Comparison of overall survival after neoadjuvant and adjuvant chemotherapy in patients with early breast cancer with immediate breast reconstruction after mastectomy: A retrospective, matched case-control study

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Abstract. Immediate breast reconstruction after mastectomy combined with chemotherapy is the preferred option for patients with early-stage breast cancer who require both superior clinical and aesthetic outcomes. The present study aimed to determine the survival benefits of neoadjuvant and adjuvant chemotherapy for patients with early-stage breast cancer who have undergone immediate breast reconstruction after mastectomy in Taiwan. The present study compared overall survival (OS) following neoadjuvant or adjuvant chemotherapy in 139 patients with early-stage breast cancer who underwent immediate breast reconstruction after mastectomy. Patient data were used retrospectively as an unmatched cohort. Next, 37 neoadjuvant cases were matched with 37 adjuvant controls through 1:1 age-, clinical stage-, and molecular subtype-matching. OS differences between the cases and controls were determined using Kaplan-Meier survival curve analyses. Here, 77.7 and 81.1% of the unmatched and matched cohort patients were aged <50 years, respectively. Of the matched neoadjuvant cases, 10 (15.6%) reached pathologic complete response after neoadjuvant chemotherapy, whereas 5 (13.5%) neoadjuvant cases succumbed during the study period. The neoadjuvant matched cases demonstrated a significantly poor OS with their adjuvant matched controls (P=0.044); nevertheless, the stratification analysis results demonstrated that the survival differences between the neoadjuvant and the adjuvant controls decreased after matching. Targeted therapy demonstrated the same OS benefits for both the neoadjuvant matched cases and adjuvant matched controls (P=1.000). This study provided matched case-control evidence for the feasibility of neoadjuvant chemotherapy combined with targeted therapy for patients with early-stage breast cancer with immediate breast reconstruction after mastectomy in a Taiwanese female population.

Introduction

Breast cancer is the most common type of cancer in the female population; based on the National Comprehensive Cancer Network (NCCN) guidelines, the main treatment for breast cancer is mastectomy (1). Although mastectomy affords a favorable survival outcome in patients with breast cancer, studies have indicated that distorted breast appearance after mastectomy is associated with an increased risk of mental health disorders, such as depression (2,3). Breast reconstruction after mastectomy may improve the cosmetic appearance and body image of patients with breast cancer, thereby enhancing their mental health and quality of life (4,5).

Growing global interest in breast reconstruction research and the growth of related studies have indicated that breast reconstruction is becoming an increasingly common options for both surgeons and patients, particularly for younger patients with breast cancer (6,7). Postmastectomy breast reconstruction may be performed immediately after the mastectomy or after systemic treatment, local treatment (radiotherapy) or both. Immediate breast reconstruction after mastectomy has provided favorable prognostic outcomes, including simultaneous superior clinical and aesthetic outcomes, in patients with breast cancer; hence, it has become a preferred option among cancer surgeons (8-10).

In addition to mastectomy, systemic therapy (including chemotherapy, hormone therapy and targeted therapy), determined according to the breast cancer subtype, is a commonly used breast cancer treatment (11-13). The major concern related to postmastectomy breast reconstruction is the delay in adjuvant treatment it may cause; a delayed adjuvant treatment course is associated with worse breast cancer survival outcomes (14,15). However, breast reconstruction has been noted to increase the risk of surgical wound complications but not necessarily delay chemotherapy initiation; as such, neoadjuvant chemotherapy could be an alternative treatment option for patients with early-stage breast cancer who undergo breast reconstruction (16,17). Moreover, the reconstructive complication rates between a neoadjuvant and adjuvant chemotherapy cohort were similar in a Taiwanese breast cancer population with immediate breast reconstruction (18).

Chemotherapy applied in both neoadjuvant and adjuvant settings can provide further survival benefits for patients with early-stage breast cancer who undergo immediate breast reconstruction after mastectomy (19,20). Moreover, additional radiotherapy, hormone therapy and targeted therapy can be considered depending on the clinical indications of the patient with breast cancer, such as the tumor size, lymph node invasion and molecular subtype. Survival outcome, rather than reconstruction outcome, after neoadjuvant and adjuvant chemotherapy has not been compared sufficiently in patients with early-stage breast cancer who have undergone immediate breast reconstruction after mastectomy in Taiwan. Therefore, a comparison has been made in this study.

Materials and methods

Data set. This retrospective case-control study was approved by the Institutional Review Board (IRB no. CE21406B) of Taichung Veterans General Hospital (TCVGH; Taichung, Taiwan); all data were retrospectively collected from the health information system of TCVGH under this approved protocol The inclusion criteria for the study population were: i) Patients with early-stage breast cancer treated with breast reconstruction immediately after mastectomy between 1 January 2011 and 31 December 2018, and ii) completion of the chemotherapy treatment course in an adjuvant or neoadjuvant setting; breast cancer diagnosed at clinical stages I and IIIB was considered early-stage. Patients who did not meet the inclusion criteria were excluded. Data of 139 women with breast cancer met the inclusion criteria. The clinical characteristics and treatment characteristics of the study population were extracted from the patients' medical records or the cancer registry database.

Post hoc power analysis. A post hoc power analysis for two independent groups with dichotomous outcomes was used to evaluate the statistical power of the population in the current study. It was assumed that the probability of type I error (α) was 0.05, the population size of the current study cohort was 136; the sample size of neoadjuvant cases was 64, with a mortality rate of 23.4%, and the sample size of adjuvant controls was 75, with a mortality rate of 1.3%. The case-control sample size ratio was 1.172 and the absolute difference between the two groups was 0.221. With the power estimation formula, the estimated critical Z value for the assumed α was ~2.122 (Φ), equal

to the power of 0.983, indicating that the assumed sample size may lead to results with 99.5% statistical power.

For the matched case and control cohorts, there was an assumed sample size of 37 for both the neoadjuvant cases and adjuvant controls, with mortality rates of 14 and 0%, respectively; the case-control sample size ratio was 1 and an absolute between-group difference was 0.14. With the power estimation formula, Φ was ~0.416, equal to the power of 0.661, indicating the assumed sample size may lead to results with 66.1% statistical power. In other words, the findings of the matched cohort may only provide conservative inference.

Clinical characteristics. Several clinical characteristics were considered, including age, clinical stage and molecular subtype at diagnosis. The molecular subtypes of all patients were classified according to the results of standard histological examinations, including microscopic analysis with standard immunohistochemistry (IHC) for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), which was performed on tissues from the primary tumor excised during mastectomy. Pathohistological testing was conducted in the Department of Pathology and Laboratory Medicine at TCVGH. Cases with + (mild), ++ (moderate) or +++ (strong) IHC results (according to the intensity of staining) for ER and PR were defined as ER$^+$ and PR$^+$ cases, respectively, whereas the remaining patients were defined as ER$^-$ and PR$^-$. Moreover, cases with +++ IHC result for HER2 were defined as HER2$^+$ cases, whereas those with - or + IHC results for HER2 were defined as HER2$^-$ cases. In cases with ++ IHC results for HER2, fluorescence *in situ* hybridization (FISH) was performed using VENTANA HER2 Dual ISH DNA Probe Cocktail assay to analyze the HER2-neu gene amplification status. Subsequently, cases with ++ IHC and + FISH results for HER2 were defined as HER2$^+$, whereas the remaining cases were defined as HER2$^-$. In accordance with the classification system for molecular subtypes presented in the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 (21), breast cancer was classified as luminal A (ER$^+$/PR$^+$ and HER2$^-$), luminal B (ER$^+$/PR$^+$ and HER2$^+$), HER2-enriched (ER$^-$/PR$^-$ and HER2$^+$) or triple-negative (ER$^-$/PR$^-$ and HER2$^-$).

Overall survival (OS) was considered a primary endpoint; patients who succumbed during the within-study follow-up duration were considered left-censored, whereas the remaining patients were considered right-censored. The follow-up interval was between the date of initial diagnosis and the date of censoring.

Treatment characteristics. The treatment characteristics of the study population were classified according to the treatment type: Chemotherapy, radiotherapy, hormone therapy or targeted therapy (e.g. anti-HER2 therapy). In all patients, the treatment selection was mainly dependent on the individual clinical indications (i.e., age, tumor size, lymph node invasion and molecular subtype at diagnosis), as suggested by the NCCN guidelines for breast cancer treatment (1). The chemotherapy drugs used in the current settings included an anthracycline (epirubicin) with an alkylating agent (cyclophosphamide) followed by a taxane (paclitaxel or docetaxel). An antineoplastic agent (carboplatin) was used for patients with triple-negative

breast cancer (TNBC) or HER2-enriched breast cancer. Most patients with T3, T4 or lymph node metastasis received intensity-modulated radiotherapy, whereas a few patients were treated with external beam radiation therapy. The hormone therapy agents used in premenopausal and postmenopausal patients were tamoxifen and an aromatase inhibitor (letrozole or anastrozole), respectively. Dual-blockade anti-HER2 agents (i.e. pertuzumab and trastuzumab) were used for HER2-enriched patients. Here, pertuzumab was administered at 840 mg in the first cycle and then at 420 mg in the following cycles, whereas trastuzumab was administered at 8 mg/kg in the first cycle and then at 6 mg/kg in the following cycles. All HER2-enriched patients received complete dual-blockade or single-blockade therapy for one year.

Unmatched and matched cohort. The overall study population that underwent immediate breast reconstruction after mastectomy was considered an unmatched cohort, comprising 75 patients who received adjuvant chemotherapy and 64 control patients who received neoadjuvant chemotherapy. The treatment responses after neoadjuvant chemotherapy were reported. Furthermore, age group, clinical stage and molecular subtype at diagnosis were used as matching criteria to generate a well-balanced case-control subgroup matched at a 1:1 ratio, to further reduce the bias and clarify the feasibility role of neoadjuvant and adjuvant chemotherapy in the study population. In this study, 37 neoadjuvant cases were well matched with 37 adjuvant controls, which was used as a matched cohort (n=74).

Statistical analysis. The clinical characteristics, treatment characteristics and OS rates of the study population are presented the mean ± SD or as frequencies and percentages. All analyses were performed using R (version 4.1.2; R core team, 2021). The distribution difference of baseline characteristics between the cases and controls was estimated using an independent two-sample Student's t-test, χ^2 test or Fisher's exact test. The survival rates and the correspond 95% confidence interval (CI) of different subgroups were computed using Kaplan-Meier estimators, and OS was compared between the subgroups using the log-rank test. A post-hoc pairwise log-rank test were performed for multiple comparison correction. All P-values were two-sided, and P<0.05 was considered to indicate a statistically significant difference.

Results

Patient clinical characteristics. Table I summarizes the clinicopathological characteristics, treatment and OS of the unmatched cohort. The mean age at diagnosis of the unmatched cohort was 43.0±8.6 years; 31 (22.3%) of the patients were aged ≥50 and 108 (77.7%) were <50 years. The mean ages at diagnosis of the adjuvant controls and neoadjuvant cases were 44.1±9.2 and 41.8±7.8 years, respectively, and the differences between the adjuvant controls and neoadjuvant cases were non-significant (P=0.117). Similar ratios were obtained for the age group distribution between the adjuvant controls and neoadjuvant cases. However, the clinical stages at diagnosis differed significantly between the adjuvant controls and neoadjuvant cases. For example, significantly more neoadjuvant cases

were at clinical stages II and III compare with the adjuvant controls (79.7 vs. 45.3% and 15.6 vs. 1.3%, respectively; both P<0.001). Moreover, more neoadjuvant cases received radiotherapy compared with the adjuvant controls (53.1 vs. 32.0%; P=0.012). According to the clinical tumor staging, the tumor sizes ranged between 2 and 5 cm; most patients were at stages T1 (n=51; 36.7%) or T2 (n=76; 54.7%), followed by those at T3 (n=8; 5.8%). One (0.7%) patient in the adjuvant group was at TisN1; the remaining 3 (2.2%) patients were neoadjuvant cases at stage T4 at diagnosis. However, their tumor size decreased after neoadjuvant chemotherapy to a pathological tumor stage of T3, T4b or T1a. In total, 19 (13.7%) HER2-enriched breast cancer, 87 (62.6%) luminal A breast cancer, 26 (18.7%) luminal B breast cancer and 7 (5.0%) TNBC cases were identified in the unmatched cohort; the adjuvant controls and neoadjuvant cases demonstrated a similar molecular subtype distribution (P=0.453). The proportions of neoadjuvant cases and adjuvant controls receiving hormone and targeted therapy demonstrated a non-significant difference. In addition, 10 (15.6%) of the 64 neoadjuvant cases reached pathologic complete response (pCR) after neoadjuvant chemotherapy. However, 16 (11.5%) patients succumbed during follow-up; this proportion was higher among neoadjuvant cases compared with adjuvant controls (23.4 vs. 1.3%; P<0.001).

OS comparison in the unmatched cohort. Fig. 1 presents the Kaplan-Meier plots for OS of the different subgroups in the unmatched cohort. The OS rates (95% CI) of the neoadjuvant cases and adjuvant controls were 50 (28.5-87.7) and 98.5% (95.5-100), respectively (Fig. 1A), with the neoadjuvant cases exhibiting significantly poorer OS compared with the adjuvant controls (P<0.001). Among the neoadjuvant cases, the OS rate was higher in patients who achieved pCR compared with those who did not [100 vs. 42.9% (95% CI, 21.4-86.1); P=0.072; Fig. 1B].

OS comparison based on molecular subtypes in the unmatched cohort. Fig. 1C and D present a comparison of the OS according to different molecular subtypes among the adjuvant controls and neoadjuvant cases, respectively. The difference in OS between the adjuvant controls with different molecular subtypes was significant (P<0.001; Fig. 1C). The survival curves of individuals with HER2-enriched, luminal A and luminal B breast cancer overlapped because they had similar survival outcomes; their OS rates were all 100%, whereas the OS rate in individuals with TNBC was 66.7% (95% CI, 30-100). However, the post-hoc pairwise comparison results revealed that individuals with TNBC had significantly poorer OS only when compared with those with luminal A breast cancer (P<0.001). By contrast, the differences in the neoadjuvant cases with different molecular subtypes were not significant (P=0.029; Fig. 1D). The discrepancy between neoadjuvant cases with TNBC and those with other subtypes was large in the post-hoc pairwise comparison: The differences between neoadjuvant cases with TNBC (40.0% OS; 95% CI, 13.7-100) and those with HER2-enriched (83.3% OS; 95% CI, 58.3-100; P=0.560), luminal A (44.0% OS; 95% CI, 21.0-92.3; P=0.300) and luminal B (84.4% OS; 95% CI, 66.6-100; P=0.300) breast cancer were not significant. Taken together, both the neoadjuvant cases and adjuvant controls with TNBC

Table I. Clinicopathological characteristics, treatment and overall survival status of patients treated with adjuvant (n=75) and neoadjuvant (n=64) chemotherapy in the unmatched cohort (n=139).

Clinicopathological characteristics	Unmatched cohort, n (%)	Adjuvant, n (%)	Neoadjuvant, n (%)	P-value[a]
Age, years (mean ± SD)	43.0±8.6	44.1±9.2	41.8±7.8	0.117
Age group				0.603
<50 years	108 (77.7)	57 (76.0)	51 (79.7)	
≥50 years	31 (22.3)	18 (24.0)	13 (20.3)	
Clinical tumor staging				<0.001
is	1 (0.7)	1 (1.3)	0 (0.0)	
1	51 (36.7)	41 (54.7)	10 (15.6)	
2	76 (54.7)	32 (42.7)	44 (68.8)	
3	8 (5.8)	1 (1.3)	7 (10.9)	
4	3 (2.2)	0 (0.0)	3 (4.7)	
Clinical node staging				<0.001
0	92 (66.2)	68 (90.7)	24 (37.5)	
1	42 (30.2)	7 (9.3)	35 (54.7)	
2	5 (3.6)	0 (0.0)	5 (7.8)	
Clinical stage				<0.001
I	43 (30.9)	40 (53.3)	3 (4.7)	
II	85 (61.2)	34 (45.3)	51 (79.7)	
III	11 (7.9)	1 (1.3)	10 (15.6)	
Molecular subtype				0.453
HER2-enriched	19 (13.7)	10 (13.3)	9 (14.1)	
Luminal A	87 (62.6)	51 (68.0)	36 (56.3)	
Luminal B	26 (18.7)	11 (14.7)	15 (23.4)	
TNBC	7 (5.0)	3 (4.0)	4 (6.3)	
Treatment response, pCR	n/a	n/a	10 (15.6)	n/a
Treatment				
Radiotherapy	58 (41.7)	24 (32.0)	34 (53.1)	0.012
Hormone therapy	105 (75.5)	59 (78.7)	46 (71.9)	0.353
Targeted therapy	41 (29.5)	17 (22.7)	24 (37.5)	0.056
Mortality	16 (11.5)	1 (1.3)	15 (23.4)	<0.001

[a]P-values were calculated using independent two-sample t-test, χ^2 and Fisher's exact test. HER2, human epidermal growth factor receptor 2; n/a, not applicable; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

demonstrated poor OS, whereas neoadjuvant therapy led to no OS benefits in the patients with luminal A breast cancer (blue lines in Fig. 1C and D; the adjuvant controls achieved improved OS outcome compared to neoadjuvant cases). Moreover, the patients with HER2-enriched and luminal B breast cancer in both the neoadjuvant and adjuvant cohorts demonstrated similar OS improvement.

OS comparison based on treatment subgroups in the unmatched cohort. Fig. 2 presents a comparison of the OS between the adjuvant controls and neoadjuvant cases in the unmatched cohort according to their treatment characteristics. In both the adjuvant and neoadjuvant settings, the combined use of chemotherapy either with radiotherapy [95.7% (95% CI, 87.7-100) vs. 54.4%, (95% CI, 33.4-88.7), respectively; P=0.058; Fig. 2A] or with targeted therapy [91.7% (95% CI,

77.3-100) vs. 40.7% (95% CI, 10.0-88.7), respectively; P=0.314; Fig. 2C] led to different OS outcomes which were not significant. The neoadjuvant cases demonstrated significantly poorer OS than did the adjuvant controls in the subgroups without radiotherapy (100 vs. 0%, respectively; P=0.001; Fig. 2B) and without therapy [91.7%, (95% CI, 77.3-100%) vs. 40.7% (95% CI, 29.1-100%); P<0.001; Fig. 2D].

The patients who received hormone therapy combined with neoadjuvant chemotherapy demonstrated significantly poorer OS than those who received hormone therapy combined with adjuvant chemotherapy [100 vs. 52.4%, respectively; 95% CI, 27-100%, P<0.001; Fig. 2E]. By contrast, no significant difference was identified between the patients who did not receive hormone therapy in the adjuvant control [90.9% (95% CI, 75.4-100%)] and neoadjuvant case [47.3% (95% CI, 20.1-100%) groups (P=0.171; Fig. 2F)].
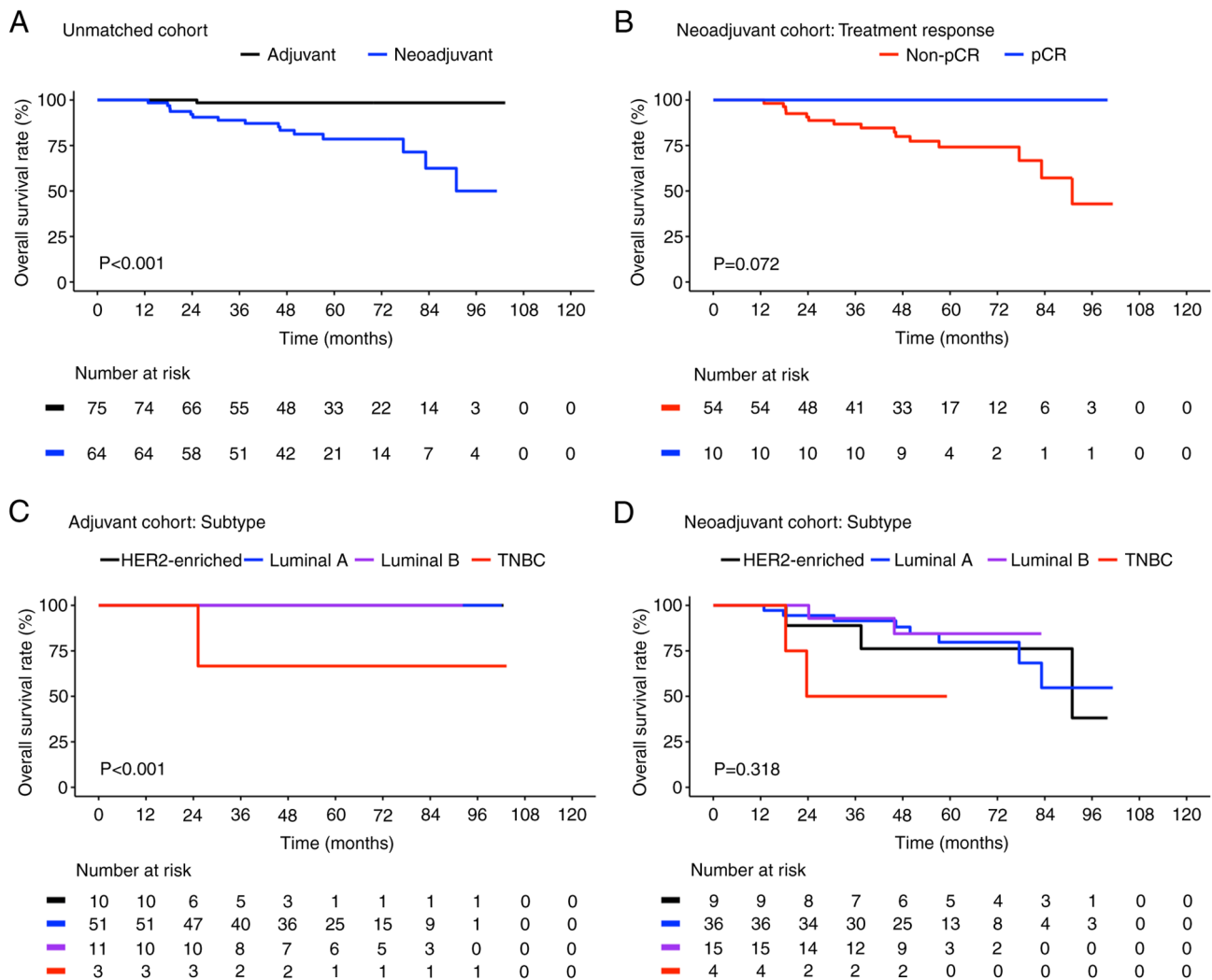
Figure 1. Kaplan-Meier plots of overall survival in the unmatched cohort. (A) Overall survival of the adjuvant and neoadjuvant subgroups in the unmatched cohort. (B) Overall survival comparison within the unmatched neoadjuvant cohort according to treatment response to neoadjuvant chemotherapy. Overall survival comparisons according to the molecular subtype were also made within the unmatched (C) adjuvant and neoadjuvant (D) cohorts. HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

Clinical characteristics of the matched cohort. To further understand the survival differences between the matched neoadjuvant cases and adjuvant controls, an age-matched, clinical stage-matched and molecular subtype-matched cohort was generated comprising 74 patients (n=37 patients/group). Table II presents the distribution of the clinicopathological characteristics, treatment characteristics and OS rates in the matched cohort. The mean age at diagnosis in the matched cohort was 42.0±8.4 years; 60 (81.1%) patients in this cohort were <50 years old. Because one adjuvant control at clinical stage III did not match with any of the neoadjuvant cases based on the aforementioned criteria, the matched cohort did not include patients at clinical stage III. The matched cohort contained 6 (8.1%) clinical stage I and 68 (91.9%) clinical stage II cases. The distribution of molecular subtypes was similar to that of the unmatched cohort; thus, the treatment characteristics also demonstrated a similar distribution between the matched neoadjuvant cases and adjuvant controls. In total, 5 (13.5%) of the 37 matched cases achieved pCR after neoadjuvant chemotherapy. However, 5 (13.5%) patients died during the follow-up duration; all of these patients were matched neoadjuvant cases (P=0.054) not in receipt of pCR.

OS comparison in the matched cohort. Fig. 3 presents the Kaplan-Meier plots for the OS of the different subgroups in the matched cohort. The neoadjuvant cases demonstrated significantly poorer OS compared with the adjuvant controls [63.3% (95% CI, 37.5-100) vs. 100%, respectively; P=0.044; Fig. 3A]. However, in terms of treatment characteristics and molecular subtypes, the neoadjuvant cases and adjuvant controls demonstrated differences which were not significant (Fig. 3B-D). In addition, similar survival curves were noted in the population with poor OS, as shown in Fig. 3A (blue line, matched neoadjuvant cases), B (red line, non-pCR matched neoadjuvant cases) and D (blue line, luminal A matched neoadjuvant cases). Mortality events were also only noted in the neoadjuvant cases with luminal A breast cancer [OS rate=71.8% (95% CI, 49.3-100%); Fig. 3D, blue line].

OS comparison based on treatment subgroups in the matched cohort. As shown in Fig. 4, the matched neoadjuvant cases and adjuvant controls demonstrated similar survival outcomes for those without radiotherapy (P=1.000; Fig. 4B) and hormone therapy (P=0.480; Fig. 4F). While the matched
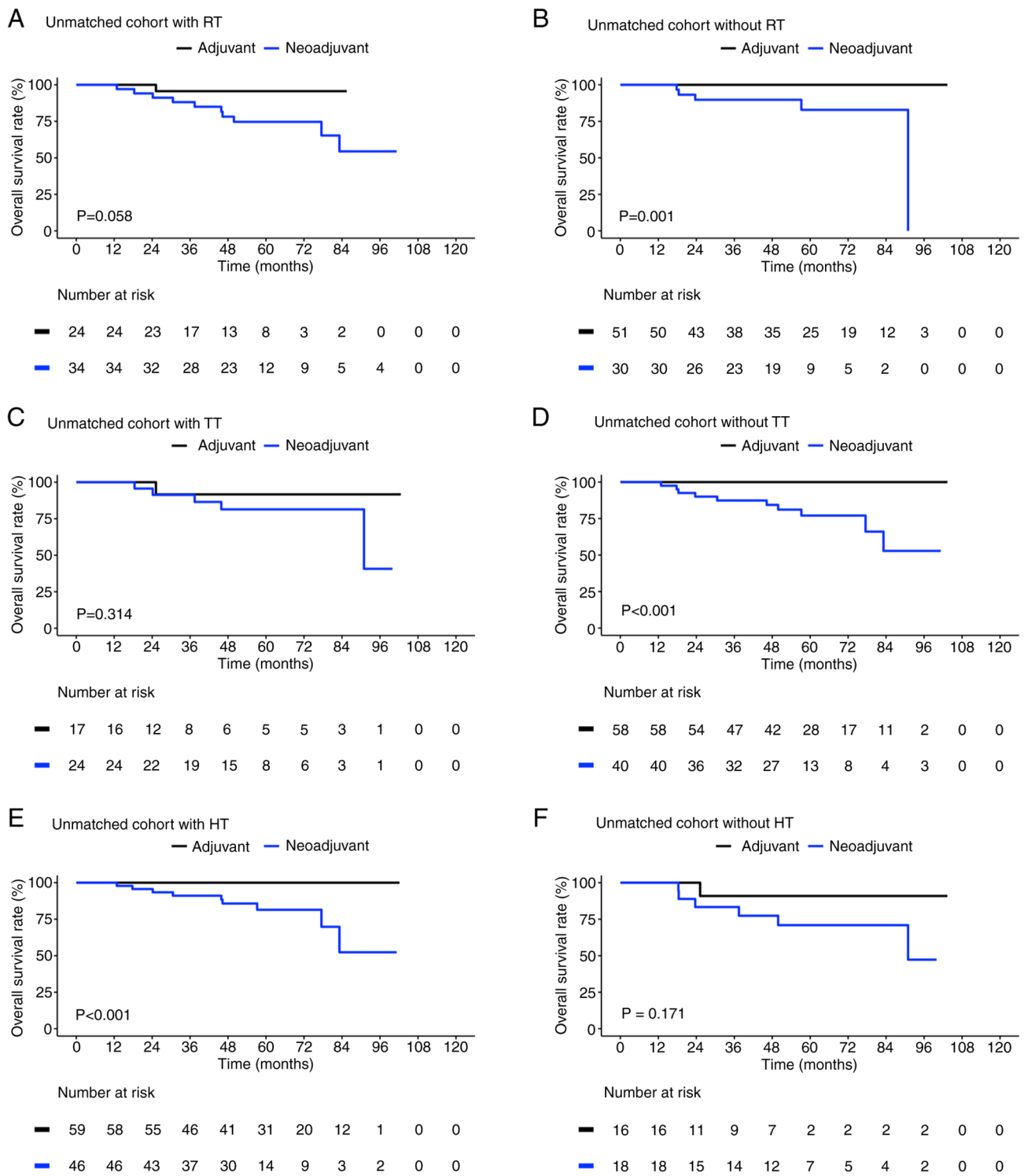
Figure 2. Kaplan-Meier plots of overall survival comparison between the adjuvant controls and neoadjuvant cases in the unmatched cohort according to different treatment characteristics. (A) RT, (B) non-RT, (C) TT, (D) non-TT, (E) HT and (F) non-HT subgroups. HT, hormone therapy; RT, radiotherapy; TT, targeted therapy.

adjuvant controls with radiotherapy (P=0.171; Fig. 4A) and hormone therapy (P=0.074; Fig. 4E) showed improved survival outcomes compared with matched neoadjuvant cases. However, the matched neoadjuvant cases who did not receive targeted therapy [OS rate=60.4%; 95% CI, 34.8-100] demonstrated significantly poorer OS than the matched adjuvant controls who did not receive targeted therapy (OS rate=100%; 95% CI; P=0.044; Fig. 4D). However, the combined use of

targeted therapy and chemotherapy led to the same favorable OS in both the matched adjuvant controls and neoadjuvant cases (P=1.000; Fig. 4C).

Discussion

In this study, a comparison was made on the long-term OS outcomes after neoadjuvant and adjuvant chemotherapy

Table II. Clinicopathological characteristics, treatment characteristics, and overall survival status of patients treated with adjuvant (n=37) and neoadjuvant (n=37) chemotherapy, in the matched cohort (n=74).

Clinicopathological characteristics	Matched cohort, n (%)	Adjuvant, n (%)	Neoadjuvant, n (%)	P-value[a]
Age, years (mean ± SD)	42.0±8.4	42.7±9.3	41.2±7.4	0.458
Age group[b]				1.000
<50 years	60 (81.1)	30 (81.1)	30 (81.1)	
≥50 years	14 (18.9)	7 (18.9)	7 (18.9)	
Clinical stage[b]				1.000
I	6 (8.1)	3 (8.1)	3 (8.1)	
II	68 (91.9)	34 (91.9)	34 (91.9)	
III	-	-	-	
Molecular subtype[b]				1.000
HER2-enriched	6 (8.1)	3 (8.1)	3 (8.1)	
Luminal A	56 (75.7)	28 (75.7)	28 (75.7)	
Luminal B	10 (13.5)	5 (13.5)	5 (13.5)	
TNBC	2 (2.7)	1 (2.7)	1 (2.7)	
Treatment response, pCR	-	-	5 (13.5)	-
Treatment				
Radiotherapy	30 (40.5)	12 (32.4)	18 (48.6)	0.155
Hormone therapy	60 (81.1)	31 (83.8)	29 (78.4)	0.553
Targeted therapy	13 (17.6)	5 (13.5)	8 (21.6)	0.359
Mortality	5 (6.8)	-	5 (13.5)	0.054

[a]P-value is estimated using independent two-sampled t-test, χ^2 and Fisher's exact test. [b]Matching criteria including clinical stage and HER2 status. HER2, human epidermal receptor-2; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

in Taiwanese women with breast cancer who had received immediate breast reconstruction after mastectomy, by using a retrospective matched case-control design. The OS outcome was similar between the matched neoadjuvant cases and adjuvant controls who also received targeted therapy combined with chemotherapy. Moreover, the patients with luminal A breast cancer who received neoadjuvant chemotherapy, including those who received the therapy in combination with hormone therapy or radiotherapy, demonstrated poorer OS.

The benefits of undergoing adjuvant chemotherapy after immediate breast reconstruction have been well studied over the last ten years (22,23). Neoadjuvant chemotherapy was introduced to facilitate tumor shrinkage and thus improve the outcomes of mastectomy or other relevant treatment modalities (24). In the findings of present study, relatively more neoadjuvant cases were at clinical stage II or III because of the beneficial effects of neoadjuvant chemotherapy, which were particularly notable in the patients with breast cancer with advanced tumor sizes or aggressive tumor characteristics. Although the application of neoadjuvant chemotherapy after breast reconstruction has been controversial (i.e. the accuracy of lymph nodes status following neoadjuvant chemotherapy), studies have suggested that neoadjuvant chemotherapy is a safe therapeutic option for patients with breast cancer who undergo immediate breast reconstruction after mastectomy (25). Studies involving Taiwanese populations have also indicated that neoadjuvant chemotherapy leads to further advancement

of tumor characteristics and that local recurrence rates over a limited follow-up interval are comparable, which is consisted with the present findings (18).

In the current study, the OS benefits were similar in both the matched neoadjuvant cases and adjuvant controls who also underwent targeted therapy. A previous study suggested that neoadjuvant chemotherapy is the preferred treatment strategy for patients with TNBC and HER2-enriched breast cancer (26), and the addition of an anti-HER2 regimen in both adjuvant and neoadjuvant settings can lead to favorable survival outcomes (27-29). However, in the present study, the treatment benefits of chemotherapy in both adjuvant and neoadjuvant settings were not observed in the patients with luminal A breast cancer following matching, which contrasts with the findings of a previous study (30). This may be due to the small sample size used in the current study. Therefore, the present findings should be interpreted with caution.

The current results reveal that 77.7% of the unmatched and 81.8% of the matched patients were <50 years old, indicating that the preference for immediate breast reconstruction after mastectomy decreases with age. Studies have demonstrated that compared with older patients, younger patients with breast cancer are physiologically healthier, which makes them better candidates for breast reconstruction (7,31). Breast cancer in younger patients is likely to be more aggressive, leading to poorer quality of life and more mental health issues; however, the younger breast cancer cohort is also preferred for
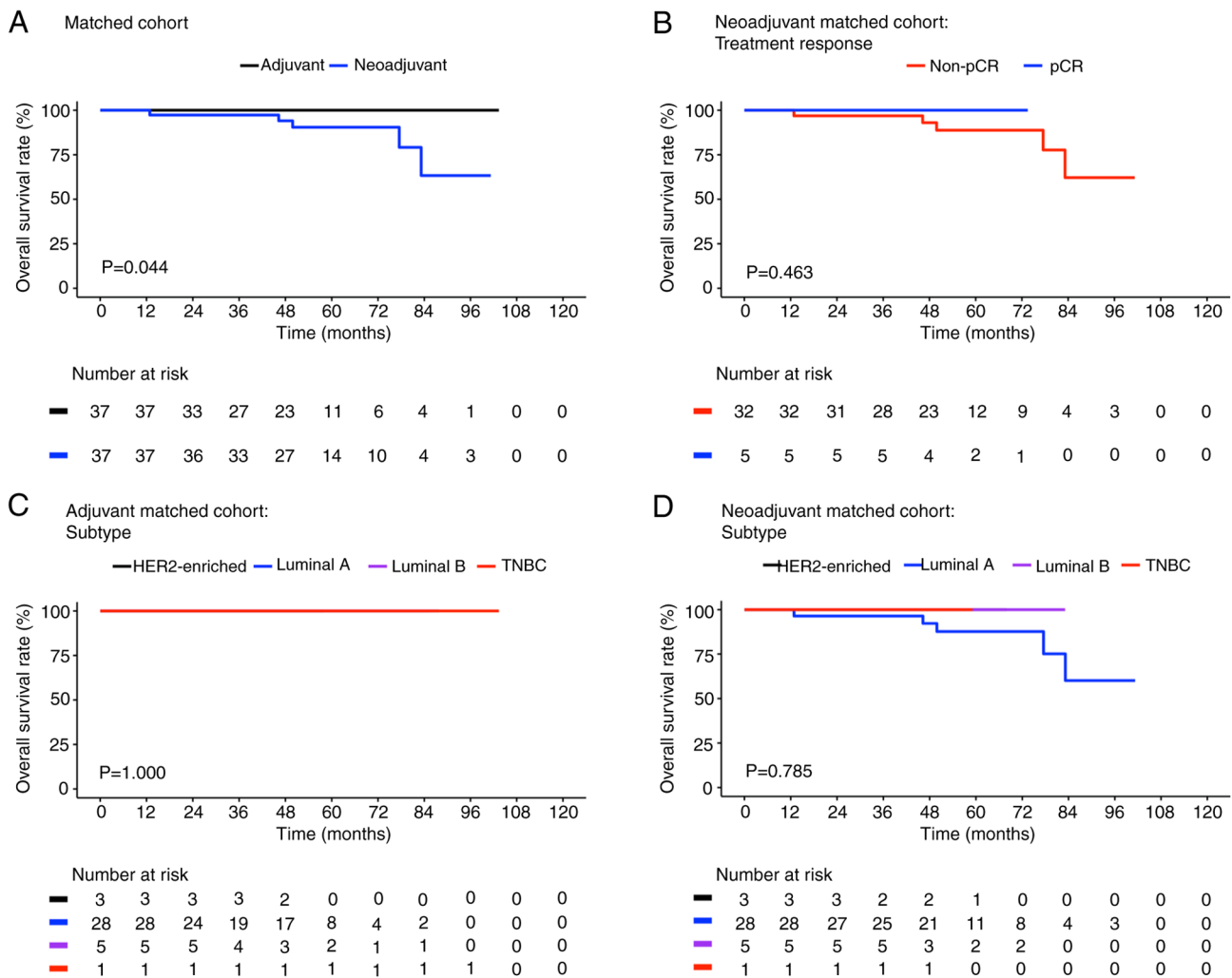
Figure 3. Kaplan-Meier plots of overall survival in the matched cohort. (A) Overall survival of the adjuvant and neoadjuvant subgroups in the matched cohort. (B) Overall survival comparison within the matched neoadjuvant cohort according to treatment response to neoadjuvant chemotherapy. Overall survival comparison according to the molecular subtype were also made within the matched (C) adjuvant and (D) neoadjuvant cohorts. HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response after neoadjuvant; TNBC, triple-negative breast cancer.

reconstructive options (7,31,32). Moreover, the recent increase in the awareness and knowledge of, the increase in communication with professionals on and the development of decision support tools related to breast reconstruction may have also led to the increase in the preference for breast reconstruction among the younger breast cancer cohort (33,34). Nevertheless, breast reconstruction outcomes have demonstrated no notable differences among different age groups (31,35).

The retrospective nature of this study limited the inclusion of additional OS-related characteristics. In addition, all data were collected from a single institution, potentially limiting the generalizability of the current findings; the small sample size possibly also limited the practical analysis. Furthermore, because of the imbalance in the distribution of the OS rates between the cases and controls, Cox regression analysis could not be applied to our data. Therefore, the survival analysis was performed using only non-parametric methods, including the Kaplan-Meier estimator and log-rank test. Despite these limitations, the present study, using both unmatched and matched case-control cohorts, provides reasonable evidence for OS differences after neoadjuvant and adjuvant chemotherapy in

patients with early-stage breast cancer who undergo immediate breast reconstruction after mastectomy.

In conclusion, the present study demonstrated that the long-term OS outcomes between neoadjuvant and adjuvant chemotherapy combined with targeted therapy groups were comparable in patients with early-stage breast cancer with immediate breast reconstruction after mastectomy. This supports the feasibility of neoadjuvant chemotherapy combined with targeted therapy in Taiwanese female patients with early-stage breast cancer with immediate breast reconstruction after mastectomy. However, the low power of our matched cohort restricts the generalizability of this finding. Therefore, in a future study, a multicenter prospective design to increase the sample size and statistical power to verify the current findings will be implemented. Moreover, additional relevant clinical characteristics and outcomes, such as drug information, treatment responses to specific drugs, laboratory measurements and disease progression status will be included. Finally, the future study will use a longitudinal model to investigate the time-varying or dose-varying effects of chemotherapeutic and targeted therapeutic agents.
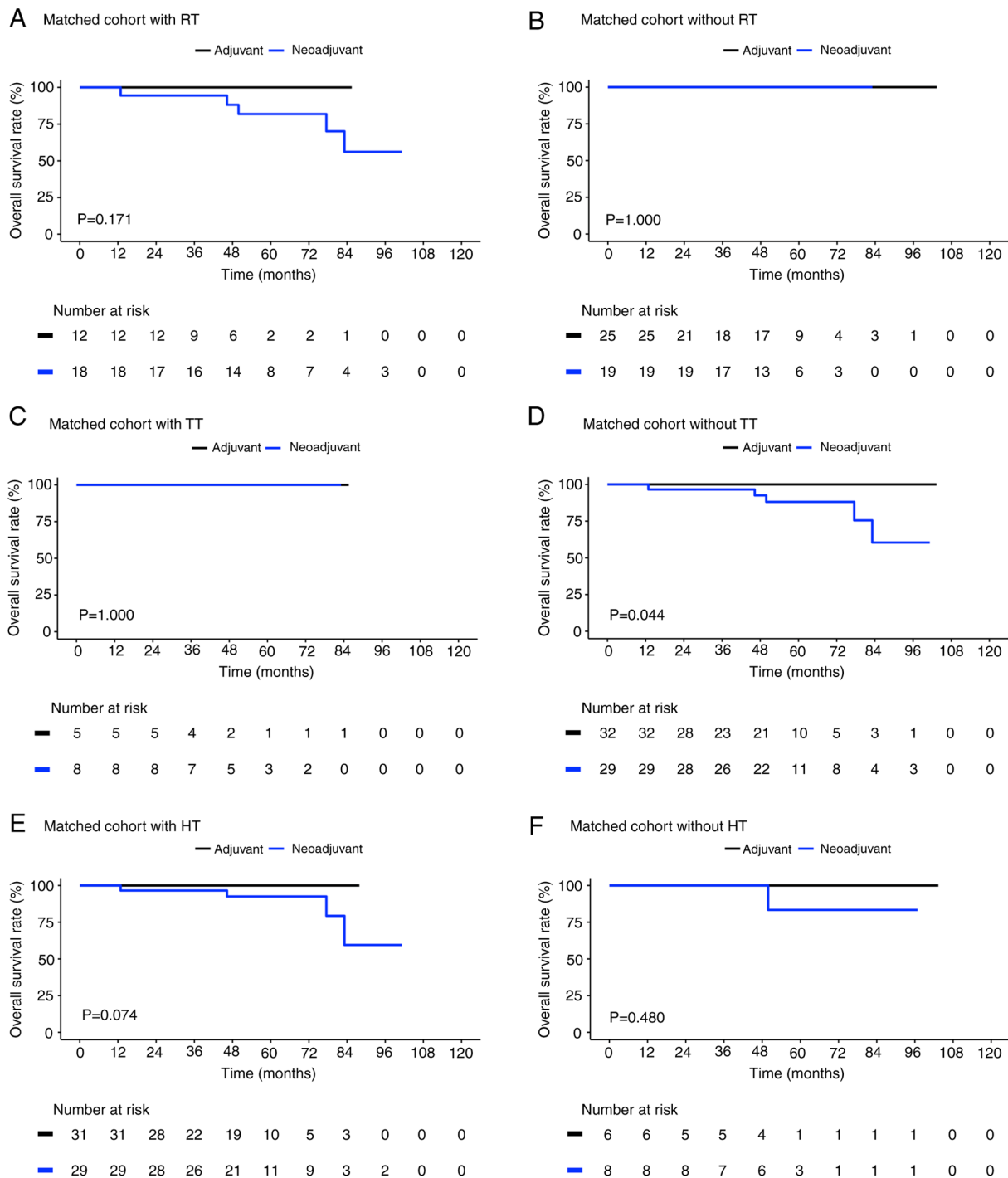
Figure 4. Kaplan-Meier plots of overall survival comparison between the adjuvant controls and neoadjuvant cases in the matched cohort according to different treatment characteristics, including (A) RT, (B) non-RT, (C) TT, (D) non-TT, (E) HT and (F) non-HT subgroups. HT, hormone therapy; RT, radiotherapy; TT, targeted therapy.

Acknowledgements

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CHL and CCH conceptualized the study, reviewed the literature and wrote and revised the manuscript. JRY and ICT collected the data and revised the manuscript. CYH and

LCY analyzed the data and interpreted the results. All authors have read and approved the final manuscript. CCH and CYH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The data protocol of this study was approved by the Institutional Review Board Taichung Veterans General Hospital (IRB no. CE21406B) with a waiver of informed consents.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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