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Cancer-specific survival patterns in patients with bone metastasis: a registry-based analysis of 13,742 patients

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Title: Cancer-Specific Survival Patterns in Patients with Bone Metastasis: A Registry-Based Analysis of 13,742 Patients

Running Title: Cancer-Specific Survival Patterns in Patients with Bone Metastasis

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Abstract

Background With increasing opportunities for patients with bone metastasis (BM) to benefit from local surgical intervention, accurate survival analysis across different primary cancers remains challenging. Current analytical frameworks commonly rely on single-center, pan-cancer cohorts and provide insufficient integration of cancer-specific characteristics. This retrospective, multicenter, registry-based cohort study aimed to analyze survival differences among BM patients across multiple primary cancers and to explore cancer-specific clinical factors associated with survival, providing a reference for clinical risk stratification to support surgical decision-making.

Methods Baseline demographic and clinical characteristics of 13,742 patients with AJCC stage IV or TNM stage M1 metastatic cancer were collected from 42 studies registered in the cBioPortal for Cancer Genomics database. Overall survival (OS) after metastatic diagnosis was the primary outcome. Univariate analyses were performed using Kaplan–Meier methods, log-rank tests, and non-parametric tests. Variables with $p<0.20$ were included in multivariable Cox proportional hazards models to examine independent associations with survival. Multiple imputation was applied to address missing data.

Results Among the 25 primary cancers analyzed, approximately half showed observable survival differences between BM and other-site metastasis, with 6 cancers reaching statistical significance. Based on median survival, all cancers

could be stratified into 3 distinct survival tiers, ranging from prolonged survival exceeding 15 months to markedly shorter survival of 3–10 months, with multivariable analyses further demonstrating that primary cancer type was the strongest factor associated with survival heterogeneity among BM patients (HR=1.422–1.758, p<0.001). Moreover, poorly differentiated or undifferentiated histology was independently associated with worse OS (HR=1.249, p<0.001), and age >60 years was also associated with shorter survival (p<0.001). Notably, no single metastatic site demonstrated a consistent adverse association with survival across cancer types.

Conclusions BM demonstrates cancer-specific and heterogeneous associations with survival compared with other metastatic sites. All primary cancers could be stratified into 3 groups, representing the most important factor associated with survival differences. Moreover, pathological differentiation was significantly associated with survival among BM patients with bone metastasis. Notably, no metastatic site functions as a universal prognostic factor across cancers. Large-scale, multicenter, registry-based analyses provide a valuable framework for cancer-specific survival analysis and for identifying clinically relevant factors that may serve as a reference for risk stratification in surgical decision-making.

Keywords: Bone Metastasis, Survival, Registry-Based, Multicenter, Cancer-Specific

Introduction

Bone metastasis (BM) represents a prevalent and debilitating complication in patients with advanced cancer, frequently leading to severe neurological pain, pathological fractures, spinal instability, sensory disturbance, and sphincter dysfunction, significantly compromising the quality of life [1-3]. Over the past decade, with rapid advancements in comprehensive oncological management, including stereotactic body radiation therapy, immunotherapy, and molecular targeted therapy, the life expectancy patients with advanced malignancies have been markedly improved [4-9]. Therefore, the indications for local surgical intervention aimed at alleviating pain and preserving neurological function have expanded substantially compared with the past. According to the four-point consensus for preoperative assessment established by the World Federation of Neurosurgical Societies (WFNS), the clinically realistic survival analysis and estimation of life expectancy are primarily crucial in the determination of surgical intervention [10]. In this context, precise identification of survival risk factors related to life expectancy is critically needed to inform clinical decisions on whether patients are expected to survive long enough to meaningfully benefit from surgical intervention.

However, survival risk assessments derived from existing prognostic models do not always translate well to real-world clinical practice. This limitation largely stems from the fact that many such models are applied across heterogeneous cancer types and rely on risk factors whose stability and interpretability may vary

substantially between different primary cancers [11-15]. From a methodological perspective, most previous studies mainly relied on single-center cohorts, resulting in pan-cancer analyses with relatively small sample sizes. Such designs are inherently subject to bias arising from unbalanced distributions of different cancer types within the population. The internal heterogeneity in survival across different cancers may introduce systematic errors, including overfitting bias, thereby precluding robust cancer-specific survival analysis and further limiting the applicability of these models across cancer types [11, 13, 16-26]. Moreover, previous analyses of survival risk factors for survival estimation have insufficiently integrated histopathological and molecular indicators that are highly specific to cancer subtypes, leading to an incomplete assessment of the biological characteristics of primary tumors [27-31]. Meanwhile, the continuous improvement in survival outcomes among BM patients with necessitates updated survival analyses that reflect contemporary clinical advances [32, 33].

These dilemmas raise the question of how to implement a cancer-specific analytical framework to identify clinically meaningful, cancer-specific variables that exert significant influence on survival even at advanced stages, thereby providing an effective reference for surgical decision-making. Therefore, in this study, we assembled a cohort of 13,742 patients with metastatic cancer diagnoses across 25 primary cancers and documented survival outcomes from 42 clinical studies registered in the cBioPortal for Cancer Genomics database. The heterogeneity of survival patterns associated with bone metastasis,

compared with other-site metastasis (OSM), was systematically examined across different primary cancers, demonstrating that BM patients represent a heterogeneous subgroup among those with advanced cancer. Cancer-specific survival-related factors that could not be adequately explored in previous studies because of limited sample sizes—such as primary cancer type, histopathological subtype, and metastatic sites—were carefully evaluated, thereby providing more precise evidence for life expectancy estimation and serving as a reference for surgical decision-making in patients with bone metastasis.

Methods

Study design and setting

This study strictly followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was conducted in accordance with the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement [34, 35]. Informed consent was waived owing to the retrospective design of the study and the anonymization of all patient information. All data used in this research were obtained from the accessible cBioPortal for Cancer Genomics database. The study was conducted with the support of a tertiary hospital in Beijing, China. Ethical approval was granted by the Research Ethics Committee of our institution (approval number: LM2025366).

Patients

Clinical djata of patients diagnosed with metastatic cancer between 2015 and 2025 were extracted from the cBioPortal for Cancer Genomics database (publicly accessible) [36]. Recruited cases were diagnosed with tumor-node-metastasis (TNM) stage M1 or American Joint Committee on Cancer (AJCC) stage IV and had a clear survival outcome (n = 17,533, including 31 cancers) [37, 38]. Histopathological classifications were based on standard diagnostic criteria consistent with the WHO Classification of Tumours, 5th Edition [39]. Studies were excluded if the number of BM patients was fewer than 5 in a single study, the specific cancer type was undefined (e.g., cancer of unknown primary), or the study cohort consisted of patients with primary bone tumors (n = 3,791). BM was identified when metastatic site labels included “bone” or specific skeletal sites (n = 6,011), regardless of the presence of metastases at other anatomical sites. OSM was defined as metastatic involvement at non-bone sites (n=7,731). Only bone metastasis (OBM) was defined as the presence of BM in the absence of metastases at any other sites. Ultimately, a total of 13,742 patients with metastatic cancer were included in the final analysis (Figure 1).

Primary Outcomes

The primary outcome was the overall survival (OS) defined as the time from the diagnosis of metastatic cancer (TNM stage M1 or AJCC stage IV) to death.

Data Sources and Variables

In total, 42 clinical studies were obtained from the cBioPortal for Cancer Genomics database involving 25 distinct cancer types and 189 histopathological subtypes. The clinical variables included study identity document (ID), patient ID, sample ID, metastatic sites (lung, liver, intra-abdominal region, pelvis including reproductive system, bladder, and rectum, central nervous system, adrenal gland, bone, spine, and vertebrae), primary cancer type, detailed histopathological subtype, overall survival status, overall survival time, age at diagnosis, current age, age at surgical procedure, sex, race, religion, body mass index (BMI), Gleason score, prior treatment regimen, comorbidities, TNM stage, and AJCC stage.

Data Preprocessing

Gene-related variables that were not associated with clinical information were removed. Clinical variables with the same meanings but different names across studies were merged: (1) variables differing only in letter case, (2) variables representing synonymous terms, and (3) age at diagnosis was missing but replaced by age at sampling in individual studies. Variables with a missing rate greater than 30% (e.g., BMI, religion, prior treatment regimen, etc.) were excluded [40]. Multiple imputation was applied to handle missing values in continuous variables, such as age at diagnosis [41, 42]. Both structured clinical data (e.g., laboratory test results) and unstructured information (e.g., electronic medical records and imaging reports) were adopted to determine the metastatic sites.

Statistical Analysis

The normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov (K–S) test [43]. The Mann–Whitney test and Kruskal–Wallis test were respectively applied to compare differences in variable distribution between two or more groups in non-normally distributed data [43]. Variables not following a normal distribution were summarized as median with interquartile range (IQR). The coefficient of variation was used to reflect the degree of dispersion in survival time among different populations.

A specific cancer type was included in univariate analyses when the number of patients experiencing the event of interest for the primary outcome was approximately 30 or higher [44]. The Kaplan–Meier curve and log-rank (Mantel–Cox) test were used to evaluate the effect of a single risk factor on survival time [41]. Variables with a $p<0.2$ in the univariate analysis were included in the multivariate model [45, 46]. To account for multiple comparisons, the false discovery rate (FDR) was controlled using the Benjamini–Hochberg procedure. Multivariate analysis was performed using the Cox proportional hazards model [47]. The collinearity was assessed using the variance inflation factor (VIF) with an acceptable threshold of <5. The proportional hazards (PH) assumption was verified using the Schoenfeld residuals test.

Exhaustive search, tree models, and the maximally selected rank statistics (MAXSTAT) were applied to identify optimal cut-off values for age-related risk of survival time [48]. The model stability was evaluated using the bootstrap method, and 95% confidence intervals (CIs) were reported. Statistical significance was defined as $p<0.05$. The clinical effect size of the significant difference was further assessed using Cliff's δ and the probability of superiority (PS) both with 95% CIs. Statistical analyses were performed using IBM SPSS Statistics (version 31.0.0.0; IBM Corp., Armonk, NY, USA) and R (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria). Survival curves were generated using GraphPad Prism (version 10.0.0; GraphPad Software, Boston, MA, USA).

Results

Patient Baseline Characteristics

A total of 13,742 patients were included in the final analysis involving 25 different cancer types. The number of BM patients exceeded 100 in 11 cancer types, and the proportion varied substantially across cancer types, ranging from 10.1% to 74.7%. Approximately half of the cancers showed a predominant distribution of pathological subtypes (Supplementary Table 1).

BM vs. OSM

Significant differences in survival between BM and OSM patients were observed in 6 cancers: uterine sarcoma (p=0.002), colorectal cancer (p=0.010), prostate cancer (p=0.047), endometrial cancer (p=0.012), salivary gland cancer (p=0.030),

and melanoma (p<0.001) (Table 2). In addition, there were 8 other cancers that demonstrated a p-value ranging between 0.05 and 0.20. Cancer-specific survival analysis in 9 of 14 cancers described above showed that BM patients tended to have shorter survival compared with OSM patients except for thyroid, colorectal, prostate, endometrial, and head and neck cancer. The absolute values of Cliff's δ ranged from 0.033 to 0.464. The most pronounced difference was observed in melanoma (p<0.001, PS=0.268, |Cliff's δ|=0.464) (Table 1).

Cancer Types

Significant survival differences were observed among BM and further OBM patients across different cancer types (both p<0.001; Figure 2). The CV of BM and OBM patients ranged from 76.04% to 103.81% and 69.40% to 138.20% (Supplementary Table 2 and Table 3). All cancer types were stratified into three groups based on median survival (IQR) (Table 1). Cancers in the first survival tier exhibited median survival times exceeding 15 months, including breast cancer (19.39, 10.13-34.82), thyroid cancer (17.79, 10.77-27.4), uterine sarcoma (16.59, 9.52-28.16), colorectal cancer (16.45, 8.63-29.52), soft tissue sarcoma (15.41, 7.85-24.36), and prostate cancer (15.36, 6.70-28.81). In contrast, cancers in the third survival tier demonstrated the poorest survival outcomes, with median survival times ranging from 3 to 10 months: hepatobiliary cancer (10.09, 4.57-19.70), bladder cancer (9.76, 3.94-15.70), head and neck cancer (9.07, 3.70-15.69), pancreatic cancer (8.94, 3.93-17.47), cervical cancer (8.68, 2.69-18.12),

small cell lung cancer (8.42, 4.83-13.52), germ cell tumor (8.20, 1.80-9.70), skin cancer (7.72, 5.63-21.14), and appendiceal cancer (3.84, 3.27-11.88)

Metastatic Sites

Patients with different single metastatic sites were further compared within cancer-specific groups. Different metastatic sites were associated with significantly different survival across cancers involved (Figure 3, Supplementary Table 4), such as brain metastasis in breast cancer (p<0.001), liver metastasis in prostate cancer (p<0.001), and abdominal metastasis in soft tissue sarcoma (p<0.001). However, no metastatic site consistently functioned as an independent risk or protective factor for survival across all cancer types. Notably, when OBM was regarded as an independent prognostic factor (Figure 3).

Pathological Subtypes

BM patients with poorly differentiated or undifferentiated pathological subtypes demonstrated significantly shorter survival compared with other pathological subtypes in multiple cancer types, such as ovarian cancer (low-grade serous ovarian cancer, p=0.042), thyroid cancer (anaplastic thyroid carcinoma, p<0.001), pancreatic cancer (undifferentiated carcinoma of the pancreas, p<0.001), non–small cell lung cancer (NSCLC) (poorly differentiated NSCLC, p<0.001), breast cancer (triple negative, p<0.001), and soft tissue sarcoma (dedifferentiated liposarcoma, p<0.001) (Figure 4, Supplementary Table 5). Particularly, this difference was mostly obvious within the first 12 months. Notably, no significant

survival differences were observed among the remaining differentiated pathological subtypes. Moreover, in NSCLC, patients with lung adenocarcinoma demonstrated a better survival outcome.

Sex and Age

Sex-specific analyses were conducted only in cancer types with relatively balanced sex distributions; cancers with a strong sex predominance, such as breast cancer and primary reproductive system cancers, were therefore excluded. Among the 13 primary cancer types included in the analysis, the proportion of male patients ranged from 38.5% to 81.0%. Except for NSCLC (p=0.028), no significant survival differences were observed between male and female (Supplementary Table 6). Age thresholds associated with significant survival differences were identified in 18 cancer types, ranging from 40 to 76 years, with 12 cancers clustering between 55 and 70 years (Supplementary Table 7). Patients older than 60 years showed significantly poorer survival (p<0.001) when a threshold of >60 years was applied for all cancers (Supplementary Figure 1).

Cox Proportional Hazard Regression Model

After controlling for multiple testing in the univariate screening stage using false discovery rate (FDR) adjustment (Supplementary Table 8), the multivariate Cox proportional hazard regression model incorporated the following covariates: primary cancer type (tier 1, 2, and 3 according to Table 1), age at diagnosis, pathological subtype (poorly differentiated or undifferentiated vs. differentiated),

sex, OBM, central nervous system metastasis, lung metastasis, and liver metastasis (Figure 5). The results indicated that the primary cancer type (2 vs. 1, HR=1.422, p<0.001; 3 vs. 1, HR=1.758, p<0.001), poorly differentiated or undifferentiated (HR=1.249, p<0.001), and male sex (HR=1.086, p=0.002) were identified as independent risk factors for survival in BM (Figure 5).

Discussion

Clinical Relevance of Cancer-Specific Survival Stratification in Bone Metastasis

Patients with bone metastasis (BM) constitute a heterogeneous and clinically important population. Over the past decade, substantial advances in radiotherapy, systemic chemotherapy, immunotherapy, and targeted therapies have markedly prolonged survival in patients with advanced cancers. In this contemporary context, the management of BM-related complications—such as neurological compression, refractory pain, and spinal instability—has emerged as an increasingly important clinical focus, as patients with BM may now live long enough to meaningfully benefit from pain alleviation, preservation of neurological function, and improvements in quality of life following local surgical interventions.

Historically, survival analyses and prognostic studies in patients with bone (or spinal) metastasis aimed at identifying survival-associated risk factors to inform surgical decision-making have largely relied on single-center cohorts and pooled, pan-cancer analyses [49-58]. Although such designs may reduce variability related to inter-institutional practice patterns, they preclude meaningful cancer-

specific risk stratification based on distinct survival patterns across different cancer types. As a result, the clinical factors identified in these studies were often influenced by cancer-type distribution, leading to biased or unstable conclusions when applied to real-world surgical decision-making.

In this multicenter, public database–based cohort study, rather than developing or validating prognostic models, we approached the problem from a more fundamental perspective by identifying survival-associated factors that reflect recent advances in oncologic management. A total of 13,742 patients with metastatic cancer across 25 primary cancer types were analyzed, enabling a cancer-specific evaluation of survival among BM patients. Compared with OSM patients, heterogeneous survival patterns among BM patients were observed in more than half of the analyzed cancer types, supporting the necessity of cancer-specific survival analyses and risk stratification in this distinct clinical population. Based on overall survival distributions, all primary cancers were further stratified into three distinct survival tiers, highlighting the strong cancer-specific association between primary tumor origin and survival among BM patients. In addition to primary cancer type, pathological differentiation and age at diagnosis were also significantly associated with survival. From a cancer-specific perspective, these findings provide a objective reference to support survival risk stratification and clinical judgment in local surgical intervention, particularly in identifying patients who are less likely to benefit from invasive procedures.

Heterogeneous Survival Patterns of BM Across Cancer Types

In contrast to previous studies, our study demonstrates that the survival pattern of BM patients, when compared with OSM patients, is not uniform across different primary cancer types [59, 60]. In several cancers identified in this study, including thyroid, prostate, colorectal, endometrial, renal cell carcinoma, and bladder cancer, BM did not consistently shorten survival relative to OSM. By contrast, in uterine cancer, salivary gland cancer, melanoma, hepatobiliary cancer, and small cell lung cancer, BM patients exhibited significantly worse survival than those in the OSM cohort. These observations are partly consistent with previous reports by Bollen, Luksanapruksa, and et al., which suggested that BM occurring in breast or thyroid cancer may be associated with a more favorable prognosis than visceral metastasis [60-63]. However, our findings further illustrate the heterogeneity of the clinical impact of BM across different cancer types and highlight the methodological relevance of cancer-specific survival analysis.

Primary Cancer Type

Primary cancer type emerged as the most influential determinant of survival, which is partly consistent with previous studies [60, 61]. However, prior clinical assessments have often relied on empirical judgment regarding primary tumor behavior, such as intrinsic growth rate reflected in the Tomita and Katagiri scoring systems or radiotherapy responsiveness incorporated in the neurologic, oncologic, mechanical, and systemic (NOMS) framework [54, 57, 64]. By

leveraging large-scale, cancer-specific survival analyses, our study provides a more systematic and objective data-driven characterization of survival heterogeneity across primary cancers. Based on observed survival distributions, different primary cancers were stratified into three survival tiers, yielding a survival hierarchy that partially parallels the stratification principles used in scoring systems developed by Tokuhashi, Katagiri, and et al., while substantially expanding the range of cancer types examined and more comprehensively reflecting contemporary treatment paradigms [11, 54, 55].

Furthermore, when these results are interpreted in the context of existing clinical knowledge, part of the observed survival heterogeneity may be related to differences in osteotropic behavior (affinity for skeletal tissue) across cancer types. For cancers with intrinsically weak affinity for skeletal metastasis (e.g., skin cancer, germ cell tumors, bladder cancer, and hepatobiliary cancer), the presence of BM more often reflects concomitant multi-organ involvement and a higher systemic tumor burden. In contrast, for cancers with strong osteotropic behavior (e.g., breast, thyroid, and prostate cancer), BM may occur in the setting of limited visceral dissemination and a relatively lower overall tumor burden. Consistent with our findings, patients in the former group tend to exhibit a higher short-term mortality risk than those in the latter. However, osteotropic behavior alone does not fully explain the observed survival stratification (e.g., small cell lung cancer also demonstrates strong bone tropism), and given the retrospective nature of this study, mechanistic overinterpretation would be inappropriate.

Age and Sex

The association between age above 60 years and shorter survival may be related to poorer baseline functional status, reduced treatment tolerance, age-related immune decline, and a higher burden of comorbidities [65-67].However, given that detailed information on baseline health status and comorbid conditions was largely unavailable in the this study, and that age reached statistical significance only in univariate analyses, the underlying clinical implications of this association require further investigation [65-67]. In addition, sex did not remain a significant prognostic variable after adjustment for primary cancer type, suggesting that previously reported sex-related differences in survival may have been confounded by the unbalanced distribution of sex-specific cancers rather than reflecting an independent effect. As such, sex may not be broadly applicable for survival estimation in patients with bone metastasis [68-72]. Taken together, these findings indicate that not all demographic variables exert a meaningful influence on survival, whereas cancer-specific characteristics—such as primary cancer type and pathological differentiation—appear to have more consistent and interpretable associations with survival outcomes in this population.

Histopathological Differentiation: an Underappreciated Survival Risk Factor

Both univariate analyses and multivariable Cox regression demonstrated that histopathological differentiation represents a robust, cancer-specific factor associated with survival among BM patients. Although previous studies have

reported that histologic grade independently influences survival after adjustment for age, metastatic pattern, and treatment [63, 73-76], its role has not been consistently incorporated or emphasized in survival analyses, particularly within prognostic frameworks focused on BM patients. Several well-recognized prognostic scoring systems for bone (or spinal) metastasis do not explicitly include histopathological differentiation as a core variable [11, 49, 77].

From this perspective, our study does not aim to redefine histopathological differentiation as a novel biological concept. Rather, it highlights its underrepresented and often overlooked role in large-scale, heterogeneous survival analyses. By systematically re-evaluating this established pathological feature across multiple cancer types with BM, we observed that poorly differentiated or undifferentiated tumors—such as triple-negative breast carcinoma, anaplastic thyroid carcinoma, and undifferentiated pancreatic carcinoma—were associated with significantly shorter survival, particularly within the first year after diagnosis. This early survival period is clinically critical as it often determines whether patients are likely to derive meaningful benefit from local surgical intervention.

Notably, our results further indicate that among diverse histopathological classifications, only clearly defined degrees of differentiation show consistent associations with survival. In the current era of molecular profiling, basic histological grading is frequently underemphasized in large registry-based analyses. However, our findings suggest that in real-world clinical scenarios—

particularly when molecular data are unavailable or when urgent surgical decision-making is required, such as in cases of impending neurological compromise—histopathological differentiation remains an accessible and clinically meaningful surrogate of tumor biological behavior.

Metastatic Sites

Our findings regarding metastatic sites represent a departure from prior literature. In most existing prognostic scoring systems for BM patients, metastatic site is treated as a uniformly adverse factor (e.g., visceral or brain metastasis) [11, 60], implicitly assuming site-specific effects that are independent of cancer type. In contrast, our analyses demonstrate that the survival impact of metastatic sites is cancer-dependent rather than universal. Certain sites are associated with significantly worse survival only within specific cancers (e.g., brain metastasis in breast cancer, liver metastasis in prostate cancer, and abdominal metastasis in soft tissue sarcoma), while no single metastatic site confers a consistent survival disadvantage across all cancers. These findings indicate that metastatic site, as a survival risk factor, should be interpreted within a cancer-specific context, which is precisely the analytical framework adopted in our study. Notably, this conclusion further reinforces the rationale for primary cancer–based stratification in BM patients, as even bone involvement itself carries different prognostic implications across cancers.

Limitations

This study incorporated a large, multicenter, registry-based cohort of patients with metastatic cancer and leveraged survival data collected over the past decade to characterize survival-associated risk factors from a cancer-specific perspective, thereby providing a reference for clinical decision-making regarding local surgical intervention in BM patients. Data preprocessing procedures—including standardized data curation, imputation of missing values, and bootstrap-based validation—together with univariate and multivariate survival analyses, were performed in accordance with recently published statistical frameworks and guidelines for survival and prognostic research [11, 41, 42, 78, 79].

Nonetheless, several limitations should be acknowledged. First, for approximately 50% of the included primary cancer types, the number of patients with bone metastasis was fewer than 100; together with heterogeneity in data collection quality and reporting across contributing centers, this may partially limit the generalizability of the findings. To partially mitigate this issue, analyses were restricted to survival data from the most recent decade and conducted within a cancer-specific framework using a unified statistical approach, with consistent clinical and histopathological diagnostic criteria ensured across studies. Second, incomplete data from immunohistochemical and radiological examinations, as well as baseline functional assessments—including Frankel grading and Eastern Cooperative Oncology Group (ECOG) performance status—limited the incorporation of these clinically relevant variables into the survival analyses. This limitation is inherent to large-scale registry-based studies and may constrain the

comprehensiveness of the survival analyses. In addition, bone metastasis was frequently recorded simply as “bone” without specification of anatomical location, which restricts the applicability of the findings to more specific clinical scenarios (e.g., patients with spinal or extremity metastases). Future studies that integrate institutional cohorts with more detailed clinical evaluations and multicenter public databases may help to address these limitations. Finally, treatment-related information was incomplete and heterogeneous across the included studies, particularly with respect to molecular targeted therapies and surgical details. To avoid introducing substantial bias, therapeutic variables were therefore not incorporated into the survival analyses, a limitation commonly shared by registry-based studies [60, 80-84]. To partially mitigate the impact of missing treatment information, we focused on other factors closely associated with treatment selection in advanced cancer (e.g., histopathological differentiation) and emphasized that the findings are applicable to baseline survival assessment prior to treatment initiation or before treatment response becomes available. This helps ensure that survival analyses remain interpretable even in the absence of detailed treatment data.

Conclusion

BM demonstrates an independent and cancer-specific impact on survival when compared with other-site metastasis. Patients with primary cancers classified in the third survival tier, poorly differentiated or undifferentiated histopathological subtypes, and diagnosis at an age above 60 years were associated with

significantly poorer survival in the presence of bone metastasis. These findings suggest that such patients should be approached with particular caution when considering local surgical interventions aimed at pain relief or preservation of neurological function. In contrast to conventional prognostic analyses, no single metastatic site served as a universal prognostic factor across all cancer types. Instead, our results indicate that metastatic patterns should be interpreted within a cancer-specific analytical framework. Leveraging real-world data from large public databases to identify and update survival-associated factors in patients with bone metastasis is both feasible and clinically meaningful, providing a valuable reference for clinical decision-making.

List of abbreviations

AJCC: American Joint Committee on Cancer; BM: Bone Metastasis; BMI: Body Mass Index; CI: Confidence Interval; CV: Coefficient of Variation; EGFR: Epidermal Growth Factor Receptor; EMT: Epithelial-Mesenchymal Transition; ECOG: Eastern Cooperative Oncology Group; HF: Hazard Ratio; IHC: Immunohistochemistry; IQR: Interquartile Range; K–S: Kolmogorov–Smirnov; MAXSTAT: Maximally Selected Rank Statistics; NSCLC: Non–Small Cell Lung Cancer; OBM: Only Bone Metastasis; OS: Overall Survival; OSM: Other-site Metastasis; PH: Proportional Hazards; PS: Probability of Superiority; RECORD: Reporting of Studies Conducted using Observational Routinely-Collected Health Data; STROBE: Strengthening the Reporting of Observational Studies in

Epidemiology; TNM: Tumor-Node-Metastasis; VIF: Variance Inflation Factor; WFNS: World Federation of Neurosurgical Societies.

Declarations

Ethics approval and consent to participate

The study is retrospective and registry-based without clinical or experimental intervention, and the data used were collected from a public database. For these reasons, informed consent was applied for exemption. The study was conducted with the support of Peking University Third Hospital. Ethical approval was granted by the Research Ethics Committee (approval number: LM2025366)

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this study are available from the corresponding author on reasonable request or can be accessed from the cBioPortal for Cancer Genomics (https://www.cbioportal.org/).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Z.L. Yun, Y.C. Tang, and J. Sun conceived and designed the study. Z.L. Yun, J.C. Lei, and G.Q. Zhang collected the data. Z.L. Yun and Y.C. Tang performed the statistical analysis. Z.L. Yun drafted the manuscript. F. Wei and X.G. Liu supervised the study and were responsible for manuscript revision and correspondence. All authors read and approved the final manuscript.

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Figures

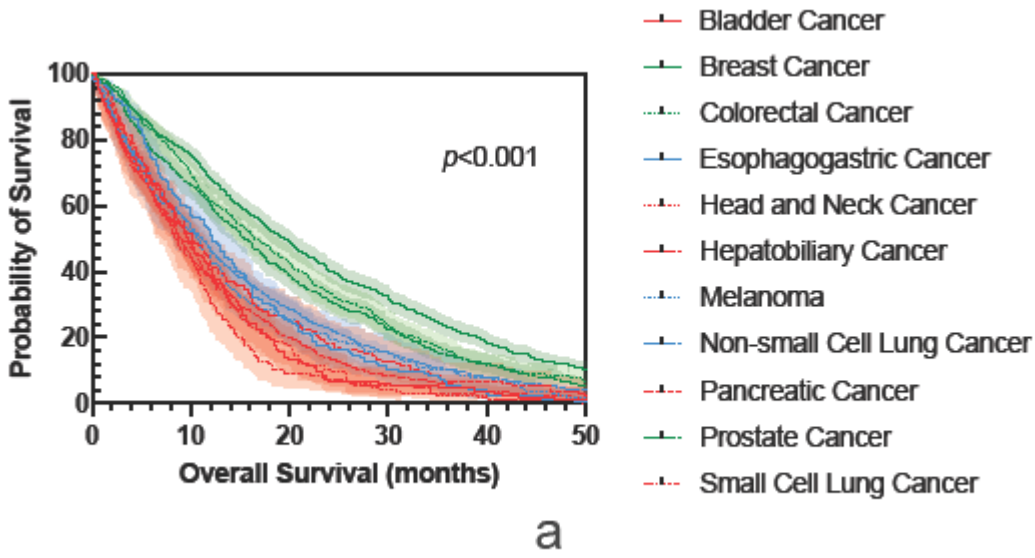
Figure 1 Flow chart of included patients.

Figure 2 Kaplan–Meier survival curves of survival comparisons among different primary cancers. a: patients with bone metastasis possibly combined with other sites of metastasis; b: patients only with bone metastasis. Cancers were stratified into three survival tiers based on primary cancer type, with different colors indicating each tier (green for the first tier, blue for the second tier, and red for the third tier).

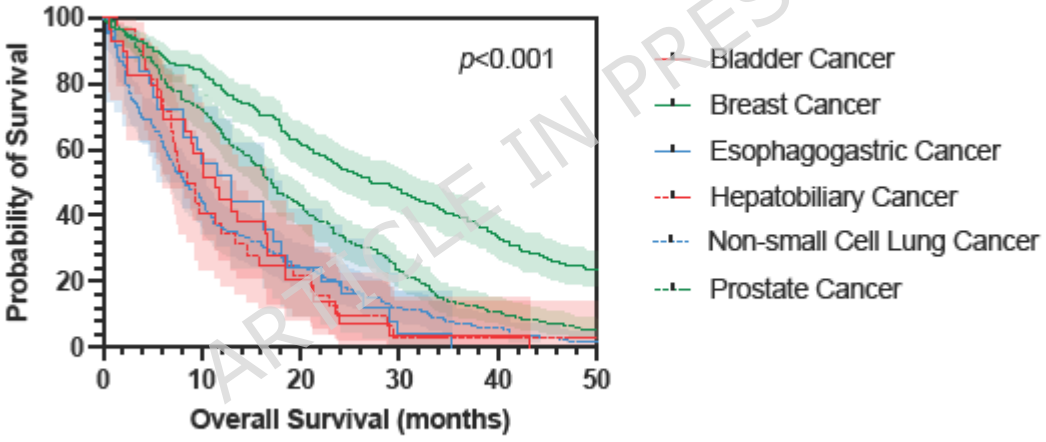
Figure 3 Kaplan–Meier survival curves according to metastatic sites in BM patients. NSCLC=non-small cell lung cancer, BM=bone metastasis.

Figure 4 Kaplan–Meier survival curves according to pathological differentiation and histological subtypes in BM patients. NSCLC=non-small cell lung cancer, BM=bone metastasis.

Figure 5 Forest plot based on multivariate Cox proportional hazards model. Survival-associated factors in patients with bone metastasis were identified. HR=hazard ratio, CI=confidence interval, UD=undifferentiated, CNS=central nervous system.



a



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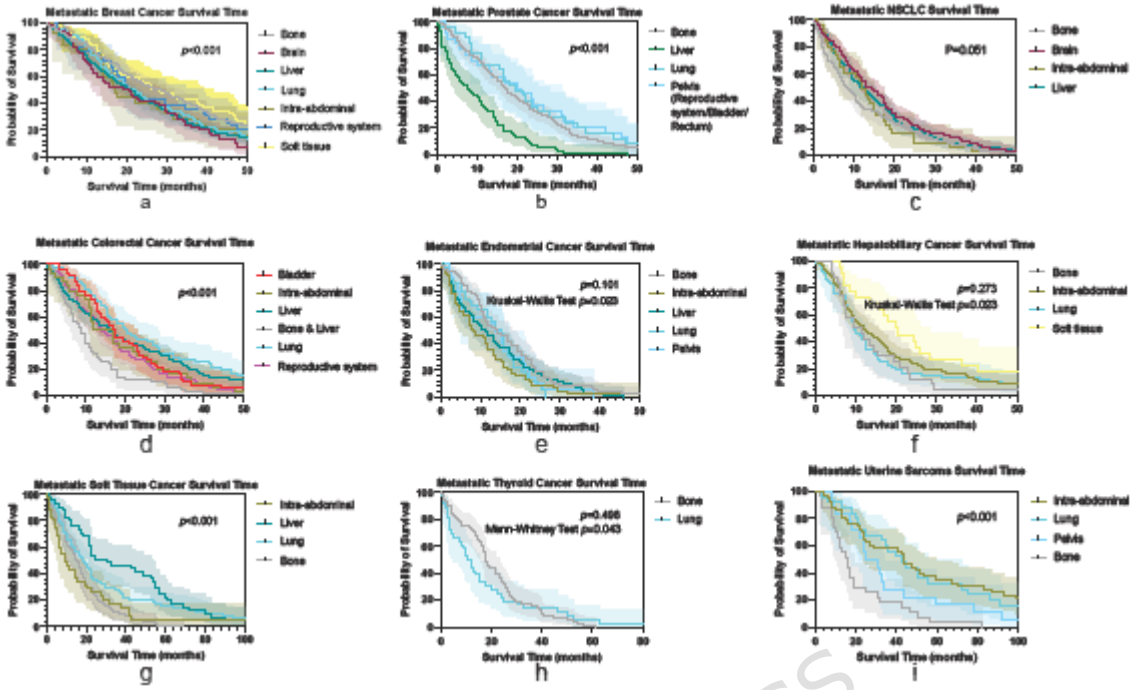

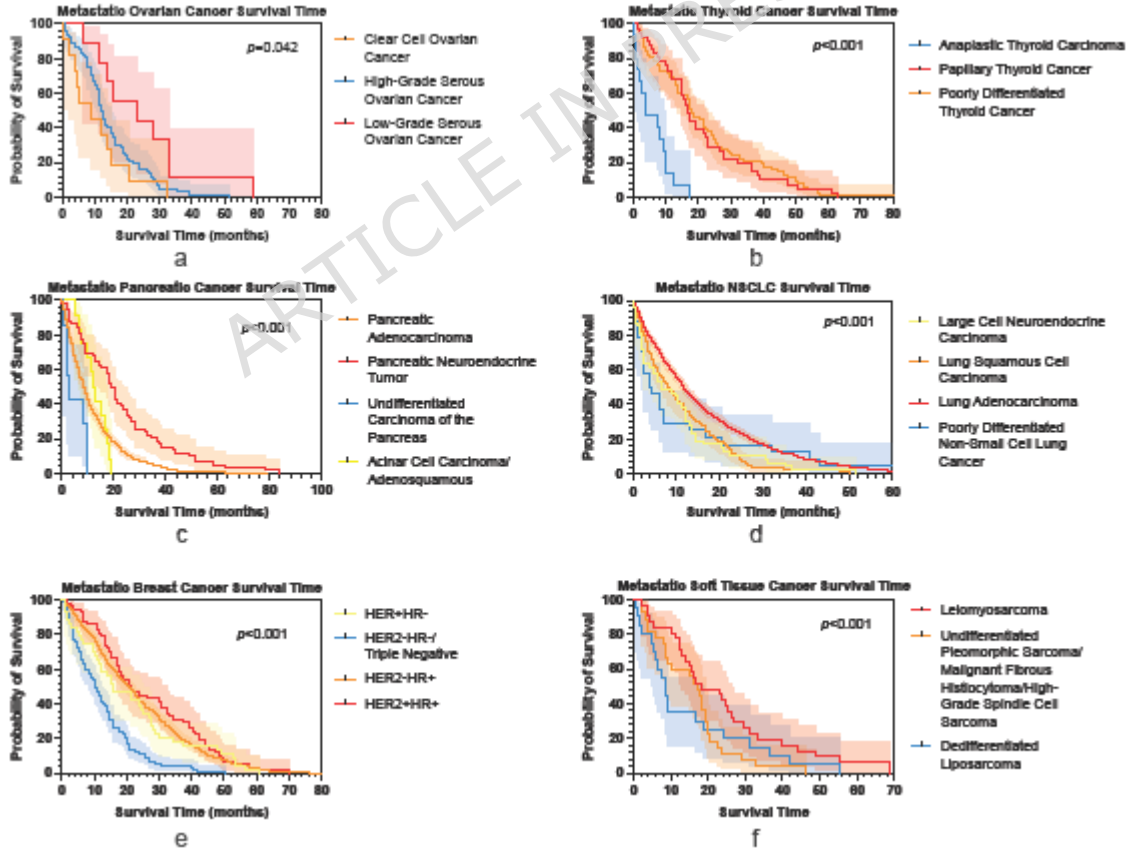

Event	HR	HR 95% CI	*p*
Primary Cancer Category (2 vs.1)	1.422	(1.335, 1.515)	<0.001
Primary Cancer Category (3 vs.1)	1.758	(1.638, 1.887)	<0.001
Age at Diagnosis (>60 vs. ≤60)	1.013	(0.960, 1.069)	0.643
Differentiation (Poorly/UD vs. Differentiated)	1.249	(1.135, 1.374)	<0.001
Sex (Male vs. Female)	1.086	(1.030, 1.145)	0.002
Only Bone Metastasis (Yes vs. No)	1.029	(0.907, 1.167)	0.657
CNS Metastasis (Yes vs. No)	0.940	(0.885, 0.998)	0.043
Lung Metastasis (Yes vs. No)	0.859	(0.881, 0.909)	<0.001
Liver Metastasis (Yes vs. No)	1.066	(1.006, 1.129)	0.029

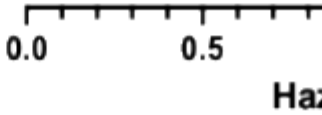

Table 1: Comparison of survival between BM and OSM population

	Overall Survival (months)	BM Survival (months)	OSM Survival (months)	*p*	PS (BM>OS 95% CI
Breast Cancer	19.95 (9.75-36.28)	19.39 (10.13-34.82)	20.40 (9.52-37.93)	**0.200**	0.483 (0.45 0.507)
Thyroid Cancer	16.51 (7.52-26.24)	17.79 (10.77-27.4)	12.32 (4.8-23.02)	**0.055**	0.595 (0.49 0.690)
Uterine Sarcoma	27.78 (13.24-60.90)	16.59 (9.52-28.16)	35.28 (15.84-75.00)	0.002*	0.314 (0.21 0.412)
Colorectal Cancer	15.31 (7.62-27.09)	16.45 (8.63-29.52)	14.73 (7.30-26.02)	0.010*	0.542 (0.51 0.573)
Soft Tissue Sarcoma	17.12 (7.96-32.75)	15.41 (7.85-24.36)	18.17 (8.08-38.54)	**0.054**	0.430 (0.36 0.499)
Prostate Cancer	14.98 (6.29-28.18)	15.36 (6.70-28.81)	13.13 (5.25-24.34)	0.047*	0.545 (0.50 0.592)
Small Bowel Cancer	12.45 (7.05-18.66)	14.79 (7.36-19.60)	11.79 (7.05-18.66)	0.632	
Endometrial Cancer	11.93 (5.45-20.49)	14.39 (9.21-23.00)	11.79 (4.86-18.79)	0.012*	0.589 (0.58 0.595)

Renal Cell Cancer	13.34 (5.65-27.12)	13.34 (5.54-28.62)	13.09 (5.81-24.59)	1.000	
Ovarian Cancer	12.85 (7.18-18.56)	12.32 (7.63-20.45)	13.08 (6.45-18.02)	0.582	
Esophagogastric Cancer	12.75 (6.40-20.76)	12.22 (5.92-19.67)	13.05 (6.54-20.90)	0.437	
Anal Cancer	11.96 (6.80-19.77)	12.17 (6.80-20.50)	11.96 (6.93-19.60)	0.941	
Salivary Gland Cancer	13.40 (7.99-24.94)	11.53 (6.47-23.59)	18.77 (10.45-30.96)	0.030*	0.361 (0.24 0.479)
Gastrointestinal Neuroendocrine Tumor	12.65 (7.25-22.41)	11.30 (7.21-22.03)	12.85 (7.26-22.11)	0.964	
Non-Small Cell Lung Cancer	11.30 (4.90-22.02)	11.05 (4.34-22.14)	11.40 (4.95-21.56)	0.325	
Melanoma	14.04 (6.21-38.36)	10.81 (4.30-20.63)	30.00 (11.00-60.46)	<0.001*	0.268 (0.21 0.321)
Hepatobiliary Cancer	11.56 (5.71-21.57)	10.09 (4.57-19.70)	12.06 (6.21-22.80)	**0.099**	0.454 (0.39 0.509)
Bladder Cancer	9.96 (4.06-15.96)	9.76 (3.94-15.70)	10.14 (4.17-16.09)	0.815	
Head and Neck Cancer	8.05 (3.31-14.84)	9.07 (3.70-15.69)	7.00 (3.03-13.13)	**0.128**	0.553 (0.48 0.619)
Pancreatic Cancer	9.11 (4.14-17.40)	8.94 (3.93-17.47)	9.30 (4.37-17.39)	0.208	
Cervical Cancer	10.64 (5.08-16.86)	8.68 (2.69-18.12)	10.64 (6.00-16.34)	0.776	
Small Cell Lung Cancer	9.55 (4.77-14.53)	8.42 (4.83-13.52)	11.06 (4.79-15.40)	**0.114**	0.439 (0.36 0.508)
Germ Cell Tumor	8.41 (2.52-18.55)	8.20 (1.80-9.70)	10.91 (3.96-25.53)	**0.116**	0.368 (0.33 0.406)
Skin Cancer	9.78 (5.50-17.78)	7.72 (5.63-21.14)	9.89 (5.55-17.41)	1.000	
Appendiceal Cancer	11.50 (6.93-18.56)	3.84 (3.27-11.88)	12.64 (7.74-18.89)	**0.058**	0.279 (0.23 0.321)

BM=bone Metastasis, OSM=other sites metastasis, PS=probability of superiority, CI=confidence interval. *p**: $p<0.05$, ***p***: $0.05<p\leq0.20$, PS and Cliff's δ were calculated only for cancers with $p\leq0.20$.