OUTCOMES OF BREAST CONSERVATION SURGERY

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COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (WIA)

ADYAR

CHENNAI- 600020

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CERTIFICATE

I hereby certify that this is the bonafide work done by **DR. D. SURESH KUMAR** who is appearing for **M Ch Surgical Oncology Branch VII** examination in February 2009, under my guidance in the College of Oncological Sciences, Cancer Institute (WIA), Adyar, Chennai

Dr. E.HEMANTH RAJ M Ch, PhD
Professor and Chairman
Division of Surgical Oncology
Cancer Institute (WIA)
Adyar, Chennai

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The task would have been more difficult without the help of the staff of Tumor Registry at Cancer Institute (WIA), specifically **Mr. Shivakumar** who had the unenviable task of procuring all the case records instantaneously on demand.

Last but not the least, I thank all my patients for their kind co-operation in this study. May God Almighty bestow upon them good health.

CONTENTS

INTRODUCTION

Breast conserving therapy is becoming widely used method for treating breast cancer, since major clinical trials have demonstrated that subsequent survival was equivalent to that of mastectomy. In breast conserving therapy, post operative breast radiation has been reported to reduce cancer recurrence in the breast. Despite the abundance of literature there has been no analysis of the outcomes of patient undergoing this procedure in patients from South India, we therefore present our experience with breast conservation surgery.

Breast cancer is the most common malignancy among females in our cancer registry.

	1983-87CIR	1988-92CIR	1993-97CIR	1998-02CIR	2003-05CIR
Cervix	33.6	26.8	23.9	24.3	19.8
Breast	15.3	16.8	20.9	24.5	30.1

The number of patients undergoing breast conservation surgery is limited in our center because of -

1. Advanced stage of presentation

2. Preference for mastectomy compared to conservation.

HOSPITAL CANCER REGISTRY-CANCER INSTITUTE (WIA)

TUMOR STAGE	1980-89		1990-2000		2004-05	
	NO	%	NO	%	NO	%
I	30	1.4	58	1.3	17	1.4
II	447	21.3	884	21.9	345	29.1
III	908	43.2	1371	43.3	585	49.3
IV	454	21.6	412	15.5	101	08.5
SNP(stage not possible)	262	12.5	600	18.0	139	11.7
TOTAL	2101	100	3325	100	1187	100

AIM AND OBJECTIVES

1. To evaluate the outcome, pattern of failure and survival of breast conservation surgery performed at Cancer Institute.

2. To compare the recurrence, overall and disease free survival from neoadjuvant chemo and concurrent chemoradiation group.

3. To study the relationship of various risk factors influencing the outcome of BCS

REVIEW OF LITERATURE

Although radical and modified radical mastectomy (MRM) were the historical mainstay of the treatment for stage 1 and 2 breast cancer for decades and MRM continue to be appropriate for some patients, breast conservation treatment has become the preferred method of treatment for many patients. The results of prospective randomized trial as well as the results of large retrospective non randomized studies from single institutions have demonstrated the equivalence of mastectomy and breast conservation treatment for appropriately selected patients in early breast cancer

PROSPECTIVE RANDOMISED TRIALS

Six modern prospective randomized trials have compared mastectomy with conservative surgery and radiation for stage I and II breast cancer shown in table1,[1-9]

TABLE 1-Prospective randomised trials comparing conservative surgery and radiation with mastectomy for early breast cancer

Trial	Treatment period	Total no of patients	Stage	Surgery for primary	Adjuvant therapy
Milan[1,2]	1973-80	701	I	Q,RM	CMF
Institute gustave-roussy[3]	1972-1980	179	I	WE,MRM	NONE

NSABPB-06 [4,5]	1976-84	1,219	I-II	WE,MRM	Mel
National cancer institute[6]	1979-87	237	I-II	WE,MRM	AC
EORTC [7,8]	1980-86	868	I-II	LE,MRM	CMF
Danish breast cancer group [9]	1983-89	904	I-III	Q,WE, MRM	CMF, Tam

Mel- Melphalan, Tam - Tamoxifen

Whole breast irradiation with doses of 45 to 50 Gy was used in all trials, and boost to primary site was employed in five of the six trials .in the national surgical adjuvant breast and bowelproject(NSABP) trial ,a dose of 50 Gy was delivered to the entire breast without a boost, this trial required histological negative margin of resection for patients undergoing conservative surgery and radiation. For the remaining five trials,the total dose to the primary site was greater than or equal to 60 Gy. The resluts of these trials are presented in table 2 and 3

Table 2

Survival Comparisons for Conservative Surgery and Radiation (CS and RT) Versus Mastectomy in Prospective Randomized Trials					
Trial	End point In years	Overall Survival %		Disease –free Survival %	
		CS and RT	Mastectomy	CS and RT	Mastectomy
Milan 1[10]	18	65 (NS)	65		
Institut Gustave – Roussy[3]	15	73 (0.19)	65		
NSABP B - 06[4]	12	63 (012)	59	50 (0.21)	49
NCI [6]	10	77(0.89)	75	72 (0.93)	69
EORTC [7]	10	65 (NS)	66		
D B Cancer Group [9]	6	79 (NS)	82	70 (NS)	66

Table 3

Comparisons of Local Recurrence Following Conservative Surgery and Radiation (CS and RT) or Mastectomy in Prospective Randomized Trials			
Trial	Endpoint	CS and RT %	Mastectomy %
Milan 1[10]	Cumulative incidence at 18 years	7 (NS)	4
Institut Gustave – Roussy[3]	Cumulative incidence at 15 years	9 (NS)	14
NSABP B - 06[4]	Cumulative incidence	10	8
National Cancer Institute [6]	Crude incidence median follow – up at 10.1 years	19 (0.01)	6
EORTC [7]	Actuarial at 10 years	20 (0.01)	12
Danish Breast Cancer Group [9]	Crude incidence median follow – up at 3.3 years	3 (NS)	4

There are no significant differences in overall and disease-free survival rates when comparing the two treatments in any of the trials. In particular, patients with histologicaly positive nodes treated with chemotherapy have not been found to have improved survival rates when treated with mastectomy either in the NSABP B-6 trial or the MILAN I trial. [5,10]

In four of the six randomized trials, there was no significant difference in the risk of a recurrence in the treated breast or chest wall following mastectomy. In the National Cancer Institute (NCI) trial, a significantly higher local recurrence rate was observed in the breast conservation group. However in this trial, only gross tumor excision was required for study entry. Similarly EORTC trial, 81 percent of the patients in the BCS arm had T2 tumor and 48 percent had microscopically positive margins.

Local recurrence after breast preservation may be due to inappropriate patient selection, inadequate surgery or radiation therapy or biologically aggressive disease. Inadequate surgery may have contributed to the increased risk of breast recurrence in the NCI and the EORTC trials. Overall, the incidence of a recurrence in the treated breast ranges from 3 to 20 percent (table3). [3,4,6,7,9,10] The majority of failures in the treated breast can be salvaged with mastectomy, and survival following such treatment is appropriately 70 percent at five years. Primary mastectomy does not guarantee freedom from local recurrence in stage I and II breast cancer. The incidence of chest wall recurrence ranges from 4 to 14 percent.

A desire to avoid local recurrence is not a reason to encourage a patient who otherwise is a good candidate for breast conservation to choose mastectomy, since the procedures are associate with an equal risk of local failure in appropriately selected and treated women. A meta-analysis [11] of nine prospective randomized trials comparing conservative surgery and radiation to mastectomy has demonstrated no survival

differences. Local recurrence was reported in 6.2 percent of the mastectomy patients and in 5.9 percent of the patients treated with breast conservation.[11] The randomized trials have also addressed the issue of second malignancy related to radiation. There has been no difference in the incidence of contralateral breast cancer or a second non breast cancer malignancy.

In addition to the randomized trials comparing breast conservation (with excision and radiation) with mastectomy, ten randomized trials have compared conservative surgery alone with conservative surgery and radiation. The published results of nine of these trials are summarized in table 4 and 5.[10,12-19]

Table 4

Prospective Randomized Trials Comparing Conservative Surgery With and Without Radiation Therapy					
Comparisons of local recurrence following conservative surgery and radiation (CS and RT) or Mastectomy in prospective randomized trials.					
Trial	No of Pts	Tumor Size (cm)	Pathologic Nodal Status	Surgery	Systemic Therapy
Swedish [12]	381	< 2	N-	Q	None
Milan III[10, 13]	601	< 2.5	N – or N +	Q	CMF/Tam N+
Ontario [14]	837	< 4	N -	L	None
NSABP B – 06[4]	1,265	< 4	N + or N -	L	L – Pam5FU for N+
NSABP B – 21[15]	1,009	< 1	N-	L	Tam
Scottish [16]	556	< 4	N – of N+	WE	CMF /Tam N+
British [17]	399	≤ 5	N – or N +	WE	CMF or Tam
BASO II [18]	241	≤ 2	N-	WE	Tam
West Midlands [19]	707	≤ 4	Clin N -	WE	Tamoxifen

Table 5

Local Recurrence and Survival in Prospective Randomized Trials Comparing Conservative Surgery With and Without radiation Therapy					
	Breast Recurrence %		Overall Survival %		Interval Results
Trial	CS	CS + RT	CS	CS + RT	Reported
Milan III [10],[13]	18	2	92	92	5 – year actuyrial
Swedish [12]	24	9	78	78	10-year actuarial
Ontario [14]	40	18	72	74	10-year actuarial
NSABP B-06[4]	35	10	58	62	12-year actuarial
NSABP B-21[15]	12	6			Crude 6.1-year mean
Scottish [16]	28	6	85	88	5-year actuarial
Positive ER	25	3			
Negative ER	44	14			
British [17]	35	13			5-year actuarial
BASO II[18]	5	2	98	98	Crude 4-year median
West Midlands [19]	13	4			Crude 2-year mean

The trials vary with regard to patient selection, extent of surgery and radiotherapy, and the use of adjuvant systemic therapy. Quadrantectomy was employed in the Milan and Swedish studies, and adjuvant chemotherapy and /or tamoxifen was used in NSABP, MILAN, BRITISH, SCOTTISH, AND WEST MIDLANDS trials. Despite these

differences all of the trials demonstrated a reduction in the rate of recurrence in the breast in the irradiated group (an average crude rate of reduction of 84 percent, ranging 73 to 97 percent). Recent metaanalysis of ten randomized trials comparing conservative surgery to conservative surgery and radiation reported an absolute reduction in breast recurrence rates with radiation of 17 percent for axillary node negative women(25 versus 7.8 percent) and 19 percent for axillary node positive women(35.4 vs16.1 percent).[11] The absolute benefit from radiation for any recurrence was 16 percent for node negative group(44.7 vs 28.6 percent, p= <.00001) and 8 percent for the node positive group (58 versus 49.8 percent, p=.002)

Subset analyses within these trials have identified older women (greater than 55 yrs of age) with small primary infiltrating ductal tumors (less than 1to 2 cm) and negative axillary nodes that lack an extensive intraductal component (EIC) or lymphatic invasion as having lowest risk of recurrence when radiation is omitted.[10,12-14] In the Swedish trial ,the breast recurrence rate at ten years in this subset of patients was 11 percent after quardrantectomy alone, compared with 6 percent for quadrantectomy and radiation. Therefore, even in the lowest risk group, radiation decreased the risk of a breast recurrence. In a single arm prospective study of 81 women (median age 66 years) with primary tumors less than or equal to 2 cm without an EIC or lymphatic invasion excised with negative margin greater than or equal to 1 cm and with negative axillary nodes treated without radiation, the crude recurrence rate was 23 percent (median follow up of 7.2 years).[20]

The NSABP B-21 addressed this question in axillary node negative women with primary tumor less than or equal to 1 cm. Patients were randomized to tamoxifen alone, radiation, or radiation and tamoxifen. With a median follow up of 6.1 years, ipsilateral breast tumor recurrence were reported in 12 percent of the 336 patients who received tamoxifen, 6 percent in the 336 women treated with radiation and 2 percent in the 337 women treated with tamoxifen and radiation. [15] there was no difference in overall survival and cause specific survival. This study suggests that tamoxifen cannot replace radiation even in most favorable tumors.

The British association of surgical oncology (BASO) II trial randomized women with primary tumors less than 2 cm, histologicaly grade1, and negative axillary nodes to wide excision with or without tamoxifen or wide excision and radiation with or without tamoxifen. With median follow up of 4 years, ipsilateral breast tumor recurrence rate in the 120 patients who did not received radiation was five percent compared with two percent in the 121 women who received radiation.[18] Radiation therefore appears to benefit all women with early stage invasive breast cancers, although magnitude of this benefit varies depending upon the selection of the patients.

Non randomized studies

The results of multiple, non randomized studies further support the equivalence of breast conservation treatment and mastectomy in appropriately selected patients (tables 6 and 7)[2,21-30]

Table 6

Survival Following Conservative Surgery and Radiation for Early-stage Breast Cancer (Nonrandomized Studies)		
Studies	Number of Patients	10 – year Survival
Stage I and II		
Fowble et al. [21]	697	83
Haffty et al. [22]	278	67
Leung et al. [23]	493	68
Mansfield et al. [24]	1,070	80†
Spitalier et al. [25]	1,133	80
Stotter et al. [26]	490	74
Kini et al. [27]	390	74
Stage I		
Dewar et al. *[28]	757	79
Veronesi et al. [2]	1,232	78
Perez et al. [29]	520	85†
Zafrani et al. *[30]	434	86
Kini et al. [27]	281	88

Table 7

Recurrence in the Breast After Conservative Surgery and Radiation for Early – stage Breast Cancer (Nonrandomized Studies)			
Study	Number of Patients	Maximum Primary Tumor Size (cm)	Breast Recurrence at 10 years (%)
Gage et al[31]	1,628	5	13
Kurtz et al. 32,33	1,593	5	14
Meric34	1,236	5	10
Veronesi et al. 1	1,232,	2	8
Clark et al. 35	1,130	5	14
Mansfield et al [24]	1,070	5	14
Dewar et al. 34	757	3	8
Fowble et al. 36	697	5	18
Fourquet et al. 37	518	5	11
Halverson et al. 38	511	5	14
Leung et al. 23	493	5	10
Haffty et al. 22	433	5	19
Kini et al. 27	390	5	10

At ten years, overall survival has ranged from 67 to 88 percent depending upon the stage of the disease (table 6). Disease – free survival at ten years is approximately 70 percent. These series have also demonstrated excellent long- term control within the treated breast with primary tumors less than or equal to 5 cm in diameter (table7). [1,2,22-24,27,28,31-38] At ten years , local recurrence rate ranges from 8 to 19 percent. For patients with negative margin of resection, the ten years actuarial risk of breast recurrence is 10 percent or less. The overall survival and local control rates in the breast reported by these retrospective series are comparable to the results of the six prospective randomized trials.

Neoadjuvant chemotherapy offers several advantages compared with traditional postoperative regimens. Invasive breast cancer patients have significant risk of harboring occult micrometastatic disease in distant organs. Neoadjuvant chemotherapy allows for earlier exposure of these micrometastases to chemotherapy agents, and an observed response to chemotherapy in the primary breast disease site indicates that the regimen has effective antitumor activity. Additionally, for women who experience significant regression of their tumor, neoadjuvant chemotherapy can allow for a more conservative surgical procedure.

NSABP B-18 trial compared outcomes between patients receiving adjuvant and neoadjuvant chemotherapy, using survival and breast conserving surgery as end points. In this study, more than 1500 women who had operable breast cancer were randomized to four cycles of doxorubicin and cyclophosphamide either pre- or post operatively, with 9 years of follow up reported. There were no significant difference in overall survival or disease free survival between women who received neoadjuvant chemotherapy and women who received adjuvant chemotherapy, with overall survival for both groups was 70% at 9 years of follow up. DFS for both groups ranged between 53%and 55%. Among women receiving neoadjuvant chemotherapy, tumor size was reduced in 80%, 36% had a complete clinical response, and 13% had a complete pathologic response. Survival rates were significantly higher among the complete pathologic responders compared to other subsets. Despite using a wide variety of chemotherapeutic agents, the majority of studies have shown that neoadjuvant chemotherapy offers similar overall survival and

DFS compared with adjuvant regimens. Both DFS an OS from these studies range from 55%to 89%. A recent meta-analysis by Mauri et al summarized nine randomized controlled trials that randomized women to either neoadjuvant or adjuvant chemotherapy. These authors report no difference in mortality between patients who received neoadjuvant and adjuvant chemotherapy (RR-1.0, 95% CI, .9-1.12).

One of the most important benefits of neoadjuvant chemotherapy is that it offers tumor down-staging, expanding the number of women eligible for BCS, but the cosmetic results improved with smaller tumors. NSABP B-18 trial reported that women who received preoperative chemotherapy were significantly more likely to receive a lumpectomy compared with women who received adjuvant therapy (60% vs67%, $p<.002$), with greatest increase in lumpectomy rates among women who had tumors larger than 5 cm. Other authors have studied BCS in the setting of neoadjuvant chemotherapy with comparable results. Rates of BCS range from 37%to 89%. In fact approximately one-quarter of women who are not initially eligible for BCS, but who receive neoadjuvant chemotherapy, may safely receive BCS following chemotherapy because of tumor shrinkage.

There is not much evidence on concurrent chemoradiation in literature, however there are few studies, our own institute study published earlier by V. Shanta et al, shown that combination of radiation and chemotherapy achieved a tumor sterility rate of 45% [41]. Other studies done in the University of Southern California conducted a pilot study

using continuous infusion of 5FU during radiotherapy in 35 patients with LABC. The overall clinical response was noticed in 72 %. The pathological CR rate was 20%. Johnny kao and colleagues reported the results from two consecutive phase I/II trials where concurrent paclitaxel +/- vinorelbine with radiotherapy in unresectable LABC shown a pathological CR was 46%. Present study pathological CR following neoadjuvant concurrent chemoradiation was 56% [42]. Formenti and colleagues reported a trial of forty four T3-T4 N0-3 breast cancers twice weekly with neoadjuvant radiation with concomitant twice weekly paclitaxel. A 16% complete pathological response rate[43]. There is no literature evidence for in-breast recurrence following neoadjuvant chemoradiation in breast conservation surgery.

MATERIALS AND METHODS

Pooled data from patients undergoing breast conservation surgery for early breast cancer over a 11 year period from 1995 to 2005 was retrospectively evaluated and analyzed.

A total number of breast cancer patients treated in our institute from 1995 to 2005 was 5589, of this 1564 case were early breast cancer. In this period 145 breast conservation surgery were performed from this early breast cancer group and selected stage III A patients. The numbers of conservation surgeries are low in our institute because of advanced stage at presentation and the preference for Mastectomy in our patients.

All patients underwent thorough clinical examination, with initial staging work-up, which included FNAC / Tru-Cut biopsy of primary lesion, for patients who underwent excision biopsy outside, the slides were reviewed in the institute. Routine hemogram, renal function test, liver function test, chest x-ray, electrocardiogram, CECT-chest, bone scan and echocardiogram were done for all patients. Predictive factors like estrogen and progesterone receptors and Cerb2 were done for some patients.

Neoadjuvant treatment, like chemotherapy and concurrent chemoradiation were used in some patients. Chemotherapy regimens used were CMF, FAC, FEC and TAXANE based, alone or concurrently with radiation. Radiation dose used was 40 GY to Breast and Axilla as per our Institute protocol.

Surgical treatment consisted of wide local excision and axillary dissection with gross tumor surgical margin of 2cm or more, frozen section was used to confirm negative margins. For patients who received neoadjuvant therapy underwent surgery after third or fourth cycle of chemo therapy, patients who received concurrent chemoradiation underwent surgery after four weeks from last date of radiation. Patients, who underwent straight surgery, did so after confirming diagnosis and completing staging work-up. Those who underwent excision biopsy outside were reexcised with 2 cm gross margins.

Surgical morbidity like seroma, marginal necrosis, wound infection and flap loss, hematoma were assessed postoperatively. Pathological assessment include primary tumor size, histological type, grade, margin status, pathological response, lymph nodes dissected and involved.

ADJUVANT TREATMENT

All patients received adjuvant treatment according to tumors characteristic, adjuvant treatment given are, radiation therapy –for those who received preoperative radiation ,post operatively received boost to tumor bed doses of 20-30 GY, other patient received 40 GY radiation to breast and axilla and boost to tumor bed doses of 20-30GY. As indicated radiation to SCL and INTERNAL MAMMARY NODES are used. Chemotherapy were used in indicated patients with various regimen like CMF, FAC, FEC, TAXANE based, totally 6 cycles were used , those patients who received pre operatively completed there remaining cycle postoperatively. Hormone therapy like

tamoxifen and aromatase inhibitors were used as indicated for 5 years duration.

FOLLOW UP

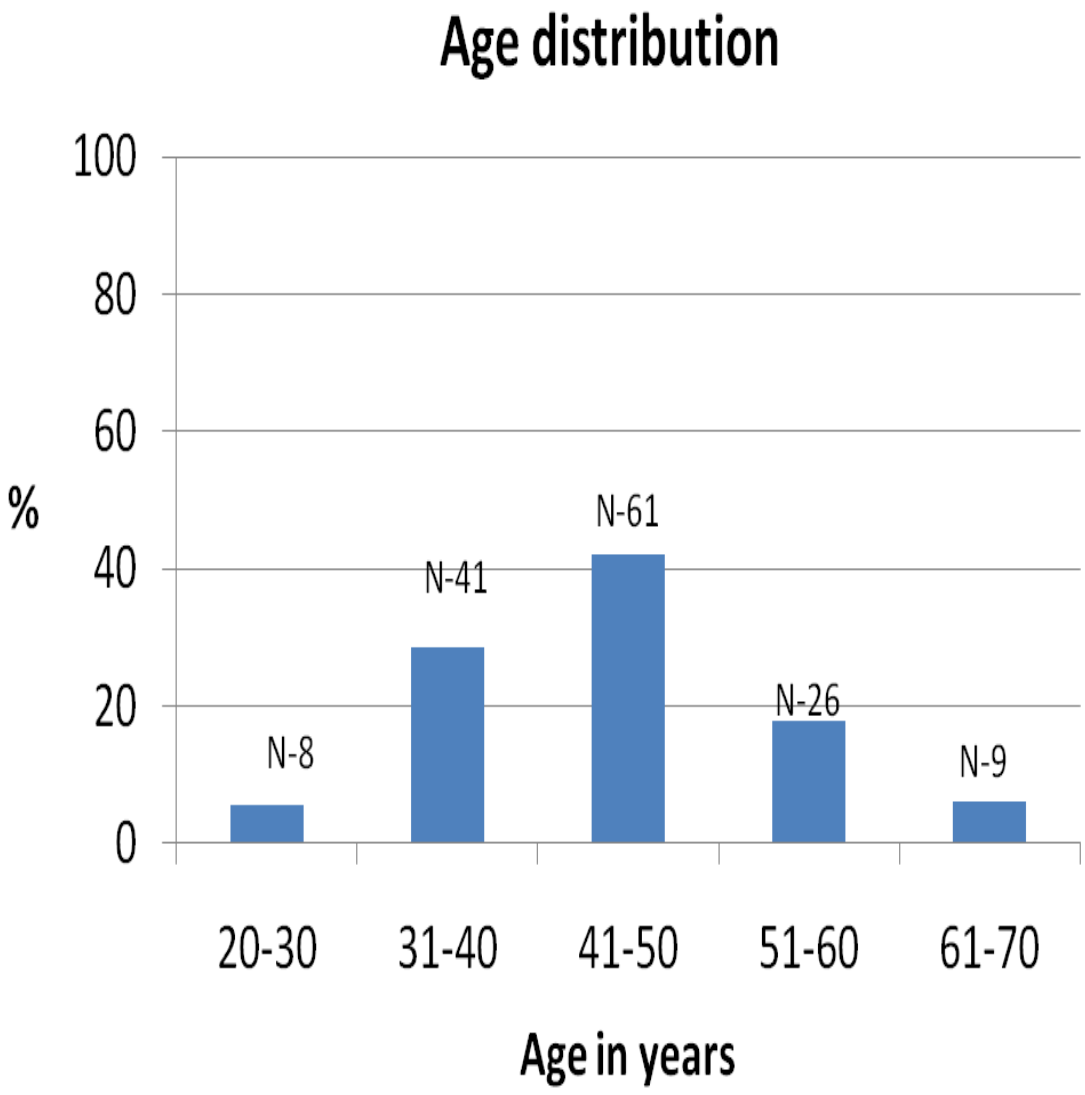
All patients were followed up for 3monthly for first three years, and 6 monthly for next two years and yearly thereafter. In each visit, history, through clinical examination was done, annually ultrasound liver, ipsilateral and contra lateral mammogram, liver function tests were done. Symptoms oriented investigations were done whenever indicated.

STATISTICAL ANALYSIS

Done by actuarial methods calculated using SPPS software.

RESULTS

Most of our study patients belongs to age group 30-50yrs . This is one decade earlier than western population.



CLINICAL CHARACTERSTICS OF PATIENTS

Variables		No of pts	%
Tumor size	1cm&<1cm	5	3.0
	1.1-2cm	23	15.8
	2.1-5cm	110	73.7
	>5cm	7	4.8
Stage	Stage I	17	11.7
	StageIIA	51	35.7
	StageIIB	66	45.5
	StageIIIA	11	7.5
Menopausal status	Premenopausal	92	63.3
	postmenopausal	53	36.5
Receptor status	Positive	60	41.3
	Negative	68	46.8
	Unknown	17	11.7
Underwent excision	Yes	51	35
biopsy outside	No	94	65

TREATMENT CHARACTERSTICS

Out of 145 patients 23 patients underwent straight surgery and the rest received neoadjuvant therapy either as chemo alone or concurrent CTRT.

	No of pts	%
STRAIGHT SURGERY +POST OP RADIATION	23	15.9
NEOADJUVANT CHEMOTHERAPY	41	28.3
NEOADJUVANT CHEMORADIATION	81	55.9

PATHOLOGICAL ASSESMENT FOLLOWING NEOADJUVANT TREATMENT (EXCLUDING PATIENTS WHO UNDERWENT EXICISION OUTSIDE)

PATHOLOGICAL RESPONSE	NEO ADJUVANT CHEMOTHERAPY %	NEOADJUVANT CHEMORADIATION %
CR	6	43
PR	68	52
NO RESPONSE	26	5

COMPLICATIONS

- Radiation toxicity in CT-RT - grade III desquamation 8(10%)

Among 81 patients in concurrent CT-RT 8 patients developed grade 3 desquamation, rest fell into grade 1&2

Surgical morbidity

	SEROMA	WOUND INFECTION	WOUND GAPING
STRAIGHT	4(17%)	3(13%)	3(13%)
NEOADJUVANT CHEMO	9(21%)	5(12%)	4(9%)
NEOADJUVANTCHEMORA -DIATION	10(12%)	18(22%)	18(22%)

RECURRENCE

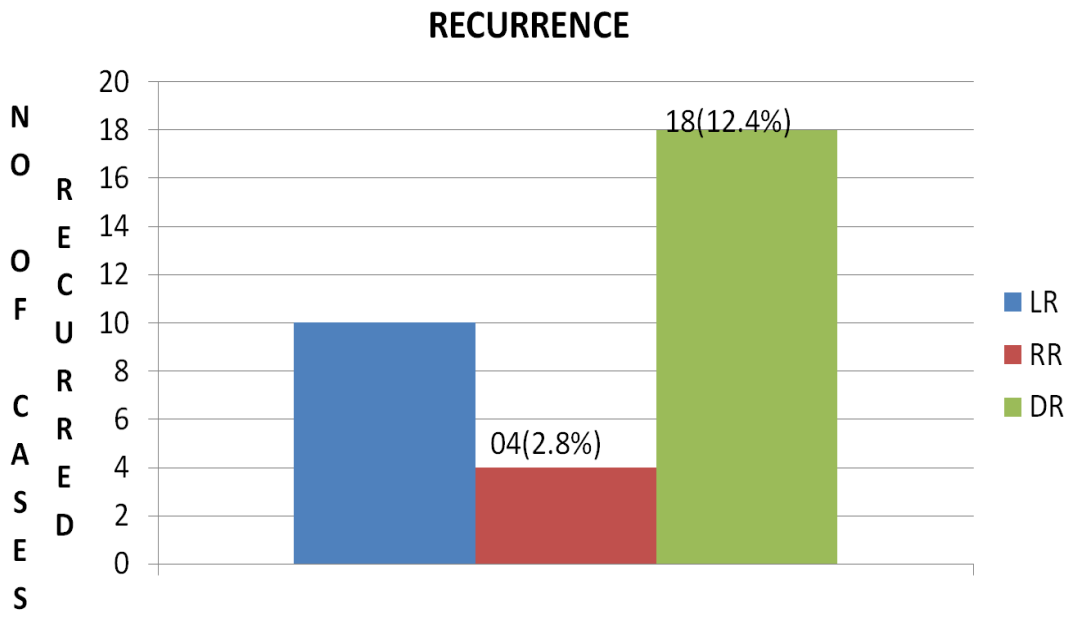
Recurrence pattern following breast conservation treatment.

14 patients developed local recurrence.

Median time to recurrence is 31 months, duration range from (7months- 89 months)

Site	%

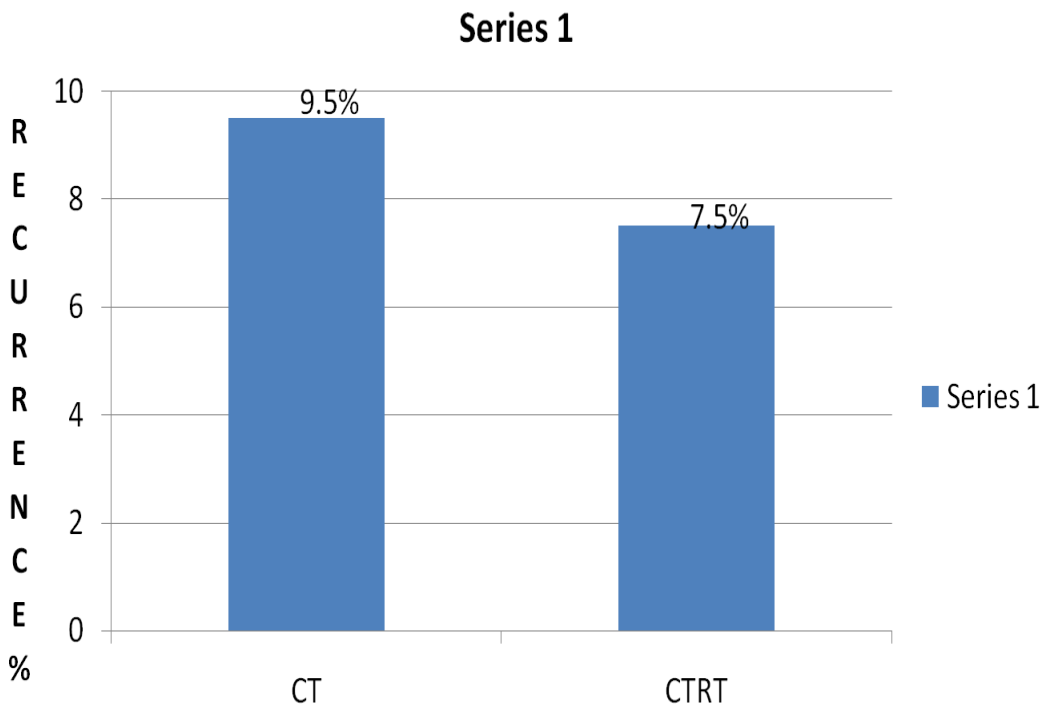
LOCAL RECURRENCE	6.9
NODAL RECURRENCE	2.8
DISTANT FAILURE	12.4



LOCAL RECURRENCE IN CT &CTRT ARM

Local recurrence following neoadjuvant chemotherapy and concurrent chemoradiation

NEOADJUVANT CHEMOTHERAPY	9.5%
NEOADJUVANT CONCURRENT CHEMORADIATION	7.5%



RECURRENCE IN RELATION TO INITIAL SIZE OF TUMOR

	RECURRENCE PRESENT	NO RECURRENCE	TOTAL
<1cm	O	5	5
1.1-2cm	2 (8.7%)	21(91.3%)	23
2.1-5cm	11(10%)	99(90%)	110
>5cm	1(14.3%)	6(85.7%)	7
	14	131	145

Not statistically significant p=.58

RECURRENCE IN RELATION TO MARGIN STATUS

	RECURRENCE PRESENT	NO RECURRENCE	TOTAL
>1cm	11(9.2%)	108(90.8%)	119
1mm-10mm	1(4.8%)	20(95.2%)	21
Positive margin	2(40%)	3(60%)	5

p-value=.53

RECURRENCE IN RELATION TO STAGE GROUP

STAGE	RECURRENCE PRESENT	NO RECURRENCE	TOTAL
I	2 (11.8%)	15(88.2%)	17
IIA	3 (5.6%)	48(94.4%)	51
IIB	8 (12.1%)	58(87.9%)	66
IIIA	1 (9%)	10(91%)	11
	14	131	145

P-VALUE=.829

RECURRENCE IN RELATION TO MENSTRUAL STATUS

	RECURRENCE PRESENT	NO RECURRENCE	TOTAL
PREMENOPAUSE	11(12%)	81(88%)	92
POSTMENOPAUSE	3(5.7%)	50(94.3%)	53
	14	131	145

P-VALUE=.257

RECURRENCE IN RELATION TO RECEPTOR STATUS

	RECURRENCE PRESENT	RECURRENCE ABSENT	TOTAL
ER ,PR-POSITIVE	4(6.7%)	56(93.3%)	60
ER,PR-NEGATIVE	9(13.2%)	59(86.8%)	68
UNKNOWN STATUS	1(5.9%)	16(94.1%)	17
	14	131	145

P-VALUE=.254

RECURRENCE IN RELATION TO EXICISION OUTSIDE

	RECURRENCE PRESENT	RECURRENCE ABSENT	TOTAL
EXICISION BX NOT DONE	8 (8.5%)	86(91.5%)	94
DONE	6 (11.7%)	45(88.3%)	51
	14	131	145

P-VALUE=.563

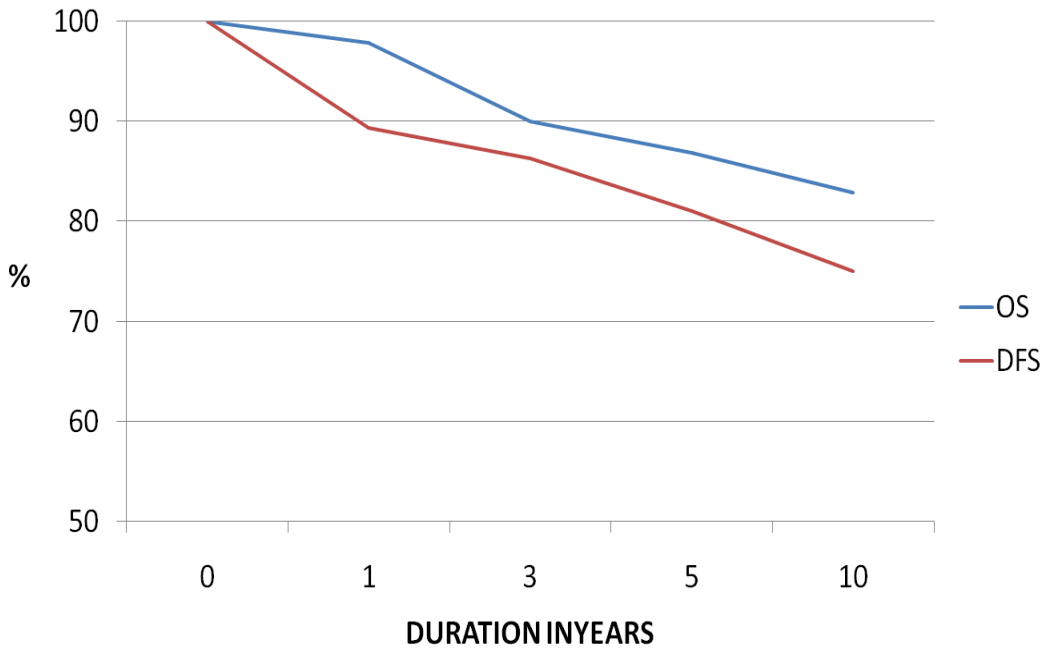
OVERALL SURVIVAL AND DISEASE FREE SURVIVAL

5 yrs and 10 yrs Overall survival and disease free survival in this study is 86.9%,

82.9%and81.0%, 75.0% respectively,

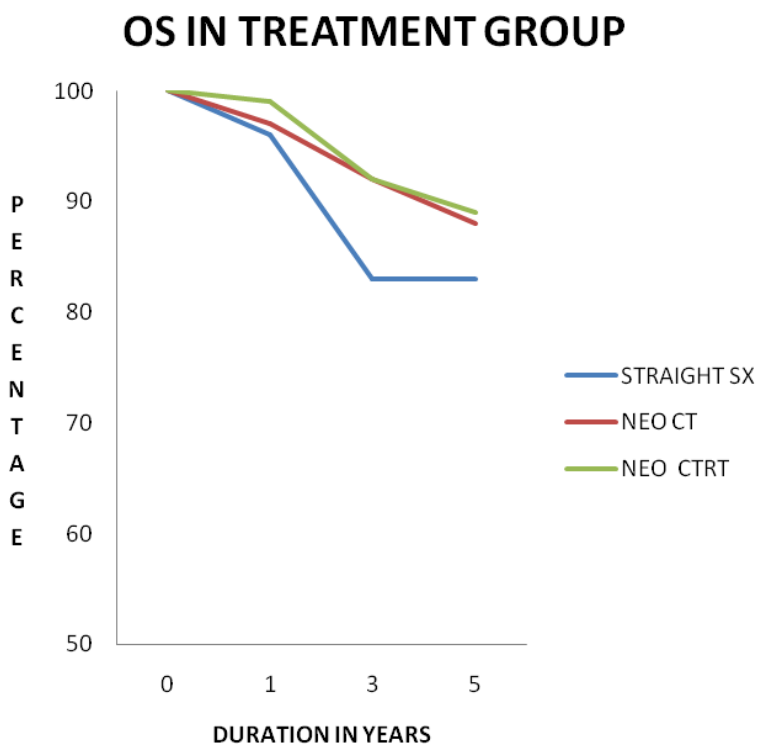
	OVERALL SURVIVAL	DISEASES FREE SURVIVAL
5 YRS	86.9%	81.0%
10YRS	82.9%	75.0%

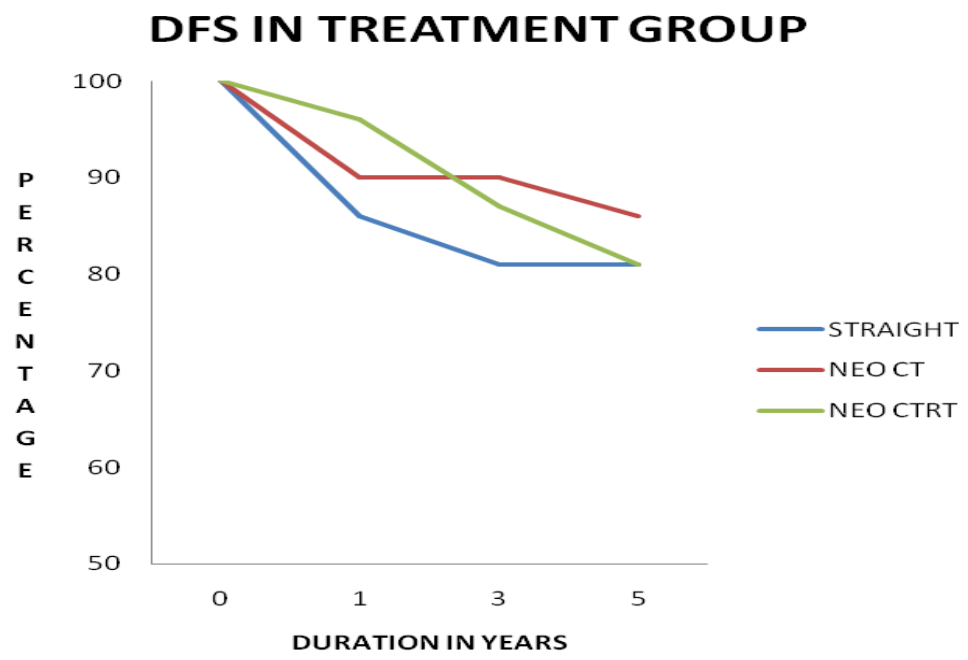
5 yrs DFS-81% & OS-86%.



OUP

	5 YRS OVERAL SURVIVAL	5 YRS DFS
STRAIGHT SURGERY	83.4%	81%
NEOADJUVANT CHEMO	88.1%	86%
NEOADJUVANT CHEMORADIATION	88.6%	83%
	P= .956	P=.975


OS IN TREATMENT GROUP
PERCENTAGE
100
90
80
70
60
50
0
1
3
5
DURATION IN YEARS
STRAIGHT SX
NEO CT
NEO CTRT



5 YRS OS AND DFS IN RELATION TO PATHOLOGICAL RESPONSE, STAGE WISE, MENOPAUSAL AND RECEPTOR STATUS.

	5 YRS DFS	P VALUE	5YRS OS	P-VALUE
PATHOLOGICALRESPONSE				
CR	83.2%	P=.786	86.4%	P=.698
PR& NO RESPONSE	83.3%		85.0%	
STAGE				
I	88.2%		93%	
IIA	84.7%	P=.841	87.9%	P=.903
IIB	79.8%		86.9%	
IIIA	88.8%		90.0%	

MENOPAUSAL				
PRE	83%	P=.776	87%	P=.7235
POST	83.9%		89%	
RECEPTORS				
ER,PR POSITIVE	90%	P=.6796	90%	P=.455
ER,PR-NEGATIVE	83%		83%	

DISCUSSION

This study was conducted to analyses the results of breast conservation treatment performed in Cancer Institute (WIA) Chennai, South India. To evaluate the outcomes of breast conservation treatment compared to historical studies. Totally 145 patients were included, out of which 16 % of patient underwent straight surgery , 28% received neoadjuvant chemotherapy and 56% received neoadjuvant chemoradiation followed by surgery.

Most of our study patients belong to 30-50 years of age group. This is one decade earlier than the western population. Breast conservation surgery was performed only for stage I to IIIA. Most of the patients were in stage IIA and IIB (35.7%& 45.5%). Regarding receptor status 41% were receptor positive, 46.8% were receptor negative, with unknown receptor status around 11%

Neoadjuvant chemotherapy and chemoradiotherapy often referred to as an emerging concept, has been practiced at the Cancer Institute since 1960. Multimodality treatment of LABC is the accepted standard care today. Primary chemotherapy has been reported widely in operable breast cancer and LABC.[40]

Analysis of pathological response in our study shows that complete response following neoadjuvant chemotherapy shown similar results with literature; it has been reported in literature that rates of complete pathological response ranges from 3-30 % with neoadjuvant chemotherapy alone, with promising results seen with dose-dense,

multiagent chemotherapy.

There is not much evidence on concurrent chemoradiation in literature, however there are few studies, our own institute study published earlier by V.Shanta et al , shown that combination of radiation and chemotherapy achieved a tumor sterility rate of 45% [41]. Other studies done in the university of southern California conducted a pilot study using continuous infusion of 5FU during radiotherapy in 35 patients with LABC. The overall clinical response was noticed in 72 %. The pathological CR rate was 20%. Johnny kao and colleagues reported the results from two consecutive phase I/II trials where concurrent paclitaxel +/- vinorelbine with radiotherapy in unresectable LABC shown a pathological CR was 46%. Present study pathological CR following neoadjuvant concurrent chemoradiation was 56% [42]. Formenti and colleagues reported a trial of forty four T3-T4 N0-3 breast cancer twice weekly with neoadjuvant radiation with concomitant twice weekly paclitaxel. A 16% complete pathological response rate.[43]

Complete pathological response excluding patients who underwent excision outside was in chemotherapy was 6% and chemoradiation group achieved 43%. There is no literature evidence so far for chemoradiation for early breast cancer. This increased complete pathological response does not translate into overall survival in our study.

Commonest complications were seroma, wound infection and wound gaping. Wound infection and gaping were slightly more in patients underwent concurrent chemoradiation as compared to straight or neoadjuvant chemotherapy which was not

statistically significant. Jayananad SB et al studied wound morbidity after neoadjuvant chemotherapy radiotherapy in breast surgery ,were they shown a greater than usual seroma collection for about 7- 10 days in about 15% cases , no margin skin morbidity, such as skin necrosis or breakdown of incision related to chemoradiation , wound infection rate was 5.8% [44].

The overall survival and disease free survival at 5 yrs was 86.1% and 81% and at 10 yrs was 82.9% and 75 % respectively, survival rate of our study were similar to those found elsewhere [1,2,3,4,5,6,7,8,9] . Six modern prospective randomized trials have compared mastectomy with conservative surgery and radiation for stage I and II. NSABP B-06 at 12 yrs follow up shows overall survival was 63% and disease free survival was 50%, In NCI and EORTC at 10 yrs follow up OS was 77% and 65% .Danish breast cancer group at 6 yrs follow OS and DFS were 79% and 70%. Milan I at 18 yrs follow up OS was 65%, DFS was not reported.

Whole breast irradiation with doses of 45 to 50 Gy was used in all trials, and boost to primary site was employed in five of the six trials . In the national surgical adjuvant breast and bowel project(NSABP) trial ,a dose of 50 Gy was delivered to the entire breast without a boost. For the remaining five trials,the total dose to the primary site was greater than or equal to 60 Gy.In our study,dose of 40 GY was deliverd to breast and axilla with boost dose 20-30 GY.

The results of multiple, non randomized studies further support the equivalence of

breast conservation treatment and mastectomy in appropriately selected patients. At ten years, overall survival has ranged from 67 to 88 percent depending upon the stage of the disease .Disease – free survival at ten years is approximately 70 percent.[2,21-30]

We also compare the overall survival and disease free survival in patients who underwent upfront surgery, neoadjuvant chemo and neoadjuvant chemoradiation which did not reveal any statsitical difference.

The local recurrence rate in our study was 6.9% and the distant failure rate was 12.4% which is comparable with historical studies [1-9].comparing our study with literature, in four of the six well conducted randomized trials, there was no significant difference in the risk of a recurrence in the treated breast or chest wall following mastectomy. In the National Cancer Institute (NCI) trial, a significantly higher local recurrence rate was observed in the breast conservation group. However in this trial, only gross tumor excision was required for study entry. Similarly EORTC trial, 81 percent of the patients in the BCS arm had T2 tumor and 48 percent had microscopically positive margins.

Local recurrence after breast preservation may be due to inappropriate patient's selection, inadequate surgery or radiation therapy or biologically aggressive disease. Inadequate surgery may have contributed to the increased risk of breast recurrence in the NCI and the EORTC trials. Overall, the incidence of a recurrence in the treated breast ranges from 3 to 20 percent. The majority of failures in the treated breast can be

salvaged with mastectomy, and survival following such treatment is appropriately 70 percent at five years. Primary mastectomy does not guarantee freedom from local recurrence in stage I and II breast cancer. The incidence of chest wall recurrence ranges from 4 to 14 percent.

A meta-analysis [11] of nine prospective randomized trials comparing conservative surgery and radiation to mastectomy has demonstrated no survival differences. Local recurrence was reported in 6.2percent of the mastectomy patients and in 5.9 percent of the patients treated with breast conservation.[11]

In addition to the randomized trials comparing breast conservation (with excision and radiation) with mastectomy, ten randomized trials have compared conservative surgery alone with conservative surgery and radiation. The trials vary with regard to patient selection, extent of surgery and radiotherapy, and the use of adjuvant systemic therapy. Quadrantectomy was employed in the Milan and Swedish studies, and adjuvant chemotherapy and /or tamoxifen was used in NSABP, MILAN, BRITISH, SCOTTISH, & WEST MIDLANDS trials. Despite these differences all of the trials demonstrated a reduction in the rate of recurrence in the breast in the irradiated group (an average crude rate of reduction of 84 percent, ranging 73 to 97 percent). Recent metaanalysis of ten randomized trials comparing conservative surgery to conservative surgery and radiation reported an absolute reduction in breast recurrence rates with radiation of 17 percent for axillary node negative women(25 versus 7.8 percent) and 19 percent for axillary node

positive women(35.4 vs16.1 percent).[11] The absolute benefit from radiation for any recurrence was 16 percent for node negative group(44.7 vs 28.6 percent, p= <.00001) and 8 percent for the node positive group (58 versus 49.8 percent, p=.002).

Subgroup analysis done in our study shown that breast recurrence following neoadjuvant chemoradiation is 7.5% and following chemotherapy is 9.5%.There is no literature evidence for in-breast recurrence following neoadjuvant chemoradiation in breast conservation surgery.

Table

	END POINT	LOCAL RECURRENCE	DFS %	OS%
OUR STUDY	5YRS	6.9%	81%	86.9%
MILANI	18YRS	7%	-	65%
INSTIUTE GU	15YRS	9%	-	73%
NASBP06	12YRS	10%	50%	60%
NCI	10YRS	19%	72%	77%
EORTC	10YRS	20%	-	65%
DBCG	6YRS	3%	70%	79%

Various factors studied in relation to recurrence in our study. None of the factors was

statistically significant.

The recurrence in relation to tumor size there were no recurrence in tumor size <1cm and most of the recurrence in the tumors with 2-5cm. In relation to margin, most of the recurrences occur in margin more than 1 cm. Two out of 5 patients with positive margin developed recurrence.

Menopausal status, receptor status and prior excision outside does not influence in recurrence pattern. In literature various factors have been studied, like histology type, presence of necrosis, lymphovascular invasion, lymphocyte infiltration, the presence of DCIS in association with an invasive ductal carcinoma, margins of resection, and pathologic nodal status.

The presence of vascular or lymphatic invasion, tumor necrosis, and an inflammatory infiltrate has been associated in a few studies with a somewhat increased risk of breast recurrence. This risk is approximately 10 to 15 percent at five years. Some series have also found an increased risk of breast recurrence in patients with high histologic – grade tumors compared with low – grade tumors, although this has not been a consistent finding. Histologic subtype other than invasive ductal carcinoma does not appear to be associated with an increased or decreased risk of breast recurrence.

The impact of the final resection margin on breast recurrence rates varies. Long – term data on the use of breast – conserving therapy in patients with positive margins is limited. In the majority of the reported series, positive margins of resection have been

associated with an increased risk of breast recurrence, The variation in these results may be related to the extent of the surgical resection for the primary tumor, the presence or absence of an EIC, the definition of a positive margin, the number of margins that are positive, and the extent of the margin positivity.

In the Milan II trial, [10] the breast recurrence rate for patients with positive margins was 12 percent for those undergoing a quadrantectomy compared with 17 percent for those whose primary surgical procedure was lumpectomy. At the JCRT, patients with positive margins had a considerably higher risk of breast recurrence than patients with negative margins. The eight – year crude rate of breast recurrence was 18 percent for patients with positive margins. Additional experience is needed to confirm this finding, and negative margins should be the goal of breast-conserving therapy

Analyses of risk factor did not reveal any statistical significance with regards to outcome as measured by DFS and OS.

Our study results of breast conservation results comparable with literature, addition of neoadjuvant therapy especially neoadjuvant chemoradiation did not show any advantage. As for breast conservation surgery is concerned radiation therapy is a must . So, why not radiation can be combined with chemotherapy in neoadjuvant protocol, so that we can reduce the duration of treatment? Additional experience is needed to confirm this finding.

CONCLUSION

In conclusion in our study there was an increased pathological complete response and partial response in patients undergoing neoadjuvant chemo radiation, but it was not translated into overall survival when comparing with neoadjuvant chemotherapy and straight surgery. The results of breast conservation surgery from our institute are comparable with those in literature. Since our study is limited by the small samples, it needs to be validated in a larger study.

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