

Original Article

Prognosis of gastric cancer with liver metastases after simultaneous primary tumor and liver resections

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Abstract: Objective: To investigate the prognostic factors of gastric cancer with liver metastases after simultaneous primary tumor and liver resections. Methods: The clinical data of 21 gastric cancer cases with liver metastases that were treated with simultaneous primary tumor and liver resections during the period of February 1999 to December 2010 were retrospectively analyzed. Results: The in-hospital mortality was 0%, the 1-year cumulative survival rate for gastric cancer patients with liver metastases that were treated with simultaneous primary tumor and liver resections was 71.4%, the 3-year cumulative survival rate was 22.2%, and the 5-year survival rate was 14.8%. Univariate analysis showed that an intravascular tumor embolus ($P = 0.002$), N stage ($P = 0.010$), and D2 resection ($P = 0.014$) were prognostic factors of gastric cancer with liver metastases after simultaneous primary tumor and liver resections. Multivariate analysis showed that N stage ($P = 0.001$), the distribution of metastatic lesions ($P = 0.032$), and D2 resection ($P = 0.037$) were independent prognostic factors. Conclusion: Simultaneous primary tumor and liver resections for the treatment of gastric cancer with liver metastases was safe, and selective surgical treatment can improve the prognosis.

Keywords: Gastric cancer, liver metastases, simultaneity liver resection, prognosis

Introduction

Gastric cancer was the one of the most common gastrointestinal cancers, and its incidence rate is ranked fourth worldwide. Distant metastasis was the most important cause of death in gastric cancer, and approximately 4-14% of patients were found to have liver metastases upon diagnosis [1]. Although liver metastases indicate an advanced cancer state, with the progress of surgical techniques and improvement in comprehensive treatment efficacy, surgical resection of liver metastases of certain primary tumors such as colorectal cancer [2], and neuroendocrine cancer [3] can yield encouraging treatment results. In particular, the 5-year survival rate of colorectal cancer with liver metastases after surgical treatment can be up to 35-61% [2, 4]. Unlike colorectal cancer, due to differences in the biological behavior of tumors, gastric cancer with liver metastases has a low surgical resection rate, poor adjuvant chemotherapy efficacy, and poor

overall surgical treatment effects. The 5-year survival rates vary greatly in the range of 0-60%, with an average of approximately 13.4% [1].

Only limited numbers of studies have reported the efficacy of simultaneous primary tumor and liver resection for gastric cancer with liver metastases, and the efficacy of this treatment remains controversial. Ambiru S et al. [5] reported that the 5-year survival rate of gastric cancer with metachronous liver metastases after liver resection was 29%, while that of gastric cancer with synchronous liver metastases after liver resection was 6%, and the difference was statistically significant. These authors suggested that hepatectomy for synchronous liver metastases are a relative contraindication. However, most of the later reports did not reach the same conclusion. A meta-analysis of 19 retrospective studies on the surgical treatment of gastric cancer with liver metastasis showed that 18 studies suggest that simultaneous resection is not a negative factor affecting the

Table 1. Clinicopathological factors

| Factor | No. | Percentage (%) |
|-------------------------------------|-----|----------------|
| Gender | | |
| Male | 15 | 71.4 |
| Female | 6 | 28.6 |
| Age | | |
| ≥60 years | 9 | 42.6 |
| <60 years | 12 | 57.4 |
| Differentiation degree | | |
| Moderate | 9 | 42.6 |
| Moderate to poor | 6 | 28.7 |
| Poor | 6 | 28.7 |
| Intravascular tumor embolus | | |
| Yes | 12 | 57.4 |
| No | 9 | 42.6 |
| Site of primary tumor | | |
| Proximal | 9 | 42.6 |
| Distal | 12 | 57.4 |
| T staging | | |
| T2 | 2 | 9.5 |
| T3 | 16 | 76.2 |
| T4 | 3 | 14.3 |
| N staging | | |
| N0-1 | 7 | 33.3 |
| N2-3 | 14 | 66.7 |
| Number of metastatic foci | | |
| Single | 14 | 66.7 |
| Multiple | 7 | 33.3 |
| Distribution of metastatic foci | | |
| Single lobe | 19 | 90.5 |
| Multiple lobes | 2 | 9.5 |
| Size of metastatic foci | | |
| ≥3 cm | 12 | 54.7 |
| <3 cm | 9 | 45.3 |
| Degree of radical gastric resection | | |
| D2 | 15 | 71.4 |
| D1 | 6 | 28.6 |
| Preoperative adjuvant therapy | | |
| Yes | 4 | 19.0 |
| No | 17 | 81.0 |

prognosis [1]. It was also found that 17 of the 29 cases with a long-term survival more than 5 years had synchronous liver metastases, and 7 of 9 patients with a survival longer than 10 years had synchronous liver metastases [1]. The purpose of this study was to investigate the prognostic factors of gastric cancer with liver

metastases after simultaneous primary tumor and liver resections.

Patients and methods

A total of 781 cases of gastric cancer with liver metastases were treated at our hospital during the period of February 1999 to December 2010, of which 21 patients (21/781, 2.7%) underwent resection of the primary tumors and simultaneous resection of the liver metastases. These patients included 15 males and 6 females with a median age of 56 years (range, 40-77 years). The conditions of the primary tumors were as follows: The maximum tumor diameter was 4-10 cm, 12 cases had tumors in the distal end, and 9 cases had the tumors in the proximal end. The conditions of the liver metastases were as follows: 19 cases (left lobe in 14 cases and right lobe in 5 cases) had the metastases in a single liver lobe, and 2 cases had the metastases distributed in multiple lobes. The number of metastatic tumors was as follows: 14 cases had one metastatic tumor, and 7 cases had multiple metastatic tumors (up to 4 tumors distributed in a single lobe). The size of the metastatic tumors was 0.4-8 cm: 12 cases had a tumor size ≥3 cm, and 9 cases had a tumor size <3 cm. All of the patients had normal pre-operative liver function.

The indicators for surgical resection of liver metastases from gastric cancer were as follows: there was no evidence of distant metastasis and peritoneal metastasis, and the primary tumor and liver metastases could be completely resected. Surgical approaches were as follows: 12 cases received distal subtotal gastrectomy, 6 cases that received proximal subtotal gastrectomy, and 3 cases received total gastrectomy. Four cases received heplobectomy, and 17 cases received irregular hepatectomy (including one case that had simultaneously undergone anhydrous ethanol injection into multiple lesions). All of the cases were pathologically confirmed. A total of 15 cases of primary tumors completed D2 radical resection, and the surgical margins of the primary tumor and liver metastases were all negative. There were nine cases of moderately differentiated adenocarcinoma, six cases of moderately to poorly differentiated adenocarcinoma, and six cases of poorly differentiated adenocarcinoma. There were 12 cases with intravascular

Gastric cancer with liver metastases

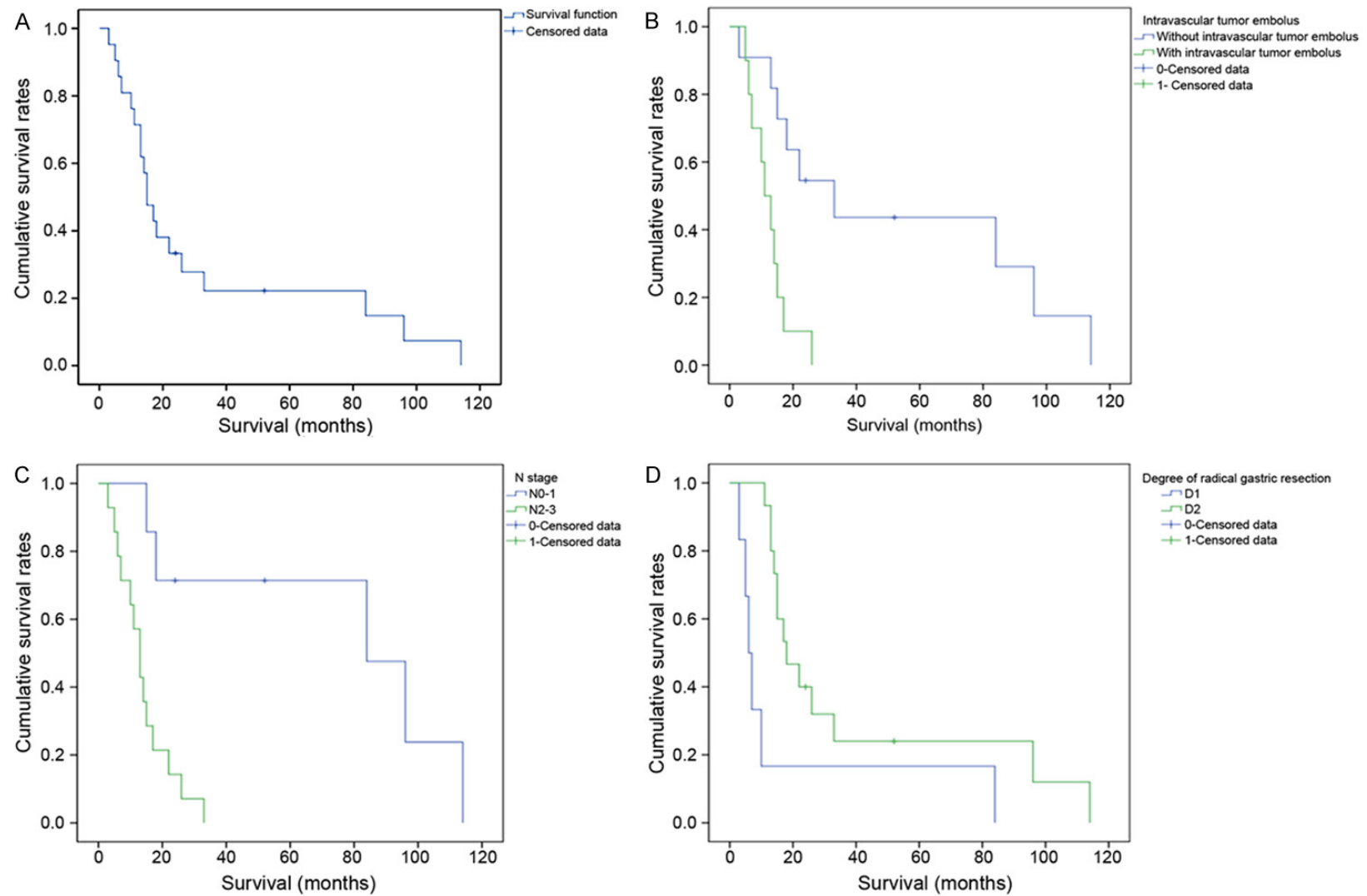


Figure 1. Cumulative Kaplan-Meier survival curves. A. Gastric cancer with liver metastasis after simultaneous primary tumor and liver resections; B. Intravascular tumor embolus ($P = 0.002$); C. N stage ($P = 0.010$); D. D2 surgery ($P = 0.014$).

Table 2. Distribution of first-relapse sites in 19 cases of death

| Sites of first relapse | No. (%) |
|--|-----------|
| Intrahepatic | 10 (52.6) |
| Extrahepatic | 9 (47.4) |
| Peritoneal seeding | 3 (15.8) |
| Celiac retroperitoneal lymph node metastasis | 2 (10.5) |
| Lung metastases | 2 (10.5) |
| Bone metastases | 1 (5.3) |
| Recurrence in the gastric remnant | 1 (5.3) |

tumor emboli. Pathological staging was conducted based on the 2010 seventh edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis staging system. There were 7 cases of NO-N1 stage and 14 cases of N2-N3 stage. There were 2 cases of T2 stage, 16 cases of T3 stage, and 3 cases of T4 stage (**Table 1**). All of the patients underwent adjuvant chemotherapy treatment after surgery. There were three cases that received preoperative embolization chemotherapy, and one case that received preoperative chemotherapy of oxaliplatin or cisplatin + leucovorin + 5-fluorouracil regimen with 2-3 cycles. The study was conducted with the approval of the institutional ethics board of our institute.

Statistical analysis

SPSS 17.0 statistical software was used for statistical analysis, and the Kaplan-Meier method was used to plot survival curves and calculate survival, followed by univariate analysis of prognostic factors. The stepwise regression method was used to introduce potential factors affecting prognosis in the Cox proportional hazards model to perform multivariate analysis of prognostic factors. A *P* value less than 0.05 was considered to be statistically significant.

Results

Overall survival

This group of patients was followed up by telephone, outpatient re-examination and letters. The median follow-up time was 15 months (range, 3 to 114 months). The follow-up endpoint was death, and the follow-up rate was 100%. One case developed the postoperative

complication (1/21, 4.8%) of adhesive intestinal obstruction, which was improved after conservative treatment. The in-hospital mortality and 30-day postoperative mortality were 0. The 1-year cumulative survival rate was 71.4%, the 3-year cumulative survival rate was 22.2%, and the 5-year survival rate was 14.8%. Cumulative survival curves are shown in **Figure 1**. During follow-up, 2 cases achieved recurrence-free survival, and 19 cases died. Analysis of the first relapse sites in patients who died showed that 1 case (1/19, 5.3%) died 8 years later due to cancer of the gastric remnant, and the remaining 18 cases (18/19, 94.7%) died of postoperative intrahepatic recurrence and extrahepatic metastasis (**Table 2**). None received a second surgical resection after relapse.

Prognostic factors

The Kaplan-Meier method was used to conduct univariate analysis of the relationship between prognosis and various clinicopathological factors of gastric cancer patients with liver metastases who received simultaneous primary tumor and liver resections. The results showed that an intravascular tumor embolus (*P* = 0.002), N stage (*P* = 0.01) and D2 resection (*P* = 0.014) were prognostic factors of overall survival (**Figure 1**). Multivariate analysis using the Cox proportional hazards model showed that N stage (*P* = 0.001), the distribution of metastatic lesions (*P* = 0.032), and D2 resection (*P* = 0.037) were independent prognostic factors (**Table 3**).

Discussion

The present study of 781 gastric cancer patients with liver metastases who were treated at our hospital over 10 years, 21 of those cases had synchronous liver metastases and received simultaneous resection, with a resectable rate of 2.7%. The 1-year cumulative survival rate was 71.4%, the 3-year cumulative survival rate was 22.2%, and the 5-year survival rate was 14.8%. The overall efficacy was similar to that reported in the literature. In addition, from the perspective of surgical safety, the meta-analysis [1] reported an in-hospital mortality of 3.5% (12/340), and 30-day mortality of 0.9% (3/340). The present study showed that there were no in-hospital mortalities and no deaths within 30 days. Except one case with

Gastric cancer with liver metastases

Table 3. Multivariate analysis of overall survival in gastric cancer with liver metastases

| Factors | Characteristics | | Hazard ratio | 95% CI | P-value |
|---------------------------------|-----------------|-------------|--------------|-----------------|---------|
| | Unfavorable | Favorable | | | |
| N staging | N2-3 | N0-1 | 127.841 | 7.1837-2085.325 | 0.001 |
| Intravascular tumor embolus | Yes | No | 1.297 | 0.259-6.482 | 0.752 |
| T staging | T4 | T2-3 | 0.177 | 0.017-1.851 | 0.148 |
| Number of metastatic foci | Multiple | Single | 1.866 | 0.354-9.833 | 0.462 |
| Distribution of metastatic foci | Multiple lobes | Single lobe | 8.960 | 1.202-66.786 | 0.032 |
| D2 surgery | No | Yes | 0.131 | 0.020-0.882 | 0.037 |

CI, confidence interval.

Table 4. Analyses of independent prognostic factors for gastric cancer with liver metastases

| Author | Country | Year | Number of cases | 5-Year survival | Independent prognostic factors |
|-----------------|-----------|------|-----------------|-----------------|--|
| Fujii [6] | Japan | 2001 | 10 | 10% | Liver metastasis size, timing of surgery |
| Ambiru [5] | Japan | 2001 | 40 | 18% | Timing of surgery, resection margin of liver metastasis >10 mm |
| Zacherl [7] | Australia | 2002 | 15 | None | Single-lobe distribution |
| Okano [9] | Japan | 2002 | 19 | 34% | Timing of surgery, solitary metastasis |
| Saiura [15] | Japan | 2002 | 10 | 20% | Lymph node metastasis, intravascular tumor embolus |
| Shirabe [10] | Japan | 2003 | 36 | 26% | Solitary metastasis, intravascular tumor embolus |
| Roh [11] | Germany | 2005 | 11 | 27% | Solitary metastasis |
| Kaga [12] | Japan | 2007 | 42 | 42% | Solitary metastasis, T stage |
| Sakamoto [8] | Japan | 2007 | 37 | 11% | Single-lobe distribution, size of gastric tumor >4 cm |
| Thelen [16] | Germany | 2008 | 24 | 15% | Liver metastases resection margin |
| Morise [14] | Japan | 2008 | 18 | 27% | T stage, intravascular tumor embolus |
| Tsujimoto [13] | Japan | 2010 | 15 | 31% | Size of gastric tumor >6 cm, D2 surgery |
| Kerkar [1] | Japan | 2010 | 436* | 26.5% | None |
| Schildberg [19] | Germany | 2012 | 31 | 13% | None |

*Meta-analysis.

postoperative adhesive intestinal obstruction, which was improved after conservative treatment, there were no serious complications.

There is no consensus concerning the prognostic factors for the surgical treatment of gastric cancer liver metastasis (**Table 4**). In the present study, N stage, the distribution of metastatic foci, and D2 resection were found as independent prognostic factors. Comprehensive analysis of the literature identified many prognostic factors, such as metastatic factors (including the size of metastases [6], distribution of metastatic foci [7, 8], number of metastatic foci [9-12], and metachronous liver metastases [5, 6, 9]), primary tumor factors (including the size of the primary tumor [6, 8, 13], T stage [12, 14], lymph node metastasis [15], and intravascular tumor embolus [10, 14, 15]) and surgical factors such as D2 lymphad-

enectomy [13], as well as the margins of the metastatic lesions [5, 16]. These factors are independent prognostic factors. However, almost all of the studies have the limitations of a small sample size, long time span, and high selectivity of cases. Therefore, these factors still need to be further confirmed by uniformed, large-sample, multi-center clinical studies.

Adjuvant chemotherapy is an important method for the comprehensive treatment of advanced cancers. Gastric cancer with liver metastases is often associated with extensive extrahepatic metastases and invasion of surrounding organs and the surgical resection rate is low, with only 0.3-2.4% of patients suitable for hepatectomy [17]. Most patients undergo comprehensive treatment with a focus on chemotherapy, but the effective rate of conventional therapy is only approximately 50%, and the

5-year survival rate of chemotherapy alone is less than 2% [1, 18]. Other studies [19, 20] have suggested that chemotherapy followed by surgery could improve the prognosis of advanced gastric cancer with metastasis. In the present study, only four patients underwent preoperative chemotherapy and/or interventional treatment to achieve remission before surgery. However, univariate analysis showed that there was no statistically significant difference in survival between patients with preoperative adjuvant chemotherapy and those without preoperative treatment. It was reported that the overall recurrence rate was 76%, and the intrahepatic recurrence rate was 56% [1]. Yoshihiro et al. [21] reported that, among 37 gastric cancer patients with liver metastases who received surgical resection, 62% of them had intrahepatic recurrence within 2 years. Tiberio et al. reported that postoperative adjuvant therapies, including systemic chemotherapy or intervention therapy, only increased the local control rate, rather than prolonged survival [18]. In the present study, the first relapse site was intrahepatic metastasis in 52.6% (10/19) of patients. This high recurrence rate may indicate that there might be occult metastasis in the liver that cannot be identified by imaging at the time of surgery.

In conclusion, we believe that it is safe to perform simultaneous resections of the primary tumor and liver metastases in patients with resectable gastric cancer and liver metastases. With the extensive application of laparoscopy, screening patients with no peritoneal metastasis, having earlier lymph node staging and recommending localized metastases for radical surgical treatment can achieve better results. At the same time, actively exploring more effective perioperative chemotherapy regimens, improving the surgical resection rate, and reducing the risk of recurrence and metastasis are effective ways to improve the survival of gastric cancer patients with liver metastases.

Disclosure of conflict of interest

None.

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