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Original Article

Early capecitabine metronomic chemotherapy improves patient prognosis and safety in early-stage triple-negative breast cancer

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Abstract: Objective: To evaluate the effect of different initiation times of capecitabine metronomic chemotherapy on prognosis and safety in patients with early-stage triple-negative breast cancer (TNBC). Methods: This retrospective study included 206 early-stage TNBC patients treated between March 2018 and January 2022. The patients were divided into early (≤ 4 weeks after surgery, n = 104) and delayed (> 4 weeks, n = 102) initiation groups. Clinical data, laboratory indicators (carcinoembryonic antigen [CEA], carbohydrate antigen 125 [CA125], neutrophil-to-lymphocyte ratio [NLR]), survival, and adverse reactions were compared between the two groups. Results: The early initiation group showed significantly longer 3-year progression-free survival (PFS) ($P < 0.05$) but similar overall survival (OS) ($P > 0.05$). Reductions in CEA, CA125, and NLR were more prominent in the early initiation group ($P < 0.05$). Subgroup analysis indicated a PFS advantage for T2-stage patients. Adverse reactions, mainly hand-foot syndrome and bone marrow suppression, were comparable between groups, with most cases being grade 1-2. Conclusion: Early initiation of capecitabine metronomic chemotherapy can improve the PFS in early-stage TNBC patients, especially for patients with T2 stage, with manageable safety.

Keywords: Triple-negative breast cancer, capecitabine, metronomic chemotherapy, treatment timing, progression-free survival, safety

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 8-13% of all breast cancer cases. Its pathologic features include the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [1, 2]. Due to the lack of specific therapeutic targets, TNBC patients do not benefit from endocrine therapy or HER2-targeted therapy, resulting in a significantly higher recurrence risk than in other subtypes. In particular, the 5-year recurrence rate of early-stage patients after surgery is high, often accompanied by distant metastases, making TNBC a major cause of breast cancer-related death [3]. Although neoadjuvant chemotherapy combined with surgery has significantly improved the pathologic complete remission rate of early TNBC, some patients still face the risk of recurrence due to chemotherapy resistance or tumor heterogeneity [4]. Therefore, exploring effective and safe adjuvant treatment strategies to extend disease-free survival (DFS) and reduce the toxicity burden is a core challenge of current clinical research.

Metronomic chemotherapy is a chemotherapy model with low-dose and frequent administration. Compared to traditional high-dose chemotherapy, it can continuously inhibit tumor angiogenesis and induce tumor cell apoptosis, with less toxic side effects [5]. Capecitabine, an oral fluorouracil drug, has unique anti-tumor activity [6]. It is converted into 5-fluorouracil in the body through a series of enzymatic reactions, thereby exerting a cytotoxic effect [7, 8]. The convenience of oral administration improves patient compliance and is a new method for the treatment of TNBC [9]. However, existing stud-

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ies mostly focus on capecitabine in combination therapy or fixed-course designs, with limited information on the effect of administration time variation (such as treatment initiation time, duration of treatment, and dosing interval) on efficacy and safety. This knowledge gap may lead to insufficient standardization of treatment regimens in clinical practice, thus affecting patient prognosis.

Early intervention may improve prognosis by inhibiting the proliferation of micrometastatic foci, but may also increase the treatment interruption rate due to cumulative chemotherapy toxicity. This study aims to explore the impact of differences in the timing of capecitabine metronomic chemotherapy on the prognosis and safety of early-stage TNBC through systematic analysis and observation, with a goal to provide more precise and effective guidance for clinical treatment.

Patients and methods

Study design

A retrospective cohort study was conducted on patients with early-stage TNBC treated at Xi'an People's Hospital (Xi'an No. 4 Hospital) between March 2018 and January 2022. A total of 206 eligible women were included and stratified into two groups based on the interval from surgery to initiation of capecitabine metronomic chemotherapy. There was an Early Initiation Group (≤ 4 weeks post-surgery; n = 104) and a Delayed Initiation Group (> 4 weeks post-surgery; n = 102).

This study was approved by the Medical Ethics Committee of Xi'an People's Hospital (Xi'an No. 4 Hospital). Due to the retrospective nature of this study, the ethics committee waived the requirement for obtaining individual informed consent from patients.

Inclusion and exclusion criteria

Inclusion criteria: 1. Histologically confirmed TNBC; 2. Clinical stage I-II per American Joint Committee on Cancer (AJCC), 8th edition; 3. Received capecitabine metronomic chemotherapy as adjuvant treatment; 4. Age 18-80 years.

Exclusion criteria: 1. Presence or history of other malignancies; 2. Severe hepatic or renal impairment; 3. Receipt of neoadjuvant systemic therapy; 4. Incomplete medical records or loss to follow-up.

Treatment protocol

All patients received standard chemotherapy regimens based on anthracyclines and taxanes after surgery. After completion of standard postoperative chemotherapy, all patients received capecitabine metronomic chemotherapy at a dose of 0.5 g orally three times daily for 12 months. Patients undergoing breast-conserving surgery received adjuvant radiotherapy after the operation using three-dimensional conformal radiotherapy (3D-CRT). The target volumes encompassed the entire affected breast (or chest wall) and the corresponding regional lymphatic drainage areas. The prescribed dose was 50 Gy administered in 25 fractions to the entire breast/chest wall, followed by a booster dose of 10-16 Gy to the tumor bed. Follow-up assessments were performed every 3-6 months and included: 1. Serum tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen 15-3 (CA 15-3), CA12-5 by chemiluminescence); 2. Complete blood counts for calculation of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR); 3. Liver and renal function tests; 4. Breast and regional lymph node ultrasound; 5. Abdominal and pelvic ultrasound.

Adverse events were monitored throughout treatment and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Data collection

Patient information was extracted from electronic inpatient and outpatient records, supplemented by telephone and text-message follow-up. The following variables were recorded: 1. Demographics and baseline tumor characteristics: age, parity, menopausal status, tumor size (maximum diameter on imaging), laterality, TNM stage [10], histologic grade and subtype, Ki-67 index. 2. Treatment details: surgical procedure (modified radical mastectomy vs. breast-conserving surgery), time to capecitabine initiation. 3. Laboratory values: serum CEA, CA15-3, CA12-5, NLR, PLR at baseline and 3 months post-chemotherapy. Peripheral fasting venous blood (5 mL) was collected for analysis. Levels

of CEA, CA15-3, and CA12-5 were detected using an automatic chemiluminescence immunoanalyzer (Roche E601). A Sysmex XN-9000 automatic hematology analyzer (Sysmex Corporation, Japan) was used to measure the levels of neutrophils, platelets, and lymphocytes in whole blood, and NLR and PLR were calculated based on these measurements. 4. Efficacy outcomes: disease recurrence, metastasis, and death within 36 months post-surgery. 5. Safety and quality of life: adverse events per CTCAE v5.0; Functional Assessment of Cancer Therapy-Breast (FACT-B) scores at baseline and 12 months (range 0-152; higher scores indicate better quality of life) [11].

Statistical analysis

All analyses were performed using SPSS v26.0. Continuous variables were presented as mean ± SD and compared using Student's t-test. Categorical variables were expressed as n (%) and analyzed by χ^2 or Fisher's exact test, as appropriate. Cumulative incidence function (CIF) curves were constructed for survival endpoints. Pearson's correlation was used to assess associations between initiation time and laboratory/inflammatory markers. A two-sided *P*-value < 0.05 was considered significant.

Results

Comparison of baseline data between the two groups

No significant differences were observed in age, tumor diameter, childbearing history, KI-67, tumor location, T stage, N stage, menopausal status, pathologic grade, lymph node metastasis, or pathologic type between the two groups of patients (P > 0.05, **Table 1**).

Comparison of laboratory indicator changes between the two groups of patients

There were no significant differences in the laboratory indicators CEA, CA153, CA125, NLR, or PLR between the two groups of patients before chemotherapy (P > 0.05). After chemotherapy, the levels of CEA, CA153, CA125, NLR, and PLR in both groups decreased compared to those before chemotherapy. Notably, the levels of these markers in the early initiation group were significantly lower than those of the delayed initiation group (P < 0.05, **Figure 1**).

Relationship between initiation time and laboratory indicators after chemotherapy

Pearson's correlation analysis revealed that the levels of CEA (r = 0.557), CA153 (r = 0.518), CA125 (r = 0.618), NLR (r = 0.509), and PLR (r = 0.495) after chemotherapy were all significantly and positively correlated with capecitabine initiation time (P < 0.001 for all), as shown in **Figure 2**. Among these, CA125 demonstrated the strongest correlation with the administration initiation time.

Comparison of prognosis between the two groups of patients

CIF curves were plotted to evaluate the 3-year cumulative all-cause mortality and the 3-year cumulative incidence of disease progression events (including death). The analysis revealed no significant difference in 3-year cumulative mortality between the two groups of patients (P > 0.05). However, the 3-year cumulative incidence of events was significantly lower in the early initiation group compared to the delayed initiation group (P < 0.05) (**Figure 3**).

Comparison of recurrence types between the two groups

A total of 56 patients experienced disease progression at the third follow-up year, excluding 3 non-breast cancer-related deaths. The recurrence sites of these patients were analyzed, distinguishing between local recurrence and distant metastasis (**Figure 4**). The results showed that the rate of distant metastasis in the early initiation group was significantly lower than that of the delayed initiation group (P < 0.05), particularly for the rate of visceral metastases (liver, lung) (P < 0.05). However, no significant difference was found in the local recurrence rates between the two groups (P > 0.05).

Correlation analysis of factors affecting prognosis

According to the 3-year PFS results, the patients were divided into a Non-progression Group and the Disease Progression Group. The comparison revealed that the initiation time of chemotherapy, tumor diameter, Ki-67 index, T stage, and N stage were associated with patients' 3-year PFS (all P < 0.05). Spearman correlation analysis showed that the initiation time of chemotherapy was negatively correlat-

Table 1. Comparison of baseline data between early- and delayed-initiation groups

	Early Initiation Group (n = 104)	Delayed Initiation Group (n = 102)	χ^2	P
Age			0.958	0.328
≤ 50 years	71 (68.27)	63 (61.76)		
> 50 years	33 (31.73)	39 (38.24)		
Tumor diameter			0.729	0.393
≤ 2 cm	50 (48.08)	43 (42.16)		
> 2 cm	54 (51.92)	59 (57.84)		
Childbearing history			0.728	0.393
Childbearing	76 (73.08)	69 (67.65)		
Not childbearing	28 (26.92)	33 (32.35)		
KI-67			0.295	0.587
≤ 20%	43 (41.35)	46 (45.1)		
> 20%	61 (58.65)	56 (54.9)		
Tumor location			0.325	0.569
Left	54 (51.92)	57 (55.88)		
Right	50 (48.08)	45 (44.12)		
T stage			0.496	0.481
T1	52 (50.00)	56 (54.9)		
T2	52 (50.00)	46 (45.1)		
N stage			0.692	0.406
N0	70 (67.31)	63 (61.76)		
N1	34 (32.69)	39 (38.24)		
Menopausal status			0.992	0.319
Not menopausal	50 (48.08)	47 (41.18)		
Menopausal	54 (51.92)	55 (58.82)		
Surgical method			0.645	0.422
Modified radical mastectomy	81 (77.88)	84 (82.35)		
Breast-conserving surgery	23 (22.12)	18 (17.65)		
Pathologic grade			0.489	0.485
Moderate to low differentiation	75 (72.12)	69 (67.65)		
High differentiation	29 (27.88)	33 (32.35)		
Pathologic type			0.554	0.457
Invasive ductal carcinoma	83 (79.81)	77 (75.49)		
Invasive lobular carcinoma	21 (20.19)	25 (24.51)		

ed with the 3-year disease progression of the patients, while the tumor diameter, Ki-67 index, T stage, and N stage were positively correlated with the 3-year disease progression (**Table 2** and **Figure 5**).

Comparison of outcomes in related populations

The 3-year CIF curves of all-cause mortality and progression-related mortality were plotted for patients with different chemotherapy initiation times (**Figure 6**). A significant difference was observed in the 3-year progression-related mortality CIF between the early-initiation and delayed-initiation groups in the T2-stage population ($P < 0.05$). However, no significant differences were observed in the 3-year all-cause mortality or progression-related mortality CIFs between the two groups in populations with tumor diameter > 2 cm, Ki-67 > 20%, or N1 stage, nor in the 3-year all-cause mortality CIF in the T2-stage population ($P > 0.05$).

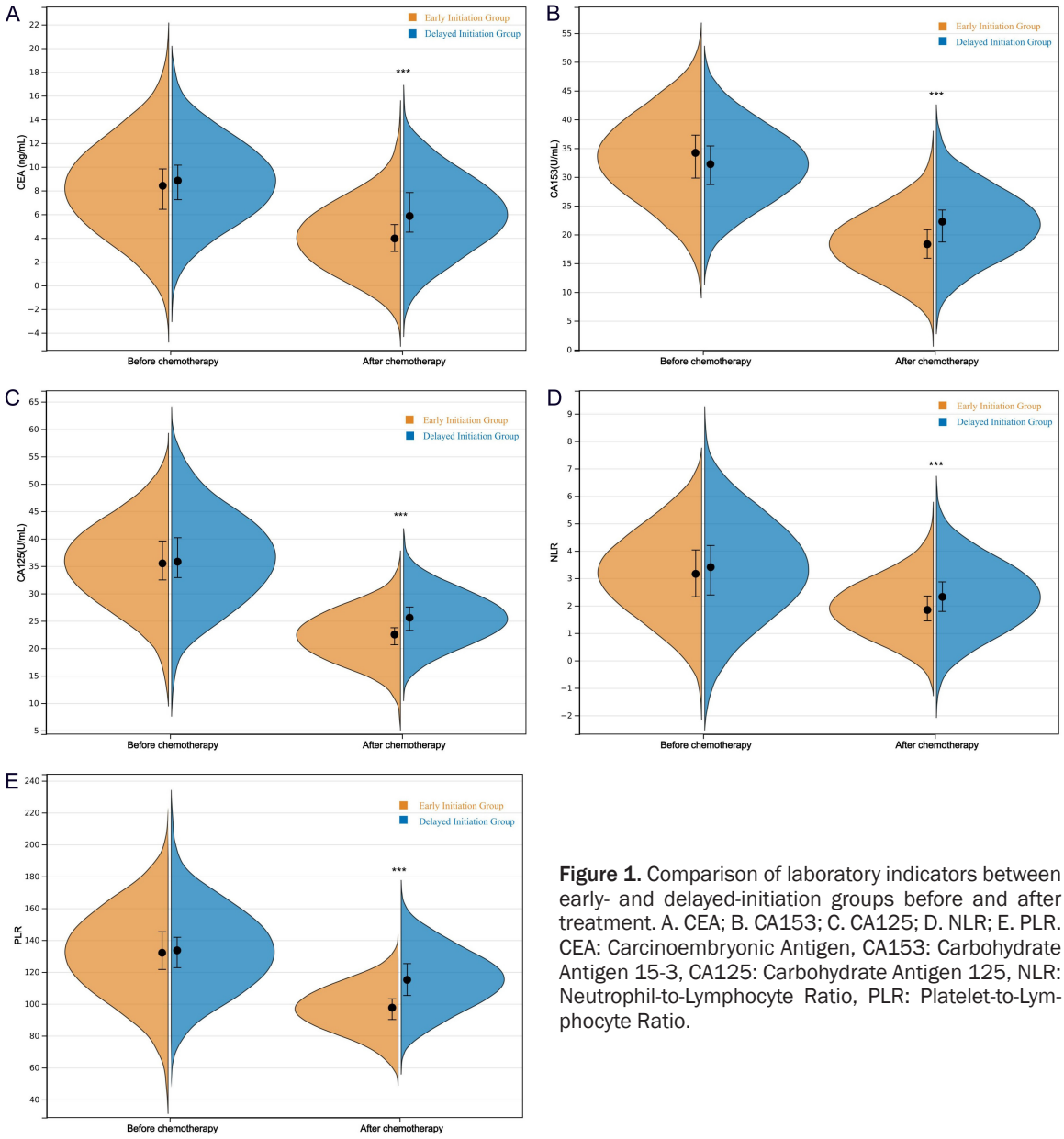

Figure 1. Comparison of laboratory indicators between early- and delayed-initiation groups before and after treatment. A. CEA; B. CA153; C. CA125; D. NLR; E. PLR. CEA: Carcinoembryonic Antigen, CA153: Carbohydrate Antigen 15-3, CA125: Carbohydrate Antigen 125, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio.

Comparison of adverse reactions between the two groups of patients

The incidence of grade ≥ 3 adverse reactions was low in both groups ($P > 0.05$), with hand-foot syndrome being the most common. For patients who developed grade ≥ 2 hand-foot syndrome or grade ≥ 3 other adverse events, corresponding dose adjustments (e.g., suspending drug administration until symptoms resolved to grade ≤ 1, then resuming treatment at 75% of the original dose) and symptomatic supportive care (e.g., use of urea ointment, analgesics, etc.) were implemented. There were no significant differences between the two groups in the proportion of patients requiring dose adjustment or temporary treatment interruption, nor in the proportion of patients with no adverse reactions ($P > 0.05$) (**Table 3**).

Comparison of quality of life between the two groups

Before treatment and 1 year after chemotherapy, the quality of life of the two groups of patients was compared according to the FACT-B scoring system. There were no significant differences between the two groups in terms of phys-

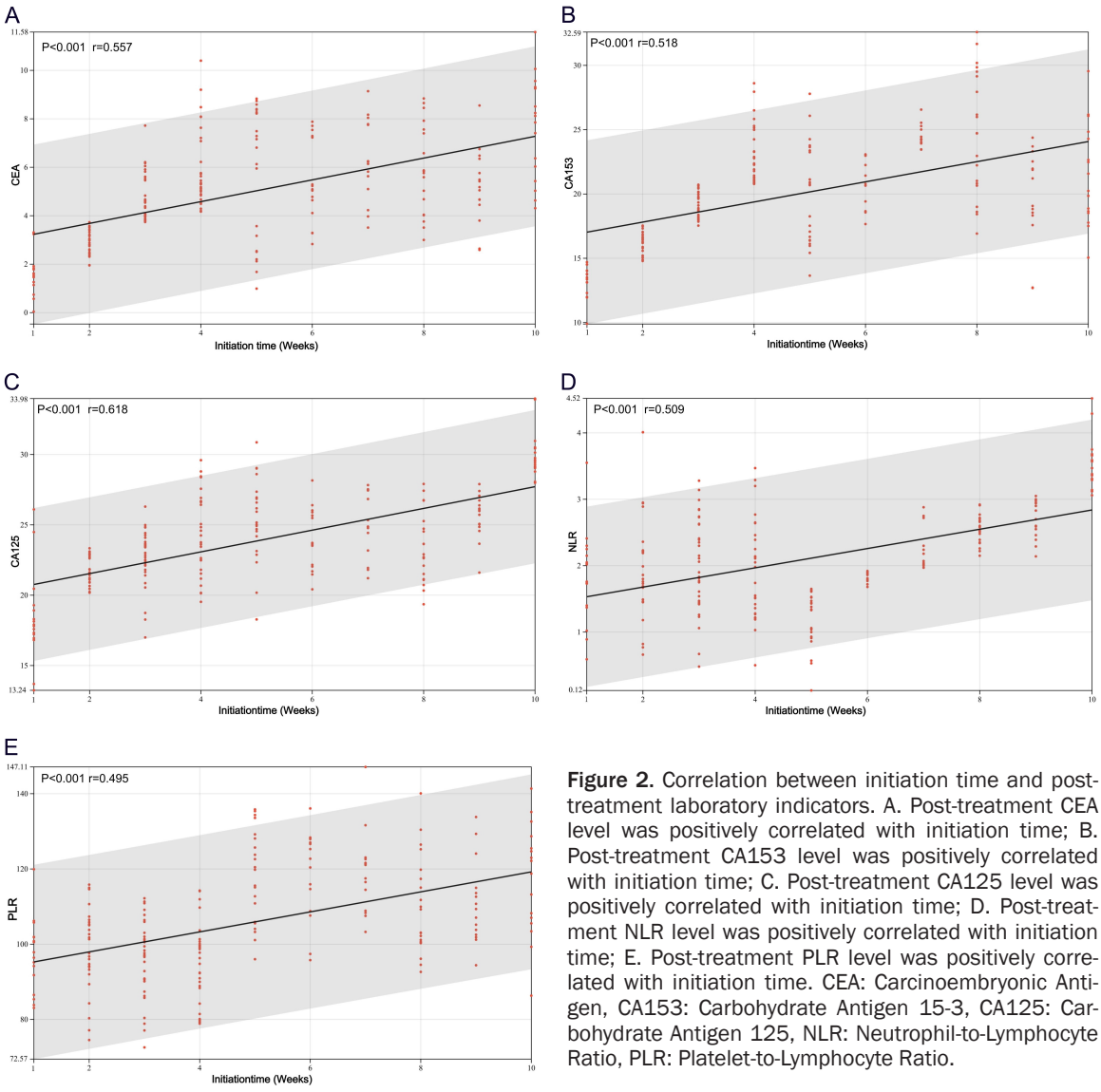

Figure 2. Correlation between initiation time and post-treatment laboratory indicators. A. Post-treatment CEA level was positively correlated with initiation time; B. Post-treatment CA153 level was positively correlated with initiation time; C. Post-treatment CA125 level was positively correlated with initiation time; D. Post-treatment NLR level was positively correlated with initiation time; E. Post-treatment PLR level was positively correlated with initiation time. CEA: Carcinoembryonic Antigen, CA153: Carbohydrate Antigen 15-3, CA125: Carbohydrate Antigen 125, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio.

ical well-being, social/family well-being, emotional well-being, functional well-being, Breast Cancer Subscale scores, or total scores before treatment. However, 1 year after treatment, the Breast Cancer Subscale score and total score of the early initiation group were significantly higher than those of the delayed initiation group ($P < 0.05$). There were no significant differences between the two groups in other module scores 1 year after treatment ($P > 0.05$), as shown in **Table 4**.

Discussion

This study retrospectively analyzed the effect of different initiation times of capecitabine metronomic chemotherapy after surgery on the prognosis of early-stage TNBC patients. It revealed a significant advantage of early-initiation treatment over delayed-initiation in terms of PFS and also clarified the dynamic relationship between laboratory indicators (e.g., CEA, CA125) and treatment timing. Although there was no statistical difference in OS between the two groups, this finding provides an important basis for optimizing adjuvant treatment strategies for TNBC.

The core finding of this study was that early initiation of capecitabine metronomic chemotherapy significantly improved the 3-year PFS of patients, while there was no difference in OS. The study by Wang et al. [12] found that early-stage TNBC patients who received low-dose capecitabine maintenance treatment after sur-

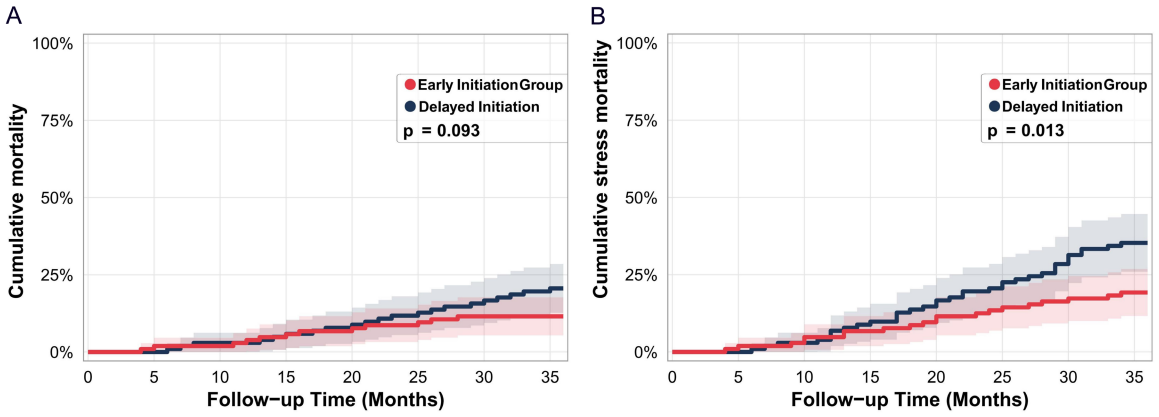

Figure 3. CIF curves for 3-year cumulative mortality and cumulative incidence of disease progression events in the two groups of patients. A. CIF curve of 3-year cumulative all-cause mortality for the two groups of patients; B. CIF curve of 3-year cumulative incidence of PFS events for the two groups of patients. CIF: Cumulative Incidence Function.

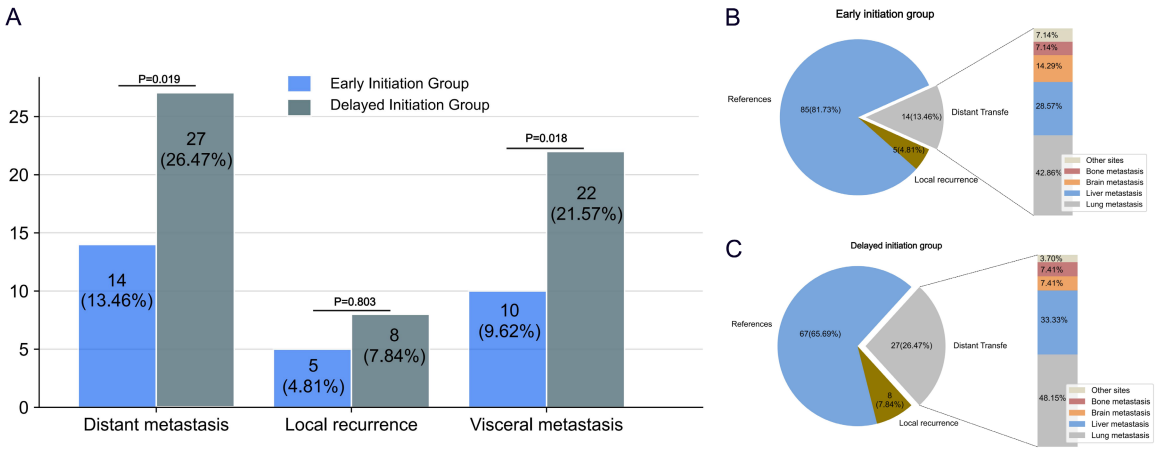

Figure 4. Comparison of recurrence types between early- and delayed-initiation groups. A. Comparison of recurrence types between the two groups; B. Recurrence type distribution in the early-initiation group; C. Recurrence type distribution in the delayed-initiation group.

gery had a significantly higher 5-year DFS rate (82.8% vs. 73.0%), which is consistent with the PFS advantage observed in this study, further verifying the value of metronomic chemotherapy for adjuvant treatment. This may be attributed to the disease characteristics of TNBC and the specificity of the postoperative treatment window. Residual micrometastatic foci may exhibit high proliferative activity in the early stage (especially within 4 weeks after surgery), when angiogenesis signals and immunosuppressive factors in the tumor microenvironment have not yet been fully re-established [13, 14]. As a fluorouracil precursor drug, capecitabine can continuously inhibit thymidylate synthase at low doses, suppress the proliferation of vascular endothelial cells, and limit the formation of new tumor blood vessels [15]. Early intervention may delay disease progression through a dual mechanism: directly killing residual tumor cells and blocking the vascular nutrient supply to micrometastatic foci. Literature has shown that capecitabine may block the proliferation of micrometastatic foci earlier by continuously inhibiting thymidylate synthase and angiogenesis signals [16], which provides a mechanistic explanation for the significant decrease in tumor markers (CEA, CA125) in the early-initiation group in this study. The significant reductions in tumor markers

Table 2. Comparison of clinicopathologic characteristics between disease progression and non-progression groups

	Non-progression Group (n = 150)	Disease progression Group (n = 56)	χ^2	P
Initiation time of chemotherapy			6.713	0.010
Early initiation	84 (56.00)	20 (35.71)		
Delayed initiation	66 (44.00)	36 (64.29)		
Age			0.020	0.888
≤ 50 years	98 (65.33)	36 (64.29)		
> 50 years	52 (34.67)	20 (35.71)		
Tumor diameter			8.531	0.004
≤ 2 cm	77 (51.33)	16 (28.57)		
> 2 cm	73 (48.67)	40 (71.43)		
Childbearing history			3.667	0.056
Has given birth	100 (66.67)	45 (80.36)		
Has not given birth	50 (33.33)	11 (19.64)		
KI-67			5.173	0.023
≤ 20%	72 (48.00)	17 (30.36)		
> 20%	78 (52.00)	39 (69.64)		
Tumor location			0.788	0.375
Left side	78 (52.00)	33 (58.93)		
Right side	72 (48.00)	23 (41.07)		
T stage			17.548	< 0.001
T1	92 (61.33)	16 (28.57)		
T2	58 (38.67)	40 (71.43)		
N stage			13.339	< 0.001
N0	108 (72.00)	25 (44.64)		
N1	42 (28.00)	31 (55.36)		
Menopausal status			0.051	0.821
Premenopausal	67 (44.67)	26 (46.43)		
Postmenopausal	83 (55.33)	30 (53.57)		
Surgical method			0.202	0.653
Modified radical mastectomy	119 (79.33)	46 (82.14)		
Breast-conserving surgery	31 (20.67)	10 (17.86)		
Pathological grade			0.153	0.696
Moderately and poorly differentiated	106 (70.67)	38 (67.86)		
Well-differentiated	44 (29.33)	18 (32.14)		
Pathological type			0.316	0.574
Invasive ductal carcinoma	118 (78.67)	42 (75.00)		
Invasive lobular carcinoma	32 (21.33)	14 (25.00)		

(e.g., CEA, CA153, CA125) and inflammatory indicators (NLR, PLR) in the early-initiation group after chemotherapy indicate that early treatment more effectively controls tumor burden and systemic inflammatory response, and the latter has been proven to be closely related to the invasiveness and immune escape of TNBC [17, 18]. It is worth noting that the strong correlation between CA125 and the initiation time (r = 0.618) may reflect its sensitivity to peritoneal or ovarian micrometastases, but its specificity in breast cancer needs further verification. Although CA125 is not a specific biomarker for breast cancer, its significant decrease in the early-initiation group may reflect more extensive inhibition of systemic inflammation or micrometastatic activity, and this warrants further research.

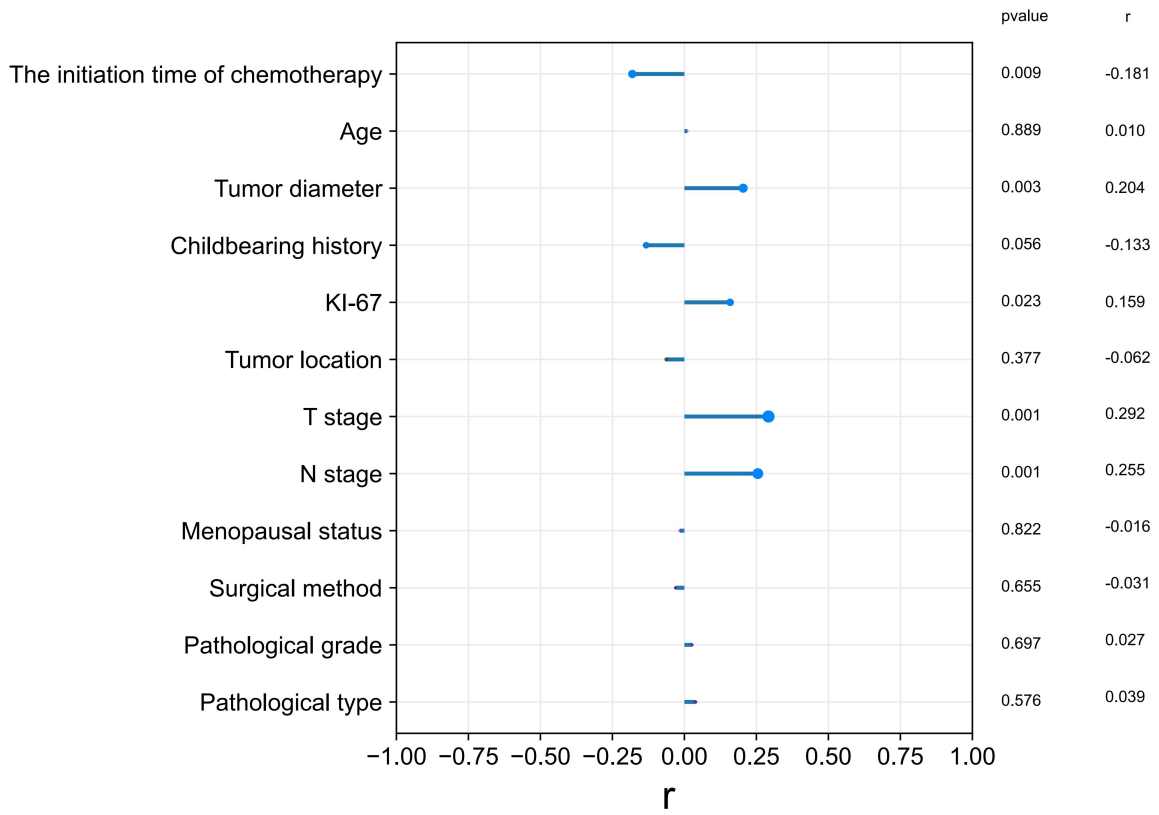

Figure 5. Correlation between clinicopathological characteristics and 3-year disease progression.

The absence of a significant difference in OS may be attributed to a relatively short follow-up period and advances in treatment methods after recurrence. The recurrence peak of TNBC usually occurs 2-3 years after surgery, and most deaths occur 1-2 years after recurrence. Therefore, extending the follow-up to 5 years may be more conducive to detecting differences in OS. Ignatiadis et al. [19] further pointed out that the failure of adjuvant immunotherapy may be related to treatment timing or patient selection, supporting the need to extend the follow-up to more than 5 years in this study to detect differences in OS. In addition, the application of immunotherapy and targeted therapy for recurrent and metastatic TNBC in recent years may partially offset the final impact of early PFS differences on survival [20, 21]. Nevertheless, the improvement of PFS itself has important clinical significance because it is directly related to the patient's quality of life, treatment burden, and psychological stress.

Subgroup analysis further revealed the interaction between treatment timing and patient characteristics. In patients with T2 stage, the 3-year PFS of the early-initiation group was significantly better than that of the delayed-initiation group, while other high-risk factors did not show such a trend. This may reflect the dynamic relationship between tumor burden and treatment sensitivity. High proliferative activity (Ki-67 > 20%) itself already indicates sensitivity to cytotoxic drugs, so the effect of treatment timing is partially masked. This finding supports the preferential use of early-initiation strategy in T2-stage patients and highlights the need to further refine the patient selection by combining molecular subtyping. This result is also consistent with the benefit trend of high-risk populations in the trial by Wang et al. [12], indicating that patients with a larger tumor burden may get greater benefit from early continuous treatment.

In this study, reductions in tumor markers such as CEA and CA125 and inflammatory indicators after chemotherapy were significantly correlated with early initiation, and these indicators were positively correlated with the initiation

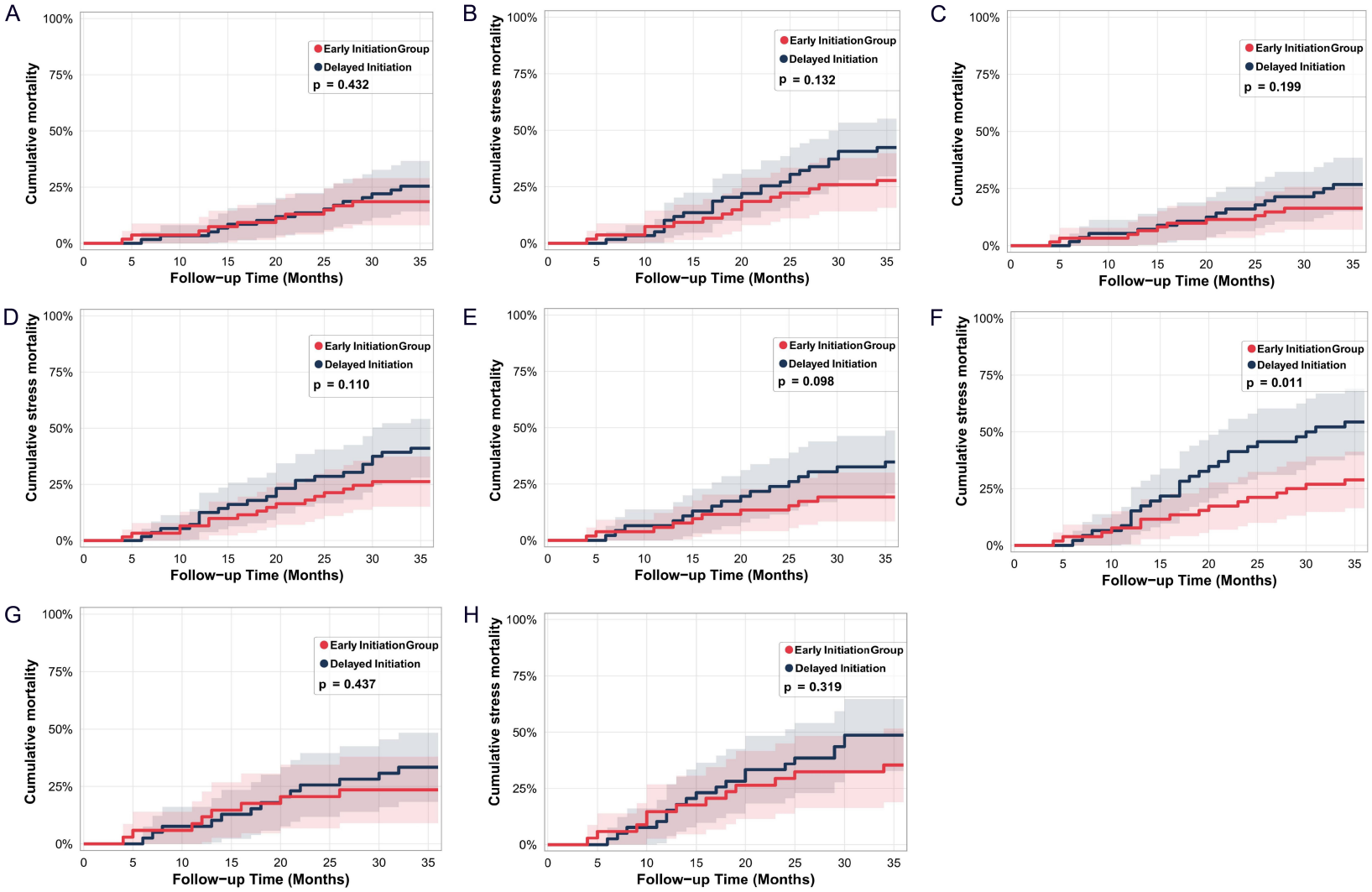

Figure 6. Comparison of outcomes in related populations. (A, B) CIF curves of 3-year all-cause mortality (A) and progression-related mortality (B) for the population with tumor diameter > 2 cm. (C, D) CIF curves of 3-year all-cause mortality (C) and progression-related mortality (D) for the population with Ki-67 > 20%. (E, F) CIF curves of 3-year all-cause mortality (E) and progression-related mortality (F) for the T2-stage population. (G, H) CIF curves of 3-year all-cause mortality (G) and progression-related mortality (H) for the N1-stage population. CIF: Cumulative Incidence Function.

Table 3. Comparison of adverse reactions between early- and delayed-initiation groups

	Early-Initiation Group (n = 104)		Delayed-Initiation Group (n = 102)		χ^2	P
	Grade 1-2	Grade 3 and above	Grade 1-2	Grade 3 and above		
Hand-foot syndrome	29 (27.88)	4 (3.85)	25 (24.51)	1 (0.98)		
Bone marrow suppression	20 (19.23)	5 (4.81)	25 (24.51)	2 (1.96)		
Elevated bilirubin	13 (12.50)	0 (0.00)	12 (11.76)	0 (0.00)		
Stomatitis	4 (3.85)	0 (0.00)	1 (0.98)	0 (0.00)		
Diarrhea	2 (1.92)	0 (0.00)	4 (3.92)	0 (0.00)		
Nausea	5 (4.81)	0 (0.00)	3 (2.94)	0 (0.00)		
Total incidence of Grade 3 and above	9 (8.65)		3 (2.94)		3.063	0.080
No adverse reactions	42 (40.38)		47 (46.08)		0.680	0.410

Table 4. Comparison of quality of life scores between early- and delayed-initiation groups before and after treatment

Dimension	Time Point	Early Initiation Group (n = 104)	Delayed Initiation Group (n = 102)	t	P
Physical Well-Being	Baseline	22.10±3.22	22.80±3.01	1.632	0.104
	1 Year After	21.31±3.66	22.09±4.02	1.457	0.147
Social/Family Well-Being	Baseline	18.91±3.09	18.38±2.78	1.297	0.196
	1 Year After	19.71±2.32	19.12±3.10	1.556	0.121
Emotional Well-Being	Baseline	23.23±2.67	23.50±2.73	0.715	0.475
	1 Year After	22.41±2.87	22.83±2.79	1.066	0.288
Functional Well-Being	Baseline	19.21±3.67	19.05±4.17	0.297	0.767
	1 Year After	18.28±2.67	17.84±4.17	0.891	0.374
Breast Cancer Subscale	Baseline	31.66±5.04	32.32±5.11	0.934	0.352
	1 Year After	35.01±4.70	31.84±5.72	4.335	< 0.001
Total Score	Baseline	115.12±8.46	116.06±8.99	0.775	0.439
	1 Year After	116.72±7.42	113.73±8.09	2.768	0.006

time. This finding suggests that these readily available and low-cost biomarkers may serve as dynamic tools for monitoring treatment response. For example, a rapid decrease in CA125 may indicate the effective inhibition of micrometastatic foci, while a sustained increase in NLR/PLR may warn of early recurrence. However, the specificity of these markers is limited: CEA is more sensitive for gastrointestinal tumors, CA125 is closely related to gynecological tumors, and inflammatory indicators are easily affected by infections or comorbid diseases [22, 23]. Future research needs to explore the relationship between TNBC-specific markers and treatment timing and construct a multidimensional prediction model by combining radiomics or metabolomics. Notably, patients receiving immunotherapy were not included in this study. As suggested by Mo et al. [24], the potential synergistic effect between early metronomic chemotherapy and immunotherapy represents a promising direction for future prospective trials. Previous study has proven [25] the synergistic effect between metronomic chemotherapy and targeted therapy in HER2-positive breast cancer, and future research is needed to explore its cross-subtype application potential in TNBC.

This study has several limitations. First, its retrospective, single-center design carries the risk of selection bias and unmeasured confounding factors, despite statistical adjustment for known baseline variables. Confounding factors such as patient adherence, specific comorbidities, and detailed postoperative recovery status could not be fully controlled. Second, the sample size - particularly for subgroup analyses

- was limited, and no multiple testing correction was performed, which increases the risk of Type I errors. Third, the 3-year follow-up period may have been too short to detect differences in overall survival. Fourth, although the underlying principles are similar, the specific regimen of previous standard chemotherapy may have varied among individuals, which could have influenced the results. Fifth, the assessment of adverse reactions was not conducted in a blinded manner, which may have introduced observer bias.

In conclusion, early initiation of capecitabine metronomic chemotherapy can improve the progression-free survival of early-stage TNBC patients without increasing treatment toxicity. This strategy is particularly suitable for patients with T2 stage.

Disclosure of conflict of interest

None.

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