What is the optimal time of adjuvant radiotherapy in breast cancer?

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Received: 15 July 2021
Accepted: 17 August 2021

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Abstract:

Background: Breast cancer is the most common cancer in female, Adjuvant radiotherapy is one of important part in management of non-metastatic patients, Optimum time of adjuvant radiotherapy in patients with breast cancer still unclear, the aim of our study was to evaluate the impact of time to radiotherapy (TTR) after surgery in breast cancer outcome.

Patients and Methods: Data of 304 female patients with a pathologically confirmed breast cancer (clinical stage I, II, III according to AJCC 8th 2018) who treated with definitive surgery and received adjuvant breast radiotherapy from 2005 to 2015 were retrospectively reviewed. We divided the entire group according to time to start of radiation therapy into (group A) who receive radiotherapy less than 24 weeks or (group B) more than 24 weeks and correlated to Loco regional recurrence (LRR) and Disease-free survival (DFS) overall survival (OS).

Results: Overall (304) patients were enrolled. Median DFS in group A was 5±0. 175 (95% C I 4.66 - 5.34) years, versus 3±0. 347 (CI 2.32 -3.68) years in group B (P<0.003). In terms of OS, no significant difference between the two treatment groups was found. the impact of the prognostic factors on DFS and OS in this study revealed significant impact of tumor grade, stage and her2 neu status P-value (P<0.02, P<0.01, P<0.001 respectively) in group A, while in group B there was significant impact of tumor grade on DFS (P<0.04). Analysis TTRs in group A&B with local recurrent revealed significant impact of her2 neu status only P-value (P<0.002, P<0.001 respectively).

Conclusion: adjuvant radiotherapy should be given to the patients within six months of surgery especially to those patients with high risk factors in order to increase the likelihood of achieving good local control and improve DFS.

Introduction:

Adjuvant radiotherapy in breast cancer has an important role in breast cancer as it reduces the incidence of local recurrence and improves overall survival (1-3).

Number of previous studies reported that long time between surgery and adjuvant radiotherapy increase risk of local recurrence (4-8), while other showed no effect on prognosis (9-14)

An optimal time Adjuvant radiotherapy still unclear, in patients received Adjuvant Chemotherapy, time to chemotherapy is an important factor affect time to start adjuvant chemotherapy (15)while literature suggesting that radiotherapy should not be delayed more than 20 weeks after surgery when adjuvant chemotherapy is not administered [16].

Patients and Methods:

Patients:

Our study was carried out at Assuit university hospital from (2005-2015). Ethics committee of Assuit university hospital approved this protocol before data collection. Data were extracted from medical records of 304 female patients over 18 years of age diagnosed with a pathologically confirmed breast cancer (clinical stage I, II, III according to AJCC) who treated with definitive

surgery and received adjuvant breast radiotherapy were retrospectively reviewed.

Patients who received neoadjuvant treatment and who had a missing date of surgery or initiation of RT were excluded. Data extracted included the patient, tumor, and treatment characteristics.

Treatments:

The study population was divided according to type of surgery into two groups, Group A Patients who receive Adjuvant radiotherapy less than 24 weeks or (group B) more than 24 weeks Adjuvant CT before initiation of RT, endocrine therapy was administered to patients with HR-positive tumors, usually after completion of RT.

Time to radiation (TTR) was defined as the time interval between the dates of definitive breast surgery to the initiation date of RT. We divided the entire group according to time to start of radiation therapy into (group A) who receive radiotherapy less than 24 weeks or (group B) more than 24 weeks.

All patients received irradiation to the ipsilateral chest wall or whole breast. Additional regional nodal irradiation was generally administrated in node-positive patients. The dose prescription was 50 Gy in 25 fractions. A boost of 10–16 Gy in 5–8 fractions to the tumor bed (boost) was delivered sequentially with whole breast irradiation. Time to recurrence was defined as (any first recurrence within the ipsilateral chest wall or breast or regional nodes) and length of follow-up were calculated from the date of initiation of RT

Statistical Analysis:

TTR was defined for group A and group B and correlated to Loco regional recurrence (LRR) and Disease-free survival (DFS) overall survival (OS).

Statistical analysis was done with the statistical package of social since Anova and T tests were used to test between-group differences. The survival curves were estimated using the Kaplan–Meier method. Analyses were performed using SPSS software version 24.

Results:

Overall treatment number were (304) patients classified into two groups, group A “n=256”, group B n=48”. Patints in group A were more likely to be larger tumor size than those in group B (P<0.001), more ER, PR +ve & Her2new –ve versus in group B (P<0.02, P<0.04& P<0.005) respectively. Patient characteristic details stratified by TTR in group A &B are listed in Table1.

There is a significant difference in Median DFS in group A versus in group B (CI, 4.657 TO 5.343, P<0.003). In terms of OS, no significant difference between the two treatment groups was found (P<0.766). Table 2,3 figures 1,2

Table 4 shows an analysis of the impact of the prognostic factors on DFS which revealed significant impact of tumor grade, stage and her2 neu status P-value (P<0.02, P<0.01, P<0.001 respectively) in group A, while in group B there was significant impact of tumor grade on DFS (P<0.04).

Analysis TTRs in group A&B with local recurrent revealed significant impact of her2 neu status only P-value (P<0.002, P<0.001 respectively) Table 5

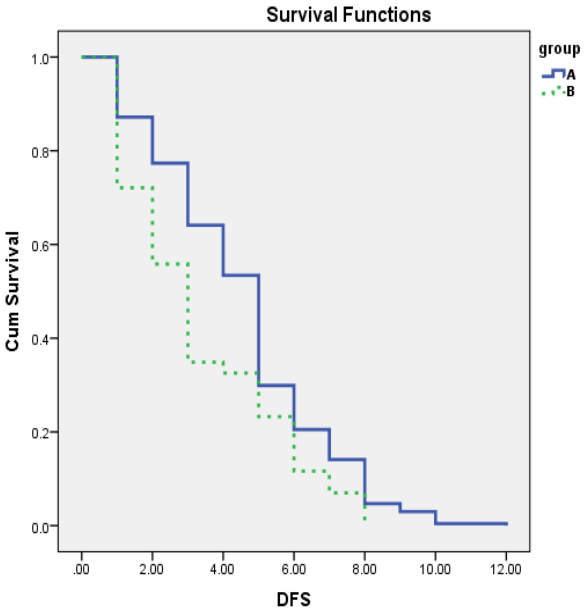

Figure (1) Kaplan Meier curve for disease free survival

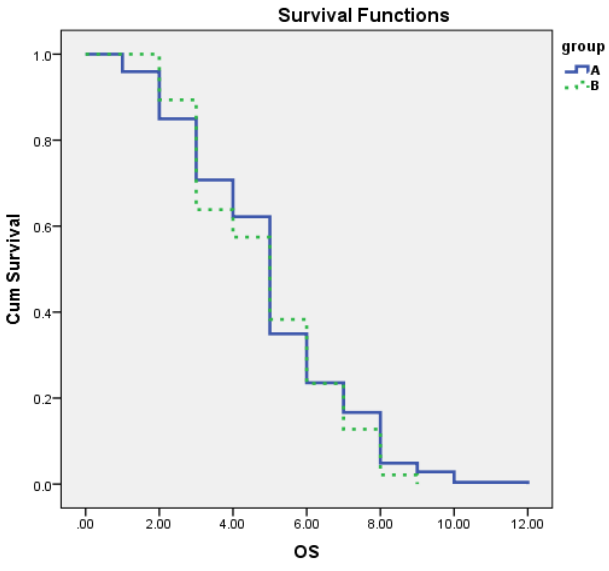

Figure (2) Kaplan Meier curve for overall survival

Table (1) Patient characteristic details stratified by TTR in group A &B

Item	Group A "n=256"	Group B" n=48"	P-value
1-Age "yrs."	49.24±11.04	47.31±10.25	P=0. 262n.s
2-Tumer size:			
• T1	22((8.6%)	10(14.9%)	
• T2	171(66.8%)	20(41.7%)	P<0.001**
• T3	49(19.1%)	12(25.0%)	
• T4	14(5.5%)	8(16.7%)	
3-Lymph node:			
• No	56(21.9%)	5(10.4%)	
• N1	63(24.6%)	10(20.8%)	P=0. 270n.s
• N2	83(32.4%)	18(37.5%)	
• N3	54(21.1%)	15(31.2%)	
4-Mets.:			
• M0	248(96.9%)	46(95.8%)	P=0. 530n.s
• M1	8(3.1%)	2(4.2%)	
5-Grade:			
• I	26(10.2%)	4(8.3%)	P=0. 906n.s
• II	185(72.3%)	36(75.0%)	
• III	45(17.6%)	8(16.7%)	
6-Stage:			
• I	6(2.3%)	1(2.1%)	P<0.007**
• II	133(52.0%)	12(25.0%)	
• III	117(45.7%)	35(73.0%)	
7-Menopause:			
• Premenopausal	131(51.2%)	26(54.2%)	P=0. 412n.s
• Postmenopausal	125(48.8%)	22(45.8%)	
8-ER:			
• -ve	59(23.0%)	18(37.5%)	P<0.02*
• +ve	197(77.0%)	30(62.5%)	
9-PR:			
• -ve	72(28.1%)	20(41.7%)	P<0.04*
• +ve	184(71.9%)	28(58.3%)	
10-Her2new:			
• Not done	166(64.8%)	40(83.3%)	P<0.005**
• -ve	72(28.12%)	3(6.2%)	
• +ve	18(7.03%)	5(10.4%)	

Table (2): Means and Medians for DFS Survival Time

Group	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
A	4.551	.156	4.245	4.858	5.000	.175	4.657	5.343
B	3.372	.347	2.691	4.053	3.000	.347	2.319	3.681
Overall	4.368	.145	4.085	4.652	5.000	.177	4.652	5.348

a. Estimation is limited to the largest survival time if it is censored.

Table (3): Means and Medians for overall Survival Time

Group	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
A	4.976	.141	4.699	5.252	5.000	.112	4.781	5.219
B	4.872	.291	4.302	5.443	5.000	.370	4.274	5.726
Overall	4.959	.127	4.710	5.208	5.000	.108	4.789	5.211

a. Estimation is limited to the largest survival time if it is censored.

Table (4): Univariate analysis TTRs in group A&B with DFS

Item	Group A	P-value	Group B	p-value
Age:				
• <40yrs.	4.39±2.45	P=0. 550n.s	3.25±2.56	P=0. 830n.s
• ≥40yrs	4.60±2.37		3.41±2.20	
Tumor size:				
• T1	4.57±2.63		3.37±2.38	
• T2	4.63±2.38	P=0. 717n.s	3.58±2.09	P=0. 822n.s
• T3	4.40±2.38		3.81±2.27	
• T4	5.34±2.48		2.81±2.47	
Lymph node:				
• N0	5.10±2.36		4.25±1.70	
• N1	4.44±2.16		4.33±2.31	
• N2	4.63±2.56	P=0. 190n.s	2.86±2.47	P=0. 093n.s
• N3	3.90±2.37		2.22±1.39	
Metastasis:				
• No	4.55±2.37		3.39±2.33	
• Yes	3.40±2.50	P=0. 283n.s	3.00±0.00	P=0. 816n.s
Grade:				
• I	4.64±1.49		6.00±1.41	
• II	4.35±2.41	P<0.02*	3.06±2.18	P<0.04*
• III	3.25±2.61		3.25±2.31	
Stage:				
• I	5.16±2.78		5.00±1.24	
• II	4.96±2.39	P<0.01*	4.09±2.34	P=0. 553n.s
• III	3.84±2.50		3.06±2.32	
Menopause:				
No	4.70±2.45	P=0. 308n.s	3.52±2.35	P=0. 650n.s
Yes	4.38±2.31		3.20±2.23	
ER:	4.70±2.45		2.64±2.20	
-ve	4.38±2.31	P=0. 308n.s	3.72±2.26	P=0. 147n.s
+ve				
PR:			2.93±2.40	
-ve	4.12±2.31	P=0. 085n.s	3.60±2.21	P=0. 362n.s
+ve	4.72±2.40			
HER2:				
-ve	4.09±2.60	P<0.001**	3.60±2.40	P=0. 261n.s
+ve	2.71±1.72		3.33±1.5	

Table 5: Univariate analysis TTRs in group A&B with local recurrent

Item	Group A		P-value	Group B		P-value
	no	yes		no	yes	
Age:						
<40yrs.	60(23.9%)	2(40.0%)	P=0.351	13(28.9%)	1(50.0%)	P=0.659
≥40yrs	191(76.1%)	3(60.0%)	n.s	33(68.5%)	1(50.0%)	n.s
Tumor size:						
T1	21(8.4%)	1(20.0%)		8(17.39%)	0	P=0.642
T2	172(68.5%)	1(20.0%)	P=0.181	19(41.30%)	0	n.s
T3	44(17.5%)	3(60.0%)	n.s	11(23.9%)	1(50.0%)	
T4	14(5.6%)	0		8(17.40%)	1(50.0%)	
Lymph node:						
N0	55(21.9%)	2(40.0%)		4(8.9%)	0	
N1	63(25.1%)	0	P=0.665	9(20.0%)	1(50.0%)	P=0.736
N2	81(32.3%)	1(20.0%)	n.s	19(40.0%)	0	n.s
N3	52(20.7%)	2(40.0%)		14(31.1%)	1(50.0%)	
Metastasis:						
No	242(96.4%)	5(100%)	P=0.911	43(93.47%)	2(100%)	P=0.899
Yes	9(3.6%)	0	n.s	3(6.52%)	0	n.s
Grade:						
I	25(10.0%)	0	P=0.376	4(8.69%)	0	P=0.271
II	180(71.7%)	5(100%)	n.s	33(71.73%)	1(50.0%)	n.s
III	46(18.3%)	0		9(19.56%)	1(50.0%)	
Stage:						
I	6(2.4%)	1(20.0%)	P=0.082	1(2.17%)	0	P=0. 962
II	132(52.6%)	1(20.0%)	n.s	11(23.9%)	0	n.s
III	113(45.0%)	3(60.0%)		34(73.91%)	2(100%)	
Menopause:						P=0. 540
No	126(50.2%)	4(80.0%)	P=0.195	25(54.34%)	1(50.0%)	n.s
Yes	125(49.8%)	1(20.0%)	n.s	21(45.65%)	1(50.0%)	
ER:						P=0. 242
-ve	60(23.9%)	0	P=0. 260n.s	19(41.30%)	0	n.s
+ve	191(76.1%)	5(100%)		27(58.69%)	2(100%)	
PR:						
-ve	70(27.9%)	1(20.0%)	P=0. 575n.s	20(43.47%)	0	P=0.
+ve	181(72.1%)	4(80.0%)		26(56.52%)	2(100%)	242n.s
HER2:						
-ve	67(26.9%)	5(100%)		3(6.52%)	0	
+ve	16(6.4%)	0	P<0.002	3(6.52%)	2(100%)	P<0.001

Discussion:

The incidence of local recurrence increases 1-2% with every month delay in initiation of adjuvant radiotherapy. Optimal time between surgery and radiotherapy still unclear [17].

Delaying RT may allow loco regional residual cancer cells to repopulate and spread to distant sites. [18].

Previous studies of TTR aimed to clarify the sequence of upfront CT or RT in the adjuvant phase, Current guidelines support upfront CT followed by RT.

Dose escalation of chemotherapy schemes prior to radiotherapy frequently resulted in a prolonged surgery-radiotherapy interval. However, these studies were not designed to evaluate the effect of delayed-onset radiotherapy [19, 20].

There are multiple factors effect on TTR especially after chemotherapy as length of chemotherapy treatment, a delay in referral to a radiation oncologist, fatigue after CT, waiting list for starting RT or inevitable interruption of adjuvant therapy, such as the current outbreak of COVID-19 worldwide [21] adjuvant RT trials usually predefined a maximum acceptable TTR after CT, although this is more empirical than an evidence-based restriction, however timely initiation of RT after CT should be granted in regular clinical practice

Buchholz and his colleagues classified 105 patients with local-regional breast cancer into two groups like us They found that, delay in the initiation of radiation for a period of 6 months or greater from diagnosis resulted in a higher local failure rate and decreased overall survival rate [22].

Our data suggest that receipt of early TTR may result in an improved DFS& local recurrence, while the OS show no significant difference in both groups.

Intervals between surgery and Radiotherapy depend on various patient-, tumor-, and treatment-related factors. [23]

In our study early TTR show a significant impact of tumor grade, stage and her2 neu status on DFS while local recurrent in both groups significantly correlated to HER2 status.

Adjuvant radiotherapy for breast cancer tends to involve long waiting times due to the lack equipment, and the poor wound healing.

Based on our study we suggested an adjuvant radiotherapy should be administered within six months of surgery especially to those patients with high risk factors in order to increase the likelihood of achieving good local control.

This study had some limitations. First, the retrospective design has undermined its importance when compared with prospective clinical trials, lack correlation of survival with treatment line, subgroup analysis according to type of surgery and the number of cases in arm B is small.

Conclusion:

Timely adjuvant radiotherapy should be given to the patients within six months of surgery especially to those patients with high risk factors in order to increase the likelihood of achieving good local control and improve DFS.

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