Original Article

Clinical and pathological response to neoadjuvant chemotherapy with different chemotherapy regimens predicts the outcome of locally advanced breast cancer

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Background: This retrospective analysis was designed to research whether clinical response partial response (PR)/complete response (CR) and pathological response (PCR) to neoadjuvant chemotherapy can translate into prognosis benefit pathological response in patients with locally advanced breast cancer and whether different chemotherapy regimens will influence the outcomes.

Methods: One hundred and thirty-five patients with breast cancer patients who received neoadjuvant chemotherapy were included in the retrospective analysis. Patients were followed up strictly. Overall survival (OS) was evaluated by the Kaplan-Meier analysis. The comparison of the clinical and pathological characteristics and recurrence was performed using the carried out by chi-squared and Fisher's exact tests. Univariate and multivariate analyses were performed by the Cox regression analysis.

Results: Clinical response was strongly correlated with lymph nodes status (P=0.032). The OS comparison of pathological response between the pCR group and non-pCR groups did not exhibit statistically significant differences (P=0.400). A similar non-significant response result was observed in the comparison of clinical response between the PR/CR and SD/PD groups group (P=0.108). Univariate and multivariate analyses did not support clinical response (P=0.156 P=0.095 respectively) or pathological response (P=0.600 P=0.144 respectively) as the predictors of prognosis. There were no significant differences in either the comparison of the clinical response group it seems no statistically significance (P=0.496) or the comparison of the pathological response group (P=0.460). OS analyses across different neoadjuvant chemotherapy regimens demonstrated no significant differences (P=0.307). In the PR/CR and PD/SD comparison of every single regimen, there were no significant differences. However, for patients with PR/CR patients from the comparison of five regimens, namely, TAC, FAC, AC-T, AT and TCBP demonstrated a significant difference (P=0.022). In the group of patients with luminal A breast cancer, the result of the Fisher's exact test approached significant (P=0.059).

Conclusions: Neither PR/CR nor pCR can translate into long-term outcome benefit. PR/CR and PCR are not independent predictors in patients with advanced breast cancer. Patients who received a taxane + anthracycline regimen exhibited a higher recurrence rate than any other regimens, especially those patients with luminal A breast cancer.

Keywords: Response; neoadjuvant chemotherapy; breast cancer; outcome

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Introduction

Breast cancer is the most common female malignant tumor worldwide (1,2). Although a combination of topical and systemic treatments provides better prognosis than previously (3), patients with advanced breast cancer patients even if it is locally advanced breast cancer (4) continue to have poor outcomes. The development of novel methods for predicting responses and outcomes is necessary.

Neoadjuvant chemotherapy is a conventional treatment for locally advanced breast cancer (5,6). This kind of treatment plays a significant role in reducing staging and breast-conserving and even axillary-conserving treatment (7-10). Whether the clinical response (CR) or pathological response (PR) to neoadjuvant chemotherapy can translate into prognostic benefit remains controversial. Romero (11) and his colleagues reported that the pathological assessment (pCR) or clinical assessment (PR/CR) of tumor response might signify the prognosis in locally advanced breast cancer patients. Asaoka (12) carried out a retrospective analysis of 1,599 patients with breast cancer who were treated with neoadjuvant chemotherapy. The results showed that patients achieving pCR to neoadjuvant chemotherapy had excellent prognosis. Cancer recurrence was predicted by high clinical staging, large tumor size, lymph node metastasis and human epidermal growth factor receptor-2-positive (HER2+) status at baseline. Similar results were observed by LeVasseur *et al.* in their retrospective analysis of 267 patients who had received neoadjuvant chemotherapy (13). Their research showed that five-year relapse-free survival and breast cancer-specific survival were higher in the pCR group compared to the non-pCR group. However, in the subtypes analysis, they reported that patients with triple negative breast cancer who achieved pCR improved breast cancer-specific survival and relapse-free survival significantly, but a non-significant trend was seen in the patients with human epidermal growth factor receptor-2-positive (HER-2+) and estrogen receptor-positive (ER+) subtypes. Chen (14) and his colleagues retrospectively analyzed the outcomes of 569 patients with locally advanced breast cancer who had received neoadjuvant chemotherapy before surgery. They showed that the value of clinical and pathological responses across different breast cancer subtypes: is correlated to survival in patients with ER+/progesterone receptor (PR)+ breast cancer rather than ER/PR- locally advanced breast cancer. However, different results were reported by Glück *et al.* (15), who used the BluePrint and MammaPrint systems to divide patients into different recurrence risks groups across different subtypes. The researchers highlighted the finding that patients with luminal A breast cancer who had been designated as low risk with MammaPrint, had a good prognosis and did not seem to benefit from chemotherapy, but a marked benefit in response survival to neoadjuvant chemotherapy was observed in patients with HER-2+ and triple negative breast cancer.

Three well-known meta-analyses were carried out to address the controversy of whether CR/PR or pCR to neoadjuvant chemotherapy results in better outcomes. The CTNeoBC pooled analysis of 12 identified international trials and 11955 patients was carried out by the US Food and Drug Administration and was published in The Lancet by Cortazar *et al.* (16). The results highlighted that tumor eradication from the breast and lymph nodes was associated with improved event-free survival (EFS) and overall survival (OS) than tumour eradication from the breast alone. In further analyses of the ypT0/is ypN0 group, the researchers found the association between pCR and outcomes were the strongest in patients with triple negative breast cancer and patients with HER-2+ and ER- breast cancer who had received trastuzumab treatment. However, two other meta-analyses showed a different conclusion with the CTNeoBC analysis. Korn (17) demonstrated that pCR could not be a trial-level surrogate for EFS or OS, nor is there evidence that pCR could be used reliably to screen out non-promising agents from further drug development. A similar conclusion was obtained by Berruti *et al.* (18) who analyzed 29 heterogeneous neoadjuvant trials that included 14,641 patients. The results of this meta-analysis did not support the use of pCR as a surrogate end point for DFS and OS in patients with breast cancer. However, pCR may potentially meet the criterion of surrogacy with specific systemic therapies.

Based on the current research, we carried out this retrospective analysis to determine whether the PR/CR and pCR to neoadjuvant chemotherapy can translate into prognostic benefits and also research whether the administration of different chemotherapy regimens influences outcomes. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-20-209).

Methods

Patients and ethics statement

A total 300 Chinese women who was diagnosed with

invasive breast cancer through core needle biopsy and the node status was assessed through fine needle aspiration before neoadjuvant chemotherapy were initially enrolled into this study. Among these, 67 (22.3%) patients were treated before or have been treated elsewhere, 52 (17.3%) patients' treatment information were incomplete, 19 (6.3%) patients' contact information they registered was unavailable, 17 (5.7%) patients rejected follow-up, 10 (3.3%) did not underwent regular follow-up were excluded. The rest 135 (45%) patients were included in the present study.

A retrospective analysis was carried including 135 patients diagnosed with locally advanced breast cancer, who were included in a prospective database of the Third Affiliated Hospital of Kunming Medical University, Yunnan Cancer Hospital from January 2012 to December 2015. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of the Third Affiliated Hospital of Kunming Medical University, Yunnan Cancer Hospital (No.: QT 202003) and informed consent was taken from all the patients.

Neoadjuvant chemotherapy treatment

The neoadjuvant chemotherapy strategies were classified into six subgroups as follows:

(I) Thirty patients received 4–6 cycles of an anthracycline + taxane + cyclophosphamide (TAC) regimen administered intravenously (IV) every three weeks as docetaxel 75 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, and cyclophosphamide 500 mg/m^2 on day 1.

(II) Fifteen patients received 2–5 cycles of a 5-fluorouracil + anthracycline + cyclophosphamide (FAC) regimen administered IV every three weeks as 5-fluorouracil 600 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, and cyclophosphamide 500 mg/m^2 on day 1.

(III) Twenty-five patients were treated with an anthracycline + cyclophosphamide sequential taxane (ACT) regimen administered IV as four cycles of doxorubicin 50 mg/m^2 on day 1 and cyclophosphamide 500 mg/m^2 on day 1 every two or three weeks followed by four cycles of docetaxel 75 mg/m^2 on day 1 every two or three weeks.

(IV) Thirty-eight patients received four cycles of an anthracycline + taxane (AT) regimen every three weeks, administered IV as docetaxel 75 mg/m^2 on day 1 and doxorubicin 50 mg/m^2 on day 1.

(V) Eleven patients received four cycles of a carboplatin + taxane (TCBP) regimen every three weeks, administered IV as docetaxel 75 mg/m^2 on day 1 and carboplatin AUC 6 on day 1.

(VI) Sixteen patients received another neoadjuvant chemotherapy regimen.

Clinical and pathological response

Clinical and pathological responses to neoadjuvant chemotherapy were assessed based on the clinical and pathological data. The clinical response to neoadjuvant chemotherapy was evaluated by MRI and ultrasound examinations and in accordance with the response evaluation criteria in solid tumors RECIST 1.1 version (19,20). The pCR after neoadjuvant chemotherapy was defined as eradication of carcinoma from both the breast and lymph nodes.

Follow-up

After systemic treatment of surgery, chemotherapy, and radiotherapy, all of the patients underwent regular follow-up including a tumor marker test, ultrasonography examination, and chest X-ray at every 2–3 months in the first year after surgery and every 6 months during the following 5 years and then every 12 months thereafter. Radiographs with a molybdenum target tube, breast MRI an investigation, the isotope bone scan and curettage, and general CT scans were carried out once a year (21). The results and events of all of the patients were recorded in the database.

Statistical analysis

The comparisons of clinical and pathological characteristics and recurrence were made using the chi-squared test. Fisher's exact test was used when the cell expectation was less than 6. The Student's *t*-test was used to analyze the differences between the variables reported as continuous data. Kaplan-Meier analysis was used for survival analysis, and group results were compared using the log rank test. Univariate and multivariate analyses were performed using the Cox regression analysis. All of the statistical analyses were performed with SPSS22.0 (Chicago, IL, USA) and Graphpad Prism 6.0. A P value of less than 0.05 was considered to be statistically significant.

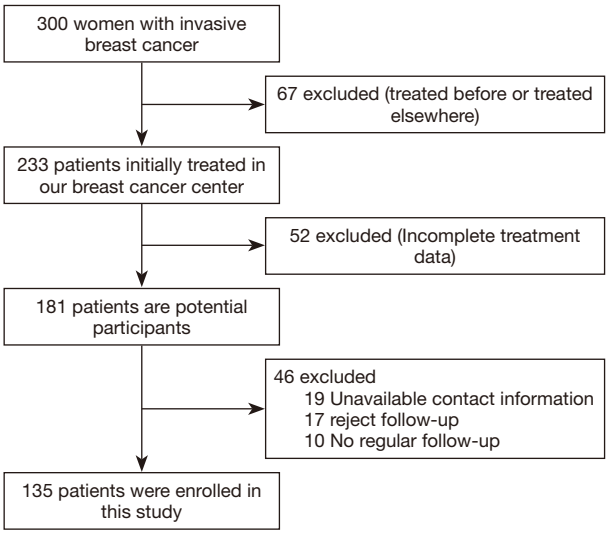

Figure 1 The flow diagram of case screen.

Results

Patient and cancer characteristics

The including of participants was exhibited in *Figure 1*. We first divided the patients into the PR + CR group and stable disease (SD) + progressive disease (PD) group according to the clinical response data. The clinical and pathological characteristics of the 135 patients with locally advanced breast cancer are summarized in *Table 1*. We analyzed the correlation across two clinical response arms at the level of age, tumor size, lymph nodes status, menstruation status, chemotherapy times, Ki67 value, and molecular subtypes. The results indicated that clinical response had a tight correlation with lymph nodes status (P=0.032). There were no significant differences in the response between age (P=0.086), tumor size (P=0.398), menstruation status (P=0.631), chemotherapy times (P=0.261), Ki67 value (P=0.992) and molecular subtypes (P=0.455).

In the further subtype analysis, we compared the clinical response in every subtype, as summarized in the *Tables S1-S4*. We found that the clinical response correlated with the lymph nodes status in the luminal B arms (P=0.045, *Table S2*). There were no significant differences in other characteristics across the subtypes There was no significant difference in other subtypes across the characteristics.

Outcomes in the different clinical and pathological response groups

After comparing the clinical and pathological characteristics, we explored whether the PR/CR and pCR to neoadjuvant chemotherapy could translate into long-term prognosis benefits. We carried out a Kaplan-Meier test for the 5-year OS analysis. The 5-year OS comparison of the pathological response between the pCR and non-pCR groups exhibited no significant differences (P=0.400, *Figure 2A*). A similar result was observed in the comparison of the clinical response between the PR/CR and SD/PD groups (P=0.108, *Figure 2B*). Then we used the Cox regression analysis to detect whether CR and PR are the independent factors influencing the prognosis. The results from the univariate and multivariate analyses did not support CR and PR as predictors of prognosis (*Table 2*). Furthermore, we researched the cancer recurrence in the patients who had shown clinical and pathological responses. In the comparison of the clinical response group there was no significant difference in cancer recurrence (P=0.496, *Table 3*), nor was there a significant result in the comparison of pathological response (P=0.460, *Table 4*). The recurrence sites of the pCR and non-pCR groups are shown in the pie chart (*Figure 2C,D*), and recurrence sites of different subtypes are shown in *Figure 2E,F,G,H*.

Long-term outcomes between different neoadjuvant chemotherapy regimens

We wanted to detect whether different neoadjuvant chemotherapy regimens exhibited different survival rates using the Kaplan-Meier analysis for 5-year OS. The results demonstrated there were no significant differences in survival between different regimens (P=0.307, *Figure 3A*). The recurrence sites of different regimens are shown in *Figure 3B,C,D,E,F,G*. We focused on those patients with clinical response PR/CR and PD/SD who received different neoadjuvant chemotherapy regimens. In the PR/CR and PD/SD comparison of every single regimen, the result showed no significant differences in survival (*Table 5*). However, for those PR/CR patients, results demonstrated a significant difference in a comparison of the regimens with P 0.022 (*Table 6*).

Table 1 Comparison of clinicopathological characteristics between CR + PR group and SD + PD group

Variables	Total (n=135)	CR + PR (n=97)	SD + PD (n=38)	Chi-square value	P value	Hazard ratio	95% CI
Age (years)				0.020	0.886	1.058	0.490–2.281
<50	83	60	23				
≥50	52	37	15				
Tumor size				2.157	0.398	NS	NS
T1–2	111	78	33				
T3	11	10	1				
T4	13	9	4				
Lymph nodes status				4.581	0.032	0.429	0.196–0.940
–	42	25	17				
+	93	72	21				
Menstruation status				0.231	0.631	0.828	0.434–1.947
Postmenopausal	49	34	15				
Premenopausal	86	63	23				
Chemotherapy times				1.266	0.261	1.824	0.633–5.250
≤4	26	21	5				
>51097633≤426215>51097633≤426215>51097633≤426215>5	109	76	33				
Ki67 value				0.000	0.992	1.004	0.437–2.307
<14	38	27	11				
≥14	93	66	27				
Molecular subtypes							
Luminal A	23	15	8	2.612	0.455	NS	NS
Luminal B	68	48	20				
HER-2 +	16	14	2				
TNBC	25	17	8				

NS, no significance; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Different treatment regimens in different subtypes

Based on the findings above, we further examined how different neoadjuvant chemotherapy regimens influenced cancer recurrence in different subtypes. We focused on comparing the five main regimens: TAC, FAC, AC-T, AT and TCBP regimens. In the group of patients with luminal A group breast cancer, results from the Fisher's exact test approached significance (P=0.059, *Table 7*). There were no significant differences in cancer recurrence among patients with luminal B breast cancer (P=0.715, *Table 8*), those with HER-2+ tumors (P>0.999, *Table 9*), or those who were treated with TNBC (P>0.999, *Table 10*).

Discussion

The correlation between the pCR to neoadjuvant chemotherapy and outcomes was first reported in the landmark National Surgical Adjuvant Breast and Bowel Project B-18 and B-27 trials (22,23). The FDA and the European Medicines Agency declared that, after accelerated

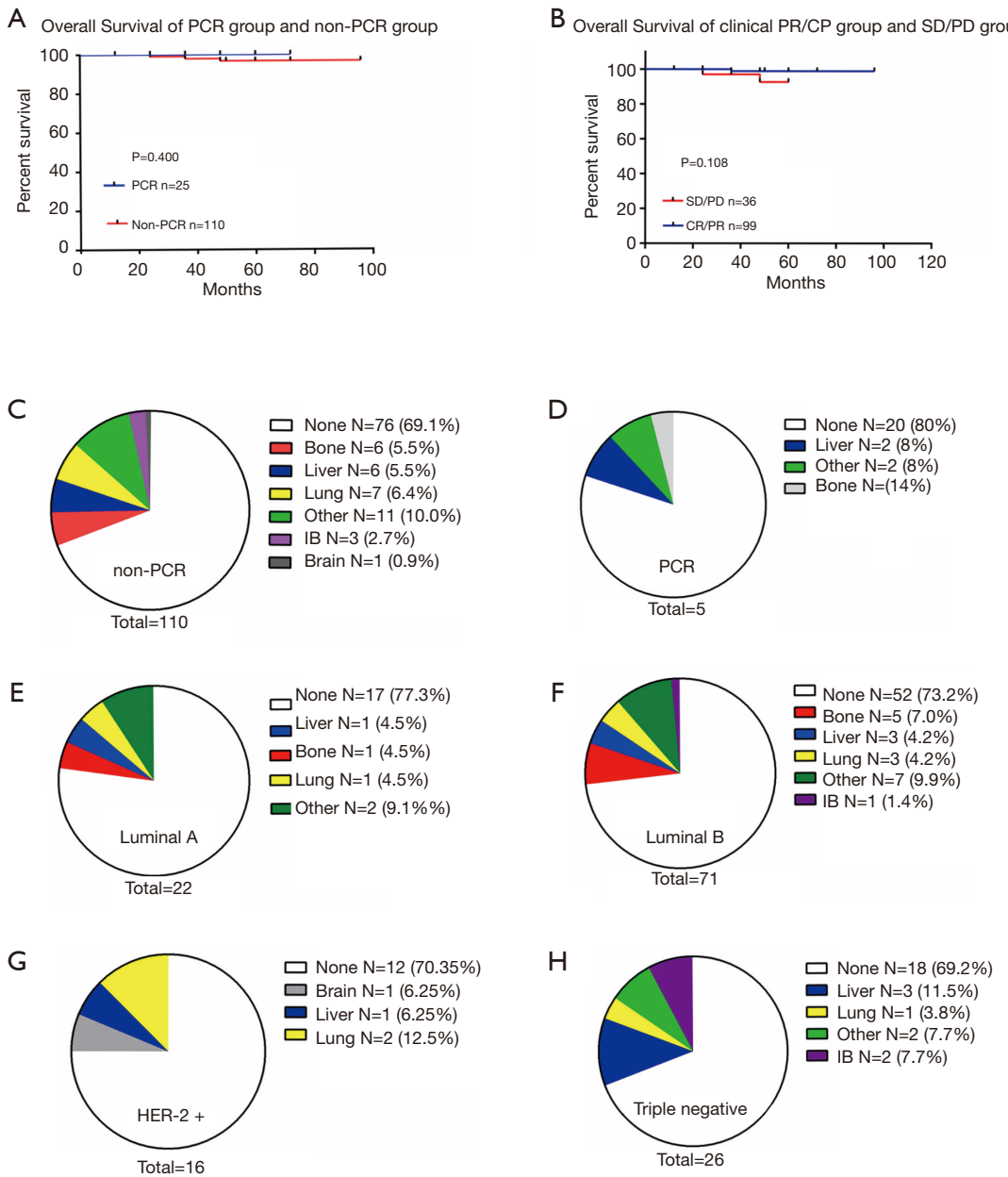

Figure 2 Overall Survival of pathology and clinical response. (A) OS analyzed by Kaplan-Meier curves for breast cancer patients with pathology PCR group (n=25) versus non-PCR group (n=110). (B) OS of patients with PR/CR group (n=99) versus SD/PD group (n=36). (C,D) Pie charts of PCR group and non-PCR group recurrent sites. (E) Recurrence pie chart of luminal A patients (n=22). (F) Recurrence pie chart of luminal B patients (n=71). (G) Recurrence pie chart of HER-2 + patients (n=16). (H) Recurrence pie chart of triple negative patients (n=26).

approval, demonstration of an improvement in OS and disease-free survival after neoadjuvant chemotherapy would be required (24,25).

In this study, we analyzed the clinical and pathological characteristics of patients and the response to neoadjuvant chemotherapy and found that the lymph nodes status correlates with response to therapy meaning patients with lymph node metastasis may obtain a better response to neoadjuvant chemotherapy. The result is similar to the finding of Caudle (26) and Tee (27). This phenomenon was

Table 2 Cox regression analysis for overall survival

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Age	0.991	0.856–1.148	0.906	0.980	0.732–1.312	0.890
Tumor invasion depth	1.790	0.488–6.567	0.380	1.861	0.460–7.531	0.384
Lymph node metastasis	35.099	NS	0.504	0.861	0.595–1.244	0.425
Menstrual status	0.886	0.080–9.777	0.922	0.648	0.013–32.352	0.828
KI67 expression	35.176	NS	0.503	NS	NS	0.983
Chemotherapy times	0.456	0.041–5.034	0.618	0.139	0.04–4.849	0.276
Pathology response to NCT (PCR)	27.818	NS	0.600	1.389	0.894–2.156	0.144
Clinical response to NCT (PR/NonPR)	35.478	0.516–62.986	0.156	12.252	0.639–274.661	0.095

NS, no significance; PCR, pathologic complete response; PR, partial response.

Table 3 The recurrence between clinical PR/CP group and SD/PD group

Events	Total (n=135)	PR/CR (n=98)	SD/PD (n=37)	Chi-square value	P value	Hazard ratio	95% CI
Recurrence	38	26	12	0.463	0.496	0.752	0.331–1.711
Non-recurrence	97	72	25				

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

Table 4 The recurrence between pathology PCR group and non-PCR group

Events	Total (n=135)	PCR (n=24)	non-PCR (n=111)	Chi-square value	P value	Hazard ratio	95% CI
Recurrence	38	5	33	0.772	0.460	0.622	0.214–1.806
Non-recurrence	97	19	78				

CI, confidence interval; PCR, pathologic complete response.

highlighted in patients with luminal B breast cancer. Breast cancer with luminal B may potentially contribute to axillary lymph node conservation and sentinel lymph node biopsy after neoadjuvant chemotherapy.

In the present study, we researched the key scientific problem of whether PR/CR and pCR to neoadjuvant chemotherapy can transfer into long-term prognosis benefits. Our research demonstrated that neither clinical response PR/CR nor pCR translated into long-term prognosis benefit. Univariate and multivariate analyses performed with the Cox regression analysis also showed that PR/CR and pCR are not the factors influencing prognosis. Our research findings differ from the findings of Romero (11), Asaoka (12), and Cortazar (16). However, our results were similar to those reported by Korn (17) and Berruti (18). It is possible that most of the clinical trials data or retrospective analyses have the sample patients from homogeneous populations such that a meaningful correlation of pCR or PR/CR between EFS or OS trial results might not have been seen. Our results also differ from those of Chen (14), although both our research and Chen's included Chinese patients. Most patients from our sample lived in Yunnan Province, an area with many ethnic minorities. This sample may have provided different outcomes than would have been observed if we had sampled Han people, who represent the largest population in China. We also noticed that some of our patients showed a clinical response PR and SD. Most of these patients had undergone surgery treatment before completion of their entire course of neoadjuvant chemotherapy and after the surgery, most of them received a different chemotherapy regimen. Switching to a different regimen may have been an important factor

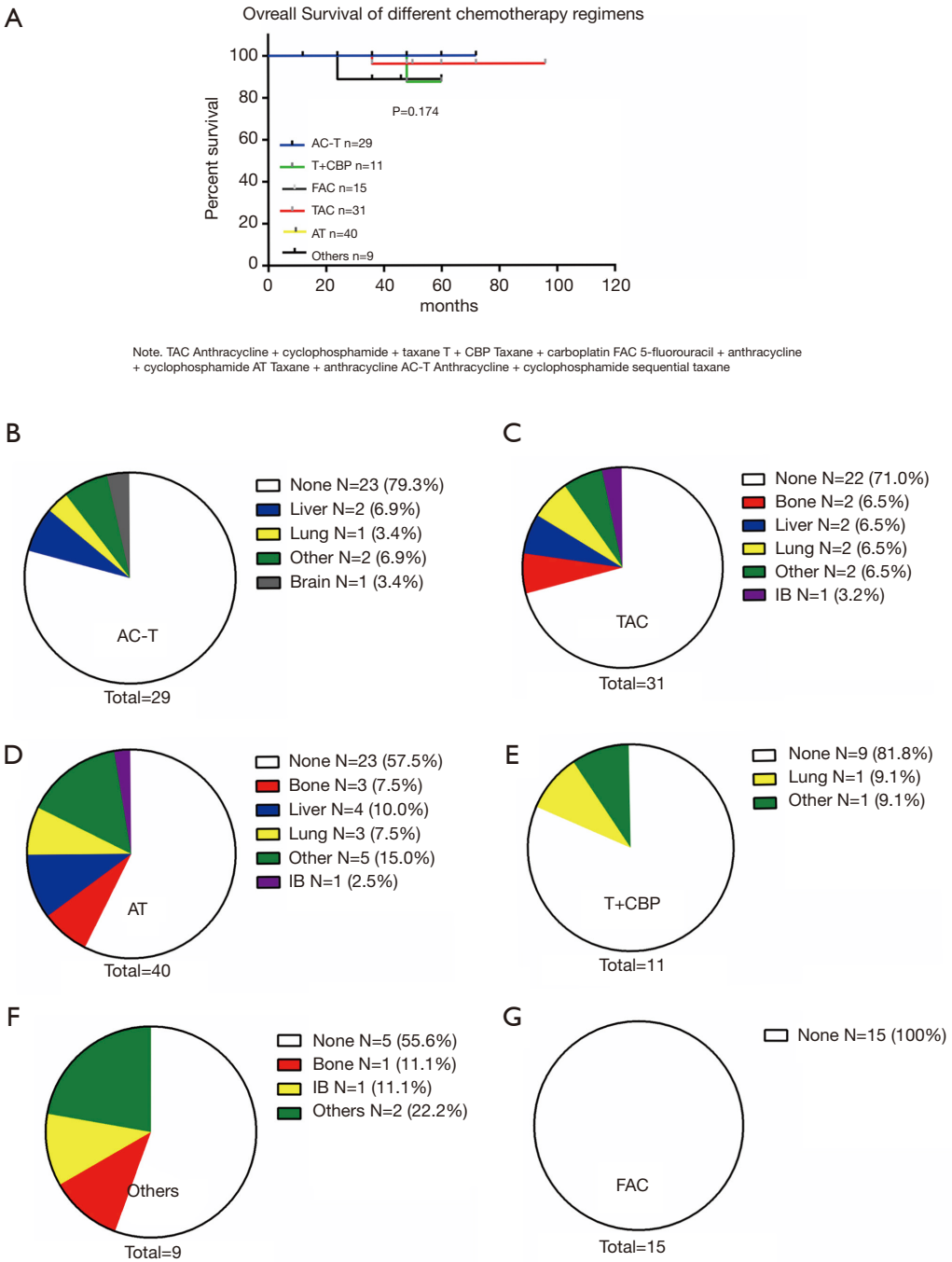

Figure 3 (A) OS analyzed by Kaplan-Meier curves for breast cancer patients with different chemotherapy regimens (anthracycline + cyclophosphamide sequential taxane n=29, anthracycline + cyclophosphamide + taxane n=31, taxane + carboplatin n=11, 5-fluorouracil + anthracycline + cyclophosphamide n=15, taxane + anthracycline n=40, others n=9). (B) Pie charts of recurrent site in patients with anthracycline + cyclophosphamide sequential taxane regimen. (C) Pie charts of recurrent site in patients with anthracycline + cyclophosphamide + taxane regimen. (D) Pie charts of recurrent site in patients with taxane + anthracycline regimen. (E) Pie charts of recurrent site in patients with taxane + carboplatin regimen. (F) Pie charts of recurrent site in patients with others regimens. (G) Pie charts of recurrent site in patients with 5-fluorouracil + anthracycline + cyclophosphamide regimen.

Table 5 Recurrence of PR/CR group comparison SD/PD group between different chemotherapy regimens

Regimens and clinical response	Total (n=135)	Recurrence (n=41)	Non-recurrence (n=94)	Chi-square value	P value	Hazard ratio	95% CI
Anthracycline + cyclophosphamide sequential taxane (n=29)				0.075	>0.999	1.389	0.131–14.779
PR/CR	23	5	18				
PD/SD	6	1	5				
Anthracycline + cyclophosphamide + taxane (n=31)				0.067	>0.999	0.778	0.115–5.246
PR/CR	25	7	18				
PD/SD	6	2	4				
Taxane + carboplatin (n=11)				4.278	0.109	NS	NS
PR/CR	7	0	7				
PD/SD	4	2	2				
5-fluorouracil + anthracycline + cyclophosphamide (n=15)				NS	NS	NS	NS
PR/CR	9	0	9				
PD/SD	6	0	6				
Taxane + anthracycline (n=40)				0.395	0.530	0.647	0.166–2.527
PR/CR	28	11	17				
PD/SD	12	6	6				
Others (n=9)				0.032	>0.999	0.750	0.032–17.507
PR/CR	4	3	1				
PD/SD	5	4	1				

NS, no significance; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

Table 6 Recurrence of PR/CR group between different chemotherapy regimens

Regimens and clinical response	Total (n=96)	Recurrence (n=26)	Non-recurrence (n=70)	Chi-square value	P value	Hazard ratio	95% CI
Anthracycline + cyclophosphamide sequential taxane	23	5	18	13.048	0.022	NS	NS
Anthracycline + cyclophosphamide + taxane	25	7	18				
Taxane + carboplatin	7	0	7				
5-fluorouracil + anthracycline + cyclophosphamide	9	0	9				
Taxane + anthracycline	28	11	17				
Others	4	3	1				

NS, no significance; CI, confidence interval; CR, complete response; PR, partial response.

Table 7 Recurrence of PR/CR group between different chemotherapy regimens of luminal A patients

Regimens and clinical response	Total (n=13)	Recurrence (n=4)	Non-recurrence (n=9)	Chi-square value	P value	Hazard ratio	95% CI
Anthracycline + cyclophosphamide sequential taxane	5	1	4	9.244	0.059	NS	NS
Anthracycline + cyclophosphamide + taxane	2	0	2				
Taxane + carboplatin	1	0	1				
5-fluorouracil + anthracycline + cyclophosphamide	2	0	2				
Taxane + anthracycline	3	3	0				

NS, no significance; CI, confidence interval; CR, complete response; PR, partial response.

Table 8 Recurrence of PR/CR group between different chemotherapy regimens of luminal B patients

Regimens and clinical response	Total (n=46)	Recurrence (n=12)	Non-recurrence (n=34)	Chi-square value	P value	Hazard ratio	95% CI
Anthracycline + cyclophosphamide sequential taxane	12	2	10	2.397	0.715	NS	NS
Anthracycline + cyclophosphamide + taxane	14	5	9				
Taxane + carboplatin	1	0	1				
5-fluorouracil + anthracycline + cyclophosphamide	3	0	3				
Taxane + anthracycline	16	5	11				

NS, no significance; CI, confidence interval; CR, complete response; PR, partial response.

Table 9 Recurrence of PR/CR group between different chemotherapy regimens of HER-2 positive patients

Regimens and clinical response	Total (n=11)	Recurrence (n=2)	Non-recurrence (n=9)	Chi-square value	P value	Hazard ratio	95% CI
Anthracycline + cyclophosphamide sequential taxane	4	1	3	2.597	>0.999	NS	NS
Anthracycline + cyclophosphamide + taxane	2	0	2				
Taxane + carboplatin	1	0	1				
5-fluorouracil + anthracycline + cyclophosphamide	2	0	2				
Taxane + anthracycline	2	1	1				

NS, no significance; CI, confidence interval; CR, complete response; PR, partial response.

Table 10 Recurrence of PR/CR group between different chemotherapy regimens of TNBC patients

Regimens and clinical response	Total (n=17)	Recurrence (n=3)	Non-recurrence (n=14)	Chi-square value	P value	Hazard ratio	95% CI
Anthracycline + cyclophosphamide sequential taxane	0	0	0				
Anthracycline + cyclophosphamide + taxane	7	2	5	1.436	>0.999	NS	NS
Taxane + carboplatin	2	0	2				
5-fluorouracil + anthracycline + cyclophosphamide	2	0	2				
Taxane + anthracycline	6	1	5				

NS, no significance; CI, confidence interval; CR, complete response; PR, partial response, TNBC, triple negative breast cancer.

influencing the long-term outcomes.

Besides the correlation between long-term outcomes and clinical response or pathological response to neoadjuvant chemotherapy, many scholars have focused on the relationship of other aspects of neoadjuvant chemotherapy with outcomes. Alba (28) reported that a Ki67 proliferation index greater than 50% may be an independent predictor for pCR to neoadjuvant chemotherapy, and they declared that cell proliferation may be tightly correlated with chemosensitivity. Baulies *et al.* (29) illustrated time-dependent prognostic factors. Distant recurrence-free intervals in patients with breast cancer who receive neoadjuvant chemotherapy are influenced by achieving pCR and the cancer subtype. Patients with more aggressive biological behaviour have poorer outcomes during the first 5 years and patients with HR+ breast cancer remain at risk for distant recurrence for many years. These scholars focused more on the biological behavior of breast cancer and outcomes rather than the correlation of chemotherapy regimens and prognoses. Schettini (30) and Li (31) performed meta-analysis and reported that most research focused on the chemotherapy regimens on HER-2+ and triple negative breast cancer. There are no reports comparing multiple types of regimens across clinical response and pathological response or comparing these outcomes across all kinds of subtypes. This is the first study to research this aspect of breast cancer treatment, and we found no significant differences in outcomes in the comparison of regimens, including TAC, AC-T, FAC, TCBP, AT and others. Moreover, in the PR/CR and PD/SD comparison of every single regimen, the result showed no significant differences. However, for the PR/CR patients, results from the comparison of regimens showed a significant difference. We believe the use of all of the regimens presented here is feasible for clinicians who use the PR/CR response to guide treatment of patients with breast cancer. However, we noticed that 40 patients who received the taxane + anthracycline regimen exhibited a higher recurrence rate than the rate in any other regimens, this concerning phenomenon was particularly observed in the recurrence comparison of regimens in the PR/CR group. Therefore, we recommend avoiding the taxane + anthracycline regimen in the neoadjuvant chemotherapy to improve outcomes. Conversely, cyclophosphamide treatment exhibited a significant effect, as patients treated with taxane and anthracycline combined with cyclophosphamide showed a lower recurrence rate than taxane and anthracycline alone. According to our findings, we recommend cyclophosphamide be added to neoadjuvant chemotherapy regimens of taxane and anthracycline.

When we compared the results across each neoadjuvant chemotherapy subtype, we detected five main regimens for comparison. In the group of patients with luminal A breast cancer, results of the Fisher's exact test approached significance. We examined the data and found that cancer in all of the patients with luminal A breast cancer who received taxane + anthracycline recurred. The phenomenon was not exhibited in other subtypes and in other regimens administered to patients with luminal A breast cancer. Thus, we strongly recommend avoiding the use of the taxane + anthracycline neoadjuvant chemotherapy regimen for patients with luminal A breast cancer. Because the clinical samples in this study were small, we hope to obtain more convincing conclusions by increasing the sample size in future research.

To sum up, in this novel study, we illustrated that neither clinical response PR/CR nor pCR can transfer into long-term outcome benefit. Clinical response PR/CR and pathological response pCR are not the independent prognostic predictors in breast cancer. We are the first to report that patients who received taxane + anthracycline regimen exhibited a higher recurrence rate than any other regimens, especially for those patients with luminal A breast cancer. We hope our research can help guide clinicians in choosing the appropriate neoadjuvant chemotherapy regimens for breast cancer.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of the Third Affiliated Hospital of Kunming Medical University, Yunnan Cancer Hospital (No. QT 202003) and informed consent was taken from all the patients.

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Supplementary

Table S1 Comparison of clinicopathological characteristics between CR + PR group and SD + PD group in luminal A patients

Variables	Total (n=23)	CR + PR (n=15)	SD + PD (n=8)	Chi-square value	P value	Hazard ratio	95% CI
Age (years)				0.171	0.679	0.667	0.097–4.580
<50	16	10	6				
≥50	7	5	2				
Tumor size				4.329	0.115	NS	NS
≤2 cm	17	9	8				
2–5 cm	3	3	0				
>5 cm	3	3	0				
Lymph nodes status				1.806	0.179	0.300	0.050–1.795
–	10	5	5				
+	13	10	3				
Menstruation status				0.289	0.591	1.650	0.264–10.313
Postmenopausal	16	11	5				
Premenopausal	7	4	3				
Chemotherapy times				0.494	0.482	0.462	0.052–4.106
≤4	4	2	2				
>5	19	13	6				

NS, no significance; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table S2 Comparison of clinicopathological characteristics between CR + PR group and SD + PD group in luminal B patients

Variables	Total (n=68)	CR + PR (n=48)	SD + PD (n=20)	Chi-square value	P value	Hazard ratio	95% CI
Age (years)				0.004	0.950	0.967	0.339–2.758
<50	37	26	11				
≥50	31	22	9				
Tumor size				4.695	0.096	NS	NS
T1–2	56	40	16				
T3	5	5	0				
T4	7	3	4		0.045		
Lymph nodes status				4.032		0.333	0.112–0.995
–	22	12	10				
+	46	36	10				
Menstruation status				0.037	0.847	0.900	0.309–2.620
Postmenopausal	26	18	8				
Premenopausal	42	30	12				
Chemotherapy times				1.140	0.286	2.368	0.469–11.950
≤4	12	10	2				
>5	56	38	18				

NS, no significance; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table S3 Comparison of clinicopathological characteristics between CR + PR group and SD + PD group in HER-2+ patients

Variables	Total (n=16)	CR + PR (n=14)	SD + PD (n=2)	Chi-square value	P value	Hazard ratio	95% CI
Age (years)				0.152	0.696	1.800	0.091–35.426
<50	10	9	1				
≥50	6	5	1				
Tumor size				3.048	0.218	NS	NS
T1–2	12	11	1				
T3	2	1	1				
T4	2	2	0				
Lymph nodes status				0.152	0.696	0.000	0.000–0.000
–	1	1	0				
+	15	13	2				
Menstruation status				0.570	0.450	0.422	0.043–4.165
Postmenopausal	10	9	1				
Premenopausal	6	5	1				
Chemotherapy times				0.327	0.568	0.000	0.469–11.950
≤4	2	2	0				
>5	14	12	2				
Ki-67 value				0.762	0.383	0.273	0.013–5.769
<14	4	3	1				
≥14	12	11	1				

NS, no significance; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table S4 Comparison of clinicopathological characteristics between CR + PR group and SD + PD group in TN patients

Variables	Total (n=26)	CR + PR (n=18)	SD + PD (n=8)	Chi-square value	P value	Hazard ratio	95% CI
Age (years)				0.657	0.418	2.100	0.343–12.859
<50	19	14	5				
≥50	7	4	3				
Tumor size				0.963	0.618	NS	NS
T1–2	24	16	8				
T3	1	1	0				
T4	1	1	0				
Lymph nodes status				0.181	0.671	1.500	0.230–9.796
–	8	6	2				
+	18	12	6				
Menstruation status				0.042	0.837	1.200	0.212–6.801
Postmenopausal	17	12	5				
Premenopausal	9	6	3				
Chemotherapy times				1.811	0.178	4.455	0.447–44.415
≤4	8	7	1				
>5	18	11	7				
Ki-67 value				0.112	0.737	1.368	0.218–8.601
<14	6	4	2				
≥14	19	13	6				

NS, no significance; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.