Reg No. 5104

তারিখঃ 12/6/2024
বরাবর
চেয়ারম্যান,
ইন্সটিটিউশনাল রিভিউ বোর্ড (আই আর বি)
বঙ্গবন্ধু শেখ মুজিব মেডিকেল বিশ্ববিদ্যালয়,
শাহবাগ, ঢাকা-১০০০।

বিষয়ঃ গবেষণা প্রটোকল ইন্সটিটিউশনাল রিভিউ বোর্ড (আই আর বি) কর্তৃক অনুমোদনের জন্য আবেদন।

জনাব,
আমি ডা: নিশাত তাসনীম, অনকোলজি (ফেইজ বি), ক্লিনিক্যাল অনকোলজি বিভাগ, বঙ্গবন্ধু শেখ মুজিব মেডিকেল বিশ্ববিদ্যালয় "Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung" শিরোনামে আমার গবেষণা প্রটোকল রিভিউ এর জন্য জমাদানে ইচ্ছুক। আমি ইন্সটিটিউশনাল রিভিউ বোর্ড (আই আর বি) এর নির্দেশিত কাঠামো অনুসরণ করে গবেষণা প্রটোকলটি তৈরি করেছি। প্রটোকলটি আমার গাইড সহযোগী অধ্যাপক ডাঃ মোসা: রোকাইয়া সুলতানা, ক্লিনিক্যাল অনকোলজি বিভাগ, বঙ্গবন্ধু শেখ মুজিব মেডিকেল বিশ্ববিদ্যালয়, কর্তৃক পরিকল্পিত হয়েছে এবং তিনি এটি তত্ত্বাবধানের জন্য সদয় সম্মতি জ্ঞাপন করেছেন। তিনি আমার কার্যক্রম তদারকি করবেন এবং প্রয়োজনে আপনার সাথে যোগাযোগ রাখবেন।

অতএব, বিনীত নিবেদন এই যে, আমার গবেষণা প্রটোকলটি অনুমোদন করে আমাকে গবেষণা করার অনুমতি প্রদান করে বাধিত করবেন।

বিনীত নিবেদক,

N. Tasnim

ডাঃনিশাত তাসনীম,
এমডি, অনকোলজি (ফেইজ বি),
ক্লিনিক্যাল অনকোলজি বিভাগ,
বঙ্গবন্ধু শেখ মুজিব মেডিকেল বিশ্ববিদ্যালয়।

forwarded
12/6/24

Prof. Dr. Md. Nazir Uddin Mollah
MBBS, M.Phil (Oncology), FCPS (Radiotherapy)
Chairman
Department of Clinical Oncology
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka-1000
Reg. No. A 2547
Mob: 01552455345

বঙ্গবন্ধু শেখ মুজিব মেডিক্যাল বিশ্ববিদ্যালয়
Bangabandhu Sheikh Mujib Medical University

রেজিস্ট্রার অফিস — Office of the Registrar

No.BSMMU/2024/6815 — *Date:15-07-2024*

Institutional Review Board (I.R.B)

Registration No: 5104

Principal Investigator : **Dr. Nishat Tasnim**
MD (Oncology) Resident, Phase-B
Department of Clinical Oncology
Bangabandhu Sheikh Mujib Medical University, Dhaka.

Title of the Research Protocol : Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung.

With reference to your application this is to inform you that the ethical clearance has been approved of the above research protocol in the IRB meeting held on 01 July 2024.

Please be advised that the Institutional Review Board (IRB) needs to be informed should any part of the research protocol is changed in any way.

Kind regards

Professor Dr. Mohammed Atiqur Rahman
Pro-Vice Chancellor (Academic)
&
Chairman
Institutional Review Board
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka.

ব্লক বি (৩য় তলা), শাহবাগ, ঢাকা-১০০০, বাংলাদেশ, টেলিফোন ঃ ৫৫১৬৫৭৬০-৯৪, ফ্যাক্স ঃ ৮৮০-২-৫৫১৬৫৬০৯, E-mail : registrar@bsmmu.edu.bd
Block B (2nd Floor), Shahbag, Dhaka-1000, Bangladesh, Tel : 55165760-94, Fax : 880-2-55165609, E-mail : registrar@bsmmu.edu.bd

Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung

Dr. Nishat Tasnim
MD(Oncology) – Phase B

Bangabandhu Sheikh Mujib Medical University
Shahbagh, Dhaka.

Accepted
Sadia Sharmin
11.07.24
DR. SADIA SHARMIN
MBBS, FCPS (Radiotherapy)
Associate Professor
Department of Clinical Oncology
BSMMU, Dhaka

can be accepted.
7.7.24.
Dr. Farzana Rahman
MBBS, FCPS (Haematology)
Associate Professor
Department of Haematology
Bangabandhu Sheikh Mujib Medical University

বঙ্গবন্ধু শেখ মুজিব মেডিক্যাল বিশ্ববিদ্যালয়
Bangabandhu Sheikh Mujib Medical University
Shahbagh, Dhaka- 1000

Register No: 5104
Received Date: 12/4/'24
Meeting Date: 01.07.'24
Approved / Not approved /
Revised / Correction:

Application for Institutional Review Board (I.R.B) Clearance

• Title of the study	**Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung**
• Principal Investigator / Name of the student	Dr. Nishat Tasnim
• Name of Present Course	MD (Oncology)
• Joining date in Thesis Part / Phase-B	1st September, 2022
• Name of Institute	BSMMU
• Expected date of Examination	January, 2026
• Guide/Adviser	Associate Professor. Dr. Most. Rokaya Sultana
• Place of Study	Department of Clinical Oncology, BSMMU Lab aid Cancer Hospital Combined Military Hospital Delta Hospital Limited
• Type of Study	Quasi-Experimental Study
• Duration of Study	One year after IRB approval
• Total cost	Approximately 4,00,000 BDT
• Funding Agency	BSMMU and the investigator

We agree to obtain approval from the Institutional Review Board of BSMMU for any changes involving the rights and welfare of subjects or any changes in the Methodology before making any such changes.

N. Tasnim
Principal Investigator/Student

R. Sultana
Co-Investigator/Guide
Dr. Most. Rokaya Sultana
MBBS, MD (Oncology)
Associate Professor
Dept. of Clinical Oncology
Bangabandhu Sheikh Mujib Medical University

Put Tick sign (√) appropriate answers against each of the following statement

(If not Applicable, Please write NA)

1. Source of Population:

(a) Patients ☑ Yes ☐ No

(b) Healthy Subjects ☐ Yes ☑ No

(c) Minors or person under guardianship ☐ Yes ☑ No

2. Does the study involve:

(a) Physical risks to the subjects ☑ Yes ☐ No

(b) Social Risks ☑ Yes ☐ No

(c) Psychological risks ☑ Yes ☐ No

(d) Discomfort to subjects ☑ Yes ☐ No

(e) Invasion of the body ☑ Yes ☐ No

(f) Invasion of Privacy ☑ Yes ☐ No

(g) Disclosure of information damaging to subject or others ☐ Yes ☑ No

3. Does the study involve:

(a) Use of records :- (Hospital, Medical, Death, Birth or other) ☑ Yes ☐ No

(b) Use of fetal tissues or abortus ☐ Yes ☑ No

(c) Use of organs or body fluids ☐ Yes ☑ No

4. Are subjects clearly informed about:

(a) Nature and purposes of study ☑ Yes ☐ No

(b) Procedures to be followed including alternative used ☑ Yes ☐ No

(c) Physical risks ☑ Yes ☐ No

(d) Private questions ☑ Yes ☐ No

(e) Mental risks ☑ Yes ☐ No

(f) Benefits to be derived ☑ Yes ☐ No

(g) Right to refuse to participate or to withdraw from study ☑ Yes ☐ No

(h) Confidential handling of data ☑ Yes ☐ No

(i) Compensations: (where there are risks or loss of working time or privacy is involved in any particular procedure) ☐ Yes ☐ No

5. Signed consent form will be obtained:

(a) From Subjects(If adult) ☑ Yes ☐ No

(b) From parent or guardian (if subjects are minor) ☐ Yes ☐ No

6. Will precautions be taken to protect anonymity of subjects? ☑ Yes ☐ No

To,

The Chairman and Course Coordinator,
Department of Clinical Oncology,
Bangabandhu Sheikh Mujib Medical University,
Shahbagh, Dhaka.

Subject: Prayer for Approval of the Thesis Protocol.

Sir,

I, the undersigned, with due respect, would like to submit my thesis protocol entitled '**Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung**'. My thesis protocol is attached herewith for your kind approval.

I, therefore, pray and hope that you would be kind enough to accept my thesis protocol and oblige me thereby.

Sincerely yours,

N. Tasnim

Dr. Nishat Tasnim
Resident, Phase- B, MD (Oncology)
Department of Clinical Oncology
Bangabandhu Sheikh Mujib Medical University
Shahbagh, Dhaka.

To,
The Chairman,
Institutional Review Board,
Bangabandhu Sheikh Mujib Medical University,
Shahbagh, Dhaka.

Through: Chairman, Department of Clinical Oncology.

Subject: Application for ethical clearance of the thesis protocol titled 'Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung'.

Sir,
With due respect, I would like to submit my thesis protocol titled **'Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung'** for your kind approval. My thesis protocol is attached herewith.

I, therefore, pray & hope that you will be kind enough to accept my thesis protocol & oblige thereby.

Sincerely yours,

N. Tasnim

Dr. Nishat Tasnim
Resident, Phase-B, MD (Oncology)
Department of Clinical Oncology
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka.

To,

The Chairman,

Institutional Review Board,

Bangabandhu Sheikh Mujib Medical University,

Shahbagh, Dhaka.

Subject: Application for I.R.B Clearance of Thesis Protocol.

Sir,

With due respect, I am glad to send this thesis protocol to you for I.R.B clearance. I have gone through this protocol and will follow all steps of this thesis to be done by Dr. Nishat Tasnim on **'Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung'.**

I would be glad if you kindly approve this thesis protocol.

With regards,

Professor Dr. Md. Nazir Uddin Mollah

Chairman

Department of Clinical Oncology

Bangabandhu Sheikh Mujib Medical University

Shahbagh, Dhaka.

Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
AJCC	American Joint Committee on Cancer
BCS	Breast Conservation Surgery
BMI	Body Mass Index
BSMMU	Bangabandhu Sheikh Mujib Medical University
CMH	Combined Military Hospital
DIBH	Deep Inspiration Breath Hold
DVH	Dose Volume Histogram
ECOG	Eastern Co-operative Oncology Group
ERR	Estimated Risk Ratio
GLOBOCAN	Global Cancer Incidence, Mortality and Prevalence
HDI	Human Development Index
ICRU	International Commission on Radiation Units
IMRT	Intensity Modulated Radio Therapy
LAD	Left Anterior Descending Artery
LINAC	Linear Accelerator
MCE	Major Coronary Events
MHD	Mean Heart Dose
MRM	Modified Radical Mastectomy
NCCN	National comprehensive cancer network, USA
OAR	Organs At Risk
OSI	Optical Surface Imaging
PMRT	Post Mastectomy Radiation Therapy

PTV	Planning Target Volume
RILD	Radiation Induced Ling Disease
RP	Radiation Pneumonitis
RPM	Real time Position Management
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SGRT	Surface Guided Radiotherapy System
SPSS	Statistical Packages for Social Sciences (SPSS Inc. Chicago IL USA)
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization

Abstract for the Institutional Review Board

Background

Breast cancer is the most common cancer among Bangladeshi females. Radiotherapy (RT) is an essential treatment option for most of the patients. However, it can cause significant late cardiac and pulmonary toxicity specially in left-sided breast cancer patients which is directly correlated with dose. Newer technique like deep inspiration breath hold (DIBH) RT can reduce doses to the heart and left lung than RT with free breathing (FB) without compromising doses to the planning target volumes (PTV).

Aim and Objective:

To compare between radiation doses to the target volumes, heart and left lung with free breathing and deep inspiration breath hold technique in adjuvant radiotherapy for left sided breast cancer.

Materials and Methods:

This quasi-experimental study will be conducted in 4 different centers of Bangladesh over a period of one year. A total of 50 left sided breast cancer patients meeting the inclusion and exclusion criteria will be enrolled in this study and then divided equally into 2 arms (Arm A and Arm B). Arm A participants will undergo computed tomography (CT) simulation and RT with FB. For Arm B, CT simulation and RT will be done in DIBH technique. All participants will receive 40.05 Gray (Gy) radiation, at 2.67 Gy daily single fraction, 5 days a week, for 3 weeks by IMRT. The dose volume histograms (DVH) will then be calculated to measure the dose to PTV, heart and left lung.

Ethical Considerations and Maintenance of Confidentiality:

After conclusive recruitment of subjects, the nature, purpose, potential risks, and benefits of the study will be explained in detail to them and informed written consent will be taken. To assess current condition, detailed history will be noted as well as clinical examination will be done. Participant's confidentiality will be maintained strictly throughout the time by giving them a unique code. No papers will contain name of any participant. The selected participants will be given Bangla version of consent to read by them. If they voluntarily agree to participate and give their full informed consent, only then they will be recruited as study participants.

Statistical Method:

All the relevant data will be compiled on a master chart first and then statistical analysis of the results will be obtained by using Windows based computer software facilities with Statistical Packages for Social Sciences (SPSS-24) (SPSS Inc, Chicago IL USA). The data will be analysed using Chi-square test and 't' test. The results will be presented in tables, figures, diagrams. All reported P values are two sided and $P < 0.05$ will be considered statistically significant.

Title of the Protocol

Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung

Name of the student : Dr. Nishat Tasnim

Place of study : Department of Clinical Oncology, BSMMU

: Department of Radiation Oncology, Combined Military Hospital

: Department of Oncology, Delta Hospital Limited

: Lab Aid Cancer Hospital

Type of the study : Quasi-Experimental study

Name of the guide : Dr. Most. Rokaya Sultana

Associate Professor

Department of Clinical Oncology

Bangabandhu Sheikh Mujib Medical University (BSMMU)

Table of Contents

Introduction

‘‘Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs’’ (World Health Organization [WHO]). The incidence, prevalence and fatality of cancer is rising worldwide with the increase in life expectancy and change in lifestyle. It represents a significant global health, social and economic burden.

According to WHO in 2022, estimated new cases were approximately 20 million, about 1 in 5 people suffer from cancer in their lifetime. It has become the second leading cause of death worldwide accounting for an estimated 9.7 million deaths that is 1 in six deaths (16.8%) and 1 in 4 deaths (22.8%) from noncommunicable diseases. 1 in 9 men and 1 in 12 women die of this approximately. At the same time in Bangladesh, expected number of new cases was around 167256 with 116598 deaths and 5-year prevalence of about 346337 (Global Cancer Observatory [GLOBOCAN]- Bangladesh, 2022). Among men, the most common causes are lung, prostate, colorectal, stomach and liver cancer and for women, breast, lung, colorectal, cervical and thyroid cancer ranked as the commonest ones.

Breast cancer is the most commonly diagnosed cancer in female globally. According to WHO in 2022, there were 2.3 million women diagnosed with breast cancer. Statistics show disparity in breast cancer burden according to human development index (HDI). In a very high HDI country, 1 in 12 women will be diagnosed in their lifetime whereas in countries with low HDI, this data is about 1 in 27 women though they are at increased mortality risk from late diagnosis and inadequate access to treatment.

Also in our country, breast cancer is one of the major health concerns in female. Though there is lack of nationwide exact data but it is estimated as the most common cancer among women. It constitutes 18% of new cancer cases estimated to be 12989 new diagnoses made in 2022 with 6162 deaths (GLOBOCAN- Bangladesh, 2022,). It is also consistent with cancer registry report of National Institute of Cancer Research & Hospital over a period of 2018 to 2020 (Cancer Registry Report 2018-2020, 2022).

Breast cancer is a heterogeneous and potentially curable disease. It can occur at any age but increasing age is one of the most important risk factors. Additional predisposing factors include family history (nearly 25% of breast cancer cases are related to family history), genetic mutations (specially in high penetrance genes like BRCA1 or BRCA2), early menarche (before 12 years), late age of first pregnancy (three times higher in women who have their firstborn after 30 years), late menopause (after 55 years), use of oral contraceptives or hormone replacement therapy, exposure to radiation at early age, obesity etc (Symonds et al., 2019, p. 401).

The commonest site of breast cancer is the upper outer quadrant (~ 40%) followed by the central area (29%), the upper inner quadrant (14.2%), the lower outer quadrant (8.8%), and the lower inner quadrant (5%) (Halperin et al., 2019). In developed countries at the time of diagnosis, maximum patients usually have localized disease. But in many other parts of the world including in our country, about 60% of patients will present with locally advanced or metastatic disease (Abraham & Gulley, 2022).

Treatment modalities include different types of surgery, chemotherapy, RT depending on histology, stage, age of the patient, performance status, co morbidities etc. As many of our patients present with advanced stage due to lack of mass screening programmes and awareness, MRM is done mostly than breast conservative surgery (BCS) (Rastogi et al., 2017). As significant risk of local recurrence can still remain (Clarke et al., 2005), post mastectomy radiotherapy (PMRT) is essential for most of them to reduce the locoregional recurrence and improve overall survival (OS) (McGale et al., 2014) by eradicating the microscopic reservoirs (DeVita et al., 2022, p. 993).

PMRT is recommended in patients with 4 or more positive axillary lymph nodes (ALN) and should be strongly considered in patients with 1–3 positive ALN. In patients with negative ALN, PMRT can be considered for tumors more than 5 cm or negative pathological margin less than 1mm. It may also be considered for patients with multiple high-risk recurrence factors, including central/medial tumors or tumors ≥2 cm and at least one of the following: grade 3, ER-negative, or lymphovascular invasion LVI (National Comprehensive Cancer Network [NCCN], version 2.2024, p. BINV-3).

RT techniques include two-dimensional (2D) therapy, three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) etc. Though there have been tremendous improvements in technology, still proper dose of radiation cannot be given precisely to the area of interest only. According to the International Commission on Radiation Units (ICRU), "The normal tissues which lie adjacent to tumor & may therefore be included within the treated volume with a risk that the radiation may impair their normal functioning are known as organ at risk (OARs)" (Morris et al., 2024, p. 40). These side effects may be early or late resulting in treatment delay, increased morbidity, poor quality of life (QoL), financial burden to the patient and nation and in many cases- undue mortality.

During Left-breast RT, two of the important OARs are the heart and left lung as they receive incidental doses. Radiation to heart causes circulatory changes by damaging cardiac micro and macro vasculatures resulting in fibrosis (Correa et al., 2007). It ultimately increases the risk of major coronary events (MCE) like myocardial infarction (MI), coronary revascularization or death from ischemic heart disease (Darby et al., 2013). These effects are usually not evident immediately. Latent period ranges from months for subclinical disorders like pericarditis, to decades for clinical diseases like MCE (Sardaro et al., 2012). Preexisting risk factors (hypertension, diabetes mellitus, total cholesterol, family history of early MI, previous cardiotoxic chemotherapy, smoking) increase the absolute risk (Shapiro et al., 1998; Wilson et al., 1998).

A linear relationship has been found between the rate of MCE and Mean Heart Dose (MHD) without any threshold which means no minimum dose with the absence of risk (Hayden et al., 2012). Study reveals 7.4% relative increase in MCE risk for per Gy increase in MHD received (Darby et al., 2013). Cardiac mortality has been estimated as 0.041 Excess Rate Ratio (ERR) per Gy whole heart dose (Taylor et al., 2017).

Pulmonary toxicities also occur from RT which may be clinical or sub clinical. Documented ones are- reduced lung function, radiation pneumonitis (RP), lung fibrosis, lung cancer (Lawler et al., 2017). Pre-existing patient-related risk factors for radiation induced lung disease (RILD) are- older age, history of chronic lung disease, smoking, concurrent chemotherapy with RT etc (Marks et al., 2010). No specific threshold is there for RILD, with risks increasing as dose increases (Halperin et al., 2019).

Course of RP is divided into several phases ranging from immediate phase occurring in hours to days to final fibrosis phase occurring in 6–12 months after RT (Gokula et al., 2013) and related with surfactant producing type II pneumocytes. RP risk increases with mean dose to the lung or irradiated lung volume (Oechsner et al., 2019). Incidence of lung cancer ≥ 10 years after RT 0.11 ERR per Gy whole lung dose (Taylor et al., 2017).

As patients are becoming long survivors, more patients are at risk of late effects (Duarte et al., 2022). Advanced irradiation techniques are being developed to avoid or reduce these. RT with optimisation of beam angles, DIBH technique, using heart lung shielding Multileaf collimators (MLCs), prone positioning, partial breast irradiation (PBI), IMRT, tomotherapy, proton therapy etc are notable (Taylor et al., 2015). Among these, heart lung shielding MLCs are preferable for upper pole breast cancers and may results in underdose to target volume specially when the PTV is located at lower part; prone positioning is more suitable for sparing lungs but heart dose may vary (Varga et al., 2014) due to variable patients' anatomy and the options for PBI are very selective. Very advanced techniques are also not suitable for resource poor setting due to unavailability.

DIBH is a specialized respiratory gating system. Patients are instructed to hold their breath after a deep inspiration for an extended time. This produces a large enough window to treat the tumor with limited motion (Kepka, 2021). An inflated lung pushes the chest wall up and the heart inferiorly and posteriorly away from the treatment field. This results in substantial exclusion of irradiated heart and lung volumes from the high-dose area without compromising PTV coverage (Stranzl et al., 2008). Ultimately, the heart and left lung receive reduced radiation doses as compared to conventional technique (Yeung et al., 2015).

Precise reduction of cardiac and pulmonary doses is critical due to anatomic proximity (Rochet et al., 2014). Surface image-guided RT (SGRT) system along with optical surface imaging (OSI) is a very useful tool for this (Wolf et al., 2023) by which reproducible patient setups as well as reasonably consistent distances between the heart and the chest wall during each breath holds can be achieved (Cerviño et al., 2009). Radiation beam is on only during inspiration and when the patient's current surface is within a preset tolerance of the DIBH reference surface (Macrie et al., 2013). It ensures reliability of the procedure without compromising doses to the target volumes.

Breast Cancer Expert Panel of the German Society for Radiation Oncology (DEGRO) has recommended that MHD should be as low as <2.5 Gy (Piroth et al., 2019). Whereas in conventional tangential left-breast RT, the MHD ranges from 1.7–9.0 Gy (Latty et al., 2014). This is clearly higher than expected safe range. Studies reveal that, it can be reduced upto ~0.7–5.0 Gy by DIBH technique. CT-based studies showed the magnitude of benefit- approximately half of the patients had complete removal of heart from radiation field and 80% had overall reduction in cardiac volumes (Lu et al., 2000).

DIBH is specifically important in PMRT because reducing cardiac dose is more challenging here due to the need of treating much larger surgical bed including scars. Left lung dose reduction has also been reported with DIBH (Vikström et al., 2011). Moreover, by eliminating the breathing motion, treatment uncertainties can be reduced resulting in improved and accurate dose distribution (Rice et al., 2017).

As a whole, DIBH during PMRT is more beneficial for whom cardiac shielding may also shield the PTV resulting in underdosing, cardiac doses likely to exceed safety guidelines, maximum heart depth 1 cm on digital reconstructed radiograph (DRR), patient with established cardiac risk factor (Symonds et al., 2019, p. 417).

The most important issues with DIBH technique are individual patient's anatomical differences (high body mass index- BMI, structural abnormalities, adherence of heart to chest wall) as well as patient's cooperation and reproducibility which often limit the feasibility (Bruzzaniti et al., 2013). Another important aspect is patient-individualized variables like type of surgery, disease stage (especially nodal involvement affecting field size and shape), RT dose regimen (standard or hypofractionated) etc.

From patient's, DIBH method demands proper understanding of the procedure as well as some degree of effort and cooperation to maintain the breathing pattern during simulation and each treatment session (Borst, et al., 2009). For a complete successful RT session with DIBH, determination of patient benefit and capability, as well as optimal positioning, reproducibility and verification methods, are also required.

The main objective of this study is to evaluate dosimetric benefits of the DIBH RT over FB RT during left sided post mastectomy chest wall irradiation.

Rationale of the Study

Due to high prevalence of breast cancer and various awareness programmes, more patients are being diagnosed and treated now with curative intention.

PMRT plays a vital role in treatment plan and is associated with improved overall survival. As a result, these patients are at long-term risk of cardiac and pulmonary sequels which causes undue morbidity and mortality specially in case of left sided breast cancer. The 2005 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) shows, beneficial effects of PMRT are counterbalanced by a 30% increase in cardiac deaths. So, issue of survivorship is a big concern now.

Various treatment modalities are being developed with these concerns ranging from optimisation of beam angles to utilisation of very advanced methods like tomotherapy or proton therapy. Unique irradiation techniques are also being tailored by simple changes in treatment position or set up. Among all these, DIBH technique utilises the patient's own anatomy by reproducible shift of heart from targeted radiation area due to increased volume of left lung in between.

Maximum western studies recommend to adopt this technique for eligible left sided breast cancer patients by proving the efficacy of DIBH RT to reduce heart and left lung doses with better dose delivery to the PTVs. In countries with limited resources, it is important to distribute the available resources accordingly for best treatment outcome. DIBH RT seems to be more effective, practicable and economically feasible compared to other modalities for cardio pulmonary sparing. Thereby, it may help to decrease future disease load and the associated economic burden both for the patients and the nation.

To the best of my knowledge, there is no study comparing target volumes, heart and left lung doses in FB RT and DIBH RT in our population. So, this study will be carried out to compare the dosimetric benefits of the DIBH technique during left sided PMRT over FB RT. This study may help to optimize PMRT approaches.

Research Question

Does deep inspiration breath hold technique in adjuvant radiotherapy for left sided breast cancer reduces doses to the heart and left lung without compromising target volume doses?

Objectives

General Objective:

To compare radiation doses of target volumes, heart and left lung by free breathing technique and deep inspiration breath hold technique in adjuvant radiotherapy for left sided breast cancer.

Specific Objectives:

1. To evaluate target volume doses during adjuvant radiotherapy for left sided breast cancer with free breathing and deep inspiration breath hold technique.
2. To assess cardiac doses during adjuvant radiotherapy for left sided breast cancer with free breathing and deep inspiration breath hold technique.
3. To analyse left lung doses during adjuvant radiotherapy for left sided breast cancer with free breathing and deep inspiration breath hold technique.
4. To demonstrate other organ at risks (right lung, right breast, esophagus, spinal cord) doses during adjuvant radiotherapy for left sided breast cancer with free breathing and deep inspiration breath hold technique.
5. To observe different demographic variables.

Materials & Methods

Study Design

Quasi-Experimental study

Duration of Study

One year after approval from Institutional Review Board (IRB) of BSMMU.

Centres of Study

This study will be conducted in-

1. Department of Clinical Oncology
   Bangabandhu Sheikh Mujib Medical University (BSMMU)
   Shahbagh, Dhaka.

2. Department of Radiation Oncology
   Combined Military Hospital
   CMH road, Dhaka cantonment, Dhaka.

3. Department of Oncology
   Delta Hospital Limited
   26/2, Principal Abul Kashem Road, Mirpur 1, Dhaka - 1216.

4. Lab Aid Cancer Hospital
   26 Green Road, Dhaka.

Study Population

Carcinoma left breast patients attending the outpatient departments (OPD) of study centres for post mastectomy radiotherapy.

Sampling Technique

After meeting inclusion and exclusion criteria, participants will be enrolled in this study and then divided equally into 2 arms by purposive sampling.

Sample Size

For determination of sample size following formula has been applied:

$$n = \frac{2 \times \sigma^2 \times (Z_\alpha + Z_\beta)2}{(\mu_1 - \mu_2)2}$$

n = Sample size

μ_1 = Mean of control group (From previous study)

μ_2 = Mean of experimental group (From previous study)

σ = Standard deviation (SD) of control group

Z_α= Z- value (two tail) at a given level of significance e.g. 1.96 at 5% level of significance

Z_β= Z- value (two tail) at a given power e.g. 1.28 at 90% power

PMRT in free breathing technique is expected to give radiation doses to $V_{25\%}$ of heart in 2.5 (SD 2.4) Gy (Rochet, et al., 2014).

PMRT in DIBH technique is expected to give radiation doses to $V_{25\%}$ of heart in 0.1 (SD 0.2) Gy (Rochet, et al., 2014).

Here,

$\mu_1 = 2.5$ $Z_\alpha = 1.96$

$\mu_2 = 0.1$ $Z_\beta = 1.28$

$\sigma = 2.4$

$n = \frac{2 \times 2.4^2 \times (1.96+1.28)^2}{(2.5-0.1)^2} = 23$

With a 10% allowance for lost to follow up final sample size is 23 + 2.3 = 25

Selection of Patients

Participants will be selected after fulfilment of inclusion and exclusion criteria.

Inclusion Criteria

1. Histopathologically proven left sided invasive breast cancer patients who underwent modified radical mastectomy.
2. Post mastectomy patients for whom radiotherapy including supraclavicular irradiation is indicated.
3. Patients having ECOG performance status up to 1.

Exclusion Criteria

1. Left sided breast cancer patient underwent BCS.
2. Patient received any chemotherapy other than Doxorubicin, Cyclophosphamide and taxane (Paclitaxel/ Docetaxel) in any settings (neoadjuvant or adjuvant).
3. Patients who have comorbidities that would hinder DIBH (extreme obesity, mental disorder, hypoacusis etc.).
4. Known case of patients with respiratory diseases.
5. Known case of patients with ischemic heart diseases.
6. Patients with previous history of radiotherapy to chest.
7. Male breast cancer patients.
8. Bilateral breast cancer patients.
9. Pregnant or lactating women.
10. Age < 18 years.

Criteria of Discontinuation of Treatment

1. Patient's refusal to continue study participation.
2. Justifiable withdrawal at the investigator's discretion.
3. Occurrence of unacceptable issues requiring major modification of treatment.
4. Clear lack of clinical benefit.

Research Instrument

A semi-structured data collection form consisting of sociodemographic information, relevant history, clinical examination and investigations made by the researcher will be used as research instrument **(appendix IV).**

Grouping

Fifty post mastectomy left sided breast cancer patients who meet the inclusion and exclusion criteria will be enrolled in this study. Then they will be divided equally into 2 arms (Arm A and Arm B) by purposive sampling.

Study Procedure

For Arm A participants, CT simulation scans will be performed on a supine breast board by Brilliance, CT Big Bore (Philips, Cleveland, USA) in BSMMU, Biograph mCT Sim edition (Siemens Healthineers AG, Germany) in CMH and Somatom 16 CT (Siemens Healthineers AG, Germany) in other institutes with arms raised above head in supports with free breathing. The board will be angled around 5°-25°, to level participant's chest as horizontal as possible. The head will be extended comfortably with face turned to the right side. Radio-opaque wires will be placed over surgical scars. Skin markers, room laser alignment, and breast-board scale will be used for standard patient positioning. Scans will be acquired with a 4 mm slice width from above the shoulder to include the neck to 5.0 cm below inframammary fold (using right inframammary fold as reference).

For Arm B participants, procedure will be same except the following-

Breath Holding Technique

Participants will be trained for 2-3 days for obtaining the desired breathing cycle by trained technologists. No extra equipment will be needed. At first, they will be assured and asked to relax. Then instructed to breath in and out twice followed by a slow, deep breath in to a comfortable higher level than normal and to hold it for at least 20 seconds then again breath normally. Once they are ready with expected breath holding, simulation will be done.

During this procedure in BSMMU, SGRT system (C-RAD, Uppsala, Sweden) will be used. At the time of simulation with this system, no marker is usually needed on or around the participant; ceiling mounted laser tracking system in the room automatically monitor for consistency by matching with anterior and lateral tattoos.

In CMH, Varian RGSC (Respiratory Gating for Scanners) and in other institutes, Varian RPM^{TM} system (Varian Medical System, Palo Alto, CA) will be used. A 4-dotted reflective marker box will be placed outside the treatment field between xiphoid level and umbilicus. It will act as an external surrogate to simulate the breathing pattern and tracked by the infrared camera at the foot end of CT couch.

For all patients, audio-visual communication through in-room speakers will assist the participant to follow the optimal breathing pattern. Each participant will have 2 CT simulation scans in this arm. One just like participants in Arm A with FB, used as the reference for treatment setups; and another in DIBH position used for the actual treatment plan.

A 30-35 minute in-room time (which included participant's dressing and undressing, set-up, daily imaging, DIBH practice, and subsequent gated RT delivery) was given to each participant for first RT day. For subsequent days, 15–20-minute time was enough, which is double than the allocated time for radiation delivery with FB.

Contouring

For all participants, contouring will be done as per the Radiation Therapy Oncology Group (RTOG) protocol. For left chest wall, superiorly caudal border of the clavicle head, inferiorly loss of CT apparent right breast tissue, laterally mid axillary line excluding latissimus dorsi muscle, medially sternal–rib junction, posteriorly rib–pleural interface, anteriorly skin will be drawn. Nodal area will be contoured including supraclavicular field. For heart, the superior point is where pulmonary trunk and right pulmonary artery seen separately. The major blood vessels will be excluded but the left anterior descending (LAD) artery will be included in the heart contour as a whole. Lungs and other OARs will be contoured accordingly using the planning system.

Treatment Planning and Evaluation

In BSMMU, data acquired by CT scanner and sentinel will be transferred to central database for automatic tracking of same surface points and breathing pattern with a Catalyst™ system in the treatment room during every fraction, without any manual intervention. IMRT planning will be done by Monaco® Treatment Planning Software (TPS) 5.11 (Elekta AB, Stockholm, Sweden) consist of 6 MV tangential beams.

In other institutes, data will be imported to console automatically from RGSC and RPM™ and a treatment gate window will be established. IMRT planning will be done using TPS Eclipse v15.1(Varian Medical Systems, Palo Alto, CA, USA) in CMH and v16.1 in Lab aid.

Plans will be evaluated using dose constraint as MSKCC dosimetric planning guidelines for breast IMRT: for heart- V_{25Gy} <25%, mean dose, D_{mean}<20Gy, maximum dose, D_{max} ≤53 Gy; for lungs- V_{20Gy} ≤ 30%, mean dose, D_{mean} ≤ 22 Gy.

Case Collection

From the OPD of study centres, a total of 50 participants will be recruited after justifying inclusion and exclusion criteria. Before participating in the study, written informed consent will be taken from each selected participant. Interviews will be taken focusing their medical and relevant history by the researcher and will be documented in the preformed data-sheet in respected department with proper privacy. Also, necessary clinical examinations and investigations will be done. Many left sided post mastectomy patients come to these centres regularly for PMRT from all over Bangladesh. Therefore, it will be easy to enrol an adequate number of participants.

Pre-treatment Evaluation

Following procedures will be done to evaluate the participant's condition before treatment:

General examination:

- Complete history, performance status and general physical examination including supraclavicular lymph nodes.

Local examination:

- Right breast examination including draining lymph node areas.
- For left side, chest wall, scar and axilla.

Systemic examination:

- Respiratory system examination.
- Cardiovascular system examination.

Investigations:

- Plain chest radiograph PA view
- ECG
- Echocardiography
- Lung function test

Along with these, all pre surgical imaging and reports will be thoroughly checked.

Intervention

All participants will receive RT with Elekta Versa HD (Elekta AB, Stockholm, Sweden) machine in BSMMU and Varian TrueBeam (Varian Medical Systems, Palo Alto, CA, USA) in other institutes.

Arm A: FB RT arm

Participants will be treated with 40.05 Gy radiation, at 2.67 Gy daily single fraction, 5 days a week, for 3 weeks by IMRT in free breathing technique.

Arm B: DIBH RT arm

Participants will be treated with 40.05 Gy radiation, at 2.67 Gy daily single fraction, 5 days a week, for 3 weeks by IMRT in DIBH technique. As the sentinel (C-RAD, Uppsala, Sweden) and Varian RGSC and RPM^{TM} system (Varian Medical System, Palo Alto, CA) is linked to the corresponding linear accelerator (LINAC), beam-hold will be automatically triggered when participant's breathing falls outside the acceptable range. It will ensure radiation delivery only at deep inspiration.

Variables

Demographic variables:

- Age
- Risk factors
    - Age of menarche
    - Age at first child birth
    - Lactation history
    - Use of oral contraceptive pill

        - Age of menopause
        - Use of hormone replacement therapy
        - Pre-existing hypertension / diabetes mellitus
        - Family history breast cancer or ovarian cancer
    - Educational status
    - Body mass index (BMI)

Clinical variables:

- Involved quadrant of the breast
- Histological variety
- Tumor grade
- Hormone receptor and HER-2 receptor status
- Stage of the disease
- Performance status

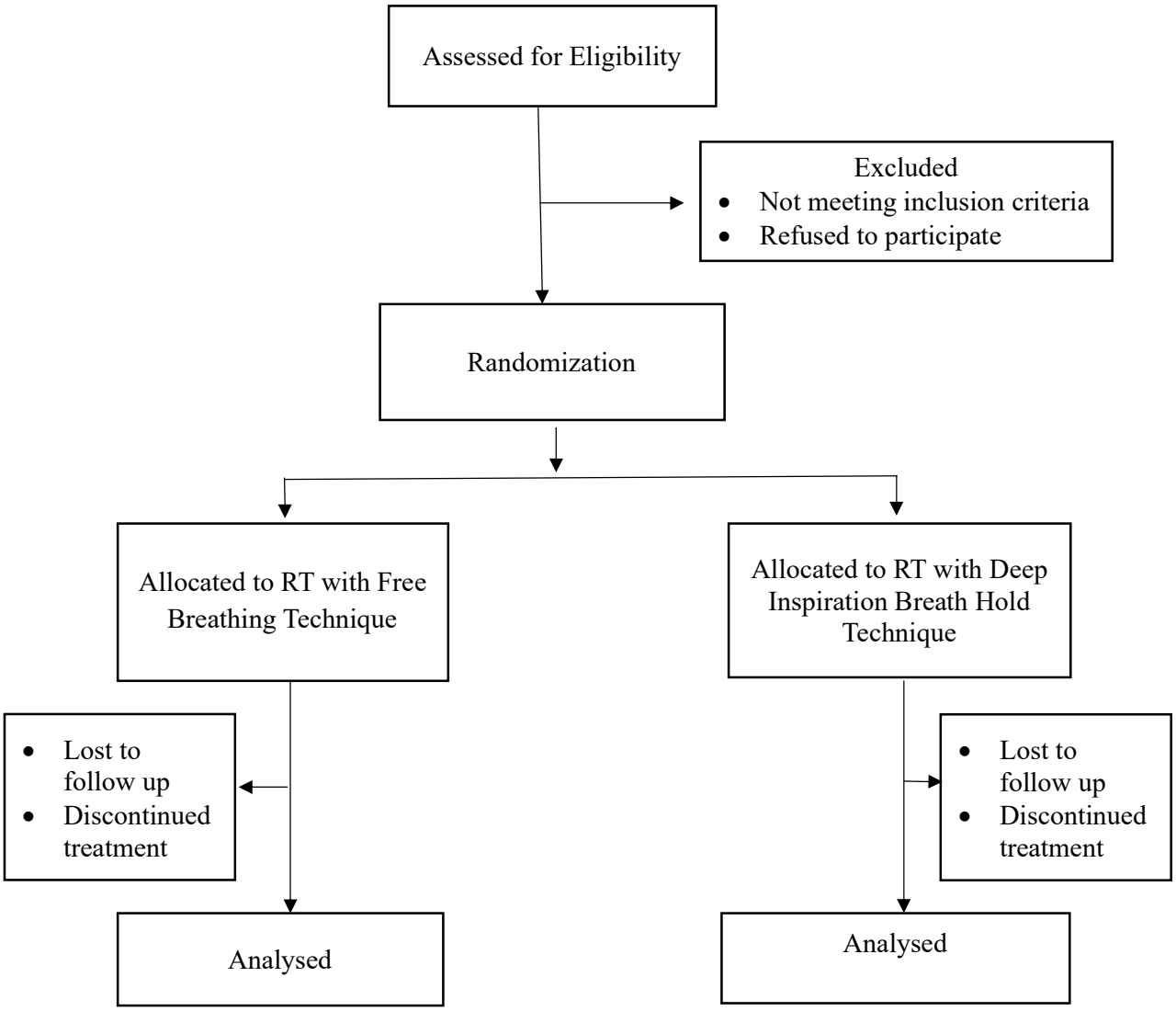
Study variables:

- Planning target volume
    - Total volume
    - Maximum dose, D_{max}
    - Mean dose, D_{mean}
    - V_{95} of PTV
- Heart
    - Mean heart dose, D_{mean}
    - Maximum heart dose, D_{max}
    - V_{25} of heart
- Left lung
    - Mean dose to left lung, D_{mean}
    - V_{20} of left lung

Data Collection

Findings will be recorded in data collection form (**Appendix-IV**).

Consort Flow Chart



Operational Definition

Deep Inspiration Breath Hold Radiotherapy

The approach of delivering prescribed radiation doses only during breath holding at deep inspiration is considered as deep inspiration breath hold radiotherapy.

Dose Volume Histogram

It is a graphical representation of the dose of radiation received by the critical structures or organs at risk per 2cc volume.

Intensity-modulated radiation therapy

It refers to a radiation therapy technique in which a nonuniform fluence is delivered to the patient from any given position of the treatment beam to optimize the composite dose distribution.

Mean dose

Statistical mean dose to the critical structure specified measured using predictive dose calculation algorithm integrated in the treatment planning system.

Maximum dose

Statistical maximum dose to the critical structure specified measured using predictive dose calculation algorithm integrated in the treatment planning system.

Organ At Risk

Normal tissues which lie adjacent to tumours and may therefore be included within treated volumes, with a risk that the radiation may impair their normal functioning.

Performance Status

Performance status refers to the level of activity to which a patient is capable of.

Respiratory Gating

Respiratory gating refers to the process of limiting the radiation beam to selected portions of the respiratory cycle, thus treating the tumor at a specific position.

Surface Guided Radiotherapy System

Surface imaging systems can help facilitate patient setup and allow for intrafraction monitoring without the use of additional ionizing radiation, this is known as Surface-Guided Radiation Therapy.

V_5

Volume of the structure receiving at least 5 Gy dose expressed as percentage of the total volume of that structure.

V_{20}

Volume of the structure receiving at least 20 Gy dose expressed as percentage of the total volume of that structure.

V_{25}

Volume of the structure receiving at least 25 Gy dose expressed as percentage of the total volume of that structure.

$V_{95\%}$

95% volume of the structure receiving the prescribed dose expressed as percentage of the total volume of that structure.

Analysis of Data

The data will be tabulated in separate tables for both Arm-A and Arm-B. It will be checked, edited, coded manually and finally saved in computer. Data analysis will be done according to the objectives of the study by using the SPSS (Statistical Package for Social Science) software program for Windows, version 21.

Data Presentation

Data will be presented using tables, graphs or charts as appropriate.

Quality Assurance

Quality will be ensured during data collection and analysis.

Timetable of the Study

	Month											
Activities	1	2	3	4	5	6	7	8	9	10	11	12
Approach to problem and designing and protocol submission	■											
Preparation of data collection sheet, pretesting and finalizing		■	■									
Data collection				■	■	■	■	■	■			
Data entry and analysis										■	■	
Report writing and submission											■	
Correction and final submission												■

Ethical Consideration

Ethical issues related to this study will be maintained carefully. In this study, following criteria will be ensured to maintain the ethical standard-

- All participants will be given an explanation of the study including the risks and benefits.
- All participants will be included in the study after taking their informed consent.
- Informed consent form will be supplied in Bengali & English versions.
- It will also be explained to them that they have the right to refuse or accept to participate in the study.
- All data obtained during the study period from the participant will remain confidential.
- Permission will be taken by the institutional review board of BSMMU.

Dummy Tables

Table 1: Distribution of participants by age in Arm A and Arm B

Age of the patients (years)	Arm A (n=25)		Arm B (n=25)		p value**
	n	%	n	%	
18-29					
30-39					
40-49					
50-59					

Table 2: Cardiac dose in Arm A and Arm B

Doses (in Gy)	Arm A (n=25)	Arm B (n=25)	p value**
D_{mean}			
D_{max}			
V_{25}			

** p value from Chi square test

S = Significant

Limitations of the Study

- Different study centres use different radiotherapy machine and treatment protocol.
- Existing risk factors are not adjusted for participants.

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Budget

A. Expenditure:

1. Papers and other stationeries			25,000 TK
2. Phone and networking bill			25,000 TK
3. Travel cost			25,000 TK
4. Data analysis			30,000 TK
5. Compose and printing			30,000 TK
6. Investigations			
i Chest xray PA view	(50×500)	=	25,000 TK
ii Lung function test	(50×2500)	=	1,25,000 TK
iii ECG	(50×300)	=	15,000 TK
iv Echocardiography	(50×2000)	=	1,00,000 TK
Total			4,00,000 TK

Total budget: Four lakh taka only

B. Funding:

1. Investigator
2. BSMMU

N. Tan

Signature of investigator

R. Sultana

Signature of guide

Dr. Most. Rokaya Sultana
MBBS, MD (Oncology)
Associate Professor
Dept. of Clinical Oncology
Bangabandhu Sheikh Mujib Medical University

APPENDIX - I
অবহিতক্রমে সম্মতিপত্র

এই সম্মতিপত্রের উদ্দেশ্য হল আপনাকে প্রয়োজনীয় তথ্য প্রদান করা যে তথ্যগুলো আপনাকে সিদ্ধান্ত নিতে সাহায্য করবে, আপনি এই গবেষণায় অংশগ্রহণ করবেন কিনা।

গবেষণার নামঃ Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung.

প্রধান গবেষকঃ ডাঃ নিশাত তাসনীম

উদ্দেশ্য ও প্রস্তুতিঃ
বাংলাদেশে স্তন ক্যান্সার একটি উল্লেখযোগ্য ক্যান্সার। স্তন ক্যান্সারের বিভিন্ন চিকিৎসা পদ্ধতি রয়েছে, যা রোগের বিভিন্ন ধাপ অনুযায়ী বিভিন্ন রকম হয়। এ রোগের চিকিৎসার একটি অন্যতম উপায় হচ্ছে রেডিওথেরাপি। রেডিওথেরাপি চলাকালীন সময় এবং চিকিৎসা পরবর্তী সময়েও বিভিন্ন পার্শ্বপ্রতিক্রিয়া দেখা যায়। চিকিৎসা পরবর্তী এসব পার্শ্বপ্রতিক্রিয়ার মাঝে হার্ট এবং ফুস্‌ফুসের সমস্যা অন্যতম বিশেষত বাম স্তনের রেডিওথেরাপি পাওয়ার পর। যার জন্য ক্যান্সার আক্রান্ত রোগীরা ক্যান্সার থেকে মুক্ত হলেও পরবর্তীতে হার্ট এটাক এবং ফুস্‌ফুসের সমস্যার বাড়তি ঝুঁকিতে পড়ে যায়। বিশ্বব্যপী বিভিন্ন গবেষণাতে দেখা গিয়েছে, যদি লম্বা করে দম নিয়ে পর্যাপ্ত সময় দম বন্ধ রাখা অবস্থায় রেডিওথেরাপি নেয়া হয়, তাহলে যেখানে রেডিথেরাপি পাওয়ার কথা সেখানেও পর্যাপ্ত ডোজ পড়ে আবার হৃৎপিন্ড এবং ফুস্‌ফুস ও রেডিয়েশন কম পায় যার ফলে পরবর্তীতে হার্ট এটাক এবং ফুস্‌ফুসের সমস্যার বাড়তি ঝুঁকি এড়ানো অনেকাংশেই সম্ভব হয়। এই গবেষণায় আপনার রেডিওথেরাপি চলাকালীন সময়ে লম্বা করে দম নিয়ে পর্যাপ্ত সময় দম বন্ধ রেখে বুকের, হৃৎপিন্ড এবং ফুস্‌ফুসের রেডিয়েশন ডোজ মেপে এই বিশেষ পদ্ধতিটির উপযোগিতা ও কার্যকারিতা দেখা হবে, যা এই গবেষণার মূল উদ্দেশ্য।

গবেষণার ঝুকিঃ
এই গবেষণায় অংশগ্রহণে আপনি খুবই সামান্য ঝুঁকির সম্মুখীন হতে পারেন। সমস্যা দেখা দিলে তা প্রশিক্ষণপ্রাপ্ত চিকিৎসকের মাধ্যমে নিয়ন্ত্রণ এবং সমাধান করা হবে।

গবেষণায় অংশগ্রহণের সুবিধাদিঃ
এই গবেষণায় অংশগ্রহণ করলে আপনি ব্যক্তিগতভাবে তেমন লাভবান না হলেও, উক্ত গবেষণা ক্যান্সারের চিকিৎসা পদ্ধতি সম্পর্কে আরও জানতে এবং অন্যান্য রোগীদেরকেও উন্নত চিকিৎসা দিতে সাহায্য করবে।

বিকল্পঃ
এই গবেষণায় অংশগ্রহণ করা কিংবা না করার বিষয়ে আপনার সিদ্ধান্তই চূড়ান্ত। অংশগ্রহণ করার পর যে কোন সময়ে আপনি নিজেকে এই গবেষণা থেকে সরিয়ে নিতে পারেন।

গোপনীয়তাঃ
গবেষণা চলাকালীন ও পরবর্তীতে সকল তথ্য কঠোর ভাবে গোপন রাখা হবে। আপনার আই ডি নম্বর সম্বলিত সব ধরনের কাগজপত্রে আপনার নাম ও ঠিকানা বসিয়ে গোপনীয়তার সাথে রাখা হবে এবং আপনার ব্যক্তিগত বিষয়াদি তথ্য বিশ্লেষণ, প্রতিবেদন তৈরিতে বা কোন প্রকাশনার কাজে ব্যবহৃত হবে না এবং গবেষণার পরীক্ষক ব্যতীত কারো কাছে প্রকাশ করা হবে না।

খরচঃ
এই গবেষণায় অংশগ্রহণের জন্য আপনার গতানুগতিক চিকিৎসার বাইরে কোন অতিরিক্ত খরচ করতে হবে না বা আপনাকে কোন অর্থ প্রদান করা হবে না।

গবেষণাকারীর দায়িত্বঃ
এই গবেষণায় অংশগ্রহণের ফলে আপনি অসুস্থ হলে গবেষণাকারী আপনার উপযুক্ত চিকিৎসার ব্যবস্থা করবে।

স্বেচ্ছামূলক অংশগ্রহণঃ
এই গবেষণায় আপনার অংশগ্রহণ স্বেচ্ছামূলক। আপনি গবেষণায় অংশগ্রহণে অস্বীকৃতি জানাতে পারেন অথবা গবেষণা চলাকালীন যে কোন সময়ে গবেষণা থেকে নিজেকে প্রত্যাহার করে নিতে পারেন। এর ফলে এই হাসপাতালে আপনার চিকিৎসায় কোন প্রভাব পরবে না। এই ফর্মে স্বাক্ষর করলে আপনার কোন আইনগত অধিকার খর্ব হবে না।

প্রশ্নাবলীঃ
যদি আপনার কোন প্রশ্ন থাকে তবে দয়া করে জিজ্ঞাসা করুন। আমরা তার উত্তর প্রদান করার যথাসাধ্য চেষ্টা করব। যদি ভবিষ্যতে আপনার অতিরিক্ত কোন প্রশ্ন থাকে, তবে গবেষণারত ডাক্তারের সাথে যোগাযোগ করতে পারবেন।

সম্মতির স্বীকারোক্তিঃ
আমি গবেষণায় নিয়োজিত চিকিৎসকের সাথে এই গবেষণা নিয়ে আলোচনায় সন্তুষ্টি প্রকাশ করছি। আমি এটা বুঝেছি যে গবেষণায় অংশগ্রহণ স্বেচ্ছামূলক এবং আমি যে কোন সময় কোন বাধ্যবাধকতা ছাড়াই গবেষণা থেকে নিজেকে বিরত রাখতে পারি। আমি উপোরোক্ত শর্তগুলো পড়েছি / আমার সম্মুখে পঠিত হয়েছে এবং স্বেচ্ছায় গবেষণায় অংশগ্রহণ করতে সম্মতি জ্ঞাপন করছি।

.....	.....	.....	.....
ডা: নিশাত তাসনীম	স্বাক্ষর / বৃদ্ধাঙ্গুলীর ছাপ	স্বাক্ষর / বৃদ্ধাঙ্গুলীর ছাপ	স্বাক্ষর / বৃদ্ধাঙ্গুলীর ছাপ
প্রধান গবেষক	স্বাক্ষীর নাম:	স্বাক্ষীর নাম:	অংশগ্রহণকারী নাম:
মোবাইল নং-			মোবাইল নং:
			কোড নং:

APPENDIX - II
Informed Written Consent

The purpose of this consent form is to provide you with the necessary information, which will help you decide to participate in the following research.

Name of the Study: Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung.

Name of the Investigator: Dr. Nishat Tasnim

Purpose of the Study:

Breast cancer is a leading cancer among Bangladeshi female. For breast cancer, there are different available treatment options according to the stage of disease. One of the important ones is radiotherapy (RT). Various side effects can occur during and after RT. Among the late side effects, numerous cardiac and pulmonary problems are significant specially in case of left sided breast cancer. In such cases, patients are being cured from cancer but the treatment itself endangering patients' general health and well-being by increasing risk of future life threatening cardiac and pulmonary diseases. Studies from around the world have shown that, during RT of left sided breast cancer, holding the breath for certain time after deep inspiration can reduce the radiation doses to heart and left lung without compromising doses to the chest wall. As a result, they can avoid the extra risk of treatment related late toxicities. This study will look at the utility and efficacy of DIBH RT over free breathing RT in reducing the heart and left lung doses without compromising the dose to the target volumes in left sided post mastectomy breast cancer patient, which is the main objective of this study.

Participating in the Study:

Your participation in the proposed study is voluntary. Your decision to participate as well as to withdraw from the study at any time without any reason after participating in the study is final. Signing this form does not waive any of your legal rights.

Obligation to Participate:

Non-participation or subsequent withdrawal from the proposed research program will not affect your treatment at this hospital.

Risk and Benefit:

By participating in the study, you may not be benefitted personally but it will help to know more precisely about better delivery of radiotherapy to other patients. Like other treatments, it has some side effects. Necessary measures will be taken to avoid or minimize complications. Even if there is any, it will be treated by trained physician.

Protection of the Confidentiality of Information:

All information will be kept strictly confidential during and after the research. Your name and address will be omitted on all documents rather an ID number will be used. All necessary information will be verified, analysed and if necessary, can be used for report preparation and publication, but your personal information, name, identity, address will not be mentioned anywhere.

Cost and Responsibilities of the Investigator:

Participation in this research program will not cost you anything or provide you with any financial or other benefits. But if you become ill while participating in this research program, the researcher will provide you with appropriate treatment.

Questions and Answers:

If you have any questions, please ask. We will try our best to answer it. If you have additional questions in the future, you can contact the researcher.

Declaration of Consent:

I have discussed this study in detail with the doctor and express my satisfaction. I understand that participation in the study is voluntary and that I may withdraw from the study at any time without obligation. I have read the above conditions / have been read in front of me and agree to participate in the study voluntarily.

……	.....	.....	.....
Dr. Nishat Tasnim	Sign / Finger print	Sign / Finger print	Sign / Finger print
Chief Investigator			
Mobile no:	Witness:	Witness:	Name of Participant
			Mobile no:

APPENDIX - III

Face-sheet

ID no -

Reg. No :

Participant's name :

Father's/Husband's name :

Mother's name :

Mobile No. :

Address :

APPENDIX – IV

Data Collection Sheet

Title of the Study:

Free Breathing versus Deep Inspiration Breath Hold Technique in Adjuvant Radiotherapy for Left Sided Breast Cancer: A Dosimetric Comparison of Target Volumes, Heart and Left Lung

Principal investigator: Dr. Nishat Tasnim

Section A: Participants Personal Information ID No:

S.N.	Questions	Options	Code	Skip
01.	What is your age?	☐☐ years		
02.	What is your religion?	Islam -1 Hinduism-2 Christianism-3 Buddhism-4 Others-0		
03.	What is your educational status?	Illiterate-1 Below primary-2 Above primary up to SSC-3 HSC-4 Graduate-5 Post graduate-6 Others-0		
04.	What is your Occupation?	Student-1 Housewife-2 Service holder-3 Business-4 Others-0		
05.	Age at menarche	☐☐ Years		

06.	What is your marital status?	Unmarried-1 Married-2 Widowed-3 Separated-4		For code 1 skip question No.6
07.	Age at marriage?	☐☐ years		
08.	Age at 1st pregnancy?	☐☐ years		
09.	Did you breastfeed your children?	Yes-1 No-2		
10.	Are you menopausal?	Yes-1 No-2		For code 2 skip question No.09
11.	Age at menopause?	☐☐ years		
12.	Do you have any history of using OCP?	Yes-1 No-2		For code 2 skip question No.11
13.	Duration of using OCP	☐☐ years		
14.	Do you have any history of using HRT?	Yes-1 No-2		For code 2 skip question No.13
15.	Duration of using HRT	☐☐ years		
16.	Do you have any family history of cancer? (mention if any)			
17.	Comorbidity (if any)			

সেকশন-এ: অংশগ্রহনকারীর ব্যাক্তিগত তথ্যসমূহ আইডি:

নং	প্রশ্ন	উত্তর	কোড	বাদ
১.	আপনার বয়স কত?	☐☐ বৎসর		
২.	আপনি কোন ধর্মের অনুসারী?	ইসলাম-১ হিন্দু-২ খ্রিষ্টান-৩ বৌদ্ধ-৪ অন্যান্য-0		
৩.	আপনার শিক্ষাগত যোগ্যতা কি?	অশিক্ষিত-১ প্রাথমিক পর্যন্ত-২ প্রাথমিক থেকে এসএসসি পর্যন্ত -৩ এইচএস সি -৪ গ্র্যাজুয়েট -৫ পোস্ট গ্র্যাজুয়েট-৬ অন্যান্য -0		
৪.	আপনার পেশা কি?	ছাত্র/ছাত্রী-১ গৃহিনী-২ চাকুরিজীবি-৩ ব্যবসায়ী-৪ অন্যান্য -0		
৫.	কত বছর বয়স থেকে আপনার রজ:ক্রিয়া শুরু হয়েছিল?	☐☐ বৎসর		
৬.	আপনার বৈবাহিক অবস্থা কি?	অবিবাহিত-১ বিবাহিত-২ বিধবা -৩ বিবাহবিচ্ছেদ-৪		কোড ১ এর জন্য ৭ নং প্রশ্ন বাদ
৭.	বিবাহ কালে আপনার বয়স কত ছিল?	☐☐ বৎসর		

৮.	প্রথম সন্তান জন্মের সময় আপনার বয়স কত ছিল?	☐☐ বৎসর		
৯.	আপনি কি আপনার বাচ্চাকে বুকের দুধ খাইয়েছিলেন?	হ্যা ১ না ২		
১০.	আপনার কি মাসিক একেবারে বন্ধ হয়ে গেছে?	হ্যা ১ না ২		কোড ২ এর জন্য ১১ নং প্রশ্ন বাদ
১১.	কত বছর থেকে মাসিক বন্ধ আছে?	☐☐ বৎসর		
১২.	আপনি কি জন্ম বিরতিকরণ পিল খেয়েছেন কখনো?	হ্যা ১ না ২		কোড ২ এর জন্য ১৩ নং প্রশ্ন বাদ
১৩.	আপনি কতদিন জন্ম বিরতিকরণ পিল খেয়েছেন	☐☐ বৎসর		
১৪.	মাসিক বন্ধ হওয়ার পরে কোনো হরমোনের ট্যাবলেট খেয়েছেন?	হ্যা ১ না ২		কোড ২ এর জন্য ১৫ নং প্রশ্ন বাদ
১৫.	আপনি কতদিন হরমোনের ট্যাবলেট খেয়েছেন	☐☐ বৎসর		
১৬.	জানামতে পরিবারের কারো কোন ক্যান্সার রোগ ছিল কি না? (থাকলে বিবরণ)			
১৭.	আপনার ডায়াবেটিস, উচ্চরক্তচাপ, কিডনী বা অন্যান্য দীর্ঘমেয়াদী সমস্যা আছে কিনা? থাকলে কোনটি?			

Section B: Clinical Examination Findings ID No:

i. General and Local Examination:

Serial No	General examination	Option	Code
01.	Performance status	☐	
02.	Body-weight (in kg)	☐☐	
03.	Height (in cm)	☐☐☐	
04.	Body mass index (in kg/m^2)	☐ kg/m^2	
05.	Anemia	Yes-1 No-2	☐
06.	Jaundice	Yes-1 No-2	☐
07.	Edema	Yes-1 No-2	☐
08.	Dehydration	Yes-1 No-2	☐
09.	Palpable lymph node (if yes, mention site)	Yes-1 No-2	☐
10.	Body temperature		
11.	Breast examination		
12.	Others		

ii. Systemic Examination:

01. Respiratory system examination

02. Cardiovascular system examination

Section C: Findings of Investigations ID No.

i. Imaging Test

- Chest xray PA view
- ECG
- Echocardiography
- Lung function test

ii. Histopathological Examination:

- Tumor size
- Nodal involvement
- Histopathological variety
- Grade

iii. Immunohistochemistry:

- Estrogen receptor, ER
- Progesterone receptor, PR
- HER-2 receptor

Section D: Previous Treatment ID No:

- Chemotherapy: □ Neoadjuvant □ Adjuvant
- Regimen of chemotherapy with doses:

- Number of cycles:
- Date of completion:
- Date of surgery:
- Duration from surgery or chemotherapy: (whichever is shorter)

Section E: Treatment Delivery ID No:

Technique of Irradiation	Arm	Code
IMRT with FB technique	Arm A =1	
IMRT With DIBH technique	Arm B = 2	

Section F: Radiation Doses ID No:

- Planning target volume
  - Total volume
  - Maximum dose, D_{max}
  - Mean dose, D_{mean}
  - V_{95} of PTV
- Heart
  - Mean heart dose, D_{mean}
  - Maximum heart dose, D_{max}
  - V_{25} of heart
- Left lung
  - Mean dose to left lung, D_{mean}
  - V_{20} of left lung

APPENDIX-V

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

0	: Normal activity; asymptomatic
1	: Symptomatic; fully ambulatory
2	: Symptomatic; in bed < 50% of time
3	: Symptomatic; in bed > 50% of time; bedridden
4	: 100% bedridden
5	: Dead

APPENDIX- VI

UICC/AJCC TNM Staging for Breast Cancer- 8th edition, 2017

Primary Tumor (T)

Tx Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis (DCIS) Ductal carcinoma in situ

Tis (Paget) Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma

T1 Tumor ≤20 mm in greatest dimension

- **T1mi** Tumor ≤1 mm in greatest dimension
- **T1a** Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm)
- **T1b** Tumor >5 mm but ≤10 mm in greatest dimension
- **T1c** Tumor >10 mm but ≤20 mm in greatest dimension

T2 Tumor >20 mm but ≤50 mm in greatest dimension

T3 Tumor >50 mm in greatest dimension

T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules) *

- **T4a** Extension to the chest wall **
- **T4b** Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
- **T4c** Both T4a and T4b are present
- **T4d** Inflammatory carcinoma

* Invasion of the dermis alone does not qualify as T4.

** Invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4.

Regional Lymph Nodes- Clinical (cN)

cNx* Regional lymph nodes cannot be assessed (e.g., previously removed)

cN0 No regional lymph node metastases (by imaging or clinical examination)

cN1 Metastases to movable ipsilateral Level I, II axillary lymph node(s)

- **cN1mi**** Micro metastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)

cN2 Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases

- **cN2a** Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
- **cN2b** Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases

cN3 Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

- **cN3a** Metastases in ipsilateral infraclavicular lymph node(s)
- **cN3b** Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
- **cN3c** Metastases in ipsilateral supraclavicular lymph node(s)

* The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.

** cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Regional Lymph Nodes- Pathological (pN)

pNx Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)

pN0 No regional lymph node metastasis identified or ITCs only

pN0(i+) ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)

pN0(mol+) Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected

pN1 Micro metastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micro metastases or macro metastases by sentinel lymph node biopsy

pN1mi Micro metastases (approximately 200 cells, larger than 0.2 mm but none larger than 2.0 mm)

pN1a Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm

pN1b Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs

pN1c pN1a and pN1b combined

pN2 Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases

pN2a Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)

pN2b Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes

pN3 Metastases in –

pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (Level III axillary lymph) nodes

pN3b pN1a or pN2a (positive Level I, II axillary lymph nodes) in the presence of cN2b (positive internal mammary nodes by imaging); or pN2a in the presence of pN1b (more than three axillary lymph nodes and micro/macro-metastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes)

pN3c Metastases in ipsilateral supraclavicular lymph nodes

Distant Metastasis (M)

M0 No clinical or radiographic evidence of distant metastases*

cM0(i+) No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases

cM1 Distant metastases detected by clinical and radiographic means

pM1 Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

* Note that imaging studies are not required to assign the cM0 category

Stage/Prognostic Grouping

Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T0-1 N1mi M0
Stage IIA	T0-1 N1 M0; T2 N0 M0
Stage IIB	T2 N1 M0; T3 N0 M0
Stage IIIA	T0-3 N2 M0
Stage IIIB	T4 N0-2 M0
Stage IIIC	Any T N3 M0
Stage IV	Any T Any N M1

APPENDIX- VII

Percentage points or critical values of standard normal distribution (Z-distribution or Z table or Z_α table)

P-Value or level of significance(α)	Confidence level	Percentage point	
		One tail	Two tail
0.5(50%)		0.00	0.67
0.4(40%)		0.25	0.84
0.3(30%)		0.52	1.04
0.2(20%)	80% C. Level	0.84	1.28
0.1(10%)	90% C. Level	1.28	1.64
0.05(5%)	95% C. Level	1.64	1.96
0.02(2%)	98% C Level	2.05	2.33
0.01(1%)	99% C Level	2.33	2.58
0.005(0.5%)	99.5% C Level	2.58	2.81
0.002(0.2%)	99.7% C Level	2.88	3.09
0.001(0.1%)	99.9% C Level	3.09	3.29
0.0001(0.01%)	99.99% C Level	3.72	3.89

APPENDIX- VIII

Critical Values (Z_β) of Standard Normal Distribution (Z-Distribution) at Different Power

Power	B (Type-II error)	Z_β
0.70	0.30	0.52
0.80	0.20	0.84(0.85)
0.90	0.10	1.28
0.95	0.05	1.64
0.99	0.01	2.33

APPENDIX – XI

HELSINKI DECLARATION:

Clinical trial involving human subjects-to indicate whether the procedures followed were in accordance with the ethical standard of responsible committee or with the Helsinki declaration of 1975, as revised in 2013.

1. Direct student should not be included in the clinical trial / research.
2. Children should not be included (unless benefit will be obtained by the children).
3. Prisoners, pregnant women and acutely ill patients should not be included.
4. Patients should not be deprived of their basic human right.
5. Patient's name, initials or hospital numbers should not be used.
6. Informed written consent of the patient should be taken after explaining the objective, risk and benefit of the experiment.
7. No incentive cash or kind for healthy volunteer should be allowed.