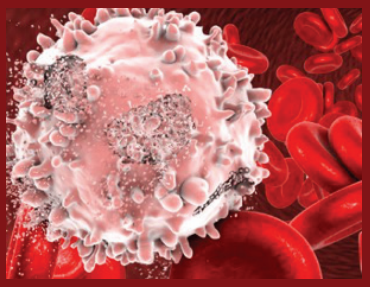
ISSN : 2766-2586

RAS ONCOLOGY & THERAPY

Research Article: Outcomes of Different Radiation Therapy Dose-splitting regimens after Radical Surgery for Early-stage Breast Cancer



Issue Type: Volume 4 Issue 1

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Citation: Mamady Keita, MD, PhD. Outcomes of Different Radiation Therapy Dose-splitting regimens after Radical Surgery for Early-stage Breast Cancer

Received Date: 9th April 2023

Published Date: 25th April 2023

Abstract

Objective: To investigate the outcomes of different dose-splitting radiotherapy regimens after radical or modified radical surgery for early-stage breast cancer.

Material and methods: Between 2015 and 2020, 412 patients treated with radiotherapy after radical or modified radical surgery for early-stage breast cancer were allocated into 3 groups according to different dose-splitting regimens of postoperative radiotherapy. Conventional radiotherapy group157 cases, 2Gy/fraction, once/day, 5 times/week, DT50 Gy; Alternate-day radiotherapy group 202 cases, 3 Gy/fraction, 3 times/week, DT45Gy; Fast radiotherapy group 53 cases, Days 1 and 3, 5Gy/fraction, Days 15 and 17, 6.5 Gy/fr, DT23Gy. Overall, 318 cases were treated with chemotherapy and/or hormone therapy. For the whole group, the 5-year overall and disease-free survival rates were 87.4% and 89.6% respectively. The 5-year disease-free survival rates for the Conventional radiotherapy group, the Alternate-day radiotherapy group, and the Fast radiotherapy group were 90.8%, 86.5%, and 84.6% (P=0.13).The locoregional recurrence rates were 7.0%, 9.9 and 5.7 respectively. There was no significant difference between the three groups in terms of local control.

Conclusion: With similar 5-year disease-free-survival rates, and the same efficacy, Alternate-day radiotherapy has the advantage of giving fewer fractions, which is suitable for a unit with limited resources. Fast radiotherapy shortens the duration of the treatment, and its efficacy and toxic effects deserve further study.

Keywords: Breast cancer, Adjuvant radiotherapy, Mastectomy, Dose splitting

Introduction

Post-operative radiotherapy following radical or modified radical mastectomy has proven to be effective in improving locoregional control and reducing the risk of death related to breast cancer [1]. For many decades, the post-operative radiotherapy regimen is mostly conventional, with DT 50 Gy, 2 Gy/fraction; 5 fractions/week, for a total duration of approximately 5 – 6 weeks. Nowadays, it is well known that the use of a high single-dose fractionation approach to shorten the duration of radiotherapy and better coordination with post-operative chemotherapy can reduce the patient's treatment burden. According to Blanco Parajón S et al [2], the efficacy of fast radiotherapy fractionation is similar to that of conventional post-operative fractionation. Given the limited resources available for radiotherapy in the country, resources could be better utilized if the duration of treatments could be reduced to reduce the workload of the treatment machine. With the introduction of the intensity-modulated radiotherapy, the Fast-Forward Trial Management Group, in the UK, searched for primary research and reviews published in English between 1980 and 2020 and found 13 randomized studies testing adjuvant breast hypofractionated radiotherapy regimens against standard fractionation ranging in sample size from 30 to 2236 patients. The results suggest further scope for simplifying curative radiotherapy for women with early breast cancer [3]. Since 2013, several studies have been conducted on postoperative radiotherapy after radical mastectomy for breast cancer with different fractionation methods in our cancer institute, the actualized results are reported as follows.

Material and methods

Clinico-pathogical characteristics

From January 2015 to December 2020, 412 women with early-stage breast cancer (stage T1-2) underwent radical or modified radical surgery followed by radiotherapy at The Fourth Affiliated Hospital of Hebei Medical University. Age 20 - 76 years, median age 47 years. Early- stage breast cancer treated with post-operative breast-conserving radiotherapy and the T3 and T4 stage post-operative radiotherapy cases were not included in the analysis. All cases were pathologically confirmed, including 388 cases (94.2%) of invasive ductal carcinoma, 15 cases (3.6%) of invasive lobular carcinoma. According to the AJCC TNM staging principles in 2017 [4], there were 103 cases (25.0%) in stage T1 and 309 cases (75.0%) in stage T2. 138 cases (33.5%) without axillary lymph node metastasis, 157 cases (38.1%) with 1 - 3 axillary lymph node metastasis, 117 cases (28.4%) with more than 3 lymph nodes metastasis.

Treatment regimes

Adjuvant treatment after radical or modified radical surgery includes post-operative radiotherapy, chemotherapy and hormone therapy. The whole group had post-operative radiotherapy, 318cases (77.2%) had chemotherapy and 118 (28.6%) cases of hormone therapy.

Radiotherapy

Post-operative radiotherapy may be given to the supraclavicular, superior axilla or complete axilla and internal mammary chain lymph nodes with or without chest wall irradiation. The supraclavicular, superior or complete axilla was irradiated with an 8MV X-ray, with a 1.5 cm thick wax block on the 20Gy clavicular, internal mammary chain area irradiated with 14 MeV electron beam or mixed with 8 MV X-rays, chest wall area irradiated with 8MV x-ray tangent or 6 – 8 MeV electron beam. According to the different dose-splitting methods of post-operative radiotherapy, patients were allocated into 3 groups: (1) Conventional radiotherapy group:157 cases (38.1%), total dose DT50Gy/5 weeks, DT 2 Gy/fraction, once /day, 5 fractions/ week; (2) Alternate-day radiotherapy group: 202 cases (49.0%), DT3Gy/fraction, 3 fractions/week, DT45 Gy/ 5 weeks; (3) Fast radiotherapy group: 53 cases (12.9%), DT 5 Gy/fraction on days 1 and 3, DT 6.5 times on days 15 and 17, total DT23 Gy/17 days. The age distribution, T-stage, type of pathology and site of radiotherapy were similar in the three groups Table 1. There were fewer N0 patients in the Alternate-day radiotherapy group than in the other two groups and more chemotherapy cases in the Fast and Alternate- day radiotherapy groups than in the Conventional radiotherapy group. Patients at high-risk of locoregional recurrence are those with ≥4 axillary lymph node metastases or 1-3 lymph node metastases and those with less than 8 lymph nodes dissected [5].There were 36 (22.9%), 98 (48.5%), and 23 (43.4%) patients with 1 – 3 lymph nodes metastasis; 56 (35.7%), 52 (25.7%), and 9 (17.0%) with more than 3 lymph nodes metastasis which are with high-risk of locoregional recurrence in the Conventional radiotherapy group, the Alternate-day radiotherapy group, and the Fast radiotherapy group, respectively. Of these, 38 (88.4%), 73 (89.0%), and 15 (100%) received chemotherapy. For the whole group, radiotherapy fields were similar in the three groups, with 214 cases (51.9%) of complete breast radiotherapy, including the chest wall, supra clavicular, superior, and complete axilla; 198 cases (48.1%) of incomplete breast radiotherapy, including the chest wall, supra clavicular, superior, and incomplete axilla, respectively, which were comparable.

Systemic treatments

118 patients received hormone therapy and 318 patients received systemic chemotherapy, respectively. Chemotherapy regimens are mainly Taxane regimens, with some patients having cisplatin or Adriamycin in their chemotherapy regimens for 6 - 12 cycles.

Follow-up and statistical analysis

The whole group was followed up for 18 - 122 months, with a median follow-up time of 68.2 months. Survival rates were calculated using the Kaplan-Meir method, differences between the three groups were tested using the log-rank test, and recurrence rates were compared using the x2 test. Cox proportional regression models were used for the multivariate analysis of local recurrence.

Results

Locoregional recurrence

Local or regional recurrence was defined as recurrence of disease in the chest wall and/or lymph node draining areas after treatment. The locoregional recurrence rate for the whole group was 8.5% (35/412cases). Among them, 16 cases (3.9%) were intra-field recurrences, all of which were positive axillary lymph nodes, 6 cases in the chest wall, 4 case in the supra clavicular, and 6 case in the axilla. There were recurrences in out of the field 19 cases (2.7%), in chest wall 12 cases (2.9%), and supraclavicular 7 cases (1.7%). The locoregional recurrence rate in the Conventional radiotherapy group, the Alternate-day radiotherapy group, and the Fast radiotherapy group is shown in Table 1. There was no significant difference recurrence within the field among the three groups (P> 0.05). Cox regression analysis showed that the number of axillary lymph node metastases was associated with recurrence in the radiotherapy field (P =0.02), while age, irradiated site, dose splitting method, pathological type, and chemotherapy were not significantly correlated.

Survival analysis:

The 5-year overall and disease-free survival rates for the whole group were 87.4% and 89.6%, respectively. The 5-year tumor-free survival rates were 90.8%, 86.5% and 84.6% in the Conventional radiotherapy group, the Alternate-day radiotherapy group, and in the Fast radiotherapy group respectively, with no significant differences between the three groups (P=0.13, X2 = 3.55).The 5-year tumor-free survival rates for high-risk patients were 80.7%, 79.6%, and 83.0%, respectively (P=0.36, X2=2.04).

Equivalent biological dose and normal tissue reaction

To facilitate the comparison of biological effects, the equivalent biological dose (BED) values of nd 1 (1+d/α /ß) were calculated by the L-Q model for the Conventional radiotherapy group, the Alternate-day radiotherapy group, and the Fast radiotherapy group, Table 2. According to the literature, the α /ßvalue for

breast cancer cells was taken to be 4Gy [6], and the α /ßvalues for normal tissue were taken to be 3 and 10 for early- and late-responding tissue, respectively, without accounting for cell repopulation during treatment [7]. The incidence of acute radiological second-degree skin reactions was 7.3%, 2.4%, and 1 in the Conventional radiotherapy group, the Alternate-day radiotherapy group, and the Fast radiotherapy group, respectively. The number of cases with regular chest X-ray reviews within three years was 98, 113, and 25 respectively. The incidence of radiation-induced localised pulmonary fibrosis in the upper lungs was 39.8% (39/98), 48.7% (55/113), and 44.0% (11/25), respectively, with chest radiographs showing dense or striated shadows in the upper lungs or the mediastinum.

Discussion

Postoperative radiotherapy for breast cancer significantly reduces the rate of local and regional lymph node recurrence and improves survival, especially in cases with ≥4 axillary lymph node metastases or T3 – T4 [8, 9]. It is generally accepted that the tumor load after radical or modified radical surgery is small and that a moderate dose of radiotherapy is sufficient for the prophylactic treatment of subclinical lesions [10]. Radiotherapy after modified radical or radical mastectomy is often performed using conventional radiotherapy with a total DT of 50Gy. The local recurrence rate after adjuvant radiotherapy and radical surgery for early-stage breast cancer is 2% [10]. Different dose splitting patterns have also been used, ranging from 36 - 50 Gy, 1.8 - 3.0 Gy/fraction, Eldeeb H[11] retrospectively reported three dose fractions for radiotherapy after modified radical surgery, DT 40 Gy/17fractions completed within 3.4 weeks versus DT 45Gy / 15 fractions completed in 4 weeks, versus DT 50Gy / 25 fractions completed in 5 weeks with no statistical difference in the local recurrence rate between the three groups. We compared three dose fractionation methods, namely the Conventional radiotherapy group, the Alternate-day radiotherapy group and the Fast radiotherapy group. Fast radiotherapy fractionation belongs to the category of hypo fractionation radiotherapy. Baillet F et al [12] first reported the results of a randomized group of 230 breast cancer patients, the majority of women were treated with radiotherapy after radical surgery or Conservative breast cancer surgery, of which 82% were stage T1, 79% stage T2, 42% had axillary lymph node metastases, and 21% had chemotherapy and radiotherapy. After lumpectomy or external beam radiotherapy in non-operated cases, the interstitial boost technique is systematically used, with a dose between 20 and 30 Gy. The results showed that the local recurrence rate was 7% in the Fast radiotherapy group compared to 5% in the control group (DT 45Gy/25 fractions, 1.8 Gy/fraction), a non-significant difference.The BED of tumors in the Fast radiotherapy group was calculated using the L-Q model to be only 56.6 Gy, which was lower than the BED of the Conventional radiotherapy group 75.0 Gy and similar to the standard fractionation method with a total of 40 Gy. Theoretically, the rate of local control may be lower in the fast radiotherapy group due to the small size, but the actual treatment effect was not significantly lower as reported by Baillet et al and in our data. Ragaz Jet al [13] reported in a prospective study that the total dose of radiotherapy after radical modified mastectomy for breast cancer with positives lymph nodes was 35 - 37.5 Gy/16 fractions were completed within 3-4 weeks. The results showed that the tumor BED value was very close to that of the Fast radiotherapy group in this study (54.1 - 59.4 Gy), the recurrence rate of the radiotherapy + chemotherapy group was 33% lower than that of the chemotherapy alone group, and the disease-free survival rate was significantly improved, indicating the effectiveness of this type of radiotherapy method. The 5-year local recurrence rate was only 5.7% in the Fast radiotherapy group, which was not significantly different from the Conventional radiotherapy group. Nowadays, the main reason why hypofractionated radiotherapy is less routinely used is that the late sequel of hypofractionated radiotherapy are significantly higher than those of Conventional radiotherapy group.

The total dose in the Fast radiotherapy group in this study was lower, and both the early response tissue BED and the late response tissue BED were lower than that in the Conventional radiotherapy group and the Alternate-day group, so the acute and late radiation response was probably lower than in the Conventional group. The results of our current study showed no acute skin reaction of grade II or higher occurred in the Fast radiotherapy group, and the incidence of pulmonary fibrosis was similar to that of the Conventional radiotherapy group. The advantage of Fast radiotherapy is that it shortens the duration of treatment, allowing time for early initiation of chemotherapy in high-risk patients with distant metastases; the number of radiotherapy fractionation is significantly reduced compared to Conventional radiotherapy, reducing the time spent in hospital or the inconvenience of travelling to and from outpatient radiotherapy. In contrast, due to the small number of cases, further observation is needed. The BED values of the early response tissue and tumour cells were similar in the Alternate-day radiotherapy group compared to the Conventional radiotherapy group, but the BED of the late response tissue was slightly higher than that of the Conventional radiotherapy group. In terms of clinical outcomes, the recurrence rates in the radiotherapy field were similar in two high-risk groups (4.9% and 4.7%), and the incidence of pulmonary fibrosis was slightly higher in the Alternate-day radiotherapy group than that in Conventional radiotherapy group, although the difference was not significant. Blomqvist et al [14] also used the same dose split for patients with stage II, positive axillary lymph nodes, and a 5-year local recurrence rate of 7% in the chemotherapy + radiotherapy group, which was better than the chemotherapy alone group (2.4%). The advantage of Alternate-day radiotherapy is that fewer treatments per week make easier for the patients and save resources and equipment, but the overall treatment time does not decrease. In this sitting, Alternate-day radiotherapy is considered an alternative to Conventional radiotherapy for units with limited radiotherapy resources. However, since late reactions were slightly higher in Alternate-day radiotherapy group, the incidence of pulmonary reactions was reduced by combining an electron beam and X-ray to reduce the dose to the apical lung field.

Conclusion: In addition to conventional dose fractionation, Alternated-days radiotherapy with 3 Gy/fractions after radical mastectomy may be an option, depending on the availability of radiotherapy resources.

Disclosure

No authors report any conflict of interest.

Authors' Contributions

Keita M. and Shen W.B. drafted the manuscript and participated in data collection, and helped to analyze the data. ZHU Shuchai participated in the coordination of the study. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Table 1 Clinicopathological characteristics and different dose-splitting groups (n=412)

Characteristics	Whole-group (n=412) n (%)	Conventional RT - group (n=157) n (%)	Alternate- day RT- group (n=202) n (%)	Fast RT- group (n=53) n (%)
Median age (range)	47 (20 – 76)	47 (20 – 76)	44 (27 – 71)	42(46– 69)
T - stage				
T1	103 (25.0)	42 (26.8)	48 (23.8)	13 (24.5)
T2	309 (75.0)	115 (73.2)	154 (76.2)	40
Lymph nodes				
N0	138 (33.5)	65 (41.4)	52 (25.7)	21(39.6)
N1-3	157 (38.1)	36 (22.9)	98 (48.5)	23 (43.4)
N4+	117 (28.4)	56 (35.7)	52 (25.7)	9 (17.0)
Histology				
IDC	388 (94.2)	148 (94.3)	192 (95.0)	48 (90.6)
ILC	15 (3.6)	4 (2.5)	8 (4.0)	3 (5.7)
Others	9 (2.2)	5 (3.2)	2 (1.0)	2 (3.7)
RT- areas				
Complete breast	214 (51.9)	52 (33.1)	126 (62.4)	36 (67.9)
Incomplete breast	198 (48.1)	105 (66.9)	76 (37.6)	17 (32.1)
Chemotherapy				
Yes	318 (77.2)	109 (69.4)	167 (82.7)	42 (79.2)
No	94 (228)	48 (30.6)	35 (17.3)	11(20.8)
Type of surgery			(	
R- mastectomy	237 (57.5)	10 (6.4)	187 (92.6)	40 (75.5)
RM- mastectomy	175 (42.5)	147 (93.6)	15 (7.4)	13 (24.5)
Hormone therapy				
Yes	118 (28.6)	39 (24.8)	67 (33.2)	12 (22.6)
No	294 (71.4)	118 (75.2)	135 (66.8)	41 (77.4)
Recurrence				
Yes	35 (8.5)	11 (7.0)	20 (9.9)	3 (5.7)
No	377 (91.5)	146 (93.0)	182 (90.1)	50 (94.3)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, R : Radical, RM : Radical modified.

Table 2 Equivalent biological dose (BED) in different dose-splitting groups

Tissue reaction	Conventional RT - group	Alternate- day RT- group	Fast RT- group
Early reactions in tissues	60.0	59.0	37.0
Late reactions in tissues	83.3	89.9	68.0
Breast tumor cell reaction	74.8	79.0	57.0

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