Clinical Trial/Experimental Study

Medicine®

OPEN

Randomized controlled trial of late-course concurrent versus sequential chemoradiotherapy after mastectomy and axillary surgery in locally advanced breast cancer

Ying Lu, MD, Haixin Huang, MS*, Hui Yang, MS, Dagui Chen, MS

Abstract

Background: Concurrent chemoradiotherapy could increase the local control rate in patients with high recurrence risk after breast-conserving surgery, but the effect of concurrent chemoradiotherapy after mastectomy and axillary dissection is not clear. The aim of the study was to compare the effects of late-course concurrent chemoradiotherapy (CCRT) versus sequential therapy (SCRT) after mastectomy and axillary surgery in locally advanced breast cancer.

Methods: This was a randomized controlled trial of 155 patients with stage pT3–4p N1–3c M0 or pAnyT pN2–3c M0 breast cancer undergoing 5-fluorouracil+epirubicin+cyclophosphamide followed by docetaxel (FEC-D) chemotherapy after mastectomy and axillary dissection. Patients were randomized to the CCRT group (intensity-modulated radiation therapy was performed concurrently with docetaxel) or to the SCRT group (radiotherapy after chemotherapy). Recurrences, adverse reactions, and short-term effects were observed.

Results: All the patients completed the planned therapy. The median follow-up was 39 (range, 16–62) months. Compared with SCRT, the 3-year local-regional recurrence-free survival (LRFS) in the CCRT group was improved (81.8% vs 92.3%, $P = .046$). There was no significant difference in 3-year disease-free survival (DFS) and overall survival (OS). In the pT3–4 pN1–3 cM0 subgroup, the 3-year local recurrence-free survival and DFS were significantly improved in the CCRT group (69.4% vs 88.2%, $P = .036$; and 41.7% vs 72.6%, $P = .049$, respectively). No significant difference was observed adverse reactions between the 2 groups.

Conclusion: LRFS of patients with locally advanced invasive breast cancer after mastectomy and axillary surgery was better with CCRT than with SCRT and with similar profiles of adverse reactions. The DFS of patients staged pT3–4 pN1–3 cM0 was also improved.

Abbreviations: CCRT = concurrent chemoradiotherapy, CMF = cyclophosphamide, methotrexate, and 5-fluorouracil, CT = computed tomography, DFS = disease-free survival, FEC = 5-fluorouracil, epirubicin and cyclophosphamide, FEC-D = 5-fluorouracil +epirubicin+cyclophosphamide followed by docetaxel, IMRT = intensity-modulated radiation therapy, LRFS = local-regional recurrence-free survival, LVEF = left ventricular ejection fraction, NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events, OS = overall survival, PFS = progression-free survival, SCRT = sequential chemoradiotherapy.

Keywords: chemotherapy, concurrent therapy, intensity-modulated radiation therapy, locally advanced breast cancer, mastectomy, sequential therapy

1. Introduction

Breast cancer is now the most common cancer in Chinese women, accounting for12.2% of all newly diagnosed breast cancers and 9.6% of all deaths from breast cancer worldwide.[1] Although the breast-conserving surgery rate is increasing, mastectomy and axillary surgery are still the main strategies for operable locally advanced breast cancer. To improve disease control and survival, a multidisciplinary approach that includes chemotherapy, radiotherapy, endocrine therapy, and targeted therapy are necessary.

It is now well-known that radiotherapy after mastectomy decreases the 10-year recurrence rate by 10.6% and 20-year breast cancer-related death by 8.1% in node-positive breast cancer patients.[2] Adjuvant radiotherapy performed after chemotherapy is currently recommended because concurrent chemoradiotherapy did not show anobvious curative effect[3,4] and may increase severe adverse reactions.[4–7] Nevertheless, the best sequence of postoperative chemoradiotherapy is still unclear.

Delayed radiotherapy may increase the risk of local recurrence.[8] Livi et al[9]showed that the timing of radiotherapy did not affect local recurrences. For patients with >4 positive lymph nodes, the 10-year recurrence risk for sequential chemotherapy and radiotherapy was over 21%.[10] However, the SECRAB trial found that the 5-year local recurrence rate of concurrent chemoradiotherapy was significantly decreased compared with the sequential therapy (2.8% and 5.1%).[11] In the ARCOSEIN

Editor: Jianxun Ding.

This work was supported by Department of Health of Guangxi Zhuang Autonomous Region Self-raised Funds Project (No. Z2014394).

All authors declared that they have no conflict of interest.

Department of Oncology, Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, Gaungxi, China.

* Correspondence: Haixin Huang, Department of Oncology, Fourth Affiliated Hospital of Guangxi Medical University, No.1 Liushi Road, Liuzhou, Gaungxi 545000, China (e-mail: 13507726193@163.com).

Medicine (2017) 96:41(e8252)

Received: 1 November 2016 / Received in final form: 21 August 2017 / Accepted: 23 August 2017

http://dx.doi.org/10.1097/MD.0000000000008252

study, all patients were treated with concurrent chemoradiotherapy after breast-conserving surgery but did not show any advantage, except for local-regional recurrence-free survival (LRFS) among patients with positive lymph nodes.[12] Therefore, these studies suggest that concurrent chemoradiotherapy could increase the local control rate in patients with high recurrence risk after breast-conserving surgery, but the effect of concurrent chemoradiotherapy after mastectomy and axillary dissection is not clear. Recent studies have shown that sequential adjuvant chemoradiotherapy was mainly performed in patients with early-stage breast cancer after breast-conserving surgery,[4,8,11,12] rather than in those who underwent mastectomy and axillary surgery.[13,14]

In addition, modern chemotherapy protocols may lead to better outcomes. The sequential administration of taxanes significantly improves progression-free survival (PFS) and overall survival (OS) of patients with positive lymph nodes.[15–17] In addition, computed tomography (CT) simulation, and three-dimensional (3D) and intensity-modulated radiation therapy (IMRT) have been recently developed, improving outcomes,[18,19] but these technologies were not tested in previous studies in relation of chemotherapy timing.

A recent Chinese preliminary trial showed that 5-fluorouracil +epirubicin+cyclophosphamide followed by docetaxel (FEC-D) given concurrently with IMRT increased the local control rate.[20] Therefore, the aim of the present study was to compare the effects of late-course concurrent chemoradiotherapy (CCRT) versus sequential therapy (SCRT) after mastectomy and axillary surgery in locally advanced breast cancer.

2. Materials and methods

2.1. Study design and patients

This was a randomized controlled trial that was carried out in female patients with breast cancer treated at the Fourth Affiliated Hospital of Guangxi Medical University between January 2009 and December 2014. Eligibility criteria were: (1) having undergone mastectomy and axillary surgery for invasive breast ductal carcinoma confirmed by pathological examination of the surgical specimen; (2) in stage pT3–4, pN1–3, cM0 or pAnyT, pN2–3, cM0 according to the American Joint Committee on Cancer (AJCC) staging system; (3) Karnofsky performance status score >60; and (4) without other tumor or severe cardiopulmonary chronic diseases. Patients who had been previously treated for any cancer, as well as those with HER2-positive breast cancer treated with trastuzumab, were excluded.

The study was approved by the ethics committee of the Fourth Affiliated Hospital of Guangxi Medical University (#KY009016). Written informed consent was obtained from each patient.

2.2. Randomization

An independent statistician prepared the allocation of patients in sequential sealed envelopes using a random number table prepared with SPSS 19.0 (IBM, Armonk, NY). The patients were randomized after the third 5-fluorouracil, epirubicin and cyclophosphamide (FEC) cycle. For the late-course concurrent therapy (CCRT) group, adjuvant radiotherapy was started concurrently during the docetaxel chemotherapy stage. For the sequential group (SCRT), adjuvant radiotherapy was started 2 weeks after completing the chemotherapy. When the chemoradiotherapy was completed, patients with a hormone receptor-positive cancer received endocrine therapy depending on their menopausal status.

2.3. Treatments

All the patients received the FEC-D adjuvant chemotherapy regimen, starting 3 weeks after operation: 5-fluorouracil (500 mg/m^2, day 1, intravenous drip), epirubicin (100 mg/m^2, day 1, intravenous drip), and cyclophosphamide (500 mg/m^2, day 1, intravenous drip). One cycle lasted 21 days and a total of 3 cycles were administered. Then, docetaxel was administrated (100 mg/m^2, day 1, intravenous drip). One cycle lasted 21 days and a total of 3 cycles were administered.

Adjuvant radiotherapy was performed using 6-MV x-ray, 50 Gy in 25 fractions of 2 Gy. IMRT was applied to the chest wall and a single tangential beam was applied to the clavicle lymph nodearea. A 1-cm thick tissue compensation membrane was used in patients with cutaneous involvement. The axilla and internal mammary lymph node regions were not irradiated.

2.4. Assessments

All assessments were performed by the oncologist. The appearance of lesions in the chest wall and lymph node drainage area were termed as loco-regional recurrence. The appearance of lesions in the head, bone, any viscera, or non-regional lymph nodes was diagnosed as distant metastasis.

Acute adverse reactions were divided into grade 0 to 4 according to the NCI-CTCAE (3.0) adverse reaction evaluation criteria.[21] The late-stage adverse reactions, which occurred 90 days after radiotherapy was finished, were divided into grade 0 to 4 according to the Radiation Therapy Oncology Group late-stage radiotherapy reaction criterion.[22]

2.5. Outcomes

The primary outcome was recurrence. Secondary outcomes included, degree and improvement time of skin and mucous membrane reaction, and cardiopulmonary adverse reaction during radiotherapy.

2.6. Follow-up

The first follow-up was performed 1 month after the whole therapy was completed. During follow-up, skin condition, myocardial enzymes, electrocardiogram, and chest x-ray (chest CT and pulmonary function test for patients with symptoms) were monitored to assess acute adverse reaction recovery and late-stage adverse reaction. The disease condition was monitored and the efficacy was assessed. The follow-up was performed every 3 months for 3 years, and every 6 months after thereafter.

2.7. Statistical analysis

Power analysis was performed based on a difference in LRFS of 10%. Using a power of 80% and α threshold of 0.05, the power analysis suggested that a sample size of 74/group should be sufficient to detect an eventual difference in LRFS. Continuous variables are presented as mean $\pm$ standard deviation and were analyzed using the Student t test. Categorical variables are presented as frequencies and were analyzed using the Fisher exact test. Survival was analyzed by the Kaplan–Meier method and the

log-rank test. The Cox proportional hazard model was used to perform multivariate analyses. SPSS 19.0 (IBM, Armonk, NY) was used for analysis. Two-sided P values <0.05 were considered as statistically significant.

3. Results

3.1. Characteristics of the patients

In this study, 155 patients were enrolled between January 2009 and December 2014, 78 in the CCRT group, and 77 in the SCRT group (Fig. 1). The median age was 46 years (range 23–65 years), and all patients were staged pT3–4p N1–3 cM0 or pAnyT pN2–3 cM0. The clinical characteristics of the patients are shown in Table 1.

3.2. Curative effect

All patients from the 2 groups completed the planned treatments. The follow-up lasted still December 2015, and the median follow-up time was 39 months (range, 16–62 months). The 3-year LRFS of the CCRT and SCRT groups was 92.3% and 81.8%, respectively ($P=.046$), and the 3-year DFS and OS were 76.9% and 64.9%, and 87.2% and 81.8%, respectively, but without significant difference ($P=.073$ and .342, respectively) (Fig. 2).

The subgroup analysis showed no significant difference of 3-year LRFS, DFS, and OS of patients with pAnyT pN2–3 cM0 between the 2 treatment models, but for patients with stage pT3–4p N1–3 cM0, the 3-year LRFS and DFS were significantly improved in the CCRT group (88.2% vs 69.4%, $P=.036$; 72.6% vs 41.7%, $P=.049$), without significant difference in OS (79.4% vs 69.4%, $P=.313$) (Fig. 3).

3.3. Adverse reactions during therapy

The acute adverse reactions during therapy were mainly leukopenia, gastrointestinal reactions, and radiation skin lesion. The occurrence rates of adverse reactions between the 2 groups had no significant difference (Table 2). The comparison of severe adverse reactions showed that grade 3 to 4 leukopenia occurrence rates in the CCRT and SCRT groups were 29.5% and 31.2%, respectively ($P=.858$), and grade 3 gastrointestinal reaction occurrence rates were 11.8% and 8.8% ($P=.548$). All the adverse reactions could be improved after appropriate treatments, and no patient withdrew from therapy. In the 2 groups, no grade 3 to 4 radiation skin lesion was found. The occurrence of grade 1 to 2 radiation skin reactions was similar in the 2 groups (89.7% and 88.3%, $P=.803$), and they were all dry dermatitis cases. The symptoms gradually improved 7 to 10 days after radiotherapy. No symptomatic cardiovascular and pulmonary adverse reactions were observed.

Table 1

Characteristics of the patients.

	Number of patients (n)			
	Total	CCRT	SCRT	P
Eligible patients	155	78	77	
Median age (range), y	46 (23–65)	44 (23–63)	47 (25–65)	.491
<35	27	16	11	
35–59	121	58	63	
≥60	7	4	3	
Disease stage				
T1–2 N2–3	85	44	41	.792
T3–4 N1	36	17	19	
T3–4 N2–3	34	17	17	
T stage				
pT1	7	3	4	.955
pT2	77	40	37	
pT3	58	28	30	
pT4	13	7	6	
N stage				
pN1	36	17	19	.638
pN2	83	42	41	
pN3	36	19	17	
Side				
Left	83	41	42	.872
Right	82	37	35	

CCRT = concurrent chemoradiotherapy, SCRT = sequential chemoradiotherapy.

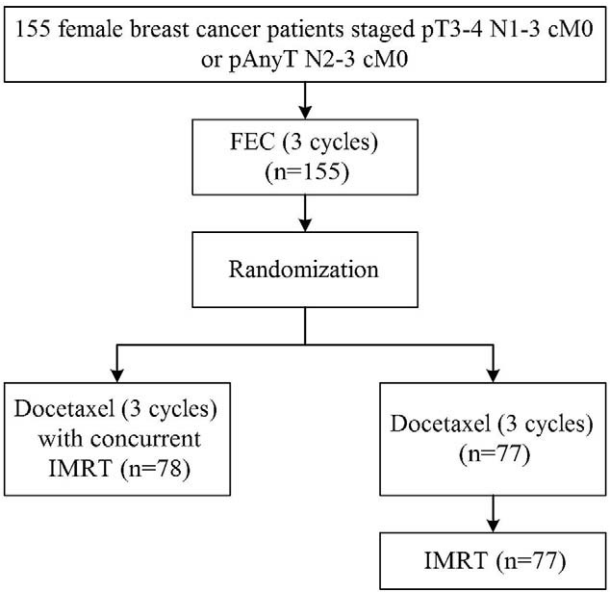

Figure 1. Patient flowchart. CCRT = concurrent chemoradiotherapy; IMRT = intensity modulated radiotherapy; SCRT = sequential chemoradiotherapy.

3.4. Adverse reactions after therapy

All the patients with radiation skin reactions recovered within 1 month after radiotherapy. During the median follow-up of 39 months (range, 16–62 months), no local pain, chest wall fibrosis, or angiotelectasis was found. One patient in each group showed moderate edema in the affected upper limb after 30 months.

The rates of patients with asymptomatic electrocardiogram changes in the CCRT and SCRT groups were 60.3% and 58.5% ($P=.473$), respectively, and the left occurrence rates were 63.0% and 57.0% ($P=.360$), respectively. These patients mainly showed mild ST segment depression, and T-wave changes were not accompanied by abnormal myocardial enzymes. No case of severe electrocardiogram, abnormal myocardial enzymes, or decreased left ventricular ejection fraction (LVEF) was noted.

Asymptomatic pulmonary imaging changes could be observed in both groups, mainly showing as apex pulmonis petechial and patchy high-density shadow in sternums on the affected side, and no stripe fibrosis or interstitial inflammation change was observed. The occurrence rates of asymptomatic pulmonary imaging change were 43.2% and 41.2% ($P=.843$). No evident drug or radiation-related ventilatory disorder cases were observed.

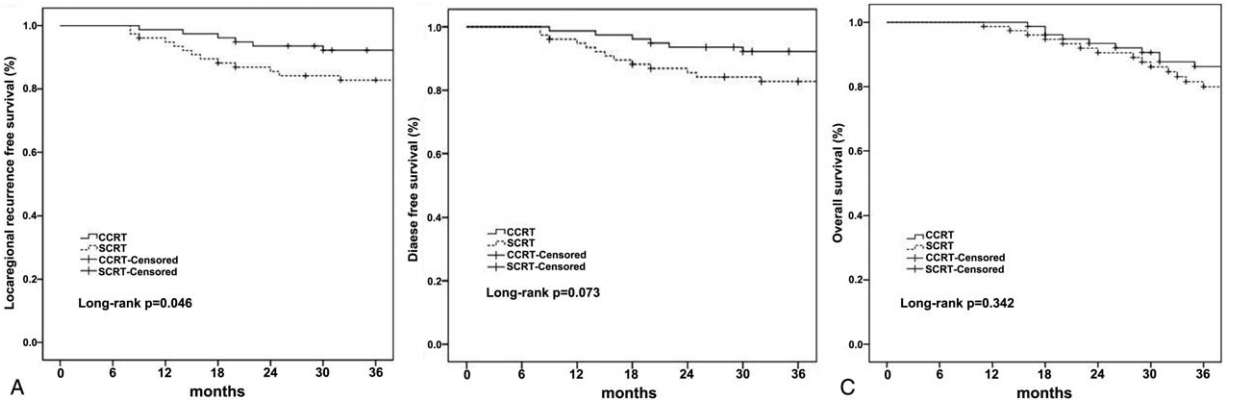

Figure 2. Kaplan–Meier estimates of local-regional recurrence-free survival (A), disease-free survival (B), and overall survival (C) according to concurrent (CCRT) or sequential chemoradiotherapy (SCRT).

There was no case of chemoradiotherapy-related death.

4. Discussion

Concurrent chemoradiotherapy could increase the local control rate in patients with high recurrence risk after breast-conserving surgery, but the effect of concurrent chemoradiotherapy after mastectomy and axillary dissection is not clear.[11,12] Therefore, the aim of this study was to compare the effects of late-course concurrent chemoradiotherapy (CCRT) versus sequential therapy (SCRT) after mastectomy and axillary surgery in locally advanced breast cancer. All the patients completed the planned therapy. LRFS of patients with locally advanced invasive breast cancer after mastectomy and axillary surgery was better with CCRT than with SCRT and with similar profiles of adverse reactions. The DFS of patients staged pT3–4 pN1–3 cM0 was also improved.

In the present study, a significant difference in 3-year LRFS was observed between the CCRT and SCRT groups. Kim et al[13] reported a study on different chemoradiotherapy approaches after mastectomy for stage I–IIIB breast cancer; they reported that there was no difference in LRFS, DFS, or OS between sequential and concurrent therapy. However, this previous study included early-stage low-risk patients and different chemotherapy regimens, probably influencing the results. In the present study, the patients in the pT3–4 pN1–3 cM0 subgroup had a better LRFS and DFS with CCRT than patients with pT1–2 pN2–3 cM0 cancer. This is supported by the study by Kim et al,[13] which indicated that concurrent chemoradiotherapy could improve the survival of patients with high-risk factors such as positive or close margins. Another study reported that concurrent radiotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) showed an increased local control rate compared with sequential therapy, especially for patients with large mass, multiple positive lymph nodes, and young patients.[23] Therefore, concurrent chemoradiotherapy might be a good option for patients with high-risk locally advanced breast cancer after mastectomy and axillary surgery.

Radiation adverse reactions, especially radiation skin reaction, radiation pneumonitis, and myocardial damage, are the focus of attention when comparing different chemoradiotherapy approaches. In the SECRAB study, the occurrence rate of acute skin toxicity reaction in the concurrent chemoradiotherapy group was 24%, significantly higher than that of sequential therapy (15%), especially for grade 3 radiodermatitis.[11] Rouesse et al[5] compared CMF concurrent chemoradiotherapy with FEC sequential chemoradiotherapy; in the concurrent therapy group, febrile neutropenia was observed, grade 3–4 leukopenia events were increased, and the occurrence rate of subclinical myocardial dysfunction was higher; furthermore, decreased left ventricular

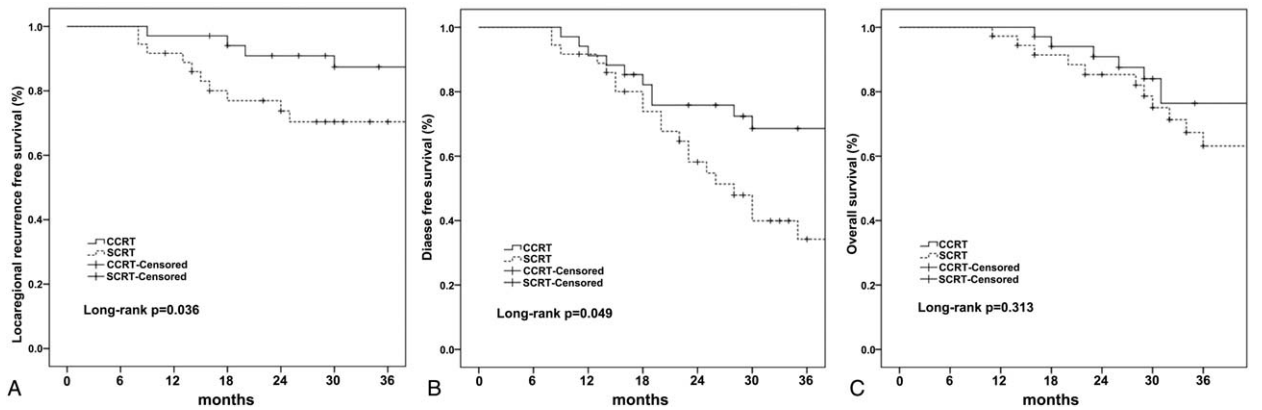

Figure 3. Kaplan–Meier estimates of local-regional recurrence-free survival (A), disease-free survival (B), and overall survival (C) according to concurrent (CCRT) or sequential chemoradiotherapy (SCRT) for the pT3–4 N1–3 cM0 subgroup.

Table 2

Acute treatment-related toxicity.

Type of toxicity	CCRT (n = 78)	SCRT (n = 77)	P
Leukopenia			
Grade 1–2	45	43	.887
Grade 3	17	19	
Grade 4	6	5	
Thrombocytopenia			
Grade 1–2	27	22	.525
Anemia			
Grade 1–2	31	40	.173
Gastrointestinal reactions			
Grade 1–2	61	58	.466
Grade 3	16	17	
Skin toxicity at end of radiotherapy			
Grade 1	52	53	.702
Grade 2	18	15	
Cardiotoxicity			.694
Grade 1	29	32	
Lung dysfunction	0	0	

CCRT = concurrent chemoradiotherapy, SCRT = sequential chemoradiotherapy.

ejection fraction (LVEF) was more frequent 1 year after therapy. In the present study, both the CCRT and SCRT groups both showed good tolerance, no grade 3–4 radiation adverse reaction occurred, and the occurrence rate of adverse reaction in the CCRT group was not significantly higher than that in the SCRT group. The development of modern radiotherapy approaches might be a key factor. Indeed, previous studies used CO^{60} or 2D radiotherapy. Although it could meet the requirements of breast cancer radiotherapy, eventual hotspots generated by non-uniform doses could lead to acute or late-stage adverse reactions, especially radiation skin damage. In the present study, IMRT was used, which could effectively increase the uniformity of planned dosage and personalization to each individual's anatomy, ensuring that neighboring organs such as lung and heart do not receive a large dose of radiations. Indeed, a Canadian study of IMRT versus 2D approaches showed that the occurrence rate of acute skin wet dermatitis has significantly decreased with IMRT.[24]

The selection of the drugs for concurrent chemoradiotherapy may also influence the outcomes. Anthracycline followed by a taxane is the current therapy recommended for high-risk patients with positive lymph nodes.[15–17] Nevertheless, hematotoxicity, radiation skin reaction, and cardiotoxicity are more common with an anthracycline-based therapy compared with other regimens. Ismaili et al[6,7] reported that anthracycline concurrent chemoradiotherapy improved the LRFS and DFS, but significantly increased hematological and non-hematological adverse reactions. Thus, avoiding concurrent radiotherapy and anthracycline might alleviate hematotoxicity, cutaneous reactions, and cardiotoxicity. Burstein et al[25] studied the adjuvant doxorubicin-cyclophosphamide (AC) regimen followed by 3-week paclitaxel or weekly paclitaxel concurrent with chemoradiotherapy; the dosage-limiting toxicity was evident in weekly paclitaxel concurrent therapy, and the occurrence rate of radiation pneumonitis was significantly increased. Another clinical trial studied AC with paclitaxel concurrent chemoradiotherapy and showed no serious adverse reactions during the 5-year follow-up.[26] On the other hand, Chow et al[27] used FEC sequential weekly paclitaxel concurrent neoadjuvant chemoradiotherapy, but 8 patients showed grade 3 radiation pneumonitis and 1 died from respiratory distress syndrome. Thus, the dose intensity of paclitaxel may influence adverse reactions.

In the present study, the CCRT group used radiotherapy only with the docetaxel as part of the chemotherapy, which avoided the concurrence with anthracycline. Previous studies showed that concurrent chemoradiotherapy was the best regimen for bi-weekly paclitaxel or 3-week docetaxel.[28,29] We found in our current trial that the occurrence rates and degrees of hematotoxicity and radiation adverse reactions in the CCRT group showed no difference with the SCRT group. Compared with similar studies,[25–27] the radiation skin reactions were slight, without symptomatic heart and lung damage. However, due to the short follow-up, the influence of concurrent chemoradiotherapy on heart needs a longer follow-up time to be confirmed.

A previous study showed that breast cancer subtype is an independent prognostic factor.[30] Another study found that the pathological remission rate of positive estrogen and progesterone receptor patients were different after paclitaxel concurrent neoadjuvant chemotherapy.[31] The influence of hormone receptors and HER2 positivity needs to be further explored.

The present study is not without limitations. The sample size was relatively small. The pathological diagnostic criteria of hormone receptor-positive changed during the period of enrollment. So in this paper did not discuss the receptor status of hormone. The follow-up was relatively short, and long-term follow-up should be contributed to assess adequately the differences between the 2 approaches in terms of LRFS, DFS, OS, and long-term toxicity.

5. Conclusion

LRFS of patients with locally advanced invasive breast cancer after mastectomy and axillary surgery was better with CCRT than with SCRT and with similar profiles of adverse reactions. The DFS of patients staged pT3–4 pN1–3 cM0 was also improved. Nevertheless, the long-term effects and adverse reactions still need to be confirmed.

Acknowledgment

The authors would like to thank the patients and the members of the Fourth Affiliated Hospital of Guangxi Medical University Oncology Department. They also like to thank Professors Guisheng Li and Dongning Huang for their help in patient data management.

References

[1] Fan L, Strasser-Weippl K, Li JJ, et al. Breast cancer in China. Lancet Oncol 2014;15:e279–89.
[2] McGale P, Taylor C, et al. EBCTCG (Early Breast Cancer Trialists' Collaborative Group)Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35.
[3] Recht A, Come SE, Henderson IC, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. N Engl J Med 1996;334:1356–61.
[4] Arcangeli G, Pinnarò P, Rambone R, et al. A phase III randomized study on the sequencing of radiotherapy and chemotherapy in the conservative management of early-stage breast cancer. Int J Radiat Oncol Biol Phys 2006;64:161–7.
[5] Rouëssé J, de la Lande B, Bertheault-Cvitkovic F, et al. A phase III randomized trial comparing adjuvant concomitant chemoradiotherapy versus standard adjuvant chemotherapy followed by radiotherapy in

operable node-positive breast cancer: final results. Int J Radiat Oncol Biol Phys 2006;64:1072–80.
[6] Ismaili N, Elmajjaoui S, Lalya I, et al. Anthracycline and concurrent radiotherapy as adjuvant treatment of operable breast cancer: a retrospective cohort study in a single institution. BMC Res Notes 2010;3:247.
[7] Ismaili N, Mellas N, Masbah O, et al. Concurrent chemoradiotherapy in adjuvant treatment of breast cancer. Radiat Oncol 2009;4:12.
[8] Huang J, Barbera L, Brouwers M, et al. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003;21:555–63.
[9] Livi L, Borghesi S, Saieva C, et al. Radiotherapy timing in 4,820 patients with breast cancer: university of florence experience. Int J Radiat Oncol Biol Phys 2009;73:365–9.
[10] Katz A, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. J Clin Oncol 2000;18:2817–27.
[11] Fernando I, Bowden S, Brookes C, et al. Synchronous chemo-radiation can reduce local recurrence in early stage breast cancer: results of the SECRAB Trial (ISRCTN: 84214355) presented on behalf of the SECRAB Steering Committee. Eur J Cancer 2011;47:2.
[12] Toledano A, Azria D, Garaud P, et al. Phase III trial of concurrent or sequential adjuvant chemoradiotherapy after conservative surgery for early-stage breast cancer: final results of the ARCOSEIN trial. J Clin Oncol 2007;25:405–10. Erratum in: J Clin Oncol. 2007 Jun 1;25 (16):2334.
[13] Kim HJ, Kim JS, Chie EK, et al. The sequencing of chemotherapy and radiotherapy in breast cancer patients after mastectomy. Tumori 2010;96:28–33.
[14] Piroth MD, Pinkawa M, Gagel B, et al. Sequencing chemotherapy and radiotherapy in locoregional advanced breast cancer patients after mastectomy—a retrospective analysis. BMC Cancer 2008;8:114.
[15] Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 2007;357:1496–506.
[16] Coudert B, Asselain B, Campone M, et al. Extended benefit from sequential administration of docetaxel after standard fluorouracil, epirubicin, and cyclophosphamide regimen for node-positive breast cancer: the 8-year follow-up results of the UNICANCER-PACS01 trial. Oncologist 2012;17:900–9.
[17] Martin M, Ruiz A, Ruiz Borrego M, et al. Fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus FAC followed by weekly paclitaxel as adjuvant therapy for high-risk, node-negative breast cancer: results from the GEICAM/2003-02 study. J Clin Oncol 2013;31:2593–9.
[18] Greenbaum MP, Strom EA, Allen PK, et al. Low locoregional recurrence rates in patients treated after 2000 with doxorubicin based chemotherapy, modified radical mastectomy, and post-mastectomy radiation. Radiother Oncol 2010;95:312–6.
[19] Jagsi R. Progress and controversies: radiation therapy for invasive breast cancer. CA Cancer J Clin 2014;64:135–52.
[20] Lu Y, Hang H, Li G. Comparison of the effect of synchronous chemoradiotherapy and sequential schedule as adjuvant therapy after surgery in locally advanced breast cancer. Chin J Cancer Prev Treat 2014;21:854–7.
[21] Available at: http://ctep.info.hih.gov/reporting/ctc_v30.html. CTCfAEv.
[22] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
[23] Kim K, Chie EK, Han W, et al. Concurrent versus sequential administration of CMF chemotherapy and radiotherapy after breast-conserving surgery in early breast cancer. Tumori 2011;97:280–5.
[24] Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008;26:2085–92.
[25] Burstein HJ, Bellon JR, Galper S, et al. Prospective evaluation of concurrent paclitaxel and radiation therapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for Stage II or III breast cancer. Int J Radiat Oncol Biol Phys 2006;64:496–504.
[26] Chen WC, Kim J, Kim E, et al. A phase II study of radiotherapy and concurrent paclitaxel chemotherapy in breast-conserving treatment for node-positive breast cancer. Int J Radiat Oncol Biol Phys 2012;82: 14–20.
[27] Chow TL, Louie AV, Palma DA, et al. Radiation-induced lung injury after concurrent neoadjuvant chemoradiotherapy for locally advanced breast cancer. Acta Oncol 2014;53:697–701.
[28] Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/ Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431–9. Erratum in: J Clin Oncol. 2003 Jun 1;21(11):2226.
[29] Sparano JA, Zhao F, Martino S, et al. Long-term follow-up of the E1199 Phase III trial evaluating the role of taxane and schedule in operable breast cancer. J Clin Oncol 2015;33:2353–60.
[30] Minicozzi P, Bella F, Toss A, et al. Relative and disease-free survival for breast cancer in relation to subtype: a population-based study. J Cancer Res Clin Oncol 2013;139:1569–77.
[31] Adams S, Chakravarthy AB, Donach M, et al. Preoperative concurrent paclitaxel-radiation in locally advanced breast cancer: pathologic response correlates with five-year overall survival. Breast Cancer Res Treat 2010;124:723–32.