Evaluation of the Role of Radiotherapy in Early Breast Cancer

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Abstract: Purpose: Retrospective study for evaluation of the role of radiotherapy in early breast cancer patients T1-2 M0 with (0-3 positive axillary LNs) as regard disease free survival (DFS) and over all survival (OS). Patients and methods: Between January 1999 to December 2004, ninety patients pathologically confirmed early breast cancer were classified into two groups, 50 patients in the first group were treated with Modified Radical Mastectomy (MRM) + adjuvant radiation therapy + systemic therapy (Chemotherapy and/or hormonal therapy) and 40 patients in the second group were treated with MRM + adjuvant systemic therapy. All patients entered in this study were monitored for treatment related events, toxicity, loco-regional and distant failure, time to death and survival. The (OS) rates and(DFS) rates depicted on Kaplan Meier plots. Results:Patients in the first group who received radiation therapy developed less loco-regional recurrence rate (8% vs 22.5%) than did those receiving no radiation therapy in the second group with no significances statistical, p=>0.05. According to the time gap since surgery to radiation therapy, twenty six percent of patients who received radiation therapy in period more than 3 months from the surgical interference had developed loco-regional failure vs no patients in population who received radiation therapy in period less than 3 months since surgical interference with statistical significant difference (P<0.005). Within 50 patients in the first group, skin desquamation was the most common acute complication of radiation therapy (20%) and hyperpigmentation was the most common late effect of radiation therapy (30%). There was statistical significant difference for the 5- year loco-regional recurrence free survival rates according to the treatment modalities in the first group versus those in the second group(88.24% vs 73.16 respectively ,P=0.0308). There was insignificant improvement in the 5-year (OS) rates and the 5-year (DFS) rates according to treatment modalities in the first group versus the second group, (70.62% vs 61.00%, p=0.2145) for (OS) rates and (51.54% vs 44.38%, p=0.111) for (DFS) rates respectively. Nodal and hormonal status was the only two prognostic factors that significantly influence (OS) and (DFS) rates. Bone was the most common site of distant failure in this retrospective study. Conclusions: Despite the improvement in loco-regional recurrence rates, loco-regional recurrence free survival rates, five-year (OS) and 5-year (DFS) rates for patients in the first group who received radiation therapy, still the value of routine use of radiation therapy in early breast cancer is unclear.
[Laila A. Korashy; Mahmoud M. Elgantiry and Fatma Zakaria. **Evaluation of the Role of Radiotherapy in Early Breast Cancer.** Life Science Journal. 2011;8(1):145-153]. (ISSN:1097-8135). http://www.lifesciencesite.com.

Key words: Breast cancer- early stage disease ¨C surgery- radiation therapy-systemic therapy.

1. Introduction:

Breast cancer remains as a common disease through out the world. Early detection and treatment can often lead to cure. Cure is most likely in women whose breast cancer is confined to the breast. Substantial number of women with spread to the loco-regional lymph nodes can also be cured with appropriate therapy [(1)].

The prognosis of early breast cancer is generally favorable. There fore, early diagnosis and early treatment are essential for better results [(2)]. During the 30 years time period of DBCG (Danish Breast Cancer Cooperative Group) post-operative radiotherapy in breast cancer has moved from orthovoltage treatment based on direct clinical (set up) to megavoltage radiation with 2D and 3D treatment planning[(3)]. Through these studies, DBCG has contributed with important evidence about the role of postoperative radiotherapy in early breast cancer, and thereby also supported the current paradigm that optimal loco-regional tumor control has influence on survival [(4)].

2. Patients and Methods

Between January 1999 and December 2004, ninety patients with early breast cancer (T1-2,0-3 +ve axillary lymph nodes, M0) to whom MRM was performed ,had been treated inclusively at Clinical Oncology Department, Tanta University. Exclusion criteria were including history of contralateral breast cancer, presence of serious nonmalignant diseases (eg, cardiovascular or pulmonary), presence of severe mental or physical disorder, presence of connective tissue disease, and pregnant women. Eligible patients were including, female patients with histologically or cytologically proven breast cancer, patients with clinical performance status (PS) grade 0-2 according to WHO,[(5)] patients with stage I-IIB disease, patients with tumor size < 5 cm, adequate negative surgical margin,

dissected lymph nodes at least 10 nodes, no evidence of distant metastasis on clinical or radiological examination at the beginning of treatment, patients with have adequate renal, hepatic, and bone marrow parameters at the time of presentation, patients compliance and geographic proximity that allow adequate follow up.

PRE_treatment assessment

The following data were obtained from the files of the patients that fulfilled the clinco-pathlogical criteria of early breast cancer (stage I and II) [6]: Historyphysical examination, investigations and histopathological examination.

Study Design and Treatment:

The patients were categorized into two treatment groups : The first group , included 50 patients with early breast cancer treated with surgical interference, modified radical mastectomy + adjuvant radiation therapy + systemic therapy (chemotherapy and/or hormonal therapy).The second group, included 40 patients with early breast cancer treated with modified radical mastectomy plus adjuvant systemic therapy (chemotherapy and\or hormonal therapy) i.e, did not received post operative radiotherapy

Modified radical mastectomy (MRM) was the surgical procedure performed for 90 patients (50 patients of them received postoperative radiation therapy due to high risk factors for local recurrence as microscopic residual, vascular invasion, lymphatic permiation , high grade and age less than 35years). Axillary dissection with clearance of at least 10 lymph nodes was done for all patients. All patients were planned through 2-D simulator- planning system using isocentric technique. Eligible patients received irradiation to the breast and chest wall through two tangential fields and the draining lymph nodes. Dose in the range of 5000 cGy was delivered in five weeks, 200 cGy, daily for five days weekly. Patients with risk factors like -ve hormonal receptors, +ve axillary lymph nodes, stage IIB, large tumor size or –ve nodal status with risk category like tumor size more than 2cm,-ve hormonal receptors, grade II-III and age less than 35 years were received chemotherapy regimens like CMF (cyclophosphamide 600mg/m^2, methotrexate 40 mg/m^2, and 5FU 600mg/m^2)(10 patients), FAC(5FU 500 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500mg/m^2)(30 patients), FEC (5FU 500mg/m^2, epirupcin 100 mg/m^2 and cyclophosphamide 500mg/m^2) (37 patients). All three chemotherapy regimens was administrated I.V. every 21 days for average 4-6 cycles $\pm$ Tamoxifen 10 mg twice daily according to ER and PR receptors status for 5 years (65 patients).Her-2 receptors (human epidermal growth factor) were not available for all patients in this study and so were not evaluated in our results as a high risk factor.

Endpoints and statistical methodology:

All patients entered in this study were monitored for treatment related events and toxicity according to RTOG and EORTC Radiation Morbidity [7], loco-regional failure ,distant failure, time to death and survival. The overall survival and disease free survival rates depicted on Kaplan-Meier methodology[8].The influence of the various variables on overall survival and disease free survival rates was assessed by using the Log Rank test[9], Pearson Chi-Square test and Fisher's Exact tests were used whenever appropriates. Differences were considered significant when P-value was < or =0.05.Analysis was done using (SPSS) version 9.

3. Results:

Patients characteristics

This retrospective study included ninety patients with early breast cancer (T1-T2, 0-3 +ve LNs, M0) presented at Clinical Oncology Department, Tanta University Hospital, during the period from January 1999 to December 2004. Patients demographics and baseline characteristics were listed in table (1).The mean age was 45.62 years+/-9.56 years old (range 16-77 years). Forty seven percent were premenopausal, 86% with negative family history of breast cancer, infiltrating ductal carcinoma was 90%, seventy two percent had +ve hormonal receptors and fifty three percent presented with stage IIB. MRM was the surgical interference that had been done for all patients. Among the 50 patients in the first group who were assigned to receive radiation therapy, the loco-regional recurrence rate was 8% (4\50) vs 22.5% (9\40) for the second group with no significance difference, p=>0.05, table (2).

Table (3) shows that 26.7% (4\15) of patients within the first group who received radiation therapy developed loco-regional failure with time gap >3 months since surgery in comparison to zero percent (0\35) of patients within the same group with the time gap <3 months since surgery with significant p value =< 0.001.

The toxicity profile with radiation therapy was recorded according to RTOG and EORTC Radiation Morbidity (1995)[7]. Acute complications of the 50 patients in the first group who received radiation therapy were skin desquamation, radiation pneumonitis and radiation carditis (20% G3, 10% G3, 2%G2) respectively. While late complications were hyperpigmentation, radiation ulcer, lung fibrosis and

ischemic heart diseases (30% G1, 4%G4, 2% G3,4% G2) respectively, Table (4). Sites of distant failure in 90 patients with early breast cancer were summarized as followed bone, liver, lung and brain (5.6, 2.2, 4.4 and 2.2%) respectively, Table (5).

Survival:

At time of analysis ,the median duration of follow up was 72 months ,(range,12-90). On the basis of Kaplan-Meier estimates, the median overall survival (OS) for all patients in this study (n=90) was 74 months (range 12-92 months) (95% CI, 0.55-0.96) with the 5- year OS 67.15%, Fig (1). The median DFS was 56 months (range,10-90 months) ,(95% CI,0.59-0.86) with the 5- year DFS 48.55%, Fig, (2).

According to treatment modalities, the 5-year OS rates were (70.62 % vs 61.00%, p=0.2141) in the first and the second group respectively with no statistical significant difference, Fig (3).For 5-year DFS rates were (51.54% vs 44.38 %, p=0.111) respectively for the first to second groups with no statistical significant differences, Fig,(4). Finally, there was statistical significant differences for the 5-year loco-regional recurrence free survival in the first and second group according to treatment modalities (88.24% vs 73.16%, p=0.03) respectively, Fig, (5).

Prognostic factors:

The 5-year OS rates were not significantly correlated with age (p=0.20), menstrual status (p=0.459), tumor site (p=0.9513), tumor size (p=0.89), pathological subtypes (p=0.202), tumor grades (p=0.636), stage (p=0.70), lines of treatment modalities (p=0.21) (Fig 4). The only two prognostic factors with statistical significance were, hormonal receptor status (p=0.02) Fig (6) and nodal status (p=0.04) Fig (7), Table (6).

For the 5- year DFS, there was statistical significant difference for the same two prognostic factors, hormonal receptors status (P=0.004), and nodal status (P=0.0042). There was no statistical significant difference for all other prognostic factors, table (7).

Table (1): Patients demographics and baseline disease characteristics in 90 patients with early breast cancer.

	Characteristics	No	%
Age in years	<35	28	31.1
	>35	62	68.9
Mean	45.62		
Median	45		
SD	9.56		
Menstrual status	Premenopause	43	47.8
	Postmenopause	47	52.2
Number of pregnancy	Nullipara	9	10.0
	Unipara	20	22.2
	Multipara	61	67.8
History of contraceptive pills	-ve history	28	31.1
	+ve history:	62	68.1
	> 2 years	52	57.9
	< 2 years	10	11.1
Family history	+ve family history	12	13.3
	-ve family history	78	86.8
Tumor site	Upper outer quadrant	55	61.1
	Upper inner quadrant	10	11.1
	Lower outer quadrant	14	15.6
	Lower inner quadrant	10	11.1
	Central	1	1.1
Tumor grade	Grade I & II	67	74.4
	Grade III	23	25.6
Pathological type	IDC	81	90
	Others	9	10
Hormone receptors status	HR +ve	65	72.2
	HR –ve	25	27.8
Nodal status	-ve	30	33.3
	+ve (1-3)	60	66.7
Tumor status	T1	7	7.8
	T2	83	92.2
Disease stage	I	2	2.2
	IIA	40	44.4
	IIB	48	53.4
Lines of treatments	MRM+Rth+ Systemic therapy	50	55.6
	MRM+Systemic therapy	40	44.4

Table (2): Loco-regional recurrence in all patients with early breast cancer according to treatment modality.

Treatment modality / Site of Recurrence	S+Rth+Systemic therapy (50)		S+ Systemic therapy (40)		Total	
	No.	%	No.	%	No.	%
Chest wall	0/50	0.0	5/40	12.5	5/90	5.6
Axillary LNs.	3/50	6	1/40	2.5	4/90	4.4
Supraclavicular LNs.	1/50	2	3/40	7.5	4/90	4.4
Total	4/50	8	9/40	22.5	13/90	14.4

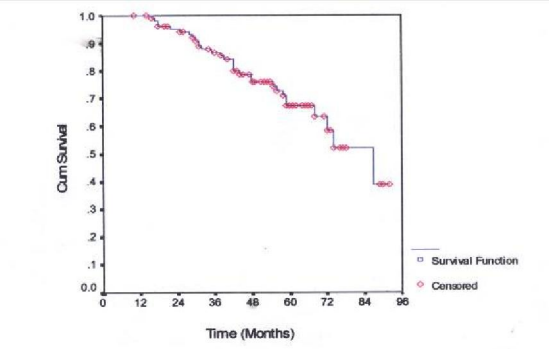


Fig. (1): Overall survival rate for the whole patients.

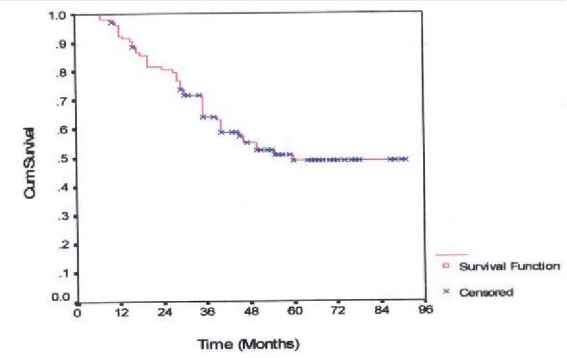
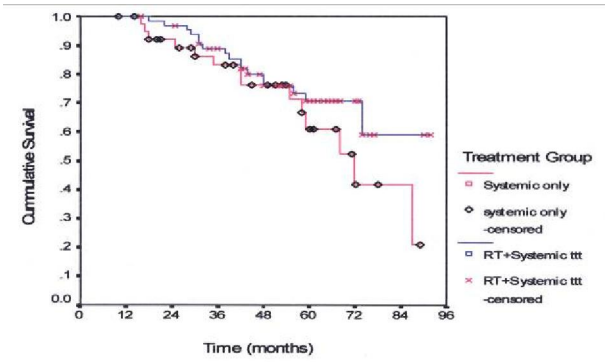


Fig. (2): Disease free survival rate for the whole patients



Fig, (3): Survival rate of all patients according to treatment modality

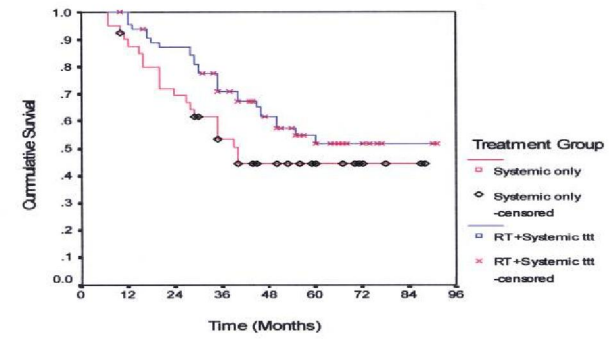
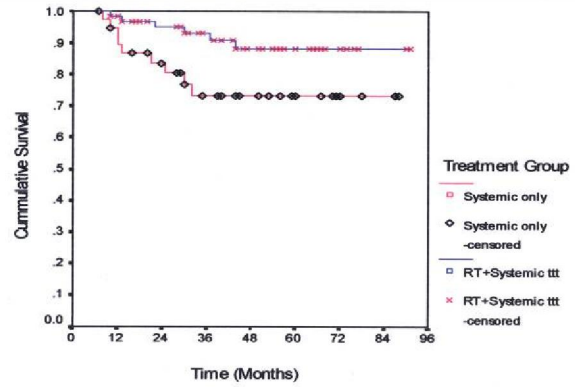
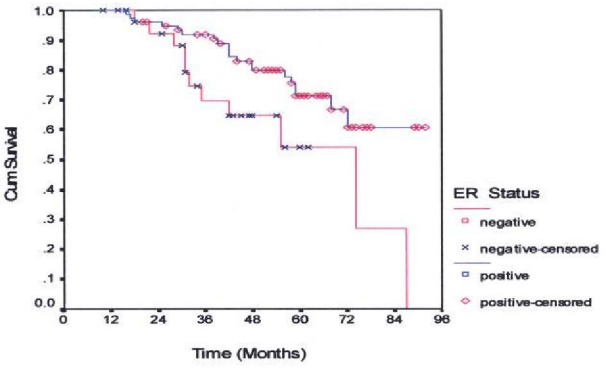


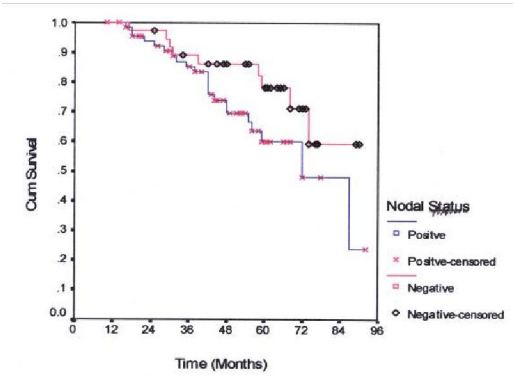
Fig. (4):Disease free survival rate of all patients according to treatment modality



Fig, (5): Loco-regional recurrence free survival rates of all patients according to treatment modality.



Fig, (6): survival rate of all patients according to hormonal receptor status



Fig, (7): Survival rate of all patients according to lymph nodes status.

Table (3): Frequency of loco-regional recurrence according to the time gap (surgery to radiation therapy) in 50 patients in the first group.

Time gap / Site of Recurrence	< 3 months		> 3 months	
	No.	%	No.	%
Chest wall	0/35	0	0/15	0.0
Axillary LNs.	0/35	0	3/15	20
Supraclavicular LNs.	0/35	0	1/15	6.7
Total	0/35	0	4/15	26.7

Table (4): Acute and late complications of radiation therapy in 50 patients received adjuvant radiotherapy.

	Complications	G1	G2	G3	G4	No.	%
Acute	Skin desquamation			-		10/50	20
	Radiation pneumonitis radiation			-		5/50	10
	cardities		-			1/50	2
Chronic	Hyper pigmentation	-				15/50	30
	Radiation ulcer				-	2/50	4
	Lung fibrosis			-		1/50	2
	Ischemic cardiac diseases		-			2/50	4

Table (5): Sites of distant metastases according to nodal status and tumor status.

	NO. of cases	Bone		Liver		Lung		Brain	
		No.	%	No.	%	No.	%	No.	%
Node –ve	30	2	6.7	0	0.0	0	0.0	0	0.0
Node +ve	60	3	5	2	3.3	4	6.7	2	3.3
T1	7	1	14.2	0	0	1	14.2	0	0.0
T2	83	4	4.8	2	2.4	3	3.6	2	2.4
Total	90	5	5.6	2	2.2	4	4.4	2	2.2

Table (6): The 5-year overall survival rates for the whole patients according to different prognostic factors

Prognostic factors	Number of cases	5-years survival rate %	Relative risk& 95% confidence interval	p-value
Age				
≤35	28	58.17	0.91(0.82 - 1.55)	0.2089
>35	62	74.63		
Menstrual status:				
Premenopause	43	62.97	0.93 (0.70-1.40)	0.4595
Postmenopause	47	71.66		
Tumor site:				
Upper O.Q.	55	63.48		
Upper I.Q.	10	77.78		
Lower O.Q.	14	70.91	0.81 (0.41-0.89)	0.9513
Lower I.Q.	10	68.18		
Central	1	53.33		
Tumor size:				
T1	7	72.19	0.76 (0.46-0.90)	0.8980

T2	83	60.43		
Pathological types:				
IDC	81	61.34	0.68 (0.44-0.74)	0.2027
Others	9	88.42		
Tumor grade:				
I & II	67	69.55	0.85 (0.60-1.52)	0.6369
III	23	61.22		
Nodal status:				
-ve	30	78.17	0.50 (0.52-0.81)	0.0438#
+ve (1-3)	60	59.98		
Disease stage:				
Stage I	2	-	1.20 (0.84-1.15)	0.7029
Stage IIA	40	67.65		
Stage IIB	48	66.26		
Line of treatment:				
Surgery+Rth+systemic therapy	50	70.62	0.49 (0.54-0.69)	0.2145
Surgery+systemic therapy	40	61.00		
Hormone receptors status:				
HR +ve	65	71.27%	0.66 (0.52-0.61)	0.0210#
HR –ve	25	53.81%		

Significant.

Table (7): The 5-year disease free survival rate for whole patients according to different prognostic factors

Prognostic factors	Number of cases	5-years DFS rate %	Relative risk & 95% confidence relative	p-value
Age:				
≤35	28	45.36	0.98 (0.72 - 1.32)	0.8043
>35	62	49.38		
Menstrual status:				
Premenopause	43	36.25	1.00 (0.74-1.35)	0.0579
Postmenopause	47	60.35		
Tumor site:				
Upper O.Q.	55	50.78	0.76 (0.45-0.99)	>0.05
Upper I.Q.	10	51.95		
Lower O.Q.	14	38.18		
Lower I.Q.	10	36.36		
Central	1	57.17		
Tumor size:				
T1	7	54.55	0.86 (0.71-0.93)	0.7522
T2	83	47.41		
Pathological types:				
IDC	81	47.50	0.48 (0.38-0.56)	0.3465
Others	9	55.58		
Tumor grade:				
I & II	67	51.82	0.75 (0.74-1.110)	0.5675
III	23	41.34		
Nodal status:				
-ve	30	61.67	0.58 (0.42-0.70)	0.0405#
+ve (1-3)	60	41.50		
Disease stage:				
Stage I	2	0	1.00 (0.74-1.35)	0.0873*
Stage IIA	40	60.40		0.1918**
Stage IIB	48	41.90		0.1069***
Line of treatment:				0.1110
Surgery+Rth+systemic therapy	50	51.54	0.48 (0.34-0.60)	
Surgery+systemic therapy	40	44.38		
Hormone receptors status:				
HR +ve	65	54.38	0.46 (0.43-0.57)	0.0042#
HR –ve	25	28.24		

Significant.* Stage I vs. IIA. ** Stage I vs. IIB. ***Stage IIA vs. IIB.

4. Discussion:

Parallel to the development in radiotherapy with more effective high-energy equipment and new treatment techniques the results have clearly demonstrated the proof of principle that primary loco-regional tumor control has impact on survival even in patients who also receive an adjuvant systemic therapy. The first convincing results of adjuvant systemic therapy in early breast cancer appeared in the mid

seventies, especially premenopausal women with node positive diseases seemed to obtained a pronounced improvement in diseases –free survival [10].These results led to a paradigm shift in the treatment of early breast cancer towards a more multidisciplinary approach in high-risk patients [11].

In this study, the incidence of breast cancer accounted for 27.6% of all female malignancy and 13% of all cases registered in our department. These figures are slightly lower than other registry [12]. Carcinoma of the breast is the most prevalent cancer among Egyptian women and constitutes 34% of National Cancer Institute cases.[13]

The median age of the patients in our study was 45 years and the mean age was 45.62 years (range: 16-77 years) [14], other study reported that the mean age of early breast cancer patients was 66 years [15, 16]. Concerning tumor size11.54% for T1 tumors, and 88.46% for T2 tumors, while in a series of 1234 cases, T1 tumors constituted 80% followed by T2 (20%) [17]. The lower incidence ofT1 tumors in Egypt may be explained by relatively late presentation due to lake of health education, screening programs and low socioeconomic factors leading to delay in seeking medical advise. In contrast, western countries programs of self breast examination and screening mammography are frequently carried out. Regarding the prognostic effect of the age, our results revealed that the younger the age, the worse the prognosis, as the five-year survival rates were 58.17% vs. 74.63% for the patients age group <35 years vs. >35 years respectively and the difference was statistically not significant,[15,18,19]. No, statistical significant difference for T1 versus T2 tumors for OS and DFS [20,21]. The axillary lymph nodes status and hormonal status were the most important factors in determining the prognosis, the 5-year survival rates for node negative patients were higher than that with 1-3 positive nodes (78.17% and 59.98% respectively) OS[22,23,24], where lymph node metastasis was a dependent factor for local failure, locoregional failure, distant failure, DFS and OS. As regard HR, (71.27% and 53.15%) OS For +ve HR versus –ve HR were respectively. ER (Estrogen reseptor)expression in the breast sample analyzed was associated with good prognostic factors, such as low histological and nuclear grade, smaller tumor size and fewer metastatic axillary lymph nodes. In general, ER expression was higher in patients in earlier clinical stages of the diseases. Determination of the presence of this receptor is fundamental, not only for its prognostic value but also for its unquestionable predictive value of response over time to sustained cancer – specific therapy. The same has not occurred with PR (progesterone receptor) which lost its independent predictive value during 1990s.[25]

As regard loco-regional recurrence, the incidence of loco-regional recurrence for whole patients was 14.44% (13\90), recurrence in chest wall was5.55%(5\90), reccurance in axillary lymph nodes was 4.44% (4\90) and supraclavicular lymph nodes was 4.44%(4\90).In previous clinical trial, loco-regional failure was 49%, chest wall recurrences was 23%, loco- regional nodes was 13%[26] and this conflict may be due to small number of patients in our study.

Twenty six percent of patients who received radiation therapy within more than 3 months from the surgical interference had developed loco-regional failure compared to no patients in the category who received radiation therapy within 3 months since the surgical treatment , and this difference was statistically significant, delays in initiation of radiation therapy more than 3 months were associated with higher loco-regional failure, overall mortality, cancer specific mortality and associated with poor survival[27].On the other hand , the 5-year local recurrence rate was significantly higher in patients treated with adjuvant radiotherapy more than 8 weeks after surgery than in those treated within 8weeks since surgery but there was little evidence about the impact of delay in radiotherapy on the risk of metastases or the probability of long term survival.[28]

Five-year OS rates were 70.62% vs 61.00% for the first versus the second treatment groups. Many authors had reported the treatment results for patients treated with modified radical mastectomy only without radiotherapy in early breast cancer, [29] (84%), [30] (64%),[31] (42%),[32,33] (49%),[34] (58%) and [35].

The five-year loco-regional recurrence free survival rates of all patients according to presence or absence of radiation therapy were 88.24% vs. 73.16% respectively and this difference was statistically significant (p=0.0308), adjuvant radiation therapy improve local control and provide a significant survival benefit for early breast cancer patients.[36]

In the present study the adverse events with radiation therapy were reported according to RTOG common toxicity criteria [7], skin desquamation was the most common acute side effect of radiation therapy (20%), moist desquamation was reported in 31.4% patients [37]. The incidence of radiation pneumonitis was very low (1.2%) [38] unlike pneumonitis represented by 10% among our patients, and this may be due to the difference in the physical and treatment consideration such as the conformal 3D-planning and treatment with linear accelerator with much exclusion of the lung volume included in the irradiated field. Ischemic heart diseases represented by 4%, in this trial may be due to inclusion of the anterior part of the heart which results in excess cardiac morbidity and mortality. Further, the standard adjuvant chemotherapy

in most patients now includes more cardiotoxic drugs, such as anthracyclins and Herceptin[39]. EORTC (22922\ 10925) was decided that in high risk ,irrespective of lumpectomy or mastectomy, the target should not include the internal mammary nodes (IMN) in patients with left-sided breast cancer whereas the target in patients with right-sided breast cancer if possible should include the IMN .The challenge for on-going trials in early breast cancer is to design more focused treatment planning in the individual patients with optimized tumor control and reduced radiation dose to critical tissues[40,41,42].

In conclusion, early stage breast cancer, radiation therapy is considered as cornerstone and the standard of care not only to decrease loco-regional failure but also to improve survival (DFS and 0S). It is the ambition to continue to do trials and answer questions regarding optimal radiotherapy in early breast cancers in Egypt. Systemic therapy should be added in early breast cancer patients guided by the developed prognostic and predictive knowledge to confer survival improvements (DFS and OS).

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12/12/2010