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COMMENTARY

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Proposal of new treatment algorithm for gastric cancer liver metastases: Up-front surgery or conversion surgery?

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Abstract: Hepatectomy for gastric cancer liver metastases (GCLM) has a 5-year survival rate of 9-42%; however, indications for hepatectomy remain unclear. Many researchers have reported prognostic factors for GCLM after hepatectomy, but surgical indications vary according to the literature. Furthermore, the indication for optimal candidates for neoadjuvant chemotherapy and intensive chemotherapy is also unclear. To understand the indications for surgery and chemotherapy intended for hepatectomy for GCLM, a new treatment algorithm was created based on previously reported evidence from the viewpoint of hepatic surgeons.

***Keywords*:** gastric cancer liver metastases, treatment algorithm, conversion surgery, up-front surgery

Introduction

The prevalence of gastric cancer has been reported to have declined in recent decades (*1,2*); however, it is still the third leading cause of death in Japan (*2*), has the sixth highest incidence rate of all cancers, and is the third leading cause of death worldwide (3). The liver is one of the most frequent sites of distant metastasis from gastric cancer (*4,5*). In the past, gastric cancer liver metastasis (GCLM) has been regarded as a contraindication for surgery because of its poor prognosis (*6*). Conversely, the recent literature has reported a 9-42% 5-year survival rate and 12-41 months median survival time after hepatectomy for GCLM with curative resection (*5,7-15*). Based on these reports, prognostic factors after hepatectomy of GCLM have been reported to include large tumours (*5,8,11,15*), multiple tumours (*8,10,13-15*), depth of the primary gastric cancer (*5,8,9,13,14*), lymph node metastasis of the primary gastric cancer (*10*), age (*15*), non-curative resection (*9,15*), and disease-free interval after resection of the primary gastric cancer (*15*) in multivariate analyses.

Although few reports have evaluated the effect of neoadjuvant chemotherapy (NAC) for the treatment of GCLM, Fukuchi *et al*. and Yamaguchi *et al*. reported the usefulness of NAC for stage IV gastric cancer, including patients with peritoneal metastasis and/or hepatic metastasis (*16,17*). Yoshida *et al*. proposed that multiple GCLM, GCLM greater than 5 cm, and GCLM with vascular invasion can be categorized as marginally resectable metastases and are indications for intensive chemotherapy (*18*). If metastatic diseases are technically resectable, metastasectomy is recommended. They categorized solitary GCLM less than 5 cm without vascular invasion as marginally resectable; however, its condition is neither a poor prognostic risk factor nor marginally resectable unless it infiltrates the hepatic hilum. From the perspective of hepatic surgeons, there is a discrepancy between their indications and previously reported prognostic factors for GCLM. To solve this discrepancy, we created a new treatment algorithm for GCLM based on previously reported prognostic factors.

Previous evidence of gastric cancer liver metastases

There are many reports discussing the significance of hepatic resection for GCLM; however, all of them are retrospective studies and no randomized studies have been conducted in this setting. Although the evidence is limited, reports including more than 50 patients with GCLM who underwent hepatectomy were selected (*5,8-15*). The reported prognostic factors for overall survival among these studies include the depth of the primary tumour (*5,8,9,13,14*) (most studies identified serosal invasion (*i.e*. T4) of the primary tumour (*5,8,14*)), tumour size (*5,8,11,15*) (two of them are more than 5 cm (*5,8*) and the others are 3 cm (*11,15*), multiple tumours (*7-10,13-15*) (two of which are more than three nodules

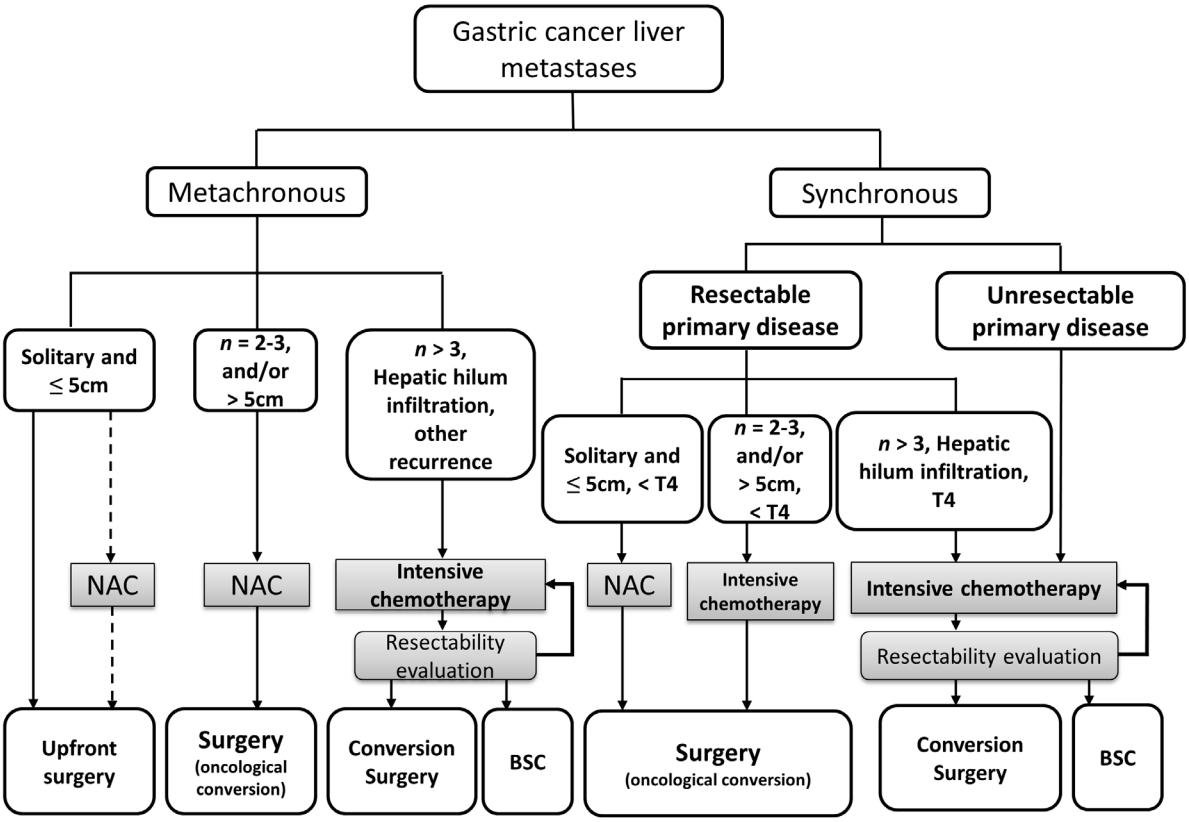

Figure 1. Suggestion of treatment algorithm for GCLM. T4 means serosal invasion of the primary gastric cancer. *Abbreviations*: GCLM, gastric cancer liver metastases; NAC, neoadjuvant chemotherapy; BSC, best supportive care.

(*8,15*)), non-curative resection (*9,15*), lymph node metastasis of the primary tumour (*10*), age (*15*), and disease-free interval (*15*). Prognostic factors for survival reported in two or more studies were included in the treatment algorithm for GCLM.

Proposal of treatment algorithm for gastric cancer liver metastases

Based on the evidence mentioned above, a treatment algorithm for GCLM was created (Figure 1). The best candidate for hepatectomy is a metachronous solitary small GCLM less than 5 cm in diameter that does not have any poor prognostic factors. In these patients, up-front surgery or occasional NAC followed by surgery are suggested. NAC is suggested for patients with one or two poor prognostic risk factors in the metachronous group, that is, two or three tumours and/or solitary large tumours without hepatic hilum invasion. In patients with more than three GCLM and/or GCLM with hepatic hilum infiltration or with other sites of metastasis, chemotherapy is the first treatment choice; if chemotherapy leads to remarkable tumour shrinkage, conversion surgery can be considered as a treatment option. Regarding synchronous primary gastric cancer with liver metastasis, chemotherapy is first suggested both in a neoadjuvant setting and as intensive chemotherapy according to the standard treatment for stage IV gastric carcinoma, even if the tumour is resectable. If the patients have only one poor prognostic factor, that is, solitary synchronous GCLM less than 5 cm in diameter without serosal invasion (< T4), surgery followed by NAC is suggested. In patients with synchronous GCLM with fewer than three tumours without serosal invasion, surgery followed by intensive chemotherapy is the suggested indicated therapy. Patients with multiple poor prognostic factors, including more than three tumours, hepatic hilum infiltration, serosal invasion (T4), or unresectable primary gastric cancer are candidates for standard intensive chemotherapy same to that for stage IV gastric cancer.

Discussion

Yoshida *et al*. first created a treatment algorithm for stage IV gastric cancer in 2018 (*18*). It is simple and easy to apply in daily clinical practice for patients with stage IV gastric cancer; however, considering the treatment choice, especially for GCLM, the structure of their algorithm is partly not based on the previously reported evidence for GCLM. As a result, we created a new treatment algorithm especially for GCLM based on the previously presented evidence from the perspective of hepatic surgeons. In this algorithm, risk factors that were reported to be prognostic factors two or more times in relatively large cohort studies including more than 50

patients were used to create the algorism. Candidates for hepatectomy for GCLM are highly limited; it has been reported that 10-20% of all patients with GCLM because of a coexisting advanced cancer condition, such as peritoneal metastases, para-aortic lymph node metastases, or locally advanced primary disease (*4,12*). However, some of these patients can be cured using hepatectomy (*5,7-15*). With the recent advances in chemotherapy for gastric cancer (*16-18*), regulation of the indications for up-front surgery, neo-adjuvant chemotherapy, and intensive chemotherapy with the aim of conversion surgery (if remarkable tumor shrinkage is achieved) is needed. Consequently, we created a new treatment algorithm for GCLM according to previously reported evidences.

In Yoshida's algorithm for stage IV gastric cancer, GCLM with vascular invasion was selected for algorithm branching and was considered an inoperable factor. From the standpoint of a hepatic surgeon, vascular invasion of metastatic liver tumour is not considered a contraindication for hepatectomy unless the tumour has deeply invaded the hepatic hilum or the estimated volume of future liver remnant is insufficient for safe hepatectomy. To date, few reports have detected vascular invasion as a prognostic factor for GCLM. Unlike vascular invasion, multiple GCLM, large GCLM, and synchronous GCLM are technically resectable, but they are often considered oncologically unresectable due to the high malignant potential of advanced gastric cancer. In these situations, postoperative recurrences occur frequently because of the accompanying poor prognostic factors. However, chemotherapy might change these difficult situations to better ones, where long-term survivals is expected due to the effect of chemotherapy itself and having time to confirm the absence of new lesions. We use the term "oncological conversion" to explain these situations.

In patients with synchronous GCLM, the treatment strategy of this algorithm is similar to that of Yoshida's algorithm. Chemotherapy is proposed to control the primary disease, whether its role is as NAC or intensive chemotherapy. Picado *et al*. reported a relatively better prognosis in patients who underwent preoperative chemotherapy for synchronous GCLM (*19*). Therefore, the first branching of this algorithm was set as whether GCLM was diagnosed as synchronous or metachronous metastasis. Uggeri *et al*. recently conducted a systematic review of GCLM and indicated two prognostic factors; < 5 cm in size and single or > 3 metastases (*20*). This algorithm contains these two factors as branches.

Given the recent advancements in chemotherapy for gastric cancer, further prognostic improvements for patients with GCLM are expected. However, disease cure with chemotherapy alone has rarely been achieved, even in the recent era. Attention should be paid to not miss the best timing for surgery, which is the only potentially curative treatment. This algorithm is not based on the results of a randomized controlled study, which is quite difficult to conduct in patients with GCLM; therefore, the evidence level is not very high. Treatment selections are not recommended but are suggested in the algorithm. Validation studies of this algorithm are needed in the future. Since the treatment of GCLM is highly limited, further discussion motivated by this study will be expected to better understanding the surgical indications for GCLM and to improve patients' prognosis.

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