

# Chinese consensus on the diagnosis and treatment of gastric cancer with liver metastases

Kecheng Zhang and Lin Chen

## Abstract

**Background:** The incidence of gastric cancer with liver metastases (GCLM) is 9.9–18.7%, with a median survival time of 11 months and a 5-year survival rate <20%. Multidisciplinary treatment (MDT) is gradually gaining recognition as the most important method. However, specific treatment plans remain unclear. The aim of study was to provide a consensus to improve the diagnosis and treatment of GCLM.

**Methods:** We brought together experts from relevant medical fields across China, including the Chinese Research Hospital Association Digestive Tumor Committee, Chinese Association of Upper Gastrointestinal Surgeons, Chinese Gastric Cancer Association, and the Gastrointestinal Surgical Group of Chinese Surgical Society Affiliated to Chinese Medical Association, to discuss and formulate this consensus.

**Results:** A consensus was reached on the diagnosis and treatment of GCLM. Moreover, we have developed a new clinical classification system, the Chinese Type for Gastric Cancer Liver Metastases, based on the likelihood of a surgical treatment being successful.

**Conclusions:** The MDT mode should be implemented throughout all treatment of GCLM.

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**Keywords:** Chinese consensus, gastric cancer, liver metastases

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## Introduction

Gastric cancer (GC) is highly heterogeneous and has a high degree of malignancy. Hematogenous dissemination is one of the main ways in which gastric tumor cells spread; the liver is the organ most frequently involved.<sup>1</sup> The incidence of GC with liver metastases (GCLM) is 9.9–18.7%.<sup>2,3</sup> The incidence of synchronous GCLM is 73.3%, and that of metachronous GCLM is 26.7%.<sup>4</sup> The median liver metastases-free interval for patients with metachronous GCLM is 14 months, with a median survival time of 11 months and a 5-year survival rate <20%.<sup>5</sup> Excision of primary tumors and liver metastases can increase the 5-year survival rate to 23.8%.<sup>6</sup>

Modern technologies and new approaches to treatment provide more options for GCLM patients. Multidisciplinary treatment (MDT), where experts from different medical fields are involved in patient care, is gradually gaining recognition as the most important method. However, specific treatment plans remain unclear. In an effort to develop guidelines aiming to improve the diagnosis and treatment of GCLM, we brought together experts from relevant medical fields across China to discuss and formulate this consensus. Recommendation of ‘high’, ‘medium’ and ‘low’ indicated a favorable voting rate of at least 90%, 75–90%, and less than 75%, respectively.

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Association



### Pathological characteristics and diagnosis

The pathological types of gastric primary tumors and liver metastases are usually the same. Most gastric primary tumors and liver metastases tend to be adenocarcinomas. According to the Lauren classification, adenocarcinomas can be classified as diffuse, intestinal, or mixed types.<sup>7</sup> Additional rare types include adenosquamous carcinoma, medullary carcinoma, hepatoid adenocarcinoma, squamous cell carcinoma, and undifferentiated carcinoma. In addition to the pathological characteristics of the gastric primary tumor, the number and size of liver metastases also affect the prognosis.<sup>8</sup> Synchronous liver metastases were defined as cases in which detection occurs before or during surgery, or within 6 months after primary tumor resection. Liver metastases occurring more than 6 months after primary tumor resection were classified as metachronous.<sup>9</sup>

### Imaging examinations

Magnetic resonance imaging (MRI) and contrast-enhanced ultrasonography (CEUS) are necessary for the diagnosis of liver metastases in GC. The use of liver-specific contrast agent increases the likelihood of detection of even small liver metastases.<sup>10–14</sup> MRI can show the exact size, number, and position of the lesions, as well as the adjacent structures; however, intraoperative ultrasound is indispensable for detection of metastases that cannot be seen preoperatively.<sup>15</sup> In addition, positron emission tomography (PET) can show the patient's general condition, and, if present, the extrahepatic metastases, both of which are of great significance in the evaluation of cancer severity preoperatively and postoperatively.<sup>16</sup> In addition, early metabolic changes on 18F-fluorodeoxyglucose (FDG) PET have been shown as a possible predictive marker for therapeutic response in advanced GC.<sup>17</sup> Specifically, early changes in the FDG-uptake rate in liver metastases might be a useful prognostic factor.

*Recommendations:* PET should be performed wherever possible to confirm extrahepatic metastases and to increase the accuracy of clinical staging.

*Recommendation level:* high

### Laparoscopic exploration

A laparoscopic exploration with extensive intraoperative peritoneal lavage can be used to rule out peritoneal carcinomatosis.<sup>18,19</sup>

*Recommendations:* This examination should be performed for all GCLM patients scheduled for surgeries.

*Recommendation level:* high

### Pathological examination

In addition to pathomorphological examination, certain immunohistochemistry and molecular tests are required, such as those for HER2,<sup>20</sup> PD1/PD-L1,<sup>21</sup> and MSI/MMR.<sup>22</sup> Percutaneous biopsy with pathological examination is the gold standard for confirming liver metastases. As percutaneous biopsy is an invasive test, it can be recommended only to GCLM patients with rare pathological types or lesions that cannot be confirmed by imaging examinations.

### Serologic examination

High preoperative levels of serum tumor markers, such as CEA, CA19-9, CA72-4, CA125, or AFP, have been reported as significant risk factors for cancer recurrence rate in GCLM patients.<sup>8,23–29</sup> Low blood lymphocyte-to-monocyte ratio in GC patients after radical-intent surgery is associated with high recurrence rate, especially in livers.<sup>30</sup> The levels of serum tumor markers increased 2–3 months ahead of the imaging findings in some patients.<sup>31</sup>

### Clinical typing

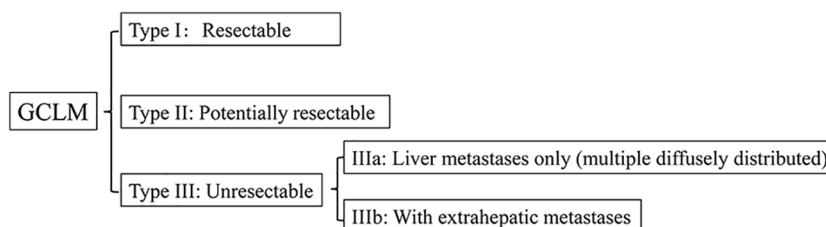
Excision of both gastric tumors and liver metastases can increase the 5-year survival rate of GCLM patients to >20%,<sup>6,8,32–34</sup> especially in selected narrow group of patients who meet strictly defined criteria.<sup>9,35–38</sup> However, the existing classification systems, such as the synchronous/metachronous system and the Japanese classification of gastric carcinoma, have limited value in clinical guidance. Therefore, based on existing studies,<sup>3,4,6,8,10,32–36,39–69</sup> and following recommendations from experts, we have developed a new clinical classification system, the Chinese Type for Gastric Cancer Liver Metastases (C-GCLM), based on the likelihood of a surgical treatment being successful (Figure 1 and Table 1).

### Multidisciplinary treatment mode

The MDT mode should be implemented all through the treatment of GCLM.<sup>14,70</sup> The diagnosis, clinical typing, therapeutic schedule, and follow-up plan should be discussed and decided by the MDT expert team.<sup>71</sup>

**Table 1.** Summary of the C-GCLM, a proposed classification system based on the likelihood of a surgical treatment being successful.

Type I	Gastric tumors: depth of invasion $\leq$ T4a; lymph node metastases within D2 lymph node dissection (not including Bulky N2) Bulky N2: at least one node of $\geq$ 3 cm in diameter, or at least three consecutive nodes each of diameter $\geq$ 1.5 cm, along the coeliac, splenic, common, or proper hepatic arteries
	Liver metastases: 1–3; maximal diameter $\leq$ 4 cm or limited to one liver lobe without involving important vessels or bile ducts Assessment of resectability: Technological resectability of liver metastases judged by a hepatobiliary surgeon; Meets the resection standard of hepatic reservational function assessment.
Type II	Gastric tumors: depth of invasion = T4b or Bulky N2 or Bulky No. 16a2, b1.
	Liver metastases: out of the range of Type I, with potential technological resectability
Type III	Gastric tumors: Primary lesion directly and considerably invades adjacent tissues or organs; Regional lymph nodes such as mesenteric lymph nodes or paraaortic lymph nodes fixed, fused, or not resectable, as confirmed by imaging examinations or biopsy.
	Metastases: IIIa: multiple diffusely distributed metastatic lesions in both lobes without extrahepatic metastases; IIIb: extrahepatic metastases (one or more organs) with or without peritoneal carcinomatosis.
C-GCLM, Chinese type for gastric cancer liver metastases.	

**Figure 1.** Chinese type for GCLM.  
GCLM, gastric cancer with liver metastases.

- (1) Synchronous resections of both primary and metastatic lesions are recommended to patients with the possibility of R0 resection.
- (2) If either primary or metastatic lesions are unresectable, the MDT team should develop a comprehensive treatment plan for the patient, with periodic appraisal and evaluation.
- (3) Comprehensive treatment plans based on chemotherapy are recommended to patients with unresectable lesions, both primary and metastatic.
- (4) Best supportive treatment will be applied to patients with poor performance status.
- (5) Palliative surgeries to relieve serious symptoms, such as bleeding or obstruction, should be considered when necessary.
- (6) The MDT team should discuss specific treatment plans for patients with extrahepatic metastases.

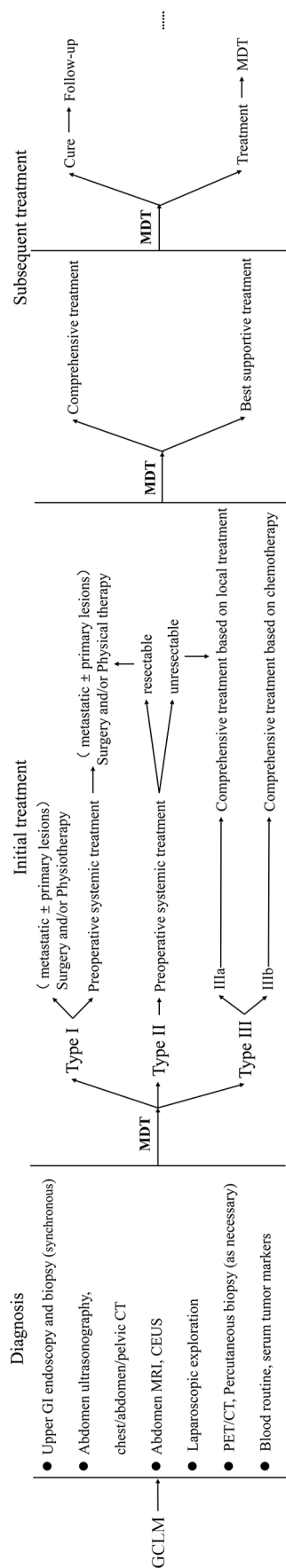
The flow chart of diagnosis and treatment by the MDT team is shown in Figure 2.

### Comprehensive treatment

The comprehensive treatment for GCLM includes systemic treatments (chemotherapy, targeted treatment, and immunotherapy), surgeries, and radiotherapy.

#### Type I

According to the MDT assessment, Type I patients can choose surgical treatments or preoperative



**Figure 2.** Flow chart of diagnosis and treatment. CEUS, contrast-enhanced ultrasonography; CT, computed tomography; GI, gastrointestinal; GCLM, gastric cancer with liver metastases; MDT, multidisciplinary treatment; MRI, magnetic resonance imaging; PET, positron emission tomography.

systemic treatments. Targeted treatment combined with chemotherapy is applied to HER2-positive patients.<sup>72</sup> Standards of surgical treatments are gastrectomy with D2 lymph node dissection for primary gastric tumor and R0 resection for liver metastases. Excision extension of liver is classified as partial hepatectomy, segmentectomy, and hemihepatectomy. Types of surgeries include open surgery, laparoscopic surgery, and robotic surgery. Radiofrequency ablation (RFA) has been considered a less invasive therapeutic choice for liver metastases. It can be used alone,<sup>42,73,74</sup> or combined with surgical resection.<sup>41,53</sup> Postoperative chemotherapy is necessary, and should include at least 4–8 cycles. Response evaluation should be performed every 2–3 months.

*Recommendations:* Preoperative systemic treatments should be applied to Type I patients.

*Recommendation level:* high

### Type II

Preoperative systemic treatments should be administered to patients who are in good performance status to ensure that surgery can take place as soon as possible. Additionally, local treatments for liver metastases such as transcatheter arterial chemoembolization (TACE)<sup>5,42,75–77</sup> and hepatic artery infusion chemotherapy (HAIC)<sup>78–80</sup> are recommended, as they can deliver high-concentration drugs to metastatic lesions as well as reduce the overall toxicity. TACE and HAIC can be used preoperatively or postoperatively. Conformal radiotherapy combined with chemotherapy can also be applied to preoperative therapy.<sup>18</sup> Stereotactic radiation therapy or intensity modulated radiation therapy can handle the lesions at difficult locations, such as hepatic hila, and are especially suitable for single lesion with a diameter <5 cm. For patients in poor performance status who cannot undergo surgery, RFA is an appropriate alternative and can be used repeatedly.<sup>81–83</sup> In addition, microwave ablation,<sup>84</sup> percutaneous cryoablation,<sup>85</sup> proton beam therapy,<sup>86</sup> and radioembolization with 90Y microspheres,<sup>87</sup> have shown promising preliminary results in the treatments of GCLM. All these therapies were recommended for tumors <3 cm in diameter and ≤5 in number in each treatment.

*Recommendations:* Surgical treatments should be performed only when R0 resection is intended.

*Recommendation level:* high

**Table 2.** Follow up.

Items	Interval time (months)
History, physical examination, nutritional status assessment, blood routine, blood biochemistry, serum tumor markers, and abdomen ultrasonography	1, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60; thereafter once a year
Chest/abdomen/pelvic CT	6, 12, 18, 24, 36, 48, 60; thereafter as necessary
Abdomen MRI, PET-CT, upper GI endoscopy	Important clinical decision; when necessary

CT, computed tomography; GI, gastrointestinal; MRI, magnetic resonance imaging; PET, positron emission tomography.

### Type III

Chemotherapy is the preferred recommendation for Type III patients in good performance status. In Type III, immunotherapy plays an important role.<sup>88</sup> Immunotherapies include immune checkpoint inhibitors (PD-1/PD-L1 inhibitors),<sup>89,90</sup> chimeric antigen receptor T cells, and heat shock protein gp96. TACE and HAIC can also be used with patients who do not achieve disease control with first-line and second-line chemotherapy; in some cases, radiotherapy might be a more suitable approach. Palliative surgeries should only be considered to relieve major symptoms such as bleeding, perforation, or obstruction.

*Recommendations:* Cytoreductive surgeries are not encouraged. Patients can participate in clinical trials on immunotherapy under the guidance of the MDT group.

*Recommendation level:* high

### Follow up

The items and interval time were summarized in Table 2.

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### Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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