Research Square

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A novel risk stratification for predicting prognosis of colorectal cancer patients with bone metastasis

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Abstract

Backgroud: Our understanding in prognosis of bone metastasis (BM) from colorectal cancer (CRC) is limited. We aimed to establish a clinical risk stratification for individually predicting the survival of CRC patients with BM.

Methods: A total of 200 CRC patients with BM were included in this study. Survival time from BM diagnosis was estimated using the Kaplan-Meier method. The multivariable COX regression model identified the risk factors on cancer specific survival (CSS). Based on weighted scoring system, the stratification model was constructed to classify patients with BM according to prognostic risk. Discrimination power and calibration ability of risk stratification were measured.

Results: The median CSS time was 11 months after BM diagnosis. Lymph node metastasis, CA199 levels, bone involvement, KPS scores, primary tumor resection, bisphosphonates therapy and radiotherapy were identified as predictors of CSS. Four risk groups were stratified according to weighted scoring system, including low risk, medium risk, medium-high risk and high risk group, with 35, 16, 9 and 5 months of median CSS, respectively (P = 0.000). The risk stratification displayed good accuracy in predicting CSS, with acceptable discrimination and calibration.

Conclusion: This novel risk stratification predicts CSS in CRC patient with BM using easily accessible clinicopathologic factors, which is recommended for use in individualized clinical decision making in patient with BM.

Introduction

As the most common cancer and the second most common cause of death worldwide, colorectal cancer (CRC) is likely to metastasize to liver, followed by lungs and peritoneal cavity, yet rarely to bone [1, 2]. Bone metastasis (BM) is a rare and special type of metastasis, presenting with very poor prognosis (5). It is reported that the incidence of BM from CRC is 6.0-10.4% [3] but has gradually increased in recent years [4]. BM is completely a special distant metastasis compared to liver or lung metastases, and its uniqueness and particularity should be attracted more attention in current clinical practice.

The diversity and complexity of metastasis provide a big challenge in the treatment of CRC with BM. How to make treatment plan and predict the treatment effect is very crucial. Either overtreatment or undertreatment for BM could have an adverse impact on prognosis and quality of life of patients. However, because of low incidence and poor prognosis of BM, the current treatment strategy for this group of patients has relatively been ignored. Previous studies with regard to the treatment plan decision of CRC patients with BM mainly originated from clinical experience and lack standardized guidance, because of the relative rarity of BM in CRC patients.

Previous studies have reported about the characteristics and clinical outcomes of BM from CRC [5, 6]. However, risk model for predicting survival outcome for CRC patients with BM are scarce. Construction of

a clinically useful risk stratification based on clinicopathologic factors will allow classification of patients according to different prognosis, which have important clinical value in guiding follow-up care and treatment. Therefore, the aims of our study were to (1) identify the clinicopathological characteristics and prognostic factors of BM from CRC; (2) to develop a comprehensive and practical risk stratification for evaluation of prognosis of CRC patients after BM diagnosis.

Materials And Methods

Data resources and study population

Patients who were diagnosed with BM from CRC between January 2008 and December 2017 at Cancer Hospital, Chinese Academy of Medical Sciences, were retrospectively identified. Patients without follow-up information or patients with BM from other malignant tumors were excluded from our study. The primary CRC lesion was confirmed by histopathological examination. The American Joint Committee on Cancer (AJCC) TNM stage and BM were identified by histopathological or imaging examinations such as standard X-rays, whole-body bone scans, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT). For the number of bone metastases, two adjacent vertebral metastases were classified into the solitary bone involvement, while non-consecutive metastases or more than 2 consecutive vertebral metastases were classified as multiple bone involvement. Synchronous BM refers to bone metastases found within 3 months after the diagnosis of colorectal cancer. Metachronous BM refers to bone metastases found more than 3 months after the diagnosis of colorectal cancer. The cancer specific survival (CSS) was defined as the time from the BM diagnosis until cancer-associated death or the end of follow up. This study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.

Prognostic factors

Clinicopathological data and treatment methods were collected from medical records or via telephone follow-ups. The last follow-up time was January 2020. Several variables were analyzed including age (< 60 vs. ≥ 60 years), sex (female vs. male), basic disease (no vs. yes), timing of BM diagnosis (metachronous vs. synchronous), primary tumor location (rectum vs. left hemicolon vs. right hemicolon), pathological type of tumor (adenocarcinoma vs. mucinous adenocarcinoma vs. signet-ring cell carcinoma vs. others), tumor grade (I/II vs. III/IV), AJCC T stage (T1/T2 vs. T3/T4), AJCC N stage (N0 vs. N1/N2), carcinoembryonic antigen (CEA) levels at BM diagnosis (negative vs. positive), carbohydrate antigen199 (CA199) levels at BM diagnosis (negative vs. positive), alkaline phosphatase (ALP) levels at BM diagnosis (negative vs. positive), bone involvement (solitary vs. multiple), KPS at BM diagnosis (≥ 80 vs. <80), extra-osseous metastases (no vs. yes), primary tumor resection (no vs. yes), systemic treatment for BM (chemotherapy alone vs. chemotherapy plus targeted therapy), bisphosphonates for BM (no vs. yes), radiotherapy for BM (no vs. yes) and operation for BM (no vs. yes).

Risk Stratification

We developed a weighted scoring system and assigned points for each adverse prognostic factor according to its beta coefficients (β) value. The insignificant risk factors ($P > 0.05$) received 0 point. Adverse factors ($P < 0.05$) with $0 < \beta < 0.5$ received 1 point; those with $0.5 \leq \beta < 1$ received 2 points. Risk groups were stratified based on total risk scores of prognostic factors.

Statistical analysis

The CSS was assessed with Kaplan-Meier method, with the log-rank tests used to compare subgroups. In order to reduce the impact of sample size, factors with $P < 0.20$ in univariate Kaplan-Meier analyses [7] were finally tested in multivariable COX regression analysis via a backward stepwise selection process. Hazard ratio (HR), corresponding 95% confidence interval (CI) and β were also calculated by COX regression model. The discrimination power of risk stratification was measured by calculating the area under the time-dependent receiver operating characteristic (AUROC) curve. Calibration curves were provided to internally evaluate the calibration ability of risk stratification. All statistical analyses were performed with SPSS version 25.0 for Mac or R version 3.6.0. It is considered as statistically significant when $P < 0.05$.

Result

Patients characteristics

Finally, 200 patients with BM from CRC were enrolled in our study, with 195 deaths (97.5%). The median age was 58 years (range from 19 to 84 years), and most of patients were male (59.5%). There was predominance of metachronous BM (68.5%) and rectal cancer (55.0%) in cohort. Most of patients were diagnosed with adenocarcinoma (86.0%), advanced AJCC T stage (68.5%) and N stage (71.5%). Patients with KPS ≥ 80 points accounted for 75.5% at the time of BM diagnosis. Table 1 summarizes the clinicopathological features of the patients.

Table 1

Clinicopathological characteristics, treatment and univariate survival analysis

Variables	No. patients (N = 200)	%	Median CSS (months)	P
Age at BM diagnosis, years				0.433
< 60	112	56.0	10	
≥ 60	88	44.0	11	
Sex				0.615
Female	81	40.5	11	
Male	119	59.5	11	
Basic disease *				**0.198**
No	123	61.5	11	
Yes	77	38.5	10	
Timing of BM diagnosis				0.571
Metachronous	137	68.5	11	
Synchronous	63	31.5	11	
Primary tumor location				0.277
Rectum	110	55.0	11	
Left hemicolon	40	20.0	11	
Right hemicolon	50	25.0	9	
Pathological type of tumor				0.453
Adenocarcinoma	172	86.0	11	
Mucinous adenocarcinoma	11	5.5	9	
Signet-ring cell carcinoma	13	6.5	8	
Others	4	2.0	4	
Tumor Grade				0.522
Grade I, II	117	58.5	12	
Grade III, IV	49	24.5	9	

Bold values indicate P < 0.20. ***Potential prognostic variables with P < 0.20. Median CSS time was performed by Kaplan-Meier, and P value is obtained by Log-Rank test.

Variables	No. patients (N = 200)	%	Median CSS (months)	P
UK	34	17.0	9	
AJCC T stage *				**0.011**
T1/T2	19	9.5	19	
T3/T4	137	68.5	11	
UK	44	22.0	8	
AJCC N stage *				**0.000**
N0	29	14.5	21	
N1/N2	143	71.5	10	
UK	28	14.0	8	
CEA levels at BM diagnosis *				**0.005**
Negative	44	22.0	11	
Positive	130	65.0	10	
UK	26	13.0	12	
CA199 levels at BM diagnosis *				**0.000**
Negative	77	38.5	13	
Positive	96	48.0	9	
UK	27	13.5	13	
ALP levels at BM diagnosis *				**0.019**
Negative	148	74.0	11	
Positive	43	21.5	8	
UK	9	4.5	8	
Bone involvement *				**0.050**
Solitary	108	54.0	12	
Multiple	92	46.0	10	
KPS at BM diagnosis *				**0.041**

Bold values indicate P < 0.20. ***Potential prognostic variables with P < 0.20. Median CSS time was performed by Kaplan-Meier, and P value is obtained by Log-Rank test.

Variables	No. patients (N = 200)	%	Median CSS (months)	P
≥ 80	151	75.5	12	
< 80	49	24.5	6	
Extra-osseous metastases *				**0.051**
No	23	11.5	8	
Yes	177	88.5	11	
Primary tumor resection *				**0.001**
No	66	33.0	9	
Yes	134	67.0	12	
Systemic treatment for BM				0.478
Chemotherapy alone	121	60.5	11	
Chemotherapy plus targeted therapy	79	39.5	12	
Bisphosphonates for BM *				**0.000**
No	115	57.5	9	
Yes	85	42.5	13	
Radiotherapy for BM *				**0.000**
No	143	71.5	9	
Yes	57	28.5	15	
Operation for BM *				0.496
No	197	98.5	11	
Yes	3	1.5	21	
Mortality	195	97.5		

Bold values indicate P < 0.20. ***Potential prognostic variables with P < 0.20. Median CSS time was performed by Kaplan-Meier, and P value is obtained by Log-Rank test.

Patterns of BM and extra-osseous metastasis

In total of 200 patients, there were 108 patients (54.0%) having BM to solitary site and 92 patients (46.0%) having BM to multiple sites respectively (Table 1). The most common metastatic sites were the spine (n = 141, 70.5%), pelvis (n = 121, 60.5%), long bones (n = 53, 26.5%) and ribs (n = 49, 24.5%), respectively. Only 8 patients (4.0%) were diagnosed with skull metastasis.

There were 23 patients (11.5%) having isolated BM, while the remaining 177 patients (88.5%) having metastases to other distant organs (Table 1). The most common site of extra-osseous metastases was lung (n = 104, 52%), followed by liver (n = 101, 50.5%), distant lymph nodes (n = 90, 45%), ovary (n = 28, 14.0%), adrenal gland (n = 14, 7.0%), brain (n = 12, 6.0%) and peritoneum (n = 10, 5.0%).

Treatments for BM

The treatments for patients after diagnosis of BM were seen in Table 1. There were 66 patients skipped surgery for primary tumor mainly due to the inability of radical resection. All patients received chemotherapy after diagnosis of BM, and some (n = 79, 39.5%) also received targeted therapy. There were 85 patients (42.5%) and 57 patients (28.5%) receiving bisphosphonates and radiotherapy, respectively. Only 3 patients (1.5%) took surgery for metastatic tumors of bone because of spinal cord compression.

CSS and prognostic factors

Median CSS after BM diagnosis was 11 months (95% CI 9.7–12.3). The 1-, 2- and 3-year CSS rate after BM diagnosis was 30.0%, 17.0% and 7.0%, respectively.

Potential prognostic variables with $P < 0.20$ in univariate Kaplan-Meier analyses were represented in Table 1, which were identified for multivariate analysis. The COX multivariate analysis revealed high AJCC N stage (HR: 1.652, 95%CI: 1.055–2.587, P = 0.028), positive CA199 levels (HR: 1.460, 95%CI: 1.061–2.009, P = 0.020), multiple bone involvement (HR: 1.534, 95%CI: 1.117–2.105, P = 0.008) and KPS < 80 at BM diagnosis (HR: 1.527, 95%CI: 1.071–2.176, P = 0.019) as independent variables related to worse CSS. While primary tumor resection (HR: 0.627, 95%CI: 0.429–0.916, P = 0.016), bisphosphonates therapy (HR: 0.581, 95%CI: 0.429–0.788, P = 0.000) and radiotherapy for BM (HR: 0.578, 95%CI: 0.407–0.822, P = 0.002) were independent variables related to better CSS (Table 2). Kaplan-Meier curves of each significant prognostic factor were shown in Fig. 1.

Table 2
Multivariable COX analysis of prognostic factors for CSS

Variables	HR (95% CI)	P	β
Basic disease (yes vs. no)	NA	0.328	-
AJCC T stage (T3/T4 vs. T1/T2)	NA	0.719	-
AJCC N stage (N1/N2 vs. N0)	**1.652 (1.055–2.587)**	**0.028**	**0.502**
CEA levels at BM diagnosis (positive vs. negative)	NA	0.367	-
CA199 levels at BM diagnosis (positive vs. negative)	**1.460 (1.061–2.009)**	**0.020**	**0.379**
ALP levels at BM diagnosis (positive vs. negative)	NA	0.827	-
Bone involvement (multiple vs. solitary)	**1.534 (1.117–2.105)**	**0.008**	**0.428**
KPS at BM diagnosis (< 80 vs. ≥ 80)	**1.527 (1.071–2.176)**	**0.019**	**0.423**
Extra-osseous metastases (yes vs. no)	NA	0.101	-
Primary tumor resection (yes vs. no)	**0.627 (0.429–0.916)**	**0.016**	**0.467**
Bisphosphonates for BM (yes vs. no)	**0.581 (0.429–0.788)**	**0.000**	**0.542**
Radiotherapy for BM (yes vs. no)	**0.578 (0.407–0.822)**	**0.002**	**0.548**
Bold values indicate statistical significance at P < 0.05			

Risk stratification for CSS

We developed a weighted scoring system according to β value of prognostic factors identified from the multivariable analysis. The details were seen in Table 2. Adverse factors including positive CA199 levels, multiple bone involvement and KPS scores < 80 at BM diagnosis were assigned for 1 point, respectively. Other adverse factors including AJCC N1 or N2 stage, no primary tumor resection, no bisphosphonates and no radiotherapy were assigned for 2 points, respectively. For the 150 patients (after excluding 50 patients with unknown AJCC N stage and serum CA199 levels), the risk scores ranged from a minimum of 0 to a maximum of 10. Considering equal risk stratification, four groups were finally divided: low risk (0–2 points), medium risk (3–5 points), medium-high risk (6–8 points) and high risk (≥ 9 points) with 35 months, 16 months, 9 months and 5 months of median CSS, respectively (P = 0.000) (Table 3). Medium risk (HR: 2.919, 95%CI: 1.307–6.517, P = 0.009), medium-high risk (HR: 6.382, 95%CI: 2.875–14.166, P = 0.000) and high risk (HR: 14.149, 95%CI: 5.060-39.564, P = 0.000) patients had worse CSS compared with low risk patients. The 1-, 2- and 3-year CSS rate in low risk group was 81.8%, 72.7% and 36.4%, while in high risk group decreased dramatically with 11.1%, 0.0% and 0.0%, respectively. The time-dependent receiver operating characteristic (timeROC) curves suggested good discrimination of risk stratification to identify the CSS with 1-, 2- and 3-year AUROC of 0.721, 0.810 and 0.823, respectively (Fig. 2). Calibration

curves for 1-, 2-, and 3-year CSS estimates showed good correlation between the CSS estimates of risk stratification and Kaplan-Meier estimates (Fig. 3).

Table 3
CSS of four risk groups based on weighted scoring system

Risk group	Points	No. patients (N = 150)	Median CSS (months)	95%CI	1-year CSS rate (%)	2-year CSS rate (%)	3-year CSS rate (%)
Low	0–2	11	35.0	20.6–49.4	81.8	72.7	36.4
Medium	3–5	49	16.0	10.5–21.5	69.4	26.5	8.2
Medium-high	6–8	81	9.0	7.7–10.3	33.3	4.9	1.2
High	≥ 9	9	5.0	3.6–6.4	11.1	0.0	0.0

Discussion

Our study retrospectively reviewed the clinicopathological characteristics of 200 patients with BM from CRC, discussing prognostic factors and a novel risk stratification for CSS. Many researches have been reported that spine is the leading site of BM from solid tumors [8, 9]. And the common sites of BM from CRC are reportedly the spine, followed by the pelvis and long bones, which is highly consistent with our study [10].

The prognosis of patients with BM from CRC is very poor because of advanced disease stage, with a median survival time of 7.0 to 17.8 months after BM diagnosis [6, 10, 11]. In our study, the overall median CSS time was 11 months (95%CI: 9.7–12.3) from the time of BM diagnosis, with 30.0%, 17.0% and 7.0% of 1-, 2- and 3-year CSS rate. Although the median CSS of patients with adenocarcinoma was longest than those with mucinous adenocarcinoma, signet-ring cell carcinoma and other pathological types (11 months, 9 months, 8 months, 4 months, respectively), there was no statistical significance (P = 0.453). Median CSS time of patients with metachronous BM and synchronous BM were both 11 months. The CSS did not differ significantly between the two groups (P = 0.571) in univariate analysis. Hidetaka et al. also found there is no significant difference in survival between metachronous and synchronous groups after BM diagnosis(P = 0.59) [8].

Then we analyzed the prognostic factors based on multivariable analysis, which revealed the CSS in patients with regional lymph node metastasis was found to be shorter than patients who were without. In addition, patients with positive serum CA199 levels at BM diagnosis had poorer prognosis in CRC

patients than those with negative. High CA199 levels is one of indicators of colorectal tumor, but there are rarely reports about the its role in prognosis of CRC, while most of researches show it plays a key role in CRC diagnosis [12, 13]. We also found high serum CEA levels and LHD levels were significant prognostic indicators for CSS by univariate analysis, which had been shown in many reports [10, 14]. So, we suggest careful surveillance in those indicators for patients with BM from CRC.

The multiple bone involvement was found to be an independent prognostic factor for CSS, similar to some previous studies [15, 16]. However, Lun et al. reported there was no association between the number of bone metastases and survival [17]. Such differences might due to the sample size and selection bias in different studies. In our study, KPS scores at BM diagnosis less than 80 were associated with a worse prognosis compared to scores ranging from 80 to 100. This is in line with previous researches that have identified performance status as one of the most valuable prognostic factors for survival of BM patients [16–18].

There exists controversy regarding to the benefit of primary tumor resection in advanced CRC. Many prior studies suggest a clinical benefit to improve survival with surgery [19–21], while others report there is no benefit [22, 23]. We found the patients with BM from CRC could significantly be beneficial from primary tumor resection with improved CSS. That might be because removal of primary tumor could prevent tumor-related complications such as bleeding, obstruction and perforation, further improving quality and survival of patients with BM.

The treatment of bisphosphonates and radiotherapy for CRC patients with BM is strongly recommended. Bisphosphonates have been used for prevention of skeletal-related events and reduction of pain from BM in recent years [24, 25]. According to our study, 42.5% of patients received bisphosphonates therapy for BM and the remaining patients didn't. The difference in median CSS between two groups is significant (13 months vs. 9 months, respectively), showing that patients who took bisphosphonates were associated with better prognosis.

Radiotherapy was found to be associated with longer CSS, although quality-of-life data were lacking. In patients with palliative radiotherapy for BM, median CSS time after BM diagnosis was prolonged obviously (15 months vs. 9 months, respectively). Previous researches have verified that radiotherapy is the approach most commonly used to treat severe pain from BM, which could improve survival directly and indirectly [26–28]. In addition, the chemotherapy can notably improve survival of BM as many researches have demonstrated [26, 29, 30]. However, because all patients had received adjuvant chemotherapy in our study, the utility of chemotherapy in improving CSS was not investigated.

Here, we developed a weighted scoring system to facilitate risk stratification for patients with BM from CRC. As an example, a CRC patient, with regional lymph node metastasis, negative CA199 levels, KPS ≥ 80 and multiple bone involvement, received primary tumor resection, bisphosphonates therapy and radiotherapy for BM, then he would be assigned for 0 point with a median CSS benefit of up to 35 months (95%CI: 20.6–49.4). In contrast, patients with all adverse factors (10 points) showed the worst CSS of only 5 months (95%CI: 3.6–6.4). So, we suggest that more medical care might be necessary for high risk

patients. And individualized medical care should be considered for patients in different risk groups. This risk stratification had good discrimination and calibration, implying a clinical value in predicting prognosis of CRC patients with BM.

Our study had some limitations. First, this was a retrospective designed study, and some data might have missed. For example, not every patient showed complete AJCC TNM stage. In addition, this was a single-center study. Because of the low incidence of BM from CRC, the number of patients was small, which limited the external validation. Nonetheless, we believe our study will be useful to both clinicians and patients.

Conclusion

Given the poor survival of BM from CRC, information regarding how to evaluate the prognosis of such patients should be considered in diagnosis and treatment. Here, we found AJCC N stage, CA199 levels, multiple bone involvement, KPS scores, primary tumor resection, bisphosphonates and radiotherapy were prognostic factors significantly affecting survival. Four risk groups showed significant differences in CSS, which could help physicians determine the prognosis of CRC patients with BM. The novel risk stratification has considerable practical implications and may be useful in selection of appreciate care and treatment.

Abbreviations

AJCC: American Joint Committee on Cancer; ALP: Alkaline phosphatase; AUROC: Area under the time-dependent receiver operating characteristic; BM: Bone metastasis; CA199: Carbohydrate antigen199; CEA: Carcinoembryonic antigen; CI: Confidence interval; CRC: Colorectal cancer; CSS: Cancer specific survival; CT: Computed tomography; HR: Hazard ratio; MRI: Magnetic resonance imaging; N=number; PET-CT: Positron emission tomography-computed tomography; UK= unknown; β: Beta coefficients.

Declarations

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Authors' contributions

CXM: Conceptualization, Investigation, Supervision, Writing-original draft. XG: Conceptualization, Software, Writing-original draft. JCQ: Software, Formal analysis. ZXZ: Validation, Data curation. HPC: Resources. Hai-yang Huang: Validation. RW: Investigation, Project administration. ZL: Data curation, Supervision. ZJ: Writing-review & editing, Supervision. XSW: Writing-review & editing, Supervision, Funding acquisition.

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Availability of data and materials

The dataset can only be used after getting the approval from Cancer Hospital, Chinese Academy of Medical Sciences.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were approved by the medical ethical committee of the Maxima Medical Center in Veldhoven, The Netherlands (number 0822) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients signed informed consent.

Consent for publication

All authors have approved the submission of this manuscript.

Competing interests

All authors declare that they have no conflict of interest.

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Figures

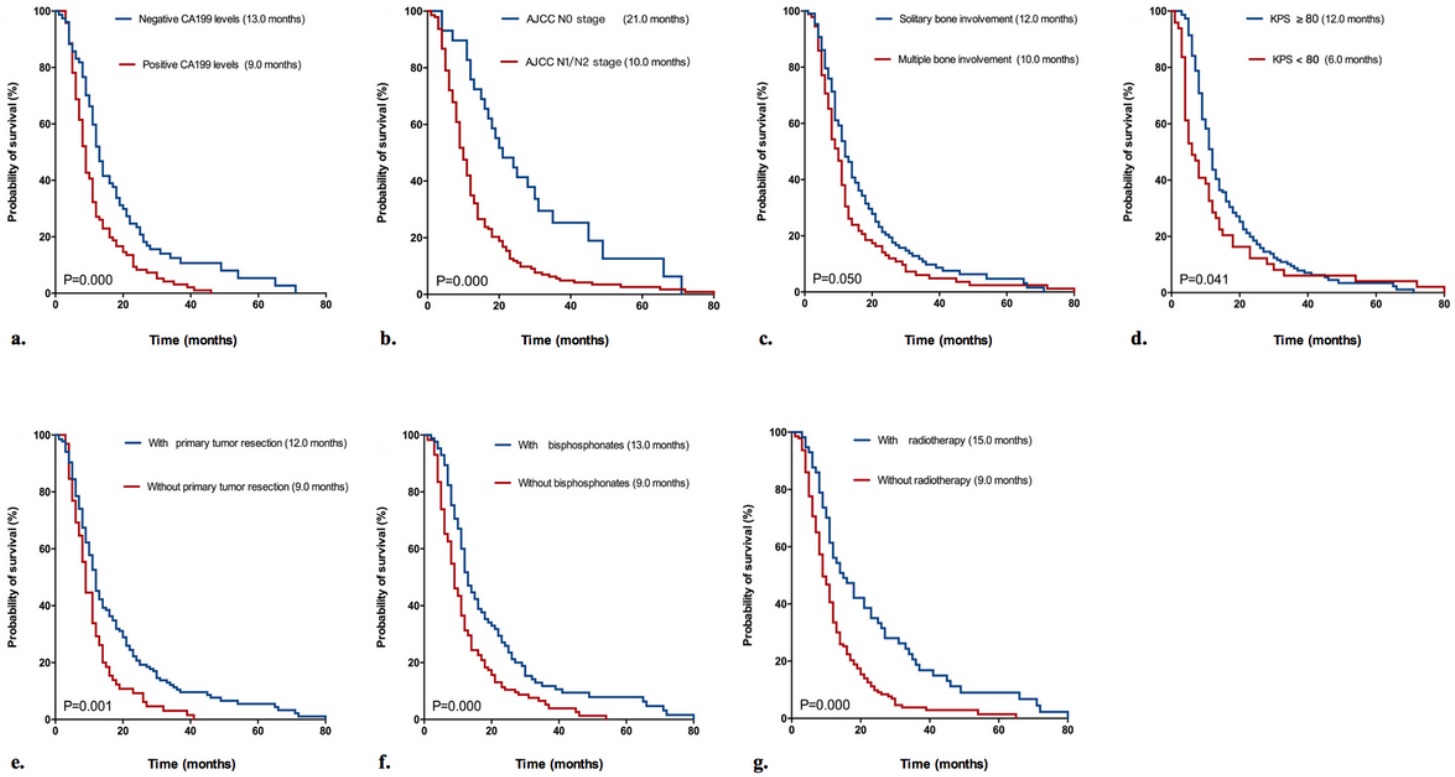

Figure 1

Kaplan-Meier curves of cancer specific survival according to different prognostic variables with P<0.05. (a) Serum CA199 levels at BM diagnosis. (b) AJCC N stage. (c) Bone involvement. (d) KPS at BM diagnosis. (e) Primary tumor resection. (f) Bisphosphonates therapy. (g) Radiotherapy.

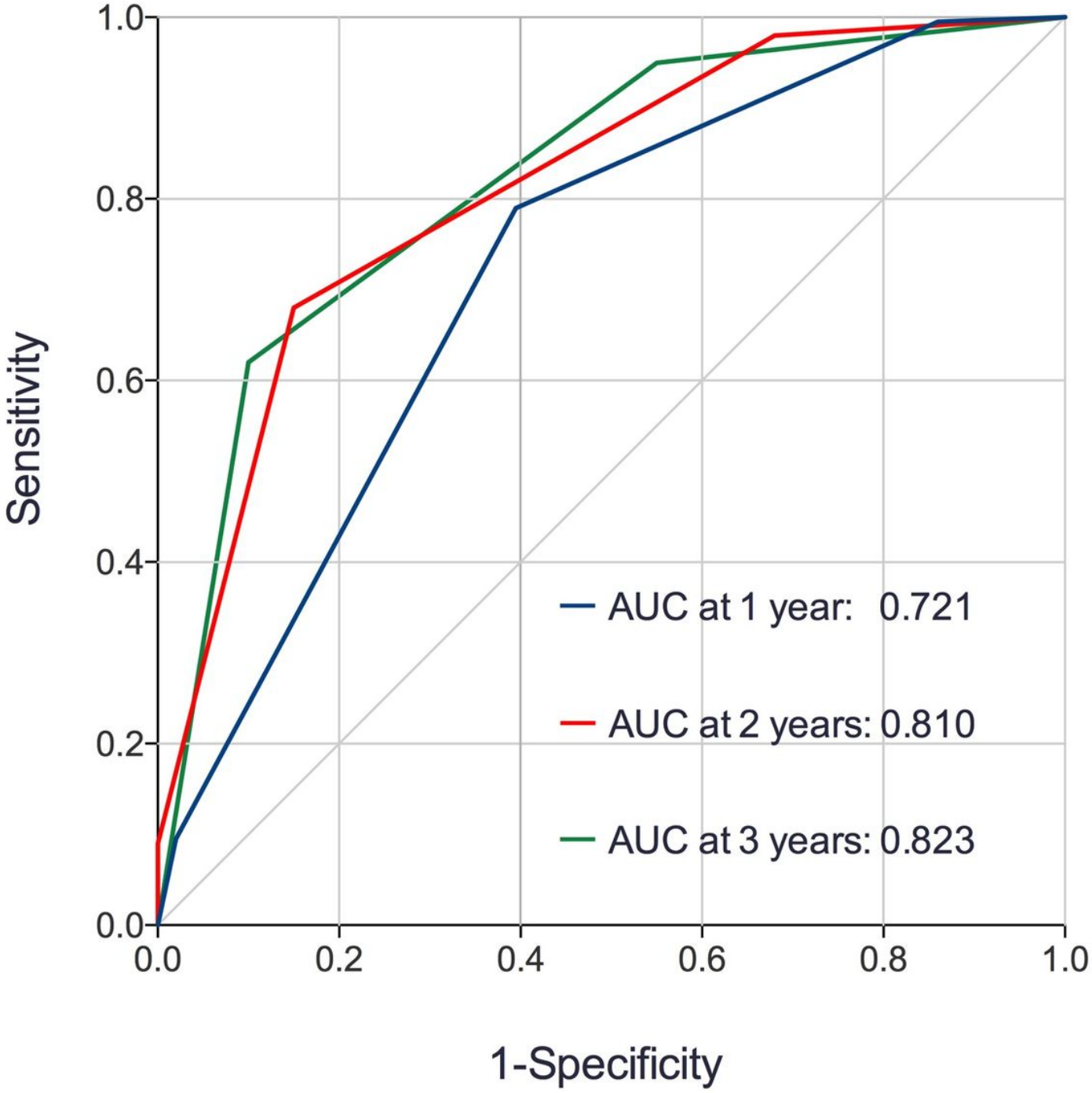

Figure 2

Time-dependent ROC curve for risk stratification.

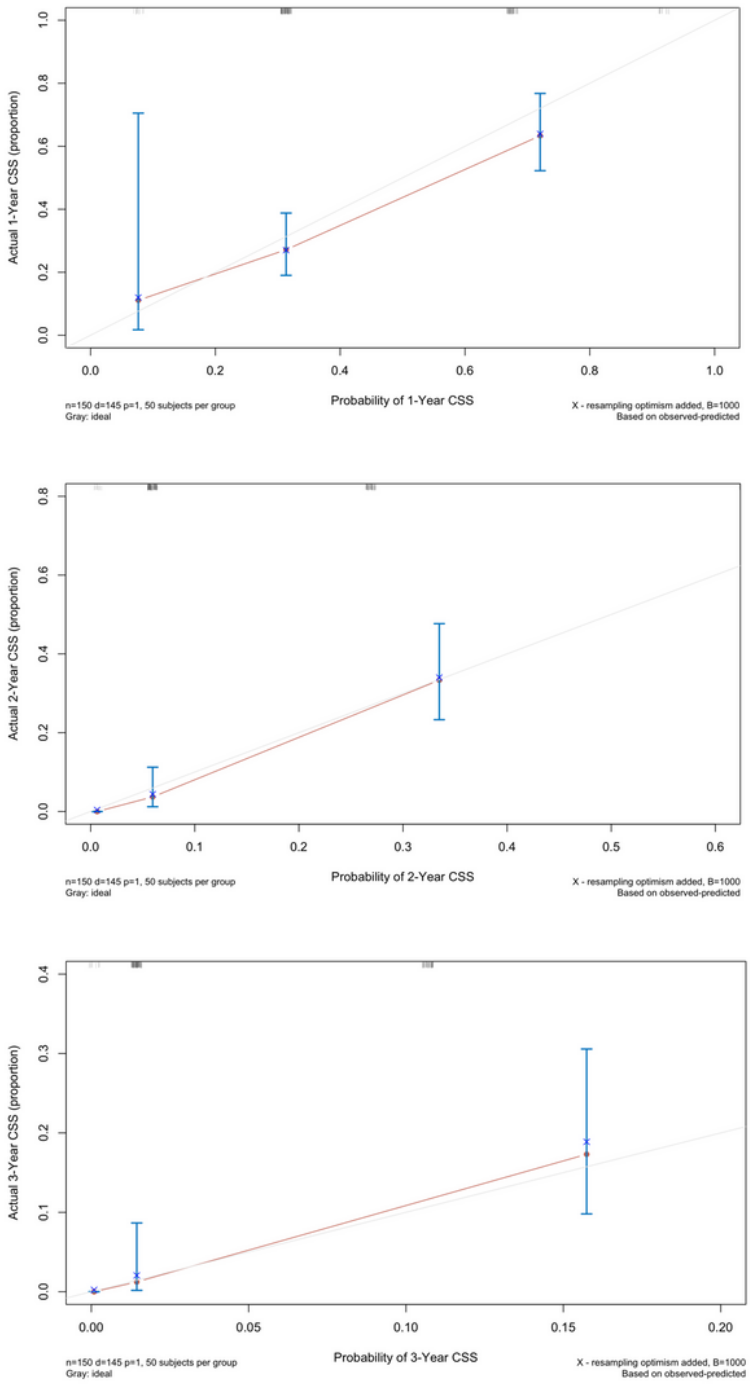

Figure 3

Calibration curves of actual CSS with 95% CI by decile (y-axis), over predicted CSS (x-axis) by risk stratification: (A) 1-year CSS calibration curve. (B) 2-year calibration curve. (C) 3-year calibration curve.