

# Time to metastasis predicts prognosis and improves the Bellmunt score in metastatic urothelial carcinoma

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## Article

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# Abstract

Prognostic models for metastatic urothelial carcinoma (mUC) have limited accuracy and additional clinically meaningful factors are needed to improve risk stratification. Time to metastasis from initial diagnosis (TTM) is an established prognostic variable in other urologic malignancies; however, its significance in mUC has not been fully defined. We conducted a retrospective multicenter study of 388 patients with mUC who received first-line platinum-based chemotherapy to evaluate the prognostic impact of TTM and to develop a modified risk model incorporating this factor. Patients were categorized as having synchronous (TTM < 6 months) or metachronous (TTM ≥ 6 months) metastasis. Overall survival (OS) was the primary endpoint. In the multivariate analysis, liver metastasis, hemoglobin levels < 10 g/dL, and synchronous metastasis were independent predictors of shorter OS. Incorporating TTM into Bellmunt score significantly improved prognostic performance, increasing the C-index from 0.575 to 0.613. Time-dependent analyses demonstrated superior C-indices for the modified scores at 12 and 24 months, and decision curve analysis showed a greater net clinical benefit. Net reclassification improvement was also significant, driven primarily by the event-NRI. These findings indicate that TTM is an independent prognostic factor and that its incorporation enhances the clinical utility of Bellmunt score for risk stratification in mUC.

## Introduction

Urothelial carcinoma, including bladder cancer and upper urinary tract carcinoma, is characterized by high recurrence and metastatic potential despite standard treatments <sup>1,2</sup>. The prognosis of metastatic urothelial carcinoma (mUC) remains poor, with 5-year survival rates of only 5–15% <sup>3–5</sup>, even though several new systemic therapies have been developed over the past three decades <sup>6–11</sup>. Therefore, more reliable prognostic models that incorporate additional clinically meaningful factors are required to better stratify the heterogeneous risk profiles of patients with mUC.

Prognostic models for mUC, such as the Bellmunt <sup>12</sup> score, have been established. This model incorporates clinical factors, including hemoglobin level, Eastern Cooperative Oncology Group performance status (ECOG-PS), and liver metastasis, and their prognostic utility has been demonstrated across different treatment lines <sup>13,14</sup>.

The timing of metastasis has emerged as an important prognostic factor for other malignancies. Time to first systemic therapy from diagnosis is used in metastatic renal cell carcinoma (mRCC) <sup>15</sup>, and synchronous versus metachronous metastasis is incorporated into risk stratification for metastatic hormone-sensitive prostate cancer (mHSPC) <sup>16</sup>. In other words, the time to metastasis from initial diagnosis (TTM) is now recognized as a meaningful prognostic variable in both mRCC and mHSPC. However, only a few studies have evaluated TTM in mUC <sup>17,18</sup>, and its prognostic significance remains unclear.

Therefore, in this study, we aimed to clarify the prognostic significance of TTM in patients with mUC and develop a more accurate risk model incorporating TTM to improve prognostic stratification.

## Results

### Patient characteristics

We retrospectively reviewed 444 patients; after excluding 56 patients based on the exclusion criteria, 388 patients were included in this study. The clinical characteristics of the study population are presented in Table 1. The median follow-up period was 15.2 months (IQR, 8.0–28.0 months), and the median age was 74 years (IQR, 68–79). A total of 242 patients died during follow-up, 232 of which were due to UC. The estimated OS rates at 12, 36, and 60 months were 66.2%, 32.9%, and 21.6%, respectively.

Table 1  
Comparison of patients characteristics between Synchronous and Metachronous groups

| Variables                                              | Overall Cases (n = 388) | Synchronous group (n = 266) | Metachronous group (n = 122) | P-value |
|--------------------------------------------------------|-------------------------|-----------------------------|------------------------------|---------|
| Time to metastasis (months), median (IQR)              | 0 (0–9.7)               | 0 (0)                       | 16.5 (10.4–29.1)             | < 0.001 |
| Follow-up periods (months), median (IQR)               | 15.2 (8.0–28.0)         | 13.2 (6.7–24.0)             | 19.9 (10.1–33.1)             | < 0.001 |
| Age at start of systemic therapy (years), median (IQR) | 74 (68–79)              | 73 (68–78)                  | 75 (68–80)                   | 0.136   |
| Gender, n (%)                                          |                         |                             |                              | 0.274   |
| Male                                                   | 292 (75.3)              | 205 (77.1)                  | 87 (71.3)                    |         |
| Female                                                 | 96 (24.7)               | 61 (22.9)                   | 35 (28.7)                    |         |
| Tumor Location, n (%)                                  |                         |                             |                              | 0.999   |
| Lower urinary tract                                    | 191 (49.2)              | 131 (49.2)                  | 60 (49.2)                    |         |
| Upper urinary tract                                    | 197 (50.8)              | 135 (50.8)                  | 62 (50.8)                    |         |
| Performance status, n(%)                               |                         |                             |                              | 0.893   |
| 0                                                      | 284 (73.2)              | 193 (72.6)                  | 91 (74.6)                    |         |
| 1                                                      | 88 (22.7)               | 61 (22.9)                   | 27 (22.1)                    |         |
| 2–                                                     | 16 (4.2)                | 12 (4.5)                    | 4 (3.3)                      |         |
| History of cystectomy or nephroureterectomy, n (%)     | 182 (46.9)              | 60 (22.3)                   | 122 (100)                    | < 0.001 |
| Perioperative treatment, n (%)                         | 62 (16.0)               | 18 (6.8)                    | 44 (36.1)                    | < 0.001 |
| Hemoglobin (g/dl), median(IQR)                         | 12.1 (10.9–13.2)        | 12 (10.6–13.1)              | 12.3 (11.2–13.4)             | 0.037   |
| Metastatic site, n (%)                                 |                         |                             |                              |         |
| Lymph node                                             | 300 (77.3)              | 215 (80.8)                  | 85 (69.7)                    | 0.021   |
| Liver                                                  | 38 (9.8)                | 25 (9.4)                    | 13 (10.7)                    | 0.828   |
| Others                                                 | 240 (61.9)              | 166 (62.4)                  | 74 (60.7)                    | 0.839   |
| History of immunotherapy, n (%)                        | 280 (72.2)              | 192 (72.2)                  | 88 (72.1)                    | 0.999   |
| IQR, interquartile range                               |                         |                             |                              |         |

| Variables                            | Overall Cases (n = 388) | Synchronous group (n = 266) | Metachronous group (n = 122) | P-value |
|--------------------------------------|-------------------------|-----------------------------|------------------------------|---------|
| History of enfortumab vedotin, n (%) | 89 (22.9)               | 54 (20.3)                   | 35 (28.7)                    | 0.09    |
| IQR, interquartile range             |                         |                             |                              |         |

## Comparison of patient characteristics and survival between synchronous and metachronous metastasis

We assigned 266 and 122 patients to synchronous and metachronous groups, respectively. The synchronous group had a significantly shorter follow-up period than the metachronous group ( $p < 0.001$ ). In addition, the synchronous group had significantly lower rates of prior cystectomy or nephroureterectomy ( $p < 0.001$ ) and perioperative systemic therapy ( $p < 0.001$ ), higher rates of lymph node metastasis ( $p = 0.021$ ), and lower hemoglobin levels ( $p = 0.037$ ) compared with the metachronous group (Table 1). In contrast, the distribution of individual systemic therapy regimens did not differ significantly between the two groups (Table 1, S1).

## Synchronous metastasis is a strong predictor of OS for mUC

Kaplan-Meier analysis demonstrated that the synchronous group had significantly poorer OS than the metachronous group ( $p = 0.001$ ) (Fig. 1). To determine the predictive factors for OS, we performed univariate and multivariate Cox proportional hazards regression analyses, including TTM, and established clinical prognostic indicators. The multivariate analysis demonstrated that liver metastasis (hazard ratio [HR], 3.32;  $p < 0.001$ ), hemoglobin  $< 10$  g/dL (HR, 1.66;  $p = 0.008$ ), and synchronous metastasis (HR, 1.69;  $p = 0.016$ ) were independent predictors of shorter OS (Table 2).

Table 2  
Univariate and multivariate analyses for overall survival

|                                                          | Univariate       |         | Multivariate     |         |
|----------------------------------------------------------|------------------|---------|------------------|---------|
|                                                          | HR (95% CI)      | p value | HR (95% CI)      | p value |
| Time to metastasis (Synchronous vs. Metachronous)        | 1.73 (1.30–2.31) | < 0.001 | 1.69 (1.10–2.62) | 0.016   |
| Age ( $\geq 70$ vs. $<70$ )                              | 1.17 (0.89–1.54) | 0.256   | 1.07 (0.81–1.42) | 0.625   |
| Gender (Male vs. Female)                                 | 1.20 (0.90–1.61) | 0.211   | 1.18 (0.87–1.61) | 0.277   |
| Location (Upper vs. Lower)                               | 1.32 (1.03–1.71) | 0.029   | 1.30 (0.99–1.71) | 0.057   |
| Performance status ( $\geq 1$ vs. 0)                     | 1.28 (0.96–1.72) | 0.091   | 1.18 (0.86–1.60) | 0.301   |
| History of cystectomy or nephroureterectomy (yes vs. no) | 0.61 (0.47–0.79) | < 0.001 | 0.88 (0.59–1.31) | 0.592   |
| Perioperative treatment (yes vs. no)                     | 0.63 (0.43–0.94) | 0.024   | 0.80 (0.50–1.28) | 0.358   |
| Hemoglobin ( $< 10$ vs. $\geq 10$ )                      | 1.85 (1.29–2.64) | < 0.001 | 1.66 (1.14–2.43) | 0.008   |
| Lymph node metastasis (yes vs. no)                       | 0.91 (0.68–1.23) | 0.552   | 0.80 (0.58–1.11) | 0.181   |
| Liver metastasis (yes vs. no)                            | 2.97 (2.04–4.33) | < 0.001 | 3.32 (2.21–4.99) | < 0.001 |
| CI, confidence interval; HR, hazard ratio                |                  |         |                  |         |

## Modified novel classification of Bellmunt score

In the multivariate analysis, including the components of the Bellmunt score, TTM remained an independent predictor of poorer OS. Based on this finding, we developed a modified Bellmunt score incorporating hemoglobin levels, ECOG-PS, liver metastasis, and TTM. Risk groups were defined according to the number of adverse prognostic factors: hemoglobin  $< 10$  g/dL, ECOG-PS  $\geq 1$ , presence of liver metastasis, and synchronous metastasis. Patients with no adverse factors were classified as the good-risk group, whereas those with one, two, and three or four factors were classified as the intermediate-, poor-, and very poor-risk groups, respectively (Fig. 2A,B).

We evaluated the discriminatory performance of the modified Bellmunt score using several approaches. Adding TTM to the original Bellmunt score significantly improved the discrimination of OS. The C-index

increased from 0.575 to 0.613 ( $\Delta = 0.038$ ;  $p = 0.002$ ). Given the median follow-up of 15.2 months, time-dependent C-indices were primarily assessed at 12 and 24 months, where adequate numbers of patients remained at risk. Time-dependent ROC analysis demonstrated that the modified score achieved higher C-indices than the original score at both 12 (0.639 vs. 0.596;  $p = 0.010$ ) and 24 months (0.692 vs. 0.648;  $p = 0.026$ ). DCA further showed that the modified Bellmunt score provided a greater net clinical benefit across a wide range of threshold probabilities at both 12 and 24 months (Fig. 3). Additionally, the event-NRI and non-event-NRI were 0.112 (95% confidence interval [CI], 0.050–0.179) and  $-0.037$  (95% CI,  $-0.062$  to  $-0.015$ ), respectively, resulting in an overall NRI of 0.075 (95% CI, 0.009–0.143), indicating a statistically significant improvement in risk reclassification. Consistent with these findings, the reclassification flow diagram (Fig. S1A) illustrates the overall pattern of movement across risk categories. Because the modified Bellmunt score only allows upward or unchanged transitions, the diagram visually depicts how patients shift toward higher-risk categories under the new classification scheme. Although the Sankey diagram did not distinguish events from non-events, the accompanying upward-reclassification plot stratified by event status (Fig. S1B) clarified that upward transitions occurred predominantly among patients who experienced events, consistent with the positive event-NRI.

## Discussion

In this study, we revealed that synchronous disease was significantly associated with poorer OS than metachronous disease in patients with mUC. Although a previous study reported shorter OS in synchronous mUC<sup>17</sup>, another study showed no significant association between TTM and survival outcomes<sup>18</sup>, leaving the prognostic impact of TTM in mUC uncertain. However, in our study, synchronous disease remained an independent predictor of worse OS alongside liver metastasis and low hemoglobin levels in the multivariate model. Both liver metastasis and low hemoglobin levels are well-established strong prognostic factors in mUC<sup>12</sup>, and the consistent association observed here suggests the clinical impact of TTM. Furthermore, TTM has been established as an important prognostic variable in other urologic malignancies<sup>15,16</sup>, supporting its potential utility in risk stratification for mUC.

The Bellmunt score, which incorporates hemoglobin level, ECOG-PS, and liver metastasis, is a well-established risk classification tool for patients with mUC across different treatment lines<sup>12–14</sup>. To enhance its prognostic performance, we developed a modified Bellmunt score by incorporating TTM. This modification resulted in a higher C index than the original Bellmunt score. Consistently, time-point analyses demonstrated superior C-indices for the modified score across multiple time horizons. In addition, the modified Bellmunt score provided a greater net benefit across a wide range of threshold probabilities in the DCA. Furthermore, the NRI was statistically significant, indicating that the incorporation of TTM improved risk reclassification, particularly by appropriately upclassifying patients who experienced events. These findings suggest that the modified Bellmunt score offers a more refined and clinically useful framework for the risk stratification of mUC.

The optimal cut-off value for TTM remains controversial. In this study, we adopted 6 months to categorize patients into synchronous or metachronous disease based on a previous report <sup>19</sup>. In addition, our analysis showed no significant difference in OS between patients with TTM of 0 months and those with TTM between 0 and 6 months (Table S2). Therefore, using 6 months as the cut-off appears reasonable and clinically meaningful for distinguishing synchronous from metachronous disease. However, different cut-off values have been used in mRCC <sup>15</sup> and mHSPC <sup>16</sup>, and further investigation is needed to determine the optimal threshold for prognostic stratification in patients with mUC.

This study had several limitations. First, as a retrospective multicenter study, the choice of systemic therapy, assessment of metastatic disease, and follow-up schedules were not standardized across institutions. Second, external validation was not performed, and analyses using an independent cohort are required to confirm the prognostic significance of TTM. Third, patients who recently received approved combination therapies were not included in this study. These limitations may have influenced our findings and should be considered when applying the results to current clinical practice in the combination-therapy era.

In conclusion, we demonstrated that patients with synchronous (TTM < 6 months) disease had significantly shorter OS than those with metachronous (TTM ≥ 6 months) disease and that TTM was an independent prognostic predictor in mUC. Furthermore, we developed a modified and enhanced risk classification by incorporating TTM to estimate the prognosis of patients with mUC. Taken together, these findings highlight the clinical relevance of TTM and support its incorporation into refined risk stratification for patients with mUC.

## Methods

### Study design and patient selection

This retrospective study was conducted at Hiroshima University and its affiliated hospitals, and was derived from the Hiroshima Cancer Registry Project (H-CARP). The study protocol was approved by the Ethics Committee of Hiroshima University, Japan (authorization number: E-2016-0326). Written informed consent was waived because of the retrospective design of the study, which used de-identified patient data and posed no potential risk to participants. In accordance with institutional policy, an opt-out approach was implemented to provide patients with the opportunity to decline participation. All analyses were conducted in accordance with the ethical standards in place at the time of data collection and the principles of the Declaration of Helsinki. Patients with mUC who received first-line platinum-based chemotherapy between April 2009 and May 2025 were included. Exclusion criteria were as follows: receipt of enfortumab vedotin plus pembrolizumab as first-line systemic therapy and incomplete clinicopathological data. All patient data were managed using the Research Electronic Data Capture (REDCap) system hosted at Hiroshima University <sup>20,21</sup>.

## Patient characteristics

Data on follow-up period, age, sex, primary tumor location (lower or upper urinary tract), ECOG-PS, hemoglobin levels (g/dL), metastatic sites, time to metastasis (TTM), and treatment history (cystectomy or nephroureterectomy, perioperative systemic therapy, platinum-based chemotherapy, immunotherapy, and enfortumab vedotin therapy) were extracted from medical records.

Patients were categorized according to TTM into two groups; synchronous (TTM < 6 months) and metachronous (TTM ≥ 6 months) groups, based on a previous study <sup>19</sup>.

## Outcomes

Overall survival (OS) was assessed as the primary outcome. OS was defined as the time from the initiation of first-line platinum-based chemotherapy to death from any cause.

## Statistical analysis

Continuous variables are presented as medians (interquartile range [IQR]) and categorical variables as numbers and percentages. Group comparisons were performed using Pearson's chi-square test, Fisher's exact test, Wilcoxon rank-sum test, or Kruskal–Wallis test, as appropriate. OS was estimated using the Kaplan–Meier method and compared using the log-rank test. Factors associated with OS were evaluated using univariate and multivariate Cox proportional hazards regression models.

To compare the discriminatory performance of the new risk model with that of the Bellmunt model, Harrell's concordance index (C-index) was calculated for each model using Cox proportional hazards regression. The difference in C indices was assessed using paired nonparametric bootstrap resampling (1,000 iterations). Time-dependent changes in the C-index were also examined <sup>22</sup>. Decision curve analysis (DCA) was performed to evaluate the net clinical benefit of each model <sup>23</sup>, and net reclassification improvement (NRI) was calculated using the category-based method proposed by Pencina et al. <sup>24</sup>.

Statistical significance was defined as  $p < 0.05$ . All analyses were conducted using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

## Declarations

## Ethics declarations

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board of Hiroshima University Hospital (approval no. E-2016-0326).

# Competing interests

The authors declare no conflicts of interest.

# Funding

No funding was received for this study.

# Author Contribution

Conceptualization was performed by TH. Material preparation, data collection, and analysis were performed by TH, YN, RY, HS, ST, NN, YK, MN, SM, KK, YS, HK, and KH. The first draft of the manuscript was prepared by TH. Review and editing of the manuscript were performed by KG. Supervision was provided by NH.

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# Data Availability

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

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## Figures

Figure1

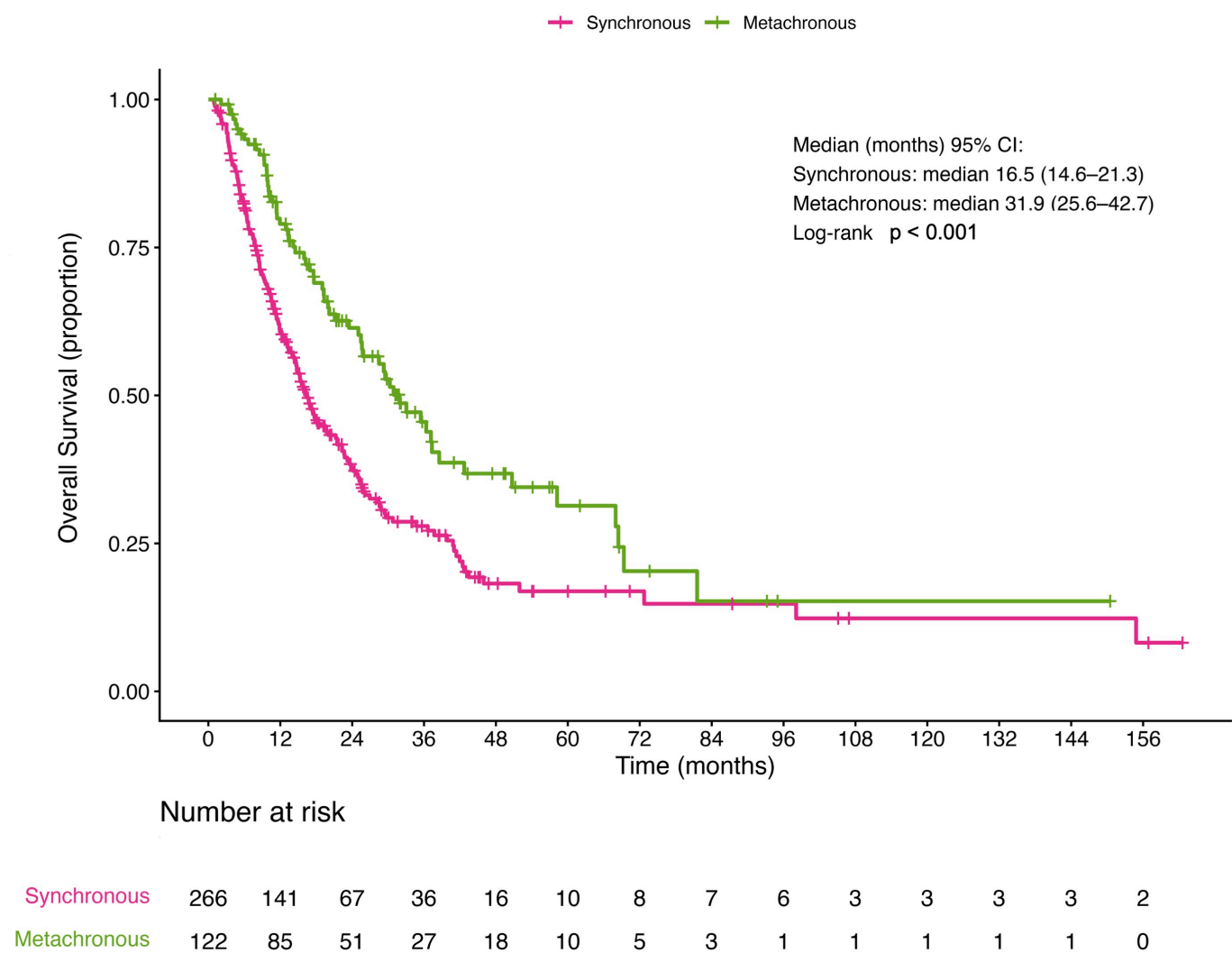


Figure 1

Comparison of overall survival between synchronous and metachronous disease.

CI, confidence interval

Figure 2A

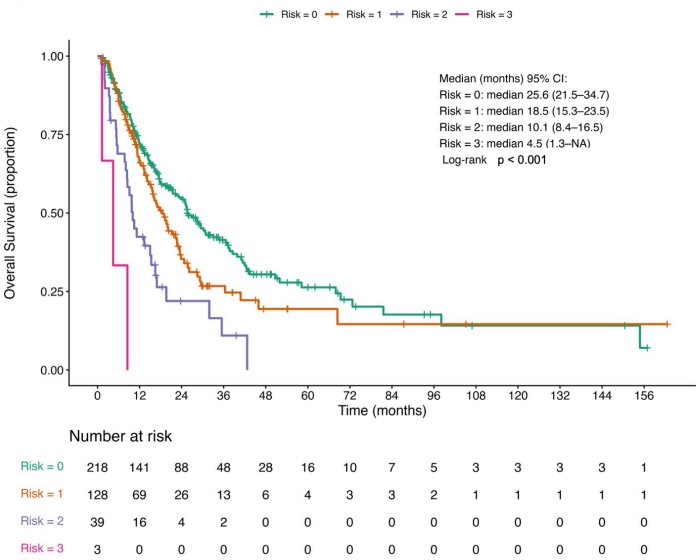


Figure 2B

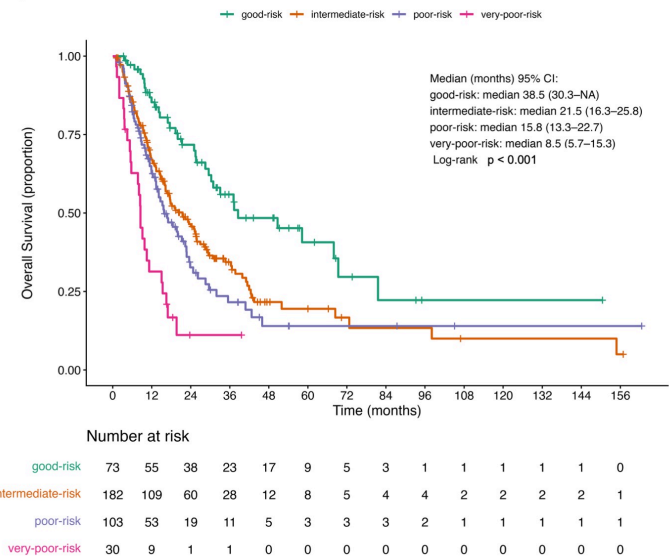


Figure 2

Comparison of overall survival by risk classification.

A, Kaplan–Meier curves stratified by the Bellmunt score. B, Kaplan–Meier curves stratified by the modified Bellmunt score. CI, confidence interval

Figure 3

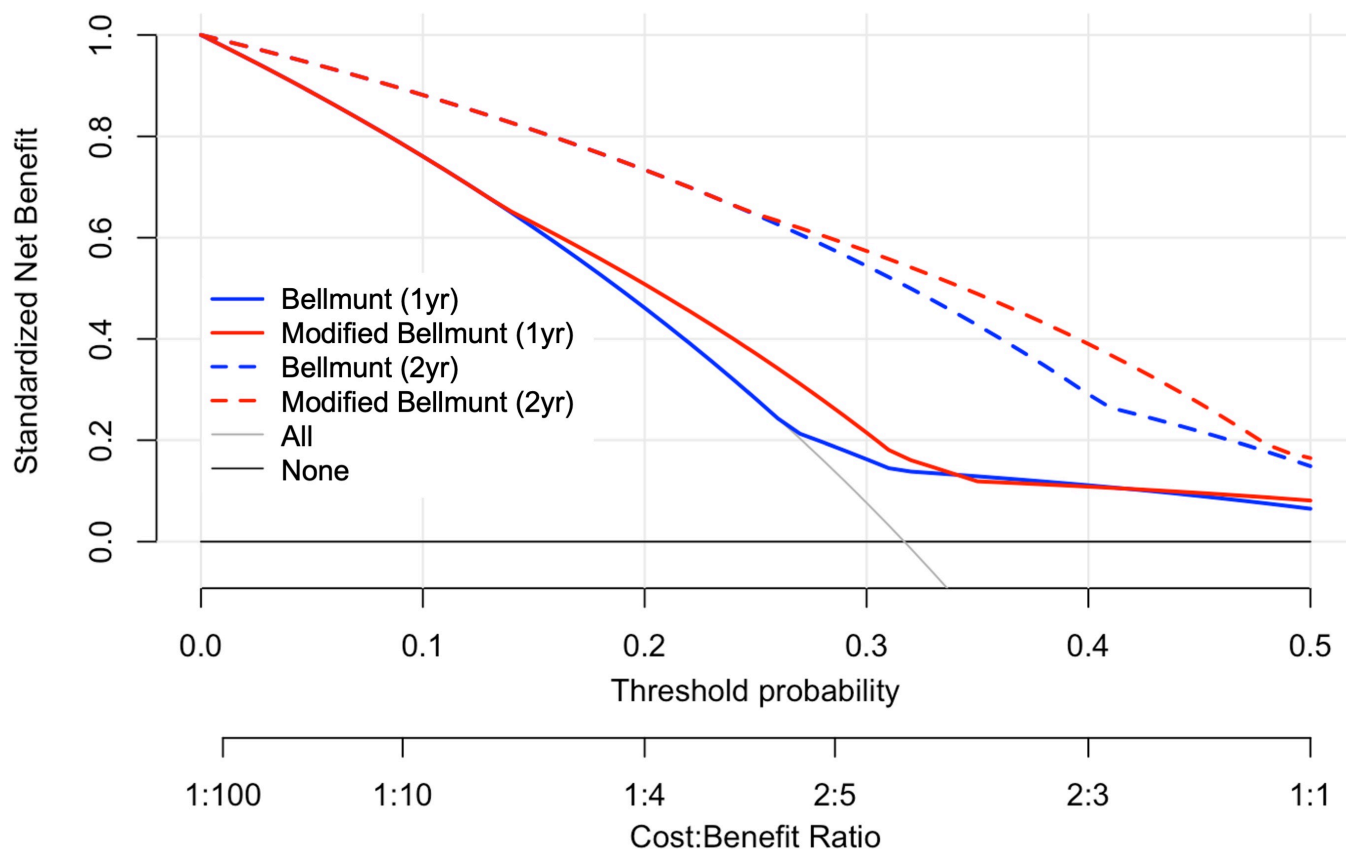


Figure 3

Decision curve analysis based on overall survival evaluated the clinical net benefit of the modified Bellmunt score compared to the Bellmunt score for survival prediction.

## Supplementary Files

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- [SupplementalFigure1.pdf](#)