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Original Article

EFFECTS OF TIMING OF RADIOTHERAPY ON TREATMENT OUTCOMES IN PATIENTS WITH BREAST CANCER

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ABSTRACT

Background: Adjuvant radiotherapy (RT) after mastectomy for breast cancer reduces the risk of locoregional recurrence (LRR) and improves survival in patients receiving systemic therapy. The aim of the study was to evaluate the impact of the interval between surgery and RT on the risk of LRR and to identify risk factors for LRR.

Patients and Methods: The study included 335 cases with breast cancer who presented to the department of Clinical Oncology, Assiut University hospital between January 2001 and December 2004. Follow up was performed for 274 cases with stage II and III who were treated with mastectomy followed by RT. These, 34 patients received early RT after surgery followed by hormone therapy. Ninety five patients received early RT after the third chemotherapy cycle (CT). Delayed RT after the sixth CT cycle was given to 145 patients.

Results: The 5-year overall survival (OS) of breast cancer was 31.2%. Overall survival of patients receiving early and delayed RT was 34.2% and 28.4%, respectively after a median follow-up of 60 months and 36 months (P=0.03). The incidence of LRR (early and delayed) was 32.8% and 67.2% (P=0.004) .The incidence of distant metastasis subsequent to LRR was 60.9% and without LRR was 46.2% (P=0.03). Prognostic factors for LRR were high tumor grade (P=0.001) and number of lymph nodes (P=0.013).

Conclusion: Delay in radiation treatment was associated with increase in the risk of LRR of breast cancer. Prognostic factors for LRR were tumor grade, number of involved nodes, age and timing of RT.

Key Words: Breast cancer, breast radiotherapy, breast cancer prognostic factors, breast loco regional recurrence.

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INTRODUCTION

Breast cancer is a major public health problem for women throughout the world. In the United States breast cancer remains the most frequent cancer in women and the second cause of cancer death[1]. The prevalence of breast cancer in Europe and the USA is estimated between 8 to 10%. However the lowest prevalence is seen in Asian countries, about 1%.[2]. Modified radical mastectomy is the standard surgical procedure for patients whom breast–conservative therapy is contraindicated. The type of surgery (mastectomy versus wide tumor excision) had no significant impact on breast cancer–specific survival[3].

Adjuvant radiotherapy after modified radical mastectomy and breast–conserving surgery for early-stage invasive breast cancer substantially reduces the risk of locoregional failure and is evidence–based[4]. Using traditional clinical and pathological factors, patients can be classified into subgroups by the risk of locoregional recurrence. In the high risk groups the absolute benefit of irradiation is larger. Adjuvant radiotherapy not only reduces locoregional recurrence rates but also improves cancer-specific survival in patients receiving systemic therapy. The highest mortality reduction is observed in mastectomy patients with good prognostic factors (< 4 positive nodes, tumor size < 2 cm, grade 1 malignancy, estrogen and progesterone receptors positive, HER-2 negative)[4].

The timing of surgery and postoperative radiotherapy–especially if combined with chemotherapy has been a subject of interest over the past years[5].

The risk of local recurrence increases with increasing waiting times for radiotherapy. The increase in local recurrence rate may translate into decreased survival in some clinical situations[6].

This study analyzed data concerning the interval between surgery and radiotherapy correlated with

locoregional control, incidence of distant metastasis and survival. Other prognostic factors for local recurrence were also analyzed.

PATIENTS AND METHODS

This study included 335 women with breast cancer in the period between 1 January 2001 and December 2005 in the department of Clinical Oncology, Assiut University hospital. Follow up was performed on 274 cases of who was operable stage II-III. These patients underwent surgery (modified radical mastectomy) and received radiotherapy, chemotherapy or hormonal treatment (tamoxifen). These three treatment options have been offered in three sequences, surgery followed by radiation and then hormonal treatment, surgery followed by 3 courses of chemotherapy and then by radiation, surgery followed by 6 cycles chemotherapy and then by radiation.

Locoregional radiotherapy (RT) was delivered within 3 weeks after initial surgery in hormonal treatment (HT) group. Radiotherapy was delivered within 20 days after the third chemotherapy cycle (CT) or the sixth CT cycle. The delivered dose to the chest wall was 45 Gy with conventional fractionation over 5 weeks (2Gy daily. 5 weekly fractions) by 2 tangentially, collimated, wedge fields on Cobalt-60 or 6 MV linear accelerator. The upper margin of the tangents was placed at the head of the clavicle. The medial margin was at 1cm over the midline if no internal mammary field was drawn, if it was drawn, the medial tangential portal was located at the lateral margin of internal mammary field. The lateral posterior margin was placed at the mid axially line. The inferior margin was drawn at the level of the sixth rib anteriorly.

Boost to the tumor bed was given to all patients after chest wall irradiation by electron beam 9-16 Me V electrons, 16Gy/8 fractions.

Radiotherapy to supraclavicular area was indicated in patients with more than 4 lymph nodes positive and in patients with 1-3 lymph nodes positive associated with high risk prognostic factors. The inferior border of the supraclavicular field was matched to the tangential field. The medial border was 1cm across the midline extending upward following the medial border of the sternocleidomastoid muscle to the thyrocricoid groove. The lateral border was a vertical line at the level of the coracoid process just medial to the humeral head. The total dose to supraclavicular field was 45Gy at 2Gy per day 5 fractions /week (calculated at a depth of 3cm).

Posterior axillary field was used to supplement the dose at the midplane of the axilla. The medial border was drawn to allow 1.5 to 2cm of the lung, shown on the portal film, to be included. Inferior border was at the same level as the inferior border of the supraclavicular field. Lateral border just blocks falloff across the posterior axillary field. Superior border splits the clavicle and the superolateral border shields or splits the humeral head. Dose to the axillary midplane was adjusted to complete 45Gy (2Gy daily, 5 fractions weekly) for 5weeks.

Internal mammary nodes irradiation was indicated in patients with positive axillary lymph nodes, central and medially located tumors and stage III patients. Medial border of internal mammary field was in the midline. The lateral border was 5cm laleral to the midline, superior border abuts the inferior border of the supraclavicular field and inferior border was at the xiphoid. The dose to internal mammary node field (45Gy at 2Gy per day) calculated at a point 4 to 5cm beneath the skin surface depending on the thickness of anterior chest wall.

For chemotherapy, antiemetic was prescribed routinely before each cycle Toxicity evaluated according to WHO criteria. Chemotherapy combination FAC (fluorouracil, adriamycin, cyclophosphamied) was prescribed to 251 patients (92%) CMF was administered in 23 patients (8%).

Patients underwent clinical assessment every 3 months for the first year following diagnosis and had regular six months follow up for 5-years.thereafter. A radiological assessment (chest radiograph, abdominal ultrasound and bone scan) was performed if the patient had symptoms or after detectable abnormality on physical examination.

STATISTICAL METHODS

The overall survival was calculated according to the Kaplan and Meier method[7]. The comparison between the survival curves of the early and delayed radiotherapy groups was performed using Log–rank statistics. Chi–square test was used to compare the distribution of frequencies among various groups.

RESULTS

Out of the 335 breast cancer patients, 32 had metastases at presentation, 20 were lost during follow up and 9 had inoperable locally advanced disease. So, 274 patients were included in the analysis. Follow

up time was calculated from the first pathological diagnosis until death or the end of the study at 31 December 2009. Mean age at diagnosis was 48.7 years (ranged from 29 to 70 years).

Ninety-five patients (35%) received RT after the third CT cycle (60 days after surgery), 34 (12%) patients received RT after surgery followed by HT and these considered group 1 (early RT). One hundred and forty five patients (53%) received surgery followed by 6 CT cycle and then by RT (140 days after surgery), group 2 (delayed RT).

Postmenopausal women constitute 57% (156 patients), while premenopausal women were 43% (118 patients). Hormonal receptor positive were 139 patients 51%(estrogen receptor positive 85 patients 61.2%, progesterone receptor positive 54 patients 38.8%) and 93 patients 34% were hormonal receptor negative (estrogen receptor negative 38 patients 41%, progesterone receptor negative 55 patients 60%) while 15% (42 patients) were unknown receptor status.

Table (1) shows the pathological characteristics of the 274 assessable patients. It was observed that there was no statistically significant difference in the incidence of distant metastasis (DM) between the two groups who received early (group 1) or delayed RT (group 2).

Table (2) shows the prognostic factors for local recurrence

It was observed that local recurrence was significantly higher in patients who received delayed RT than in patients who received early RT P=0.004).

Analysis of the prognostic factors for LRR, the number of involved nodes (N0 and N 1 versus N 2) P=0.013, tumor grade (1 and 2 vs. 3) P=0.001 and timing of RT (early vs. delayed) P=0.004, were significant prognostic factors.

The incidence of DM subsequent to LRR is significantly higher than in patients who had no LRR (P=0.03).

Table (3) shows the multivariate analysis of the prognostic factors. Younger age and delayed RT were strong prognostic factors for LRR. Local recurrence was a strong prognostic factor for DM.

Figure (1) shows the 5–year overall survival (OS) of 274 breast cancer patients which was 31.2% after a median follow up 48 months.

Figure (2) shows the 5–year OS of 274 breast cancer patients received early and delayed RT which was 34.4% and 28.4%, respectively. The median follow–up for patients received early RT was 60 months and for delayed RT was36 months (P=0.03).

Table 1: Pathological characteristics of 274 assessable breast cancer patients.

		Radiotherapy		P-value
		Early (n=129)	Delayed (n=145)	
Tumor size	T2	79 61%	81 56%	0.7
	T3	27 21%	29 20%	
	T4	18 14%	25 17%	
	Unknown	5 4%	10 7%	
Lymph Nodes	N0	63 49%	47 33%	0.03
	N1	20 16%	31 21%	
	N2	38 29%	55 38%	
	Unknown	8 6%	12 8%	
Grade	1	1 .7%	0 .0%	0.34
	2	85 66%	83 57%	
	3	37 29.3%	54 37%	
	Unknown	6 4%	8 7%	
Distant Metastasis	Yes	65 50.3%	71 49%	0.9
	No	64 49.6%	74 51%	

Table 2: Prognostic factors for local recurrence (univariate analysis).

		Local recurrence		P-value
		Yes No (total =64) (%)	No No (total =210) (%)	
Tumor size	T2	36 (56.2)	131 (62.4)	0.379
	T3 and T4	28 (43.8)	79 (37.6)	
Lymph Nodes	N0 and N1	30 (46.9)	135 (64.3)	0.013
	N2	34 (53.1)	75 (35.7)	
Grade	1 and 2	30 (46.9)	148 (70.5)	0.001
	3	34 (53.1)	62 (29.5)	
Radiotherapy	Early	21 (32.8)	111 (52.9)	0.004
	Delayed	43 (67.2)	99 (47.1)	
Distant Metastasis	Yes	39 (60.9)	97 (46.2)	0.03
	No	25 39.1%	113 53.8%	
Age Groups	30 -50 y	21 32.8%	89 42.4%	0.13
	50- 65 y	35 (54.7)	88 (41.9)	
	< 35 y	2 (3.1)	19 (9.0)	
	>65y	6 (9.4)	14 (6.7)	
Tumor Location	Lateral	42 (21.8)	150 (78.2)	0.26
	Medial	17 (34)	33 (66)	
	Central	5 (15.6)	27 (84.4)	

Table 3: Prognostic factors for local recurrence (multivariate analysis).

Variables	B	Wald	Sig.	Odd's ratio	95.0% C.I	
					Lower	Upper
Age	0.037	6.555	0.010	1.038	1.009	1.067
Distant metastasis (1)	0.641	4.170	0.041	1.898	1.026	3.511
Early radiotherapy	-0.903	7.799	0.005	0.405	0.215	0.764
R^2	0.2					

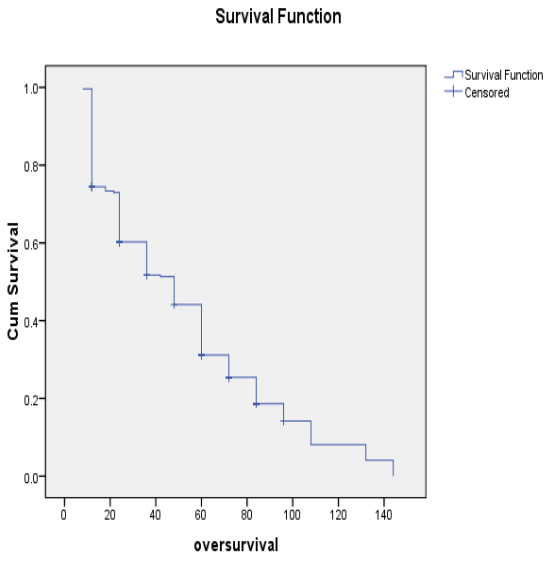

Figure 1: 5-year overall survival of 274 breast cancer patients diagnosed between 1/1/ 2001 and 31/12/2004 (OS=31.2%)

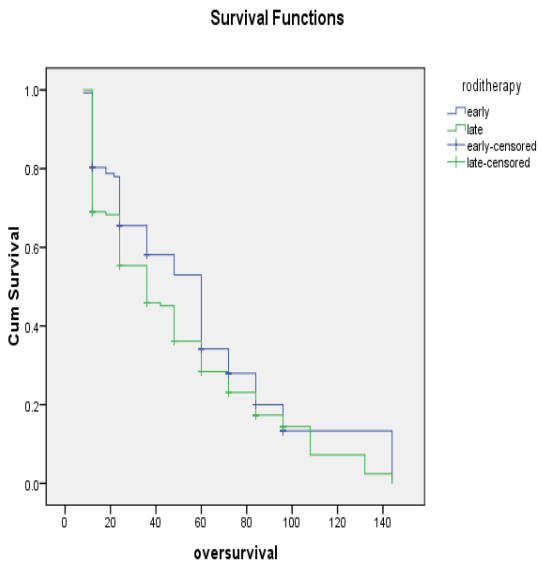

Figure 2: 5-year survival of 274 breast cancer patients who received early (OS=34.2%) and delayed (OS=28.4%) radiotherapy

DISCUSSION

Breast cancer is the most commonly diagnosed malignancy among women in developed countries[8,9] and in some developing countries[10,11].

Adjuvant systemic therapy reduces the likelihood of both local and distant recurrence Metaanalysis of local therapy reveal that the use of radiotherapy (RT) after mastectomy in node–positive patients improved 15–year survival in patients who also received adjuvant systemic therapy and not in patients who were treated with mastectomy alone[12].

Adjuvant chemotherapy is well established as an important strategy for lowering the risk of breast cancer recurrence and improving survival. Long term follow–up demonstrated benefit from chemotherapy for women irrespective of age, tumor estrogen receptor status, or whether patients also receive adjuvant endocrine therapy[13].

Post mastectomy RT in high–risk breast cancer patients can reduce locoregional recurrences (LRR) and improve disease–free and overall survival[14]. The optimal integration of chemotherapy and radiation with early-stage breast cancer remains uncertain. It was shown previously that a delay in the initiation of RT resulted in a higher local recurrence rate[15].

In this study, the risk of local recurrence increased with increasing waiting times for radiotherapy. Locoregional recurrence after delayed RT (group 2) was significantly higher than early RT (group 1) (P=0.004). The incidence of distant metastasis in relation to waiting time of RT did not differ significantly between the two groups.

Few studies reported the results of clinical evidence relating waiting times (WTs) for RT to the outcomes of RT. Chen Z et al.[6] did a systematic review of the literature between 1975 and 2005 to identify clinical studies describing the relationship between WTs and outcomes of RT. For postoperative RT for breast cancer, relative risk recurrence / month=1.11, 95 % CI, but there was little evidence of any association between WTs and the risk of distant metastasis. These results were in agreement with the present study results.

Another trial done by Knauerhase H et al.[16] concluded that tumor location, interval between surgery and RT and boost technique might influence local control of breast cancer treated by breast conservative surgery and RT.

Benchalal M et al.[15] did a prospective trial on three groups of patients, RT directly after breast conservative surgery, RT after the third CT cycle and RT after the sixth CT cycle. In the multivariate analysis, the timing of RT was not associated with a higher rate of LRR, where tumor size >2 cm and no hormone therapy were prognostic factors.

There was no sufficient clinical trial describing when the interval between surgery and RT is considered to be delayed. Punglia RS et al.[17] suggested that an interval of over six weeks from surgery to the start of RT was associated with an increased likelihood of local recurrence (in older women with breast cancer and conservative surgery). Knauerhase H et al.[16] defined also delayed RT as an interval > 2 months between surgery and the start of RT.

Forty seven percent of patients remained free of LRR despite receiving delayed RT and 32.8% develop LRR despite early RT (Table 2). So other prognostic factors influence LRR as the time interval. These factors are number of involved nodes, tumor grade and age. These results were in agreement with Benc V et al.[18] who concluded that the risk of LRR was associated with young age, higher histological grade and time to radiation treatment.

Fodor J et al.[3] also reported that after mastectomy in univariate analysis, nodal status (negative vs. positive) and RT (no vs. yes) were significant predictors of local control, but tumor size (T1 vs. T2) and histological grade (1-2 vs. 3) were not. In multivariate analysis both nodal involvement and omission of RT remained independent significant negative predictors of local control.

In this trial, the incidence of DM subsequent to LRR is significantly higher than in patients with no LRR (P=0.03). This is in agreement with the results done by Danish Breast Cancer Cooperative Group et al.[14], who reported DM subsequent to LRR and no LRR 35% and 6%, respectively (P<0.001).

The 5–year overall survival (OS) in this trial was 31.2 % which was much lower than in Iran which was reported to be 58% by Rezaianzadeh A et al.[19]. The

possible reasons for this may be the late consultation of the physician for a painless breast masses in our country, so this result in delaying in diagnosis and hence late stage disease and hence decreased survival. For more explanation, analysis of a wide range of factors affecting survival must be done as they did in their trial.

In this trial the median follow–up of patients received early RT was significantly higher than patients received delayed RT (P=0.03). Improvement in survival is due to prevention of local recurrence by RT. This is inagreenent with Fodor J[4].

CONCLUSION

Among breast cancer patients treated with mastectomy, short interval between surgery and radiotherapy was associated with decrease in the risk of local recurrence. So waiting times for radiotherapy should be short as reasonably achievable. Based on the results of this study radiotherapy should not delayed more than 2 months from surgery. Prognostic factors for local recurrence were, number of involved nodes, tumor grade and age. Further researches are needed to estimate accurate time to radiation treatment after surgery.

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