Am J Cancer Res 2026;16(7):2838-2847
www.ajcr.us /ISSN:2156-6976/ajcr0173678

Original Article

Temporal trends in the incidence and prognosis of lung metastasis in gallbladder cancer: risk stratification and survival analysis

Yang Yu[1*], Xuan Li[2*], Jia-Jun Hui[2], Dong Li[3]

[1]Hepatobiliary and Pancreatic Surgery, Wuxi Huishan District People's Hospital, Affiliated Huishan Hospital of Xinglin College, Nantong University, Wuxi, Jiangsu, China; [2]Department of Medical Oncology, Wuxi Huishan District People's Hospital, Affiliated Huishan Hospital of Xinglin College, Nantong University, Wuxi, Jiangsu, China; [3]Department of Gastroenterology, Wuxi Huishan District People's Hospital, Affiliated Huishan Hospital of Xinglin College, Nantong University, Wuxi, Jiangsu, China. [*]Equal contributors.

Received April 29, 2026; Accepted June 25, 2026; Epub July 15, 2026; Published July 30, 2026

Abstract: Lung metastases are the second most common visceral metastatic site in gallbladder cancer (GBC); however, population-based evidence regarding this metastatic pattern remains limited. In this study, we sought to define the incidence trend of lung metastasis in GBC, identify risk factors associated with its occurrence, and comprehensively assess survival outcomes in this patient population. Data on GBC patients diagnosed 2010-2022 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. Joinpoint regression was used to evaluate temporal trends. Multivariate logistic regression was performed to identify independent risk factors. Overall survival (OS) was analyzed via Kaplan-Meier, multivariate Cox regression, and propensity score matching (PSM). The incidence of lung metastasis in GBC patients showed a modest but statistically significant increasing trend from 2010 to 2022, with an average annual percent change of 3.6% (95% CI 1.4%-5.8%, P<0.05). Independent risk factors for lung metastasis included advanced N stage (N1 and N2) and synchronous bone, liver, or brain metastases. GBC patients with lung metastasis exhibited poor prognosis, with a median OS of 5.0 months (95% CI 4.0-6.0). The 1-, 2-, and 3-year OS rates were 18.1%, 4.3%, and 1.0%, respectively. Isolated lung metastasis conferred better survival than concurrent other distant metastases (median OS: 7.0 vs. 4.0 months, P<0.001). Chemotherapy significantly improved survival (HR=0.39, 95% CI 0.32-0.49), whereas primary tumor resection showed no benefit after PSM. Survival rates in this population did not change significantly between 2010 and 2022. In conclusion, this comprehensive, population-based analysis provides contemporary insights into the epidemiology and management of this challenging patient population.

Keywords: Gallbladder cancer, lung metastasis, SEER database, propensity score matching, prognosis

Introduction

Gallbladder cancer (GBC) is one of the most aggressive malignancies in the digestive system, typically characterized by rapid disease progression and poor prognosis [1]. Because the gallbladder lies in a relatively concealed anatomical location, the clinical symptoms of GBC patients tend to be insidious. As a result, some patients are diagnosed at an advanced or metastatic stage, with a 5-year survival rate of approximately 3% [2-4]. Lung metastasis is the second most common metastatic site in GBC patients, following only liver metastasis. Given the dismal prognosis of metastases GBC, it represents a clinically significant condition that urgently requires improved management [5, 6]. Previous studies have explored the metastatic patterns and prognostic features of metastatic GBC [5, 7]. For example, some analyses have identified race, advanced T stage, and N stage as independent risk factors for distant metastasis [8]. However, research specifically focusing on GBC patients with lung metastases remain limited, particularly population-based evidence. The lack of large-scale population data has left several gaps in the understanding of GBC with lung metastases, including contem-

porary epidemiological features and temporal trends over the past decade, as well as the key factors associated with lung metastasis. In addition, as treatment strategies for advanced cancers move forward, especially with the introduction of immunotherapy, the prognostic profile of this population remains uncertain.

Given the limitations of small sample sizes and single-institution designs in most existing studies on this specific population, the present study was conducted using a population-based design utilizing data from the Surveillance, Epidemiology, and End Results (SEER) database to address these clinical questions. Specifically, we aimed to: (1) analyze the epidemiological features and temporal trends of GBC with lung metastasis between 2010 and 2022; (2) identify the independent risk factors for lung metastasis; (3) assess the prognosis of these patients, including survival stratified by patient characteristics and treatment strategies; and (4) determine independent prognostic factors associated with overall survival in this population and further explore changes in survival. Through this comprehensive population-based analysis, this study aimed to facilitate clinical decision-making and optimize surveillance strategies for high-risk individuals facing this challenging clinical entity.

Method

Study design and patients' selection

This population-based retrospective cohort study utilized data from the SEER database (SEER Research Data, 17 Registries, November 2024 Submission 2000-2022). Due to the de-identified nature of the data, the study was exempt from institutional review board approval, and informed consent was not required. We identified patients diagnosed with GBC between 2010 and 2022 using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) site code C23.0. The inclusion criteria were: (1) histologically confirmed primary GBC; (2) diagnosis between 2010 and 2022; (3) known metastatic status regarding lung metastases at diagnosis; and (4) GBC as the only primary cancer. Patients were excluded if they: (1) were diagnosed based on autopsy or death certificate only; (2) had a history of other malignancies; or (3) had missing data on metastases to other organs. For survival analysis, patients with a survival time of zero or unknown survival status were excluded.

Data extraction

Demographic characteristics, tumor features, metastasis status, treatment modalities, and survival variables were extracted. These included age at diagnosis (analyzed both as a continuous variable and categorized as ≤50 years, 50-69 years, and ≥70 years), sex (male or female), race (White, Black, or other), marital status (married, unmarried/domestic partner, or widowed/divorced/separated), tumor grade (I, II, III, or IV), AJCC-T stage, AJCC-N stage, metastases to the lung, bone, liver, and brain, as well as the use of surgery, chemotherapy, or radiotherapy.

Survival analysis

The primary survival endpoint was overall survival (OS), defined as the time from the initial diagnosis of GBC to death from any cause. To assess annual trends, patients were grouped by individual year of diagnosis (2010-2022). Survival rates (6-month, 1-year, and 2-year OS) were calculated for each calendar year. To evaluate temporal trends in survival, patients were categorized into three periods: 2010-2015, 2016-2020, and 2021-2022.

Statistical analysis

Categorical variables were presented as counts and percentages and compared using Pearson χ^2 test or Fisher's exact test, as appropriate. Continuous variables were summarized as mean ± standard deviation (SD) and compared with t-test. We used joinpoint regression analysis to describe temporal trends in the incidence of lung metastasis among GBC patients, with up to two joinpoints allowed. The annual percent change and average annual percent change were further calculated. Multivariable logistic regression was performed to identify factors associated with the development of lung metastasis. The Kaplan-Meier method and the log-rank test were used to compare OS. To assess the influence of surgery on GBC patients with lung metastases, propensity score matching (PSM, 1:1 ratio) was used to establish a matched cohort via balancing baseline characteristics between patients with and without surgery. Multivariable Cox regression analysis was carried out to determine independent prognostic factors associated with OS. Results are presented as odds ratios (ORs) and hazard ratios (HRs) with corresponding 95%

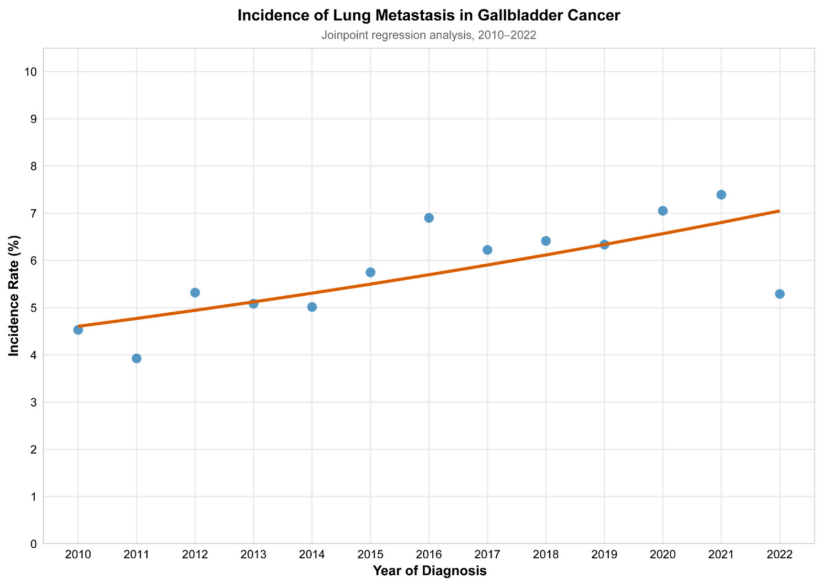


Figure 1. Joinpoint regression analysis of lung metastasis incidence in gallbladder cancer, 2010-2022. Observed annual incidence rates (points) and fitted trends (red line) derived from joinpoint regression.

confidence intervals (CIs). All statistical analyses were performed using R software (version 4.4.3) and MedCalc Statistical Software (version 22.018, Ostend, Belgium). A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Temporal trends in the incidence of lung metastasis in GBC patients

During the study period (2010-2022), the overall incidence of lung metastases in GBC patients increased from 4.5% (26/574) in 2010 to 5.3% (40/756) in 2022. Joinpoint regression analysis detected no statistically significant joinpoints; therefore, a single linear trend was fitted over the entire period. The average annual percent change was 3.6% (95% CI 1.4% to 5.8%, P<0.05), indicating a modest but statistically significant increasing trend in the incidence of lung metastases over time (**Figure 1**).

Baseline characteristics of GBC patients with lung metastases

Baseline characteristics stratified by lung metastasis status are summarized in **Table 1**. Patients with lung metastasis were more likely to have a higher tumor grade (P<0.01), advanced T stage (P<0.01) and N stage (P<0.01). Lung metastasis was strongly associated with the presence of concurrent bone, liver, and brain metastases (all P<0.01). Additionally, patients with lung metastasis were less frequently treated with surgery (19.5% vs. 67.7%, P<0.01) or radiotherapy (8.3% vs. 11.2%, P= 0.04), but more frequently received chemotherapy (54.0% vs. 45.7%, P< 0.01).

Factors associated with lung metastasis

Multivariable logistic regression analysis was conducted to identify independent risk factors for lung metastasis (**Figure 2**). After adjusting for all variables, N stage and the presence of metastases in other organs were independently associated with lung metastasis. Compared with N0, patients with N1 (OR=1.65, 95% CI 1.27-2.14) and N2 (OR=1.79, 95% CI 1.22-2.63) had a significantly higher risk of lung metastasis. The presence of bone metastases (OR=4.29, 95% CI 3.14-5.86), liver metastases (OR=3.94, 95% CI 3.18-4.87), and brain metastases (OR=4.88, 95% CI 2.24-10.6) also conferred a substantially increased risk.

Survival analysis

GBC patients with lung metastasis had a significantly worse prognosis than those without, with a median OS of 5.0 months (95% CI: 4.0-6.0) (**Figure 3A**). The 1-, 2-, and 3-year OS rates were 18.1%, 4.3%, and 1.0%, respectively. Among patients with lung metastasis, those with isolated lung metastasis had significantly better OS than those with lung metastasis and concurrent distant metastases at other sites (median OS: 7.0 months, 95% CI: 6.0-8.0 vs. 4.0 months, 95% CI: 3.0-5.0; P<0.01) (**Figure 3B**). In subgroup analyses, no significant difference in OS was observed according to N stage (P=0.06). Similarly, the presence of concurrent

Table 1. Baseline characteristics of gallbladder cancer patients stratified by lung metastasis status

Characteristic	Total (N=8,844)	Lung Metastases (N=517)	No-Lung Metastases (N=8,327)	*P* value
Age (years)				0.47
Mean ± SD	8,844	68±11.4	68.4±12.3	
Age categories				0.82
≤50 years	736	41	695	
51-69 years	3785	228	3557	
≥70 years	4323	248	4075	
Sex				0.59
Female	6152	354	5798	
Male	2692	163	2529	
Race				0.14
White	6414	367	6047	
Black	1168	74	1094	
Other	1191	69	1122	
Unknown	71	7	64	
Marital status				0.27
Married	4425	254	4171	
Single/Unmarried/Domestic Partner	1465	97	1368	
Divorced/Separated/Widowed	2584	150	2434	
Unknown	370	16	354	
Grade				<0.01
I	890	14	876	
II	2843	74	2769	
III	2271	113	2158	
IV	44	4	40	
Unknown	2796	312	2484	
T stage				<0.01
T0-1	1329	57	1272	
T2	2624	56	2568	
T3	3253	193	3060	
T4	441	32	409	
TX	1197	179	1018	
N stage				<0.01
N0	4995	164	4831	
N1	1863	111	1752	
N2	419	41	378	
NX	1567	201	1366	
Bone metastases				<0.01
No	8597	438	8159	
Yes	247	79	168	
Liver metastases				<0.01
No	6445	163	6282	
Yes	2399	354	2045	
Brain metastases				<0.01
No	8810	502	8308	
Yes	34	15	19	
Surgery				<0.01
No	3103	416	2687	

Yes	5741	101	5640	
Radiation				0.04
No	7870	474	7396	
Yes	974	43	931	
Chemotherapy				<0.01
No	4762	238	4524	
Yes	4082	279	3803	

bone metastasis (P=0.11) or brain metastasis (P=0.94) did not significantly affect survival. However, patients with lung metastasis and concurrent liver metastasis had significantly worse OS compared with those without liver metastasis (P=0.01) (Supplementary Figure 1).

Impact of treatment modalities on survival

In the overall cohort of 445 patients with available survival data, 94 patients (21.1%) underwent primary tumor resection, 38 (8.5%) received local radiotherapy, and 272 (61.1%) received systemic chemotherapy. Survival analysis demonstrated that primary tumor resection was associated with a significantly prolonged median OS in the overall cohort (**Figure 4A**, P<0.01). However, after PSM to balance baseline characteristics, no significant survival benefit was observed for surgery in the matched cohort (**Figure 4B**, P=0.35; Supplementary Table 1). Similarly, radiotherapy did not significantly affect OS in the overall population (**Figure 4C**, P=0.98). In contrast, systemic chemotherapy was associated with a significant improvement in OS (**Figure 4D**, P<0.01).

Independent prognostic factor for OS

Multivariable Cox regression analysis identified several factors independently associated with OS in GBC patients with lung metastasis (**Table 2**). Compared with married patients, those who were single, unmarried, or had a domestic partner had a significantly higher risk of death (HR=1.29, 95% CI 1.01-1.64; P=0.04). Higher tumor grade was also associated with a worse prognosis; patients with grade III disease had a significantly increased mortality risk compared with those with grade I disease (HR=1.85, 95% CI 1.01-3.40; P=0.04). The presence of liver metastasis independently predicted poorer survival (HR=1.48, 95% CI 1.18-1.85; P< 0.01). In contrast, the use of chemotherapy was strongly associated with improved OS (HR=0.39, 95% CI 0.32-0.49; P<0.01).

Temporal trends in survival of GBC patients with lung metastases

When analyzed by individual year of diagnosis from 2010 to 2022, the 6-month, 1-year, and 2-year overall survival rates fluctuated without significant changes (**Figure 5A**). Patients were categorized into three chronological periods: 2010-2015, 2016-2020, and 2021-2022. Survival analysis revealed no significant differences in OS across the three groups (P=0.81) (**Figure 5B**).

Discussion

Using a population-based cohort design, we comprehensively explored the epidemiology, risk stratification, and clinical management of GBC patients with lung metastasis. The findings showed a significant upward trend in the incidence of lung metastasis over time, with advanced N stage and concurrent metastases in other organs identified as independent risk factors for lung metastasis development. Survival analysis indicated that patients with isolated lung metastasis had superior survival compared to those with concomitant metastases at additional sites, particularly involving the liver. Over the past decade, overall survival has not significantly changed. As for treatment modalities, the use of chemotherapy was significantly associated with better survival, whereas primary tumor resection did not improve prognosis in the matched cohort. Taken together, these findings suggest the importance of routine chest imaging for high-risk patients, highlight the prognostic significance of different metastatic patterns, and reinforce the role of chemotherapy as the cornerstone of systemic therapy.

Several factors could contribute to the observed increase in the incidence of lung metastasis

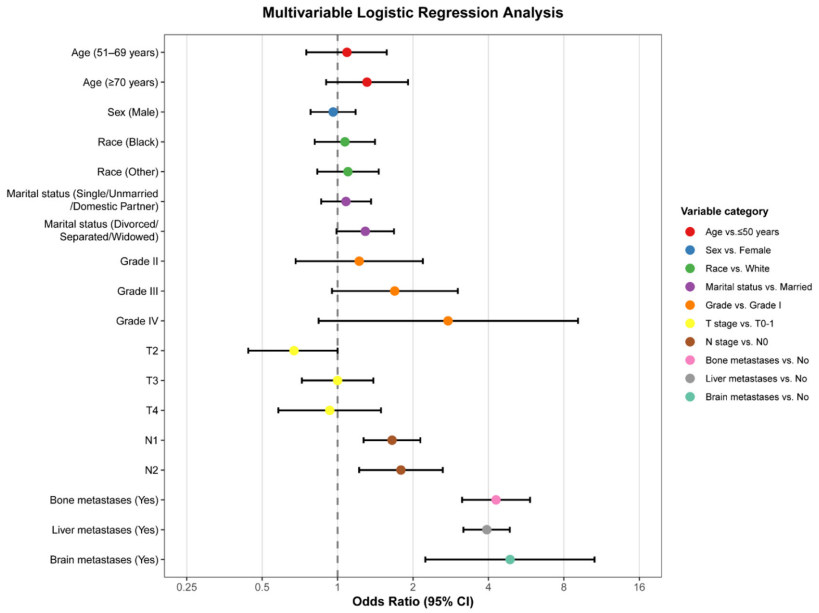


Figure 2. Forest plot of multivariable logistic regression analysis showing risk factors associated with lung metastasis in GBC patients. Odds ratios (ORs) with 95% confidence intervals (CIs) are presented. Variables with 95% confidence intervals that do not cross 1 are considered statistically significant. GBC, gallbladder cancer.

among GBC patients. For example, advances in imaging techniques, including high-resolution computed tomography (CT) and positron emission tomography (PET)-CT, have improved the detection rate of pulmonary lesions [9]. Meanwhile, the introduction of more effective systemic therapies including targeted therapies and immunotherapies, has prolonged the survival of advanced GBC patients. The longer survival may increase the likelihood of clinically detectable lung metastases [5, 10-12]. In addition, increased awareness and more standardized staging evaluations in clinical practice may also contribute to this trend. A similar pattern has also been observed in other digestive system malignancies, where better systemic control has been associated with altered patterns of metastasis [13].

The findings on risk factors for lung metastasis are biologically plausible. Patients who have lymph node involvement or who already have other organ metastases are more likely to develop lung metastases. From a mechanistic perspective, this suggests that tumor cells in these patients already carry the biological features needed for distant spread [14]. These findings also suggest that patients with positive lymph nodes or metastases at other organs warrant close screening or monitoring for lung metastases.

The poor prognosis associated with lung metastasis in GBC is consistent with the generally aggressive nature of this malignancy. The finding that isolated lung metastasis confers better outcomes than lung metastasis with concurrent involvement of other sites underscores the prognostic heterogeneity within the metastatic GBC population. This observation aligns with previous SEER-based analyses demonstrating that patients with isolated lung or distant lymph node metastases have more favorable survival compared to those with bone or multiple organ involvement [5]. Among patients with lung metastasis, the presence of concomitant liver metastasis was associated with a significantly worse prognosis. In contrast, differences by N stage, brain metastasis, or bone metastasis were not statistically significant. This likely reflects the central role of the liver as the primary filtration site for splanchnic venous drainage from the gallbladder, and the high tumor burden associated with hepatic involvement may drive overall disease progression to a greater extent than other metastatic sites. The adverse prognostic impact of liver metastasis underscores the clinical significance of hepatic involvement. This subgroup may represent a particularly high-risk population, warranting more intensive treatment strategies or consideration for clinical trials of novel therapeutic strategies [15].

The findings regarding treatment efficacy also have important clinical implications. The significant survival benefit associated with chemotherapy aligns with established evidence from prior randomized controlled trials [10]. The lack of survival benefit from radiotherapy in this population is unsurprising, as radiotherapy plays a limited role in managing of metastatic

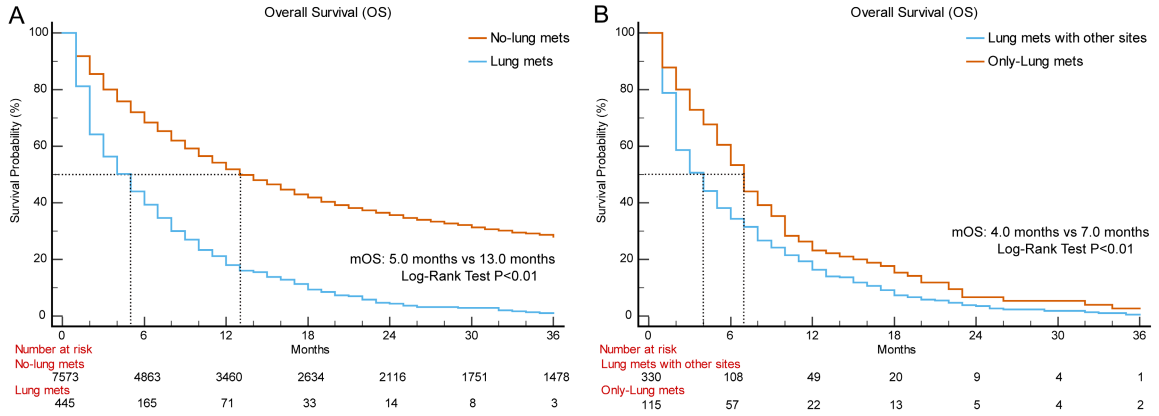


Figure 3. Kaplan-Meier curves comparing overall survival (OS) in GBC patients. A. OS comparison between patients with and without lung metastasis. B. OS comparison between patients with lung-only metastasis and those with lung metastasis involving other distant organs. Dashed lines indicate median OS times, and differences between groups were assessed using the log-rank test. OS, overall survival; GBC, gallbladder cancer.

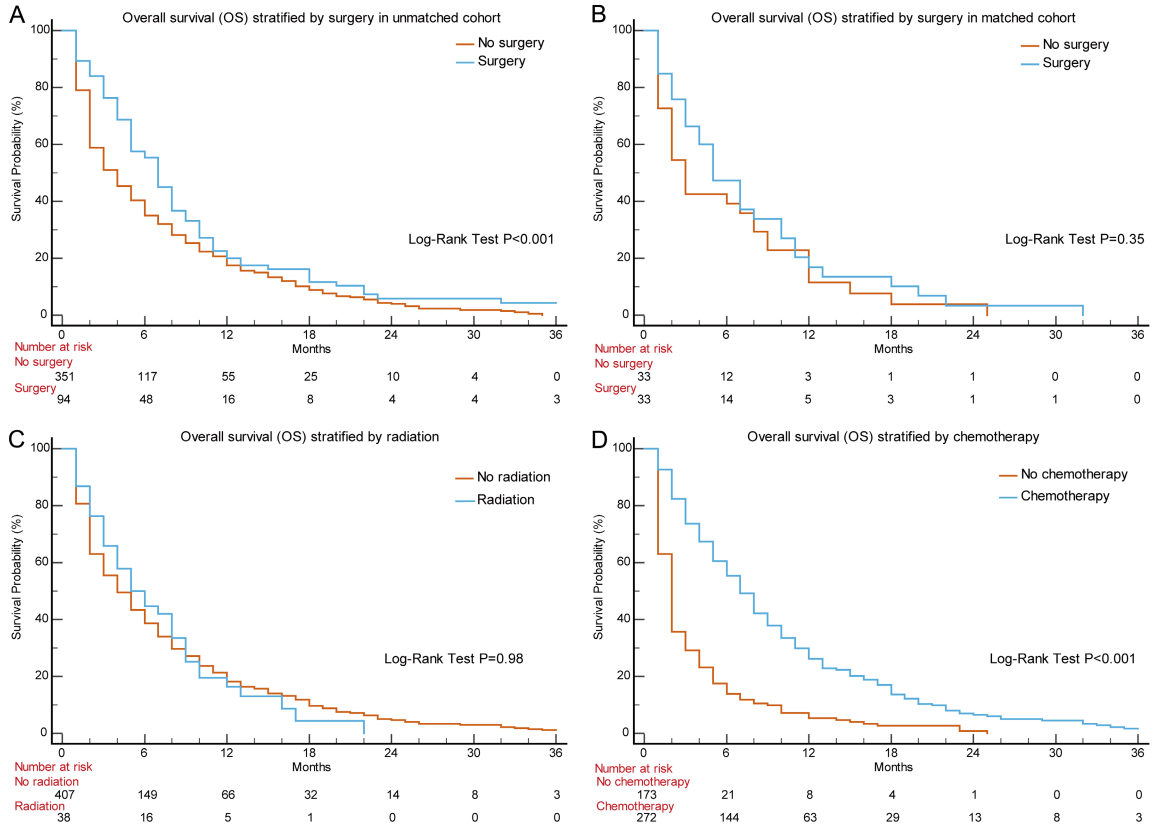


Figure 4. Kaplan-Meier curves comparing overall survival (OS) in GBC patients with lung metastasis according to different treatment modalities. (A, B) OS comparison between patients who underwent primary tumor resection and those who did not, in the unmatched cohort (A) and after PSM (B). (C) OS comparison according to radiotherapy status. (D) OS comparison according to chemotherapy status. Differences between groups were assessed using the log-rank test. OS, overall survival; GBC, gallbladder cancer; PSM, propensity score matching.

GBC, primarily for palliative symptom control [16]. The observation that primary tumor resection appeared to confer a survival benefit in the overall cohort but was no longer significant

Table 2. Multivariate Cox regression analysis of overall survival in gallbladder cancer patients with lung metastases

Characteristic	HR with 95% CI	*P* value
Age categories		
≤50 years	Reference	
51-69 years	1.41 (0.95-2.09)	0.09
≥70 years	1.25 (0.84-1.85)	0.28
Sex		
Female	Reference	
Male	0.97 (0.77-1.21)	0.77
Race		
White	Reference	
Black	1.04 (0.78-1.40)	0.77
Other	0.81 (0.59-1.10)	0.18
Marital status		
Married	Reference	
Single/Unmarried/Domestic Partner	1.29 (1.01-1.64)	0.04
Divorced/Separated/Widowed	1.18 (0.87-1.59)	0.29
Grade		
I	Reference	
II	1.24 (0.66-2.33)	0.50
III	1.85 (1.01-3.40)	0.04
IV	2.13 (0.67-6.81)	0.20
T stage		
T0-1	Reference	
T2	0.92 (0.56-1.52)	0.75
T3	0.86 (0.61-1.22)	0.39
T4	0.64 (0.39-1.07)	0.09
N stage		
N0	Reference	
N1	0.79 (0.60-1.05)	0.10
N2	0.90 (0.60-1.35)	0.60
Bone metastases		
No	Reference	
Yes	1.28 (0.95-1.72)	0.11
Liver metastases		
No	Reference	
Yes	1.48 (1.18-1.85)	<0.01
Brain metastases		
No	Reference	
Yes	0.81 (0.42-1.56)	0.54
Surgery		
No	Reference	
Yes	0.77 (0.54-1.09)	0.14
Radiation		
No	Reference	
Yes	1.04 (0.69-1.58)	0.84
Chemotherapy		
No	Reference	
Yes	0.39 (0.32-0.49)	<0.01

after PSM or in multivariate analysis warrants careful consideration [17, 18]. This discrepancy suggests that the apparent survival advantage associated with surgery may be attributable to selection bias rather than a true causal treatment effect. For example, patients selected for primary tumor resection in the setting of metastatic disease are more likely to have factors associated with improved survival, such as favorable performance status, lower disease burden, and better overall clinical condition.

The protective effect of chemotherapy reinforces its role as the cornerstone of systemic management for this patient population. Additionally, we observed no significant improvement in survival outcomes for GBC patients with lung metastases between 2010 and 2022. Before 2022, no immunotherapy regimen had been formally approved for advanced GBC. The landmark TOPAZ-1 and KEYNOTE-966 trials have demonstrated significant survival benefits with chemoimmunotherapy, further underscoring the importance of future investigations into immunotherapy in this population [19, 20]. Collectively, these results establish a critical baseline for future evaluations of immunotherapy's impact on this historically poor-prognosis group.

Several limitations of this study should be acknowledged. First, as a retrospective analysis of a population-based database, the SEER registry lacks detailed information on potentially important confounders, including performance status, comorbidities, chemotherapy regimens, and surgical margin status. Second, the absence of information on molecular markers, such as HER2 expression, microsatellite instability, and IDH1/2 mutations, precludes analysis of targeted therapy and immunotherapy, which may have influenced outcomes in more recent years [21, 22]. Due to the

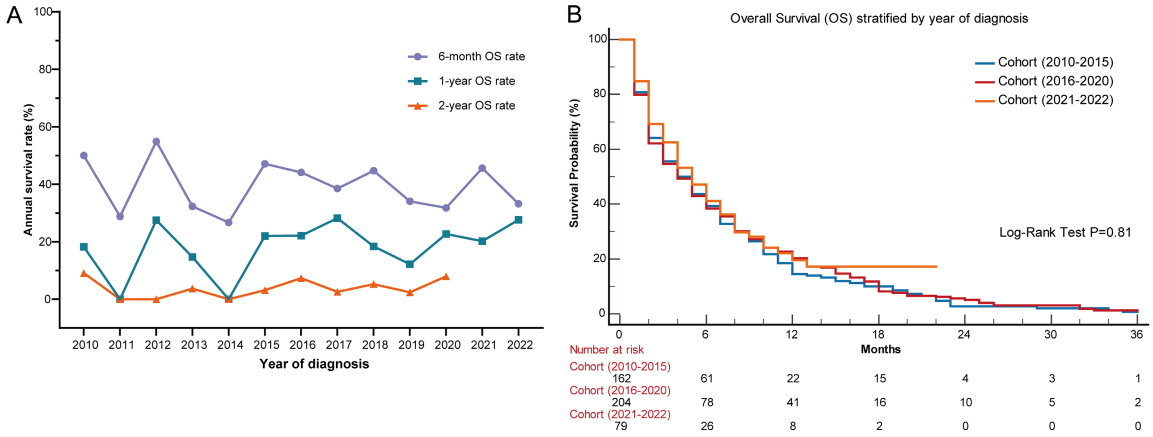


Figure 5. Temporal trends in overall survival (OS) among GBC patients with lung metastasis from 2010 to 2022. A. Annual survival rates at 6 months, 1 year, and 2 years (2010-2020). Due to insufficient follow-up time, the 2-year survival rate was not present for 2021 and 2022. B. OS comparison across three periods: 2010-2015, 2016-2020, and 2021-2022. The log-rank test was used for between-group comparisons. OS, overall survival; GBC, gallbladder cancer.

lack of sufficient information on surgery, local ablation, and radiotherapy for lung metastases in the SEER database, it is not feasible to assess the value of local therapy for this patient population. Third, although our PSM analysis and multivariate analyses reduced selection bias to some extent, unmeasured confounding cannot be entirely excluded. Fourth, the relatively small number of patients in certain subgroup analyses, particularly those receiving radiotherapy or with brain metastases, limited the statistical power for some comparisons.

Conclusions

In this comprehensive, population-based analysis of GBC patients with lung metastases, we provide contemporary evidence on the epidemiology, risk stratification, and treatment considerations for this challenging patient population. These findings may offer valuable insights to support evidence-based clinical decision-making.

Acknowledgements

The authors would like to thank the National Cancer Institute (NCI) for providing access to the Surveillance, Epidemiology, and End Results (SEER) database. The data used in this study were derived from the SEER program, and we are grateful for their efforts in collecting and maintaining this valuable resource. During the preparation of this paper, the authors used DeepSeek (DeepSeek V3.2) to improve the language and readability.

Disclosure of conflict of interest

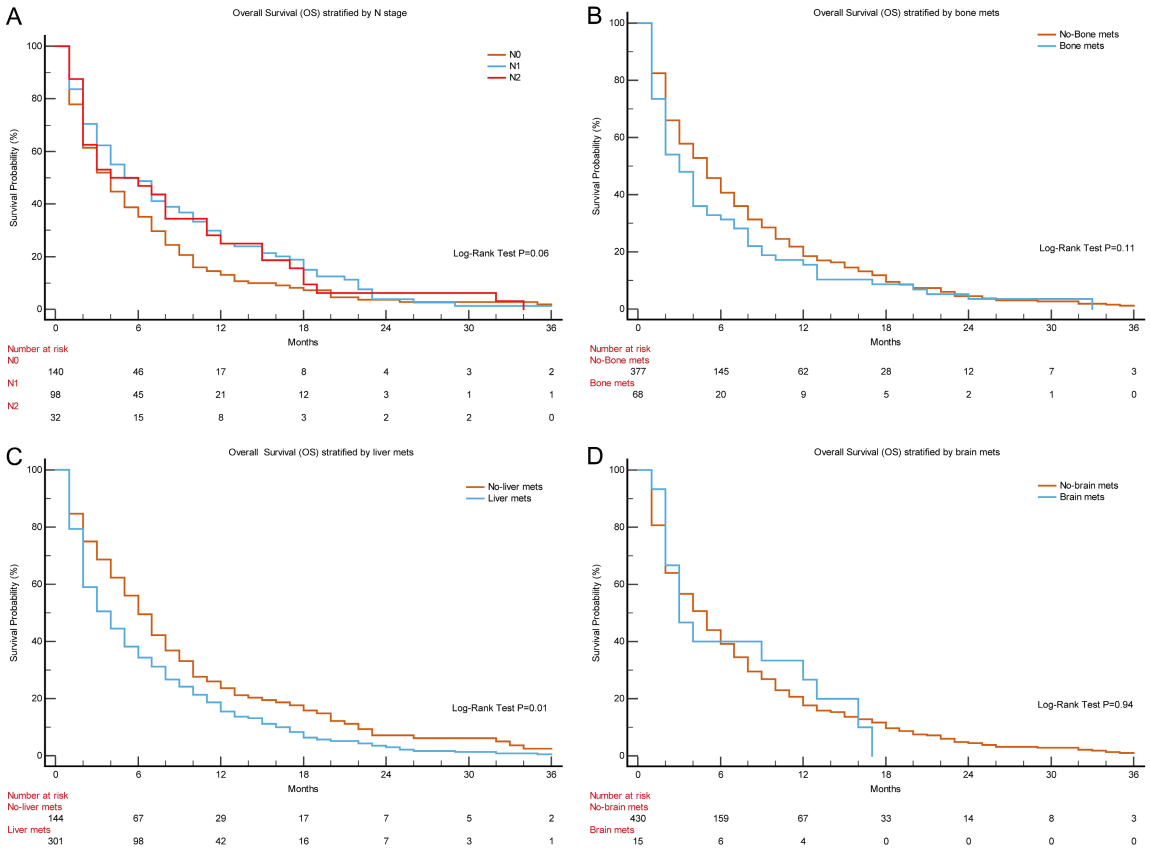
None.

Address correspondence to: Jia-Jun Hui, Department of Medical Oncology, Wuxi Huishan District People's Hospital, Affiliated Huishan Hospital of Xinglin College, Nantong University, No. 2 Zhanqian North Road, Huishan District, Wuxi 214187, Jiangsu, China. E-mail: doctorhuijiajun@163.com; Dong Li, Department of Gastroenterology, Wuxi Huishan District People's Hospital, Affiliated Huishan Hospital of Xinglin College, Nantong University, No. 2 Zhanqian North Road, Huishan District, Wuxi 214187, Jiangsu, China. E-mail: 503954591@qq.com

References

[1] Roa JC, García P, Kapoor VK, Maithel SK, Javle M and Koshiol J. Gallbladder cancer. Nat Rev Dis Primers 2022; 8: 69.
[2] Sturm N, Schuhbaur JS, Hüttner F, Perkhofer L and Ettrich TJ. Gallbladder cancer: current multimodality treatment concepts and future directions. Cancers 2022; 14: 5580.
[3] Hundal R and Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014; 6: 99-109.
[4] Brañes A. Surviving gallbladder cancer: when overall survival is not enough. Ann Surg Oncol 2025; 32: 5378-5379.

[5] Yang Y, Tu Z, Ye C, Cai H, Yang S, Chen X and Tu J. Site-specific metastases of gallbladder adenocarcinoma and their prognostic value for survival: a SEER-based study. BMC Surg 2021; 21: 59.
[6] Xu ZP, Gong JH, Gong JP and Li JH. A nomogram predicting the outcome of gallbladder cancer patients with different target organ metastases. Eur Rev Med Pharmacol Sci 2023; 27: 10016-10030.
[7] Liu R, Wu S, Kuang T, Gao X, Wang J, Ye J, Liu W, Shi Q, Zhao K, Yu J and Wang W. Prediction system for gallbladder cancer distant metastasis a retrospective cohort study based on machine learning. Int J Surg 2025; 111: 7906-7920.
[8] Xiao Z, Nie G, Xiao X, Li B and Jiang H. Predictive and prognostic models and visualizations of distant metastasis in gallbladder cancer. Medicine (Baltimore) 2025; 104: e43369.
[9] Labrunie L, Nahoum L, Carpentieri-Primo P, Mendes G, Amorim VB and Parente DB. Imaging of Gallbladder Cancer. In: Correia MM, Choti MA, Rocha FG. Gallbladder Cancer: A Comprehensive Guide to Management. Cham: Springer Nature Switzerland; 2024. pp. 67-84.
[10] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M and Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362: 1273-1281.
[11] Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DV, Borad MJ, Bridgewater J, Harris WP, Murphy AG, Oh DY, Whisenant J, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Fan B, Wu B, Chamberlain CX, Jiang L, Gliser C, Pandya SS, Valle JW and Zhu AX. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020; 21: 796-807.
[12] Sun Y, Gong J, Li Z, Han L and Sun D. Gallbladder cancer: surgical treatment, immunotherapy, and targeted therapy. Postgrad Med 2024; 136: 278-291.
[13] Riihimäki M, Hemminki A, Sundquist J and Hemminki K. Patterns of metastasis in colon and rectal cancer. Sci Rep 2016; 6: 29765.
[14] Chaffer CL and Weinberg RA. A perspective on cancer cell metastasis. Science 2011; 331: 1559-1564.
[15] Fang C, Li W, Wang Q, Wang R, Dong H, Chen J and Chen Y. Risk factors and prognosis of liver metastasis in gallbladder cancer patients: a SEER-based study. Front Surg 2022; 9: 899896.
[16] Gupta A, Gupta S, Chauhan U, Kumar U, Sharma N, Ahuja R, Rajput D and Gupta M. Symptom palliation in advanced gallbladder cancer: an institutional experience. Indian J Palliat Care 2019; 25: 514-516.
[17] Breitenbach M, Burchard P, Kothari V and Carpizo D. Surgical management of locally advanced and metastatic gallbladder cancer. Cancers (Basel) 2025; 17: 3952.
[18] Gao T, Tang H, Zhou B, Bai D, Jin S, Zhang C and Jiang G. Can patients with gallbladder adenocarcinoma and liver metastases obtain survival benefit from surgery? A population-based study. Updates Surg 2022; 74: 1353-1366.
[19] Oh DY, He AR, Bouattour M, Okusaka T, Qin S, Chen LT, Kitano M, Lee CK, Kim JW, Chen MH, Suksomboon charoen T, Ikeda M, Lee MA, Chen JS, Potemski P, Burris HA 3rd, Ostwal V, Tanasanvimon S, Morizane C, Zaucha RE, McNamara MG, Avallone A, Cundom JE, Breder V, Tan B, Shimizu S, Tougeron D, Evesque L, Petrova M, Zhen DB, Gillmore R, Gupta VG, Dayyani F, Park JO, Buchschacher GL Jr, Rey F, Kim H, Wang J, Morgan C, Rokutanda N, Żotkiewicz M, Vogel A and Valle JW. Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. Lancet Gastroenterol Hepatol 2024; 9: 694-704.
[20] Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, Yau T, Klümpen HJ, Chan SL, Ozaka M, Verslype C, Bouattour M, Park JO, Barajas O, Pelzer U, Valle JW, Yu L, Malhotra U, Siegel AB, Edeline J and Vogel A; KEYNOTE-966 Investigators. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023; 401: 1853-1865.
[21] Javle M, Churi C, Kang HC, Shroff R, Janku F, Surapaneni R, Zuo M, Barrera C, Alshamsi H, Krishnan S, Mishra L, Wolff RA, Kaseb AO, Thomas MB and Siegel AB. HER2/neu-directed therapy for biliary tract cancer. J Hematol Oncol 2015; 8: 58.
[22] Goeppert B, Roessler S, Renner M, Loeffler M, Singer S, Rausch M, Albrecht T, Mehrabi A, Vogel MN, Pathil A, Czink E, Köhler B, Springfeld C, Rupp C, Weiss KH, Schirmacher P, von Knebel Doeberitz M and Kloor M. Low frequency of mismatch repair deficiency in gallbladder cancer. Diagn Pathol 2019; 14: 36.



Supplementary Figure 1. Kaplan-Meier curves comparing overall survival (OS) in GBC patients with lung metastasis according to N stages (A), concurrent bone/liver/brain metastases (B-D).

Supplementary Table 1. Baseline characteristics of gallbladder cancer patients stratified by the use of surgery in matched cohort after PSM

Characteristic	Without surgery (N=33)	With surgery (N=33)	*P* value
Age			0.414
≤50 years	3 (9.1)	3 (9.1)	
51-69 years	21 (63.6)	16 (48.5)	
≥70 years	9 (27.3)	14 (42.4)	
Sex			1.000
Female	22 (66.7)	21 (63.6)	
Male	11 (33.3)	12 (36.4)	
Race			0.685
White	24 (72.7)	27 (81.8)	
Black	5 (15.2)	4 (12.1)	
Other	3 (9.1)	2 (6.1)	
Unknown	1 (3.0)	0 (0.0)	
Marital status			0.438
Married	16 (48.5)	18 (54.5)	
Single/Unmarried/Domestic Partner	8 (24.2)	4 (12.1)	
Divorced/Separated/Widowed	9 (27.3)	11 (33.3)	
Grade			0.068
I	3 (9.1)	0 (0.0)	
II	9 (27.3)	6 (18.2)	
III	12 (36.4)	20 (60.6)	
IV	0 (0.0)	2 (6.1)	
Unknown	9 (27.3)	5 (15.2)	
T stage			0.976
T0-1	3 (9.1)	2 (6.1)	
T2	4 (12.1)	3 (9.1)	
T3	21 (63.7)	22 (66.7)	
T4	1 (3.0)	1 (3.0)	
TX	4 (12.1)	5 (15.2)	
N stage			0.942
N0	13 (39.4)	15 (45.5)	
N1	9 (27.3)	7 (21.2)	
N2	2 (6.1)	2 (6.1)	
NX	9 (27.3)	9 (27.3)	
Bone metastases			1.000
No	30 (90.9)	29 (87.9)	
Yes	3 (9.1)	4 (12.1)	
Liver metastases			0.587
No	8 (24.2)	11 (33.3)	
Yes	25 (75.8)	22 (66.7)	
Brain metastases			1.000
No	32 (97.0)	33 (100)	
Yes	1 (3.0)	0 (0.0)	
Radiation			1.000
No	29 (87.9)	30 (90.9)	
Yes	4 (12.1)	3 (9.1)	
Chemotherapy			0.455
No	16 (48.5)	12 (36.4)	
Yes	17 (51.5)	21 (63.6)	