Screening Optimal Candidates with Operable, Early-Stage Triple-Negative Breast Cancer Benefitting from Capecitabine Maintenance: A Post-Hoc Analysis of the SYSUCC-001 Study

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Research Article

Keywords: triple-negative breast cancer, ideal patients, capecitabine maintenance, disease-free survival, predicting model

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Abstract

Background

Recent clinical trials and meta-analyses suggest that addition of capecitabine to standard chemotherapy could be beneficial in early-stage triple-negative breast cancer (TNBC). We aimed to develop an individualized prediction model to quantify the clinical benefit of capecitabine maintenance in TNBC.

Methods

Data of patients from the SYSUCC-001 trial (NCT01112826), randomized to standard treatment with or without metronomic capecitabine maintenance, were analyzed. Candidate covariates included age, menstrual status, type of surgery, postoperative chemotherapy regimen, Ki-67 percentage, histologic grade, primary tumor size, lymphovascular invasion, node status, and capecitabine medication. The primary endpoint was disease-free survival (DFS). The nonlinear effects of continuous covariates were modeled by restricted cubic spline. A survival prediction model was constructed using Cox proportional hazards regression analysis.

Results

The data of 434 patients (306 in the development cohort and 128 in the validation cohort) were analyzed. The estimated 5-year DFS in the development cohort and validation cohort were 77.8% (95% CI, 72.9%-82.7%) and 78.2% (95% CI, 70.9%-85.5%), respectively. Age and node status had significant nonlinear effects on DFS. The prediction model constructed using four covariates (node status, lymphovascular invasion, capecitabine maintenance, and age) demonstrated satisfactory calibration and fair discrimination ability, with C-index of 0.722 (95% CI, 0.662–0.781) and 0.764 (95% CI, 0.668–0.859) in the development cohort and validation cohort, respectively. An easy-to-use online calculator for predicting benefit of capecitabine maintenance was also designed.

Conclusions

The evidence-based prediction model may help identify patients most likely to benefit from metronomic capecitabine maintenance and thus help in decision making in daily clinical practice.

Introduction

Triple-negative breast cancer (TNBC) presents with heterogeneous molecular and clinicopathological characteristics, but the treatment strategy is the same, with chemotherapy being the only adjuvant treatment option [1–5]. Multiple clinical trials have shown that addition of capecitabine to standard chemotherapy can reduce relapse risk in early-stage TNBC [6–10]. However, any benefit is at the cost of
increased toxicity, longer treatment duration, and higher costs. Therefore, it is important to identify those who are most suited for capecitabine treatment.

Tumor relapse after curative treatment is basically due to revival of minimal residual disease that is seldom detected on routine clinical examination [11, 12]. Traditionally, the possibility of minimal residual disease-and hence the need for intensive capecitabine therapy in TNBC-has been determined by assessing the anatomic stage of the disease, but this overly simple probabilistic model does not consider various patient-specific clinicopathological characteristics that influence treatment efficacy and outcomes. An individualized prognostic model using clinicopathological information for predicting disease-free survival (DFS) and quantifying the expected benefit from capecitabine would be extremely meaningful for clinicians.

The aim of this study was to reanalyze the data of the SYSUCC-001 trial [6] and develop a clinically applicable tool to identify patients most likely to derive survival benefits from capecitabine therapy after surgery.

**Methods**

**Study Population and Design**

The SYSUCC-001 trial (Clinicaltrials.gov: NCT01112826) was an open-label, prospective, multicenter, randomized, phase III study that enrolled patients from 13 institutions in China [6]. The participants were women with hormone receptor (HR) negative (< 1% positive cells by immunohistochemistry staining) and ERBB2 negative stage T1b-3 N0-3c M0 invasive breast ductal carcinomas of any type scheduled to receive either metronomic capecitabine maintenance or observation after completion of standard treatments based on institutional guidelines (including surgery). The specific study protocol and statistical analysis plan of the SYSUCC-001 trial can be downloaded from the published article in JAMA [6]. This study was reviewed and approved by the ethics committee of Sun Yat-sen University Cancer Center (No. B2010-001-03), we performed current study following the Declaration of Helsinki and all participants provided their written informed consent. During current post-hoc analysis, we re-randomized the 434 female patients enrolled in SYSUCC-001 trial (in a 7:3 ratio) to a training cohort and a validation cohort.

**Objectives and variables of interest**

The primary outcome of this study was DFS, defined as the time from randomization to the first occurrence of any one of the following: local relapse, distant metastasis, contralateral breast cancer, or death from any cause. The secondary outcome was overall survival (OS), defined as the time from randomization to death from any cause.

Choice of candidate variables was based on a previous study and consultation with South China Breast Cancer Group experts [1, 6, 13–17], the variables included demographic characteristics (age); clinical characteristics (menstrual status); treatment-related characteristics (type of surgery, postoperative
chemotherapy regimen, capecitabine medication); and histopathologic characteristics (Ki-67 percentage, histologic grade, primary tumor size, lymphovascular invasion, node status).

**Statistical analysis**

Continuous data were presented as medians with interquartile ranges (IQR) and compared with the Wilcoxon rank-sum test. Categorical data were reported as frequencies with percentages and compared with the chi-square test, continuity-corrected chi-square test, or Fisher exact test, as appropriate. Survival analysis was performed using the Kaplan-Meier method, and comparisons between groups were performed via the log-rank test. Time-varying, nonlinear effects were explored using survival analysis with generalized additive and restricted cubic spline models, represented as three-dimensional surfaces and contour maps [18]. The last-observation-carried-forward and imputation method were used for handling missing outcome data. Univariate and multivariate analyses were conducted using the Cox proportional hazards model. The proportional hazards assumption was confirmed based on the Schoenfeld residuals [19]. A prediction model was developed and graphically presented as a nomogram. Calibration curves were plotted, and discrimination was assessed using the Harrell C-index and the area under time-dependent receiver-operating characteristic (tROC) curve. The optimal risk score cutoff value was determined by maximally selected rank statistics. All statistical tests were two-tailed, with statistical significance at \( P \leq 0.05 \). Data analysis was performed using R 3.5.1 (https://cran.r-project.org/).

**Results**

**Patients and outcomes**

The flow diagram of these 434 patients enrolled in SYSUCC-001 trial is available in the previously published article in JAMA [6]. Herein, we divided them into a development cohort (\( n = 306 \)) and a validation cohort (\( n = 128 \)). Demographic and treatment characteristics at baseline were comparable between the two cohorts (**Table 1**). After median follow-up of 61.4 months (IQR, 44.3-82.4 months), 94 DFS events were observed, of which 67 events were in the development cohort and 27 events were in the validation cohort. The median follow-up was 61.1 months (IQR, 42.9-80.5 months) and 65.4 months (IQR, 46.8-84.7 months) in development and validation cohorts, respectively. The 5-year DFS was comparable between the development and validation cohorts (77.8% vs. 78.2%; HR = 0.95, 95% CI, 0.61-1.49, \( P = 0.833 \); **Supplementary Figure 1**).

**Development and validation of the predictive model**

Both node status and age had pronounced nonlinear effects without significant time-varying effects. **Figures 1A-C** showed the hazard ratio surfaces, restrictive cubic spline functions, and corresponding contour maps for node status. In the case of node status, the risk of recurrence increased steadily as the number of positive nodes increased from 0 to 6 and then plateaued; the effect was clearly nonlinear (\( P < 0.001 \)). Similar nonlinearity was detected for age (**Figures 1D-F; \( P = 0.011 \)).
Proportional hazards assumptions were confirmed in the multivariable Cox modeling (Supplementary Figure 2). Multivariable Cox regression analysis showed node status, lymphovascular invasion, and capecitabine maintenance to be independent prognostic factors for DFS (Table 2). These factors were used for model development. We also included the variable of age, which although was not significantly associated with DFS in multivariate analyses in the present study, has well-recognized prognostic value. Moreover, the time-dependent ROC curve and the area under ROC curve of the model that included age showed significantly better predictive value than the model that did not include age (P = 0.047; Supplementary Figure 3). The predictive model, named SYSU-001, constructed using the four variables showed satisfactory calibration (Supplementary Figure 4A) and fair discrimination ability (C-index, 0.72, 95% CI: 0.66-0.78) in the training cohort. The SYSU-001 model was graphically represented in a nomogram (Figure 2), and a web-based calculator was also designed (http://www.sysu001-tnbc.com). The nomogram showed satisfactory calibration in the validation cohort (Supplementary Figure 4B) and good discrimination of prognosis, with C-index of 0.76 (95% CI: 0.67-0.86).

Cutoff value for risk stratification and subgroup analysis

A cutoff value for quick classification of patients according to prognosis can be useful in clinical practice. For this analysis, it was decided to pool patients from both arms of the trial since the 3-variable risk score did not have significant interaction with the treatment (P = 0.096). The total risk score of three variables (node status, lymphovascular invasion, and age) for each patient from both arms of the study was calculated using this nomogram, and the optimal cutoff value was determined by maximally selected rank statistics (Supplementary Figure 5). This cutoff score was used to separate the patient cohort into a low-risk group (score ≤5.89) and a high-risk group (score >5.89). While 127 (29.3%) patients were classified as high risk, 307 (70.7%) patients were classified as low risk. The low-risk group included all node-negative patients and about half of the patients with 1-2 positive nodes.

In the whole cohort, the estimated 5-year DFS and OS rates were both significantly higher in the low-risk group than in the high-risk group (DFS: 88.6% vs. 51.8%; HR = 0.20, 95% CI: 0.13-0.30, P < 0.001; OS: 92.0% vs 62.7%, HR = 0.18, 95% CI: 0.11-0.30, P < 0.001; Figure 3A-B). We also performed subgroup analysis, comparing outcomes between patients receiving capecitabine maintenance and those receiving observation in the two risk groups. In the low-risk group, the estimated 5-year DFS and OS rates were both significantly better in patients receiving capecitabine maintenance than in patients receiving observation (DFS: 93.5% vs. 83.8%; HR = 0.65, 95% CI: 0.46-0.93, P = 0.014; OS: 95.1% vs. 89.0%; HR = 0.66, 95% CI: 0.43-0.99, P = 0.044; Figure 3C-D). In the high-risk group, DFS and OS rates were not significantly different between patients receiving capecitabine maintenance and patients receiving observation (57.9% vs. 45.3%; HR = 0.87, 95% CI: 0.67-1.12, P = 0.280; and 63.5% vs. 61.8%; HR = 0.97, 95% CI, 0.73-1.29, P = 0.809; Figure 3E-F).

Discussion
The present study aimed to develop and validate a model for predicting the benefit of capecitabine maintenance after standard treatment in women with early-stage TNBC. The model developed using four variables (age, node status, lymphovascular invasion, and capecitabine maintenance) showed satisfactory calibration and good discrimination. The model can provide quantified estimate of the benefits to be expected with capecitabine maintenance in individual patients. Notably, subgroup analyses demonstrated that significant improvement was to be had in both DFS and OS with capecitabine maintenance in low-risk patients.

This study has several important implications. The decision on whether or not to add capecitabine to standard therapy for early-stage TNBC is difficult. Previous clinical trials have reported inconsistent results [6–10]. Many patients have minimal residual disease after standard treatments, for these patients, capecitabine therapy is indicated to reduce the risk of disease recurrence. However, the longer duration of therapy, the additional toxicity, and the increased cost often led to discontinuation of therapy, negating any potential benefits of treatment. The SYSU-001 model, constructed using routinely available variables, might be able to quantify the expected benefits of capecitabine maintenance; when used in combination with clinical judgment, it can be very helpful during complex clinical decision making. Of course, patient preference must also be considered.

The SYSU-001 model can identify individuals likely to benefit most from capecitabine maintenance and thus can facilitate individualized therapy. The SYSUCC-001 and CBCSG010 trials showed significant DFS benefit but no significant OS benefit with capecitabine maintenance, while the CREATE-X trial showed significantly improved DFS (13.7%) and OS (8.5%). Therefore, it appears that only some of the patients with TNBC will derive DFS and OS benefits, and those would naturally be the most suitable candidates for capecitabine treatment. The current study showed notable DFS and OS benefits in 70% of low-risk patients (all node-negative patients and half of the patients with 1–2 positive nodes). This finding is consistent with the results of the CREATE-X trial, which reported that capecitabine benefit was more likely in patients with 1–3 positive nodes than in those with ≥ 4 positive nodes [7]. Further research is necessary to determine how to identify individuals for capecitabine treatment.

This study underscores the nonlinear effects of different factors in routine oncology practice. Among four variables in our final model, two (age and node status) were continuous variables with significant nonlinear effects on the model’s predictive ability. The risk of recurrence increased rapidly as the number of positive nodes increased from 0 to 6 and then plateaued, indicating the dynamically changing magnitude of impact of node status on DFS. This was also observed for age and likely occurs with other variables. These dynamic effects should not be dismissed. The nonlinear effect of node status indicates that the cutoffs typically applied in the traditional TNM classification are not compatible with the features of TNBC. Categorization of patients by the traditional TNM system entails substantial loss of information. Thus, categorizing the node status by the traditional TNM classification system may not be valid in cancers such as TNBC. Node status should be evaluated as a continuous variable to allow for the nonlinear effects.
The current study has several limitations. Firstly, we lacked an external validation of the model, as it was only validated in a cohort derived from the same population as the development cohort. Secondly, the study patients were all Chinese, suggesting that the current findings may not be applicable to patients from other geographic regions. For instance, age was one of the four variables included in the final model, but age at diagnosis of breast cancer varies quite obviously between Chinese and other populations, specifically speaking, the mean age at diagnosis of breast cancer in China is 45–55 years, which is considerably younger for Western women [20–22]. Thirdly, only a limited number of patients received neoadjuvant chemotherapy, which is a currently standard of treatment for patients with node positive TNBC [23]. And compared with other contemporary datasets, in which higher BCS rates would normally result in a higher use of adjuvant radiation therapy, the cohorts in the current study showed a higher mastectomy rate. Although there were minor differences in follow-up time and number of events between development and validation cohort, survival outcomes between them were not statistically significant, which therefore was not a concern. Clinicopathologic characteristics were found to be associated with capecitabine benefit in CREATE-X trial, but they were not considered in this study. According to GEICAM/2003-11_CIBOMA/2004-01 clinical trial [9], TNBC patients with non-basal phenotype seemed to benefit more from taking additional capecitabine treatment, but we didn’t perform in-depth exploration on heterogeneous TNBC subsets.

Conclusions

The SYSU-001 prediction model incorporating four routinely available clinicopathological variables appears to be capable of quantifying the benefit to be expected from addition of capecitabine therapy in early-stage TNBC. The SYSU-001 model could be used for identifying the ideal candidates for inclusion in future clinical trials of capecitabine in TNBC.

Abbreviations

TNBC Triple-negative breast cancer
DFS Disease-free survival
OS Overall survival
HR Hormone receptor
IQR Interquartile range
tROC Time-dependent receiver-operating characteristic

Declarations

Acknowledgements
We thank Alberto Carmona-Bayonas, MD, PhD, for help in the analysis of time-varying effects. We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

**Authors’ contributions**

FFD, XH and XWB contributed to the methodology and software. FFD and XH analyzed the data, wrote the first draft of this manuscript, and revised the manuscript critically for important intellectual content. XWB, SSW, YXS, FX, LW, JJH and ZYY collected the data. JJH, ZYY and YYH designed and supervised this study. All authors contributed to this article and approved the submitted version.

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**Data Availability**

The key raw data of this article have been deposited into the Research Data Deposit (http://www.researchdata.org.cn), with the approval number RDDA2021001968.

**Ethics approval and consent to participate**

This study was reviewed and approved by the ethics committee of Sun Yat-sen University Cancer Center (No. B2010-001-03).

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no competing interests.

**References**


Tables

Table 1. Patient demographics and clinical characteristics.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Development cohort</th>
<th>Validation cohort</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years, (IQR)</td>
<td>47 (39-54)</td>
<td>48 (41-55)</td>
<td>0.961</td>
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<tr>
<td>Menstrual status</td>
<td></td>
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<td>Premenopausal</td>
<td>207 (67.6%)</td>
<td>83 (64.8%)</td>
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<td>Menopausal</td>
<td>99 (32.4%)</td>
<td>45 (35.2%)</td>
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</tr>
<tr>
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<td></td>
<td>0.902</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>264 (86.3%)</td>
<td>111 (86.7%)</td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>42 (13.7%)</td>
<td>17 (13.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Median tumor size</strong>, mm, (IQR)</td>
<td>25 (20-35)</td>
<td>25 (20-35)</td>
<td>0.992</td>
</tr>
<tr>
<td><strong>Median positive nodes, (IQR)</strong></td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0.984</td>
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<tr>
<td><strong>Histological grade</strong></td>
<td></td>
<td></td>
<td>0.724</td>
</tr>
<tr>
<td>G 1</td>
<td>6 (2.0%)</td>
<td>2 (1.6%)</td>
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<tr>
<td>G 2</td>
<td>81 (26.5%)</td>
<td>29 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>G 3</td>
<td>219 (71.6%)</td>
<td>97 (75.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Median Ki-67 index</strong>, %, (IQR)</td>
<td>50 (30-70)</td>
<td>50 (30-70)</td>
<td>0.371</td>
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<tr>
<td>Lymphovascular invasion</td>
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<td></td>
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<td>Yes</td>
<td>45 (14.7%)</td>
<td>15 (11.7%)</td>
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</tr>
<tr>
<td>No</td>
<td>261 (85.3%)</td>
<td>113 (88.3%)</td>
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<tr>
<td><strong>Chemotherapy regimen</strong></td>
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<td>Anthracyclines and taxane</td>
<td>274 (89.5%)</td>
<td>113 (88.3%)</td>
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<td>32 (10.5%)</td>
<td>15 (11.7%)</td>
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<td><strong>Capecitabine maintenance</strong></td>
<td></td>
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<td>151 (49.3%)</td>
<td>70 (54.7%)</td>
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<tr>
<td>No</td>
<td>155 (50.7%)</td>
<td>58 (45.3%)</td>
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</table>

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\[a\] Tumor size at diagnosis was based on pathological assessment.

\[b\] Histological grade at diagnosis was based on the degree of tumor's histologic differentiation.
KI-67 index at diagnosis indicates DNA synthetic activity as measured by immunocytochemistry.

Table 2. Univariate and multivariate Cox regression analyses of disease-free survival (DFS).
<table>
<thead>
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<th>Variables</th>
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<th>Multivariate analysis</th>
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<td>Hazard ratio(95%CI)</td>
<td>P</td>
<td>Hazard ratio(95%CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
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<td>≤ 40</td>
<td>1.582 (0.807-3.103)</td>
<td>0.182</td>
<td>1.416 (0.716-2.801)</td>
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<td>41-50</td>
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<tr>
<td>≥ 51</td>
<td>2.024 (1.114-3.677)</td>
<td>0.021</td>
<td>1.718 (0.941-3.138)</td>
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<tr>
<td>Lumpectomy</td>
<td>1.555 (0.672-3.599)</td>
<td>0.302</td>
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<tr>
<td><strong>Tumor size (cm)</strong></td>
<td>1.013 (0.996-1.031)</td>
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<td><strong>Node status</strong></td>
<td>1.047 (1.024-1.070)</td>
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<tr>
<td>G 2</td>
<td>1.264 (0.167-9.573)</td>
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<tr>
<td>G 3</td>
<td>1.394 (0.193-10.087)</td>
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<td><strong>Ki-67 index</strong></td>
<td>0.995 (0.985-1.005)</td>
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<td><strong>Lymphovascular invasion</strong></td>
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<td>reference</td>
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<td>2.562 (1.491-4.402)</td>
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<td>1.964 (1.064-3.625)</td>
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<td>1.081 (0.423-2.024)</td>
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<td>reference</td>
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<tr>
<td>No</td>
<td>1.759 (1.062-2.912)</td>
<td>0.028</td>
<td>1.887 (1.133-3.146)</td>
<td>0.015</td>
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Figures

Figure 1

Three-dimensional surface, hazard ratio plot, and contour map showing the time-varying, nonlinear effects of node status and age. Panels A, B, and C show three-dimensional surface, hazard ratio plot, and contour map of node status, respectively. Panels D, E, and F show three-dimensional surface, hazard ratio plot, and contour map of age, respectively.

Three-dimensional surface plot showing the relation between node status (or age) and time on the y- and x-axes, respectively. The z-axis shows the contribution of each combination on the hazard ratio for disease-free survival.

Hazard ratio plot showing the relation between hazard ratio for disease-free survival and node status (or age) on the y- and x-axes, respectively.

Contour map that uses a color gradient to visualize the effect of the combination on the hazard ratio, with darker shades of blue indicating a decreased effect and darker shades of red indicating an increased effect on the hazard ratio.
Figure 2

Nomogram of the current model for disease-free survival (DFS) prediction
Figure 3

Kaplan-Meier estimates of disease-free survival (DFS) and overall survival (OS). Panels A and B show survival plots of DFS and OS in low-risk and high-risk patients, respectively. Panels C and D show survival plots of DFS and OS in capecitabine maintenance and observation patients in the low-risk group. Panels E and F show survival plots of DFS and OS in capecitabine maintenance and observation patients in the high-risk group.
Cumulative survival probabilities were estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Hazard ratios with 95% confidence intervals were estimated using the Cox proportional hazards model.

Supplementary Files

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