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Current Trends in the Treatment of Locally Spread Metastatic Gastric Cancer

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Abstract A single distant metastatic lesion is defined as one that has the possibility of local treatment, regardless of the primary lesion of the stomach and regional lymph nodes. There are no large-scale prospective randomized controlled clinical trials to provide evidence-based evidence for the treatment of gastric cancer with relapse or single distant metastasis. Most of the evidence comes from retrospective or small-scale studies. For patients with non-radically resectable primary tumor or PS ≥ 2, the main treatment strategy is to treat recurrent and metastatic gastric cancer or better supportive treatment. For patients with radically resectable primary lesion and regional lymph nodes and PS = 0-1, the main treatment strategy is based on the treatment of recurrent and metastatic gastric cancer, and an optional strategy is individualized decision-making. The optimal therapeutic option for such patients should be discussed in an interdisciplinary commission.

Keywords Treatment, Anastomotic, Lymph, Laparoscopic gastrectomy, Esophageal entero anastomosis

1. Treatment of Locally Recurrent Stomach Cancer after Surgery

Local recurrence is defined as the recurrence of a tumor at the site of resection after radical gastrectomy and metastasis of the regional lymph node. Most studies concerning local recurrence of gastric cancer are retrospective studies, by one institution, and there is no large-scale prospective study.

The results of one study showed that surgery can be an important prognostic factor for survival, since the mOS of patients who underwent surgery was significantly better than inoperable patients (25.8 vs. 6.0 months) [4].

Although some local recurrent diseases are amenable to surgical treatment, indications for surgical intervention must be strictly observed.

For patients with local relapse who had not received any previous radiation therapy, simultaneous chemoradiotherapy was associated with survival benefits.

A retrospective study showed that simultaneous chemoradiotherapy in patients with gastric cancer with local recurrence in the anastomotic site or regional lymph nodes was associated with ORR 61.9% and mOS 35 months [5].

Compared with chemotherapy alone, simultaneous chemoradiotherapy resulted in higher ORR (87.8% vs. 63.0%, P = 0.01), longer mOS (13.4 vs. 5.4 months, P = 0.06) and better control of symptoms such as pain, bleeding and obstruction (85.0% vs. 55.9%, P = 0.06) [6].

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Relapse in the remaining stomach after radical gastrectomy usually occurs within 10 years after surgery [7], and the possibility of resection is high. ESD can be performed for early gastric residual relapse without metastasis to the lymph nodes. It was reported that the block resection rate and the frequency of complete resection are 91%-100% and 74%-94% [8].

Resection of recurrent residual gastric cancer at a late stage should include total gastrectomy, excision of lymph nodes and combined resection of captured organs.

Regional lymph nodes that were not resected during the initial operation should be resected. It should be noted that the rate of metastasis of the jejunum mesentery and root lymph nodes near the anastomotic stoma of the Billroth II anastomosis is high and should be included in the field for excision of lymph nodes [9].

Palliative resection, bypass surgery, stent implantation or jejunum implantation may be considered for patients with inoperable and symptomatic tumors.

2. Treatment of Gastric Cancer with Peritoneal Single Distant Metastasis

Prophylactic dissection of paraaortic lymph nodes in gastric cancer was not found useful in the JCOG9501 study [10].

In the REGATTA study [11], analysis of subgroups of para-aortic lymph node metastases (No 16a2/b1) showed that

surgery in combination with chemotherapy was associated with a good therapeutic effect.

Currently, the main method of treating metastasis to paraaortic lymph nodes is neoadjuvant chemotherapy followed by sequential surgery.

The JCOG0001 study [12] reported that 2-3 cycles of sequential chemotherapy with irinotecin and cisplatin before surgery were associated with clinical efficacy of 56%, resection rate R0 of 65% and 3-year survival of 27%.

However, due to the high mortality rate in this study, it was terminated prematurely.

The JCOG0405 study [13] reported that 2 cycles of neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with dissection of the para-aortic lymph node in gastric cancer with extensive lymph node metastasis were associated with a cure rate of 64.7%, a resection rate of R0 82% and a 3-year OV 58.8%.

In the JCOG1002 study [14], docetaxel was added to S-1 in combination with cisplatin in the JCOG0405 study (DCS mode), and it was found that the observed clinical remission rate is 57.7%, the resection rate R0 is 84.6%, and the pathological remission rate is 50.0%, suggesting that the addition of docetaxel does not increase the effectiveness treatment. S-1 in combination with cisplatin is still considered the first choice for these patients [15].

A prospective study conducted at Zhongshan Hospital affiliated with Fudan University showed that the total PFS of patients with gastric cancer with isolated para-aortic lymph node metastases after neoadjuvant chemotherapy combined with radical surgery was 18.1 months [16].

Synchronous metastasis of gastric cancer to the liver refers to liver metastasis occurring 6 months before, during, or 6 months after surgery [17].

Single distant liver metastasis refers to single hepatic metastases with a diameter of < 5 cm, and metastasis is limited to one lobe without involving blood vessels and bile ducts. Currently, there are no prospective randomized data from controlled clinical trials for the treatment of such patients.

The results of the REGATTA study showed that palliative surgery only for primary lesions was not associated with survival benefits [11]. A retrospective study showed that selective patients with gastric cancer with liver metastases, that is, including those aged <65 years, with normal levels of carcinoembryonic antigen (CEA) and cancer antigen 199 (CA199) at the time of diagnosis and non-EGJ cancer, can obtain survival benefits by consistent chemotherapy and surgery [18].

The results of the meta-analysis showed that the prognosis of patients whose liver metastases were resected was significantly better than that of non-resected patients (mOS, 23.7 vs. 7.6 months) [19].

A systematic review showed that the 1-, 2-, 3- and 5-year rates of OV in patients who underwent gastrectomy plus hepatectomy were significantly higher than in patients with gastrectomy alone [20].

A systematic review of 39 retrospective studies showed that resection of liver metastases can significantly improve the prognosis (HR = 0.50; P < 0.001), especially in the Far East compared to Western studies, as well as in patients with solitary liver metastases [21].

Meta-analysis showed that relatively early stage T and N, absence of vascular invasion, maximum diameter of liver metastases <5 cm, negative margin, normal preoperative levels of CEA and CA19-9 were important factors for a better prognosis in patients with gastric cancer with liver metastases who underwent systemic chemotherapy followed by surgery [22].

The results of the EORTC and JCOG questionnaire survey [23] conducted in 2017 in 17 European countries and 55 research centers in Japan on patients with gastric cancer with liver metastases whose primary and metastatic foci can be resected found that most centers recommend preoperative chemotherapy followed by resection of primary and metastatic foci.

For patients with solitary distant liver metastases that are not suitable for surgical intervention, systematic chemotherapy in combination with other local methods of treatment, including RFA [24], microwave ablation (MWA) [25], infusion chemotherapy of the hepatic artery (HAIC) [26], transarterial chemoembolization (TACE) may be considered [27] and stereotactic body radiotherapy (SBRT) [28].

A retrospective multicenter study from Japan found no significant difference in survival between patients who underwent surgical resection and those who underwent local treatment, but also noted that patients who underwent stage N0/N1 after resection of their only metastatic and primary lesion had significantly better results from surgery or local treatment [29].

The results of the meta-analysis showed that, compared with systemic chemotherapy, systemic chemotherapy in combination with RF in patients with liver metastases (diameter <3 cm) can significantly prolong the survival time of these patients, with a mOE of 22.93 months [30].

Krukenberg tumors are a metastatic lesion of stomach cancer that has been metastasized to the ovary. Systematic chemotherapy is still the main treatment for these patients. However, some retrospective studies have shown that systematic chemotherapy combined with surgical resection of the primary tumor and/or ovarian metastasis may provide some survival benefits for these patients, increasing their average survival from 6-9 months to 19-23.7 months [31].

The most determining prognostic factors of these patients were ECOG PS 0-1, resection R0 (radical resection of primary lesion and metastatic ovarian lesion) and postoperative systemic chemotherapy [32], while pathology of peritoneal ring cells and metastasis of peritoneal semen were poor prognostic factors [33]. For patients with single distant ovarian metastasis, it was found that only some highly selected patients benefit from surgery in combination with systemic chemotherapy. However, there is no definite consensus on the choice of patients, the timing of treatment and methods of such operations.

3. Treatment of Metachronous Single Distant Metastasis of RV without Peritoneal Metastasis

Liver metastases detected more than 6 months after radical gastrectomy are defined as metachronous liver metastases. The results of a retrospective study and meta-analysis showed that patients who underwent hepatectomy for metachronous lesions had a better survival rate than non-resected tumors, with a mOS of 22-26 months versus 3-7 months ($P < 0.001$) [21,34].

In addition, for similar treatment, no differences in survival were found between patients with synchronous and metachronous liver metastases. It was also reported that the prognosis of patients with metachronous liver metastases was better than in patients with synchronous liver metastases [35].

A retrospective study showed that percutaneous RFA for metachronous metastases of RV in the liver was limited to patients with single metastasis without extrahepatic metastatic lesions, but the combination with systemic chemotherapy was useful for prolonging OV [36].

Ovarian resection in combination with drug therapy is an important method of treating patients with metachronous ovarian metastasis after gastric cancer surgery. Compared with monochemotherapy, ovarian resection in combination with chemotherapy can increase mOS [37].

Compared with synchronous ovarian metastasis, surgical resection of metachronous metastases in the ovaries was associated with an excellent survival advantage; mOS was 36 months and 17 months, respectively [38].

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