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Retrospective analysis of concurrent docetaxel and epirubicin neoadjuvant versus adjuvant chemotherapy

Which leads to better outcomes for different subtype breast cancer patients?

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Abstract

Different biological subtype breast cancers respond differently to neoadjuvant chemotherapy, but it is unknown whether neoadjuvant or adjuvant chemotherapy leads to different long-term survival in each specific subtype although equal outcomes have been reported in general population. This study sought to clarify whether the selection of either neoadjuvant or adjuvant chemotherapy was linked to a differential survival benefit based on breast cancer subtypes.

A prospectively maintained breast cancer database was queried from 2000 to 2008. All patients with a diagnosis of stage II and III breast cancer who received neoadjuvant or adjuvant chemotherapy were identified, only patients receiving docetaxel and epirubicin (TA) regimen were included. Patients were divided according to the administration of neoadjuvant or adjuvant chemotherapy. The biological subtypes were determined by immunohistochemical tests. The outcomes between neoadjuvant and adjuvant chemotherapy were compared in each different subtype. Kaplan–Meier curves were generated, and the Cox model was used to estimate the association between death risk and chemotherapy timing while adjusting for potentially confounding factors. P values $< .05$ were considered statistically significant.

Of the 406 patients included, 201 (49.5%) received neoadjuvant chemotherapy, and 205 (50.5%) received an adjuvant TA regimen. Patients with the HER2+ and TNBC subtypes showed significantly higher pCR rates than patients with luminal types ($P < .05$). In general population, the neoadjuvant and adjuvant chemotherapy groups showed little survival variance (HR=1.15, 95% confidence interval (CI) .69–1.91, P=.60). In luminal B-like patients, neoadjuvant chemotherapy led to worse overall survival (OS) than adjuvant therapy (HR=2.92, 95% CI 1.20 to 8.31, P=.02). In patients with the HER2+ subtype, neoadjuvant treatment corresponded to better OS (HR=.10, 95%CI .02–.58, P=.01). In contrast, patients with luminal A-like (HR=1.14, 95%CI .53–2.43, P=.74) and TNBC disease (HR=1.00, 95%CI .27–3.73, P=>.99) who underwent neoadjuvant chemotherapy showed equivalent OS when compared to patients undergoing adjuvant therapy.

Neoadjuvant versus adjuvant chemotherapy results in a disparate impact on overall survival among patients with variant subtype breast cancer. When neoadjuvant chemotherapy was given, luminal B-like patients showed worse outcome, while patients with HER2+ disease had better OS. Prospective studies are necessary to determine and optimize the timing of chemotherapy for breast cancers with different molecular backgrounds.

Abbreviations: AC = adjuvant chemotherapy, CI = confidence interval, EBCTCG = Early Breast Cancer Trialists' Collaborative Group, FISH = fluorescence in situ hybridization, HR = hazard ratio, NAC = neoadjuvant chemotherapy, OS = overall survival, pCR = pathological complete response, TA = taxane and anthracycline (docetaxel and epirubicin), TNBC = triple-negative breast cancer.

Keywords: breast neoplasms, neoadjuvant therapy, triple-negative breast neoplasms, tumor subtype

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1. Introduction

Breast cancer is the most common maliganancy and the second death cause in women worldwide.[1] In spite of the rapid evolution of the theory and practice of comprehensive treatment,[2,3] chemotherapy still plays a very important role in the cure of high-risk nonmetastatic breast cancer. A meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated that adjuvant chemotherapy (AC) reduced the risk of death by at least 15%, regardless of age and hormone receptor status.[4] Chemotherapy administered preoperatively, known as neoadjuvant chemotherapy (NAC), was initially used only for locally advanced breast cancer but has become widely accepted as the treatment of choice for patients with operable disease for improving surgical options and defining responses.[2–6] However, data from randomized clinical trials and meta-analyses have suggested that NAC is equivalent to AC in terms of overall patient survival,[5–11] which are inconsistent with the hypothesis that preoperative NAC might act as advantageous treatment by reducing cell growth of "micro-metastases" and improving survival by preclinical animal models.[12,13] What was the science behind the gap of the laboratory and clinical data? Many scientists hypothesized that unselected population might be the main reason. In Fisher's animal experiment, the "breast cancer" used in the laboratory were obtained from spontaneous mouse mammary models which were confirmed as biological unique. On the contrary, the subsequent clinical trials consist of mixed subtypes of breast cancer that are highly heterogeneous in their chemo-sensitivity, and biological nature,[14–16] therefore may compromise the survival benefit in some specific population.

In this retrospective study, we analyzed a cohort of patients receiving neoadjuvant or adjuvant taxane and anthracycline-based (TA) regimens. All patients were categorized into the luminal A-like, luminal B-like, HER2+, and triple-negative breast cancer (TNBC) subtypes using immunohistochemical tests. The overall survival (OS) between the NAC and AC groups was compared according to breast cancer subtypes.

2. Methods

2.1. Patients

This retrospective study was approved by the Ethics Committee of Peking University People's Hospital prior to commencement. The written and informed consent of patients was not required. To identify all patients with a diagnosis of stage II and III invasive breast cancer who received NAC or AC, the surgical database was queried from January 1, 2000, to December 31, 2008. We included all consecutive patients meeting the following inclusion/exclusion criteria. The inclusion criteria consisted of patients who received a taxane and anthracycline combination treatment regimen and patients who had not previously received any chemotherapy, endocrine therapy, target therapy, or radiation therapy. The exclusion criteria consisted of inflammatory breast cancer and HER2+ patients who received trastuzumab. We identified 406 patients with stage II and III breast cancer out of 1531 cases in the database (Fig. 1). Patients were divided according to administration of neoadjuvant or adjuvant TA (docetaxel and epirubicin) chemotherapy.

The specific regimen was the concurrent use of docetaxel and epirubicin. Epirubicin was given at a dose of 75 mg/m^2, and docetaxel by 75 mg/m^2 every 3 weeks. The standard 3-day course of steroids pre- and postmedication was used. G-CSF was given if grade 3 to 4 nonhematological toxicity or febrile neutropenia had developed. The supportive treatment protocol was the same between NAC and AC patients. Around 85% of patients in NAC group received 4 cycles of chemotherapy in the neoadjuvant setting, and followed by 2 to 6 cycles of chemotherapy after surgery. In the AC group, most of patients received 6 cycles of chemotherapy.

2.2. Pathologic assessment

Histological diagnosis, ER status, PR status, HER2 status, and Ki67 indices were determined by standard immunohistochemical methods. Tumors with <1% positive cells were considered to have a negative receptor status. HER2 status was confirmed by fluorescence in situ hybridization (FISH) if 2+ immunohistochemical staining was present. A Ki67 index higher than 20% was defined as Ki67-positive. The immunohistochemical subtypes were defined as follows: luminal A-like, ER+/PR+/HER2-/Ki67-; luminal B-like, ER+/PR+/HER2+ or Ki67+; HER2+, ER-/PR-/HER2+; and TNBC, ER-/PR-/HER2-. Pathological complete response (pCR) was defined as the absence of invasive breast cancer both in the breast and lymph nodes upon final pathologic assessment.

2.3. Statistical analysis

The primary endpoint of this study was OS, which was defined as the time from treatment to the date of death due to any cause. Survivors were censored at the date of the last follow-up. The distributions of clinical characteristics across different chemotherapy groups were compared using Fisher's exact test or analysis of variance (ANOVA) as appropriate. The OS within the various groups was estimated using the Kaplan-Meier method and compared by log-rank test. To identify the correlation between chemotherapy timing and OS in various subtypes while adjusting for confounding factors including age, T stage, N stage, and TNM stage, a Cox proportional hazard model was fitted by a backward stepwise (likelihood ratio) selection method. P values $< .05$ were considered statistically significant. All statistical calculation was performed using PASW statistics version 18 (IBM, NY).

3. Results

During the study period from 2000 to 2008, 406 patients were identified with stage II and III breast cancer and were treated with at least 4 cycles of NAC or AC. Patient and tumor characteristics are listed in Table 1. Of the 406 patients, 201 (49.5%) received NAC, and 205 (50.5%) received an adjuvant TA regimen. The mean follow-up time was 6.5 years and did not differ between the 2 groups.

The 2 groups also did not differ with regard to patient age, surgical type choice, or histological type. However, patients who received NAC showed larger tumor sizes ($P < .001$) (T stage) and more axillary lymph nodes involvement ($P = .003$) (N stage).

Among the patients undergoing NAC, the pCR rate was 12.9% (26/201) in total and 7%, 14%, 33.3%, and 19.4% for the luminal A-like, luminal B-like, HER2+ and TNBC subtypes, respectively (Fig. 2). HER2+ and TNBC patients showed significantly higher rates of pCR than those of luminal types ($P < .05$).

In general, univariate analyses did not reveal significantly different OS between the NAC and AC treatment groups (HR = 1.15, 95% confidence interval [CI] .69–1.91, $P = .60$). Similarly, there was no statistically significant difference between the 2 arms

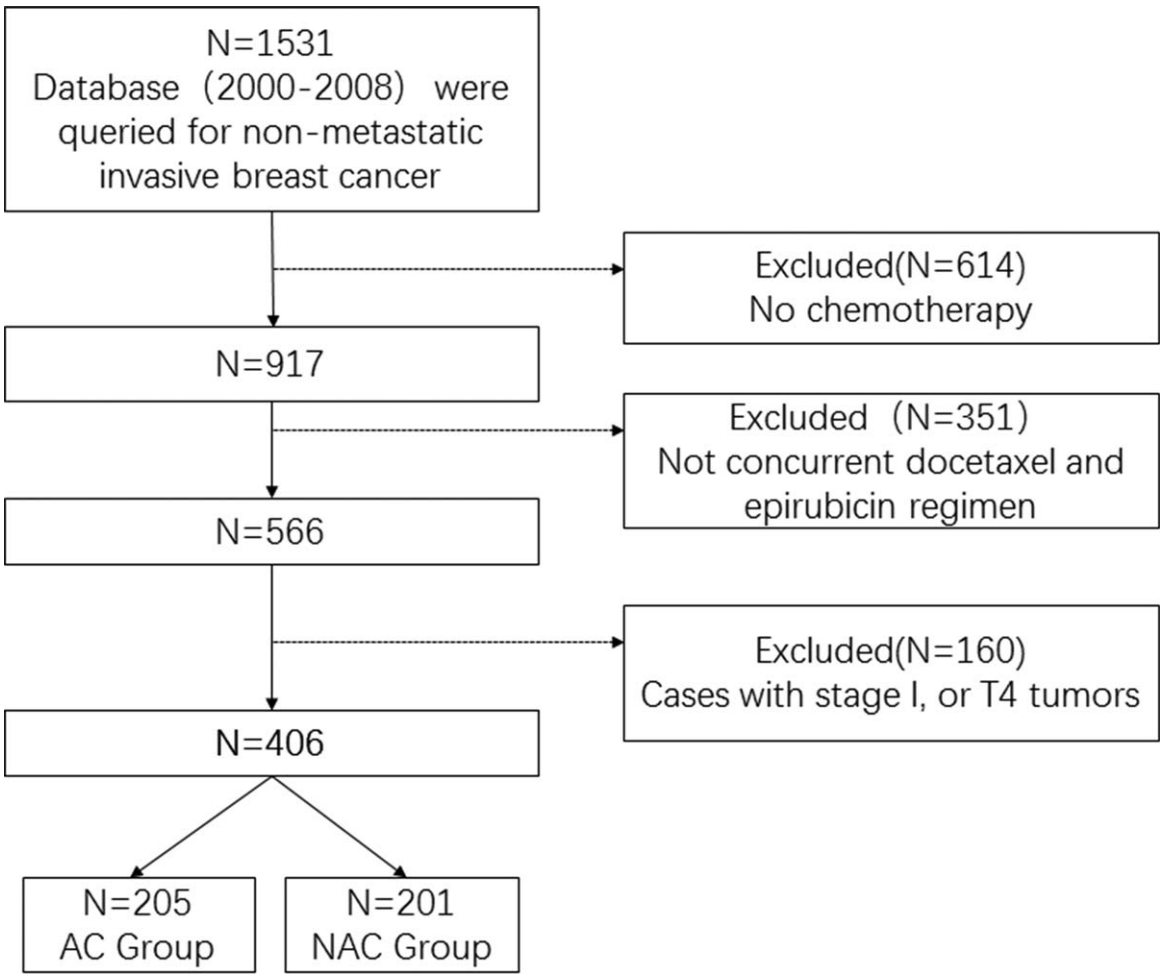

Figure 1. Flowchart of selection of patients.

Table 1

Clinical and histological characteristics of 406 patients.

		NAC (n=201)	AC (n=205)	χ^2	*P*
Age	≤50	96 (47%)	116(53%)	1.417	.234
	>50	105(53%)	89(47%)		
T, cm	≤2	19(9%)	25(12%)	59.581	.000
	2~5	118(59%)	174(85%)		
	>5	64(32%)	6(3%)		
LN	Positive	92(46%)	64(31%)	9.083	.003
	Negative	109(54%)	141(69%)		
Histological type	Invasive ductal	153(76%)	164(80%)	1.361	.506
	Invasive Lobular	27(13%)	26(13%)		
	Unknown/ other	21(10%)	15(7%)		
Molecular subtype	Luminal A like	100(50%)	69(34%)	17.450	.001
	Luminal B like	50(25%)	90(44%)		
	HER2+	15(7%)	15(7%)		
	Triple negative	36(18%)	31(15%)		
Surgical type	Modified mastectomy	159(79%)	141(69%)	.525	.469
	Breast Conserving surgery	42(21%)	64(31%)		
Chemothreapy cycles		7.8(5.2–8.8)	6(5.8–6.5)		.028
Hormone therapy	Yes	152(76%)	148(72%)	.618	.432
	No	49(24%)	57(28%)		

AC=adjuvant chemotherapy, LN=lymph node status, NAC=neoadjuvant chemotherapy.

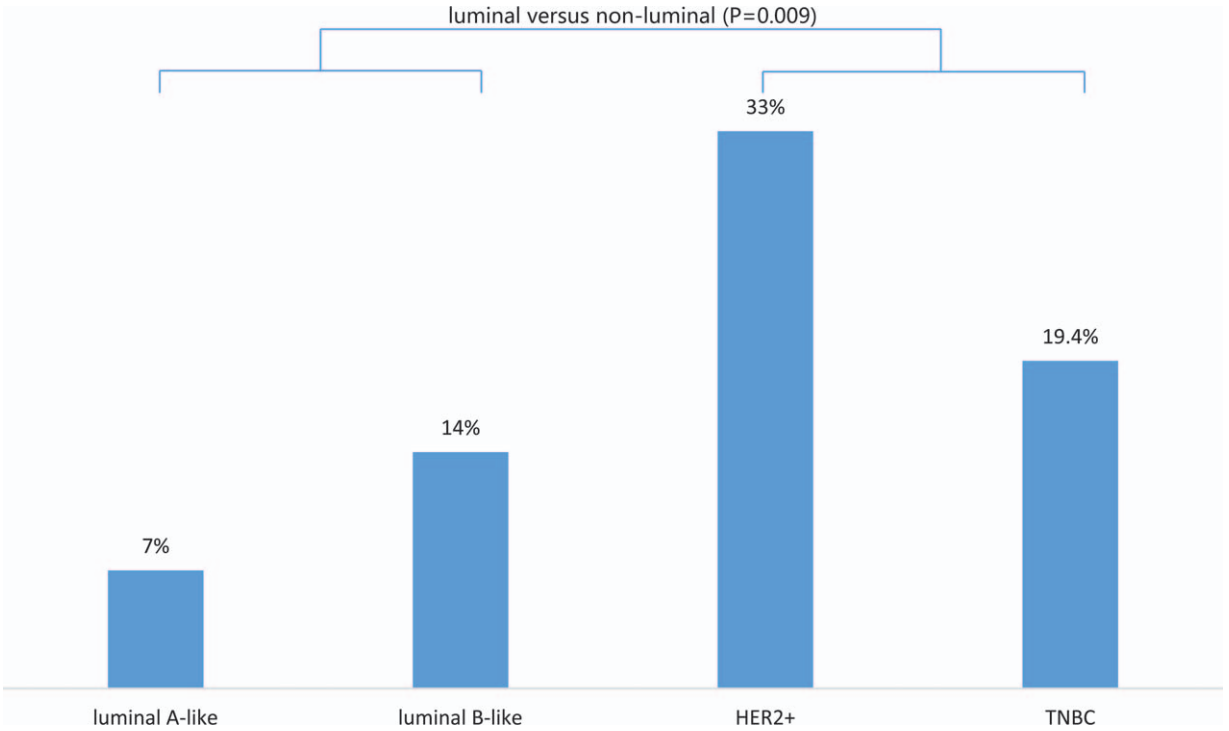

Figure 2. pCR rate in patients receiving neoadjuvant chemotherapy with different subtypes. pCR = pathological complete response.

among patients with luminal A-like or TNBC disease (for luminal A-like, HR = 1.14, 95% CI .53–2.43, $P = .74$; for TNBC, HR = 1.00, 95% CI .27–3.73, $P > .99$). In the luminal B-like subtype, patients receiving NAC showed a worse OS (HR = 2.92, 95% CI 1.20–8.31, $P = .02$), while those with HER2+ disease benefited from NAC (HR = .10, 95% CI .02–.58, $P = .01$). Figure 3 illustrates the survival curves for the NAC and AC treatment groups based on disease subtype. No significant difference of OS was shown in variant age, tumor size, lymph node metastasis, ER and HER2 status (Fig. 4).

In the luminal B-like group, a multivariable Cox regression analysis was used to evaluate the association between death risk and factors related to survival including chemotherapy timing, age, T stage, N stage and TNM stage. We found that the choice of NAC ($P = .035$) and advanced TNM stage ($P = .001$) were independent negative predictive factors for OS. For the HER2+ subtype, the number of cases was too small to fit any model.

We also analyzed the OS benefit between patients achieved pCR or non-pCR in the neo-adjuvant setting and patients receiving adjuvant chemotherapy in each subtype (Fig. 5). In the luminal B-like group, OS for patients receiving adjuvant therapy was prolonged compared with patients who received neo-adjuvant chemotherapy and had residual disease following treatment (HR = .29, 95% CI .09–.67, $P = .006$), but was not significantly difference compared with those receiving neo-adjuvant therapy with pCR (HR = 2.95, 95% CI .18–48.50, $P = .45$). In the HER2+ group, the sample size was too small to detect an OS difference among neoadjuvant with pCR, non-pCR, and adjuvant groups with interpretable significance.

4. Discussion

The results of this analysis of a consecutive cohort of women with stage II and III breast cancer showed that the selection of chemotherapy timing had a different impact on OS among patients with varying subtypes of disease. For instance, compared with AC treatment, NAC treatment might result in worse survival for patients with luminal B disease but might correlate with better OS for HER2+ patients. Moreover, multivariate analyses revealed that chemotherapy timing was an independent risk factor for long-term survival in patients with the luminal B subtype.

The potential survival advantage of moving chemotherapy from after surgery to before surgery was first discovered in animal studies. In these studies, preoperative cytotoxic therapy inhibited the accelerated growth of distant metastases after removal of the primary tumor and consequently improved long-term outcomes in mice.[12,13] However, randomized trials conducted in the 1980s and 1990s comparing the same regimens failed to confirm this concept and demonstrated similar disease recurrence and death risk in patients treated with pre- or postoperative chemotherapy.[5–11] Some researchers have ascribed this failure to translate the survival benefit observed in animal models to inadequate patient selection in previous studies. This point is best illustrated with the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 study.[5,7] Despite no significant survival difference between the NAC and AC treatment groups, this large prospective trial revealed that, compared with standard AC, there was an OS trend in favour of NAC in women younger than 50 years old; conversely, there was a trend in favour of AC in women ≥ 50 years old at entry. The authors considered that one possible explanation for this treatment-age interaction could be that older women are more likely to be hormone receptor-positive, which correlates with worse chemosensitivity. Many studies have observed that hormone receptor-positive patients (luminal subtypes) have lower pCR rates in NAC settings compared to patients with HER2+ and TNBC subtypes.[16–19]

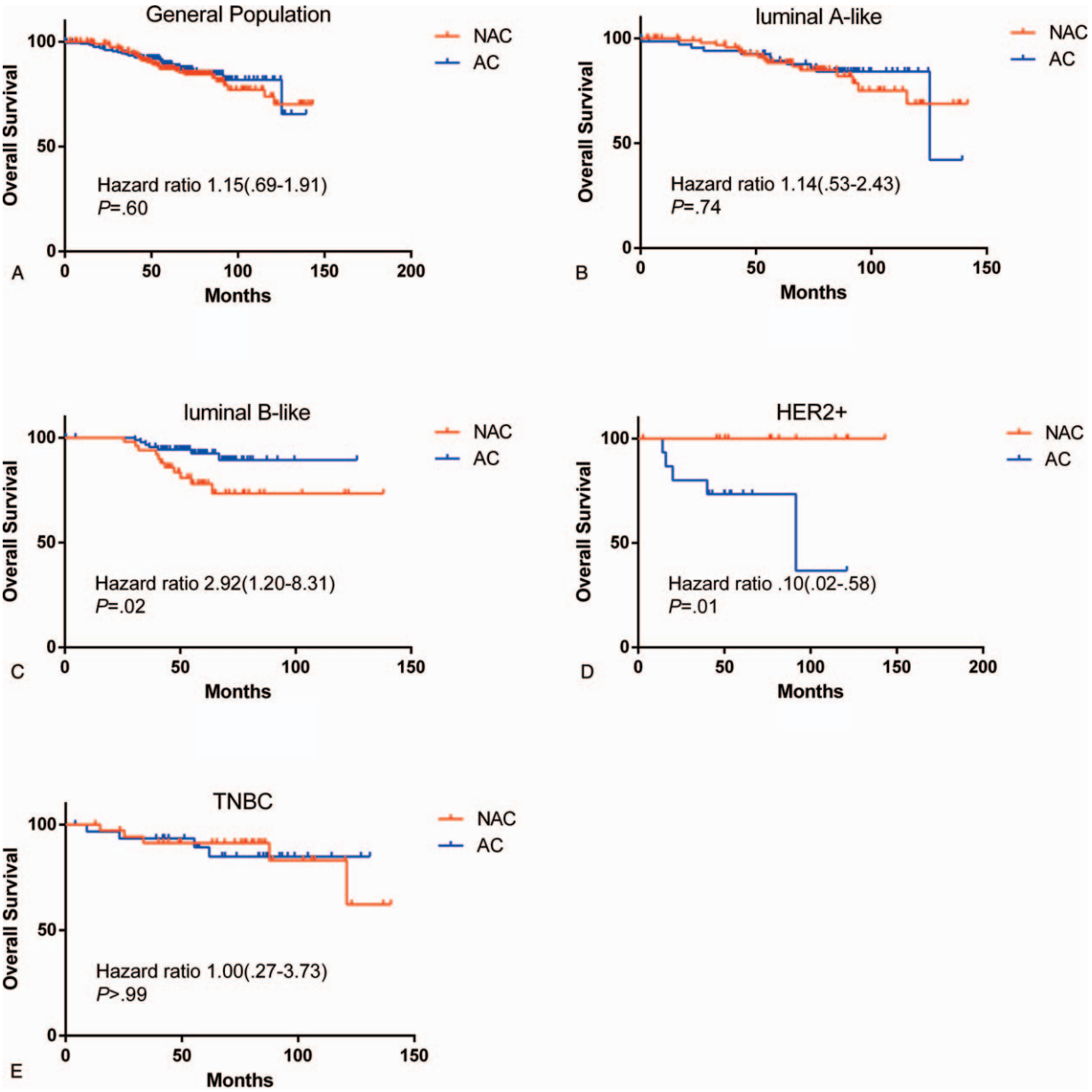

Figure 3. Overall survival comparing patients with different subtypes according to administration of neoadjuvant chemotherapy (NAC), or adjuvant chemotherapy (AC). A = general population, AC = adjuvant chemotherapy, B = luminal A-like, C = luminal B-like, D = HER2+, E = TNBC, NAC = neoadjuvant chemotherapy.

The current study revealed similar results in patients with luminal A like disease that showed relatively low chemosensitivity to NAC.

The most important finding of this study was that the luminal B-like subgroup, defined as ER+/PR+ with either HER2+ or a high Ki67 index, showed moderate sensitivity to the TA regimen. Patients with luminal B disease showed a worse outcome if they received chemotherapy before surgery especially in the majority of the patients (86%) who did not achieve pCR. Luminal B-like group is a mixture of HER2+ and Ki67 high, when analysing them separately, they showed the same worse survival trend in NAC group (HR = 3.43, 95%CI 1.44–13.02, $P = .009$ for luminal B-like Ki67 high; HR = 7.22, 95%CI .45–115.5, $P = .16$ for luminal B-like HER2+. Detailed data not shown). This survival disadvantage related to preoperative chemotherapy might be explained by a "delay effect" propagated through postponing effective surgery and relatively effective endocrine therapy by at least 3 months in some patients. Unlike luminal B-like disease, luminal A-like breast cancer carries a better natural prognosis, and patients are less likely to develop relapses and metastases. Hence, the "delay effect" may be minimized and masked in this subtype. HER2+ disease and TNBC are more sensitive to taxane and anthracycline-based regimens despite their aggressive biological nature.[13] In HER2+ patients, NAC treatment appeared to provide a greater survival benefit compared with AC treatment, which is consistent with other studies.[20] However, it is noteworthy that the total number of patients with this subtype was small, making this conclusion less durable. Moreover, the regimen for chemotherapy did not include trastuzumab, which might be less effective for HER2+ patients and is not a standard of care today.[21] Hence, our results in HER2+ patients should be cautiously clarified by current practice.

Subgroup	No of Patient	AC *No of events(%)*	NAC	Hazard Ratio (95%CI)	P Value
Overall	406	205(15.6)	201(15.9)	1.146 (0.688-1.910)	0.601
Age					
≤50	212	116(12.9)	96(15.6)	1.212 (0.592-2.493)	0.597
> 50	194	89(13.5)	105(16.2)	1.080 (0.518-2.253)	0.837
T					
≤2cm	44	25(12)	19(10.5)	0.931 (0.158-5.512)	0.938
2-5cm	292	174(13.8)	118(14.4)	0.960 (0.517-1.782)	0.897
> 5cm	70	6(0)	64(20.3)	2.970 (0.349-25.220)	0.322
LN					
Negative	249	141(11.3)	108(12)	0.954 (0.459-1.980)	0.899
Positive	157	64(20.3)	93(33.3)	1.275 (0.616-2.620)	0.519
HR					
Negative	78	46(19.6)	32(9.4)	0.452 (0.155-1.535)	0.221
Positive	328	159(11.3)	169(17.2)	1.448 (0.814-2.560)	0.212
HER2					
Negative	346	167(12.6)	179(16.8)	1.306 (0.754-2.262)	0.344
Positive	60	38(15.8)	22(9)	0.506 (0.131-2.218)	0.393

Figure 4. Hazard ratio for the overall survival in traditional prognostic subgroups. AC = adjuvant chemotherapy, NAC = neoadjuvant chemotherapy.

TNBC is a unique subtype, it was reported that, compared with non-TNBC patients, patients with TNBC had significantly higher pCR rates but decreased 3-year progression-free survival and 3-year OS.[22] Further analysis showed that patients with pCR had excellent survival, whereas, compared with non-TNBC patients, TNBC patients with residual disease after NAC had significantly worse survival, particularly in the first 3 years.[23] In 2010, Kennedy et al.[24] reported a retrospective study investigating the differences in OS of patients with triple-negative disease according to the administration of NAC or AC. In this study more patients with prognostic poor criteria like increased tumor size (T2, T3, T4), nodal positivity, advanced stage (IIB, III) and

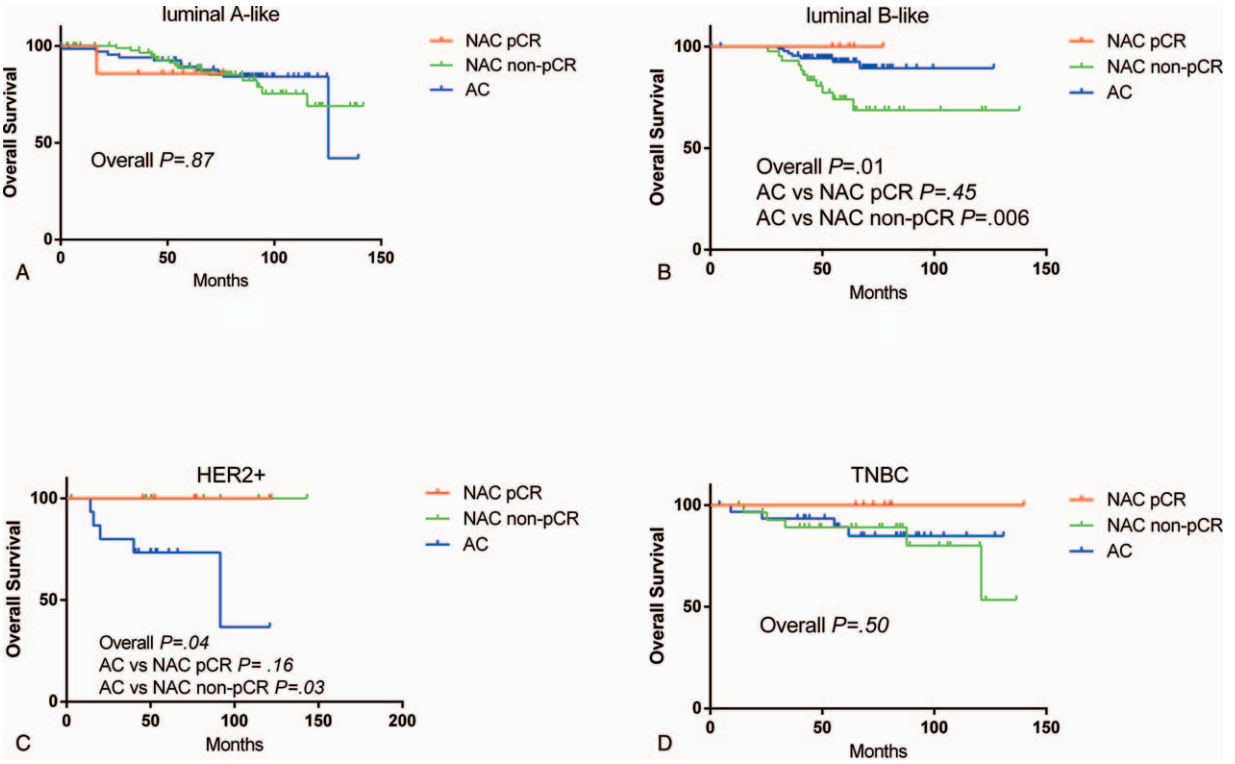

Figure 5. Overall survival comparing patients with different subtypes according to administration of neoadjuvant chemotherapy with complete pathologic response (NAC pCR), neoadjuvant chemotherapy with residual disease (NAC non-pCR), or adjuvant chemotherapy (AC). A = luminal A-like, AC = adjuvant chemotherapy, B = luminal B-like, C = HER2+, D = TNBC, pCR = pathological complete response.

young age were included in neoadjuvant chemotherapy group. However, multivariate models were used to control the unbalanced covariates of the groups. The results of this study showed that, compared with women with TNBC who received NAC, those who underwent AC were 52% less likely to die overall.[24] Further analysis revealed that patients unlikely to achieve pCR during NAC would have even worse survival than patients who received AC.[25] Recently, MD Anderson Cancer Center analyzed another cohort consisting of 319 patients with stage I and II triple-negative breast cancer.[26] Around 187 received adjuvant chemotherapy (58.6%) and 132 received neoadjuvant chemotherapy (41.4%). About 135 were BRCA positive (42.3%) and 184 were BRCA negative (57.7%). There were no significant differences between patient subgroups (neoadjuvant BRCA positive, neoadjuvant BRCA negative, adjuvant BRCA positive, and adjuvant BRCA negative) with respect to either overall survival or disease-free survival. Different from Kennedy's study, the latter study only included stage I and II patients, reported observably higher pCR rate (54%), and achieved comparable long-term outcome. We speculate that the pCR rate is another important factor impacting OS in addition to the inclusion bias of TNBC in NAC group. From the abovementioned conflicting results, we can conclude that the true effect of chemotherapy timing in this life-threatening subtype is yet to be proven.

We identified 67 patients with TNBC, 36 received NAC and had a relatively high pCR rate. These patients showed no significant difference in OS compared with 31 patients who received AC. Our results differed from Kennedy's study but were similar to MD Anderson study. The advantage of our study was that all the chemotherapy regimens were relatively homogenous (taxane and anthracycline based), while various drugs were included in the previous articles. However, the TNBC sample size was smaller than that in the previous studies. At present, there is insufficient evidence to support either of these results. One reasonable explanation for our results is that different chemotherapy timing may have little perceptible impact on survival due to the highly aggressive biological features of TNBC and poor prognosis of TNBC patients.

There are several limitations of this study. First, we were unable to provide accurate disease-free survival or breast cancer specific survival data due to database limitations. Furthermore, in retrospective research, it is difficult to control for all of the covariates affecting long-term prognosis, such as tumor size, lymph node metastasis, and clinical stage. Even though we attempted to reduce the impact of these variations by using multivariable analysis, it was difficult to eliminate all selection bias. Thirdly, it was a pity that few HER2+ patients in China received trastuzumab because it was not approved until 2008, and we could only study the impact of regular chemotherapy. If we could do the analysis today, the result might be different, and we have to separate Luminal B-like patients to HER2+ and Ki67 high group because of the different treatment. Finally, after surgery, we did not consider any preoperative response-guided chemotherapy adjustments. For instance, data from the GeparTrio trial revealed that a treatment adjustment according to patients' early responses to 2 cycles of NAC benefited patients with specific cancer subtypes.[27] In this study, because only a small number of patients received altered post-NAC chemotherapy, we did not analyze the impact of response guidance.

Despite these limitations, after controlling for confounding variables, the current study demonstrates that chemotherapy timing has different impacts on OS for the 4 different breast cancer subtypes; in particular, patients with luminal B-like disease undergoing NAC might be more likely to die than those undergoing AC. These results suggest that chemotherapy timing should be tailored according to biological subtype. Prospective, randomized trials are imperative to determine the best approaches for unique breast cancer subtypes.

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