ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO GASTROINTESTINAL ONCOLOGY

REVIEW

# Practical management of oligometastatic gastric cancer

**Y. Narita[1], K. Muro[1] & D. Takahari[2]***

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya; [2]Department of Medical Oncology, Graduate School of Medicine, Gunma University, Maebashi, Japan

Available online 21 November 2024

Gastric cancer is one of the types of cancer with a high prevalence of morbidity. The frequency of esophagogastric junction cancer, 5-year survival rates, perioperative adjuvant therapy, and standard chemotherapeutic regimens for gastric cancer vary between Asian countries and the West. Although oligometastasis is considered an intermediate state between localized and systemic disease, no standardized definition regarding metastatic organ sites or international consensus in gastric cancer exists. Both local treatment, such as radical surgery and radiotherapy, and systemic chemotherapy can be employed for treating patients with gastric cancer with oligometastatic disease. Recently, evidence for oligometastatic gastric cancer has been accumulated, including findings from several clinical trials conducted in Asian and Western countries, focusing on both organ-specific and non-organ-specific oligometastatic gastric cancer. Here, we review the latest findings on oligometastasis in gastric cancer, including variations in treatment strategies between Western and Asian countries. Further investigation is needed to determine the most favorable practical management strategies for patients with metachronous oligometastasis in gastric cancer, including the use of molecular-targeted agents and immune checkpoint inhibitors. The results of ongoing trials may shed light on the optimal treatment approaches for oligometastatic disease.

**Key words:** chemotherapy, gastric cancer, oligometastasis, treatment strategies

## INTRODUCTION

Gastric cancer, the fifth most common type of cancer worldwide, is the fifth leading cause of cancer-related death.[1] Its incidence and mortality rates are notably high in East Asia. Although systemic chemotherapy with several cytotoxic and molecular-targeted agents or immune checkpoint inhibitors has prolonged the survival of patients with advanced gastric cancer (AGC), the median overall survival (OS) remains suboptimal.[2-8] The frequency of esophagogastric junction cancer, 5-year survival rates, perioperative adjuvant therapy, and standard chemotherapeutic regimens vary between countries in Asia and the West (Table 1).[9-11] Japan and Korea are known to have a high rate of endoscopic diagnosis for early gastric cancer, with widespread use of endoscopic mucosal resection/dissection.[12-15] In contrast, Western countries generally carry out less extensive surgical lymph node dissection compared with Asian countries. Additionally, Western countries have a higher incidence of esophagogastric junction cancer, accounting for ∼25%-30% of all cases according to clinical trials. In Asia, the incidence of gastric cancer against a background of chronic gastritis attributed to *Helicobacter pylori* (*H. pylori*) infection is high, with the diffuse type being more prevalent. Conversely, in Western regions where the infection rate of *H. pylori* is low, the common sites include the cardia, with the intestinal type being more common. Diffuse AGC has a high frequency of peritoneal dissemination, whereas intestinal AGC has a high frequency of liver metastasis.

Oligometastasis, proposed by Hellman and Weichselbaum[16] for the first time, generally refers to a small number of metastases; however, no standardized definition is available concerning the organ sites or international consensus. Recent advancements in the diagnostic techniques and therapeutic modalities have resulted in increased focus on oligometastases. The widespread adoption of positron emission tomography (PET) has facilitated the detection of oligometastases. Additionally, the development of new systemic therapies, including molecular-targeted agents or immune checkpoint inhibitors, has contributed to this heightened interest.[3,5-7,17-19] Oligometastasis is considered an intermediate state between localized (generally resectable and curable) and systemic (generally treated with palliative chemotherapy and incurable) disease. In lung cancer, prostate cancer, and breast

**Correspondence to:* Prof. Daisuke Takahari, Department of Medical Oncology, Graduate School of Medicine, Gunma University, Maebashi, 371-8511, Japan. Tel: +81-27-220-7927; Fax: +81-27-220-8609

E-mail: dtakahari@gunma-u.ac.jp (D. Takahari).

**Table 1. Comparison of gastric cancer between the Eastern and Western countries**

| | East Asia | West |
|---|---|---|
| Prevalence | High | Low |
| Proportion of gastroesophageal junction cancer | Low (gradually increasing trend) | High |
| Early cancer | Common | Rare |
| ***Helicobacter pylori*-induced gastric cancer** | Common | Rare |
| Standard surgery | D2 dissection | D1 or D2 dissection |
| 5-Year survival by surgery | 70% | 30%-40% |
| Standard perioperative chemotherapy | Post-operative chemotherapy in Japan (S-1/CapeOX/SOX/DS)<br>Perioperative chemotherapy (neoadjuvant and post-adjuvant DOS) | Perioperative chemotherapy (neoadjuvant and post-adjuvant FLOT) |
| Standard chemotherapy regimen for advanced gastric cancer | Doublet | Doublet or triplet |

CapeOX, capecitabine + oxaliplatin; DOS, docetaxel + oxaliplatin + S-1; DS, docetaxel + S-1; FLOT, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; SOX, S-1 + oxaliplatin.

cancer, the benefit of local treatment, including radiation therapy and surgery, has been reported for oligometastatic disease.[20] In this review, we outline the most recent findings on oligometastasis in gastric cancer, including variations in the treatment strategies between Western countries and Asian countries, along with discussing future perspectives.

## DEFINITION OF OLIGOMETASTASIS FOR GASTRIC CANCER

The term 'oligometastasis' has historically lacked a precise definition. For instance, it could refer to a *de novo* oligometastasis or a controlled multiple metastasis that has reduced to an induced oligometastasis. Most recently, the proposed definition of oligometastatic disease in a joint systematic review by the European Society for Radiotherapy and Oncology and the American Society for Radiation Oncology[20] classifies oligometastasis in nine clinicopathological conditions. A limited number of metastases detected at the time of initial diagnosis is considered synchronous oligometastasis (Figure 1A). A limited number of metastases detected at least 3 months after the initial diagnosis is considered metachronous oligometastasis. Resectable gastric cancer cases that recur after neoadjuvant chemotherapy are termed metachronous oligometastasis. In the field of gastric cancer, metachronous oligometastasis and

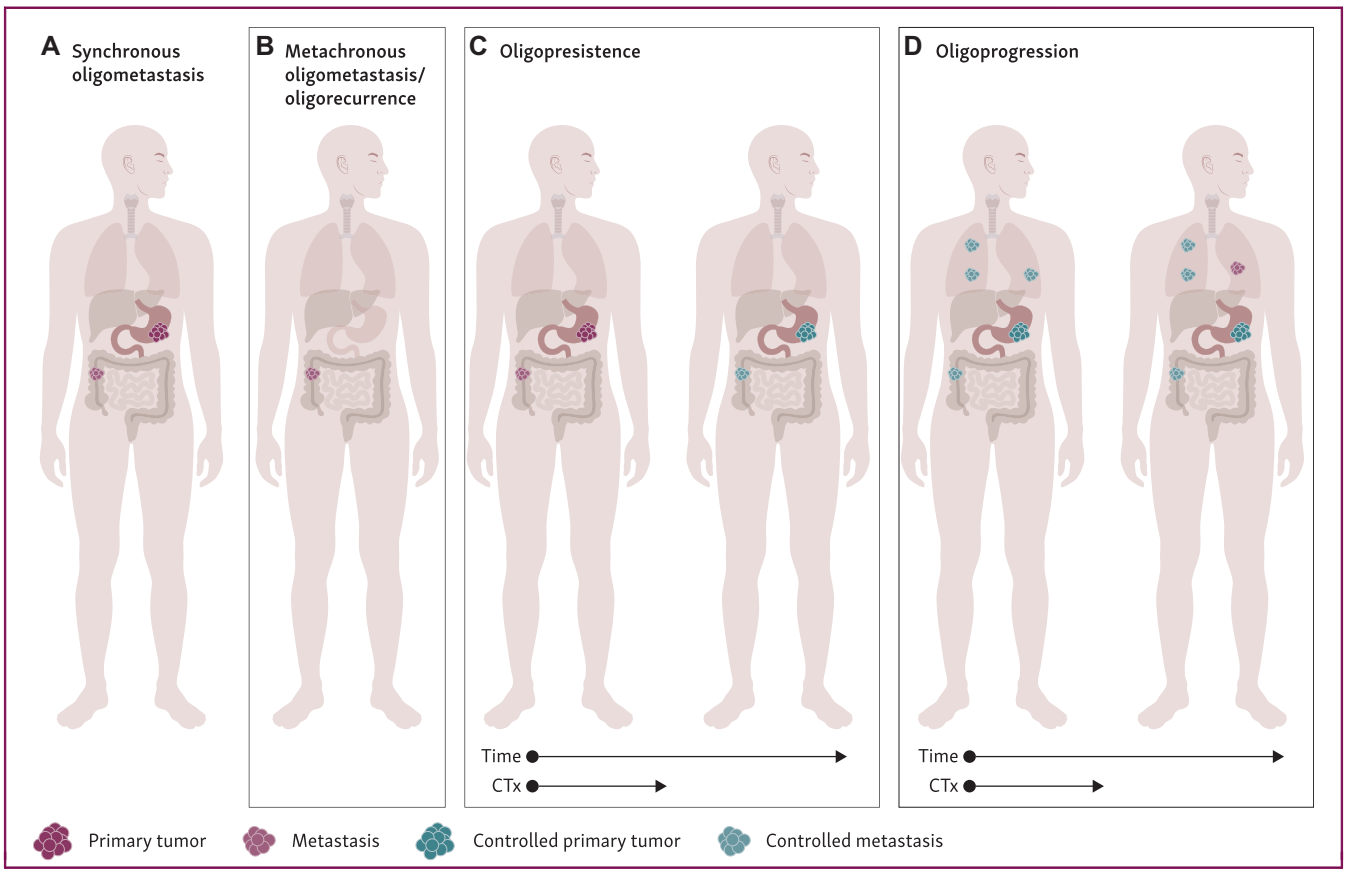


**Figure 1. Representation of oligometastatic states.**
CTx, chemotherapy.

metachronous oligorecurrence are nearly synonymous when the primary tumor has been resected (Figure 1B). Two other commonly used terms are oligopersistence and oligoprogression. In gastric cancer, oligopersistence often warrants 'conversion surgery' following systemic chemotherapy (Figure 1C). Oligoprogression refers to a small number of lesions that progress against a background of controlled metastatic disease. In recent years, with the advent of immune checkpoint inhibitors and molecular-targeted agents for gastric cancer, as well as cytotoxic agents, oligoprogression has been reported in gastric cancer (Figure 1D).[21]

For gastric cancer, the OligoMetastatic Esophagogastric Cancer (OMEC) project has developed European clinical practice guidelines for the definition, diagnosis, and treatment of esophagogastric oligometastatic disease.[22-24] These guidelines were developed by 49 European experts in esophagogastric cancer. Oligometastasis was defined as three or fewer metastases in one organ or one extra-regional lymph node metastasis. PET imaging is recommended when considering baseline and local therapy, with synchronous oligometastatic disease and a disease-free interval of $\leq$2 years; re-staging is used to assess the suitability of local therapy after systemic therapy; moreover, local therapy is recommended for patients with metachronous oligometastatic disease and a disease-free interval of $\geq$2 years.

The Japanese gastric cancer treatment guidelines only mention paraaortic lymph node and liver metastases for oligometastatic disease. Surgical resection following neoadjuvant chemotherapy is weakly recommended for a small number of No. 16a2/b1 para-aortic lymph node metastases; moreover, surgical resection is cautiously recommended for solitary liver metastases. The variations between European and Japanese gastric cancer treatment guidelines are outlined in Table 2.

The National Comprehensive Cancer Network guidelines do not include a definition of oligometastasis or a section on treatment strategies.[25] Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment, and follow-up of patients with gastric cancer have been recently published.[26] The guidelines state that the treatment of metastases cannot be recommended in general but might be considered as an individual approach in highly selected cases of oligometastatic disease, which may be responsive to chemotherapy.

## TREATMENT STRATEGY FOR OLIGOMETASTASIS OF GASTRIC CANCER

When optimizing treatment strategies for oligometastasis of gastric cancer, a multifaceted perspective is required. (i) Should systemic chemotherapy be administered first? (ii) Is surgical resection necessary even in cases of clinical complete response (CR)? (iii) Should surgical resection be carried out in cases that do not achieve clinical CR. (iv) Should molecular pathology background, including human epidermal growth factor receptor 2 (HER2), programmed death-ligand 1 (PD-L1) positivity, microsatellite instability-high (MSI-H), and positive claudin-18 isoform 2 (CLDN18.2) be considered? (v) Is the treatment strategy different for synchronous and metachronous oligometastasis? Several clinical trials on oligometastasis have been reported, differing in target populations, control groups, and chemotherapeutic regimens (Figure 2).

### *Does the RENAISSANCE trial offer insight into the preferred treatment choice for oligometastasis between chemotherapy or surgery?*

Table 3 summarizes certain characteristics and relevant outcomes of pivotal prospective trials for oligometastasis of gastric cancer,[27-30] which may also be related to the differences in the frequency of metastatic sites observed in clinical trials targeting oligometastasis in gastric cancer. Several

**Table 2. Definition and treatment of oligometastatic disease in gastric cancer**

| | | European clinical practice guidelines[22] | Japanese gastric cancer treatment guidelines[8] |
|---|---|---|---|
| Definition of oligometastatic cancer | | 1 Organ with $\leq$3 metastases or 1 extra-regional lymph node station | Often refers to a small number of metastases ($\leq$2-3) in 1-2 organs, but not strictly defined |
| | Liver | $\leq$3 Unilobar liver metastases (consensus)<br>$\leq$2 Bilobar liver metastases (fair) | Not described |
| | Lung | $\leq$3 Unilateral lung metastases (consensus)<br>$\leq$2 Bilateral lung metastases (fair) | Not described |
| | Adrenal gland | Unilateral adrenal gland involvement | Not described |
| | Bone or soft tissue | 1 Bone or 1 soft tissue metastasis<br>2 Bone metastases in 1 bone or 2 soft tissue metastases in 2 compartments | Not described |
| Treatment of oligometastatic cancer | | Synchronous or metachronous OMD with DFI $\leq$2 years: systemic chemotherapy<br>Metachronous OMD with DFI >2 years: systemic chemotherapy or upfront local treatment of OMD (another option) | General treatment strategies for OMD are not described<br>In cases of single liver metastasis, radical resection is recommended<br>In cases of aortic lymph node (16a2/b1) metastasis, neoadjuvant chemotherapy followed by radical resection is recommended |

DFI, disease-free survival; OMD, oligometastatic disease.

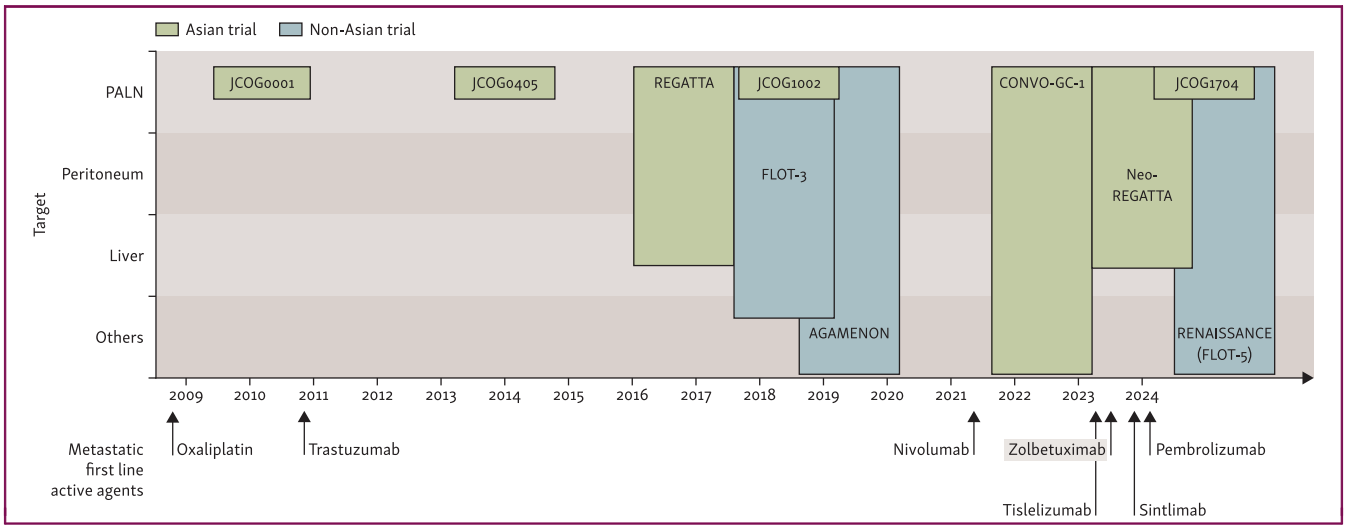


**Figure 2. Overview of studies on oligometastatic disease in gastric cancer.**
met, metastasis; PALN, para-aortic lymph node.

retrospective studies of non-organ-specific oligometastasis have been reported.[31-33] The prognosis was better in patients with gastric cancer with localized metastases who underwent chemotherapy followed by surgery compared with those who underwent chemotherapy alone (16.7-28.0 versus 9.0-15.3 months), suggesting that surgery following chemotherapy may contribute to improved outcomes (Table 4).

The REGATTA trial, which was an open-label, randomized, phase III study conducted in Japan, Korea, and Singapore, evaluated the superiority of chemotherapy (S-1 plus cisplatin) following gastrectomy over chemotherapy alone in patients with AGC localized to one noncurative factor in the liver (H1), peritoneum (P1), or para-aortic lymph nodes (16a1/b2). The trial was terminated and the median OS was 16.6 months [95% confidence interval (CI), 13.7-19.8 months] in the chemotherapy alone group and 14.3 months (95% CI 11.8-16.3 months) in the gastrectomy plus chemotherapy group [hazard ratio (HR), 1.09; 95% CI 0.78-1.52, $P = 0.70$).[27] No superiority was demonstrated for resection of the primary tumor before chemotherapy. In the 89 patients from the surgery-precedent group, radical resection was carried out in 98% of the cases. Of the 86 patients assigned to the chemotherapy arm, 5 (6%) received surgery.

The Neo-REGATTA trial conducted in China evaluated the effectiveness of docetaxel, oxaliplatin, and S-1 (DOS regimen) followed by radical resection versus chemotherapy in patients with advanced gastric adenocarcinoma with a single non-curable factor. The patients without disease progression after four cycles of DOS were divided into chemotherapy and surgery groups. The median OS was 18.0 months for the chemotherapy group; however, it was not reached in the resection group.[30] A total of 73 cases were enrolled, with 35 (48%) and 25 (34%) undergoing surgery and chemotherapy, respectively. In the REGATTA trial, ∼70% of patients had peritoneal dissemination, whereas in the NEO-REGATTA trial, it was ∼25%. Those differences may have affected the results. The NEO-REGATTA trial excluded patients with tumor progression after preoperative chemotherapy, highlighting the importance of selecting appropriate candidates, such as those who respond to chemotherapy, when considering local treatment options. While the negative outcomes of the REGATTA trial suggest that primary tumor resection cannot be universally recommended for all patients, Asian trials suggest that primary resection improves outcomes in patients with AGC with non-curative resection factors who can undergo resectable surgery without exacerbation following chemotherapy.

The AIO-FLOT3 trial, which is a prospective phase II study in patients with adenocarcinoma of the stomach or gastroesophageal junction, included three cohorts of patients with resectable and metastatic disease.[29] The cohort of patients with localized metastases received four cycles of neoadjuvant FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) followed by surgical resection. The median OS in the cohort with localized metastases was better than that in the cohort with non-localized metastases (22.9 versus 10.7 months; HR, 0.37; 95% CI 0.25-0.55; $P < 0.001$).

The RENAISSANCE trial aimed to evaluate the significance of surgical intervention following systemic therapy in limited metastatic gastric cancer/esophagogastric junction cancer. Patients with localized metastases, specifically retroperitoneal lymph node [RPLN] metastases only or a maximum of one resectable or locally controllable curatively unresectable organ site with or without RPLN metastases, were included. After four cycles of FLOT therapy, the outcomes were compared between the continued FLOT and radical complete surgical resection groups (median OS, 23.6 versus 18.5 months; HR, 1.037; 95% CI 0.691-1.556; $P = 0.8610$). Surgery was carried out after neoadjuvant chemotherapy in 54% of the 67 patients assigned to the surgery group.

The results of these trials evaluating surgical therapy following systemic chemotherapy for gastric cancer with localized metastases indicate certain differences in the patient backgrounds, chemotherapeutic regimens, and treatment outcomes. Owing to differences in the regions where the trials were conducted, the diffuse type was more common in Asian trials (34%-76% versus 25%-30%), while

**Table 3. Summary of key characteristics and outcomes from pivotal prospective trials for oligometastasis in gastric cancer**

| Study | | RENAISSANCE[28] | | | REGATTA[27] | | | FLOT-3[29] | | | Neo-REGATTA[30] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study design | | Phase III | | | Phase III | | | Prospective phase II | | | Prospective phase II | |
| Region | | Germany | | | Japan/South Korea/Singapore | | | Germany | | | China | |
| Treatment | | | FLOT + surgery | FLOT | | S-1/cisplatin | Surgery → S-1/cisplatin | FLOT + surgery (limited metastatic) | | FLOT (limited metastatic) | DOS + surgery | |
| Definition and distribution of limited/ oligometastatic lesion | Lymph node | RPLN | 22% | 18% | #16a1/b2 | 13% | 15% | RPLN | 45% | | #16a1/b2 | 51.4% |
| | Peritoneum | P1[a] | 25% | 33% | Diaphragm or caudal to the transverse colon[b] | 77% | 73% | P1 or P2[a] | 6.7% | | above the transverse colon[c] | 20.0% |
| | Liver | ≤5 | 36% | 28% | | 6% | 12% | <5, single site | 18.3% | | | 28.6% |
| | Lung | Unilateral | 1% | 6% | | | | Unilateral | 16.7% | | one lesion or limited in one lobe | NA |
| | Ovary | Uni- or bilateral | 1% | 0% | | | | Uni- or bilateral | 0% | | | |
| | Adrenal | Uni- or bilateral | 3% | 3% | | | | Uni- or bilateral | 60.1% | | | |
| | others | Extra-abdominal LN | 7% | 10% | Two to four | | | Extra-abdominal LN | | | Uni- or bilateral | |
| | | Bone | 1% | 1% | | | | | | | | |
| GEJ/gastric | | | 69%/31% | 68%/32% | | 0%/100% | 0/100% | 68.2%/31.8% | | | 25.7%/74.3% | |
| Histological type (diffuse/ intestinal/mixed) | | | 25%/36%/10% | 19%/46%/4% | | 76%/24%/0% | 75%/25%/0% | 30.0%/38.3%/13.3% | | | 34.3%/45.7%/20.0% | |
| *N* | | | 67 | 72 | | 86 | 89 | 36 | | 31 | 35 | |
| Complication rate of NAC | | | 100% | NA | | 86% | NA | NA | | NA | 100% | |
| Completion rate from NAC to surgical treatment | | | 54% | NA | | NA | 98%[d] | 60% | | NA | NA (73 enrolled, 35 underwent surgery, 25 chemotherapy) | |
| Median survival time (months) | | | 18.5 | 23.6 | | 16.6 | 14.3 | 31.3 | | 15.9 | Not reached | |
| 2-Year overall survival | | | NA | NA | | 31.7% | 25.1% | NA | | NA | 81.7% | |

DOS, docetaxel + oxaliplatin + S-1; FLOT, fluorouracil + leucovorin + oxaliplatin + docetaxel; GEJ, gastroesophageal junction; LN, lymph node; NA, not assessment; NAC, neoadjuvant chemotherapy; RPLN, retroperitoneal lymph node.

[a]P1 or P2 was defined according to guidelines by the Japanese research society for gastric cancer.

[b]The diaphragm or peritoneum caudal to the transverse colon without massive ascites or intestinal obstruction.

[c]Limited lesions in the peritoneum above the transverse colon, including the diaphragm, mesentery, and greater omentum.

[d]Ratio of the patients who underwent gastrectomy.



https://doi.org/10.1016/j.esmogo.2024.100108

**Table 4. Overview of selected studies in patients with organ-specific oligometastatic gastric cancer**

| Metastatic lesion | Study or author | Study design | Year | Metastatic number or location | *N* | Region | Type of oligometastasis | Treatment | Median OS |
|---|---|---|---|---|---|---|---|---|---|
| Not organ-specific | | | | | | | | | |
| | RENAISSANCE[28] | Phase III | 2024 | RPLN and/or 1 | 67<br>72 | Germany | Synchronous | FLOT + surgery + FLOT<br>FLOT | 18.5 months<br>23.6 months |
| | REGATTA[27] | Phase III | 2016 | Peritoneum, liver, 16a1/b2 | 89<br>86 | Japan/South Korea/Singapore | Synchronous | S-1/cisplatin + surgery<br>S-1/cisplatin | 14.3 months<br>16.6 months |
| | FLOT-3[29] | Phase II | 2017 | RPLN and/or 1 | 36<br>31 | Germany | Synchronous | FLOT + surgery +FLOT<br>FLOT | 31.3 months<br>15.9 months |
| | Neo-REGATTA[30] | Phase II | 2023 | Peritoneum, liver, 16a1/b2 | 35<br>25 | China | Synchronous | DOS + surgery<br>DOS | Not reached<br>18.0 months |
| | Kim[33] | Retrospective | 2011 | Peritoneum, liver, lung, distant LN | 42<br>185 | South Korea | Synchronous | CTx + surgery<br>CTx | 28.0 months<br>9.0 months |
| | AGAMENON[31] | Retrospective | 2018 | Liver, lung, peritoneal, LN, others | 97 | Spain | Synchronous | CTx + surgery | 16.7 months |
| | Hara[32] | Retrospective | 2023 | Liver, lung, adrenal, PALN, distant LN | 21<br>50 | Japan | Synchronous/ metachronous | CTx + surgery<br>CTx | 48.3 months<br>15.3 months |
| Organ-specific | | | | | | | | | |
| Extra-regional lymph node | | | | | | | | | |
| | RENAISSANCE[28] | Phase III | 2024 | RPLN only | 18<br>19 | Germany | Synchronous | FLOT + surgery + FLOT<br>FLOT | 29.6 months<br>17.1 months |
| | JCOG1002[35] | Phase II | 2017 | 16a2/b1 and/or bulky LN | 53 | Japan | Synchronous | DCS | 55% (5-year OS) |
| | JCOG1704[37] | Phase II | 2024 | 16a2/b1 and/or bulky LN | 47 | Japan | Synchronous | DOS | NA |
| | CONVO-GC-1[38] | Retrospective | 2021 | 16a2/b1<br>16a1/b2 | 222<br>106 | Japan/South Korea/China | Synchronous | CTx + surgery | 33.5 months<br>54.3 months |
| | Hara[32] | Retrospective | 2023 | PALN<br>Distant LN | 55<br>10 | Japan | Synchronous/ metachronous | Surgery or surgery + CTx or CTx | 21.0 months<br>28.8 months |
| Liver | | | | | | | | | |
| | RENAISSANCE[28] | Phase III | 2024 | Five or less | 24<br>20 | Germany | Synchronous | FLOT + surgery + FLOT<br>FLOT | 24.9 months<br>25.7 months |
| | CONVO-GC-1[38] | Retrospective | 2021 | Solitary<br>Two<br>Three or more | 63<br>24<br>53 | Japan/South Korea/China | Synchronous | CTx + surgery | 95.2 months<br>46.6 months<br>56.6 months |
| | Shirasu[45] | Retrospective | 2018 | Two or three | 9<br>15<br>3 | Japan | Synchronous/ metachronous | CTx<br>Surgery<br>CTx followed by surgery | 38.1 months<br>24.8 months<br>Not reached |
| | Hara[32] | Retrospective | 2023 | Three or less | 27 | Japan | Synchronous/ metachronous | Surgery or surgery + CTx or CTx | 28.8 months |
| | van Hootegem[46] | Retrospective | 2024 | Five or less | 31 | Netherlands/ Italy/Belgium | Synchronous | CTx and/or surgery/ablation | 21 months |
| Peritoneum | | | | | | | | | |
| | RENAISSANCE[28] | Phase III | 2024 | P1[a] | 17<br>24 | Germany | Synchronous | FLOT + surgery + FLOT<br>FLOT | 11.9 months<br>18.6 months |
| | CONVO-GC-1[38] | Retrospective | 2021 | P0CY1<br>Peritoneal metastasis | 107<br>99 | Japan | Synchronous | CTx + R0 resection<br>CTx + R0 resection | 42.4 months<br>41.8 months |
| | Yamaguchi[58] | Retrospective | 2021 | CY1 and/or P1a[a] | 150<br>563 | Japan | Synchronous | Initial CTx<br>Initial Surgery | 24.8 months<br>24.0 months |

CTx, chemotherapy; CY, cytology; DCS, docetaxel + cisplatin + S-1; DOS, docetaxel + oxaliplatin + S-1; FLOT, fluorouracil + leucovorin + oxaliplatin + docetaxel; LN, lymph node; NA, not assessment; OS, overall survival; PALN, para-aortic lymph node; RPLN, retroperitoneal lymph node.
[a]P1 or P1a was defined according to guidelines of the Japanese research society for gastric cancer.

gastroesophageal junction cancer was more common in Western trials (26% versus 31%-32%), indicating regional differences in the incidence of gastric cancer. Moreover, a questionnaire survey on gastric cancer with liver metastases compared clinical practice in Europe (European Organization for Research and Treatment of Cancer) and Japan (Japan Clinical Oncology Group).[34] For patients with resectable synchronous liver metastasis, 7.5% and 40.0% of European and Japanese physicians, respectively, carried out gastrectomy and hepatic resection; 43.3% and 52.7% carried out chemotherapy followed by gastrectomy and hepatic resection, respectively, and 26.9% and 3.6% carried

out chemotherapy only. Hence, if the oligometastatic lesion is resectable, radical resection is often carried out in Asian countries; however, in Western countries, chemotherapy is the main treatment strategy considered. When interpreting clinical trials on oligometastasis in clinical settings, it is necessary to adopt a multifaceted and multidimensional perspective that considers geo-regional disparities. Notably, international collaborative clinical studies may be warranted to establish treatment strategies for providing timely surgery or chemotherapy to the right patient and improving the outcomes of patients with gastric cancer.

### *Organ-specific oligometastatic gastric cancer*

In gastric cancer with extra-regional lymph node metastasis, such as metastasis to the para-aortic, supraclavicular, mediastinal, and axillary lymph nodes, the efficacy of chemotherapy followed by surgery has been reported based on the data from Asian studies (median OS, 21.0-54.3 months).[35-38] Based on data from Japanese prospective trials, chemotherapy followed by radical resection is considered one of the treatment options for 16a2/b1 lymph node metastasis.[35,37,39] The para-aortic lymph node metastases at 16a1/16b2, however, which are located in the retroperitoneum, are more advanced than those at 16a2/16b1, which are considered classically unresectable.[40-42] The RENAISSANCE trial reported numerically better survival in the chemotherapy followed by surgery group than in the chemotherapy alone group in patients with only RPLN metastases (median OS, 29.6 versus 17.1 months; $P = 0.6049$).[28] Data on distant lymph node metastases other than para-aortic lymph node metastases are lacking, and no conclusions have been drawn regarding systemic chemotherapy or chemotherapy followed by surgery in clinical settings.[32,43]

Solitary liver metastasis is weakly recommended for radical resection in the Japanese gastric cancer treatment guidelines.[8,28,32,38,44-54] Chemotherapy is commonly adapted for two to three metastatic liver lesions.[46,49,51,54,55] Surgery is beneficial in cases of oligopersistence following chemotherapy in retrospective studies.[32,45] Conversely, the subgroup analysis of liver metastasis in the RENAISSANCE trial demonstrated no difference between the chemotherapy followed by surgery and continued chemotherapy groups (median OS, 24.9 versus 25.7 months; $P = 0.9529$). This study, however, included five or fewer liver metastases and did not cover only three or fewer liver metastases as defined by OMEC or solitary liver metastasis mentioned in the Japanese gastric cancer treatment guidelines.[8,22,23] Thus, treatment strategies for localized liver metastases are controversial.

Peritoneal lavage cytology positive (CY1) is generally considered a non-curative factor. A treatment strategy of prior gastrectomy followed by chemotherapy has been reported in several retrospective studies (median 5-year OS, 26.0%-30.2%).[56-58] The JCOG0501 trial, however, comparing gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, reported no difference between the two groups for prior surgery and prior chemotherapy in the CY1 subgroup (HR, 1.05; 95% CI 0.60-1.85).[59] Conversely, the importance of R0 resection has been documented in cases where cytology-negative results are achieved following chemotherapy (conversion surgery) (median OS, 24.0-42.8 months).[38,58,60] Similar to CY1 disease, there is no established standard of care for patients with peritoneal metastases localized near the stomach, as defined by P1a in the Japanese classification of gastric carcinoma.[8,58,61] In a retrospective Japanese study of the patients with P1a, the patients in the initial chemotherapy group with P1a converting to P0 and CY0 had better survival outcomes than did patients in the initial surgery group (median OS, 32.0 versus 24.0 months; HR, 1.64; $P = 0.004$).[58] In the RENAISSANCE trial, the chemotherapy arm showed a more favorable outcome than the chemotherapy followed by surgery arm (median OS, 11.9 versus 18.6 months; $P = 0.0926$); however, the results were not obtained in cases where P0/CY0 status was confirmed.[28] Confirmation of P0/CY0 status following chemotherapy may serve as a clinical indicator for oligopersistence in P1/CY1. In these cases, surgery following chemotherapy may be recommended.

For other metastatic organs, few case series have documented lung, bone, ovarian, and adrenal metastases.[62-69] A relatively large number of case reports on surgical therapy are available for Krukenberg tumor in gastric cancer.[67,68] Median OS for patients undergoing metastasectomy of Krukenberg tumors was numerally better when compared with that for non-metastasectomy (median OS, 14 to −19 versus 8-11.8 months). The coexistence of peritoneal dissemination has been reported as a poor prognostic factor in several studies, with some suggesting that resection may not improve prognosis in patients with peritoneal dissemination. Treatment strategies, including criteria for selecting patients for surgical therapy, such as in the case of Krukenberg tumors, and decisions regarding the administration of preoperative or post-operative chemotherapy, remain to be established.

## REGIMEN SELECTION STRATEGIES FOR OLIGOMETASTATIC GASTRIC CANCER

In the era of molecular-targeted agents or immune checkpoint inhibitors and approval for AGC as first-line therapy, a strategy of adding molecularly-targeted agents (i.e. trastuzumab and zolbetuximab) or immune checkpoint inhibitors (i.e. nivolumab, pembrolizumab, sintilimab, and tislelizumab) with high antitumor effects in addition to the conventional two- or three-drug combination cytotoxic agents can be considered for patients with oligometastatic gastric cancer.[3,5-7,17,18,70,71] In fact, the data on unresectable colorectal cancer with liver metastases have demonstrated a correlation between response rate and resectability.[72] Most recently, the CAIRO-5 trial did not demonstrate any survival benefit in the panitumumab arm over the bevacizumab arm despite a 24% increase in the response rate.[73,74] In addition,

recent prospective studies on resectable gastric cancer have not yet established the efficacy of incorporating molecularly-targeted agents or immune checkpoint inhibitors.[75-79] For HER2-positive resectable or extensive lymph node metastatic gastric cancer, the JCOG1301C studies demonstrated a 4%-23% increase in the pathological CR for patients with the addition of anti-HER2 drugs.[76,77] Similarly, the KEYNOTE-585 and MATTERHORN trials have demonstrated a 10.5%-12% improvement in the pathological CR with the addition of immune checkpoint inhibitors to perioperative chemotherapy.[78,79] No reports of improved long-term outcomes, however, such as relapse-free survival or OS, exist. The addition of molecularly-targeted agents or immune checkpoint inhibitors for patients with oligometastatic gastric cancer remains controversial, and further investigations are warranted.

## IS ORGAN PRESERVATION POSSIBLE IN GASTRIC CANCER WITH OLIGOMETASTASIS?

The MSI-H status is a predictive biomarker of immune checkpoint inhibitors.[6,80-83] The integrated analysis of KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 trials in the metastatic setting demonstrated that patients with MSI-H tumors in the pembrolizumab group have a significantly high survival rate; however, OS was not reached.[83] Another subgroup analysis of the CheckMate 649 trial demonstrated a favorable prognosis for patients with MSI-H tumors treated with nivolumab plus chemotherapy or ipilimumab (HR, 0.38; objective response rate, 55% versus 39%).[6] A case report indicated that organ preservation was possible with clinical CR even with later-line treatment, >2 years after the diagnosis of unresectable disease.[84,85] In resectable cases, a higher rate of pathological CR was observed in patients with MSI-H who received immune checkpoint inhibitors (pathological CR rate, 58.6%-62.5%).[86-90] It remains uncertain whether organ preservation for patients with oligometastasis is feasible without radical resection in resectable MSI-H gastric cancer cases. Moreover, even in cases of clinical CR evaluated by imaging studies including PET scans, residual tumor is often found despite radical resection being carried out. Circulating tumor DNA (ctDNA) may serve as an indicator for determining the need for radical resection in patients with oligometastatic gastric cancer who have achieved clinical CR after chemotherapy. ctDNA refers to the portion of cell-free DNA derived specifically from the tumor cells in a patient's blood, which facilitates the detection of molecular residual disease.[91-93] Sensitivity and specificity of 85.7% (30/35) and 95.5% (85/89), respectively, were reported by the ctDNA assay in stage I-III resected upper gastrointestinal cancers.[92] In the gastric cancer subgroup, patients who were ctDNA-negative after surgery had a better prognosis than those who were ctDNA-positive (HR, 17.7; $P < 0.0001$).

## FUTURE PERSPECTIVES

Another issue is that most prospective studies have concentrated on synchronous metastases, with few focusing on metachronous metastases.[32] There is no literature consensus on the interval between resection of the primary cancer and the development of oligometastatic disease, distinguishing between synchronous and metachronous metastases.[94] The OMEC consensus proposes that local therapy is recommended for patients with metachronous oligometastatic disease.[22] Whether treatment strategies for patients with oligometastasis in post-resection recurrent cases can be extrapolated from the evidence based on synchronous oligometastasis, however, remains unclear, suggesting the need for further investigation in patients with gastric cancer with metachronous oligometastasis.

Many studies have revealed genomic complexity and heterogeneity of cancer genetic profiles in gastric cancer.[95,96] A retrospective study of 1124 patients treated with immune checkpoint inhibitors reported a better prognosis in patients with oligoprogression than in those with polyprogression (median OS, 38.5 versus 14.0 months; HR, 0.37; $P < 0.001$).[21] Oligoprogression was defined as two or fewer sites of disease progression, with varying treatment options, including radiation therapy, local treatment, and systemic chemotherapy, with no differences in the outcomes between local and systemic treatments. Many aspects of oligoprogression in gastric cancer remain unknown, warranting further study for determining the most favorable practical management.

Four prospective phase III trials are currently underway for patients with synchronous oligometastatic disease.[97-99] Two are taking place in China and Japan, while the other two are being conducted in western countries. The Chinese study is investigating two treatment arms for gastric cancer with a single non-curable factor by comparing chemotherapy alone with a combination of D2 distal gastrectomy, metastasectomy, and chemotherapy.[97] The SURGIGAST trial has been designed to evaluate the benefit of combining systemic therapy with radical resection compared with systemic therapy alone for oligometastatic disease in France.[98] The EA2183 trial from the USA is investigating whether stereotactic body radiation therapy provides an OS advantage for patients who have responded to chemotherapy, compared with continuing with chemotherapy alone.[99] The Japan Clinical Oncology Group (JCOG) is conducting a phase III trial (JCOG2301) to verify the superiority of conversion surgery over chemotherapy for stage IV gastric cancer, where distant metastatic sites show response to chemotherapy. Although the results of these trials will provide new evidence in the future, they do not address the preferred treatment strategies involving molecular-targeted agents or immune checkpoint inhibitors.

### *Conclusions*

Developing definitions, diagnoses, and treatments for oligometastatic gastric cancer is crucial for its management in clinical settings. There is an urgent need to establish and validate treatment strategies through rigorous clinical trials. The results of ongoing clinical trials will play a pivotal role in improving patient care in daily clinical practice.

## ACKNOWLEDGEMENTS

The authors thank Editage (https://www.editage.jp) for English language editing. We also thank all the study participants and their families.

## FUNDING

None declared.

## DISCLOSURE

YN: research funding to my institution from Chugai, Merck Sharp & Dohme.

(MSD), Amgen, ONO Pharmaceutical, Astellas, Sanofi, Taiho, Eisai, Daiichi Sankyo, Novartis, and Pfizer; honoraria for lectures, presentations, and speaker bureaus from Yakult Honsha, Taiho, Eli Lilly, Daiichi Sankyo, Ono Pharma, and Bristol-Myers Squibb; and participation in the advisory board of Daiichi Sankyo.

KM: research funding to my institution from Chugai, MSD, Amgen, ONO Pharmaceutical, Astellas, Sanofi, Taiho, Eisai, Daiichi Sankyo, Novartis, and Pfizer; consulting fees from AstraZeneca, ONO Pharmaceutical, Amgen, and Astellas; honoraria for lectures from ONO Pharmaceutical, Taiho, Bristol-Myers Squibb, Eli Lilly, MSD, and Daiichi Sankyo; participation on the advisory boards of ONO Pharmaceutical, Amgen, AstraZeneca, Eli Lilly, and Takeda.

DT: honoraria for lectures, presentations, and speaker bureaus from ONO Pharmaceutical, Taiho, Bristol-Myers Squibb, Eli Lilly, Astellas.

## REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263.
2. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer*. 1993;72(1):37-41.
3. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376(9742):687-697.
4. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6(10):1571-1580.
5. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27-40.
6. Shitara K, Ajani JA, Moehler M, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature*. 2022;603(7903):942-948.
7. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*. 2023;401(10389):1655-1668.
8. Japanese Gastric Cancer Association. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). *Gastric Cancer*. 2023;26(1):1-25.
9. Ohtsu A, Yoshida S, Saijo N. Disparities in gastric cancer chemotherapy between the East and West. *J Clin Oncol*. 2006;24(14):2188-2196.
10. Nakayama I, Ohashi M, Nunobe S. Perioperative or neoadjuvant chemotherapy for locally advanced gastric or gastroesophageal junction cancer: from independent evidence in the West, the East, and Japan to global collaboration. *Chin Clin Oncol*. 2024;13(1):8.
11. Narita Y, Muro K. Updated immunotherapy for gastric cancer. *J Clin Med*. 2023;12(7):2636.
12. Li Y, Feng A, Zheng S, Chen C, Lyu J. Recent estimates and predictions of 5-year survival in patients with gastric cancer: a model-based period analysis. *Cancer Control*. 2022;29:10732748221099227.
13. Office for National Statistics. Cancer survival in England adult, stage at diagnosis and childhood — patients followed up to 2018. 2019. Available at https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/latest. Accessed June 17, 2024.
14. seer.cancer.gov. Cancer Stat Facts: Stomach Cancer. Available at https://seer.cancer.gov/statfacts/html/stomach.html. Accessed June 17, 2024.
15. ganjoho.jp. Cancer Statistics in Japan 2024. 2024. Available at https://ganjoho.jp/public/qa_links/report/statistics/2024_en.html. Accessed June 17, 2024.
16. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10.
17. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med*. 2023;29(8):2133-2141.
18. Rha SY, Oh DY, Yañez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24(11):1181-1195.
19. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. *Lancet*. 2023;402(10418):2197-2208.
20. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21(1):e18-e28.
21. Zhuo N, Liu C, Zhang Q, et al. Characteristics and prognosis of acquired resistance to immune checkpoint inhibitors in gastrointestinal cancer. *JAMA Netw Open*. 2022;5(3):e224637.
22. Kroese TE, Bronzwaer S, van Rossum PSN, et al. European clinical practice guidelines for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer (OMEC-4). *Eur J Cancer*. 2024;204:114062.
23. Morgagni P, Bencivenga M, Carneiro F, et al. International consensus on the management of metastatic gastric cancer: step by step in the foggy landscape: Bertinoro Workshop, November 2022. *Gastric Cancer*. 2024;27(4):649-671.
24. Leonhardt CS, Stamm T, Hank T, Prager G, Strobel O. Defining oligometastatic pancreatic cancer: a systematic review and critical synthesis of consensus. *ESMO Open*. 2023;8(6):102067.
25. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2022;20(2):167-192.
26. Shitara K, Fleitas T, Kawakami H, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with gastric cancer. *ESMO Open*. 2024;9(2):102226.
27. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol*. 2016;17(3):309-318.

28. Al-Batran S-E, Lorenzen S, Riera J, et al. Effect of chemotherapy/targeted therapy alone vs. chemotherapy/targeted therapy followed by radical surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction: the IKF-575/RENAISSANCE phase III trial. *J Clin Oncol*. 2024;42(suppl 17):LBA4001-LBA4001.
29. Al-Batran SE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 trial. *JAMA Oncol*. 2017;3(9):1237-1244.
30. Cui Y, Yu Y, Zheng S, et al. Does resection after neoadjuvant chemotherapy of docetaxel, oxaliplatin, and S-1 (DOS regimen) benefit for gastric cancer patients with single non-curable factor? A multicenter, prospective cohort study (Neo-REGATTA). *BMC Cancer*. 2023;23(1):308.
31. Carmona-Bayonas A, Jiménez-Fonseca P, Echavarria I, et al. Surgery for metastases for esophageal-gastric cancer in the real world: data from the AGAMENON national registry. *Eur J Surg Oncol*. 2018;44(8):1191-1198.
32. Hara K, Cho H, Onodera A, et al. Long-term treatment outcomes in gastric cancer with oligometastasis. *Ann Gastroenterol Surg*. 2024;8(1):60-70.
33. Kim KH, Lee KW, Baek SK, et al. Survival benefit of gastrectomy ± metastasectomy in patients with metastatic gastric cancer receiving chemotherapy. *Gastric Cancer*. 2011;14(2):130-138.
34. Kataoka K, Kinoshita T, Moehler M, et al. Current management of liver metastases from gastric cancer: what is common practice? New challenge of EORTC and JCOG. *Gastric Cancer*. 2017;20(5):904-912.
35. Ito S, Sano T, Mizusawa J, et al. A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. *Gastric Cancer*. 2017;20(2):322-331.
36. Takahari D, Ito S, Mizusawa J, et al. Long-term outcomes of preoperative docetaxel with cisplatin plus S-1 therapy for gastric cancer with extensive nodal metastasis (JCOG1002). *Gastric Cancer*. 2020;23(2):293-299.
37. Kurokawa Y, Doki Y, Kitabayashi R, et al. Short-term outcomes of preoperative chemotherapy with docetaxel, oxaliplatin, and S-1 for gastric cancer with extensive lymph node metastasis (JCOG1704). *Gastric Cancer*. 2024;27(2):366-374.
38. Yoshida K, Yasufuku I, Terashima M, et al. International retrospective cohort study of conversion therapy for stage IV gastric cancer 1 (CONVO-GC-1). *Ann Gastroenterol Surg*. 2022;6(2):227-240.
39. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. *Gastric Cancer*. 2016;19(2):329-338.
40. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg*. 2014;101(6):653-660.
41. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med*. 2008;359(5):453-462.
42. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy — Japan Clinical Oncology Group study 9501. *J Clin Oncol*. 2004;22(14):2767-2773.
43. Marrelli D, Piccioni SA, Carbone L, et al. Posterior and para-aortic (D2plus) lymphadenectomy after neoadjuvant/conversion therapy for locally advanced/oligometastatic gastric cancer. *Cancers (Basel)*. 2024;16(7):1376.
44. Takemura N, Saiura A, Ito H, et al. Proposal of new treatment algorithm for gastric cancer liver metastases: Up-front surgery or conversion surgery? *Global Health Med*. 2022;4(1):57-60.
45. Shirasu H, Tsushima T, Kawahira M, et al. Role of hepatectomy in gastric cancer with multiple liver-limited metastases. *Gastric Cancer*. 2018;21(2):338-344.
46. van Hootegem SJM, de Pasqual CA, Giacopuzzi S, et al. Outcomes after surgical treatment of oesophagogastric cancer with synchronous liver metastases: a multicentre retrospective cohort study. *Cancers (Basel)*. 2024;16(4):797.
47. Oki E, Tokunaga S, Emi Y, et al. Surgical treatment of liver metastasis of gastric cancer: a retrospective multicenter cohort study (KSCC1302). *Gastric Cancer*. 2016;19(3):968-976.
48. Granieri S, Altomare M, Bruno F, et al. Surgical treatment of gastric cancer liver metastases: systematic review and meta-analysis of long-term outcomes and prognostic factors. *Crit Rev Oncol Hematol*. 2021;163:103313.
49. Montagnani F, Crivelli F, Aprile G, et al. Long-term survival after liver metastasectomy in gastric cancer: systematic review and meta-analysis of prognostic factors. *Cancer Treat Rev*. 2018;69:11-20.
50. Markar SR, Mikhail S, Malietzis G, et al. Influence of surgical resection of hepatic metastases from gastric adenocarcinoma on long-term survival: systematic review and pooled analysis. *Ann Surg*. 2016;263(6):1092-1101.
51. Kinoshita T, Kinoshita T, Saiura A, Esaki M, Sakamoto H, Yamanaka T. Multicentre analysis of long-term outcome after surgical resection for gastric cancer liver metastases. *Br J Surg*. 2015;102(1):102-107.
52. Liu Q, Bi JJ, Tian YT, Feng Q, Zheng ZX, Wang Z. Outcome after simultaneous resection of gastric primary tumour and synchronous liver metastases: survival analysis of a single-center experience in China. *Asian Pacific J Cancer Prevent*. 2015;16(4):1665-1669.
53. Petrelli F, Coinu A, Cabiddu M, et al. Hepatic resection for gastric cancer liver metastases: a systematic review and meta-analysis. *J Surg Oncol*. 2015;111(8):1021-1027.
54. Ohkura Y, Shinohara H, Haruta S, et al. Hepatectomy offers superior survival compared with non-surgical treatment for ≤3 metastatic tumors with diameters < 3 cm from gastric cancer: a retrospective study. *World J Surg*. 2015;39(11):2757-2763.
55. Kroese TE, Takahashi Y, Lordick F, et al. Liver oligometastatic disease in synchronous metastatic gastric cancer patients: a nationwide population-based cohort study. *Eur J Cancer*. 2023;179:65-75.
56. Kodera Y, Ito S, Mochizuki Y, et al. Long-term follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study. *Gastric Cancer*. 2012;15(3):335-337.
57. Yamaguchi T, Takashima A, Nagashima K, et al. Efficacy of postoperative chemotherapy after resection that leaves no macroscopically visible disease of gastric cancer with positive peritoneal lavage cytology (CY1) or localized peritoneum metastasis (P1a): a multicenter retrospective study. *Ann Surg Oncol*. 2020;27(1):284-292.
58. Yamaguchi T, Takashima A, Nagashima K, et al. Impact of preoperative chemotherapy as initial treatment for advanced gastric cancer with peritoneal metastasis limited to positive peritoneal lavage cytology (CY1) or localized peritoneal metastasis (P1a): a multi-institutional retrospective study. *Gastric Cancer*. 2021;24(3):701-709.
59. Iwasaki Y, Terashima M, Mizusawa J, et al. Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial. *Gastric Cancer*. 2021;24(2):492-502.
60. Yasufuku I, Nunobe S, Ida S, et al. Conversion therapy for peritoneal lavage cytology-positive type 4 and large type 3 gastric cancer patients selected as candidates for R0 resection by diagnostic staging laparoscopy. *Gastric Cancer*. 2020;23(2):319-327.
61. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer*. 2011;14(2):101-112.
62. Aurello P, Petrucciani N, Giulitti D, Campanella L, D'Angelo F, Ramacciato G. Pulmonary metastases from gastric cancer: is there any indication for lung metastasectomy? A systematic review. *Med Oncol*. 2016;33(1):9.
63. Kemp CD, Kitano M, Kerkar S, et al. Pulmonary resection for metastatic gastric cancer. *J Thorac Oncol*. 2010;5(11):1796-1805.

64. Howell GM, Carty SE, Armstrong MJ, et al. Outcome and prognostic factors after adrenalectomy for patients with distant adrenal metastasis. *Ann Surg Oncol*. 2013;20(11):3491-3496.
65. Lin X, Han T, Zhuo M, et al. A retrospective study of clinicopathological characteristics and prognostic factors of Krukenberg tumor with gastric origin. *J Gastrointest Oncol*. 2022;13(3):1022-1034.
66. Cho JH, Lim JY, Choi AR, et al. Comparison of surgery plus chemotherapy and palliative chemotherapy alone for advanced gastric cancer with Krukenberg tumor. *Cancer Res*. 2015;47(4):697-705.
67. Yu P, Huang L, Cheng G, et al. Treatment strategy and prognostic factors for Krukenberg tumors of gastric origin: report of a 10-year single-center experience from China. *Oncotarget*. 2017;8(47):82558-82570.
68. Ma F, Li Y, Li W, et al. Metastasectomy improves the survival of gastric cancer patients with Krukenberg tumors: a retrospective analysis of 182 patients. *Cancer Manag Res*. 2019;11:10573-10580.
69. Choi YJ, Kim DH, Han HS, et al. Long-term survival after gastrectomy and metastasectomy for gastric cancer with synchronous bone metastasis. *World J Gastroenterol*. 2018;24(1):150-156.
70. Xu J, Jiang H, Pan Y, et al. Sintilimab plus chemotherapy for unresectable gastric or gastroesophageal junction cancer: the ORIENT-16 randomized clinical trial. *JAMA*. 2023;330(21):2064-2074.
71. Qiu MZ, Oh DY, Kato K, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ*. 2024;385:e078876.
72. Folprecht G, Grothey A, Alberts S, Raab HR, Köhne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol*. 2005;16(8):1311-1319.
73. Bond MJG, Bolhuis K, Loosveld OJL, et al. First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. *Lancet Oncol*. 2023;24(7):757-771.
74. Punt CJA, Bond MJG, Bolhuis K, et al. LBA27 First-line systemic treatment in patients with initially unresectable colorectal cancer liver metastases (CRLM): overall survival of the phase III CAIRO5 study of the Dutch Colorectal Cancer Group. *Ann Oncol*. 2023;34:S1268.
75. Rivera F, Izquierdo-Manuel M, García-Alfonso P, et al. Perioperative trastuzumab, capecitabine and oxaliplatin in patients with HER2-positive resectable gastric or gastro-oesophageal junction adenocarcinoma: NEOHX phase II trial. *Eur J Cancer*. 2021;145:158-167.
76. Hofheinz RD, Merx K, Haag GM, et al. FLOT versus FLOT/trastuzumab/pertuzumab perioperative therapy of human epidermal growth factor receptor 2-positive resectable esophagogastric adenocarcinoma: a randomized phase II trial of the AIO EGA Study Group. *J Clin Oncol*. 2022;40(32):3750-3761.
77. Tokunaga M, Machida N, Mizusawa J, et al. Early endpoints of a randomized phase II trial of preoperative chemotherapy with S-1/CDDP with or without trastuzumab followed by surgery for HER2-positive resectable gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301C (Trigger Study). *Gastric Cancer*. 2024;27(3):580-589.
78. Janjigian YY, Al-Batran SE, Wainberg ZA, et al. LBA73 Pathological complete response (pCR) to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): interim results of the global, phase III MATTERHORN study. *Ann Oncol*. 2023;34:S1315-S1316.
79. Shitara K, Rha SY, Wyrwicz LS, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol*. 2024;25(2):212-224.
80. Nie RC, Chen GM, Yuan SQ, et al. Adjuvant chemotherapy for gastric cancer patients with mismatch repair deficiency or microsatellite instability: systematic review and meta-analysis. *Ann Surg Oncol*. 2022;29(4):2324-2331.
81. Pietrantonio F, Miceli R, Raimondi A, et al. Individual patient data meta-analysis of the value of microsatellite instability as a biomarker in gastric cancer. *J Clin Oncol*. 2019;37(35):3392-3400.
82. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1-10.
83. Chao J, Fuchs CS, Shitara K, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol*. 2021;7(6):895-902.
84. Hidaka Y, Arigami T, Osako Y, et al. Conversion surgery for microsatellite instability-high gastric cancer with a complete pathological response to pembrolizumab: a case report. *World J Surg Oncol*. 2022;20(1):193.
85. Ogata T, Narita Y, Misawa K, Hosoda W, Muro K. Marked improvement of oral intake with nivolumab monotherapy in a patient with microsatellite instability-high gastric cancer with insufficient oral intake. *Clin Case Rep*. 2021;9(1):50-56.
86. Al-Batran S-E, Lorenzen S, Thuss-Patience PC, et al. Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. *J Clin Oncol*. 2022;40(suppl 16):4003.
87. Al-Batran SE, Lorenzen S, Homann N, et al. 1429P Pathological regression in patients with microsatellite instability (MSI) receiving perioperative atezolizumab in combination with FLOT vs. FLOT alone for resectable esophagogastric adenocarcinoma: results from the DANTE trial of the German Gastric Group at the AIO and SAKK. *Ann Oncol*. 2021;32:S1069.
88. André T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPIGA phase II study. *J Clin Oncol*. 2023;41:255-265.
89. Pietrantonio F, Raimondi A, Lonardi S, et al. INFINITY: a multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastro-esophageal junction adenocarcinoma (GAC/GEJAC). *J Clin Oncol*. 2023;41(suppl 4):358.
90. Verschoor YL, van de Haar J, van den Berg JG, et al. Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial. *Nat Med*. 2024;30(2):519-530.
91. Hashimoto T, Nakamura Y, Oki E, et al. Bridging horizons beyond CIRCULATE-Japan: a new paradigm in molecular residual disease detection via whole genome sequencing-based circulating tumor DNA assay. *Int J Clin Oncol*. 2024;29(5):495-511.
92. Huffman BM, Aushev VN, Budde GL, et al. Analysis of circulating tumor DNA to predict risk of recurrence in patients with esophageal and gastric cancers. *JCO Precis Oncol*. 2022;6:e2200420.
93. Yang J, Gong Y, Lam VK, et al. Deep sequencing of circulating tumor DNA detects molecular residual disease and predicts recurrence in gastric cancer. *Cell Death Dis*. 2020;11(5):346.
94. Palma DA, Salama JK, Lo SS, et al. The oligometastatic state — separating truth from wishful thinking. *Nat Rev Clin Oncol*. 2014;11(9):549-557.
95. Nagaraja AK, Kikuchi O, Bass AJ. Genomics and targeted therapies in gastroesophageal adenocarcinoma. *Cancer Discov*. 2019;9(12):1656-1672.
96. Sindhu KK, Nehlsen AD, Lehrer EJ, et al. Oligoprogression of solid tumors on immune checkpoint inhibitors: the impact of local ablative radiation therapy. *Biomedicines*. 2022;10(10):2481.
97. ClinicalTrials.gov. A Prospective, Multicentral, Open-label, Randomized, Controlled, Phase III Clinical Trial of Chemotherapy Alone Versus D2

Gastrectomy and Metastasectomy Plus Chemotherapy for Distal Gastric Cancer With One Non-curable Factor. 2018. Available at https://clinicaltrials.gov/study/NCT03399253. Accessed July 9, 2024.
98. ClinicalTrials.gov. Surgical Resection Plus Chemotherapy Versus Chemotherapy Alone in Oligometastatic Stage IV Gastric Cancer — A Multicenter, Prospective, Open-labeled, Two-armed, Randomized, Controlled Phase III Trial. 2017. Available at https://clinicaltrials.gov/study/NCT03042169. Accessed July 9, 2024.
99. ClinicalTrials.gov. A Phase III Study of Consolidative Radiotherapy in Patients With Oligometastatic HER2 Negative Esophageal and Gastric Adenocarcinoma (EGA). 2020. Available at https://clinicaltrials.gov/study/NCT04248452. Accessed July 9, 2024.