Stratification of Prognoses based on Criteria from Clinical Trials of Metastatic Hormone-sensitive Prostate Cancer

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Research Article

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Abstract

Background: Oncologic outcomes in metastatic hormone-sensitive prostate cancer (mHSPC) are extremely heterogeneous. We aimed to (1) stratify the prognosis in mHSPC patients according to criteria for high-volume disease, as defined in clinical trials, and (2) identify the combinations of unfavorable risk factors.

Methods: This retrospective study reviewed 623 patients who were diagnosed with mHSPC between 1996 and 2014. The prognoses of mHSPC patients were stratified by criteria from the GETUG15, CHAARTED, STAMPEDE, and LATITUDE trials. The exclusion criteria were incomplete clinical data, docetaxel chemotherapy with upfront options, and metastatic disease without proper management after initial diagnosis.

Results: All 485 patients (median follow-up=36.1 months) were categorized according to stage: M1a (70, 14.4%), M1b (367, 75.7%), and M1c (48, 9.9%). Significant differences in overall survival (OS) and cancer-specific survival (CSS) were found among the groups with low-volume disease, as classified by four clinical trials (log-rank p=0.001 and p<0.001, respectively). Bone metastasis volume and liver metastasis were independent predictors of prognosis. According to disease classification under NCCN guidelines, the prognosis of CSS between low-volume disease patients and M1c patients (no bone metastasis and low-volume bone metastasis) was not significantly different. Additionally, the prognosis of CSS did not significantly differ between M1c (high-volume bone metastasis and visceral metastasis, except liver) and M1b (high-volume bone metastasis) patients.

Conclusions: The prognoses of patients with low-volume disease, based on several classification systems, were heterogeneous. Except for lung or liver metastasis, the combination of visceral metastasis with no/low-volume bone disease should be considered as a proxy of less aggressive disease in patients presenting with mHSPC.

1. Background

Prostate cancer cells are highly likely to metastasize, with metastatic hormone-sensitive prostate cancer (mHSPC) accounting for approximately < 5% of newly diagnosed cancers [1–3]. Bone metastases occur in more than 80% of cases of advanced-stage prostate cancer and have been associated with a poor prognosis, with a 5-year survival rate of 25% [4]. Nodal or axial skeleton involvement and the number of metastases have been identified as factors associated with cancer-specific survival (CSS) of prostate cancer patients [5]. Moreover, visceral metastases have been shown to negatively impact survival and are considered to be an indicator of more aggressive disease in patients with mHSPC [6].

The prognosis of mHSPC is extremely heterogeneous, according to disease volume status. Docetaxel and abiraterone acetate, in addition to androgen deprivation therapy (ADT), have been recommended as upfront options based on the results of the phase III trials GETUG15, CHAARTED, STAMPEDE, and LATITUDE for patients with mHSPC [7–11]. However, the heterogeneity of a standard definition of this

disease status among these trials required to identify whether the different prognosis among the groups according to the classification systems presents an attempt to better stratify patients within this heterogeneous group. The present study aimed to stratify the prognoses in mHSPC patients by utilizing several definitions of high-volume disease in mHSPC. Another aim was to identify combinations of unfavorable risk factors.

2. Methods

2.1. Study population

This retrospective study involved collecting data on all patients with mHSPC, and Institutional Review Board approval was obtained. We reviewed 623 consecutive patients who were initially diagnosed with mHSPC between January 1996 and December 2015. Of these, 138 patients were excluded due to incomplete clinical data, terminal-stage comorbid cancer, docetaxel chemotherapy administration with upfront options, or development of metastatic disease without proper management after initial diagnosis.

2.2. Assessments of clinicopathological variables

Age, prostate-specific antigen (PSA) level, tumor-node-metastasis (TNM) stage, Gleason score, pain level (Visual Analogue Scale [VAS] pain score), performance status (Eastern Cooperative Oncology Group Performance Status [ECOG PS]), comorbidity (Charlson Comorbidity Index [CCI]), initial treatments, PSA nadir level, time to PSA nadir (TTN) during ADT, and the sites of metastasis at diagnosis were assessed. Metastatic HSPC was defined using either demonstrable metastatic deposits on imaging (bone scan, computed tomography, magnetic resonance imaging, or positron emission tomography) or pathologic diagnosis of prostate cancer from the tissue outside the prostatic fossa [12]. TNM staging was classified according to the 7th American Joint Committee on Cancer guidelines, and patients were further stratified according to the volume of bone metastasis and site of visceral metastasis.

2.3. Assessments of treatments

For the initial treatment, all patients were treated with either ADT, including combined androgen blockade (luteinizing hormone-releasing hormone [LHRH] agonist with antiandrogen) or an LHRH antagonist, or orchiectomy. PSA levels were measured every 1–3 months. Imaging was typically indicated after clinical disease progression or during follow-up with at least a 6-month interval.

2.4. Analysis of clinical data

Patients were initially classified into three groups: M1a, M1b, and M1c. Then, the survival of the patients according to disease spread was investigated. Disease spread was defined using criteria from the clinical trials. Patients with M1c were further stratified into the following three sub-groups to evaluate the prognostic impact of visceral metastatic sites: (1) those with visceral metastasis except in the lung or liver, (2) those with lung metastasis, and (3) those with visceral metastasis including the liver. High-volume bone metastasis was defined as four or more bone metastases, with at least one metastasis

beyond the pelvis or vertebral column. Additionally, we compared patient survival according to the combination of metastatic bone spread and visceral sites. Finally, data were classified and analyzed using the CHAARTED, GETUG15, LATITUDE, and HORRAD criteria to define high- and low-volume bone metastasis. The criteria were defined as the following: (1) CHAARTED: visceral metastases and/or ≥ four bone metastases, at least one outside of the vertebral column/pelvis; (2) GETUG15: Visceral metastases and/or appendicular disease and ECOG PS ≥ 1 and PSA ≥ 65 ng/ml (Glass risk group); (3) LATITUDE: Visceral metastases. ≥ three bone metastases, Gleason score ≥ 8: 2 out of 3; and (4) HORRAD: PSA ≥ 142 ng/ml, ≥ 5 bone metastases, Gleason > 8 (higher volume).

2.5. Statistical analysis

Appropriate comparative tests, such as the Student's t-test and χ2-test, were used to compare continuous and categorical variables. For the survival analysis, the status of survival and cause of death of all patients were investigated based on data from the National Cancer Registry Database or institutional electronic medical records. This analysis utilized survival results up to July 2018. Kaplan-Meier curves were used to estimate the survival of patients, which were stratified by stage, visceral metastatic sites, and bone metastasis spread. Univariable and multivariable analyses for predicting survival were performed using Cox-proportional hazards regression models. Statistical analysis was performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). All tests were two-sided, with statistical significance set at $p < 0.05$.

3. Results

3.1. Patient characteristics

Clinicopathological features of each group are presented in Table 1. Among 485 initially diagnosed patients (median follow-up = 36.1 months) with mHSPC, 70 (14.3%), 367 (75.7%), and 48 (9.9%) patients were diagnosed with M1a, M1b and M1c, respectively. The median OS and CSS times were 48.0 months and 62.4 months, respectively (Fig. 1A, Fig. 1B).

Table 1
Clinicopathological features of patients with metastatic hormone-sensitive prostate cancer

	M1a	M1b	M1c	p value
No. of patients	70 (14.4)	367 (75.7)	48 (9.9)	
Age (yrs)	69.3 (64.6–75.5)	70.6 (65.1–76.7)	73.0 (68.0-78.2)	0.088
ECOG PS (≥ 1)	5 (7.2)	55 (16.0)	8 (12.5)	0.153
CCI (≥ 4)	3 (4.5)	18 (5.3)	5 (11.6)	0.219
VAS pain score (≥ 1)	12 (29.3)	97 (50.5)	12 (40.0)	0.037
PSA (ng/mL)	55.0 (24.8-176.5)	138.0 (39.0-544.0)	106.5 (46.3-313.8)	0.001
PSA nadir (ng/mL)	0.07 (0.02–0.40)	0.42 (0.04–3.92)	0.55 (0.04–2.54)	0.001
TTN (month)	8.2 (4.5–14.6)	7.0 (4.2–11.7)	6.9 (4.3–11.5)	0.172
Gleason score				0.592
≤7	10 (14.3)	68 (18.5)	7 (14.6)	
≥8	60 (85.7)	299 (81.5)	41 (85.4)	
T stage				0.856
≤T2	4 (5.7)	26 (7.1)	4 (8.3)	
≥T3	66 (94.3)	341 (92.9)	44 (91.7)	
N stage				< 0.001
0	10 (14.7)	153 (41.7)	20 (42.6)	
1	58 (85.3)	214 (58.3)	27 (57.4)	
High-volume disease				
CHAARTED	0 (0.0)	246 (67.0)	48 (100.0)	< 0.001
GETUG15	5 (7.1)	71 (19.3)	48 (100.0)	< 0.001
LATITUDE	0 (0.0)	217 (59.1)	45 (93.8)	< 0.001
HORRAD	9 (12.9)	150 (40.9)	16 (33.3)	< 0.001

Data are n (%) or median (interquartile range); ECOG PS, Eastern Cooperative Oncology Group performance score; CCI, Charlson Comorbidity Index; VAS, Visual Analogue Scale pain score; ADT, androgen deprivation therapy; TTN, Time to PSA nadir; ART, androgen receptor target therapy; RT, radiotherapy.

In 4 (5.7%) patients, M1a was found in the supradiaphragmatic lymph nodes. Visceral metastases were most often to the lung in 41 (85.4%) patients, followed by the liver in 11 (22.9%) patients and other sites,

including the adrenal gland and peritoneum, in 5 (10.4%) patients. Patients with M1b and M1c were more likely to have VAS pain scores ≥ 1, higher PSA, and greater PSA nadir levels than those with M1a. There were no significant differences in age, ECOG PS (≥ 1), CCI (≥ 4), time to PSA nadir, or Gleason score among the groups. The proportion of patients with high-volume disease according to the four different criteria was greater with increasing stage.

In Kaplan-Meier curves of OS according to the four different criteria, patients with low-volume disease, as defined by CHAARTED and LATITUDE, had a higher OS rate than those with HORRAD and GETUG15 criteria (log rank p = 0.001, Fig. 2A). No differences in the OS of patients with high-volume disease according to four different criteria were found. In Kaplan-Meier curves of CSS, patients with low-volume disease, as defined as CHAARTED and LATITUDE, had a higher CSS rate than those with HORRAD and GETUG15 criteria (log rank p < 0.001, Fig. 2B). No differences in the CSS of patients with high-volume disease according to the four different criteria were found.

3.2. Univariable and multivariable analyses of predictors for overall survival and cancer-specific survival

The 5-year OS and CSS rates were 58.1% and 71.7%, 29.4% and 36.4%, and 25.0% and 31.0% for M1a, M1b, and M1c subgroups, respectively. CCI (≥ 4) (HR = 2.46 (1.298–4.667), p = 0.006), VAS pain score (≥ 1) (HR = 2.03 (1.272–3.240), p = 0.003), and TTN (HR = 0.95 (0.905–0.986) were significant predictors of OS. PSA level at diagnosis, PSA nadir, Gleason score, and TNM stage were not found to be potential prognostic factors of OS in the multivariable analysis (Table 2).

Table 2
Multivariable analysis of overall survival and cancer-specific survival in patients with metastatic hormone-sensitive prostate cancer

	Overall survival		Cancer-specific survival	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age*	1.02 (0.986–1.046)	0.314		
CCI (≥ 4)	2.46 (1.298–4.667)	0.006		
VAS pain score (≥ 1)	2.03 (1.272–3.240)	0.003	2.27 (1.380–3.740)	0.001
PSA*	1.00 (1.000–1.000)	0.942	1.00 (1.000–1.000)	0.387
PSA nadir*	1.00 (0.998–1.005)	0.398	1.00 (0.998–1.004)	0.458
TTN*	0.95 (0.906–0.985)	0.007	0.92 (0.880–0.968)	0.001
Gleason score (≥ 8 vs. <8)			1.12 (0.580–2.151)	0.741
M stage		0.539		0.433
M1a	Reference		Reference	
M1b	1.37 (0.667–2.829)	0.388	1.67 (0.751–3.717)	0.208
M1c	1.70 (0.653–4.449)	0.276	1.77 (0.616–5.090)	0.289

*, continuous variables; ECOG PS, Eastern Cooperative Oncology Group performance score; CCI, Charlson Comorbidity Index; VAS, Visual Analogue Scale pain score; ADT, androgen deprivation therapy; TTN, Time to PSA nadir, ART, androgen receptor target therapy; RT, radiotherapy; CI: confidence interval.

Additionally, VAS pain score (≥ 1) (HR = 2.27 (1.380–3.740), p = 0.001) and TTN (HR = 0.92 (0.880–0.968), p = 0.001) were significant predictors of CSS. Of note, CCI (≥ 4), PSA level at diagnosis, PSA nadir, Gleason score, and TNM stage were not associated with CSS (Table 2).

3.3. Impact of bone metastasis spread and the site of visceral metastasis on overall survival and cancer-specific survival

Due to clinicopathological heterogeneity across subgroups that may have confounded our ability to determine the influence of bone metastasis spread and the site of visceral metastasis on survival outcomes, mHSPC patients were stratified according to metastatic bone volume and the site of visceral metastasis. The presence of high-volume bone disease was defined as four or more bone metastases, with at least one metastasis beyond the pelvis or vertebral column. In the analyses for CSS, patients with low-volume bone disease did not have a lower survival rate than those without bone metastasis (log-rank

p = 0.247, Fig. 3A). However, CSS prognosis was significantly different between high-volume and low-volume bone disease (log rank p < 0.001)

A sub-analysis stratifying the visceral metastatic sites showed that patients with lung metastasis did not have a lower CSS rate than those with visceral metastasis, except in the lung and liver (log -rank p = 0.321, Fig. 3B). However, CSS prognosis was significantly different between patients with lung metastasis and visceral metastasis, including the liver (p = 0.021).

3.4. Stratifying the prognosis according to the combination of unfavorable risk factors

We further stratified CSS by bone metastasis spread and the site of visceral metastasis (log-rank p = 0.002, Fig. 4). The prognosis of CSS between low-volume bone metastasis patients and M1c patients (no bone metastasis and low-volume bone metastasis) was not significantly different (log-rank p = 0.507). In addition, the prognosis of CSS was not significantly different between M1c (high-volume bone metastasis and visceral metastasis except liver) and M1b (high-volume bone metastasis) patients (p = 0.489). However, the CSS rate was significantly higher in M1b patients than in M1c patients with visceral metastasis including the liver (p = 0.016).

4. Discussion

The present study demonstrated that OS and CSS outcomes among mHSPC patients were heterogeneous. Despite no differences in prognosis for groups with high-volume disease according to stratification defined by various guidelines, the prognoses were different among groups with low-volume disease. We confirmed that OS and CSS were related to visceral metastatic sites and metastatic bone spread in mHSPC patients. Of interest, no prognostic difference was found in the CSS between M1a or M1b (low-volume bone metastasis) and M1c patients (no bone metastasis and visceral metastasis, except liver). Notably, this study found that the prognosis of patients with visceral metastasis (except in the liver) depended on the spread of the bone disease.

The current standard treatment for mHSPC is ADT, since the first description of its hormonal dependence in 1941 [13, 14]. In a new treatment paradigm shift, upfront docetaxel and abiraterone acetate administration have been performed in patients with *de novo* metastasis [7–11]. However, clinicians are confused regarding the selection of initial treatment options, due to the heterogeneity of bone disease spread in patients with visceral metastasis. Although visceral metastases without bone involvement are seldom noted in mHSPC patients, clinicians often see patients with only visceral metastasis in practice [15, 16]. In our cohort, four patients were diagnosed with M1c (lung metastasis without bone metastasis).

This study observed that some mHSPC patients were classified differently according to the several definitions of high-volume disease. Prognoses did not differ among groups with high-volume disease, but significant differences in the prognoses among the groups with low-volume disease were found. These findings suggest that some patients have the probability of missing the opportunity to receive proper

initial treatment. Importantly, the concept of high- and low-volume bone metastases has become an essential issue for mHSPC patients in cases utilizing upfront docetaxel and abiraterone acetate [7–11], as well as radiation therapy for primary lesions [17]. In practice, prostate cancer patients are treated based on the recommendations of NCCN guidelines, which categorize mHSPC into high- and low-volume disease according to the presence of visceral metastasis and the degree of bone spread, based on the CHAARTED trial [18]. In particular, the guidelines suggest that radiation therapy is limited for high-volume metastatic disease. This result was recommended based on the STAMPEDE and HORRAD trials [17, 19], which reported that radiation therapy affects survival in cases of low-volume metastases. Therefore, based on our results, careful decisions are needed regarding the use of radiation therapy for primary lesions.

Compared with bone metastasis, visceral metastasis has been shown to confer worst survival, regardless of concomitant bone spread [6]. The study by Gandaglia et al. on 3857 mHSPC patients in the Surveillance Epidemiology and End Results–Medicare database reported that the presence of visceral metastasis should be associated with more aggressive disease; this was observed after stratifying patients according to the metastatic site (lymph node alone, bone, visceral, or bone plus visceral) [20]. Our findings confirmed that visceral metastases conferred the worst survival. Results of additional analyses showed that having visceral metastasis except in the liver did not worsen the prognosis of concomitant bone disease volume.

The presence of liver metastasis have been shown to be a significant predictor of worse prognosis [21]. Armstrong et al. reported that liver metastases were included in the variables with the greatest risk of death [22]. We confirmed that liver metastasis was associated with worse OS and CSS. However, the incidence of liver metastasis with or without bone involvement following prostate cancer diagnosis was relatively low [15]. In our study, there were no patients with liver metastasis and concomitant low-volume bone metastasis.

Regarding the heterogeneous outcomes in mHSPC, our study serves to inform clinical practice by highlighting that the prognosis of patients with an mHSPC diagnosis depends on the presence of liver metastasis and tumor involvement of the bone. In cases with visceral metastasis except liver, CSS survival was associated with bone disease spread. Also, differences in the survival of patients with low-volume bone metastases suggest that physicians should be cautious when deciding on the initial treatment for *de novo* metastases. To prevent such confusion, the unification of different criteria is necessary and will require a large-scale longitudinal study. Despite the strengths of this study, there are several limitations. Only a relatively small number of patients in this cohort were evaluated by retrospective, observational design. Moreover, several treatment options, such as docetaxel, abiraterone acetate, enzalutamide, and Radium-223, have emerged during the observation period. Therefore, there might be potential biases associated with the implementation of a specific treatment, based on differences in insurance, physician discretion, and patient preference. Nevertheless, we believe that this may reflect clinical practice in the real world.

5. Conclusions

We noted heterogeneity in OS and CSS among patients with mHSPC. Additionally, we successfully stratified mHSPC patients and noted that the use of different combinations of bone metastasis volume and visceral metastasis site can help in predicting the prognosis of mHSPC patients. Results from this study will aid in the counseling and prediction of the prognosis of mHSPC patients by stratifying for different combinations of existing metastatic criteria.

Abbreviations

ADT: androgen deprivation therapy

CCI: Charlson Comorbidity Index

CSS: cancer specific survival

ECOG: Eastern Cooperative Oncology Group Performance Status

mHSPC: metastatic hormone-sensitive prostate cancer

LHRH: luteinizing hormone-releasing hormone

NCCN: National Comprehensive Cancer Network

VAS: Visual Analogue Scale

TTN: time to PSA nadir

TNM: Tumor-node-metastasis

Declarations

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Availability of data and materials:

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contributions:

Conceptualization, H.K.A. and K.S.L.; Data Curation, H.K.A., J.W.Y. and K.S.L.; Formal Analysis, H.K.A. and K.S.L.; Investigation, H.K.A. and K.S.L.; Methodology, J.W.Y. and K.C.K.; Project Administration, K.S.L.; Supervision, K.C.K. and B.H.C.; Validation, K.C.K. and B.H.C.; Visualization, H.K.A.; Writing—Original Draft, H.K.A.; Writing—Review and Editing, K.S.L.

Ethics approval and consent to participate

This study was approved by the Yonsei University Health System Institutional Review Board. Informed consent was waived by the Yonsei University Health System Institutional Review Board, as patients' information was collected during routine clinical practice, and patients were identified by using an anonymized investigator-generated code that could not be linked to their personal data. The same Institutional Review Board granted access to the institutional databases used in this study.

Consent for publication:

Not required.

Competing interests:

The authors declare that they have no competing interests.

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Figures

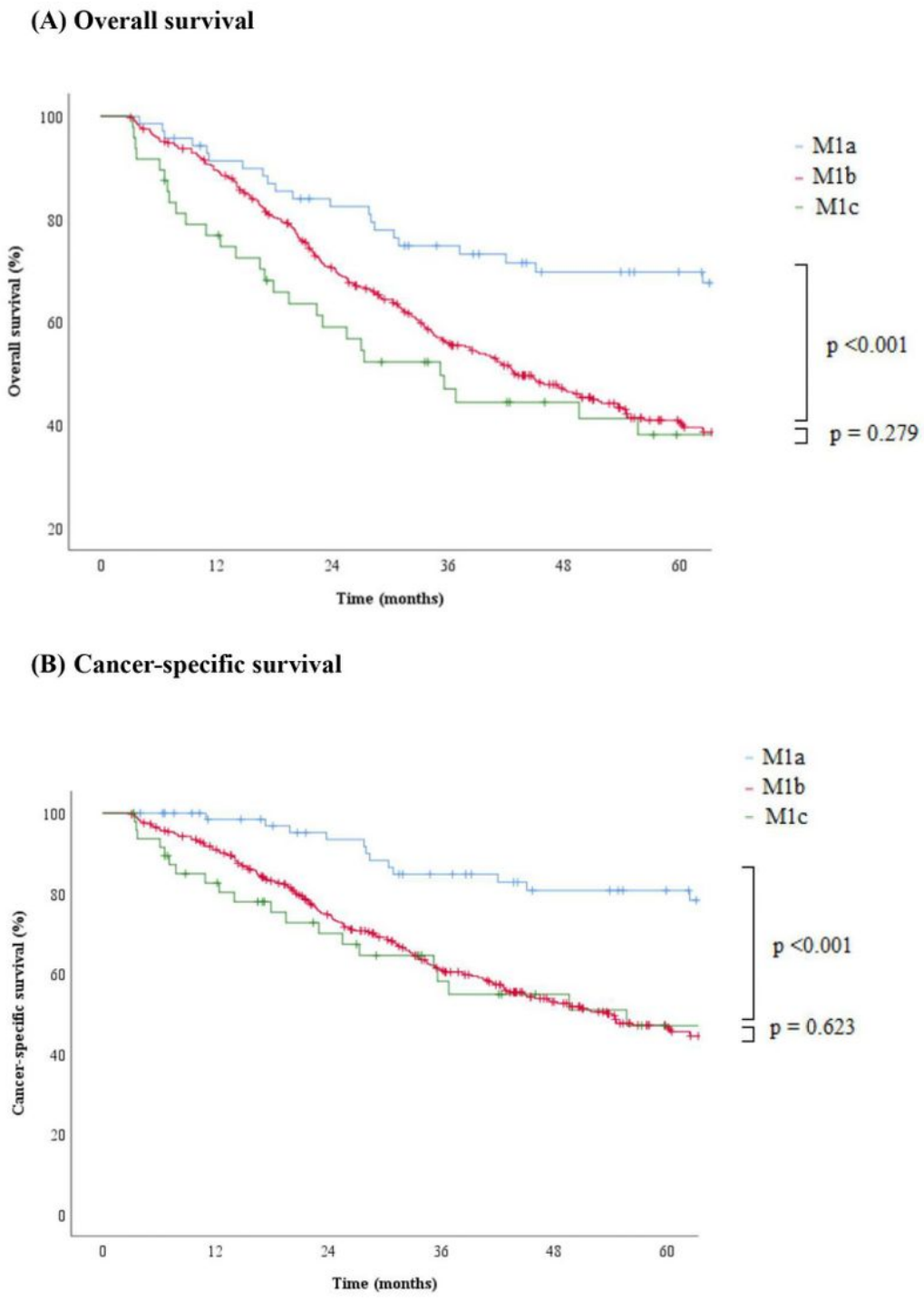

Figure 1

Comparative prognoses of patients with metastatic prostate cancer. (A) Overall survival and (B) cancer-specific survival are shown.

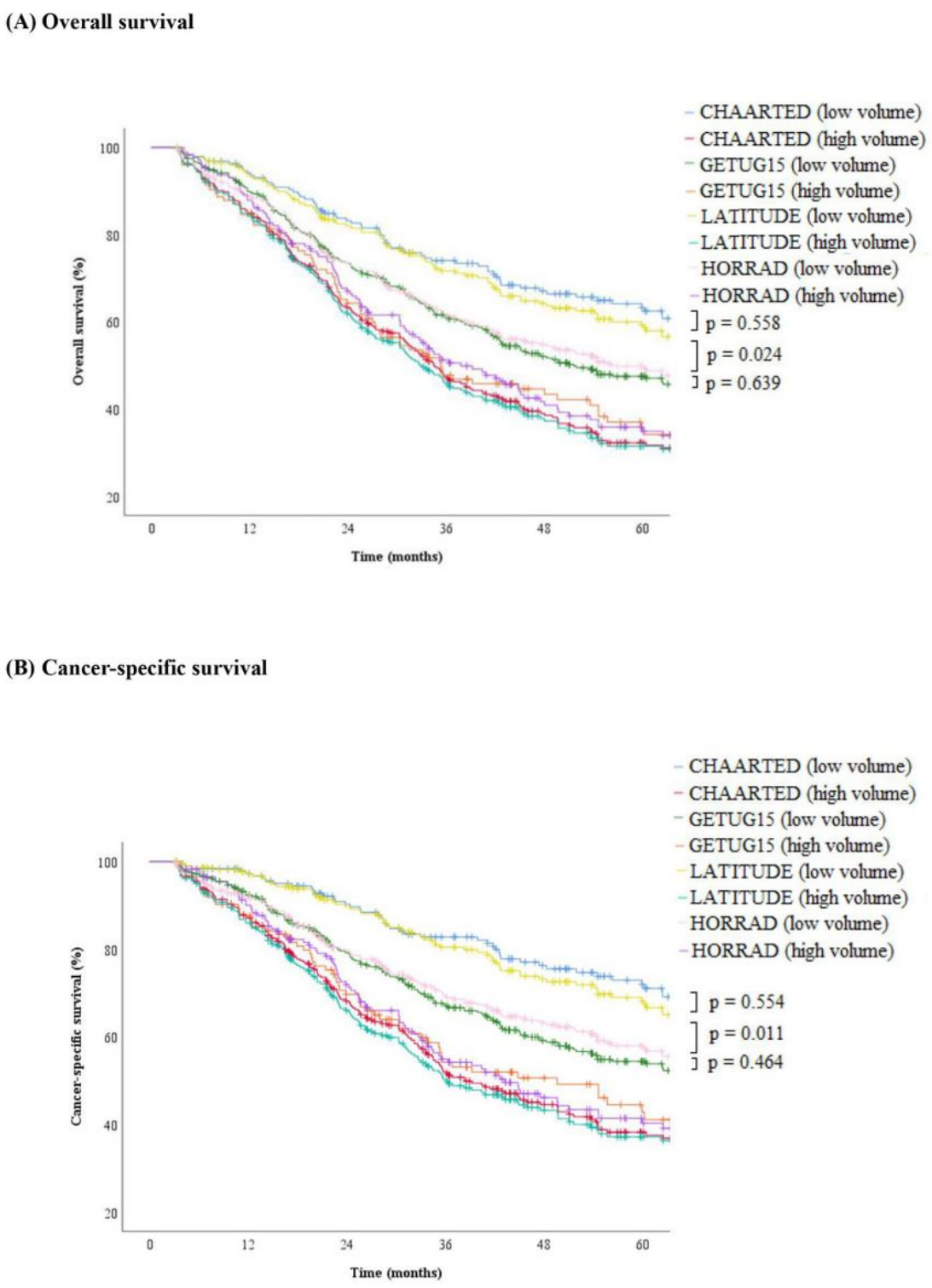

Figure 2

Comparative prognoses of patients with stratification based on criteria from several clinical trials. (A) Overall survival and (B) cancer-specific survival are shown.

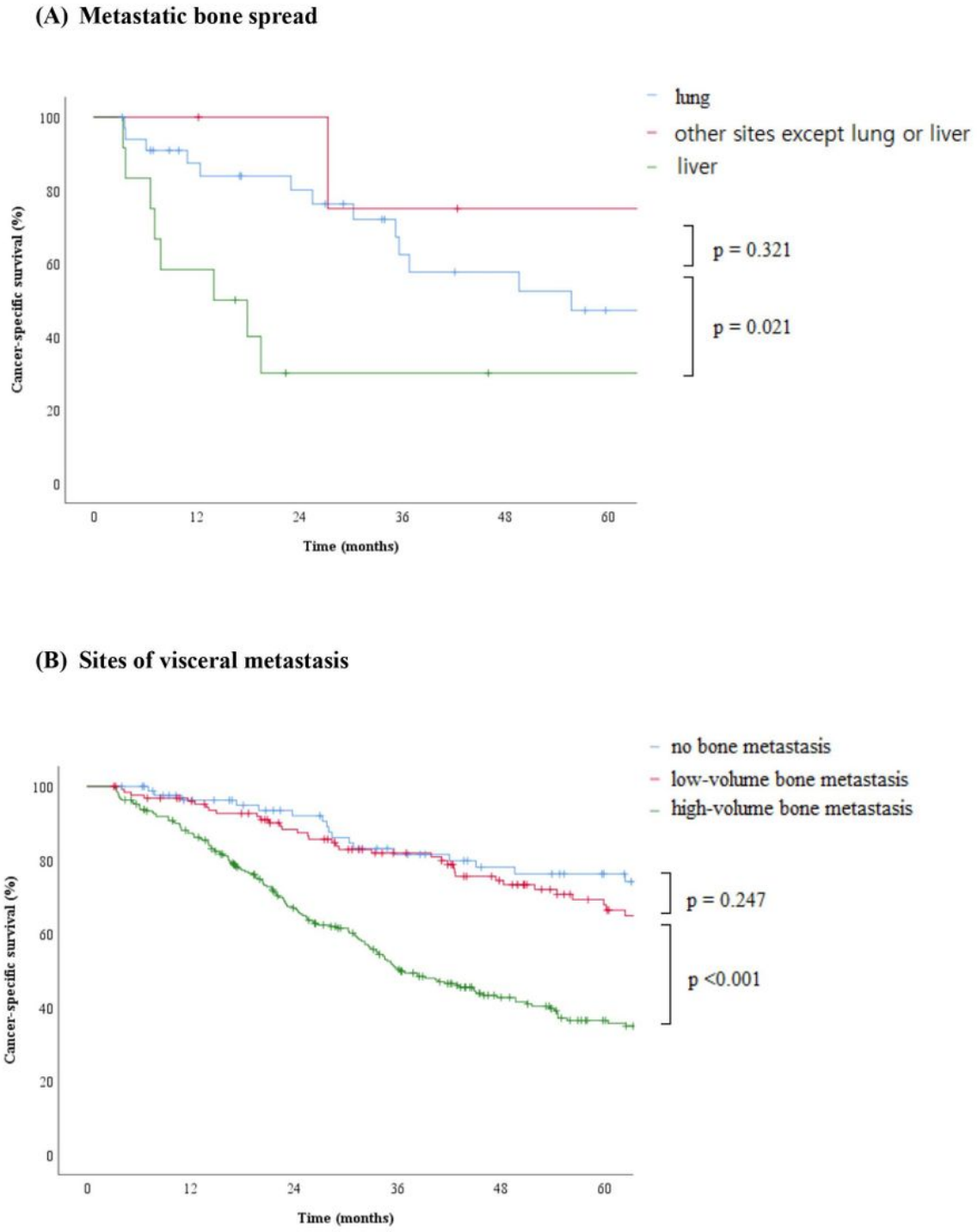

Figure 3

Comparative cancer-specific survival curves based on (A) metastatic bone spread and (B) sites of visceral metastasis.

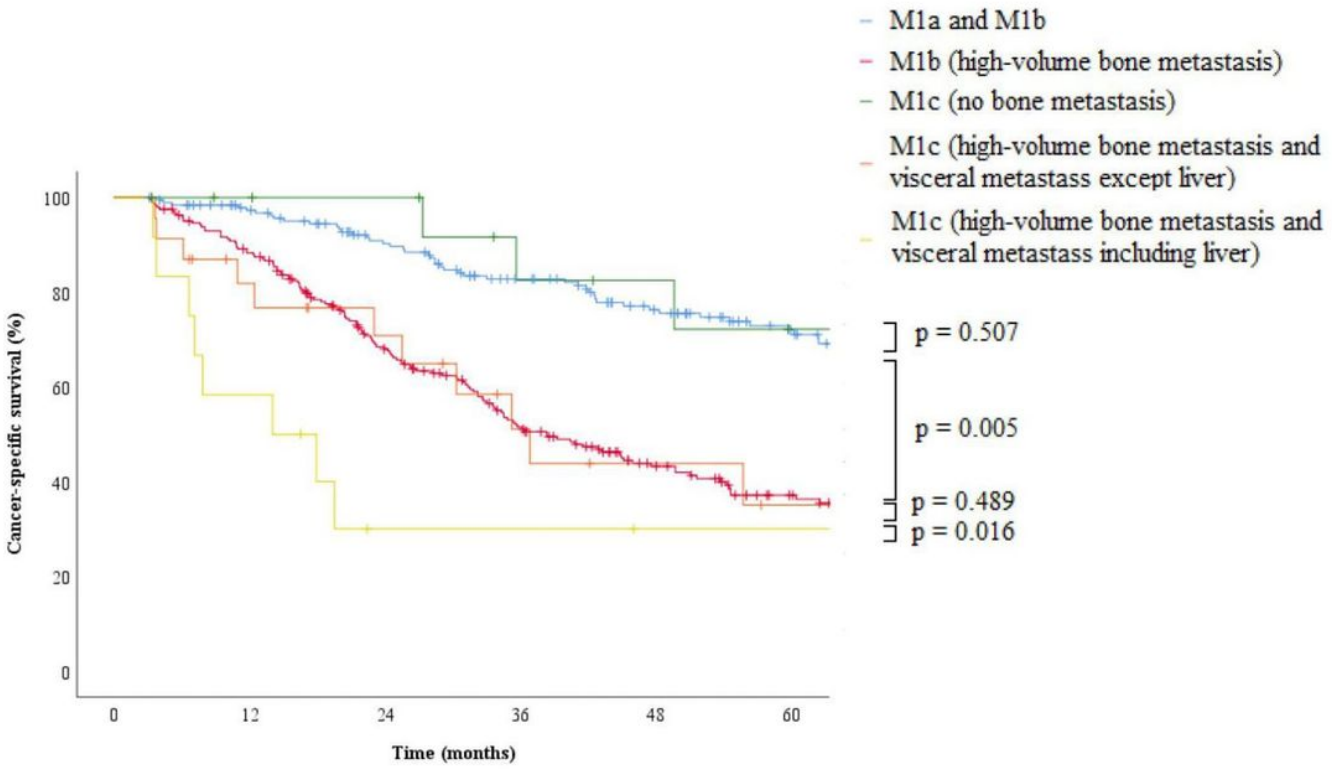

Figure 4

Comparative cancer-specific survival curves of patients with metastatic prostate cancer, according to the metastatic bone volume and sites of visceral metastasis.