May;31(5):325-9. doi:10.1097/MPH.0b013e3181923cc5.

18. Kashyap S, Meel R, Pushker N, et al. Clinical predictors of high-risk histopathology in retinoblastoma. Pediatr Blood Cancer. 2012;58(3):356-61.

19. Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. Ophthalmol Clin North Am. 2005 Mar;18(1):41-53, viii. doi:10.1016/j.ohc.2004.11.003.

20. Shields CL, Mashayekhi A, Au AK, Czyz C, Leahey A, Meadows AT, Shields JA. The International Classification of Retinoblastoma predicts chemoreduction success. Ophthalmology. 2006 Dec;113(12):2276-80. doi:10.1016/j.ophtha.2006.06.018.

21. Aschero R, Francis JH, Ganiewich D, Gomez-Gonzalez S, Sampor C, Zugbi S, et al. Recurrent somatic chromosomal abnormalities in relapsed extraocular retinoblastoma. Cancers (Basel). 2021 Feb 8;13(4):673. doi:10.3390/cancers13040673.

22. Gupta R, Vemuganti GK, Reddy VA, et al. Histopathologic risk factors in retinoblastoma in India. Arch Pathol Lab Med. 2009;133(8):1210-4.

23. Canadian Retinoblastoma Society. National Retinoblastoma Strategy Canadian guidelines for care: stratégiethérapeutique du rétinoblastome guide cliniquecanadien. Can J Ophthalmol. 2009;44(Suppl 2):S1–88.

24. Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020 Nov;68(11):2356-65. doi: 10.4103/ijo.IJO_721_20.

25. Shields CL, Fulco EM, Arias JD, et al. RB frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Eye. 2013;27(2):253-64.

26. Honavar SG, Singh AD, Shields CL, et al. Postenucleation adjuvant therapy in high-risk RB. Arch Ophthalmol. 2002;120(7):923-31.

27. Kaliki S, Shields CL, Eagle RC Jr, Iram S, Shields JA. High-risk intraocular retinoblastoma: Comparison between Asian Indians and Americans from two major referral centers. Retina. 2018;38(10):2023–9.

28. Kaliki S, Mittal P, Mohan S, Chattannavar G, Jajapuram SD, Mohamed A, et al. Bilateral advanced (group D or E) intraocular retinoblastoma: outcomes in 72 Asian Indian patients. Eye (Lond). 2019 Aug;33(8):1297-304. doi: 10.1038/s41433-019-0409-z.

29. Abramson DH, Dunkel IJ, Brodie SE, Kim JW, Gobin YP. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology. 2008 Aug;115(8):1398-404.e1. doi: 10.1016/j.ophtha.2007.12.014.

30. Yamane T, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. Int J Clin Oncol. 2004 Apr;9(2):69-73. doi: 10.1007/s10147-004-0392-6. PMID: 15108036.

31. Munier FL, Soliman S, Moulin AP, Gaillard MC, Balmer A, Beck-Popovic M. Profiling safety of intravitreal injections for retinoblastoma using an anti-reflux procedure and sterilisation of the needle track. Br J Ophthalmol. 2012 Aug;96(8):1084-7. doi: 10.1136/bjophthalmol-2011-301016.

32. Cassoux N, Aerts I, Lumbroso-Le Rouic L, Freneaux P, Desjardins L. Eye salvage with combination of intravitreal and intracameral melphalan injection for recurrent retinoblastoma with anterior chamber involvement: report of a case. Ocul Oncol Pathol. 2017 Jul;3(2):129-32. doi: 10.1159/000452305.

33. Munier FL, Gaillard MC, Decembrini S, Bongiovanni M, Beck-Popovic M. Intracameral chemotherapy (melphalan) for aqueous seeding in retinoblastoma: bicameral injection technique and related toxicity in a pilot case study. Ocul Oncol Pathol. 2017 Jul;3(2):149-55. doi: 10.1159/000453617.

34. Dittner-Moormann S, Reschke M, Abbink FCH, et al. Adjuvant therapy of histopathological risk factors of retinoblastoma in Europe: a survey by the European Retinoblastoma Group (EURbG). Pediatr Blood Cancer. 2021 Jun;68(6):e28963. doi: 10.1002/pbc.28963. PMID: 33720495.

35. Roy PS, Muhammed S, Singh U, et al. A single-blinded, randomized controlled trial of standard versus higher dose carboplatin-based intravenous chemotherapy for group D and E retinoblastoma. Pediatr Blood Cancer. 2023;70:e30444.

36. Nag A, Khetan V. Retinoblastoma - A comprehensive review, update and recent advances. Indian J Ophthalmol. 2024;72(6):778–88.