RESEARCH ARTICLE

Benefit of Post-mastectomy Radiotherapy of the Supra-/infraclavicular Lymphatic Drainage Area in Breast Cancer Patients

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Abstract

Background: This study investigated the survival benefit of radiotherapy (RT) of the supra- and infraclavicular lymphatic drainage area in Chinese women with T1-2N1M0 breast cancer receiving mastectomy. Methods: A total of 593 cases were retrospectively reviewed from 1998 to 2007. The relationship between supra- or infraclavicular fossa relapse (SCFR) and post-operative RT at the supra-/infraclavicular lymphatic drainage area was evaluated. Results: The majority of patients (532/593; 89. 8%) received no RT while 61 patients received RT. The median follow-up was 85 months. Among patients without RT, 54 (10. 2%) developed recurrence in the chest wall or ipsilateral SCFR. However, none of the 61 patients who underwent RT demonstrated SCFR. One patient who received RT (1. 6%) experienced recurrence in the chest wall. Univariate analysis revealed that age and molecular subtype (both $P < 0.05$) were two prognostic factors related to supraclavicular and infraclavicular fossa relapse-free survival (SFRFS). Multivariate analysis revealed that only Her-2 positive status ($P = 0.011$) was an independent predictor of SFRFS. RT had no influence on distant metastasis ($P = 0.328$) or overall survival ($P = 0.541$). SCFR significantly affected probability of distant metastasis ($P < 0.001$) and overall survival ($P < 0.001$). Conclusion: Although RT was not significantly associated with SFRFS, postoperative RT was significantly associated with a lower locoregional (i. e. , supraclavicular/infraclavicular and chest wall) recurrence rate. SCFR significantly influenced distant metastasis-free survival, which significantly influenced the overall survival of T1-2N1M0 breast cancer patients after mastectomy. Thus, prophylactic RT is recommended in T1-2N1M0 breast cancer patients, especially those who have Her-2 positive lesions.

Keywords: Axillary lymph nodes - breast cancer - radiotherapy - relapse-free survival - distant metastasis-free survival

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Introduction

In China, breast cancer incidence is predicted to increase to 85 per 100, 000 women by 2021 (Ziegler et al., 2008; Han et al., 2013). Current cancer treatment consists of surgery, chemotherapy and radiotherapy (RT). RT, chemotherapy and hormonal therapy are currently used as adjuvant therapy in early breast cancer, and neo-adjuvant therapy is used in locally advanced cancer, or as palliative treatment for metastatic breast cancer (Kaufmann et al., 2003; Harhra and Basaleem, 2012).

Postoperative RT is an important adjunctive therapy for patients receiving complete mastectomy due to locally-advanced breast cancer. Clinical trials have confirmed that postoperative RT is beneficial both for locoregional control of breast cancer and for overall survival (OS), especially in patients with ≥4 positive axillary lymph nodes (ALN) (Overgaard et al., 1997; Overgaard et al., 1999; Ragaz et al., 2005). However, for patients with T1-2 stage breast cancer and 1-3 positive ALN, the indications for RT after mastectomy are still unclear.

Currently, there is no consensus regarding the use of RT for intermediate risk patients (i. e., T1-2 breast cancer patients with 1-3 positive ALN). Guidelines of the National Comprehensive Cancer Network (NCCN) and the German Society for Radiooncology (DEGRO) recommend adjunctive RT in patients after mastectomy due to T1-2N1M0 breast cancer (Sautter-Bihl et al., 2008; National Comprehensive Cancer Network (NCCN), 2011). However, other studies, including the St. Gallen International Breast Cancer Conference, New Zealand Guidelines Group (NZGG), Chinese Anti-Cancer

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Association, and the European Society for Medical Oncology (ESMO), recommend adjunctive RT for patients with 1 to 3 positive ALN plus the presence of other risk factors, such as young age, negative estrogen receptor (ER) status, dissection of a small number of ALN, positive nodal ratio, lymphovascular invasion (LVI), extracapsular extension, and high nuclear grade (New Zealand Guidelines Group (NZGG), 2009; Aebi et al., 2011; Goldhirsch et al., 2011; Professional Committee of Breast Cancer of Chinese Anti-Cancer Association, 2011; Huang et al., 2012; Kong and Hong, 2013).

Whether RT at the supra- /infraclavicular fossa region provides any additional survival benefit following mastectomy remains controversial. Breast cancer recurrence via lymphatic drainage from the breast most often occurs in the axilla, followed by the internal mammary, supraclavicular, and infraclavicular nodal fields (Grotenhuis et al., 2013). Wu et al. (2010) reported that supra- or infraclavicular fossa relapse (SCFR) was higher than the recurrence rate of breast cancer in the chest wall (5. 3% vs. 2. 9%).

Studies have reported that SCFR can significantly reduce survival, making prevention of SCFR very important (Kong and Hong, 2013). SCFR rates have been shown to vary from as low as 1. 0% to as high as 9. 2% in patients with 1-3 positive ALN without RT (Strom et al., 2005; Macdonald et al., 2009; Yu et al., 2010; Yates et al., 2012; Grotenhuis et al., 2013; Yu et al., 2013). In addition, SCFR may increase the incidence of distant metastasis (Fan et al., 2010; Reddy et al., 2011; Duraker et al., 2012), which impacts the quality of life and OS. Currently, the guidelines of NCCN (2011) and DEGRO (Sautter-Bihl et al., 2008) recommend supraclavicular radiation therapy (SCRT), but the NZGG recommends SCRT only in patients with ≥4 positive ALN. The guidelines in the United Kingdom also recommend SCRT in patients with T3 (clinical staging) or G3 (pathological staging) breast cancer and 1-3 positive ALN (Yarnold, 2009).

The SCFR in breast cancer patients with 1-3 positive ALN is relatively low, and there are no phase III randomized, controlled clinical trials showing the potential side effects of SCRT. Additionally, the overall impact of RT on OS remains unclear, and concerns exist about the morbidity associated with RT. For these reasons, SCRT is not universally-recommended in these patients. Although patients in the study from the Danish Breast Cancer Cooperative Group (DBCG) received SCRT, the number of dissected lymph nodes was small and the adjunctive therapy was insufficient (Overgaard et al., 2007). Therefore, the results have poor reliability. The Selective Use of Postoperative Radiotherapy After Mastectomy (SUPREMO) clinical trial is still ongoing (Kunkler et al., 2008). We investigated the survival benefit of RT at the supra- /infraclavicular fossa region on SCFR and factors influencing SCFR in Chinese patients with T1-2N1M0 breast cancer after undergoing mastectomy.

Materials and Methods

Patients

This study was approved by the institutional review board of Sun Yat-sen University Cancer Center. Written consents were obtained from all patients. Between January 1998 and December 2007, 977 patients with T1-2N1M0 breast cancer in the Sun Yat-sen University Cancer Center were retrospectively reviewed. The following inclusion criteria were utilized for the study: 1) female patients; 2) unilateral breast cancer; 3) underwent mastectomy and dissection of axillary lymph nodes (ALN); 4) dissection of axillary level I-II lymph nodes; 5) dissected ≥10 ALN); 6) known status for ER, PR, and Her-2; 7) adjunctive chemotherapy administered for ≥4 weeks after surgery. Furthermore, all ER and/or PR positive patients received endocrine therapy, and for patients who received RT, it must have covered at least the ipsilateral chest wall and supra- /infraclavicular lymphatic drainage areas. Overall, 593 patients were included in the study.

The 593 patients were then divided into two groups: patients who received RT (n = 61) and patients who did not receive RT (n = 532). All 61 patients received RT within 6 months of surgery, and the RT was administered to the ipsilateral chest wall and supra-/infraclavicular regions. For the chest wall, RT was administered with a 6 MV X-ray tangential field or a 6 to 9 MeV electron beam with 0. 5-1. 0 cm bolus, and the dose was increased to 36 to 40 Gy. The total DT was 50 Gy (2 Gy/treatment). For the supra- /infraclavicular regions, an opto-electronic hybrid ray was used initially at 6 MV, and the dose was gradually increased to 36 to 40 Gy. Treatment was then performed with an electric ray at 12 to 15 MeV. The total DT was 50 Gy (2 Gy/treatment).

Follow-up and end points

Patients received follow-up by phone and/or clinic visit once every 3 to 6 months starting from the time of cancer diagnosis. Supra- and infraclavicular fossa relapse-free survival (SFRFS) served as the primary end point. Distant metastasis-free survival (DMFS) and overall survival (OS) served as secondary end points. SCFR refers to the recurrence of breast cancer in the ipsilateral supra- and infraclavicular lymphatic drainage area not including the chest wall. The recurrence was also confirmed by pathological examination. Distant metastasis refers to the recurrence of breast cancer at a site distant to the primary cancer and confirmed by two imaging examinations and pathological examination, if needed. OS was defined as the time from cancer diagnosis to death or the end of the study. Death refers to breast-cancer related death.

The following were analyzed as factors affecting survival in patients with T1-2N1M0 breast cancer: patient's age, menstrual cycle status (i. e., pre- vs. post-menopausal), size of the primary breast cancer (pT stage), number of positive ALN, presence of LVI, molecular subtype, chemotherapeutic regimen, and use of RT. Molecular subtypes included luminal type A (ER+, PR+, Her2-), luminal type B (ER+, PR+, Her2+), Her-2 positive type (ER-, PR-, Her2+), and triple negative type (ER-, PR-, Her2-). PR or ER positive was defined as >10% positive cells by immunohistochemistry; Her-2 positive was defined as +++ by immunohistochemistry or ++ with confirmation by FISH.

Table 1. Demographic and Clinic Characteristics between Patients who Received or did not Receive RT

Characteristics	Total (n=593)	Without RT (n=532)	With RT (n=61)	*P*-value
Age (yr)	46. 5±10. 2	46. 9±10. 2	43. 3±8. 9	0. 004*
Menstrual status, n (%)				
Pre-menopausal	410 (69. 1)	359 (67. 5)	51(86. 6)	0. 010*
Post-menopausal	183 (30. 9)	173 (32. 5)	10 (16. 4)	
Tumor stage, n (%)				
T1	185(31)	171 (32. 1)	14 (23. 0)	0. 142
T2	408(69)	361 (67. 9)	47 (77. 0)	
No. of positive ALN, n (%)				
1	283 (47. 8)	269 (50. 6)	14 (23. 0)	<0. 001*
2	166 (20. 8)	154 (28. 9)	12 (19. 7)	
3	144 (24. 3)	109 (20. 5)	35 (57. 4)	
LVI, n (%)				
No	569(96)	513 (96. 4)	56 (91. 8)	0. 089
Yes	24(4)	19 (3. 6)	5 (8. 2)	
ER status, n (%)				
Negative	228 (38. 4)	205 (38. 5)	23 (37. 7)	0. 9
Positive	365 (61. 6)	327 (61. 5)	38 (62. 3)	
PR status, n (%)				
Negative	195 (32. 9)	175 (32. 9)	20 (32. 8)	0. 986
Positive	398 (37. 1)	357 (67. 1)	41 (67. 2)	
Her-2 status, n (%)				
Negative	373 (62. 9)	345 (64. 8)	28 (45. 9)	0. 004*
Positive	220 (37. 1)	187 (35. 2)	33 (54. 1)	
Molecular subtype, n (%)				
Luminal A	301 (50. 8)	278 (52. 3)	23 (37. 7)	0. 036*
Luminal B	125 (21. 1)	105 (19. 7)	20 (32. 8)	
Her-2 positive	92 (15. 5)	80 (15. 0)	12 (19. 7)	
Triple negative	75 (12. 6)	69 (13. 0)	6 (9. 8)	
Chemotherapy regimen, n (%)				
CMF	44 (7. 4)	42 (7. 9)	2 (3. 3)	0. 145
Anthracycline and/or taxane	549 (92. 6)	490 (92. 1)	59 (56. 7)	
#Recurrence, n (%)				0. 032*
Yes	55 (9. 3)	54 (10. 2)	1 (1. 6)	
No	538 (90. 7)	478 (89. 8)	60 (98. 4)	

All numbers are mean ± SD unless otherwise specified; ALN, axillary lymph node; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; Her-2, human epidermal growth factor receptor 2; CMF, cyclophosphamide, methotrexate, fluorouracil; RT, radiation therapy; #Recurrence involves both the chest wall and the supra- /infraclavicular regions; *Indicates a significant difference between the RT and non-RT groups, $P < 0.05$

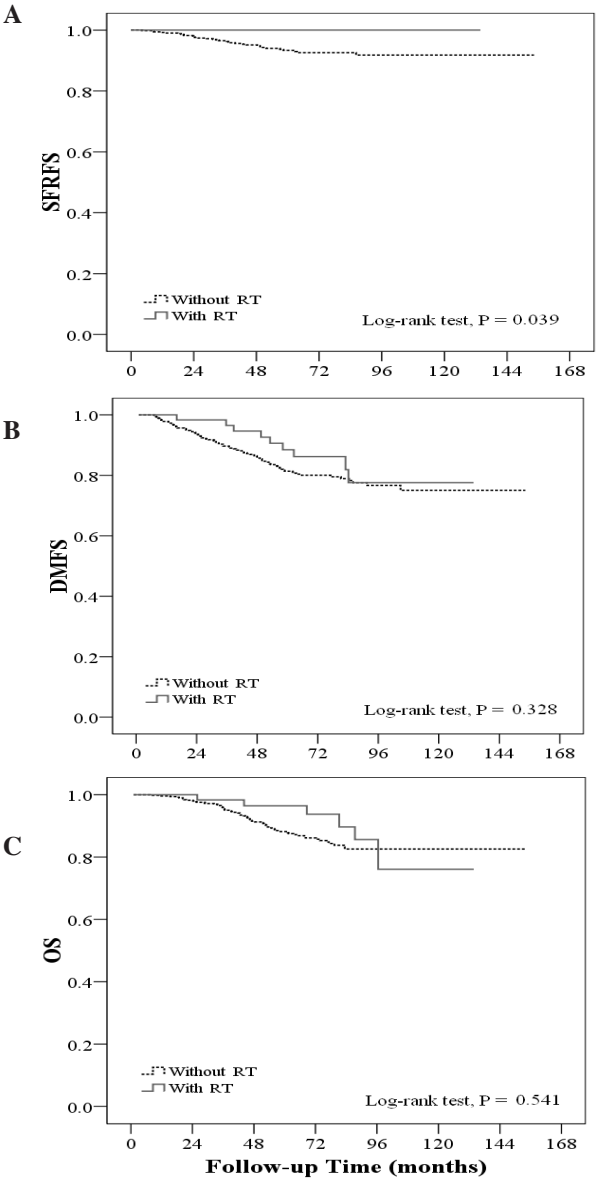

Figure 1. Kaplan-Meier Cumulative Survival Curves. (a) Supraclavicular and infraclavicular fossa relapse-free survival (SFRFS); (B) Distant metastasis-free survival (DMFS), ; and (C) Overall survival (OS)

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) and comparison between the two groups (RT vs. no RT) was made by independent t-test. Categorical data were presented as frequency (percentage) and comparison between the two groups (RT vs. no RT) was made by chi-square test or Fisher's exact test, as appropriate. The survival curves for SFRFS, DMFS, and OS were constructed using Kaplan-Meier method and compared by log-rank test.

Cox proportional hazard regression analyses were performed to calculate crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) to investigate potential prognostic factors associated with SFRFS, DMFS, and OS. Only the significant variables in the univariate analysis were included in the multivariate Cox proportional hazard regression analyses. All statistical analyses were performed using SPSS 15. 0 statistics software (SPSS Inc, Chicago, IL). A two-tailed test with a $P < 0.05$ indicated statistical significance.

Results

The 593 patients included in this study were divided into two groups: 61 patients with postoperative RT and 532 without postoperative RT. The baseline and clinical characteristics of the two groups are shown in Table 1. Patients who received RT tended to be younger ($P = 0.004$) and premenopausal ($P = 0.010$). Patients receiving RT also demonstrated more positive ALN ($P < 0.001$) and were more often Her2 + ($P = 0.004$). Significantly lower rates of recurrence (defined as including both the chest wall and supra- /infraclavicular fossa areas) were observed for patients who received RT compared with patients who did not receive RT (1. 6% vs 10. 2%, respectively; $P = 0.032$). However, when the recurrence rates were analyzed with only supra- /infraclavicular lymphatic drainage area involvement (no chest wall involvement), no significant difference was found between the patients who received RT and those who did not receive RT (0% vs. 6. 0%; $P = 0.065$).

Figure 1 presents the Kaplan-Meier survival curves for SFRFS, DMFS, and OS, respectively. The log-rank test indicated a significant difference in SFRFS between these two groups (Figure 1A; $P = 0.039$). However, there

Table 2. Results of Univariate Cox Proportional Hazards Regression Analysis of Potential Prognostic Factors

Prognostic factors	Hazard ratio (95% CI)		
	SFRFS	DMFS	OS
Age (yr)			
≤35 vs. >35	2. 25 (1. 04, 4. 86)*	1. 70 (1. 07, 2. 70)*	1. 34 (0. 75, 2. 41)
Menstrual status			
Post- vs. Pre-menopausal	0. 86 (0. 40, 1. 86)	0. 74 (0. 47, 1. 15)	0. 69 (0. 40, 1. 19)
Tumor stage			
T2 vs. T1	1. 65 (0. 71, 3. 82)	2. 61 (1. 53, 4. 60)*	2. 33 (1. 25, 4. 33)*
No. of positive ALN			
2 vs. 1	1. 94 (0. 86, 4. 40)	1. 07 (0. 68, 1. 69)	1. 11 (0. 64, 1. 91)
3 vs. 1	1. 57 (0. 65, 3. 79)	0. 87 (0. 53, 1. 43)	0. 94 (0. 52, 1. 69)
LVI			
Yes vs. No	0. 82 (0. 11, 6. 02)	0. 76 (0. 24, 2. 40)	0. 05 (0. 01. 10. 79)
Molecular subtype			
Luminal B vs. Luminal A	1. 37 (0. 50, 3. 78)	1. 51 (0. 92, 2. 48)	1. 63 (0. 88, 3. 00)
Her-2 positive vs. Luminal A	3. 41 (1. 42, 8. 20)*	1. 80 (1. 06, 3. 05)*	2. 18 (1. 16, 4. 10)*
Triple negative vs. Luminal A	2. 56 (0. 93, 7. 05)	1. 58 (0. 87, 2. 86)	2. 11 (1. 07, 4. 14)*
Chemotherapy regimen			
Anthracycline and/or taxane vs. CMF	0. 64 (0. 22, 1. 82)	0. 72 (0. 39, 1. 31)	1. 36 (0. 55, 3. 39)
Radiotherapy			
Yes vs. No	0. 04 (0. 01, 4. 58)	0. 71 (0. 36, 1. 41)	0. 78 (0. 36, 1. 71)
SCFR			
Yes vs. No	NA	6. 08 (3. 81, 9. 72)*	5. 73 (3. 31, 9. 91)*
Distant metastasis			
Yes vs. No	NA	NA	396 (55, 2854)*

SFRFS, supraclavicular/infraclavicular fossa relapse-free survival; DMFS, distant metastasis-free survival; OS, overall survival; ALN, axillary lymph node; LVI, lymphovascular invasion; CMF, cyclophosphamide, methotrexate, fluorouracil; SCFR, supra- or infraclavicular fossa relapse; *P<0. 05 (statistically significant)

Table 3. Results of Multivariate Cox Proportional Hazards Regression Analysis of Potential Prognostic Factors

Prognostic factors	SFRFS		DMFS		OS	
	aHR (95% CI)	P-value	aHR (95% CI)	P-value	aHR (95% CI)	P-value
Age (yr)						
≤35 vs. >35	2. 02 (0. 93, 4. 39)	0. 076	1. 47 (0. 92, 2. 35)	0. 108		
Tumor stage						
T2 vs. T1			2. 42 (1. 42, 4. 15)	0. 001*	1. 02 (0. 54, 1. 92)	0. 962
Molecular subtype						
Luminal B vs. Luminal A	1. 34 (0. 49, 3. 69)	0. 57	1. 42 (0. 86, 2. 33)	0. 167	1. 56 (0. 84, 2. 88)	0. 156
Her-2 positive vs. Luminal A	3. 16 (1. 31, 7. 63)	0. 011*	1. 39 (0. 81, 2. 36)	0. 232	1. 60 (0. 85, 3. 03)	0. 147
Triple negative vs. Luminal A	2. 51 (0. 91, 6. 92)	0. 074	1. 34 (0. 74, 2. 44)	0. 334	2. 00 (1. 02, 3. 95)	0. 045*
SCFR						
Yes vs. No			5. 38 (3. 33, 8. 69)	<0. 001*	1. 06 (0. 61, 1. 85)	0. 835
Distant metastasis						
Yes vs. No					385 (53, 2793)	<0. 001*

SFRFS, supraclavicular and infraclavicular fossa relapse-free survival; DMFS, distant metastasis-free survival; OS, overall survival; SCFR, supra or infraclavicular fossa relapse; aHR, adjusted hazard ratio; P< 0. 05 indicates a significant difference

were no significant differences in DMFS (Figure 1B; P = 0. 328) and OS (Figure 1C; P = 0. 541) between patients who received RT and those patients who did not receive RT.

The univariate Cox proportional hazards regression analysis was performed to analyze potential prognostic factors affecting SFRFS, DMFS, and OS (Table 2). Patient age (≤ 35 years vs. > 35 years, HR = 2. 25, 95% CI = 1. 04 to 4. 86) and molecular subtype (Her-2 positive vs. Luminal A, HR = 3. 41, 95% CI = 1. 42 to 8. 20) were significantly associated with SFRFS. Patient age (≤35 years vs. >35 years, HR = 1. 70, 95% CI = 1. 07 to 2. 70), tumor stage (T2 vs. T1, HR = 2. 61, 95% CI = 1. 53 to 4. 60), molecular subtype (Her-2 positive vs. Luminal A, HR = 1. 80, 95% CI = 1. 06 to 3. 05) and SCFR (Yes vs. No, HR = 6. 08, 95% CI = 3. 81 to 9. 72) were significantly associated with DMFS. Tumor stage (T2 vs. T1, HR = 2. 33, 95% CI = 1. 25 to 4. 33), molecular subtypes (Her-2 positive vs. Luminal A, HR = 2. 18, 95% CI = 1. 16 to 4. 10; Triple negative vs. Luminal A, HR = 2. 11, 95% CI = 1. 07 to 4. 14), SCFR (Yes vs. No, HR = 5. 73, 95% CI = 3. 31 to 9. 91), and distant metastasis (Yes vs. No, HR = 396, 95% CI = 55 to 2854) were significantly associated with OS.

The multivariate Cox proportional hazards regression model was used to identify prognostic factors associated with SFRFS, DMFS, and OS (Table 3). Molecular subtype (Her-2 positive vs. Luminal A, adjusted HR [aHR] = 3. 16,

95% CI = 1. 31 to 7. 63) was an independent prognostic factor associated with SFRFS. The tumor stage (T2 vs. T1, aHR =2. 42, 95% CI = 1. 42 to 4. 15) and SCFR (Yes vs. No, aHR = 5. 38, 95% CI = 3. 33 to 8. 69) were independent prognostic factors associated with DMFS. Molecular subtype (Triple negative vs. Luminal A, aHR = 2. 00, 95% CI = 1. 02 to 3. 95) and distant metastasis (Yes vs. No, HR = 385, 95% CI = 53 to 2793) were independent prognostic factors associated with OS.

Discussion

In the present study, the SFRFS was retrospectively reviewed in 593 patients receiving complete mastectomy due to T1-2N1M0 breast cancer, and the survival benefit of post-operative RT administered to 61 of those patients was further examined. SCFR significantly influenced the DMFS and OS. The use of RT at the supra- /infraclavicular fossa region was significantly associated with a lower locoregional recurrence rate but did not significantly impact the SFRFS, DMFS, and OS. Among potential prognostic factors affecting SFRFS, only the Her-2 positive molecular subtype significantly affected SFRFS.

Our previous study confirmed that T1-2N1M0 breast cancer patients receiving mastectomy experienced a significantly higher rate of recurrence at the supra- or infraclavicular lymphatic drainage area than at the chest wall (Wu et al., 2010). In the current study, 9. 3% (55/593) experienced recurrence in the supra- /infraclavicular area and chest wall. Among patients without RT, 10. 2% (54/532) experienced recurrence in the supra- / infraclavicular area and chest wall. However, only one patient who received RT (1. 6%) experienced a recurrence of breast cancer, and that recurrence was located in the chest wall. None of the 61 patients who underwent RT demonstrated SCFR. Although RT at the supra- / infraclavicular region was not significantly associated with SFRFS, the lack of breast cancer recurrence in the supra- /infraclavicular fossa among patients receiving RT suggests a locoregional benefit from RT compared to patients who did not receive RT. The benefits of RT were also noted in a preliminary study conducted in India on 135 women with breast cancer (the majority of whom had undergone mastectomy). They found no local recurrence after hypofractionated RT at the time of the analysis and only four patients developed metastatic disease at the time of analysis (2. 96%), although the results were preliminary (Nandi et al., 2014). The benefit of RT in early breast cancer patients was also confirmed in 143 early breast cancer patients who underwent either interoperative or routine RT after breast-conserving surgery (BCS) and showed satisfactory local control of tumor at 54-month follow up (Zhou et al., 2012).

Overall, our results confirmed that the rate of recurrence at the supra- /infraclavicular lymphatic drainage area was higher than at the chest wall. This suggests that patients receiving mastectomy due to T1-2N1M0 breast cancer should have postoperative RT targeted at the supra- /infraclavicular lymphatic drainage area. A similar conclusion was reached in a study of 113 breast cancer patients with 1 to 3 positive axillary lymph nodes who underwent BCS or modified radical mastectomy (MRM) (Kong and Hong, 2013). Kong et al. (2013) also concluded that supraclavicular nodal RT was necessary in N1 breast cancer patients. However, they limited their therapeutic approach to only a high-risk subgroup of patients featuring histologic grade 3 and ECE.

Recurrence at the supraclavicular and infraclavicular lymphatic drainage area may increase the risk for distant metastasis and ultimately affect the OS. Kong et al. (2013) reported that patients with SCFR experienced significantly decreased DMFS and OS compared to patients who did not have SCFR. Siponen et al. (2012) reported SCFR was an independent predictor of poor OS. Yates et al. (2012) reported a significantly lower 10-year survival for patients with SCFR. In the present study, patients with recurrence at the supraclavicular and infraclavicular lymphatic drainage area had a very poor prognosis, which was consistent with other studies (Fan et al., 2010; Reddy et al., 2011). These findings all highlight the importance of preventing recurrence at the supra- /infraclavicular lymphatic drainage area.

RT is an important modality used to reduce the locoregional recurrence of cancer. Our results showed RT administered at the supra- /infraclavicular region was significantly associated with lower recurrence in the supra- /infraclavicular and chest wall area compared to patients who did not receive RT; however, RT at the supra-/infraclavicular region was not significantly associated with a lower SCFR compared to patients who did not receive RT. Our results also suggested RT at this region did not significantly impact the DMFS or OS.

Numerous studies have looked at the effect of RT on the locoregional control, DMFS, and OS; however, the results have been inconsistent. Wai et al. (2010) reported on the efficacy of RT after breast-preserving surgery in patients with 1-3 positive lymph nodes and observed RT, including the supraclavicular and infraclavicular lymphatic drainage area and axilla, significantly improve the locoregional control but did not affect the DMFS and OS. Cosar et al. (2011) reported significantly better rates for locoregional recurrence, distant metastasis, and 5-year disease-free survival (but not OS) with RT in post-mastectomy T1-2 breast cancer patients with 1-3 positive ALN. Huang et al. (2012) reported a significant reduction in locoregional recurrence and a significant improvement in the 10-year disease-free survival for patients who received post-mastectomy RT; however, no significant effect was noted for the distant metastasis rate or OS. Compared to patients not receiving post-mastectomy RT, Tendulkar reported RT significantly affected the 5-year loco-regional recurrence but not the disease-free survival (Tendulkar et al., 2012). Yu et al. (2013) reported supraclavicular radiation therapy (SCRT) was a significant predictor of locoregional recurrence-free survival (but not DMFS or OS) in patients with ≥2 risk factors.

Biancosino et al. (2012) reported RT to the supraclavicular and infraclavicular lymphatic drainage area in patients with positive ALN who underwent breast-preserving surgery failed to improve the focal control, disease-free survival, and OS. Macdonald et al. (2009) compared RT at chest wall alone with RT at the chest

wall and supra- and infraclavicular lymphatic drainage area in patients who underwent complete mastectomy due to T1-2N1 breast cancer. Their results indicated that RT administered at the supra- and infraclavicular lymphatic drainage area in addition to the chest wall did not significantly improve the locoregional recurrence, disease-free survival, or OS (Macdonald et al., 2009). Taken together, all of these studies suggest that prophylactic SCRT does not seem to improve the DMFS or OS, and the effect of SCRT on regional control remains unclear.

In our study, patient age and Her-2 positive status were identified as independent predictors influencing SFRFS in the univariate analysis; however, only Her-2 positive status remained significant as a prognostic factor in the multivariate analysis. In a study on Chinese patients treated with BCS, HER2-enriched tumors had the highest risk of local recurrence and the poorest prognosis (Jia et al., 2014). However, a study on patients with operable HER-2 overexpressing breast cancer (which accounts for approximately 20- 30% breast cancer) showed that whether or not they had received RT had little effect on survival whereas lymph node metastases, LVSI, PCNA and chemotherapy cycles were independent predictors of prognosis (Liu et al., 2012).

HER2-enriched tumors have the highest risk of local recurrence in Chinese patients treated with breast conservation therapy. Other studies identified different risk factors for SCFR. Yates et al. (2012) found that 2-3 positive ALN and a high tumor grade were two independent predictors affecting SCFR. The 5-year and 10-year SCFR rates were highest in patients with grade III breast cancer and 3 positive lymph nodes (21% and 30%, respectively) (Yates et al., 2012). Yu et al. (2010) found that the presence of LVI, extracapsular extension, and the number/level of involved ALN were independently and significantly associated with SCFR. Additionally, the 5-year SCFR recurrence rates were 3. 2% for patients with 0-1 risk factor, 21. 3% for patients with 2 risk factors, and 48. 8% for patients with ≥3 risk factors. Yu et al. (2010) recommended RT be strongly considered for patients with ≥2 risk factors for SCFR. Kong et al. (2013) reported that histologic grade 3 and extracapsular extension were significant predictive factors for SCFR. Duraker et al. (2012) reported lymph node ratios > 0. 25 in patients with T1N1 breast cancer and >0. 08 in T2N1 breast cancer were associated with lower locoregional recurrences rates in patients receiving post-mastectomy RT. Siponen et al. (2012) reported that histologic tumor grade 3 and estrogen and progesterone receptor negativity were associated with an increased risk for SCFR.

Our study had several limitations including its retrospective nature. Additionally, the sample size was relatively small (only 61/593 patients received RT), and a randomized, controlled design was not used. Our results showed Her-2 positive status significantly influenced the SFRFS in patients with T1-2N1M0 breast cancer. Although trastuzumab has been shown to impact the focal recurrence of breast cancer (Panoff et al., 2011) and improve overall survival in metastatic HER2-positive breast cancer patients (Zhu et al., 2013), patients that were Her-2 positive in our study were not treated with trastuzumab. Thus, it remains unclear whether the focal recurrence rate of breast cancer in these patients would have been altered by trastuzumab treatment.

In conclusions, postoperative RT administered to the supra- and infraclavicular area along with the chest wall significantly lowered the locoregional recurrence of breast cancer in T1-2N1M0 patients who underwent mastectomy and ALN dissection. SCFR was significantly associated with DMFS, which was significantly associated with OS. Furthermore, Her-2 positive status was significantly associated with SFRFS. Therefore, prophylactic, postoperative RT directed at the supra- /infraclavicular lymphatic drainage area, is recommended for T1-2N1M0 breast cancer patients, especially those patients with Her-2 positive status.

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