



**DISEASE CONTROL AFTER DELAYED ADJUVANT RADIOTHERAPY
AMONG LOCALLY ADVANCED BREAST CANCER PATIENTS TREATED
AFTER ONE YEAR MASTECTOMY AT TIKUR ANBESSA SPECIALIZED
HOSPITAL IN 2016 GC**

**A thesis submitted to AAU, CHS, in Partial Fulfillment of Specialty Certificate in Clinical
Oncology**

Principal Investigator - Dr. Ephrem Tafesse

Advisor - Dr. Edom Seife (Consultant oncologist, Assistance Professor of Medicine, AAU)

Dr. Eva Johanna Kantelhardt

SEPTEMBER 2020

ADDIS ABABA, ETHIOPIA

Abstract

Introduction – Nearly more than half of post mastectomy patient needs adjuvant radiotherapy. Adjuvant radiotherapy should be given according to clinical recommended indication, dose and time to reduce risk of loco-regional tumor recurrence. Most post mastectomy patients do not get adjuvant radiotherapy due to long radiotherapy waiting time at the centers. Delayed initiation of adjuvant radiotherapy associated with increased risk of tumor recurrence. Radiotherapy waiting time at TASH oncology center is unknown and expected to be more than a year. All high risk post mastectomy patients will be registered and wait for adjuvant radiotherapy. Benefit of giving delayed adjuvant chest wall irradiation is unknown. Despite our routine clinical practice, such treatment delay should be evaluated.

Objective – The main objective of study was to assess the clinical benefit of delayed adjuvant radiotherapy delivery after 1 year of post mastectomy.

Methods – Institutional based retrospective cross-sectional used to assess tumor control rate among post mastectomy breast cancer patients registered at TASH radiotherapy center for the indication of adjuvant chest wall irradiation.

Result- In 2016 at TASH radiotherapy center, total of 274 high risk post mastectomy patients had registered for adjuvant chest wall irradiation. At 1 year of post mastectomy, among radiotherapy registered 67.5%(185) patients had stable disease. Nearly 38.6% (106) patients did not take adjuvant radiotherapy and 28.8% (79) patients had took sequentially adjuvant chemotherapy and radiotherapy. The mean radiotherapy waiting time was 8.8 ± 1.4 months. Among those who took delayed adjuvant radiotherapy, the mean post mastectomy adjuvant radiotherapy delivery time was 10.4 ± 1.9 months. At 4 years follow up, 62.7%(116) patients are alive, 27.6%(52) had died and 9.7%(17) had unknown status. Tumor recurrence confirmed in 28.6% (53) patients. Among sub-groups, 34.1% (27) and 24.5% (26) patients had tumor recurrence among those who took and did not take delayed adjuvant radiotherapy respectively. Adjuvant radiotherapy was not found to be association with tumor control (COR=1.5, 95% CI=0.83-3.03, P=0.16). On multivariate analysis only advanced nodal tumor showed statically significant for tumor recurrence. N2 and N3 stage patients were found to be 3.8 and 4.3 times more

likely to develop recurrence as compared to Nx& N1 patients respectively (AOR, 3.86, CI 1.72-8.65, AOR 4.34, CI 1.54-12.26)

Conclusion- Delayed adjuvant radiotherapy after median 10.4 months of post mastectomy did not associate with improved tumor control. According to our finding, most unnecessary delivery of delayed adjuvant radiotherapy can be omitted and delayed adjuvant chest wall irradiation should be given among patients having one of those poor prognostic factors age less than 55 years or advanced nodal tumor disease (N2 and N3).

Recommendations– Radiotherapy waiting time at TASH oncology center can be improved through avoiding unnecessary delayed radiotherapy delivery among breast cancer patients. since TASH oncology center is the only center having single cobalt-60 machines for the whole country, the available energy source should be used effectively and efficiently without compromising treatment quality.

Key words- Waiting time, delayed adjuvant radiotherapy, Post mastectomy patients.

Acknowledgements

I would like to thank my Advisor Dr. Edom Seife, a consultant oncologist at AAU, for her continuous advice and support during my study period and also I would like to give my deep gratitude to Dr. Wondimagegnehu Tigeneh, a senior consultant oncologist at AAU for his unconditional advice starting from proposal draft. I would like to give my special thanks to Dr. Eva Johannakantelhardt and Dr. Ahmedin Jamal for their valuable comments and the financial support to complete my project.

Acronyms

BC	Breast Cancer
BCS	Breast Conserving Surgery
Co-60	Cobalt 60
DR	Disease Recurrence
DTCDistant Site Tumor control	
EUROCHIP	European Cancer Health Indicator Project
GLOBOCAN	Global Cancer statistics
IBCSG	International Breast Cancer Study Group
LMIC	Low- and Middle-Income Country
LRC	Loco Regional Control
LVI	Lympho-Vascular Invasion
PMRT	Post Mastectomy Adjuvant Radiotherapy
OS	Overall Survival
COR	CrudesOdds Ratio
RT	Radiation Therapy
SSA	Sub-Saharan Africa
SEER	Surveillance, Epidemiology and End Results
TASH	Tikur Anbessa Specialized Hospital
WHO	World Health Organization

List of Tables and Figures

Table.1.Socio-demographic characteristic of post mastectomy adjuvant radiotherapy registered patient.....	14
Table.2. High risk Pathologic features among adjuvant radiotherapy registered patients.....	16
Table.3.Prognostic factors associated with tumor recurrenceamong locally advanced breast cancer patients.....	21
Table.4. Site and frequency of tumor Recurrence among locally advanced breast cancer patients who took and did not took delayed adjuvant radiotherapy.....	22
Figure.1. Types of adjuvant treatment delivery among registered and treated patients at TASH, Radiotherapy center.	17
Figure.2.Patient condition at 4 years of post-mastectomy.....	18
Figure.3.Post mastectomy disease control at 4 years among registered patients.....	19
Figure.4.Time and frequency of tumor recurrence among whotook and did not take delayed adjuvantradiotherapy and omitted groups.....	22

Contents

Abstract.....	ii
Acknowledgements.....	iv
Acronyms.....	v
List of Tables and Figures.....	vi
CHAPTER-ONE.....	1
1.1 Introduction.....	1
1.2 Statement of the problem	3
CHAPTER -TWO.....	5
Literature review	5
CHAPTER-THREE	8
3.1 General Objective	8
3.2 Specific objectives	8
CHAPTER- FOUR:	9
4. Methodology	9
4.1 Study setting.....	9
4.2 Study design.....	9
4.3 Source and Study Population	10
4.4 Inclusion and exclusion criteria	10
4.5 Sample size determination	10
4.6. Study variables.....	11
4.7. Definition of terms	11
4.8. Operational definitions:.....	11
4.9. Data collection procedures.....	12
4.10. Data processing and Analysis	12
4.11. Ethics and Human Subjects consideration	12
CHAPTER-FIVE	13

Result	13
5.1 Socio demographic Characteristics of adjuvant radiotherapy registered patients.....	13
5.2 Pathologic features among adjuvant radiotherapy registered patients	14
5.3. Adjuvant treatment delivery among adjuvant radiotherapy registered patients.....	17
5.4. Radiotherapy waiting time	17
5.5. Current patient condition among adjuvant radiotherapy registered patients.....	18
5.6. Tumor control rate among radiotherapy registered patients	18
5.7. Clinico- Pathologic factors associated with tumor recurrence after 1 year of post mastectomy	19
5.6. Effect of delayed adjuvant radiotherapy and time of tumor recurrence.....	21
CHAPTER - SIX.....	23
Discussion	23
CHAPTER-7	29
7.1 Strength and weakness of the study	29
7.2 Conclusion	30
7.3 Recommendations.....	30
References.....	32
Annex.....	38

CHAPTER-ONE

1.1 Introduction

Cancer is becoming one of the major health related problem among all nations. Previously cancer was considered as problem of developed nations and less attention was given among developing countries. Despite most cancers are being detected among western population, risk of life time cancer developing is increasing among developing countries due to changes in socio-economic and living style. Recent epidemiologic data showed that cancer related morbidity and mortality is increasing rapidly among developing countries. According to the 2018 global cancer reports, there were about 18.1 million new cancers were detected globally and 9.6 million cancer related deaths had occurred at the same year. Among all cancer incidences, lung cancer is the commonest cancer diagnosed accounting 11.6% followed by breast (11.6%), prostate (7.1%) and colorectal cancer (6.1%) respectively (1)

Breast cancer is the leading cancer diagnosed among females and incidence is increasing globally. According to the global burden of cancer estimations, by the year of 2030, there will be 26 million new cancer cases and 17 million cancers related deaths expected to occur globally and among the sub Saharan region nearly about 1.28 million new cancer cases and 970,000 cancer deaths are expected to occur (2). Even though, breast cancer is considered to be the fifth commonest cause of cancer related death, due to poor cancer registry and reporting system among developing countries the exact figure of breast cancer is unknown. The estimated incidence of breast cancer among different countries ranges from 19.4 in East Africa to 89.7 per 100,000 among western population (3). Incidence among developing country is generally increasing, according to epidemiological data in 2012, among 1.7 million breast cancer cases where diagnosed globally and majority of cases (56.8%) had occurred among low and middle income countries (3,4)

Breast cancer survival has improved significantly over the past 30 years due to early breast cancer detection and multi-modality treatment approach including surgery, radiation therapy and systemic treatments. Clinically stage of tumor at time of diagnosis is a major determinant factor to patients' survival where early-stage associated with better prognosis than late-stage presentation

despite delayed treatment initiation with increased relative risk of local failure of 1.16% for curative intent for adjuvant radiation delay. Although no impact on distant metastatic or overall survival was demonstrated increasing risk of local recurrence by 1.0% per month delay was observed (5). The estimated 5-year survival among locally advanced breast cancer patients living in developing countries is expected to be low due to lack of early breast cancer detection and limited accesses for cancer treatment. Recent cancer registries data from Gambia and Uganda showed relative age-standardized 5-years survival was found between 12 and 46% compared to 85% among western population (6).

Due to lack of adequate adjuvant treatment after surgery, most post mastectomy patients are at risk for local regional or distant recurrence. Adjuvant radiotherapy is one of the most effective treatment modality given alone or in combination to prevent recurrence. In order to achieve the maximum clinical benefit from treatment, delayed initiation of adjuvant treatment should be kept minimum. According to the Joint Counsel For Clinical Oncology and National Cancer Plan recommendation, the waiting time from surgery to initiation of adjuvant radiotherapy should be around 28 and 33 days respectively (7). Institutional delay by more than 3 months from presentation to primary therapy is associated with worse outcomes (8).

Delayed treatment initiation is very common among locally advanced breast cancer patients live in resource limited country due to few treatment facilities availability. Among many LMIC most radiotherapy centers have long waiting time. Even though there is gradual increment in radiotherapy machine availability among many countries still accesses to of radiotherapy remains a significant challenge. According to 2010 IAEA report, Africa had contributes only 2% of world's radiotherapy machines and nearly 80% of RT machines were found among northern part of Africa including Egypt, morocco, Libya and few in South Africa. Africa still needs for more than 703 RT machines according to the recommended radiotherapy source for the population density (9). According to 2015 EUROCHIP pilot trial involving multiple representative from different continents showed that average adjuvant RT waiting time among facilities was around 54-80 days indicating many centers in the world have significant deviation from the recommended time to initiation of adjuvant RT after mastectomy and the expected waiting time among LMICs could be even worse (10). Retrospective study from tertiary hospital in west province of South Africa showed a significant deviation of median

radiotherapy waiting time among breast cancer patients during 2013 and 2014 were found 80 and 68 days respectively (11).

There is no specific cut time regarding how long adjuvant chest wall irradiation can be safely delayed among high risk post mastectomy patients without compromising clinical benefits. Clinically, delivery of adjuvant RT up to 6-7 months after diagnosis showed clinical benefit. Delivery or omission of delay adjuvant radiotherapy beyond 7 months of post mastectomy is unknown.

1.2 Statement of the problem

Ethiopia is the 2nd most popular country having more than 100 million populations with poor health care system. There is no population-based cancer registry in Ethiopia. Most of data are generated from hospital based and from Addis Ababa cancer registry. According to 2011 WHO reports, among all deaths occurring in the country, nearly 34% were attributed to the non-communicable disease (12). Cancer accounted about 5.8% from total mortality (13). Among adult's cancers, Breast cancer accounts for 20.8 % (14). According to Addis Ababa cancer registry, higher of breast cancer incidences are observed among population living in urban (30.2%) followed by cervical (13.4%) and colorectal cancer (5.7%) (15). Breast cancer survival is not well studied and expected to be low. A recent retrospective study among 627 breast cancer patients treated at TASH showed, the estimated 5-years survival rate was only 26.4% and median survival was only 32 months.(16).

Despite advanced stage at presentation among many Ethiopian breast cancer patients, access to standard treatment is very low and most of cancer patients treated sub-optimally. Tikur Anbessa Specialized Hospital (TASH) is the only hospital providing radiotherapy service with single cobalt 60 machines for the whole population. Post mastectomy patients will be referred to this center for adjuvant radiation therapy. Due to high patient burden and long radiotherapy wait time at TASH radiotherapy center, most locally advanced breast cancer patients will not start adjuvant radiotherapy according to the recommended time. High risk post mastectomy patients will be registered and nearly wait for 1 year after first day of oncologic evaluation. Delayed

initiation of adjuvant radiotherapy among high risk group might be the contributing factor for low treatment outcomes among Ethiopian breast cancer patients.

There is no strong clinical evidence supporting the benefit of delayed adjuvant chest wall irradiation and the clinical benefit expected from adjuvant RT beyond 6-7 months of post-operative period is very minimal. Regardless of the clinical recommended period, most clinical Oncologists deliver delayed adjuvant RT among high risk post mastectomy patients to prevent possible tumor recurrence. At TASH, most of breast cancer patients took delayed adjuvant radiotherapy after 1 year of post mastectomy. Clinical decision whether the patient should take or shouldn't take delayed adjuvant radiotherapy mainly depends on physician clinical judgment. Since, the effectiveness of adjuvant RT after 1 year of mastectomy is unknown, such routine clinical practice should be evaluated.

CHAPTER -TWO

Literature review

Due to improvement in treatment modality and early cancer detection, breast cancer related morbidity and mortality is decreasing among developed countries compared developing. In 2012, more than 56.8% new breast cancer cases were detected among LMICs (3,17). Diagnosis of breast cancer among patients living in LMICs associated with higher cancer related morbidity and mortality compared to western due to patient late clinical presentation and limited accesses to standard cancer treatment. Countries breast cancer mortality index strongly related to countries economic status which directly contributes to patient survival and accesses to standard treatment.

Breast cancer patients living among high-income countries are expected to have higher 5 year survival rate reaching up to 85% compared below 60% among developing country (18). Highest breast cancer mortality to incidence ratio was observed among Central Africa breast cancer patients (0.55) compared to 0.16 in US (19). Generally, the low survival rates among developing countries were contributed to absence of early breast cancer detection, advanced clinical stage at presentation and lack of adequate compressive treatment facilities. Survival was even low among many sub-Saharan patients compared to others LMIC including Brazil (58.4%), India (52%), Algeria (38.8%) and Gambia (12%) in comparison to United States (83.9%), Sweden (82.0%), Japan (81.6%) and Australia (80.7%) (20).

Delayed treatment initiation is very common among many breast cancer patients living in LMIC due to few available treatment centers. Delayed adjuvant treatment more than 3 months associated with poor clinical outcome. Majority of countries have significant deviation from the recommendation waiting times between post mastectomy and initiation of adjuvant radiotherapy. Adjuvant radiotherapy should not be delayed beyond the clinically recommended time. Optimal adjuvant RT showed an improving local regional tumor control and overall survival compared to those who did not receive or delayed adjuvant radiotherapy. Clinical benefit from adjuvant radiotherapy increased as local regional stage of tumor increased (21). Omission of adjuvant radiotherapy in retrospective study showed increased local failure among chemotherapy only was 14 % compared to 5% among those who took chemotherapy and adjuvant radiotherapy

(22). The time gap continued to be significant and associated with low treatment outcome among locally advanced breast cancer who took sequential adjuvant treatment.. After 8 years of follow up, delayed initiation of adjuvant RT after 6 months of post mastectomy had showed decreased clinical outcome compared to those who took adjuvant RT within less than 6 month, the LRC was (98% vs 76%), DFS (71% vs 48%) and OS (80% vs 52%) respectively (23).

Intentional delay adjuvant radiotherapy until completion systemic therapy within 7 months of initial diagnosis did not affect outcome compared to early adjuvant radiotherapy initiation showed among 278 pathologic stage 0–II breast cancers who took systemic treatment. Delaying RT initiation for more than 6 weeks and less than 7 months after last treatment (chemotherapy or surgery) does not have negative impact on disease-free or overall survival (24).

Adjuvant RT associated with higher loco regional control rate patients among age less than 50 years compared to older patients. Retrospective data from 1,087 post mastectomy patients (924 without PMRT, 163 with PMRT) with T1–T2 tumors and 1 to 3 positive after 7 years median follow-up showed similar LRR, RFS and OS among patients who took and did not take adjuvant RT but only age ≤ 50 years and positive lympho-vascular invasion (LVI) were associated with increased LRR and radiotherapy showed improved loco regional tumor control rate (10.1 versus 1.1 %, $p < 0.001$) (25).

Among breast-conserving patients, adjuvant RT showed a decreased 5-year local recurrence rate from 26% to 7 % and RT showed prolonged clinical benefit up to 15 years (26). According to National Canadian clinical practice guidelines recommendation RT should be given within less than 12 weeks after BCS to keep the incidence of local failure and disease-free survival (DFS) similar to that of mastectomy (27). Despite old age and higher prevalence of co morbidity among aged 65 and older patients, data from the SEER among 13,907 stages I–II breast cancer after BCS without systemic therapy, showed delayed adjuvant RT by more than 3 months has associated with higher mortality rate (HR-1.92) and cancer specific mortality rate of (HR-3.84) compared to adjuvant RT initiation before 3 months (28). Among who took systemic therapy, delay up to 20 weeks according to British Columbia trial did not show decreased clinical outcome and use of Systemic therapy reduced the impact tumor recurrence related to delayed radiotherapy initiation.

But adjuvant RT delay without chemotherapy by more than 20 weeks has associated with inferior outcome compared to less than 20 weeks (29).

Others retrospective study among breast conserving surgery with node-negative 615 early breast cancer patient treated from 1984 to 2010 were analyzed according to RT waiting time delivery ≤ 60 , 61–120 days and >120 days after surgery, time of adjuvant radiotherapy has no correlation on local relapse and distant metastases even though year of treatment affect patients outcome (30). But in other study including more than of 7800 post breast conservative lymph node negative patients without chemotherapy showed delayed adjuvant radiotherapy by more than 20-26 weeks has significant decreased overall survival and delayed more than 9 weeks associated with relative increased risk of death but not statically significant (31).

In contrast to the above studies, adjuvant RT can be safely delivered after completion of systemic treatment and delayed RT have no significant effect had showed from meta-analysis of International Breast Cancer Study Group (IBCSG) Trial VI and VII finding showed no differences at 4 and 16-year actuarial total failure rates, risks of developing distant metastases, and overall survival regardless of adjuvant radiotherapy initiated time (4 and 7) months in premenopausal women and (2 and 4 months) among post-menopausal women who took 3 cycle or 6 cycle of systemic chemotherapy. (32).

CHAPTER-THREE

3.1 General Objective

- To assess disease control rate of post mastectomy delayed adjuvant radiotherapy delivery among locally advanced high risk breast cancer patients treated at Tikur Anbessa Specialized Hospital, Radiotherapy center in 2016 GC.

3.2 Specific objectives

- To assess 4 years loco-regional and distant tumor control rate among high risk post mastectomy locally advanced breast cancer patients who took delayed adjuvant radiotherapy and did not took delayed adjuvant radiotherapy at 1 year of mastectomy.
- To identify high risk clinic-pathologic features associated with disease recurrence among post mastectomy locally advanced breast cancer patients treated at TASH, radiotherapy center.

CHAPTER-FOUR:

4. Methodology

4.1 Study setting

The study was conducted at Tikur Anbessa Specialized Hospital (TASH) radiotherapy center. TASH is the only tertiary hospital in the country having radiotherapy service. Radiotherapy department provides all oncologic service including outpatient and inpatient and radiotherapy service. Currently there are 8 clinical oncologists and one trained physician on palliative care and 42 oncology residents on training. The center has 3 radiation physicists and 4 radiotherapy technicians and other oncology staffs including oncology nurses, social workers, chart keepers, secretaries and cleaners. TASH Radiotherapy center has two cobalt-60 machines of which only one is functional. Since 2016, brachytherapy service had started at center for cervical cancer treatment. External beam radiotherapy treatment is given for both curative and palliative intent. Post mastectomy patients referred to the center for adjuvant chest wall irradiation. After complete history, physical examination, pathology review and basic radiologic workup with CXR and U/S, those patients staged with locally advanced and having high risk features will be registered for adjuvant radiotherapy and chemotherapy. Due to long radiotherapy waiting time, most of locally advanced breast cancer patient will not start adjuvant radiotherapy according to clinically recommended and after long radiotherapy waiting period, delayed adjuvant treatment may be given or differ by treating physician at the time of adjuvant radiotherapy commencement considering the risk and benefit of delayed adjuvant radiotherapy to risk of possible tumor recurrence.

4.2 Study design

An institutional based retrospective cross sectional analytical study design used to assess the clinical benefit of delayed adjuvant radiotherapy and its tumor control rate among high risk post mastectomy locally advanced breast cancer registered at TASH radiotherapy center.

4.3 Source and Study Population

Source population: All high risk post mastectomy patients (International classification of disease-Oncology (ICD-O- 3) codes 50.0-9) diagnosed with locally advanced breast cancer and registered for adjuvant chest wall irradiation at TASH radiotherapy center.

Study population: All high risk post mastectomy patients (International classification of disease-Oncology (ICD-O- 3)codes 50.0-9) registered for radiotherapy and had stable disease after 1 year of mastectomy.

4.4 Inclusion and exclusion criteria

Inclusion criteria

- Aged between 18 -75 years
- All post mastectomy patients diagnosed with locally advanced breast cancer and registered for adjuvant radiotherapy at TASH radiotherapy center from January 1to December 30, 2016

Exclusion criteria:

- Patients who have progressed within 1 year of post mastectomy during radiotherapy waiting time
- Patients who took adjuvant chest wall irradiation within less than 1 year of post mastectomy and patient who have received neo-adjuvant chemotherapy.

4.5 Sample size determination

For statically analysis the minimum sample size should be determined

- Single population proportion formula is used to calculate sample size

- $n = Z^2 \alpha / 2^2 P(1-p) / d^2$, Where $Z = 1.96$ at 95% confidence interval, d - margin of error = 0.05
- $p =$ Assuming that 50% radiotherapy registered BC patients will develop recurrence

$$n = (1.96)^2 \times 0.5 \times (1-0.5) / (0.05)^2$$
 $n = 384$, since the population is small in size, correction factor needed.
 - Assume -3000per/year new cases of cancer patients at TASH and 21% are BC cases. Among BC patients 50% of them will require Radiotherapy
 - $n = n * N / (N + n - 1)$
 - $384 * 315 / (315 + 383) = 174$ patients
 - Adding 10% for Non-response the final sample size was $174 + 18 = 192$
 - 185 patients were actually included in the study

4.6. Study variables

Dependent variable – loco regional and distant tumor control rate at 4 years

Independent variables – Age, Sex, stage, tumor size, lymph node status, surgical margin, grade of tumor, lympho-vascular status, post mastectomy adjuvant radiotherapy and systemic therapy.

4.7. Definition of terms

Locally advanced breast cancer: Post- operative patients with pathological stage is between IIA- IIIB based on NCCN during the time of evaluation

Adjuvant radiotherapy: delivery of radiotherapy to chest wall and axillary lymph node for microscopic tumor control within the recommended time

4.8. Operational definitions:

Delayed adjuvant radiotherapy: Delivery of adjuvant chest wall irradiation among high risk patients after the recommended time for adjuvant RT had passed.

Loco regional recurrence rate -The time gap between the initial diagnoses to the time of disease recurrence over chest wall, axillary or supraclavicular area.

Distant site recurrence rate – The time gap from the initial diagnosis to the time of disease recurrence at any distant site

4.9. Data collection procedures

Patient data were retrieved and collected by two oncology residents under supervision of principal investigator. Pre-test sampling was done on 20 patients registered for adjuvant radiotherapy after identifying their medical recording number which is not included in study sample. Patient's files and radiotherapy treatment sheet were retrieved after identifying patients medical record number from radiotherapy registry log book. Completeness of data collection was checked using a checklist and missed data were filled. Patients who have no recent documentation or missed follow up for more than 6 months were traced through phone call.

4.10. Data processing and Analysis

The revised patients' record was checked for completeness, data were cleaned and manually entered in to excel spread sheet, then the final data transferred to IBM.SPSS window version 25 for additional statistical analysis. Results are presented as count (%), means and standard deviation or median based on the data type and distribution. Groups were compared using non-parametric (chi-square) tests and variables were analyzed, using binary logistic regression to assess the association between variables on disease control rate. All p values less than 0.05 were considered statically significant.

4.11. Ethics and Human Subjects consideration

An ethical clearance was obtained from ethical review committee of radiotherapy unit of TASH under, Addis Ababa University college of health science (AAU CHS). Confidentiality of the information will be maintained throughout the study by excluding names as identification in the data extraction form and the data will be used only for the purpose of the proposed study.

CHAPTER-FIVE

Result

In 2016, a total of 274 high risk post mastectomy patients had registered at TASH, radiotherapy center for adjuvant chest wall irradiation. Of those, 93.4% (256) patient's files were retrieved. Among registered patients 26% (71) were excluded from data analysis due to 5% (13) took neo adjuvant chemotherapy and 21.3 %(58) patients had tumor recurrence within less than of a year after mastectomy while waiting for adjuvant radiotherapy.

5.1 Socio demographic Characteristics of adjuvant radiotherapy registered patients

The mean age of adjuvant RT registered patients was 42.6 ± 11.1 years ranging from 23 years to 75 years? Majority of patients, 82.7% are below the age of 55. Half of cases are residents of Addis Ababa region followed by Oromia regional state. More than 75% were married. Comorbid illness was found in 12.2% of cases. Male breast cancer accounts only 2.2%. (See table 1)

Table1: Socio demographic characteristic of post mastectomy adjuvant radiotherapy registered patients at TASH radiotherapy center in 2016

Variable	Category	Took RT (n=79)		Did not took RT(n=106)		Total
		Frequency	Percent (%)	Frequency	Percent (%)	
Age	≤ 40	40	50.6	58	57.7	98
	41- 55	26	32.9	29	27.4	55
	≥ 56	13	16.5	19	17.9	32
Sex	Female	78	98.7	103	97.2	181
	Male	1	1.3	3	2.8	4
Region	AddisAbaba	36	45.6	39	36.8	78
	Oromia	17	21.5	38	35.8	55
	Amhara	11	13.9	14	13.2	25
	Tigray	1	1.3	3	2.8	4
	SNNP	10	12.7	10	9.4	20
	Others	4	5.5	2	1.2	6
Religion	Christian	62	78.5	78	73.6	140
	Muslim	14	17.7	22	20.8	36
	Others	3	3.8	6	5.7	9
Marital Status	Married	60	75.9	82	77.4	142
	Single	2	2.5	2	1.9	4
	Divorced	12	15.2	20	18.9	32
	Widowed	5	6.3	2	1.9	7
Co-morbidity	Yes	8	10.1	15	14.2	23
	No	71	89.9	91	85.8	162

5.2 Pathologic features among adjuvant radiotherapy registered patients

Among registered patients, 42.7 % had primary tumor size greater than 5cm and 73.5% didn't have adequate lymph node evaluation. The average lymph node identified was 4.86 ± 5.2 .

Advanced nodal metastasis was detected only in 25% of cases and more than 56.2% patients are stage 3 tumors. Ductal carcinoma accounts more than 91% and 29.7% patients had poorly differentiated tumor. Lympho-vascular status was mentioned only in 10% of patients and positive surgical margin was identified in 18.9%. (see table 2)

Table 2: High risk Pathologic features among adjuvant radiotherapy registered patients

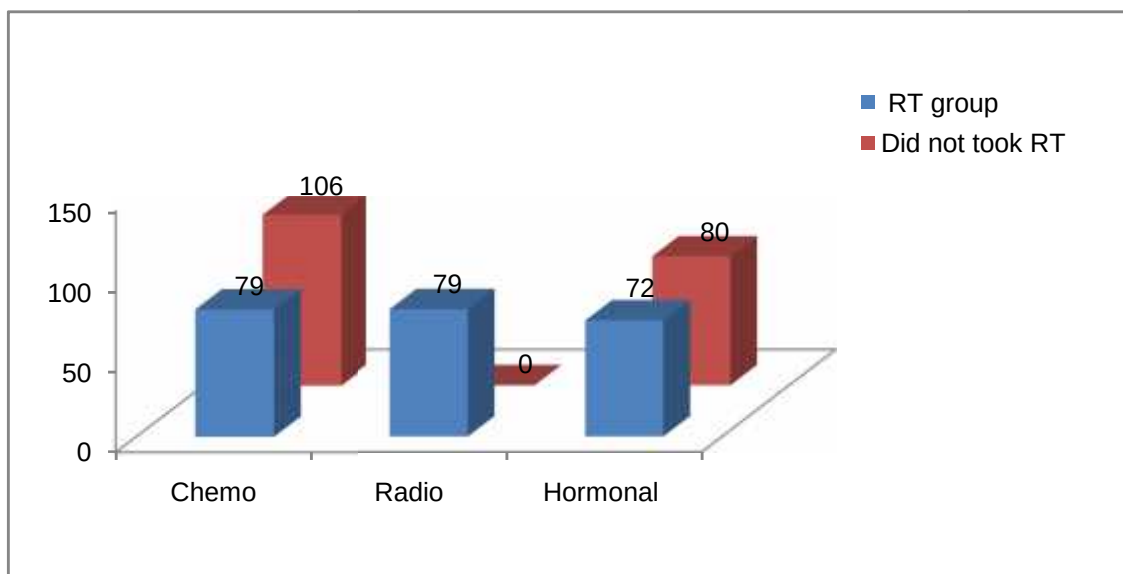
Variables	Category	Took RT (n=79)	Did not took	Total
-----------	----------	----------------	--------------	-------

		RT(n=106)				
		Frequency	Percent (%)	Frequency	Percent (%)	
T-stage	T1 & T2	40	50.6	66	62.3	106
	T3 & T4	39	49.4	40	37.7	79
N-stage	NX & N1	54	68.4	82	77.4	136
	N2	17	21.5	15	14.5	32
	N3	8	10.1	9	8.5	17
Stage	Stage 2A	8	10.1	17	16.0	25
	Stage 2B	19	24.1	37	34.9	56
	Stage 3A	26	32.9	27	25.5	53
	Stage 3B	18	22.8	16	15.1	34
	Stage 3C	8	10.1	19	8.5	17
Histology	Ductal	70	88.6	99	93.4	169
	Lobar	5	6.3	4	3.8	9
	Others	4	5.1	3	2.8	7
Grade	Well-differentiated	21	26.6	22	20.8	43
	Moderately differentiated	37	46.8	50	47.2	87
	Poorly differentiated	21	26.6	34	32.1	55
Surgical Margin	Positive	18	22.8	17	16.0	35
	Negative	55	70.9	77	72.6	133
	Unknown	5	6.3	12	11.3	17
Lympho-vascular	Present	9	11.4	3	2.8	12
	Absent	3	3.8	3	2.8	6
	Unknown	67	84.8	100	94.3	167
Lymph node ratio	≤ 20%	7	8.9	15	14.2	22
	≥ 20%	44	55.7	44	41.5	88
	Unknown	28	35.4	47	44.3	75

5.3. Types of adjuvant treatment delivery among adjuvant radiotherapy registered patients

After 1 year of post mastectomy, among registered patients 67.5% (185) had clinically stable diseases were candidate for delayed adjuvant radiotherapy treatment. Despite the indication for adjuvant irradiation, only 79 (28.8%) patients had took adjuvant radiotherapy while 106(38.6%) patient did not take adjuvant radiotherapy. Decision whether to give or omit delayed adjuvant radiotherapy were decided by the primary treating physician based on patients risk stratification into high risk and low risk for tumor loco regional recurrence.

Figure 1: Pattern of adjuvant treatment delivery among post mastectomy registered and treated patients.



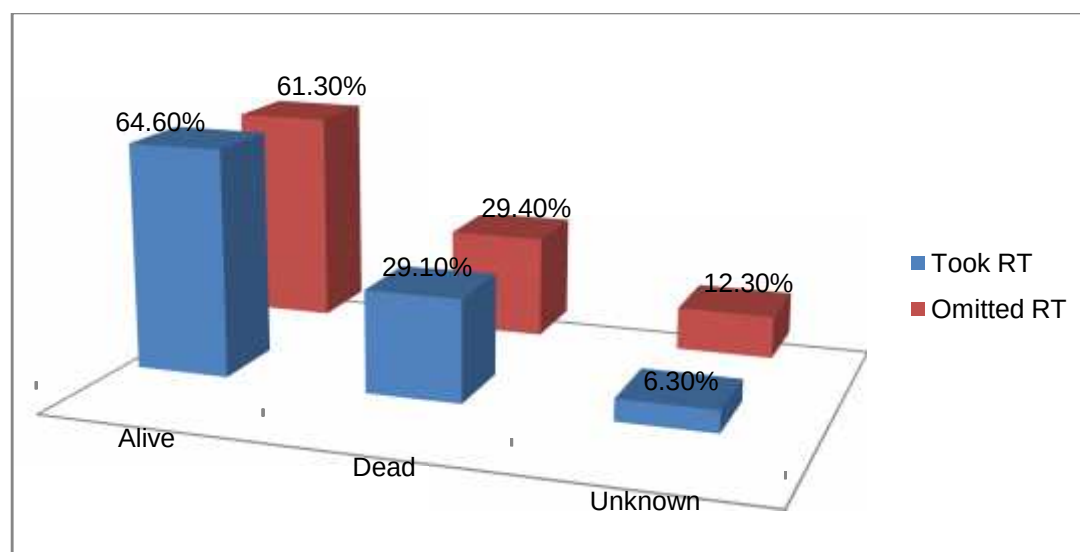
5.4. Radiotherapy waiting time

The mean radiotherapy waiting time among registered patients was 8.8 ± 1.4 months. The median time between dates of surgery to date of delayed adjuvant radiotherapy delivery among those who took adjuvant radiotherapy was 10.4 ± 3.4 months. The average post mastectomy referral time was 1.7 months ranging from 2 weeks to 6 month of post-mastectomy period.

5.5. Patient condition among adjuvant radiotherapy registered patients.

At 4 years of post-mastectomy, 116(62.7%)patients are alive,52(27.6%) had died and 17(9.7%) patients had unknown status. The mean time of disease progression among all recurred patient was 27 ± 11.1 months .Among the groups, mean time of tumor recurrence among patients those who took delayed adjuvant radiotherapy and did not took delayed adjuvant radiotherapywas 28.9 ± 4 and 28.4 ± 7 months respectively.(figure 2)

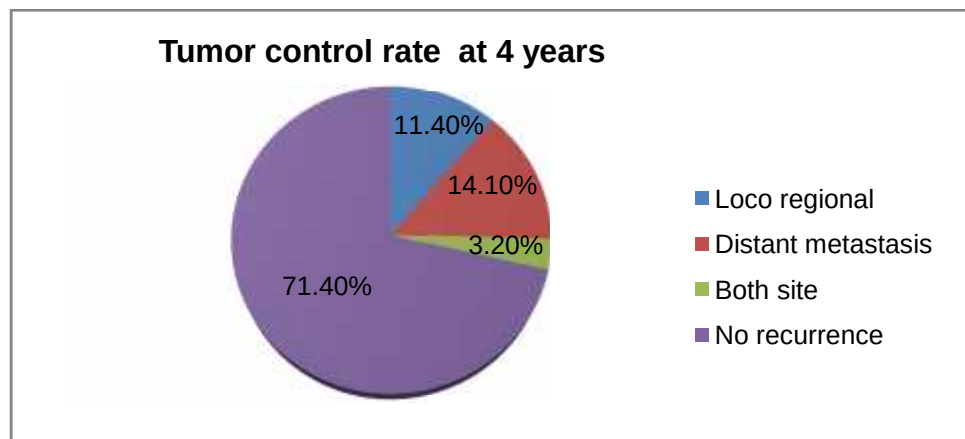
Figure.2. Patient condition after 4 years of post-mastectomy registered at TASH, radiotherapy center.



5.6. Tumor control rate among radiotherapy registered patients

At 4 years, 132(71.4%) patients had stable diseases and 53 (29.6%) patients had tumor progression. Nearly 34 %(27) patients who took delayed adjuvant radiotherapy and 24.5 %(26) patients among who did not took delayed adjuvant radiotherapy had developed tumor progression respectively. Nearly 11.4 % patients develop loco regional while 14.1% developed distant site recurrence. (figure.3)

Figure.3. Tumor control status at 4 years among locally advanced breast cancer registered in 2016



5.7. Clinico- Pathologic factors associated with tumor recurrence after 1 year of post mastectomy

Delayed post mastectomy adjuvant radiotherapy among high risk patient did not associated with decreased in overall tumor recurrence compared to those patients who did not take delayed adjuvant radiotherapy ($p = 0.16$) but sub group analysis showed improved loco regional control rate (HR=0.8). On bivariate analysis, age at less than 55 years, advanced nodal stages, advanced stage and percent of lymph node positive ratio greater than 20% were significantly associated with increased tumor recurrence. Adjuvant radiotherapy was not found to be significantly associated with tumor control (COR=1.5, 95% CI=0.83-3.03, $P=0.16$) (see table.3)

Table 3. Prognostic factors associated with tumor recurrence among locally advanced breast cancer patient treated at TASH, radiotherapy center

Variable		Category		COR	95% CI		P-value
	Group	Not recurred (%)	Recurred(%)		Lower	Upper	
Age	≤ 40	67.3	32.7	1			0.102
	41-55	69.1	30.9	0.923	0.453	1.878	0.824
	≥ 55	87.5	12.5	0.295	0.095	0.912	0.034*
T-stage	T1 & T2	71.7	28.3	1			
	T3 & T4	70.9	29.1	1.04	0.547	1.98	0.904
N-stage	NX & N1	79.4	20.6	1			0.228
	N2	50	50	3.857	1.719	8.654	0.001*
	N3	47.1	52.9	4.339	1.535	12.26	0.006*
Stage	Stage 2A	84	16	1			0.083
	Stage 2B	78.6	21.4	1.432	0.412	4.974	0.572
	Stage 3A	36	32.1	2.479	0.736	8.355	0.143
	Stage 3B	67.6	32.4	2.511	0.692	9.105	0.161
	Stage 3C	47.1	52.9	5.906	1.411	24.727	0.015*
Histology	Ductal	69.8	30.2	1			0.359
	Lobar	88.9	11.1	0.289	0.035	2.373	0.248
	Others	85.7	14.3	0.386	0.045	3.285	0.383
Grade	Well-differentiated	79.1	20.9	1			0.331
	Moderately differentiated	66.7	33.3	1.889	0.800	4.461	0.147
	Poorly differentiated	72.7	27.3	1.417	0.551	3.643	0.47

Surgical Margin	Positive	80	20	1			0.417
	Negative	69.9	30.1	1.72	0.694	4.263	0.241
	Unknown	64.7	35.3	2.182	0.598	7.961	0.237
Lympho-vascular status	Present	66.7	33.3	1			0.766
	Absent	83.3	16.7	0.4	0.034	4.681	0.465
	Unknown	71.3	28.7	0.8	0.232	2.805	0.736
Lymph node ratio	≤ 20%	86.4	13.6	1			0.001*
	≥ 20%	58	42	4.595	1.266	16.677	0.02*
	Unknown	82.7	17.3	1.328	0.342	5.156	0.682
RT	No	75.5	24.5	1			0.152
	Yes	65.8	34.2	1.598	0.841	3.035	
HT	Yes	69.9	30.1	1			0.354
	No	78.1	21.9	0.651	0.263	1.612	

On multivariate only advanced nodal tumor (N-stage) showed statically significant for tumor recurrence. N2 stage patients were found to be 3.8 times more likely to develop recurrence as compared to Nx& N1 patients (AOR, 3.86, CI 1.72-8.65) and N3 patients were found to be 4.3 times more likely to develop recurrence as compared to Nx and N1 patients (AOR, 4.34, CI 1.54-12.26)

5.6. Effect of delayed adjuvantradiotherapy and time of tumor recurrence

Delayed adjuvant radiotherapy did not showed any difference on the time of tumor recurrence compared to those patient who did not took delayed adjuvant radiotherapygroup. Most recurrence seen during the 2nd and 3rd year after mastectomy. The median time of failure among group was similar(figure 4)

Figure 4. Time and frequency of tumor recurrence among delayed adjuvant radiotherapy treated and omitted groups during follow up period.

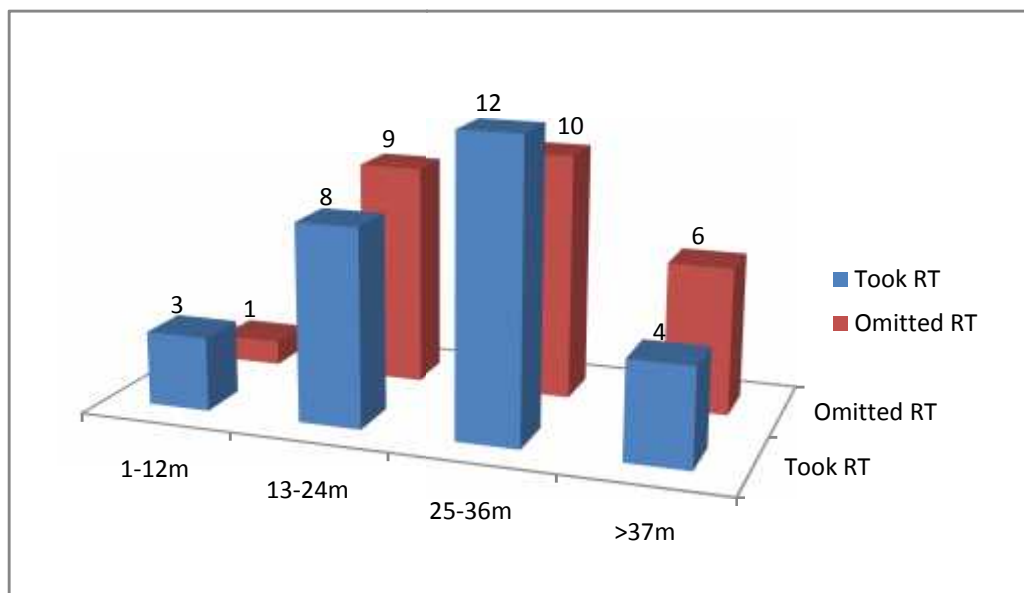


Table.4. Recurrence site and frequency of tumor recurrence among locally advanced breast cancer patient among who took and did not took adjuvant radiotherapy.

Category	Took RT group (n-79)		Did not took RT group(n-106)	
	Frequency	Percent (%)	Frequency	Percent (%)
Recurred	27	50.9	26	49.1
➤ Loco regional	7	8.9	14	13.2
➤ Distant	17	21.5	9	8.5
➤ Both site	3	3.8	3	3.8
No recurrence	52	49.4	80	50.6

CHAPTER -SIX

Discussion

Breast cancer is the second most cancer diagnosed worldwide. Nearly 40-60% post mastectomy patients need adjuvant radiotherapy. Approximately 30% post mastectomy patients will develop tumor recurrences after surgical alone (33). Among high risk post mastectomy patients, delivery of adjuvant radiotherapy improved loco regional tumor control and improved overall survival. According to Fisher et al. report of 20 years follow up from NSABP-06 study, post-operative radiotherapy showed decreased cumulative rate of ipsilateral tumor recurrence from 39.2% to 14.3% compared to among patients who did not take adjuvant radiotherapy (34). Clinically, delayed initiation of radiotherapy greater than 6-12 weeks for patients not receiving chemotherapy and greater than 6-7 months for patients receiving adjuvant chemotherapy was considered to be associated with increased risk of tumor recurrence (35). Delivery of adjuvant radiotherapy among women with positive axillary lymph nodes shown improved disease free survival and overall survival after 10 and 20 years of post-mastectomy follow up (36). But among lymph node negative patients adjuvant radiotherapy showed only improved loco regional tumor control having primary only tumor size greater than 5cm and positive surgical margin (37).

Most of breast cancer patients live among LMICs where access to radiotherapy is minimal and most of patients do not get standard treatment. Scarcity of radiotherapy source is a major contributing factor for the delayed initiation of adjuvant radiotherapy among many breast cancer patients living in sub-Saharan countries. In our study, the mean radiotherapy waiting time among locally advanced breast cancer patients was 8.8 ± 1.9 months which is long compared to previous unpublished retrospective study report from the same hospital assessing the disparity of radiotherapy receipt among cervical patients in 2014. Treatment at regular or private wing showed that the median radiotherapy waiting time among private wing treated patients was 185 days (nearly 6 months) which is relatively considered to be shorter. The finding observed in our study showed that radiotherapy waiting time had prolonged by more than 2 months which might be due to increased new cancer case detection in the country which contributed patient burden at the center or it could be

due repeatedly radiotherapy machines breakage. Most of breast cancer among Africa has no access to radiotherapy. According to World Bank countries economic classification in 2014, worldwide 139 countries grouped under LMICs and only 84 countries had documented to have radiotherapy and 55 (39.5%) countries have no radiotherapy which majorities are from sub Saharan countries. Radiotherapy Access among 80 LMICs ranges from 2.3% to 98.9% (median 39.5%) (38).

Ethiopia has only one cobalt 60 radiotherapy source machine .Most of Ethiopian breast cancer patients have no accesses to radiotherapy. According to our study, among high risk post mastectomy registered At TASH radiotherapy center from January 1 to December 30, 2016 for adjuvant radiotherapy, only 28.8 % patients had took adjuvant radiotherapy while 38.6% did not get adjuvant radiotherapy. From recent publication ,Similar finding was observed from Addis Ababa cancer registry among 588 registered patient between 2012 to 2014,median radiotherapy waiting time was 6.9 months (0.17 to 21.8) and radiotherapy was not prescribed for a high proportion of patients (38.8%) despite most of cancer patients had registration and eligibility for radiotherapy (42).Compared to developed countries,among sub Saharan country and LMICaccess to RT among breast cancer patients were worse. A study by King ham et al showed in 2010, only 10.8% of breast cancer patients had received post mastectomy adjuvant radiotherapy among Sub-Sahara Africa (39).Even though it is better than most Africans country similar situation was observed among Philippines patients, where PMRT were provide only about 20% of breast cancer cases compared to high-income countries where access to radiotherapy is above 60% (40).Despite the late clinical presentation among many Ethiopia breast cancer patients, most of breast cancer patients are getting sub optimal treatment .Delayed treatment initiation at the facility levels very common.Only few patients are getting radiotherapy according to our study .Generally radiotherapy utilization rate is very low among many African countries including Ethiopia. According to the study by kentelhardt et.al, radiotherapy utilization rate among the center asbreast cancer directed treatment was only 26 %at TASH radiotherapy center which is very low compared to other sub-Saharan centers as high as 46%in Gambia (41).

One of our major finding was most of post mastectomy high risk patients took delayed adjuvant radiotherapy after long waiting time of post- mastectomy period which significantly deviated from what clinical recommended.The median post mastectomy adjuvant radiotherapy delivery was $10.4 \pm$

4.9 months. Even though, the optimal time between surgery and post mastectomy adjuvant radiotherapy delivery remains unclear, delivery of adjuvant radiotherapy within clinically recommended time had showed improvement in clinical outcome and delayed in adjuvant radiotherapy associated increased risk of tumor recurrence.

Radiotherapy has minimal benefit if delayed in radiotherapy delivery is greater than 6-12 weeks or greater than 6-7 months after surgery without receiving chemotherapy (35). Even though most east of African countries do not have radiotherapy, radiotherapy delay at TASH was worse compared to South African radiotherapy treatment waiting time at west province hospital during 2013 and 2014 having nearly 80 and 68 days respectively treated (44). Ethiopia is the 2nd countries having high population number next to Nigeria. According to Tumba et.al study, the median radiotherapy waiting among Nigeria breast cancer patient treated at 7 center during 2010-2014 was 329 days (IQR 207–464) which is comparable to TASH radiotherapy waiting time (10.4 vs 10.9 months) indicating unbalanced demand and high patients burden among most of sub Saharan radiotherapy center compared to western country where delayed is not more than 28 days (43).

There is no randomized clinical data assessing the clinical benefit of delayed adjuvant radiotherapy among post mastectomy locally advanced breast cancer patients treated beyond 6 to 7 months of post-operative period. This is the only retrospective data which evaluate the clinical benefit of delayed adjuvant radiotherapy delivery compared to omission of delayed adjuvant radiotherapy among high risk post mastectomy patients after nearly 1 year of surgery.

In our study, delivery of delayed adjuvant radiotherapy among high risk post mastectomy patients did not associated with decreased tumor recurrence compared to patients those who did not take delayed adjuvant radiotherapy. At 4 years of follow up, a total of 53 (28.6%) patients developed tumor recurrences, of whom 27 (50.9%) among those who took delayed adjuvant radiotherapy and 26 patients (49.1%) did not take delayed radiotherapy. On sub group analysis, delayed radiotherapy was associated with improved loco regional tumor control rate compared to radiotherapy omitted groups. Only 7 (8.8%) cases developed loco regional recurrence among those who took delayed adjuvant radiotherapy while 14 (13.2%) patients developed loco regional recurrences among those who did not take delayed adjuvant radiotherapy. Despite lack of randomized clinical trial and absence of clear consensus on post-operative adjuvant period among locally advanced post mastectomy patients,

many retrospective studies showed that delaying adjuvant radiotherapy have minimal effect on tumor control rate. A study done at Harvard school of medicine among 270 post mastectomy patients after median follow up of 6 years (ranging 7 months to 15 years) showed delaying adjuvant radiotherapy by more than 7 months was not associated with increased loco regional tumor recurrence. Groups were compared, there were no significant difference on local control and distant failure from delaying post mastectomy adjuvant radiotherapy by less than 5 months, 5-7 months or by more than 7 months among who took systemic therapy even though few patients were delayed beyond 7 months (46). Similar finding were observed among 340 post mastectomy stage 3 Chinese patients who took chemotherapy after median 72 months of follow-up, delaying adjuvant radiotherapy by more than 6 months (median delay was 5 months) was not associated with increased risk of loco regional, distant tumor recurrence and decreased survival (47). The benefit observed from delayed adjuvant radiotherapy in our study can be explained by the above two trial findings in which delayed radiotherapy did not result in significant difference on tumor control rate, despite most of our patients did not take adjuvant radiotherapy and the mean post mastectomy radiotherapy treatment time in our patients was 10.8 months which is nearly two times delay can explain the absence of overall tumor control among our patients.

Studies had showed adjuvant chemotherapy was found to compensate the prolonged adjuvant radiotherapy delaying time without decreasing clinical benefit. Despite most of our patients are locally advanced and at high risk for both loco regional and distant recurrences nearly more than 94 % patients had taken systemic taxol containing regimen chemotherapy which might contributed to the observed improved loco regional control rate after delayed adjuvant radiotherapy. A study done by Meek et al among 297 stage 0-2 BCS patients who took adjuvant chemotherapy and delayed RT was initiated between 12 to 63 weeks (median 31 weeks) showed that there was no increased loco regional tumor recurrence compared to those patients in which adjuvant radiotherapy initiated within not more than 8 weeks and chemotherapy has compensated the duration (48). In Other study done at Chieti university among 802 early breast cancer patients, chemotherapy showed prolonging effect of adjuvant radiotherapy (within 8 weeks) to beyond 16 weeks without reducing loco regional tumor control. After 8 years of follow up, delaying adjuvant radiotherapy by more than 16 weeks but not more than 25 weeks among who took chemotherapy did not affect local tumor control (49). In contrast to the above, meta-analysis from 7 randomized retrospective, French adjuvant study group

having 1831 early breast with positive lymph node and took systemic chemotherapy showed that time interval between lumpectomy and initiation of adjuvant radiotherapy has no impact on loco regional tumor control rate. Among the group median time of adjuvant radiotherapy initiation was 5 weeks without chemotherapy group, 12 weeks and 25 weeks among who took 3 and 6 cycles. After 9 years of follow up, loco regional free survival rate was 92%, 81.5%, and 87.5% ($p=0.001$) respectively. According to the meta-analysis conclusion, tumor control mainly depends on number of completed chemotherapy cycles rather than time of delay in radiotherapy delivery (50). Nearly all patients had taken more than 4 cycles of chemotherapy at time of evaluation for delayed adjuvant radiotherapy treatment in our study, which might have contributed to improved loco regional control rate of delayed radiotherapy despite the time gap. Most physicians order adjuvant chemotherapy to prevent tumor progression due to long radiotherapy waiting time and most patients had incomplete pathologic evaluation and more than 56% of patients are stage 3 diseases at presentation having high chance for nodal and distant site recurrence.

Among lymph node negative patients, benefit of chemotherapy can be low and impact on delayed adjuvant radiotherapy can be masked. In the British Columbia trial initiation of adjuvant RT up to 20 weeks did not show any decreased clinical outcome but delayed by more than 20 weeks without systemic therapy associated with inferior outcome (HR, 2.00), even though at 10-year outcomes were similar (LRFS, 95.4%; DRFS, 90.5%; and BCSS, 92.5%) (26).

According to our findings, delayed adjuvant radiotherapy did not change the mean time of tumor relapse among the groups. Most recurrences among who took delayed adjuvant radiotherapy occurred at distant site compared to those who did not take. The median time of disease progression among all recurrent patients was 27 ± 11.1 months. The mean time to tumor recurrence among who took delayed adjuvant radiotherapy and those who did not take was 28.9 ± 8 and 28.4 ± 11 months respectively. A retrospective observational study done by Kapoor et al. on pattern of recurrence showed most post-mastectomy tumor recurrences were detected clinically after 3 years and after 2 years of post-mastectomy by imaging (45). In our patients, nearly 75% tumor recurrence was detected in the second and third years of follow up indicating delayed intervention had minimal clinical effect and delayed adjuvant radiotherapy had shifted pattern of tumor recurrence from loco regional to distant sites.

A Study showed that more than 50% breast cancer pathologic reports had missed some critical component which should be included in reporting system according to the American pathology reporting guideline system (51). More than 75% of patients have no adequate lymph node evaluation in our study and mean number of lymph node identified was 4.8 ± 0.6 . Only 10% of patients had documented lympho vascular status and 21 % patients had positive surgical margin. Due to incomplete pathologic reporting, most of our patients were considered to be high risk and registered for adjuvant radiotherapy even though, nearly 40% of patients did not take adjuvant radiotherapy.

Patient age might be contributing factor to the increased disease recurrences among our patients. The median age among adjuvant radiotherapy registered patients was 42.6 years and nearly 80% cases were diagnosed before the age 55 years which may contribute to tumor aggressiveness. Retrospective study among 93 post mastectomy locally advanced Sudanese patients who developed recurrences within 5 years of post-mastectomy, showed that loco regional tumor recurrence was strongly associated with age less than 40 years, surgical margin positivity and lymph node involvement despite adjuvant radiotherapy treatment (52). Most patients had unknown nodal status in our study, the benefit from the delayed adjuvant radiotherapy among advanced nodal patients (N2 and N3) can be explained by risk reduction from nodal recurrence among age less than 55 years (OR=0.87). Studies showed risk of local regional recurrence has direct proportion to the extent of axillary lymph node involvement at time diagnosis (53). Even though, impact of radiotherapy not assessed in one of retrospective study done among 513 Ethiopian breast cancer patients treated at TASH assessing predictor for recurrence among who took systemic therapy showed that higher tumor recurrence was associated with clinical stage 3 (HR-2.6), negative estrogen receptor (HR-2.2), grade 3 tumor (HR-2.2), positive surgical margin (HR-2.8) and greater than 2 positive lymph node (HR-2.6) were identified (54). Adjuvant radiotherapy should not completely omit among all patients and need patient stratification. Omitting adjuvant radiotherapy among high risk patients without having a well-defined prognostic model is very challenging and study had showed increased tumor recurrences. A retrospective study among 125 patients with T1 & T2 and 1-3 positive lymph nodes, omission of adjuvant radiotherapy increased loco regional recurrence among age less than 40 years ($p=0.006$), T2 ($P=0.04$) and tumor size greater than 3cm ($p=0.02$), LVI invasion (0.02) and no adjuvant hormonal treatment (55).

CHAPTER-7

7.1 Strength and weakness of the study

Strength of the study:

There is no clinical data assessing benefit delayed radiotherapy among Ethiopian cancer patients .This is the first clinical study done among post mastectomy patients treated at TASH assessing the clinical benefit delayed adjuvant radiotherapy after 1 year post mastectomy. The main finding achieved from this study, at most benefits the treating physician to decide the correct treatment option and reduce treatment toxicitybased on local evidences through identifying appropriate patients prognostic factors for tumor recurrence. In addition to the above, finding can be applied to solve the long radiotherapy waiting time at TASH oncology center and improving patient treatment satisfaction. We hope the finding of this study will be used as an evidence to support the effort in improving cancer care at national level as well as other among other sub Saharan country where radiotherapy is limited

Weakness of the study:

The major weakness of the study is being a retrospective study which affects accuracy and completeness of data and most of patients did not get adjuvant radiotherapy. Most of patients had incomplete pathologic report which is difficult to assess the actual prognostic factors for tumor recurrences. overall treatment outcome can be affected by different factors confounders patient performance, delay during referral and patient treatment adherence like use of chemotherapy and hormonal therapy, time gap between systemic chemotherapy to adjuvant radiotherapy, dose, fractionation field of radiotherapy and set up uncertainty which makes difficult to control and affect the outcome

7.2 Conclusion

Delayed adjuvant radiotherapy delivery among high risk post mastectomy patients did not reduce tumor recurrence compared to those who did not take delayed radiotherapy. Institutional delay and omission of adjuvant treatment was very common among breast cancer patients treated at TASH. The negative finding in our study supports other similar finding observed in trials which the overall clinical benefit of delayed adjuvant radiotherapy beyond 6 -7 months is very minimal and should be individualized and delayed adjuvant radiotherapy should be given to certain specific group patients having poor prognostic factors(younger age less than 55years or advanced nodal stage (N2 and N3).)

7.3 Recommendations

Cancer patient survival depends on and accessibility availability of standard treatment. All cancer Patient has the right to get standard treatment and should have equal accesses regardless of cancer stage due to limited compressive cancer treatment centers in Ethiopia, most locally advanced breast cancer patients don't have accesses to standard cancer treatments. Most breast cancer recurrences can be reduced through timely treatment .Comprehensive approach to cancer control is still the most effective in ensuring that the role of radiotherapy is well articulated, integrated and planned in most holistic manner and should be integrated to the current health care system. Governmental officials and other responsible stake holders should work extensively in expanding radiotherapy center in Ethiopia to increase radiotherapy accessibility among cancer patients.

Despite the limited accesses to radiotherapy among many Ethiopian cancer patients, radiotherapy waiting time at TASH oncology center should improve. The vicious cycle observed at TASH radiotherapy center, in which long radiotherapy waiting result in delayed initiation adjuvant radiotherapy and giving delayed adjuvant radiotherapy without any significant clinical benefit results again in more and more prolonging radiotherapy waiting time which finally result in poor treatment outcome and inefficient use of the available radiotherapy energy source can be improved through minimizing number of unnecessary patient irradiation. According tour study, most delayed adjuvant

radiotherapy among breast cancer can be safely omitted and radiotherapy waiting time the oncology center can be minimized through reducing time, energy and resources used to irradiate unnecessary patients. In a country like Ethiopia with single radiotherapy machine for the whole nation, center should develop effective mechanism maximally to utilize the available radiation resource without compromising treatment quality. Finally, both treatment and diagnostic modalities including pathology and radiology among breast cancer patients treated at TASH should be improved and Physician treatment decision should be made on strong clinical evidence which generated from locally or international clinical data. If not, routine clinical activity should be supported or justified by locally researches.

References

- 1.FreddieB,JacquesF,IsabellaS,RebeccaLS,Lindsey.AT,AhmedinJ.etal.:Gobalcancerstatics 2018:GLOBOCON estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J clinical.2018;68:394-424.
- 2.Negin J,Cumming R, DeRamirez S, Abimbola S ,et al.Risk factors for non-communicable diseases among older adults in rural Africa. Trop Med Int Health.2011;16: 640-6
3. Mutebi M, Edge J,. Stigma, survivorship and solutions: Addressing the challenges of living with breast cancer in low income resource areas. S Afr Med J .2014; 104(5):383.
- 4.WHO(2015).Breastcancer:preventionandcontrol.Available:http://www.who.int/cancer/detection/breast cancer/en/index1.html# 4/1/2015
5. Alon U. "How To Choose a Good Scientific Problem". Molecular Cell 35.6 (2009): 726-728.
- 6.BhikoR,SrivasaS,ChiehT,MossD,GhillaA.:Systemic review of breast cancer biology in developing countries(part1): Africa, the middle East, Eastern Europa, Mexico, the Caribbean and South america:cancer.2011,3,2358-2381
7. Kerba M, Miao Q, Zhang, Salomon J.Defining the Need for Breast Cancer Radiotherapy in the General Population: a Criterion-based Benchmarking Approach. Clinical Oncology .2007.vol 19(7): 481-489.
- 8.Mc Laughlin JM, Anderson RT, Ferketich. AK, et. al. Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. Journalof Clinical Oncology. 2012;30 (36):4493.<http://dx.doi.org/10.1200/jco.2012.39.7695>.
9. Zubizarreta Eh, Fidarova E, Healy B, Rosenblatt E: Need for radiotherapy in low and middle income countries. The silent crisis continues. Clin Oncol.2015; 27:107–114
10. Baili P and Micheli A. "Report of EUROCHIP-2 Pilot Studies" (2008).
11. Jana Bester. Retrospective Analysisof Treatment Delay in Breast Cancer Radiotherapy. Acta Scientific Cancer Biology 2.10 (2018): 43-48.

12. World Health Organization: Non communicable diseases country profiles. Geneva, World Health Organization.2011. p 207
13. Federal Ministry of Health Ethiopia. National Cancer Control Plan 2016-2020.p 67
14. Abate S., Assefa M.,Tigeneh W., et al. Trends of Breast Cancer in Ethiopia. Int J Ca
15. HaileselassieW., MulugetaT., Tigeneh W., et al .The situation of cancer treatment in Ethiopia: challenges and opportunities.JCancer Prev.2019; 24:33-42
- 16.Wondimeneh S.,Yared A. TeferaM.,et al. Survival status and predictors of mortality among Breast cancer patients at Black lion specialized hospital, Adult oncology unit, Addis Ababa, Ethiopia, 2018.bioRxiv. 2019. Doi: <http://dx.doi.org/10.1101/636431>.
17. MutebiM.,Edge J.Stigma, survivorship, and solutions: addressing the challenges of living with breast cancer in low-income resource areas. South African medical journal.2014;104(5):383.
- 18.Allemani C, Weir HK, HarewoodR.et al. Global surveillance of cancer survival 1995–2009: Analysis of individual data for 25,676,887patients from 279 population-based registries in 67 countries (CONCORD-2).Lancet. 2015; 385(9972):977-1010ncer Res Mol Mech. 2016;2(1)
19. DeSantis CE, Ferlay J, Jemal.A., etal.International variation in female breast cancer incidence and mortality rates. Cancer Epidemiology and Prevention Biomarkers.2015; 24(10):1495-506.
20. Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: A worldwide population-based study (CONCORD). Lancet Oncol.2008; 9:730–756.
21. Shafiq J,Delaney G, Barton BM.: An evidence based estimation of local control and survival benefit of radiotherapy for breast cancer.Radiotherapy and oncology.2007.84 (1).11-27
doi.org/10.1016/j.radonc.2007.03.006
- 22.GriemKL.,Henderson IC.,Gelman R. et.al : The 5-year results of a randomized trial of adjuvant radiation therapy after chemotherapy in breast cancer patients treated with mastectomyClinoncol.1987;5(10):1546-55. DOI.10.1200/JCO.1987.5.10.1546

23. Buchholz TA., Astin-seymour MM, Ellis GK., et al :Effect of delay in radiation in the combined modality treatment of breast cancer. *Int.JOncol Bio Phys.*1993: 26(1):23-35.
- 24.Raquel CC., Antxon A., Frenandez DL. et,al.:A retrospective observational study on Clinical impact of delaying initiation of radiotherapy inpatients with breast cancer: stages 0, I and II.*Journalof RadiotherapyPractice.*2015.14(3), 244-251.doi.org/10.1017/S1460396915000230).
- 25.Tracy AM, Robert M., Michelle S.,et.al :Selection Criteria for Post mastectomy Radiotherapy in T1–T2 Tumors with 1 to 3 Positive Lymph Nodes. *Annals of Surgical Oncology.* 2013.20(10), 3169–3174.
26. Clarke M, Collins R, Darby S .et al: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Early breast cancer trials’ collaborativegroup(EBCTCG). *Lancet* (2005), 366(9503),2087-106.DOI:10.1016/S0140-6736(05)67887-7
27. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer.Breast radiotherapy after breast-conserving surgery. *Can Med Assoc J.* 1998; 158(suppl 3):S35–42.
28. Dawn LH, Xiaoyan W., Judith SJ,.et al. Delay in initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival. *Int.JOncol Bio Phys* .2006;65(5):1353-1360. [dio.org/j.ijrobp.2006.03.048](https://doi.org/j.ijrobp.2006.03.048)
- 29.Ivo A, Olivotto, Mary L,.et al. Interval longer than 20weeks from breast conserving surgery to radiation therapy are associated with inferior outcome from with early-stage breast cancer who are not receiving chemotherapy. *JClinOncol.* 2009. 27:16-23, doi:10.1200/JCO.2008.18.1891
30. Raffaella C., Maria Pc., Rocco N,.et al.Waiting time for radiation therapy after breast conserving surgery in early breast cancer: A retrospective analysis of local relapse and distant metastases in 615 patients. *Eur J Med Res.*2016. 21:3 [dio10.1186/s40001-016-0226-92](https://doi.org/10.1186/s40001-016-0226-92)

31. Mikeljevic S., Haward R., Johnston C, Crellin A., et al: Trends in Postoperative Radiotherapy Delay and the Effect on Survival in Breast Cancer Patients Treated with Conservation surgery. *British Journal of Cancer*. 2004;90, 1343-1348, doi-10.1038/sj.bjc.6601693
32. Karles P. Cole FB., Price NK., et al. Timing of radiotherapy and chemotherapy following breast-conserving surgery for patients with node-positive breast cancer. Long –term results from International Breast Cancer Study Group trials VI and VII. *Int.J Radiation oncol bio phy*. 2016;96(2),273-279.
33. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med*. 1997;337(14):949–955.
34. Fisher B., Anderson S., Bryant J., et al. 20 year follow up of Randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J med*. 2002. doi:10.1056/NEJMoa022152
35. Tsoutsou PG, Koukourakis MI, Azria D, et al. Optimal timing for adjuvant radiation therapy in breast cancer: a comprehensive review and perspectives. *Crit Rev Oncol Hematol*. 2009;71(2):102–116.
36. McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomized trials. *Lancet* 2014;383:2127–2135.
37. Jagsi R, Raad RA, Goldberg S, et al. Local regional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for post mastectomy radiation. *Int J Radiat Oncol Biol Phys* 2005; 62: 1035–1039.
38. Niloy RD., Massoud S., Stephen B., et al. Radiation therapy infrastructure and human resources in low- and middle-income countries: present status and projections for 2020. *Int.J Rad. Oncol. Bio. Phys*. 2014; 89(3):448-57. doi: [10.1016/j.ijrobp.2014.03.002](https://doi.org/10.1016/j.ijrobp.2014.03.002)

39. Kingham TP, Alatisie OI, Vanderpuye V. et al. Treatment of cancer in sub-Saharan Africa. *Lancet Oncol.* 2013;14(4):e158-67.
40. Grover S, Xu MJ, Yeager A et al. A Systematic Review of Radiotherapy Capacity in Low- and Middle-Income Countries. *Frontiers in Oncology.* 2014;4:380.
41. Yvonne WJ, Lucia H, Nikolaus M. et al. Breast cancer treatment in sub Saharan Africa: A population-based registry study: *Journal of Global Oncology*:(2018). ,
doi.org/10.1200/JGO.18.10230
42. Feuchtner J, Mathewos A., Aynalem A., et.al. Addis Ababa population-based pattern of cancer therapy in Ethiopia. 2019. *PLoS ONE* 14(9) , doi.org/10.1371/journal.pone.0219519
43. Tumba.N, Adeyemi .AS. ,EguzoK A, et.al. Radiotherapy waiting time in Northern Nigeria: experience from a resource-limited setting. ***Ecancer.*** 2020, **14**:1097.
doi.org/10.3332/ecancer.2020.1097
44. Jana Bester. Retrospective analysis of treatment delay in Breast Cancer Radiotherapy. *Acta Scientific Cancer Biology* 2.10 (2018): 43-48
45. Kapoor T, Wrenn S, James TA. et.al. Analysis of patient detected breast cancer recurrence. *Breast Dis* 2017; 37:77-82.
46. Torunn Y, Alphonse G, Lisa A, et al. The effect of delaying radiation therapy for systemic chemotherapy on local-regional control in breast cancer. *Breast cancer research and treatment.* 2004;84:161-171.
47. Yock, T.I., Taghian, A.G., Kachnic, L.A. et al. The Effect of Delaying Radiation Therapy for Systemic Chemotherapy on Local-regional Control in Breast Cancer. *Breast Cancer Research and Treatment* .2004. 84:161–171. doi.org/10.1023/B:BREA.0000018414.36274.72
48. Meek AG., Park TL., Weiss TA., et.al .Effect of delayed radiation therapy on local control in breast conservation therapy. 1996. Published On
[line:https://doi.org/10.1148/radiology.200.3.8756905](https://doi.org/10.1148/radiology.200.3.8756905).

49. Giampro AC., Domenico G., Rita M., et.al . The Effect of Delaying Adjuvant Radiation Treatment after Conservative Surgery for Early Breast Cancer. *The Breast journal* .2007.13(6);575-580. <https://doi.org/10.1111/j.1524-4741.2007.00511.x>
50. Results of French Adjuvant Study Group .Influence of the Time between Surgery and Radiotherapy on Local Recurrence in Patients with Lymph Node-Positive, Early-Stage, Invasive Breast Carcinoma Undergoing Breast-Conserving Surgery .Meta analysis from 7 randomizes ,multi centric early breast cancer patients. *Cancer* 2005;104:240–50. 2005. American Cancer Society
51. Wilkinson NW, Shahryarinejad A, Winston JS, et al. Concordance with breast cancer pathology reporting practice guidelines. *J Am Coll Surg* 2003;196:38–43.
52. Gismall.MD.,Alshaihk.AA.,Elfatih .MM. ,et.al. Factors associated with local recurrence after mastectomy for invasive breastcancer in sudanese patients. *International Research on Medical Sciences*. 2014.;2;2, 026-30. <http://www.apexjournal.org>
53. Siponen, E.T., Joensuu, H., Leidenius, M.H. (2013). Local recurrence of breast cancer after mastectomy and modern multidisciplinary treatment. *Acta Oncol*.52(1): 66-72.
54. Shiferaw. W.,Ayinalem.Y.,AkaluT,et.al. Incidence and Predictors of Recurrence among Breast Cancer Patients in Black Lion Specialized Hospital Adult Oncology Unit.: Retrospective Follow-up Study with Survival Analysis. *J Cancer Prev* .2020, 25(2):111-118
55. Josenchait.HC.,Chii ming CH.,AndrewTH.,et.al. Loco regional failure of post mastectomy patients with 1–3 positive axillary lymph nodes without adjuvant radiotherapy.*Int J RadiatOncolBiolPhys* .2002; 52: 980-988. [DOI.org/10.1016/S0360-3016\(01\)02724-9](https://doi.org/10.1016/S0360-3016(01)02724-9)

Annex

Annex 1: Questionnaire for post mastectomy adjuvant RT breast cancer patient treated at TASH, Socio demographic and clinic-pathologic prognostic high-risk factor assessment tool at black lion hospital, radiotherapy center.

Socio Demographic characters:

Variables	Values
MRN	_____
1. Address	Region _____
2. Age	_____ Years
3. Sex	1. Female 2. Male
4. Religion	1. Christian 2. Muslim 3. Other
5. Marital status	1. Married 2. Single 3. Divorced 4. Widowed

Variables of Clinico pathology characters	Values
1. Any Comorbidity (Cardiac, renal, previous history of any cancer Rx)	1. Yes 2. No
2. Date of mastectomy/surgery (Biopsy date)	_____ DD/MM/YYYY)
3. Pathology Staging	Group Stage _____
4. Sub histology type	1. ductal carcinoma 2. lobular carcinoma
5. T-stage of the tumor	_____

6. Grade of the tumor	1.well differentiated2.moderately differentiated3.poorly differentiated
7. Surgical margin status	1.posative 2.negative 3.unkwon
8. Number of lymph node identified	_____
9. Number of lymph node positive	_____
10. Lymph node positivity ratio	_____
11. Lymph vascular invasion	1. Yes 2. No 3.unkwon
12. Date of registry for Radiotherapy	__(DD/MM/YYYY)
13. Date of initiation of Radiotherapy	__(DD/MM/YYYY)
14. Dose of radiotherapy	1.with boost 2.without boost
15. Date of last chemotherapy	__(DD/MM/YYYY)
16. Hormonal therapy initiation	1. Yes 2. No
17. Date recurrence confirmed	DD/MM/YYYY)
18. Site of recurrence	1.locoregional2.distant3.both
19. Loco regional Clinical tumor control after 4 years (with/without RT)	1. Stable2. Progressed3. Unknown
20. Current Status of patients	1. Alive 2. Dead3. Unknown

Annex 2: Patients treatment fellow chart

