

A Study on the Patterns of Recurrence of Liver Metastases after Curative Surgery for Gastric Cancer, Based on the SEER Database

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Abstract: Gastric cancer is a prevalent malignancy of the digestive system worldwide. Even after curative surgical intervention, distant metastasis remains the primary cause of treatment failure, with hepatic metastasis being the most common type of hematogenous spread. The Surveillance, Epidemiology, and End Results (SEER) database, a large-scale population-based cancer registry in North America, provides extensive data on gastric cancer, including demographics, clinical pathology, treatment modalities, and long-term follow-up. This data is invaluable for understanding the real-world patterns of hepatic metastasis, risk factors, prognostic features, and the development of predictive models. This paper systematically reviews research based on the SEER database related to gastric cancer hepatic metastasis, summarizing findings regarding epidemiological characteristics, clinical risk factors, prognostic factors, benefits of surgical treatment, various predictive models, and features in specific patient subgroups. The aim is to provide evidence-based guidance for clinical risk stratification, follow-up strategies, and personalized treatment decisions following gastric cancer surgery.

Keywords: Gastric cancer; SEER database; Hepatic metastasis; Risk factors; Prognosis; Scatter plot; Machine learning

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1. Introduction

Gastric cancer is highly invasive, and the majority of gastric cancer cases in China are at an advanced stage. Despite curative surgery, a considerable number still develop distant metastasis, which markedly shortens long-term survival. Metastasis from gastric cancer shows organ preference, mainly involving the peritoneum,

liver, lung, and bone. The liver is the most common site of hematogenous dissemination, and hepatic involvement can be synchronous or postoperative. Synchronous liver metastasis is found at initial diagnosis, whereas postoperative liver metastasis appears during follow-up after surgery. The two forms differ in mechanism, clinical presentation, and outcome.

In the conventional AJCC TNM system, all distant metastases are grouped as stage IV, without distinguishing the organ involved, such as the liver. As a result, prognosis within the gastric cancer liver metastasis population is not well reflected, and individualized assessment remains difficult. Because single-center samples are often small, domestic institutions have found it hard to collect enough cases for large retrospective studies of gastric cancer with liver metastasis. The SEER database covers several regions of the United States and records demographic data, tumor site, differentiation, T and N stage, treatment, and survival. It has therefore been widely used to study the epidemiology, risk factors, and predictive models of gastric cancer liver metastasis. In recent years, researchers in China and abroad have published many SEER-based studies using cohort analysis, propensity score matching (PSM), competing risk models, scatter plots, and machine learning. However, there is currently a lack of a comprehensive review article summarizing these types of studies.

This article reviews and summarizes the literature on gastric cancer metastasis to the liver, as found in the SEER database. It examines the epidemiological characteristics, risk factors, prognosis, surgical treatment outcomes, predictive models, and specific patient subgroups within the included studies. The aim is to provide a reference for clinical practice and future domestic research in this area.

2. Basic epidemiological characteristics of liver metastasis in gastric cancer

Utilizing the extensive SEER registration data, it is possible to determine the prevalence and characteristics of liver metastasis in gastric cancer at the population level. Studies by Horn et al.^[1] on the epidemiology of liver metastasis in various cancers have shown that the risk of liver metastasis varies significantly depending on the type of malignancy, with gastric cancer being a high-risk type. Qiu et al.^[2] used the SEER database to analyze the distribution of distant organ metastases in gastric cancer, finding that liver metastasis is the most common type, often manifesting as a solitary liver metastasis, but frequently occurring alongside metastasis to the peritoneum, bone, or lungs. In most cases, patients with liver metastasis do not exhibit a single, isolated lesion.

Based on the timing of metastasis, gastric cancer liver metastasis is classified as synchronous liver metastasis and metachronous liver metastasis. Synchronous liver metastasis refers to the presence of liver metastasis at the initial diagnosis; metachronous liver metastasis refers to the development of liver metastasis during follow-up after curative surgery. Due to the lack of detailed records of post-operative recurrence time in some cases, some studies combine all cases of liver metastasis in gastric cancer for analysis. Other studies focus on synchronous liver metastasis. Zhang et al.^[3] studied incidence trends of synchronous liver metastasis in gastric cancer and found that its proportion remained relatively stable over the past decade, without a clear downward trend. Overall, patients with synchronous liver metastasis have a markedly worse prognosis than those without liver metastasis.

Patient distribution also differs by age. Zhang et al.^[4] used PSM with SEER to analyze metastasis patterns in young gastric cancer patients and found a higher liver metastasis risk than in older patients. Young patients with liver metastasis also more often had multi-organ involvement, indicating a heavier disease

burden. Wang et al. ^[5] compared early- and late-stage gastric cancer and found that early-stage disease had a higher rate of liver metastasis and more frequent multi-organ metastasis. This suggests that age influences the preferred metastatic organs in gastric cancer. Wu et al. ^[6] likewise confirmed that early-stage gastric cancer is more likely to spread to the liver, while advanced disease mainly involves the peritoneum. Differences in pathological subtype distribution by age are important: young patients have more diffuse and signet-ring cell carcinoma, which is biologically aggressive and prone to hematogenous spread to the liver.

Pathological subtype also matters. Gastric neuroendocrine tumors can metastasize to the liver, not only the peritoneum. Huang et al. ^[7] constructed survival curves for gastric neuroendocrine tumors with liver metastasis using SEER and confirmed that these tumors can spread to the liver. Survival was significantly worse in patients with liver metastasis than in those without. Huang et al. ^[8] developed a personalized prediction tool for metastatic gastric neuroendocrine tumors, noting that peritoneal metastasis is most common while liver metastasis is relatively rare. Prognosis among neuroendocrine tumor patients with liver metastasis is highly heterogeneous, so individualized risk assessment is needed rather than a uniform judgment.

3. Clinical and pathological risk factors for gastric cancer metastasis to the liver

Identifying independent risk factors for liver metastasis is important for screening high-risk individuals and guiding close postoperative follow-up. Several multivariate regression analyses based on SEER have been performed.

An W et al. ^[9] conducted a SEER collaborative external validation study and confirmed that age, tumor stage, and tumor differentiation are independent risk factors for liver metastasis. Later stage, greater lymph node involvement, and poorer differentiation were associated with a significantly higher risk. Lymph node involvement was a notable predisposing factor: patients with positive nodes had a much higher risk than those with negative nodes, highlighting the link between lymphatic and hematogenous spread in gastric cancer.

At the TNM level, liver metastasis risk rises with tumor invasion depth. Song et al. ^[10] developed a machine learning model to identify liver metastasis in gastric cancer, and their study showed that patients with T2-T4 stage gastric cancer have a significantly higher risk of liver metastasis compared to those with T1 stage gastric cancer. However, even in T1-stage gastric cancer, there is a small probability of liver metastasis, and early-stage blood metastasis cannot be completely ruled out. Tumor invasion depth and lymph node status are among the most important predictors of liver metastasis. Li et al. ^[11] developed a decision tree model specifically for predicting liver metastasis in gastric cancer, which also confirmed that TN and N staging are independent and key predictors of liver metastasis. Lymph node metastasis had the highest weight, and the number of positive nodes was positively correlated with liver metastasis probability.

Tumor location can also affect risk. Wang et al. ^[12] used SEER and domestic single-center registries to study tumor subtypes associated with liver metastasis and found that gastroesophageal junction cancer has a higher risk than distal gastric cancer. Distal tumors are more prone to peritoneal metastasis, whereas proximal tumors more often spread to the liver through the bloodstream. Tumor origin may therefore serve as a reference for assessing liver metastasis risk and for planning clinical staging and examinations. Ming et al. ^[13] compared tubular and diffuse gastric cancer and found that tubular cancer has a higher liver metastasis risk than diffuse cancer, while diffuse cancer more often involves the peritoneum. Histological type is thus an

important pathological factor influencing liver metastasis risk.

4. Prognostic features in patients with gastric cancer and liver metastasis

SEER contains two core survival endpoints: overall survival (OS) and cancer-specific survival (CSS), which are essential for prognosis prediction in gastric cancer liver metastasis. Overall, the prognosis for patients with gastric cancer liver metastasis is poor, but there is significant heterogeneity in survival within the population. Factors such as the presence of other organ metastases, demographics, clinical pathology, and treatment options can all influence survival outcomes.

Lin Z et al.^[14] conducted a comparative study on the prognosis of liver, lung, bone, and brain metastasis in gastric cancer, using the SEER database. Their findings showed that isolated liver metastasis had a better prognosis than liver metastasis combined with multiple distant metastases, but a worse prognosis than isolated peritoneal metastasis. They also found that once liver metastasis was combined with metastasis to other organs such as bone, lung, and brain, the patient's survival time was significantly reduced, and the number of metastatic organs was an important prognostic indicator. Zhao QW et al.^[15] specifically investigated the heterogeneity of single-organ metastasis in gastric cancer. Their research confirmed that isolated liver metastasis had a significantly better prognosis than liver metastasis combined with multiple distant metastases. Both studies highlighted that IV-stage gastric cancer requires further stratification, rather than being treated as a homogeneous group. Meng et al.^[16] developed decision curve diagrams to predict the prognosis of liver metastasis in gastric cancer, using OS and CSS as outcome measures. Age, tumor grade, N stage, and whether the patient underwent surgery were identified as independent prognostic factors. Older age, higher tumor grade, and a greater number of lymph node metastases were associated with poorer prognosis, while patients who received tumor-related treatment had better survival outcomes compared to those receiving conservative care. Dong et al.^[17] developed two independent decision curve diagrams to predict OS and CSS in patients with liver metastasis from gastric cancer. Their study confirmed that T stage, N stage, age, tumor differentiation, and treatment method jointly determined the prognosis of liver metastasis from gastric cancer. Traditional TNM staging systems had limited predictive value for this subgroup, while the decision curve models provided individualized survival probability estimates and demonstrated superior risk stratification compared to traditional staging systems.

Wu et al.^[18] analyzed the causes of death in patients with liver metastasis from gastric cancer using the SEER database. Their research found that the primary cause of death for patients with liver metastasis from gastric cancer was the gastric cancer itself, with a low proportion of deaths due to non-tumor causes. They also found that advanced stages of the disease (high age and late T/N stages) significantly increased the risk of overall and tumor-specific mortality, highlighting the importance of controlling tumor progression for improving the prognosis of this group. Liu et al.^[19] conducted a retrospective study on the prognosis of organ-specific metastasis in late-stage gastric cancer, which also confirmed that the prognosis for patients with liver metastasis was significantly worse than that of those without distant metastasis. Furthermore, the risk of death increased when liver metastasis occurred in combination with metastasis to other organs, and the type of organ affected by metastasis was an independent prognostic factor, separate from T/N staging.

5. The impact of surgical treatment on the survival of patients with gastric cancer metastasis to the liver

The benefit of surgery for gastric cancer with liver metastases, specifically involving resection of the primary tumor and liver lesions, has always been a subject of debate. However, using a large SEER (Cancer Registries) cohort and propensity score matching, it is possible to assess the benefits of surgical treatment in real-world settings.

Studies using multiple SEER sources confirmed significant heterogeneity in the surgical treatment of gastric cancer with liver metastases. Wu et al.^[20] found that patients with surgically resectable primary tumors had improved survival, whereas those with extensive or large tumor burdens did not benefit and sometimes had increased perioperative risk. Ren et al.^[21] also used SEER propensity score matching to examine the value of palliative gastrectomy in liver metastasis. Only a small subgroup with low tumor burden and single-organ liver metastasis appeared to benefit. For patients with multiple organ metastases, surgery did not significantly improve survival. Clinicians should therefore carefully consider whether palliative gastrectomy is appropriate.

Su et al.^[22] developed a specialized decision-making model to predict survival after primary tumor resection in gastric cancer liver metastasis and to quantify potential surgical benefit. The model incorporates demographic, pathological, and staging variables and can distinguish patients likely to benefit from surgery from those unlikely to benefit, providing a quantitative tool to reduce experience-based bias. Ji et al.^[23] analyzed the impact of surgery on the prognosis of gastric cancer liver metastasis and emphasized that benefit depends heavily on baseline characteristics. Surgery should not be decided solely by the presence of liver metastasis, but by comprehensive assessment of individual clinical and pathological features.

Wang et al.^[24] developed a machine learning dynamic prediction model based on SEER to assess the prognosis of liver metastasis in gastric cancer and support treatment decisions. The model indicated that tumor burden and lymph node involvement are key prognostic factors. It can output expected survival rates under different treatment plans, helping clinicians weigh surgery and systemic therapy for personalized decisions. Li et al.^[25] investigated the prognostic value of distant metastasis sites and surgical intervention in metastatic gastric cancer using SEER. They confirmed that surgical benefit in liver metastasis gastric cancer is significantly biased: patients with single-organ metastasis and generally good condition are more likely to benefit, while systemic treatment is recommended for widespread multi-organ metastasis.

6. A prediction model for the risk and prognosis of liver metastasis in gastric cancer, based on the SEER database

Traditional TNM staging is often inadequate for assessing individualized risk and prognosis in gastric cancer patients with liver metastasis. In recent years, many studies have used SEER to develop nomograms, web-based calculators, and machine learning models. These fall into two groups: models predicting liver metastasis risk and models predicting survival after liver metastasis diagnosis.

6.1. Predictive model for risk of liver metastasis

Song et al.^[10] developed a machine learning model to identify liver metastasis risk in gastric cancer. It included demographics, T/N staging, tumor differentiation, and tumor location. Internal validation showed good discriminatory power, allowing quantification of liver metastasis probability for individual patients. The

model can help identify high-risk individuals and guide imaging surveillance and early detection. Li et al.^[11] constructed a decision tree to predict liver metastasis risk. T staging, N staging, and tumor differentiation were the most important input variables. A web-based tool was developed for clinical use to help identify high-risk individuals.

6.2. Predictive model for survival prognosis in patients with liver metastatic gastric cancer

Meng N et al.^[16] developed a prognostic nomogram based on SEER to predict liver metastasis in gastric cancer, incorporating age, sex, TNM stage, tumor grade, and treatment. The nomogram can predict 13-year survival probability and is used for risk stratification, physician-patient communication, and treatment selection. Dong Z et al.^[17] developed two independent nomograms for OS and CSS. They were internally validated and confirmed the limitations of traditional TNM staging in stratifying liver metastasis patients. Su R et al.^[22] developed a nomogram specifically for patients with liver metastasis after primary tumor resection. It incorporates survival prediction and assessment of surgical benefit, facilitating treatment decisions and showing high clinical utility. Wang Z et al.^[24] developed a machine learning-based dynamic prediction model. In addition to survival prediction, it can compare expected outcomes of different treatment strategies, expanding the use of prediction models in treatment decision-making.

7. Distinct features of gastric cancer metastasis to the liver in specific subgroups

7.1. Early-stage gastric cancer with liver metastasis

Early-onset gastric cancer is generally defined as occurring at age 50 or younger. Zhang et al.^[4] used SEER data and showed that early-onset patients had a higher risk of liver metastasis and multiple organ involvement than older patients. Wang et al.^[5] conducted a large-scale, multi-population retrospective study that also confirmed a higher incidence of liver metastasis in early-onset gastric cancer. Furthermore, early-onset gastric cancer patients with liver metastasis had a poorer prognosis compared to those with late-onset disease. This highlights the importance of regular screening and follow-up for liver metastasis in young gastric cancer patients. Wu et al.^[6] also found similar results, indicating that the distribution of pathological subtypes differs in early-onset gastric cancer, with a higher proportion of disseminated and infiltrative subtypes, which are more prone to hematogenous spread to the liver.

7.2. Metastatic liver cancer originating from gastric carcinoid tumors

Previous clinical observations suggested that gastric neuroendocrine tumors (NETs) primarily metastasize to the peritoneum. However, SEER data analysis confirmed that gastric NETs also carry a risk of liver metastasis. Huang et al.^[7] developed a survival prognostic index for gastric NETs with liver metastasis, demonstrating significantly poorer survival outcomes for patients with gastric NETs and liver metastasis compared to those without. Huang et al.^[8] established a personalized prediction tool for metastatic gastric NETs, highlighting significant differences in prognosis among different metastatic sites. Even in patients with liver metastasis, there was considerable heterogeneity in survival outcomes, necessitating individualized treatment decisions. Ji et al.^[26] analyzed the impact of surgical resection combined with chemotherapy on survival in different metastatic sites for gastric NETs. They found that only a small subset of patients with gastric NETs and liver metastasis benefited from the combined approach, with most patients opting for

systemic therapy.

7.3. Primary tumor site – Gastric cancer, metastasis to the liver

Wang et al. ^[12] found in a nationwide, single-center study that gastric cancer with metastasis to the liver at the pylorus and gastroesophageal junction has a higher risk compared to gastric cancer at the distal end of the stomach. Tumors at the distal end tend to metastasize via the peritoneum, while those at the proximal end are more likely to spread through the bloodstream. This anatomical characteristic is significant for pre-operative and post-operative imaging selection. Proximal gastric cancers require more attention to liver imaging screening and vigilance regarding metastasis. In a study by Ming et al. ^[13], patients with diffuse gastric cancer are more likely to experience metastasis to the peritoneum, while those with diffuse tumors are more prone to metastasis via the bloodstream. The histological type and tumor location jointly determine the preferred site of metastasis in gastric cancer.

8. Limitations of research on SEER databases

The SEER database is a cancer registry for the US population, providing a valuable large-sample resource for research on gastric cancer metastasis to the liver. However, the database itself has several inherent limitations, and conclusions drawn from research based on SEER data on gastric cancer metastasis to the liver should be interpreted with careful consideration of its potential biases.

Firstly, differences in population and ethnicity. The SEER data primarily reflects the epidemiology of gastric cancer in North America. There are significant differences in the causes of gastric cancer, the subtypes of tumors, screening strategies, clinical treatment patterns, and follow-up systems in North America compared to the Chinese population. Therefore, regression and machine learning models trained on SEER data cannot be directly applied to Chinese patients and must undergo multicenter external validation before implementation.

Second, key clinical and pathological information is lacking. SEER does not include biomarkers such as HER2 and MSI, so the impact of molecular subtypes on the development and prognosis of gastric cancer liver metastasis cannot be analyzed. It also lacks important pathological indicators such as vascular and nerve involvement, as well as tumor recurrence data. Specific drug regimens and durations for chemotherapy, targeted therapy, and immunotherapy are not fully documented, making it difficult to assess how different systemic treatments affect prognosis. This can bias risk factor identification.

Third, recurrence timing information is incomplete. Some studies cannot distinguish synchronous liver metastasis from postoperative delayed liver metastasis, and recurrence times are not recorded. Many studies pooled all liver metastases from gastric cancer, making it difficult to separate initial liver metastasis from postoperative recurrence. In addition, the database lacks a standardized coding system for retroperitoneal metastasis, leading to registration errors in some cases involving both liver and retroperitoneal metastasis and interfering with statistical results for multi-organ metastasis.

Fourth, the database is retrospective so that it can reveal associations but not causality. Although SEER studies use methods such as propensity score matching and multivariate regression to adjust for confounders, selection bias cannot be completely eliminated. For example, patients who undergo surgery may have better overall health and lower tumor burden, which cannot be fully ruled out and introduces baseline differences. Therefore, conclusions about surgical benefits from SEER data are real-world observational findings and

cannot replace randomized controlled trials.

Fifth, the study lacks key clinical information such as performance status scores and comorbidities, which are important for treatment and survival. Moreover, some confounding variables could not be included.

9. Conclusion

A large retrospective study of SEER data showed that liver metastasis is the most common form of distant metastasis in gastric cancer, with substantial population heterogeneity. Age, TNM staging, tumor differentiation, tumor size, primary tumor location, and histological subtype were important independent risk factors for gastric cancer liver metastasis.

Patients with gastric cancer that has metastasized to the liver generally have a poor prognosis. However, there is significant variation in survival rates depending on the specific circumstances. Patients with liver metastasis alone have a better prognosis than those with liver metastasis combined with multiple organ involvement. Age, lymph node status, tumor differentiation, presence of other metastases, and treatment approach all contribute to survival. Surgical intervention for liver metastasis in gastric cancer is highly dependent on patient selection and is only recommended for patients with low tumor burden and single-organ liver metastasis. Blind palliative surgery is not recommended for patients with widespread multi-organ metastasis. Currently, several decision diagrams and machine learning models based on SEER have been developed to predict liver metastasis risk and assess survival prognosis. These tools address the limitations of traditional TNM staging in stratifying liver metastasis patients.

It is also important to acknowledge the inherent limitations of SEER, including racial disparities, missing key pathology and treatment information, and potential biases in retrospective observations. All predictive models based on SEER data require validation in multiple geographically diverse centers in China. Future work should integrate multicenter Chinese cohorts and molecular data to improve model transferability and clinical utility.

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