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Efficacy of adjuvant capecitabine in triple-negative breast cancer with residual disease after neoadjuvant therapy: a real-world study

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ABSTRACT

Purpose: To determine the beneficiaries of capecitabine in patients with triple-negative breast cancer (TNBC) who failed to achieve pathological complete response (pCR) by analyzing the efficacy of the drug in different HER2 statuses and TNM stages.

Methods: The Kaplan–Meier survival curve was plotted to estimate the effect of capecitabine therapy on disease-free survival (DFS) and overall survival (OS). Furthermore, the Cox proportional hazards model was used to analyze the factors that influence DFS and OS.

Results: A total of 296 patients with TNBC who had non-pCR after undergoing neoadjuvant therapy (NAT) were included in this study. There were 152 patients (51.4 %) in the capecitabine group and 144 patients (48.6 %) in the no-capecitabine group. The 3-year DFS and OS rates of the capecitabine group were better than those of the no-capecitabine group (DFS 80.0 % vs. 68.0 % p = 0.012, OS 95.9 % vs. 86.9 % p = 0.011). In addition, the capecitabine group exhibited significantly better DFS and OS than the no-capecitabine group in the HER2-low (DFS p = 0.004, OS p = 0.009) and stage III (DFS p = 0.004, OS p = 0.008) populations but not in the HER2-0 or stage II population.

Conclusion: Adjuvant capecitabine therapy significantly improved the prognosis of patients with TNBC who had residual disease after NAT, and the improvements in the outcomes were significant in patients with HER2-low expression and stage III disease. Other effective treatment methods should be explored for patients with HER2-0 expression or stage II disease.

1. Introduction

Triple-negative breast cancer (TNBC) refers to the molecular subtype of breast cancer with negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [1,2]. TNBC is associated with a poor prognosis [3,4]. Neoadjuvant therapy (NAT) is one of the main systemic therapies for early-stage TNBC. NAT can enhance the surgical and breast-conserving rates and provide drug sensitivity information. NAT also serves as a screening mechanism, and based on the pathological response after NAT, patients with poor prognosis can be screened out for intensive treatment [5,6]. Pathological complete response (pCR) is a key indicator for assessing the sensitivity of NAT. Patients with TNBC who do not achieve pCR after receiving NAT have a worse prognosis than those achieving pCR [7,8]. Although capecitabine improves the survival of patients with TNBC with non-pCR [9], it does not provide a cure for all patients. Hence, the population that benefits from capecitabine must be screened out, and effective treatment methods must be identified for those who do not benefit from capecitabine.

The significant therapeutic effect of trastuzumab deruxtecan on HER2-low tumors in the DESTINY-Breast04 trial [10] suggests that, in the future, TNBC could be categorized into HER2-low and HER2-0

Abbreviations: DFS, disease-free survival; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; K–M, Kaplan–Meier; MP, Miller–Payne; NAT, neoadjuvant therapy; OS, overall survival; pCR, pathological complete response; PR, progesterone receptor; TNBC, triple-negative breast cancer.

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subtypes for treatment. Whether HER2-low expression in breast cancer has unique biological significance is yet to be elucidated [11–16]. A retrospective analysis of prospective study data incorporating four NAT trials observed that HER2-low expression was linked to better survival in patients with TNBC or those with residual tumors after NAT [11]. In a retrospective study involving nearly one million patients with breast cancer, the overall survival (OS) of patients with HER2-low tumors was better than that of those with HER2-0 tumors only in high-stage patients [17]. This finding suggests that HER2-low expression might have considerable categorization value for breast cancer in high-risk patients. Analyzing the efficacy of capecitabine in patients with non-pCR TNBC with different HER2 statuses may aid in identifying the beneficiaries of the drug.

In the CBCSG 010 trial, the addition of capecitabine improved the disease-free survival (DFS) in patients with TNBC. Subgroup analysis revealed that while patients with lymph node metastasis benefited significantly from capecitabine, those without lymph node metastasis did not [18]. In the SYSUCC-001 trial, low-dose capecitabine maintenance therapy for 1 year enhanced the DFS in the patients. Subgroup analysis suggested that patients without lymph node metastasis benefited significantly from capecitabine, whereas those with lymph node metastasis did not [19]. Furthermore, in the Create-X trial, subgroup analysis showed that the survival benefit of capecitabine was significant in subgroups with stages T2–4 or N1 [9]. These results imply that the beneficiaries of capecitabine may be related to the TNM stage, but inconsistent conclusions suggest that the sensitivity of tumors of different stages to capecitabine should be investigated further.

At present, few studies have examined the beneficiaries of capecitabine, and there have been no reports on whether there are differences in the efficacy of capecitabine in TNBCs of various HER2 statuses and stages. Therefore, in this study, the data of patients with TNBC with residual disease after NAT in our center were examined. Moreover, the impact of postoperative capecitabine enhanced therapy on survival in patients with different HER2 statuses and stages was determined, and the beneficiaries of the drug were identified.

2. Materials and methods

2.1. Patient selection

Data of patients who were diagnosed with TNBC and received NAT in Henan Cancer Hospital from January 2016 to December 2021 were analyzed retrospectively. Inclusion criteria: female, invasive cancer, TNBC, stage II–III, received at least four cycles of NAT, underwent standard radical surgery after NAT, non-pCR (presence of residual invasive cancer in the breast specimen or regional lymph node positivity) after surgery, and availability of postoperative treatment information and follow-up information. Exclusion criteria: bilateral breast cancer, advanced breast cancer, progressive (after two cycles) or stable disease (after four cycles) during NAT, presence of other primary malignant tumors at the time of diagnosis, and loss to follow-up immediately after the surgery. None of the patients enrolled in this study received treatment with pembrolizumab, poly adenosine diphosphate-ribose polymerase inhibitor, or bisphosphonates in an adjuvant setting. This study was approved by the Medical Ethics Committee of Henan Cancer Hospital (Approval Number: 2024-247).

2.2. Data collection and survival analysis

Clinicopathological characteristics (including age at diagnosis, menopausal status, ER status pre-NAT, PR status pre-NAT, HER2 status pre-NAT, Ki-67 index pre-NAT, clinical T stage, clinical N stage, clinical TNM stage, and Miller–Payne (MP) grade) and treatment information (NAT regimens, type of breast surgery, whether received radiotherapy, and whether received capecitabine therapy) of the patients were collected. TNBC was defined as the negative expression of ER, PR, and HER2. ER and PR were considered negative if the immunohistochemistry (IHC) score was <1 %. Clinical TNM staging was performed based on the American Joint Committee on Cancer TNM staging system for breast cancer, 7th edition. HER2 interpretation was based on the American Society of Clinical Oncology/College of American Pathologists guidelines. HER2-negative was defined as HER2 IHC 0, 1+, or 2+ without HER2 gene amplification as inferred from fluorescence in situ hybridization (FISH) testing. HER2-low was defined as HER2 IHC 1+ or IHC 2+/FISH−. HER2-0 was defined as HER2 IHC 0. The capecitabine group included patients who received ≥1 cycle of capecitabine therapy after the surgery, whereas the no-capecitabine group comprised patients who did not receive capecitabine therapy after the surgery. DFS was defined as the time from radical surgery for breast cancer to the date of recurrence, development of a second primary cancer, death for any reason, or the last follow-up. OS was defined as the time between the diagnosis and death of any reason or the last follow-up.

The treatment standard for capecitabine was early-stage TNBC with non-pCR after NAT. The patients who did not receive capecitabine were mainly those treated before the release of the results of the Create-X trial; the capecitabine treatment was predominantly recommended after the release of Create-X research results in 2017. The median follow-up time of the capecitabine group was significantly shorter than that of the no-capecitabine group, which may have led to inaccurate research results. The follow-up deadline for patients in the capecitabine group was May 31, 2024. Based on the median follow-up time for the capecitabine group, the follow-up deadline for the no-capecitabine groups was adjusted to May 31, 2022. After adjustment, the median follow-up time of the two groups was close.

2.3. Statistical analysis

In this study, statistical analysis was performed using the SPSS 23.0 version. The clinicopathological characteristics of the capecitabine and no-capecitabine groups were compared using the chi-square test. The Kaplan–Meier (K–M) survival curve was used to estimate the effect of capecitabine therapy on DFS and OS. Furthermore, the log–rank test was used to compare the differences, and $p < 0.05$ was considered statistically significant. The prognostic factor analysis of DFS and OS was conducted via univariate analysis, and variables with $p < 0.05$ were included in Cox proportional hazards regression models. Finally, variables with $p < 0.05$ in the Cox analysis were considered to be independent prognostic factors.

3. Results

3.1. Patient characteristics

This study collected data from 296 patients with TNBC who did not achieve pCR after receiving NAT. The median age at diagnosis was 49 years for the patients. There were 152 patients (51.4 %) in the capecitabine group and 144 (48.6 %) in the no-capecitabine group. In the capecitabine group, there were 136 patients (89.5 %) treated for 6–8 cycles and 16 (10.5 %) treated for 1–5 cycles. None of the patients in the no-capecitabine group received capecitabine treatment. The proportion of NAT regimen using anthracyclines combined with taxanes was lower in the capecitabine group than in the no-capecitabine group (78.9 % vs. 91.0 %, $p = 0.009$). The proportion of patients with HER2-low expression in the capecitabine group was similar to that in the no-capecitabine group (61.2 % vs. 53.5 %, $p = 0.18$). There were no significant differences in age at the time of diagnosis, menopausal status, clinical T stage, clinical N stage, AJCC TNM stage, Ki-67 index, type of surgery, MP grade, radiation therapy, ypT stage, or ypN stage between the two groups (Table 1).

Table 1
Clinicopathological characteristics associated with Capecitabine treatment.

Characteristics	Total	No-capecitabine N(%)	Capecitabine N(%)	Univariate Analysis
				p-Value
Age at diagnosis				0.30
≤55	233	117 (81.3)	116 (76.3)	
>55	63	27 (18.8)	36 (23.7)	
Menopausal status				0.57
Premenopausal	178	89 (61.8)	89 (58.6)	
Postmenopausal	118	55 (38.2)	63 (41.4)	
Clinical T stage				0.58
T1	19	9 (6.9)	10 (6.6)	
T2	220	103 (71.5)	117 (77.0)	
T3	41	22 (15.3)	19 (12.5)	
T4	16	10 (6.9)	6 (3.9)	
Clinical N stage				0.17
N0	80	31 (21.5)	49 (32.2)	
N1	133	69 (47.9)	64 (42.1)	
N2	16	10 (6.9)	6 (3.9)	
N3	67	34 (23.6)	33 (21.7)	
AJCC TNM stage				0.23
II	189	87 (60.4)	102 (67.1)	
III	107	57 (39.6)	50 (32.9)	
Ki-67 index				0.08
≤30 %	25	8 (5.6)	17 (11.2)	
>30 %	271	136 (94.4)	135 (88.8)	
HER2 status pre-NAT				0.18
0	126	67 (46.5)	59 (38.8)	
low	170	77 (53.5)	93 (61.2)	
NAT regimens				0.009
Anthracyclines + Taxanes	254	133 (91.0)	120 (78.9)	
Platinum-based regimens	33	8 (5.6)	25 (16.4)	
Other regimens*	12	5 (3.5)	7 (4.6)	
Type of surgery				0.11
Mastectomy	233	119 (82.6)	114 (75.0)	
Breast-conserving	63	25 (17.4)	38 (25.0)	
MP grade				0.29
1 + 2	93	40 (27.8)	53 (34.9)	
3	94	50 (34.7)	44 (28.9)	
4 + 5	109	54 (37.5)	55 (36.2)	
Radiation therapy				0.58
No	51	23 (16.0)	28 (18.4)	
Yes	245	121 (84.0)	124 (81.6)	
ypT stage				0.12
0	40	24 (16.7)	16 (10.5)	
1	154	65 (45.1)	89 (58.6)	
2	94	51 (35.4)	43 (28.3)	
3	8	4 (2.8)	4 (2.6)	
ypN stage				0.49
0	135	62 (43.1)	73 (48.0)	
1	77	39 (27.1)	38 (25.0)	
2	37	16 (11.1)	21 (13.8)	
3	47	27 (18.8)	20 (13.2)	

AJCC, The American Joint Committee on Cancer; HER2, human epidermal growth factor receptor 2; MP, Miller-Payne; NAT, neoadjuvant therapy. *, including anthracycline-based, and taxane-based regimens.

3.2. The effect of postoperative capecitabine treatment on DFS and OS

The median follow-up time for the overall population in this study was 50 months (49 months for the capecitabine group and 51 months for the no-capecitabine group). The 3-year DFS was 74.3 % (95 % CI: 69.4 %–79.6 %), and the 3-year OS was 92.1 % (95 % CI: 88.9 %–95.3 %). The DFS of the capecitabine group was 80.0 % (95 % CI: 73.9 %–86.7 %) and that of the no-capecitabine group was 68.0 % (95 % CI: 60.5 %–76.5 %). The K–M survival curve showed that the DFS of the capecitabine group was significantly better than that of the no-capecitabine group (log–rank p = 0.012, Fig. 1A). The OS of the capecitabine group was 95.9 % (95 % CI: 92.7 %–99.2 %) and that of the no-capecitabine group was 86.9 % (95 % CI: 81.2 %–92.9 %). Moreover, the K–M survival curve indicated that the OS of the capecitabine group was significantly better than that of the no-capecitabine group (log–rank p = 0.011, Fig. 1B).

In the patients with HER2-0 status, the DFS and OS of the capecitabine group were better than those of the no-capecitabine group, but the difference was not statistically significant (DFS log–rank p = 0.57, OS log–rank p = 0.36, Fig. 2A and C). In the patients with HER2-low status, the DFS and OS of the capecitabine group were significantly better than those of the no-capecitabine group (DFS log–rank p = 0.004, OS log–rank p = 0.009, Fig. 2B and D).

In the patients with stage II disease, statistically significant differences in DFS and OS were not observed between the capecitabine and no-capecitabine groups (DFS log–rank p = 0.94, OS log–rank p = 0.98, Fig. 3A and C). In the patients with stage III disease, the DFS and OS of the capecitabine group were significantly better than those of the no-capecitabine group (DFS log–rank p = 0.004, OS log–rank p = 0.008, Fig. 3B and D).

3.3. Factors influencing DFS and OS

In the analysis of factors that influence DFS, univariate analysis demonstrated that lower T (p = 0.004) and N staging (p < 0.001), higher MP grading (p < 0.001), and postoperative treatment with capecitabine (p = 0.033) were associated with better DFS (Table 2). The outcomes of multivariate analysis revealed that T staging (p = 0.013), N staging (p < 0.001), MP grading (p < 0.001), and capecitabine therapy (p = 0.036) were the independent factors that influenced DFS (Table 3).

When the factors that influence OS were analyzed, univariate analysis showed that lower T (p = 0.047) and N stage (p < 0.001), breast-conserving surgery (p = 0.023), higher MP grade (p = 0.002), and postoperative treatment with capecitabine (p = 0.028) were linked to better OS (Table 2). N staging (p < 0.001), MP grading (p = 0.004), and capecitabine treatment (p = 0.04) were the independent factors that affected OS (Table 3).

4. Discussion

To the best of our knowledge, this is the first study to combine HER2-low and HER2-0 status to analyze the efficacy of capecitabine enhanced therapy. The findings confirmed that intensified treatment with capecitabine after NAT can improve DFS and OS and further identified that capecitabine provided significant improvements in DFS and OS in HER2-low TNBC. Moreover, this research observed that in stage III TNBC, patients treated with capecitabine had significantly better DFS and OS than those who did not receive the drug. However, in stage II TNBC, DFS, and OS were not significantly improved after capecitabine therapy.

Previous studies have examined the impact of adding capecitabine on the efficacy of TNBC treatment [20]. In the GEICAM/2003-11_CIBOMA/2004-01 trial, the addition of capecitabine to the standard treatment regimen did not improve the survival of patients with breast cancer [21]. Nonetheless, in the FinXX trial, the concurrent use of capecitabine and standard chemotherapy improved the outcomes in patients with TNBC [22]. After 15 years of follow-up, the survival benefit of the overall population attained statistically significant differences [23]. Although both the CBCSG 010 trial [18] and the SYSUCC-001 trial [19] found that capecitabine improved DFS, the subgroup analysis results of the beneficiary population were inconsistent. Therefore, whether the use of capecitabine in standard adjuvant therapy or the addition of the drug for enhanced treatment after the surgery offers definite therapeutic effects remains controversial. The treatment response of the tumor can be observed during NAT, which has a unique screening value. The prognosis of patients with pCR is significantly better than that of those with non-pCR, especially in TNBC [7]. Patients with non-pCR after NAT are selected for enhanced treatment. The Create-X trial observed that postoperative capecitabine treatment improved DFS and OS in non-pCR patients with TNBC after NAT [9]. Prior to the publication of the Create-X trial results, effective treatment methods were not available for TNBC after NAT based on anthracyclines

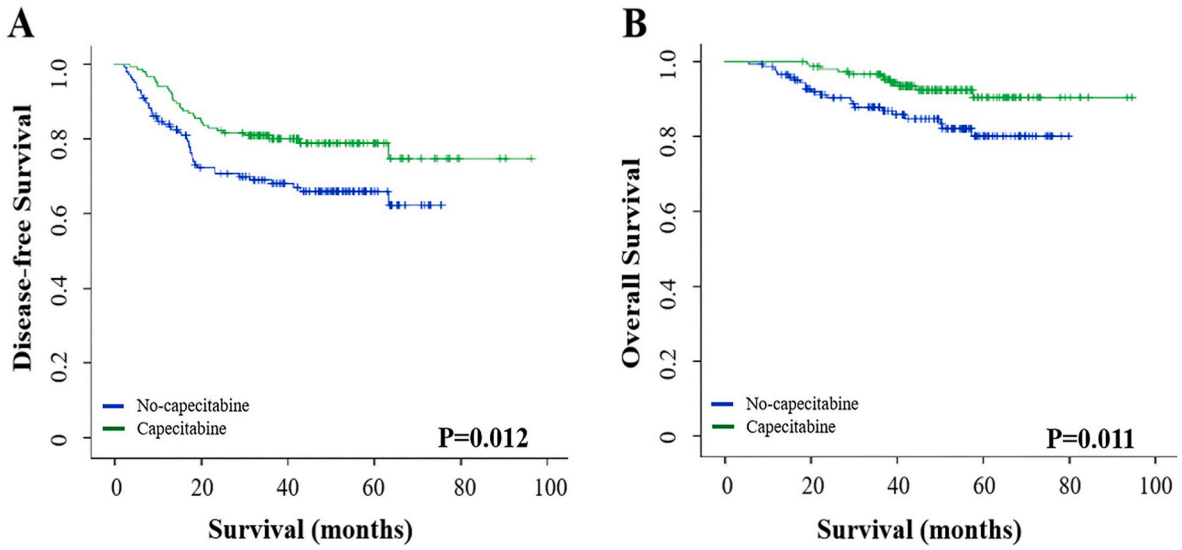

Fig. 1. Survival analysis based on capecitabine therapy. A, Disease-free survival; B, Overall survival.

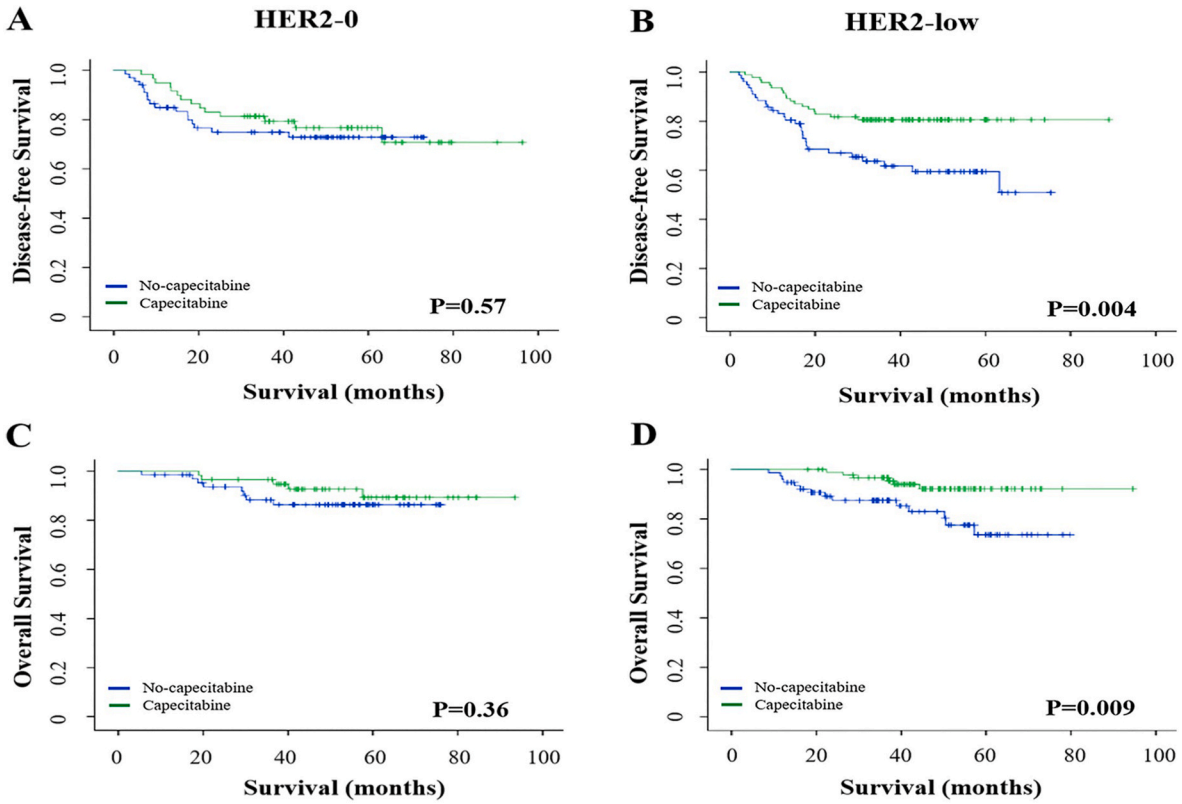

Fig. 2. Survival analysis based on capecitabine therapy and HER2 statuses. Disease-free survival analyses in the HER2-0 (A) and HER2-low (B) populations; Overall survival analyses in the HER2-0 (C) and HER2-low (D) populations. HER2, human epidermal growth factor receptor 2.

combined with taxanes. Meta analyses noted that adding capecitabine treatment in TNBC was associated with improved outcomes [24–27]. The meta-analysis conducted by van Mackelenbergh et al. found that adding capecitabine to standard chemotherapy could improve DFS and OS of patients with breast cancer [28]. Subgroup analysis revealed that only in the CREATE-X trial, both DFS and OS were improved and the improvement only occurred in TNBC. However, von Minsckwitz et al. reported that the addition of capecitabine enhanced the survival of patients with hormone receptor positivity but not those with TNBC [29]. The design of their study was different from that of the Create-X trial. However, the inconsistencies in these studies signify that further research is required on the beneficiaries of capecitabine.

In this study, the patients who did not receive capecitabine were mainly those treated before the release of the results of the Create-X trial [9], and some patients refused or could not tolerate the drug. Most patients with TNBC who underwent NAT after the release of the results of the Create-X trial received intensive treatment with capecitabine after the surgery. The capecitabine treatment was predominantly recommended after the release of Create-X research results in 2017. Along with the economic development and the popularization of scientific

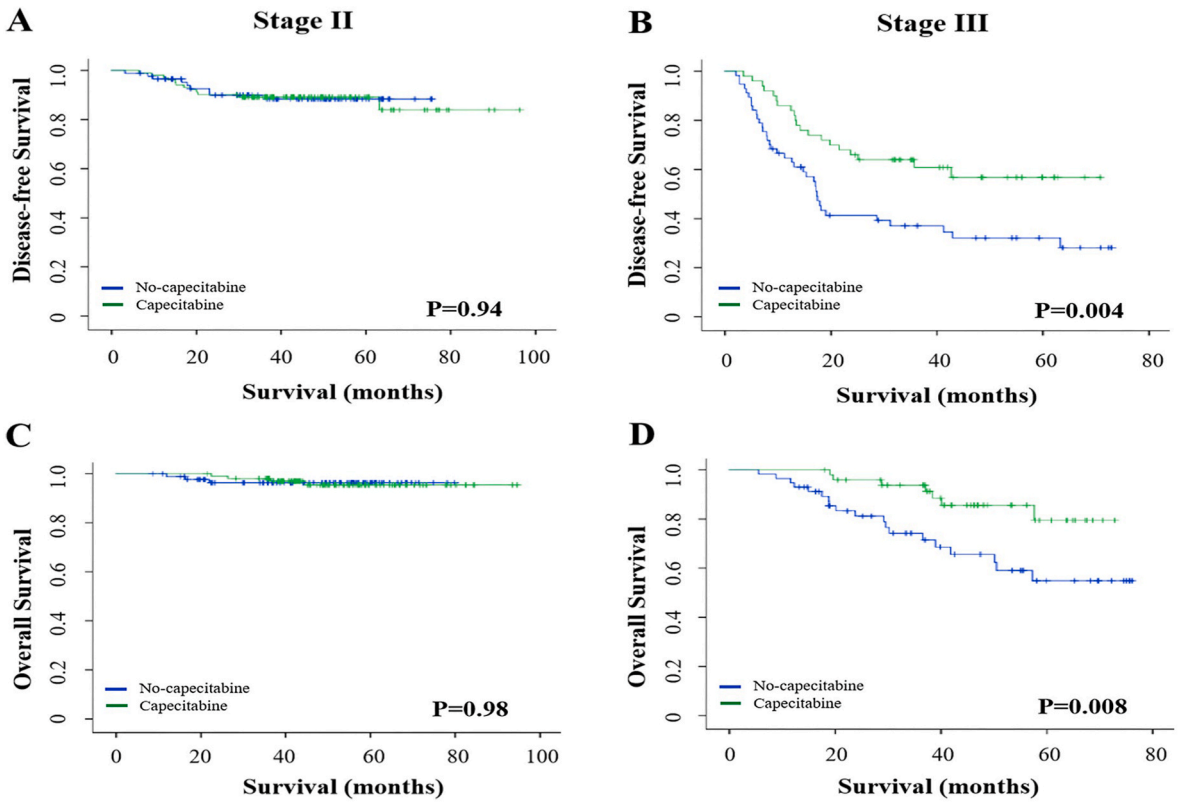

Fig. 3. Survival analysis based on capecitabine therapy and TNM stages. Disease-free survival analyses in the stage II (A) and stage III (B) populations; Overall survival analyses in the stage II (C) and stage III (D) populations.

treatment concepts, the breast-conserving rate of patients with breast cancer increased gradually in our center. Therefore, the breast-conserving rate of the capecitabine group was higher, but it did not reach statistical significance. With the addition of platinum-based drugs to the recommended NAT regimens for TNBC, the proportion of regimens combining anthracyclines with taxanes also demonstrated a decreasing trend. Therefore, the proportion of NAT using anthracyclines combined with taxanes in the capecitabine group was lower than that in the no-capecitabine group.

Although capecitabine treatment immensely improves the survival of non-pCR patients, it cannot cure all patients. Hence, it is crucial to screen out the significant beneficiary population of this treatment. For patients in whom the efficacy of capecitabine is insignificant, new clinical trials must be designed to explore effective treatment methods to improve DFS and OS. The focus of this study was to analyze the effectiveness of capecitabine treatment in different subgroups and to determine the effective population. In the GEICAM/2003-11_CIBOMA/2004-01 trial, only 16 % of the overall patients (PAM50 non-basal subtype) benefited from capecitabine [30]. This study noted that the capecitabine group exhibited better DFS and OS than the no-capecitabine group in HER2-low patients. However, in HER2-0 patients, there was no significant DFS or OS advantage. The results of the DESTINY-Breast04 trial [10] showed that the HER2-low status can be used as a basis for therapeutic categorization of advanced breast cancer. The findings of this study support HER2-low status as a predictive factor for capecitabine efficacy in TNBC. This study found that the treatment benefit of capecitabine was greater in patients with stage III disease. On the contrary, capecitabine therapy did not provide significant survival benefits to patients with stage II disease. In the subgroup analysis of the Create-X trial, subgroups with $\geq$T2 stage or 1–3 lymph node metastases obtained significant survival benefits with capecitabine therapy. The DFS subgroup analysis performed in the CBCSG 010 trial suggested that patients with lymph node positivity benefit significantly from capecitabine therapy. This observation appears to indicate that tumors with higher stages are associated with the survival benefits of capecitabine, which agrees with the results of this study.

However, there are several limitations in this study. The retrospective nature of this study is a major limitation. Being retrospective research, data on the dosage of oral capecitabine were partly reported by the patients, and the lack of supervision by researchers or third parties prevented the assurance of completeness and accuracy of the data. Moreover, obtaining accurate data about dose reduction is difficult. This study lacks data on the toxicity rates or adverse events for the capecitabine arm. The unicentric design is also one of the shortcomings of this study. In addition, the ER, PR, and HER2 status was not retested in a central laboratory. Furthermore, owing to the shortage of pathologists in our center, from the perspective of work convenience, the MP grading system was adopted instead of the Residual Cancer Burden grading system, which added to the shortcomings of this study.

5. Conclusion

This investigation confirmed that capecitabine therapy plays a role in improving the prognosis of patients with TNBC who have residual disease after NAT. For the first time, this study established that compared with HER2-0 patients; capecitabine therapy exerted a more significant therapeutic effect in HER2-low patients. In stage III patients, the efficacy of capecitabine was significant, whereas in stage II patients, the drug failed to significantly improve survival. Capecitabine significantly improved the survival in HER2-low or stage III patients; however, other effective treatment modalities must be explored for HER2-0 or stage II patients.

CRediT authorship contribution statement

Youzhao Ma: Writing – original draft, Validation, Methodology,

Table 2
Univariate analysis of clinicopathological characteristics associated with DFS and OS.

Characteristics	Total	No-DFS events N(%)	DFS events N(%)	Univariate Analysis	No-OS events N(%)	OS events N(%)	Univariate Analysis
				p-Value			*p*-Value
Age at diagnosis				0.65			0.18
≤55	233	173 (79.4)	60 (76.9)		210 (79.8)	23 (69.7)	
>55	63	45 (20.6)	18 (23.1)		53 (20.2)	10 (30.3)	
Menopausal status				0.77			0.75
Premenopausal	178	130 (59.6)	48 (61.5)		159 (60.5)	19 (57.6)	
Postmenopausal	118	88 (40.4)	30 (38.5)		104 (39.5)	14 (42.4)	
T stage				0.004			0.047
T1	19	12 (5.5)	7 (9.0)		15 (5.7)	4 (12.1)	
T2	220	168 (77.1)	52 (66.7)		201 (76.4)	19 (57.6)	
T3	41	32 (14.7)	9 (11.5)		35 (13.3)	6 (18.2)	
T4	16	6 (2.8)	10 (12.8)		12 (4.6)	4 (12.1)	
N stage				<0.001			<0.001
N0	80	76 (34.9)	4 (5.1)		78 (29.7)	2 (6.1)	
N1	133	111 (50.9)	22 (28.2)		127 (48.3)	6 (18.2)	
N2	16	7 (3.2)	9 (11.5)		11 (4.2)	5 (15.2)	
N3	67	24 (11.0)	43 (55.1)		47 (17.9)	20 (60.6)	
Ki-67 index				0.22			0.39
≤30 %	25	21 (9.6)	4 (5.1)		24 (9.1)	1 (3.0)	
>30 %	271	197 (90.4)	74 (94.9)		239 (90.9)	32 (97.0)	
HER2 status				0.56			0.70
0	126	95 (43.6)	31 (39.7)		113 (43.0)	13 (39.4)	
Low	170	123 (56.4)	47 (60.3)		150 (57.0)	20 (60.6)	
NAT regimens				0.70			0.31
Anthracyclines + Taxanes	251	183 (83.9)	68 (87.2)		220 (83.7)	31 (93.9)	
Platinum-based regimens	33	25 (11.5)	8 (10.3)		32 (12.2)	1 (3.0)	
Other regimens*	12	10 (4.6)	2 (2.6)		11 (4.2)	1 (3.0)	
Type of surgery				0.07			0.023
Mastectomy	233	166 (76.1)	67 (85.9)		202 (76.8)	31 (93.9)	
Breast-conserving	63	52 (23.9)	11 (14.1)		61 (23.2)	2 (6.1)	
MP grade				<0.001			0.002
1 + 2	93	56 (25.7)	37 (47.4)		78 (29.7)	15 (45.5)	
3	94	68 (31.2)	26 (33.3)		79 (30.0)	15 (45.5)	
4 + 5	109	94 (43.1)	15 (19.2)		106 (40.3)	3 (9.1)	
Radiation therapy				0.62			0.88
No	51	39 (17.9)	12 (15.4)		45 (17.1)	6 (18.2)	
Yes	245	179 (82.1)	66 (84.6)		218 (82.9)	27 (81.8)	
Capecitabine				0.033			0.028
No	144	98 (45.0)	46 (59.0)		122 (46.4)	22 (66.7)	
Yes	152	120 (55.0)	32 (41.0)		141 (53.6)	11 (33.3)	

DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; MP, Miller-Payne; NAT, neoadjuvant therapy; OS, overall survival. *, including anthracycline-based, and taxane-based regimens.

Table 3
Multivariate analysis of clinicopathological characteristics associated with DFS and OS.

Characteristics	DFS			OS		
	HR	95 %CI	*p*-Value	HR	95 %CI	*p*-Value
T stage			0.013			0.12
T1	1			1		
T2	0.54	0.23–1.26	0.16	0.30	0.09–0.99	0.048
T3	0.42	0.15–1.21	0.11	0.52	0.12–2.24	0.38
T4	1.65	0.61–4.49	0.32	0.79	0.18–3.47	0.76
N stage			<0.001			<0.001
N0	1			1		
N1	3.55	1.22–10.34	0.02	1.91	0.36–10.17	0.45
N2	9.54	2.84–32.11	<0.001	8.04	1.29–50.08	0.025
N3	19.20	6.82–54.03	<0.001	15.53	3.05–79.10	0.001
MP grade			<0.001			0.004
1 + 2	1			1		
3	0.73	0.44–1.24	0.25	1.11	0.47–2.21	0.97
4 + 5	0.24	0.13–0.47	<0.001	0.12	0.03–0.45	0.002
Capecitabine						
No	1			1		
Yes	0.60	0.37–0.97	0.036	0.44	0.20–0.96	0.04
Type of surgery						
Breast-conserving				1		
Mastectomy				1.26	0.25–6.45	0.78

DFS, disease-free survival; HR, hazard ratio; MP, Miller-Payne; OS, overall survival.

Conceptualization. **Mingda Zhu:** Methodology, Formal analysis. **Jingyang Zhang:** Software, Formal analysis. **Dechuang Jiao:** Funding acquisition, Data curation. **Yangyang Hou:** Data curation. **Xiuchun Chen:** Writing – review & editing. **Zhenzhen Liu:** Supervision, Resources, Project administration.

Data availability statement

The data presented in this study are available from the corresponding author on a reasonable request. The data are not publicly available due to ongoing studies and for patient privacy.

Ethics approval and consent to participate

This study was conducted in accordance with the standards set out in the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of Henan Cancer Hospital (Approval Number: 2024-247). The Medical Ethics Committee of Henan Cancer Hospital granted exemption from obtaining informed consent for the study considering its retrospective nature.

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Declaration of Competing interest

The authors of the article declare that there are no conflicts of interest related to this manuscript.

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