Original article

Adjuvant regional nodal irradiation did not improve outcomes in T1-2N1 breast cancer after breast-conserving surgery: A propensity score matching analysis of BIG02/98 and BCIRG005 trials

Wei-xiang Qi, Lu Cao, Cheng Xu, Shengguang Zhao[**], Jiayi Chen[*]

Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

ABSTRACT

Aim: To determine whether the addition of regional nodal irradiation (RNI) to whole-breast irradiation (WBI) would improve outcomes over WBI alone in T1-2N1 breast cancer after breast-conserving surgery (BCS) and adjuvant systematic therapy.
Methods: Data were obtained from two randomized controlled trials (NCT00174655 and NCT00312208). Univariate and multivariate Cox-regression analysis were performed to investigate predictors for overall survival and disease-free survival. A 1:1 propensity score matching (PSM) analysis was applied to eliminate selection bias.
Results: With median follow-up 80 months (range: 3—155 months), the 5-year local regional recurrence in the WBI group was 2% vs. 5% ($p = 0.28$) in the WBI + supraclavicular radiotherapy, and the rate of 5-year distant metastasis in the WBI group was 7% vs. 13% in the WBI + supraclavicular radiotherapy ($p = 0.0748$); In addition, the 5-year local regional recurrence in the WBI group was 3% vs. 9% ($p = 0.19$) in the WBI + internal mammary irradiation (IMI); However, the rate of 5-year distant metastasis in the in the WBI group was significantly lower than that in the WBI + IMI (8% vs. 24%, $p = 0.036$). After PSM, cox-regression analysis indicated that neither RNI nor IMI in combination with WBI in T1-2N1 breast cancer was associated with an improved overall survival and disease-free survival when compared to WBI alone.
Conclusion: The addition of RNI to WBI in T1-2N1 breast cancer after BCS and adjuvant systematic therapy did not improve outcomes in comparison with WBI alone. Further studies are still needed to identify patients who would most benefit from RNI in this patient population.

Introduction

Adjuvant radiation therapy (RT) plays a vital role in the multidisciplinary management of breast cancer after breast conserving surgery (BCS) [1,2]. Twenty-year follow-up of the National Surgical Adjuvant Breast and Bowel Project (NSABP)-04 study demonstrates that BCS followed by breast irradiation significantly decrease the incidence of a recurrence in the ipsilateral breast as compared with BCS alone (14.3% vs. 39.2%, $p < 0.001$) [3]. A larger individual meta-analysis reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) also shows that addition of radiotherapy to breast cancer after BCS nearly halves the recurrence rates and reduces the

breast cancer death independent of lymph nodes status [4]. However, the indications for regional nodal irradiation in presumed intermediate risk (pT1-2N1) breast cancer patients after BCS remains a topic of debate. In addition, internal mammary chain is a major local lymph drainages accounting for 25% of all lymphatics in breast cancer [5]. Although increasing clinical data suggest that internal mammary node irradiation (IMNI) would improve local regional control and overall survival in lymph node positive breast cancer, the survival benefits of IMNI in this patient population remains controversial due to increased risk of cardiac and pulmonary toxicity [6—8]. Due to the aforementioned issues, whether RNI with or without IMNI has additional value for T1-2N1 breast cancer after BCS remains undetermined.

Project data sphere is an independent, not-for-profit data-sharing platform, which provides one place where the research community could voluntarily share, integrate, and analyze historical, patient-level data from prospective clinical trial in order to

* Corresponding author.
** Corresponding author.
 E-mail addresses: zsg10935@rjh.com.cn (S. Zhao), chenjiayi0188@aliyun.com (J. Chen).

advance future cancer research (https://www.projectdatasphere.org/). Prior to our study, Prof. Abdel-Rahman has performed an individual data analysis, by using project data sphere, to assess the impact of postmastectomy radiotherapy (PMRT) among breast cancer patients with T1—T2 N1 after adjuvant systemic therapy and find that there is no survival beneficial of PMRT in this patient population [9]. Similarly, Zeidan YH. et al. [10]. perform a retrospective analysis of the Breast International Group 02—98 Trial and find that PMRT could improve local regional recurrence in T1-2N1 breast cancer who had undergone mastectomy and axillary nodal dissection, but not for survival benefits. However, due to the limitation of retrospective analyses and lack of quality control for radiotherapy, we are still waiting for the results of SUPREMO trial, which is a phase III international randomized trial evaluating the role of PMRT for intermediate-risk breast cancer [11]. Additionally, the survival impact of adding regional nodal irradiation (RNI) to whole-breast irradiation (WBI) among breast cancer patients with T1—T2 N1 after BCS remains unknown. As a result, in the present study, we aim to investigate whether the addition of RNI to WBI would improve outcomes over WBI alone in T1-2N1 breast cancer after breast-conserving surgery and adjuvant systematic therapy by using a propensity score matching (PSM) analysis.

Material and method

About PDS and study cohorts

The present analysis is based on the raw individual data from two phase III trials evaluating adjuvant systematic chemotherapy for operable breast cancer patients (NCT00174655 and NCT00312208). The primary results of these trials were analyzed and published previously [12—14]. Informed consent was obtained from all included participants in all included studies. Only active comparator arm datasets were available in the PDS platform for the included trials. Overall, a total of 660 patients were available from the combined dataset.

Data collection

The available data of the phase III trial contains data about age at diagnosis, number of positive lymph nodes, T and N stages, number of lymph nodes examined, hormone receptor (HR) status, grade, and adjuvant chemotherapy. Site of RNI, including the supraclavicular, axillary, or internal mammary fields were also recorded in the present. Moreover, data about locoregional relapse status and overall survival status were recorded.

Based on the inclusion criteria for clinical trials, all included patients in the present study should have adequate organ function and acceptable performance status. The primary endpoints of the current analysis are overall survival (OS) which is defined as the time from randomization till death from any cause and disease-free survival (DFS) which is defined as the time from randomization till disease progression or death.

Statistical consideration

The baseline characteristics of included patients was simply described by using frequencies and percentages. Overall survival and disease-free survival was assessed according to whether or not patients received RNI through Kaplan—Meier analysis. Univariate and multivariate Cox-regression analysis were performed to investigate predictors for overall survival and disease-free survival. A 1:1 propensity score matching (PSM) analysis was applied to eliminate selection bias. Factors significantly associated with risk of OS and DFS in the univariate analysis ($p < 0.05$) were then included

for analysis in the multivariate cox-regression analysis. A two-tailed P-value <0.05 was considered statistically significant. Statistical analyses were conducted through SPSS statistical software (IBM; NY) version 20.0 and R version 3.4.2 software (The R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org).

Results

Patients characteristics

Baseline characteristics of the included 660 patients were shown in Table 1. A total of 279 patients received supraclavicular in combination with WBI, while 381 patients received WBI alone; in addition, 62 patients received IMI combined with WBI; Among the 660 patients, 103 (15.6%) patients aged less than 40, while 557 (84.4%) patients older than 40; median tumor size is 1.8 cm (range: 0.4—5.5 cm); 403 patients presented with T1 and 257 patients diagnosed with T2 (Table 1).

Cumulative incidence of recurrence

With a median follow-up of 80 months (range: 3—155 months), the 5-year local regional recurrence in the WBI group was 2% vs. 5% in the WBI + supraclavicular radiotherapy, there was no significant difference of local regional recurrence between the two groups (Fig. 1A, $p = 0.28$). Then, we investigated the incidence difference of distant metastasis between the groups, and found that the rate of 5-year distant metastasis in the WBI group was 7% vs. 13% in the WBI + supraclavicular radiotherapy, no significant difference of distant metastasis incidence was observed between the two groups

Table 1
Baseline characteristics of 660 breast cancer patients.

Characteristic	Value
Age	
<40 years	103
≥ 40years	557
T stage	
T1	403
T2	257
No. of positive lymph node	
1	326
2	187
3	147
Resected lymph node	
< 10	112
≥ 10	548
Grade	
1—2	386
3	252
Missing	22
ER status	
Positive	156
Negative	504
PR status	
Positive	198
Negative	435
Missing	27
Supraclavicular (with or without axillary) radiotherapy	
Yes	279
No	381
Internal mammary radiotherapy	
Yes	62
No	598

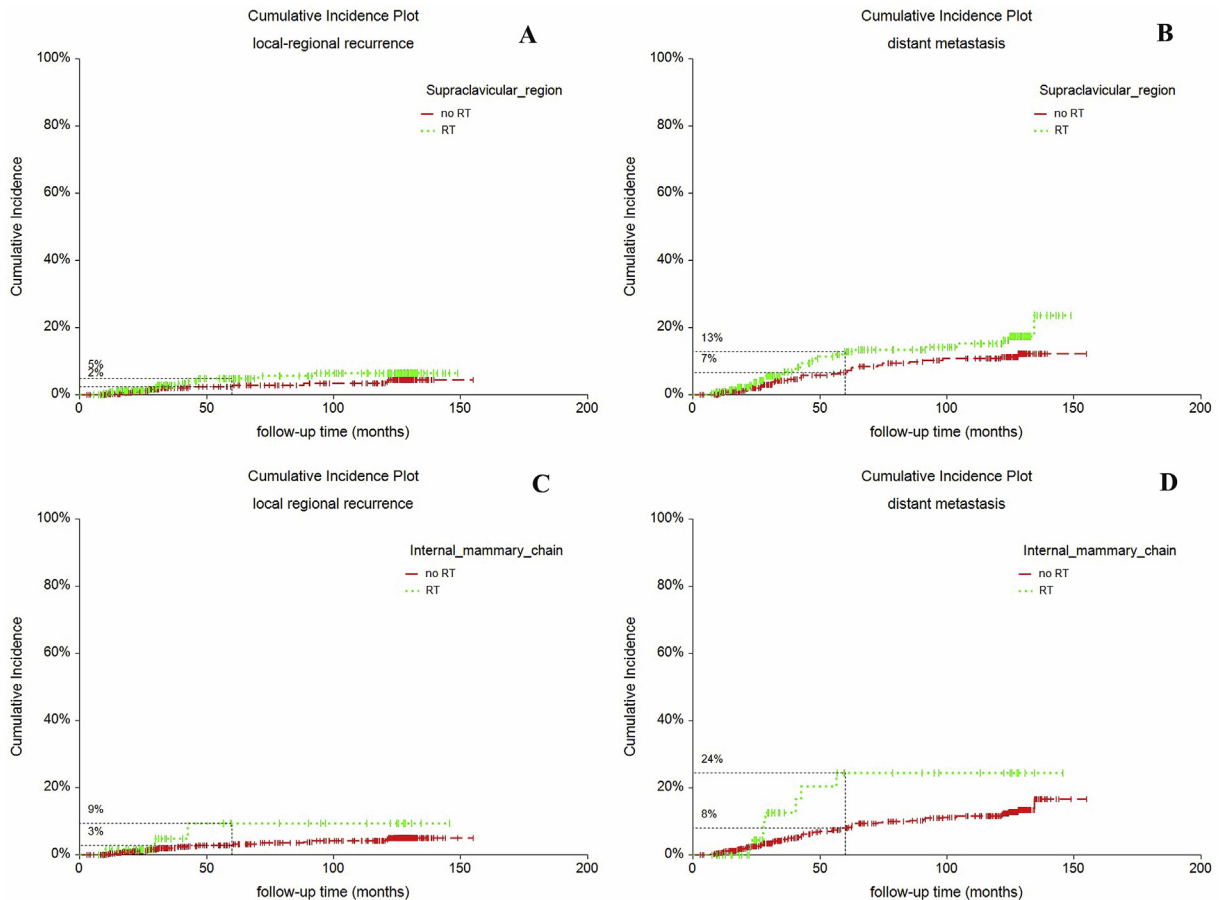Abbreviation: ER, estrogen receptors; PR, progesterone receptors.

Fig. 1. cumulative incidence of local-regional recurrence and distant metastasis according to regional nodal irradiation

(Fig. 1B, $p = 0.0748$); In addition, the 5-year local regional recurrence in the WBI group was comparable to that in the WBI + internal mammary irradiation (IMI) (3% vs. 9%, $p = 0.19$, Fig. 1C); However, the rate of 5-year distant metastasis in the in the WBI group was significantly lower than that in the WBI + IMI (8% vs. 24%, $p = 0.036$, Fig. 1D).

Survival benefits according to RNI

Kaplan-Meier analysis according to supraclavicular radiotherapy showed that the OS of patients who received combination of supraclavicular radiotherapy with WBI seems to be inferior than patients who received WBI alone ($p = 0.028$, Fig. 2A); Similarly, the DFS of patients who received combination of supraclavicular radiotherapy with WBI seem to be inferior than patients who received WBI alone ($p = 0.0022$, Fig. 2B). However, there might be selection bias for using RNI treatment because patients with higher risk had a tendency to be treated with RNI. Therefore, in order to account for heterogeneity in baseline characteristics of patients, we performed a 1:1 propensity score matching by using nearest neighbor matching. It matched patients treated with supraclavicular radiotherapy versus those not treated with supraclavicular radiotherapy according to age at diagnosis, T stage, HR status, grade, No. of positive lymph node and No. of lymph nodes examined. After PSM, A total of 442 patients with breast cancer were included after matching (221 who had been treated with supraclavicular radiotherapy + WBI, and 221 who underwent WBI alone). Multivariate analysis in the post-matching patients did not

show an impact of supraclavicular radiotherapy on OS (HR 0.52, 95%CI: 0.22—1.27; $p = 0.15$, Table 2). Additionally, supraclavicular radiotherapy did not improve DFS in univariate analyses (HR 0.59, 95%CI: 0.32—1.07;$p = 0.081$, Table 3).

Survival benefits according to IMI

Kaplan-Meier analysis according to IMI showed that the addition of IMI to WBI seems to significantly decrease the OS ($p = 0.026$, Fig. 2C) and DFS (p = 0.0098, Fig. 2D) when compared to WBI alone. However, selection bias for using IMI treatment could not be avoided. As a result, we also performed a 1:1 propensity score matching by using nearest neighbor matching according to age at diagnosis, T stage, HR status, grade, No. of positive lymph node and No. of lymph nodes examined. After PSM, A total of 116 patients with breast cancer were included after matching (58 who had been treated with WBI + IMI, and 58 who underwent WBI alone). Univariate analyses showed that the addition of IMI to WBI did not significantly improve OS (HR 0.12, 95%CI: 0.014—1.04; $p = 0.054$) and DFS (HR 0.53, 95%CI: 0.20—1.44; $p = 0.22$) in comparison with WBI alone.

Discussion

In the past decades, multiple randomized phase III trials assessing the role of adjuvant RT in breast cancer after BCS have demonstrated a remarkably consistent local control in comparison with BCS alone [15]. Based on these high-level evidence, adjuvant
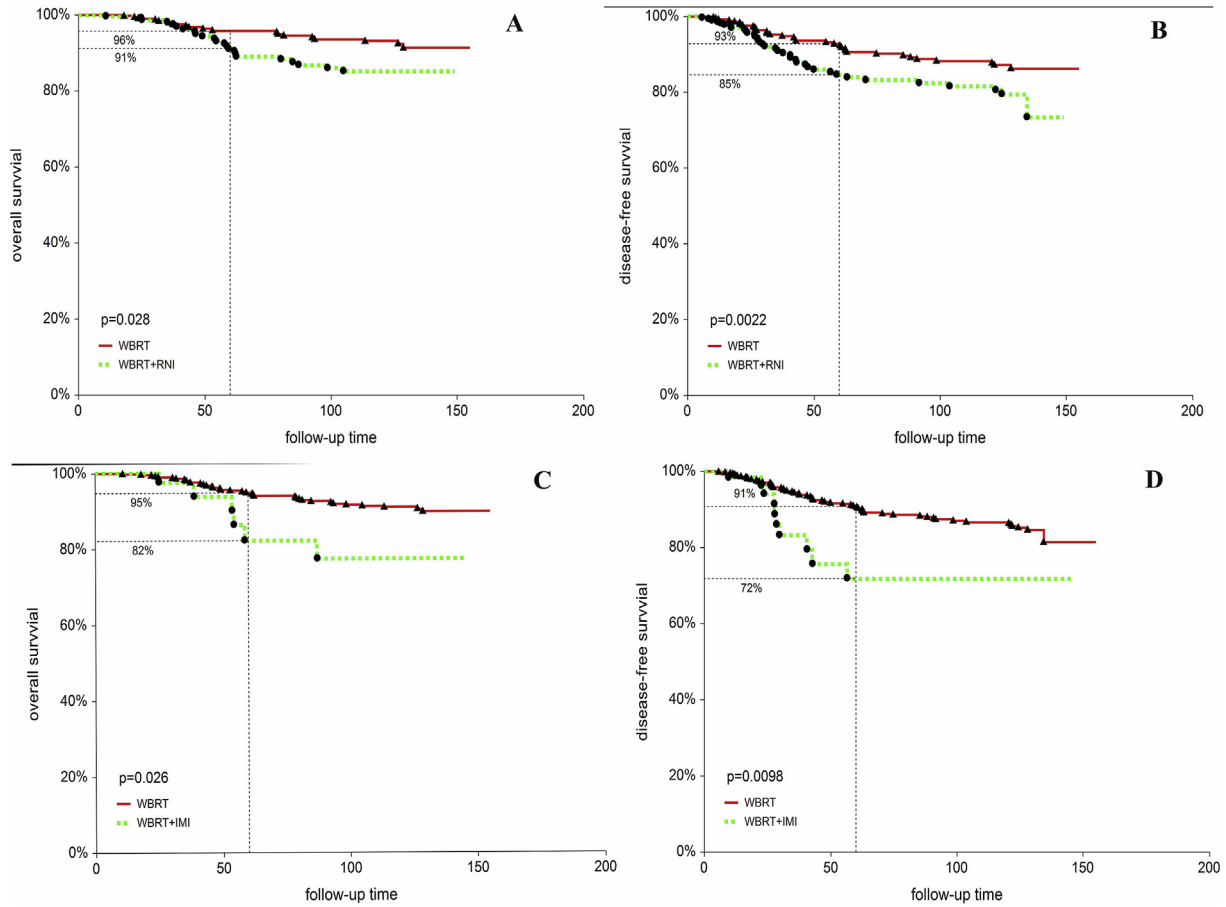
Fig. 2. overall survival and disease-free survival according to regional nodal irradiation

Table 2
Univariate and multivariate cox regression analysis for factors predicting OS after PSM for supraclavicular radiotherapy.

Characteristic	Overall survival			
	Univariate		Multivariate	
Age	HR (95%CI)	p	HR (95%CI)	p
<40 years	1		—	
≥ 40years	0.97 (0.33–2.83)	0.95	—	—
T stage				
T1	1		1	—
T2	2.32 (1.06–5.10)	0.035	2.14 (0.93–4.92)	0.07
No. of positive lymph node				
1–2	1		—	
3	0.98 (0.36–2.62)	0.98	—	—
Resected lymph node				
< 10	1		—	
≥ 10	0.76 (0.30–1.91)	0.56	—	—
Grade				
Well-moderate	1		1	
Poor	3.99 (1.65–9.62)	0.0021	3.05 (1.23–7.61)	0.016
HR status				
Positive	1		—	
Negative	1.74 (0.73–4.16)	0.22	—	—
Supraclavicular (with or without IMI) radiotherapy				
No	1		1	
Yes	0.39 (0.17–0.91)	0.028	0.52 (0.22–1.27)	0.15
Internal mammary radiotherapy				
Yes	1		1	
No	0.34 (0.12–0.98)	0.046	0.37 (0.12–1.14)	0.084

Table 3
Univariate and multivariate cox regression analysis for factors predicting DFS after PSM for supraclavicular radiotherapy.

Characteristic	Disease-free survival			
	Univariate		Multivariate	
Age	HR (95%CI)	p	HR (95%CI)	p
<40 years	1		—	
≥ 40years			—	—
T stage				
T1	1		1	—
T2	1.85 (1.03–3.33)	0.039	1.73 (0.94–3.21)	0.079
No. of positive lymph node				
1–2	1		—	
3	1.32 (0.67–2.60)	0.43	—	—
Resected lymph node				
< 10	1		—	
≥ 10	0.51 (0.27–0.95)	0.35	—	—
Grade				
Well-moderate	1		1	
Poor	2.16 (1.19–3.93)	0.012	1.53 (0.72–3.21)	0.27
HR status				
Positive	1		1	
Negative	2.10 (1.13–3.92)	0.019	1.49 (0.70–3.19)	0.30
Supraclavicular (with or without IMI) radiotherapy				
No	1		—	
Yes	0.59 (0.32–1.07)	0.081	—	—
Internal mammary radiotherapy				
Yes	1		1	
No	0.35 (0.16–0.76)	0.0077	0.31 (0.14–0.67)	0.0031

RT after BCS for early-stage disease has become an integral part of breast cancer treatment. However, the role of RNI in early stage breast cancer after BCS is less clear. As a result, two large randomized trials has been conducted to investigate the benefits of RNI: the European Organization for Research and Treatment of Cancer (EORTC) 22922 trial [8] and the National Cancer Institute of Canada (NCIC) MA.20 trial [16]. Both of these two trials aim to investigate the impact of adding comprehensive nodal (supraclavicular and internal mammary nodes with or without the axilla) to WBI on survival of breast cancer after BCS. MA.20 trials showed that there was a significant decrease in breast cancer recurrences with the addition of comprehensive RNI in women predominantly with 1–3 lymph nodes involved after a completion ALND but not for overall survival, while EORTC 22922, including both mastectomy and BCS treatment, found that the 10-year risk-adjusted overall survival was improved from 80.7% to 82.3% in the regional irradiation group ($p = 0.06$). However, the addition of IMI to WBI in presumed intermediate risk (pT1-2N1) breast cancer patients after BCS remains in a debate, and the potential benefits of comprehensive nodal therapy must be weighed against the potential toxic effects of treatment. In this study, we aim to investigate whether the addition of supraclavicular radiotherapy with or without IMI to WBI would improve the survival of T1-2N1 breast cancer after BCS in the presence of contemporary systemic therapy.

A total of 660 patients, of whom 279 patients received supraclavicular in combination with WBI, 381 patients received WBI alone and 62 patients received IMI combined with WBI are included for analysis; our study shows that the incidence of 5-year local regional recurrence and distant metastasis in the WBI group is comparable to WBI + supraclavicular radiotherapy; while the rate of 5-year distant metastasis in the in the WBI group is significantly lower than that in the WBI + IMI (8% vs. 24%, $p = 0.036$), but not for local regional recurrence, one possible explanation for this finding is the patient selection bias. For example, proportions of patients with three positive lymph node in the WBI + IMI is significantly higher than that in the WBI group (30.6% vs. 18.6%, $p = 0.029$). We thus use a 1:1 propensity score matching by using nearest neighbor matching to account for heterogeneity in baseline characteristics of patients. In consistent with MA20 and EORTC 22922/10925 studies, cox-regression analysis also find that addition of supraclavicular or internal mammary radiotherapy to WBI does not improve overall survival in multivariate analysis after PSM, which indicates that treatment volume is not an independent prognostic factor, and baseline characteristics of tumor size and tumor differentiation seem to be associated with worse outcomes in this patient population. In addition, we also do not observe an improved DFS in the RNI group, which is contrary to the above mentioned two trials. Possible reasons for this discrepancy are as follows: (1) different characteristics of included patients: both MA20 and EORTC 22922/10925 studies include a subset of patients with > N1 disease, and EORTC 22922/10925 study include patients treated with mastectomy; (2) different treatment volume of RNI: both MA20 and EORTC 22922/10925 studies investigate the impact of comprehensive nodal (supraclavicular and internal mammary nodes with or without the axilla) on survival of breast cancer, while in the present study, only 62 patients received IMI combined with WBI. Based on our findings, the routine use of adding supraclavicular or IMI to WBI among T1-2N1 breast cancer after BCS and standard systematic therapy could not be recommended, but it is needed to be confirmed in further prospective trials.

Recently, neoadjuvant chemotherapy (NCT) has been increased to be used in breast cancer treatment in order to downstage locally advanced (inoperable) disease and increase the probability of BCS (early stage) [17,18]. However, whether additional RNI following BCS would improve survival in patients with initial cN1 remains undetermined. In our previous study, post-mastectomy radiotherapy (PMRT) significantly improved locoregional recurrence-free survival (LRRFS) following NAT in breast cancer patients with cT1–2N1 disease [19]. In addition, novel clinical-pathological risk assessment is used to identify the patients who would most benefit from RNI. In our recent publication, we find that adding RNI significantly improve DFS following NAT. Patients with a Neo-Bioscore of 1–3 are more likely to benefit from RNI [20]. However, further prospective with larger sample size are still needed to confirm our findings. In addition, most of included patients received mastectomy (89%), thus the role of RNI in cN1 breast cancer after BCS remains to be clearly determined in further studies.

Several limitations needed to be concerned in the present study. Most importantly, the primary endpoint of the included studies are aimed to investigate the survival benefit of adjuvant systematic chemotherapy in breast cancer, but not for WBI with or without RNI. Thus, despite of the randomized, prospective nature of the included studies, our study is a retrospective analysis of the pooled dataset of these included studies. The finding of present study might be confounded by this pattern of study design although we use the propensity score matching (PSM) analysis to eliminate selection bias. In addition, these two trials are lack of quality control for radiation therapy, thus the characteristics of the radiotherapy used in each study, such as fractionation size, treatment volumes and fields, total dose, and tumor bed boost or no boost, might be significant different, which makes it more complicated to establish comparative similarities between the patients of both studies. Secondly, PDS only provide comparator arms of the included trials, thus the sample size in our study is relative small and statistical power is limited. Thirdly, the human epidermal growth factor receptor 2 (HER-2) status and triple-negative subtype are two risk factors for poor prognosis among breast cancer patients. However, the present data is lack of data on the distribution of HER-2 and triple-negative subtype, and the impact of these two factors on patients survival and recurrence remain unknown. Although all of included patients in the BCIRG-005 trial are HER-2 negative breast cancer, and 5.2% of included patients in BIG02/98 are HER-2 positive patients. Finally, adjuvant systematic therapies might be another source of heterogeneity among the included patients, which might affect the role of radiotherapy in this patient population.

Conclusion

The addition of RNI to WBI in T1-2N1 breast cancer after BCS and adjuvant systematic therapy did not improve outcomes in comparison with WBI alone. Patients with early stage (T1-2N1) breast cancer after BCS represent a diverse population who need an individualized risk analysis when considering RNI. Further studies are still needed to identify patients who would most benefit from RNI and those at low risk for local recurrence in whom RNI could be omitted.

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