

Sequential Vs Concurrent Adjuvant Chemotherapy for Operable Breast Cancer: A Meta-analysis

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Research

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Abstract

Background: Controversy still remains in that whether sequential or concurrent regimen of anthracyclines and taxanes benefits more for breast cancer. Here we aimed to compare these two regimens in patients with operable breast cancer based on all published data of phase III randomized controlled trials in this topic.

Methods: A literature search on PubMed, Web of science, Embase, ScienceDirect, Google scholar and clinicaltrials.gov databases was conducted up to May 2020. Meta-analysis was performed to evaluate the different efficacy on disease free survival (DFS) and overall survival (OS) for these two regimens. Subgroup analyses were further carried out in terms of node status and anthracycline selection.

Results: Compared to concurrent regimen, sequential regimen did not improve the DFS or OS in the whole population included. Subgroup analysis showed that in node-positive patients, however, sequential regimen has better DFS, but not OS, than concurrent regimen. In sequential regimen, patients received doxorubicin and taxanes had improved DFS and OS than those were given epirubicin and taxanes. Furthermore, for patients receiving doxorubicin and taxanes, compared to sequential regimen, less cycles (4 cycles) of concurrent treatment showed worse DFS and OS, whereas more cycles (6 cycles) may rescue the loss. In addition, high grade toxicity response in both groups exhibited no difference except for neuropathy, which occurred more frequently in the sequential regimen.

Conclusions: Sequential regimen of anthracyclines and taxanes for patients with breast cancer did not promise a significant benefit in neither DFS nor OS over concurrent regimen. However, sequential regimen did provide a better DFS than that in concurrent regimen for node-positive patients. Interestingly, further subgroup analysis showed that for patients with node-positive and were given doxorubicin and taxanes, more cycles (6 cycles) of concurrent regimen was not inferior to sequential regimen.

Background

Breast cancer is the most common cancer in women worldwide. In 2018, 266,120 new breast cancer cases occurred in the United States, accounting for 30% of all female malignant tumors, and 40,920 deaths, accounting for 14% of the total mortality of female malignancies[1]. In China, the incidence and the mortality of female breast cancer is about 41.82/100,000 and 9.91/100,000, respectively[2]. Despite of the great advances achieved in diagnosis and treatment, breast cancer remains to be one of the leading causes of cancer-related death[1]. Dozens of studies have indicated that adjuvant chemotherapy contributes huge benefit for early breast cancer patients after surgery[3], and at present, anthracyclines and taxanes are the basic components in chemotherapy as the addition of a taxane to an anthracycline-contained regimen is associated with better relapse-free and overall survival[4-7]. However, although the regimens containing anthracycline and taxane are reported to be more effective, the optimal schedule of drug intervention (sequentially or concurrently) remains questionable. For instance, superficially at least,

concurrent regimen requires less doses of drugs which may affect the efficiency, nevertheless, sequential administration may supply an optimal dose for each compound but requires longer time frame.

Thus, to elucidate clearly which regimen may promise more benefit for patients, we performed this meta-analysis to comprehensively evaluate the clinical effect of these two adjuvant regimens in patients after breast cancer surgery by including all phase III randomized control studies in this topic.

Methods

The methods used for this meta-analysis and generation of inclusion criteria were based on PRISMA recommendations.

Literature search strategy

Databases including PubMed, Web of science, Embase, ScienceDirect, Google scholar and clinicaltrials.gov up to May 2020 were used for literature search, with the following keywords: "breast cancer", "sequential and (concurrent or concomitant)", "adjuvant chemotherapy", "anthracyclines and taxanes", "(doxorubicin or epirubicin) and (docetaxel or paclitaxel)". In addition, the references of relevant reviews were searched for additional studies.

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) Phase III randomized control studies; (2) Breast cancer that have not spreaded beyond the breast or the axillary lymph nodes. (3) Patients whom underwent curative surgical resection and were subsequently randomized to receive either sequential or concurrent regimen. Standard post-operative radiotherapy and endotherapy protocols, either with tamoxifen or aromatase inhibitors, were allowed.

The exclusion criteria are: (1) Abstract only, (2) Duplicated publications, (3) reviews, letters or comments, (4) no available data.

Data extraction

Two investigators independently screened all the studies and extracted data. Differences were resolved by discussion until obtaining consistence. The following data were extracted and recorded in a predesigned form: study design, year of reporting, regimen details, median follow up, hazard ratio (HR) of DFS and OS, the number of outcome events, and the number of patients who experienced grade 3 and 4 toxicity.

Quality assessment

We used The Cochrane Collaboration's 'Risk of bias' assessment tool to assess the potential sources of bias in the included studies[7]. Two authors independently assessed the potential risk of bias for each study; any differences in judgement were resolved through discussion. The domains assessed according to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We assigned rating of "high", "low" or "unclear" risk of bias to each domain for each included studies.

Statistical analysis

The RevMan 5.3 was used for performing this meta-analysis. The I^2 and Cochrane Q tests were used to assess heterogeneity among the included studies, with $P < 0.1$ or $I^2 > 50\%$ being considered as significant. The risk ratio (RR) as well as the corresponding 95% confidence intervals (CIs) were pooled by an appropriate model (fixed- or random-effects model) based on the results of the heterogeneity test. Z test was used to evaluate the significant of pooled effect size. For dichotomous variables, a Mantel-Haenszel Rate Ratio with 95% confidence intervals was calculated. If significant heterogeneity was detected ($P < 0.1$), causes of heterogeneity were subsequently explored via subgroup analyses, otherwise a random effect model was selected. For continuous variables, we used a fixed effect weighted mean difference (WMD) for measurements and 95% confidence interval (95% CI) was calculated.

All analysis were performed according to the intention-to-treat principle, when appropriate data were available. The publications bias was evaluated by the Egger's and Begg's test using Stata 11.0 software. The sensitivity analyses were performed by omitting each individual study at a time. For these analyses, $p < 0.05$ indicated statistical significance.

Results

Characteristics of the included studies

After an initial literature search on PubMed, Web of science, Embase, ScienceDirect, Google scholar and clinicaltrials.gov databases, 189 articles were identified. After excluding duplicates and obvious irrelevant studies, 59 potentially relevant articles were remained. Among these, 32 articles were further excluded due to mis-matching contents (21 studies did not report the comparison between sequential and concurrent regimens; 8 reviews; 3 case reports). For the rest 27 articles, another 21 studies were excluded for the following reasons: no available data ($n=7$); no comparison between sequential and concurrent regimens($n=4$); regimens did not contain both anthracycline and taxane($n=8$); duplicates($n=2$). Finally, 6 articles were included in this meta-analysis [8-13](Figure 1).

In these 6 studies, 6866 breast cancer patients after surgery were given sequential regimen of anthracyclines and taxanes as adjuvant chemotherapy, while 6847 patients were received concurrent

treatment(Table 1). The publication year ranged from 2010 to 2017. All these studies were phase III randomized control trials.

Quality assessment

The details of the risk of bias summary was outlined(Figure 2).All studies were considered to be at median risk of bias.Randomized sequence generation was implemented in all 6 studies,and 4 studies implemented allocation concealment.All studies were performed on the intention-to-treat principle.None of these 6 studies reported blind to the participants or the outcome assessment.

Comparison of DFS between sequential and concurrent regimens

Significant heterogeneity among studies ($I^2 = 59%$, $P = 0.03$, Figure 3) was found in analysis for DFS between sequential and concurrent regimens, so we used the random effects model to pool the RR. The meta-analysis showed that sequential regimens of anthracycline and taxane seems not to add any significant improvement in DFS over to the concurrent regimens(RR: 1.05; 95%CI:0.97-1.14; $P=0.22$, Figure 3).

Comparison of DFS between sequential and concurrent regimens

As shown in Figure 4, significant heterogeneity among studies was observed for OS in comparison between sequential and concurrent regimens ($I^2=55%$, $P = 0.05$, Figure 4), so the randomized effects model should be used. The pooled estimate showed that there are no significant different OS between sequential regimens compared with concurrent regimens(RR: 1.03, 95% CI: 0.94 to 1.13, $P = 0.51$, Figure 4).

Sub-analysis in node status for DFS and OS

Eligible patients in HORG trial[11]were early breast cancer patients with high risk and node-negative, while the other trials included patients with node-positive.We conducted a sub-analysis according to the axillary lymph node status. The pooled estimate showed that there was a significant better DFS in patients with node-positive administrated with sequential regimens (RR: 1.08;95%CI:1.02-1.14, $P=0.004$, Figure 5A),yet the OS were approximate between both regimens (RR: 1.07;95%CI:0.96-1.19, $P=0.24$, Figure 5B).

The cycles of concurrent regimen with doxorubicin and taxanes also seemed to affect the heterogeneity. The patients in Big02-98[10]and NSABP B-30[9] trials only received 4 cycles of doxorubicin and taxanes. While patients in the other two trials [8, 12]weretreated for six cycles. So we then conducted another sub-analysis for this. The pooled estimate showed that less cycles (4 cycles) of concurrent treatment had worse DFS(RR:1.16;95%CI:1.06-1.27, $P=0.0009$, Figure 7A) and OS (RR:1.18;95%CI:1.05-1.33, $P=0.007$, Figure 7B) compared to sequential regimen, whereas more cycles(6 cycles) may rescue the loss.

Comparison of toxicity between sequential and concurrent regimens

Both hematologic and non-hematologic grades 3 and 4 adverse events were described in the six studies. Using prophylactic Granulocyte colony stimulating factor(G-CSF),patients with concurrent treatment did not show any significant higher risk of hematologic complications, such as febrile neutropenia and anemia. There was also no significant difference for fatigue or diarrhea. Nevertheless, the incidence of neuropathy occurred more frequently in the sequential regimen (RR = 0.17, 95% CI: 0.12 to 0.24, P <0.00001, Table 2).

Sensitivity analysis and publication bias

Sensitivity analysis showed that there was no significantly different incidence through omitting each study. No significant publication bias was found based on the Egger's and Begg's test (P > 0.05, Figure 8).

Discussion

Controversy still remains in that whether sequential or concurrent usage of anthracyclines and taxanes contributes more for operable breast cancer patients' survival. Our meta-analysis presented evidence that the sequential regimen is not associated with better DFS or OS than concurrent regimen from any cause, according to all published data of phase III randomized controlled trials.

Considering the importance of axillary lymph node status on breast cancer recurrence, DFS and OS, we conducted a sub-analysis to illuminate whether node-positive or -negative would affect the result. Data from 5 included phase III trials showed that in node-positive patients, sequential treatment provided a statistically better DFS. We further conducted another subgroup analysis in node-positive patients in regard to different choice of anthracycline. In particular, data from four trials [8-10, 12] showed patients treated with doxorubicin get both better DFS and OS than whom were treated with epirubicin. Interestingly, in the doxorubicin group given four cycles of drug treatment [9, 10], patients in sequential arm achieved better DFS and OS compared to combination arm, whereas patients receiving six concurrent cycles had the similar survival with the sequential group [8, 12]. This may be explained by two reasons. Firstly and importantly, cumulative doses of drugs would be the main factor. For patients in Big 02-98 [10] and NSABP B-30 [9] trials, the sequential arms were delivered with higher cumulative doses of both doxorubicin (225 vs 200 mg/m² in Big 02-98 trial, 240 vs 200 mg/m² in NSABP B-30 trial) and docetaxel (300 vs 300 mg/m² in Big 02-98 trial, 400 vs 300 mg/m² in NSABP B-30 trial). This is consistent with other reports that "lower doses" (30 mg/m²) of doxorubicin are correlated with inferior survival compared with "higher doses" (60 and 40 mg/m²) [14, 15]. Secondly, the dose intensity was higher in both doxorubicin (25 vs 16.7 mg/m² per week in Big 02-98 trial, 20 vs 16.7 mg/m² per week in NSABP B-30 trial) and docetaxel (33.3 vs 25 mg/m² per week in Big 02-98 trial and NSABP B-30 trial) in sequential arm, which validated the finding from NEAT trial [16] that a higher dose intensity confers a greater favorable long-term outcome. The principle behind dose density relates to the Gompertzian model and Norton-Simon hypothesis that smaller tumor grows faster so that the regrowth rate is higher between treatment cycles [17, 18], and as tumor shrinks, the regrowth rate increases to make the chemotherapy level capable of initiating regression be insufficient to maintain this regression and produce cure, indicating the

regression rate may be overcome by switching to alternative cytotoxic therapy[19]. On the contrary, the left four trials[8, 11-13] did not indicate any significant better survival in sequential regimens than that in concurrent treatment. Given these trials' patients assigned to the concurrent treatment were administered higher cumulative doses than Big02-98[10] and NSABP-30[9], it may be inferred that perhaps once the threshold of total dose is surpassed, higher cumulative doses do not add to efficacy.

According to the different choice of anthracyclines in node-positive patients, we conducted a further sub-analysis, showing that patients who received doxorubicin, but not epirubicin, had better DFS and OS in sequential treatment. It may be related to that the heart toxicity of epirubicin is lower than doxorubicin, thus patients in both groups can receive optimal dose intensity of epirubicin during the trials[20]. The toxicity response during therapy often aggravates the body burden and dampens the patients' medical compliance. Our analysis found that the incidences of adverse events such as febrile neutropenia, anemia, fatigue and diarrhea were similar for the two regimens, partially due to the more often administration of G-CSF in the concurrent treatment. However, neuropathy occurred more in the sequential regimen which may be related to a higher cumulative dose and longer treatment.

Some disadvantages of this meta-analysis should be noted. Firstly, the number of included studies is small. Secondly, heterogeneity, which may affect the result, exists in several trials. The 10/00 trial[13] included patients with pathological stage T4, while HORG trial[11] focused on patients with early breast cancer as well as node-negative and high risk. Besides, the choice of anthracyclines and the cycles of treatment in the 6 trials are different. Thirdly, subgroup analyses of some confounding factors, like country, races, hormonal receptor status and Her-2 status, could not be performed to explore the influence of these factors due to insufficient data.

Conclusions

Breast cancer patients with positive node and patients who are given doxorubicin, especially for those who want fewer cycles of chemotherapy, should be recommended with the sequential regimen. Alternatively, sufficient cycles of concomitant regimen may acquire the similar benefit with the sequential regimen does. Concurrent treatment is supposed to be administered with G-CSF prophylactically, and may be a better choice for early breast cancer patients with node-negative since they would benefit from the less duration and neuropathy rate. More RCTs with larger sample size should be performed to verify the results of this meta-analysis.

List Of Abbreviations:

disease free survival (DFS), overall survival (OS), hazard ratio (HR), risk ratio (RR), confidence intervals (CIs), weighted mean difference (WMD)

Declarations

Ethic approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The datasets used and analysed during the current study are available from PubMed, Web of science, Embase, ScienceDirect, Google scholar and clinicaltrials.gov.

Competing interests: Not applicable

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Authors' contributions: Qian Tu contributes to the inclusion criterias, Yanfei Shen contributes to the statistical analysis, Kejun Tang and Mengying Hong contribute to the data extraction. Wanjing Chen and Yong Shen contribute to the design of the work, datas analysis, interpatation of datas and submission.

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Tables

Table1: **Main characteristics of the studies included in this meta-analysis.**

Note:BCIRG-005*:either arm with G-CSF at the discretion of the investigator; CMF**,:Patients in all arms received three cycles of CMF that were given every 4 weeks as oral cyclophosphamide at 100 mg/m² on days 1–14 and intravenous methotrexate at 40 mg/m² plus intravenous 5-fluorouracil at 600 mg/m² on day 1 and day 8; CMF#:intensified CMF (cyclophosphamide at 840 mg/m², methotrexate at 57 mg/m², and 5-fluorouracil at 840 mg/m²); NSABP B-38###:all patients receive primary prophylaxis with pegfilgrastim or filgrastim; NR:no report; A:doxorubicin;E:epirubicin; C:cyclophosphamide;T:docetaxel; P:paclitaxel.

Trial	Year	Patient stage	Intervention	No. of patients	Median follow-up(M)	DFS			OS				
						HR	95%CI	P	Events	HR	95%CI	P	Events
BCIRG-005*	2016	T1-3cN0-1M0		3298	65	0.98	0.87-1.11	0.749		0.95	0.81-1.11	0.506	
			AC 60/600X4/3w→T 100X4/3w	1649				518					319
			TAC 75/50/500X6/3w	1649				523					332
Big 02-98	2013	T1-3N1-3M0		1919	93.4	0.84	0.72-0.99	0.035		0.79	0.65-0.98	0.028	
			A 75X3/3w→T 100X3/3w → CMF#X3/4w	960				318				165	
			AT 50/75X4/3w→CMF#X3/4w	959				278				201	
HE10/00	2012	pT1-4N1-2M0		1086	76	1.02	0.82-1.28	0.84		1.12	0.85-1.48	0.41	
			E 110X3/2w→P 250X3/2w → CMF#X3/2w+ G-CSF	551				327				388	
			EP 83/187X4/3w→CMF#X3/2w + G-CSF	535				313				363	
HORG	2017	T1c-3N0M0 (high risk)		658	70.5	1.591	0.990-2.556	0.055		1.89 6	0.902-3.987	0.091	
			E 90X4/3w→T 75X4/3w	329				94				102	
			ET 75/75X6/3w + prophylactic G-CSF	329				75				86	
NSABP B-30	2010	T1-3cN0-1M0		3511	73	0.83	NR	0.01		0.86	NR	0.09	
			AC 60/600X4/3w→T 100X4/3w	1753				388				240	
			TAC 75/50/500X4/3w + prophylactic G-CSF	1758				457				278	
NSABP B-38###	2013	pT1-3 pN1-3b M0		3241	64	0.87	0.74-1.01	0.07		1.01	0.82-1.23	0.96	
			AC 60/600X4/2w→P 175X4/2w	1624				294				188	
			TAC 75/50/500X6/3w	1617				327				185	
			All with prophylactic G-CSF										

Table2: The analysis of grade 3-4 toxicity between sequential and concurrent regimen.

Outcome	RCTs	RR	95%CI	P
Febrile neutropenia	6	0.66	0.41-1.07	0.09
Fatigue	4	1.06	0.84-1.33	0.62
Diarrhea	5	0.71	0.41-1.22	0.21
Neuropathy	4	5.78	4.01-8.34	< 0.01
Anemia	5	1.29	0.68-2.47	0.44

Figures

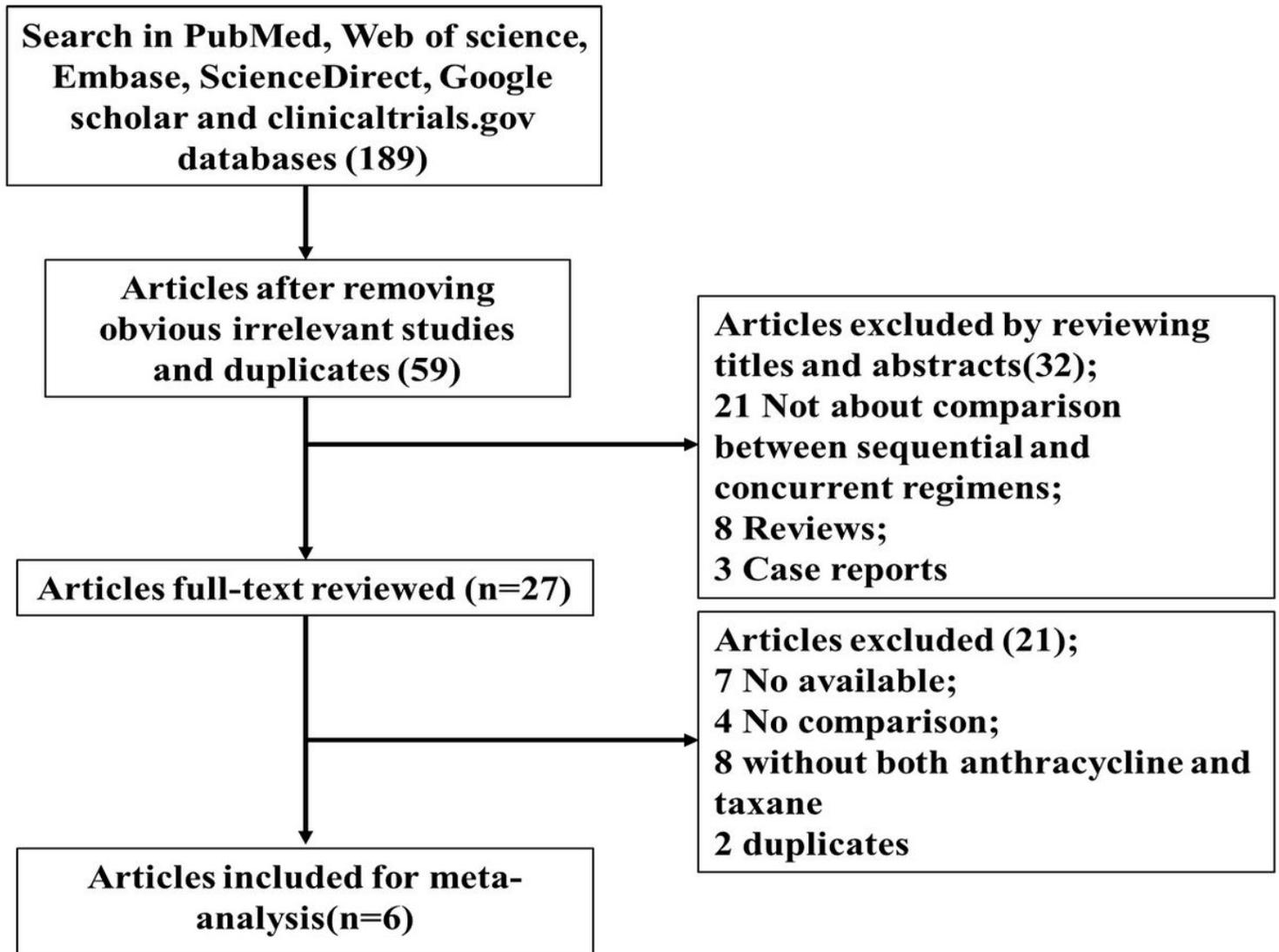


Figure 1

Figure 1. Flow diagram of the study selection process.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
BCIRG 005 2016	+	+	-	-	?	+	+
Big 02-98 2013	+	+	-	-	+	?	?
HE 10/00 2012	+	?	-	-	?	+	+
HORG 2017	+	+	-	-	+	?	?
NSABP B-30 2010	+	?	-	-	+	?	+
NSABP B-38 2013	+	+	-	-	+	+	+

Figure 2

Figure2. "Risk of bias" assessment for each risk of bias item of each included study.

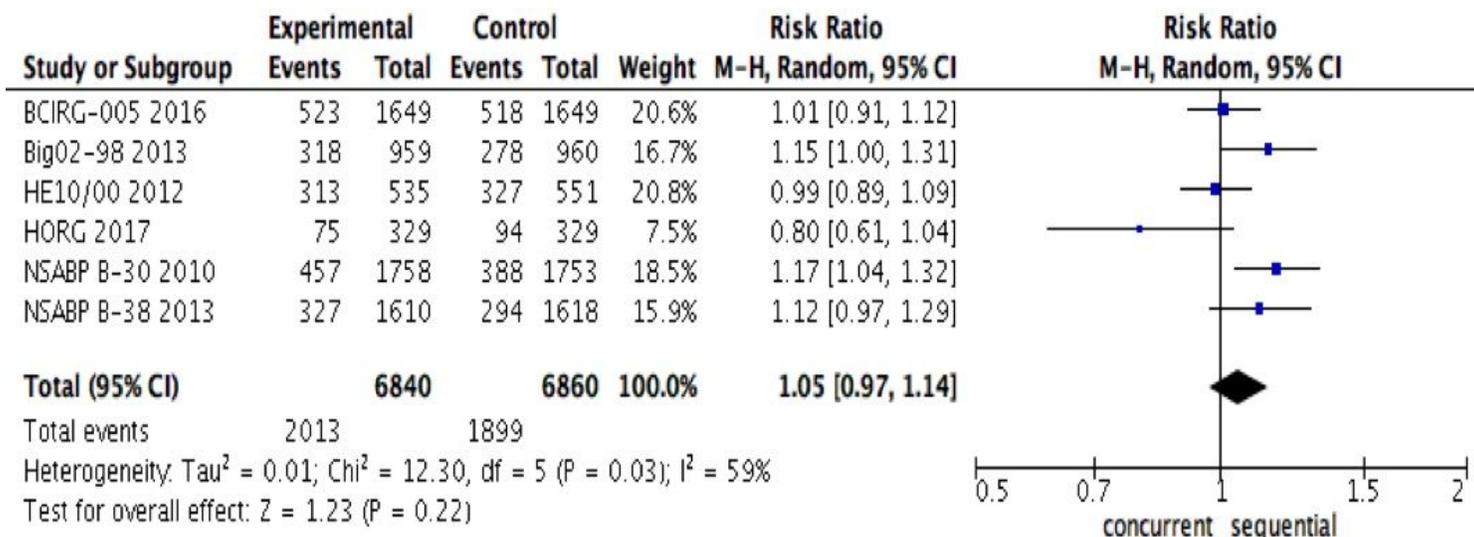


Figure 3

Figure 3. The analysis of DFS in sequential regimens compared with concurrent regimens.

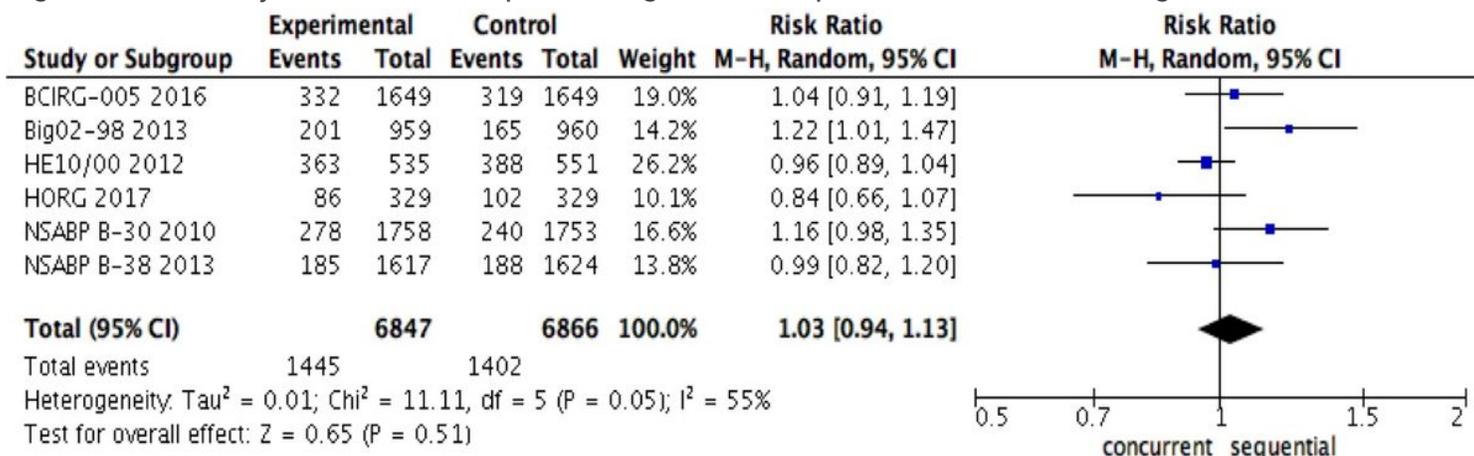


Figure 4

Figure 4. The analysis of OS in sequential regimens compared with concurrent regimens.

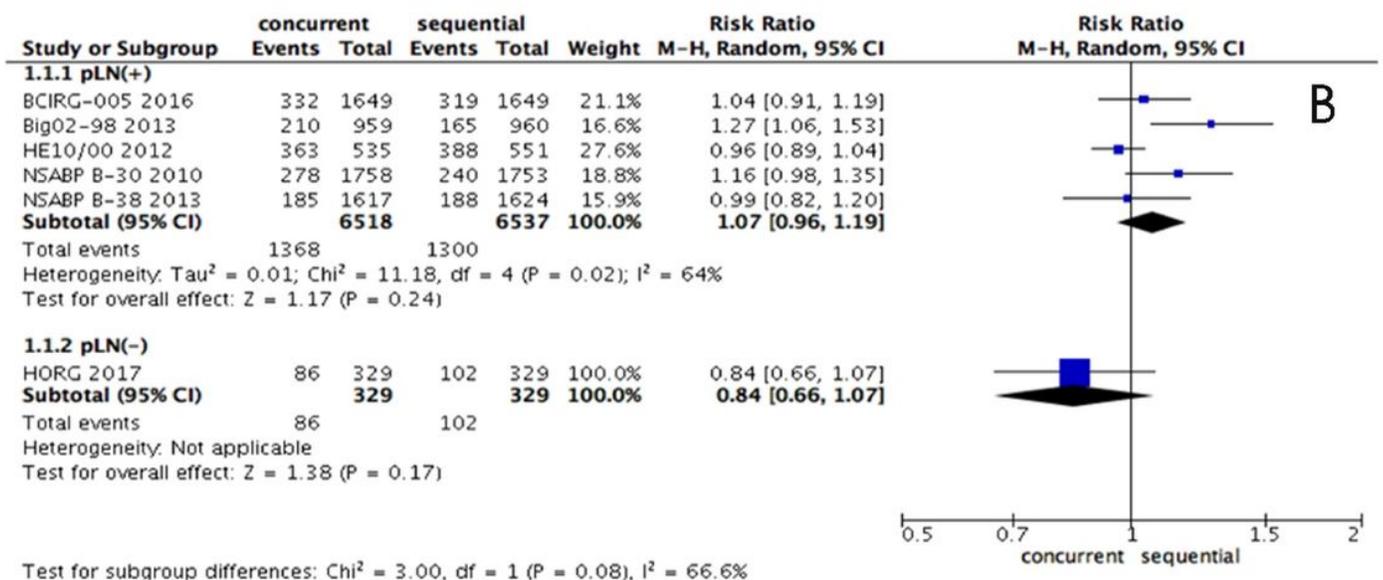
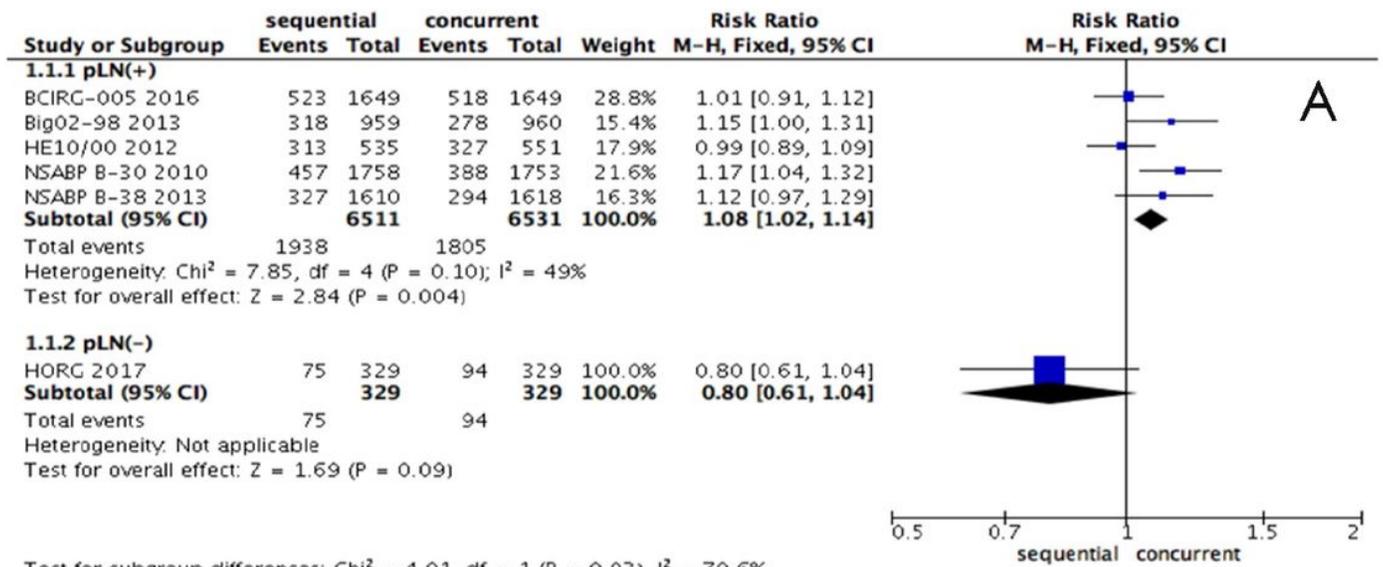


Figure 5

Figure 5A. The sub-analysis of node status effect in DFS between sequential and concurrent regimens.
 Figure 5B. The sub-analysis of node status effect inOS between sequential and concurrent regimens.

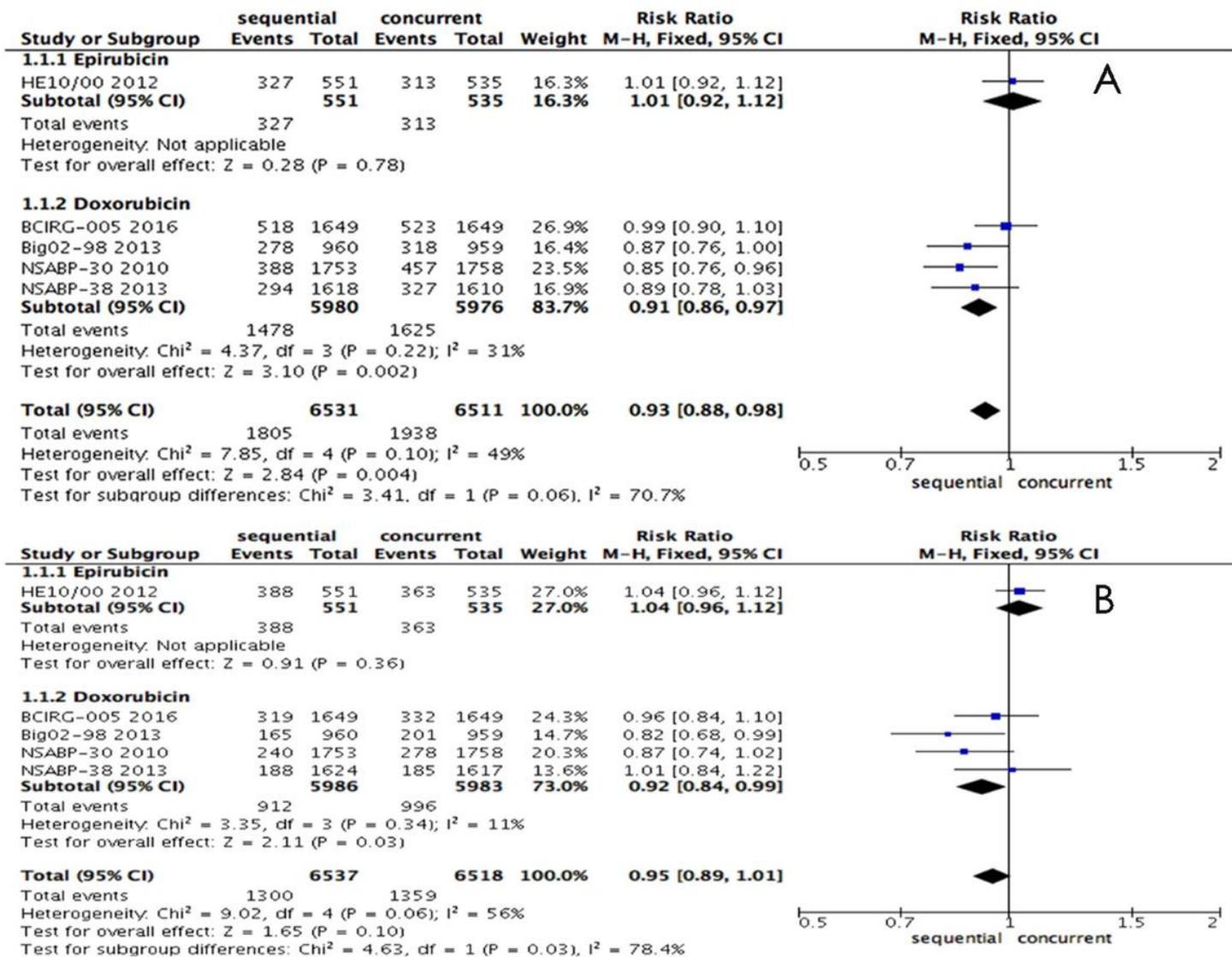


Figure 6

Figure 6A. The sub-analysis of anthracycline effect in DFS between sequential and concurrent regimens.
 Figure 6B. The sub-analysis of anthracycline effect in OS between sequential and concurrent regimens.

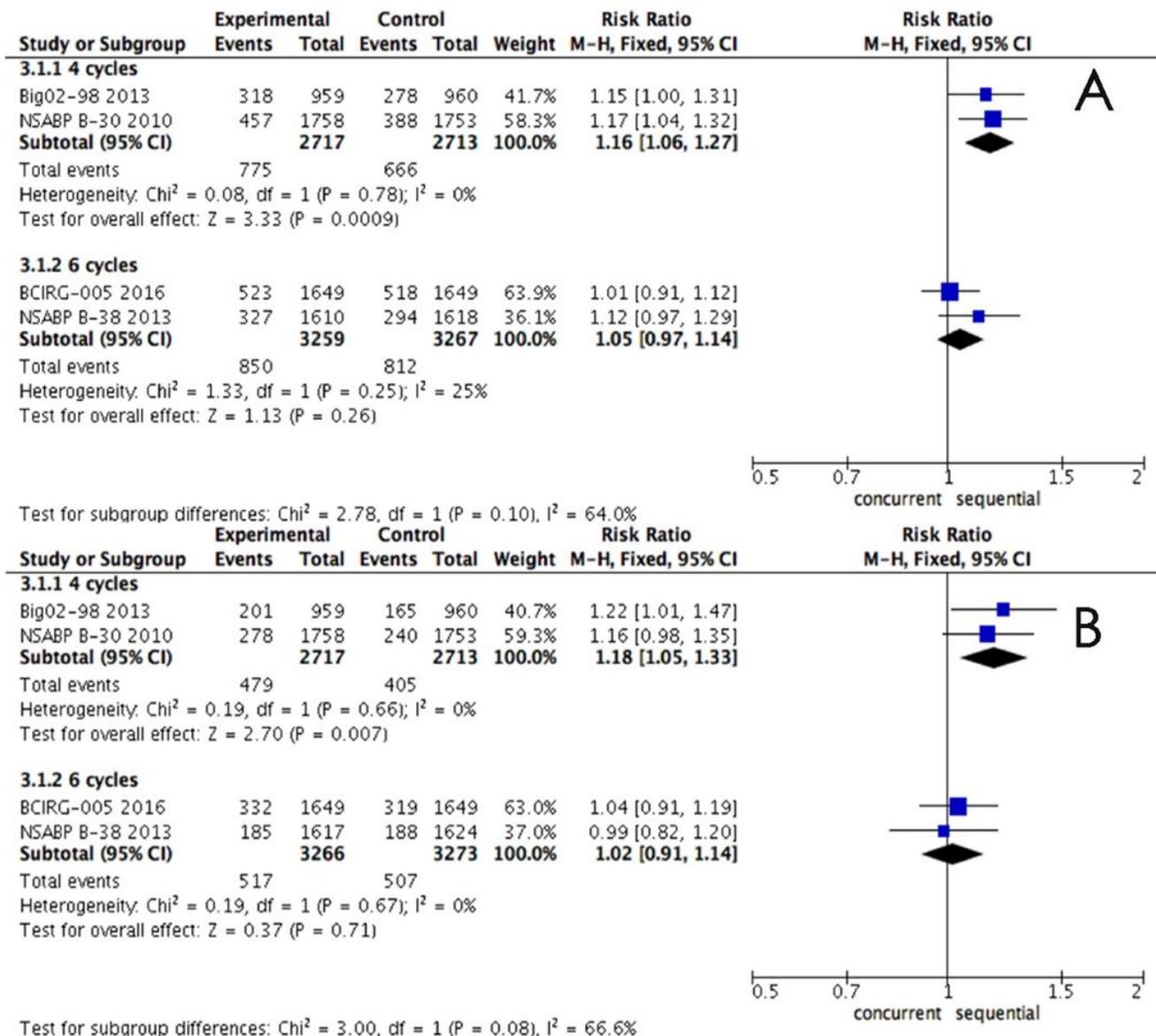


Figure 7

Figure 7A. The sub-analysis of cycle number effect in DFS in epirubicin arms between sequential and concurrent regimens. Figure 7B. The sub-analysis of cycle number effect in OS in epirubicin arms between sequential and concurrent regimens.

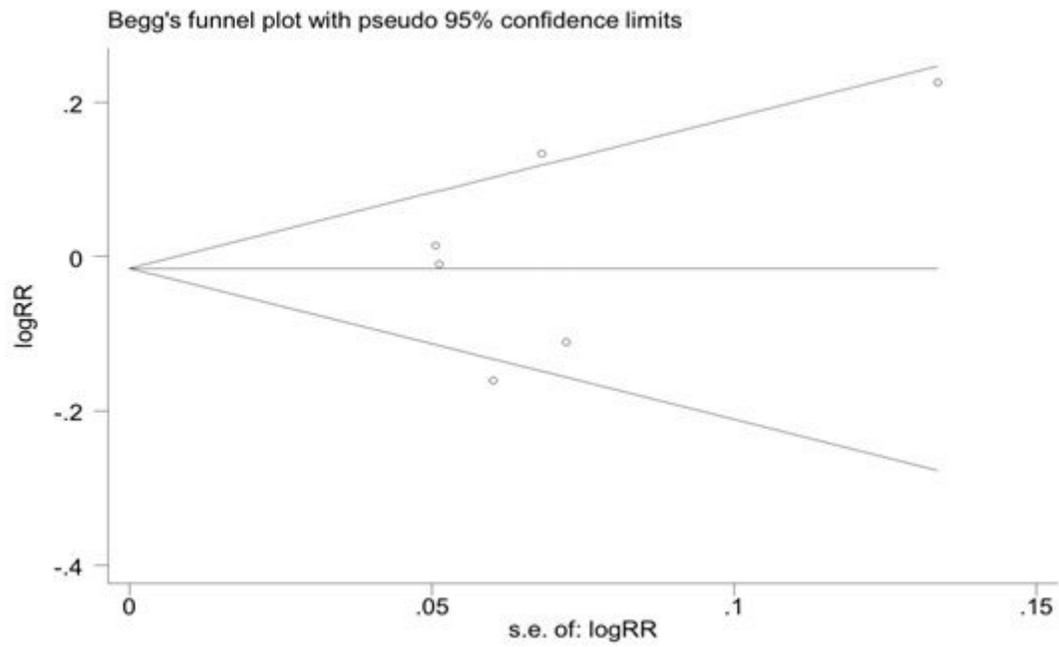


Figure 8

Funnel plot based on the risk ratio(RR) of DFS.