Surgery with curative intent for stage IV gastric cancer: Is it a reality of illusion?

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Abstract
Gastric cancer with metastases outside of the regional lymph nodes is deemed oncologically unresectable. Nevertheless, some metastatic lesions are technically resectable by applying established surgical techniques such as para-aortic lymphadenectomy and hepatectomy. At the time of compilation of the Japanese gastric cancer treatment guidelines version 4, systematic reviews were conducted to see whether it is feasible to make any recommendation to dissect both the primary and metastatic lesions with intent to cure, possibly as part of multimodality treatment. Long-term survivors were found among carefully selected groups of patients both in prospective and retrospective studies. In addition, there is a growing list of publications reporting encouraging outcomes of gastrectomy conducted after exceptionally good response to chemotherapy, usually among patients who underwent R0 resection. This type of surgery is often referred to as conversion surgery. It is sometimes difficult to define a clear borderline between curative surgery scheduled after neoadjuvant chemotherapy and the conversion surgery. This review summarizes what we knew after the literature reviews conducted at the time of compiling the Japanese guidelines and in addition reflects some new findings obtained thereafter through clinical trials and retrospective studies. Metastases were divided into three categories based on the major metastatic pathways: lymphatic, hematogenous, and peritoneal. In each of these categories, there were findings that could provide hope for patients with metastatic disease. These findings implied that the surgical technique that we already use could become more useful upon further developments in antineoplastic agents and drug delivery.

KEYWORDS
conversion surgery, gastric cancer, metastasis, multimodality treatment

1 | INTRODUCTION

Gastric adenocarcinoma remains a major health problem worldwide with 738,000 deaths annually. Although surgery is a mainstay of treatment for gastric cancer, indication for gastrectomy is limited to oncologically curable cancer. This is because gastrectomy is associated with relatively high morbidity and mortality, along with considerable decline in quality of life. Cancers, in general, can metastasize through three major pathways: lymphatic, hematogenous, and direct dissemination of cancer cells from the tumor surface.
Gastric adenocarcinoma has been feared as a particularly aggressive disease that has potential to spread through all of these pathways. Lymph node metastasis is the only pattern of disease spread that occurs during the earlier stages so that surgery with adequate lymphadenectomy has been believed to confer not only precise staging but also prognostic benefit. On the contrary, patients who harbor metastases to distant organs are considered to have little hope of cure even if the metastatic sites seem technically resectable, owing to rapid and almost inevitable growth of micrometastases that are likely to exist in such patients. This is in stark contrast with colorectal cancer in which hepatic and pulmonary metastases are often considered for surgery with intent to cure.

The present review attempts to identify situations where an aggressive surgical approach could be indicated for metastatic gastric cancer. There are two types of surgery for metastatic cancer. In one, the metastatic lesions are technically resectable, and a surgeon attempts complete resection of all lesions. The term “technically resectable” is ambiguous, may depend on the philosophy of each surgeon, and is extremely difficult to define. It may be more realistic to give the following as a typical example for each of the metastatic pathways: (i) cancer with a moderate number of swollen (≥1 cm) lymph nodes in the No. 16 a2/b1 regions which can be resected by the conventional technique of para-aortic lymph node dissection such as the one explored in a Japan Clinical Oncology Group (JCOG) randomized trial to be described later in this article; (ii) cancer with a small number of liver metastases (typically ≥3) of a size and location that can be dissected by hepatectomy without exceptional considerations; and (iii) cancer with a small number of peritoneal deposits which can be resected easily at the time of gastrectomy. Patients usually undergo systemic chemotherapy, often in the form of neoadjuvant chemotherapy to eradicate micrometastases and to avoid surgery in a cohort that suffers from rapid progression while chemotherapy is being given. In the other type, patients suffer from multiple metastases that are technically unresectable. Chemotherapy delivered to these patients sometimes results in complete or near-complete response of the metastatic lesion, which could render the primary lesion ± the remains of the metastases resectable. This type of surgery has recently been referred to as conversion surgery. Yoshida et al have recently created a comprehensive classification of gastrectomy for stage IV cancer which takes into consideration the indications for both types of surgery.

2 | LYMPH NODE METASTASIS

Before discussing metastases to various distant organs, it is necessary to discuss the value of lymph node dissection. Relevance of prophylactic lymph node dissection has been discussed thoroughly elsewhere, and various guidelines currently support standard application of D2 dissection to treat resectable advanced gastric cancer. However, cancer can spread beyond the boundary of standard D2 dissection. Thus, more extended lymphadenectomy had been proposed, but a campaign to enlarge the extent of prophylactic lymphadenectomy to include the para-aortic lymph nodes turned out to be a failure in the JCOG9501 trial, a phase III trial in which the survival curve for the para-aortic lymph node dissection group overlapped completely with that for the D2 dissection group.

Patients with metastasis to the para-aortic lymph nodes are classified as stage IV. This denotes that metastases to the para-aortic lymph nodes are considered as distant metastases. Para-aortic lymph nodes in the peritoneal cavity are classified anatomically as a1, a2, b1, and b2 (Figure 1). During the 1980s, the technique for systematic dissection of a2/b1 lymph nodes was established and conducted experimentally in high-volume hospitals throughout Japan. The JCOG9501 trial was conducted based on these techniques, and para-aortic lymph node dissection was carried out safely with mortality and complication rates of 0.8% and 28.1%, respectively. One of the limitations of the trial was that the incidence of pathological para-aortic lymph node metastasis among patients allocated to extended lymphadenectomy was unexpectedly low at 8.5%. In fact, the trial did not include patients who had enlarged lymph nodes in the para-aortic region. Thus, survival benefit of para-aortic nodal dissection cannot be denied among patients who had apparently swollen lymph nodes in the para-aortic region. Sasako proposed a neoadjuvant strategy to this patient cohort as they likely suffer from micrometastases and may benefit from tumor shrinkage. After a series of phase II trials, neoadjuvant chemotherapy with S-1 and cisplatin followed by gastrectomy and D2 plus para-aortic lymph node dissection is considered the current standard of care in high-volume centers in Japan. Para-aortic lymph node dissection in this context denotes systematic dissection of the No. 16 a2/b1 region rather than sampling of apparently swollen nodes, as that was the strategy explored in the JCOG phase II trials. Absence of peritoneal deposits and negative peritoneal washing cytology through staging laparoscopy, absence of metastasis to other organs, and absence of cancer spread to the a1 or b2 regions and mediastinal/cervical lymph nodes have been prerequisites for participation in these phase II trials. Although not clarified in the eligibility criteria, it is likely that only patients with a moderate number of swollen nodes in the No. 16 a2/b1 region were entered into this trial.

Dissection of mediastinal lymph nodes could be indicated and may, in some cases, even be recommended for patients with junctional cancer, given the presence of long-term survivors among patients with metastases to such lymph nodes. Furthermore, patients with para-aortic lymph node metastases beyond the a2 and b1 regions could still be indicated for surgery pending marked shrinkage of these nodes during chemotherapy which, originally, would have been cause for palliation. In such cases, surgeons often carry out limited or standard lymph node station dissection in order to evaluate the histological responses, but do not necessarily dissect all lymph nodes that have been swollen. This type of surgery has recently been referred to as conversion surgery. Although this term has not been defined explicitly, it could be characterized as follows: (i) surgery is not preplanned as in the case of neoadjuvant strategy, but is proposed after exceptional response of the metastatic lesions to chemotherapy; (ii) resection of all metastatic lesions that had
originally been detected is not necessarily required, especially when complete response of such lesions was achieved; and (iii) surgery is indicated when information through imaging studies, laboratory data, and other modalities suggests possibility of R0 resection. There are sporadic reports of long-term survivors among the responders who underwent conversion surgery mainly for, but not restricted to, distant lymphatic metastases in retrospective analyses (Table 1).

Approximately 30% of patients who received chemotherapy underwent surgery. Series with higher incidence of R0 resection were associated with superior survival time.17,18

### 3 | HEPATIC METASTASIS

Gastric cancer cells that enter the bloodstream first enter the portal vein to reach the liver. These cells are considered to sometimes pass through the liver and lung to eventually metastasize to more remote sites such as bone, adrenal gland, and the brain, showing their diversity and that of the microenvironments where they eventually establish themselves as metastases. Anatomically speaking, however, the liver is the most logical and frequent site of hematogenous metastasis from gastric cancer. Liver metastases often emerge as multiple nodules occupying both lobes, sometimes accompanied by other distant metastases, and are usually considered incurable. Thus, hepatic metastases that undergo hepatectomy are carefully selected based on the number and size of metastatic nodules and biological characteristics of the primary cancer.

Adam et al20 analyzed a retrospective series of a large number of resected non-colorectal and non-neuroendocrine liver metastases into three categories, stratified by the 5-year survival rate of the patients who underwent hepatectomy. Gastric cancer was classified into the intermediate group where the 5-year survival rate was approximately 25%. Most reports of hepatectomy for gastric cancer

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**FIGURE 1** Anatomical extent of para-aortic lymph node dissection that was carried out as a part of prophylactic dissection. 16a2 denotes para-aortic lymph nodes distributed between the celiac axis and the lower border of the left renal vein, and b1 denotes those between the lower border of the left renal vein and inferior mesenteric artery.

**TABLE 1** Four retrospective case series looking at conversion surgery after chemotherapy for advanced/metastatic gastric cancer

| First author | Time of accrual | Eligibility | Chemotherapeutic regimen | Indication for surgery | No. of patients | No. of patients who received R0 resection | Rate of R0 resection among all surgeries | MST of patients who received R0 resection | MST of the R0 resected patients |
|--------------|----------------|------------|--------------------------|-----------------------|----------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------|
| Yamaguchi16 | 2001-2013 | cStage IV | Various doublets/triplets | R0 resection possible | 84 | 43 | 51.2 | 30.5 | 41.3 |
| Fukuchi17 | 2003-2013 | Any one of the following: S-1/CDDP or S-1/paclitaxel | R0 resection possible | 151 | 32 | 53 | 47.9 |
| Sato18 | 2002-2014 | cStage IV | S-1/CDDP/docetaxel | R0 resection possible | 100 | 33 | 68.8 | 30.5 |

The fourth series was restricted to patients who underwent intraperitoneal chemotherapy for peritoneal metastases. MST, median survival time; IP, intraperitoneal chemotherapy; mets, metastases; NA, not available.
metastasis are single-institution case series consisting of 20-30 cases accumulated over more than two decades. By systematically reviewing these reports, the Japanese Gastric Cancer Treatment Guidelines committee came to a conclusion that a solitary nodule, lack of other non-curative factors, and favorable stage in terms of cT and cN categories of the primary tumor were among the factors that indicate better prognosis.

More recently, larger case series have been published through multi-institutional studies and combined analysis of data from high-volume hospitals (Table 2) that reported a 5-year survival rate of approximately 30%. Treatment selected in these studies was usually hepatectomy, but the amount of the liver resected varied widely depending not only on the number or size of the lesions but also on the preference of the surgeons. Two of these studies included radiofrequency ablation (RFA) as alternative treatment modalities. As the indication for RFA was limited based on the diameter and location of the metastatic tumors, it is currently impossible to see whether RFA could replace surgery. However, RFA did seem to show efficacy for a well-selected cohort of patients in these studies. Regardless of the details of treatment modalities selected, patients who were indicated for surgery in these studies usually had ≤3 nodules and, in one of the studies, a subset with a solitary nodule apparently had an outstanding outcome. When discussing the number of metastatic nodules, the influence of the evolution of novel imaging modalities cannot be ignored as, again, most of the studies accrued patients over more than a decade. In this respect, one recent single-institution study was convincing because the authors looked only at patients with ≤3 nodules which were invariably diagnosed using enhanced magnetic resonance imaging (MRI). The 5-year survival rate in that study also exceeded 30%. Based on these studies, the Japanese guidelines decided not to deny the possibility of carrying out hepatectomy for those with a “small number” of metastatic nodules.

There are multi-institutional retrospective analyses from European countries, also showing that not all hepatectomies are futile. However, their conclusions tended to be reserved, indicating that a prospective study is needed to justify hepatectomy even in favorable situations. The only consensus between the east and the west is that some form of chemotherapy is needed prior to or after hepatectomy (or gastrectomy plus hepatectomy in cases of simultaneous metastasis) in order to eliminate the micrometastases that are likely to exist. When designing an international prospective trial to explore optimal multimodality treatment for “resectable” liver metastasis, however, the European investigators continue to show prudent attitudes and insist that a control arm to be treated by chemotherapy alone is necessary to confirm the prognostic impact of hepatectomy.

### Table 2

| First author/year | Type of study | No. of cases | Type of metastatic nodules | 5-year survival rate (%) | Prognostic factors |
|-------------------|---------------|--------------|---------------------------|-------------------------|-------------------|
| Oki 201622        | Retrospective | 94           | Solitary: 56 (60%), 2 nodules: 19, 3 nodules: 9, ≥4 nodules: 10 | 42                      | Solitary metastasis, primary tumor > pN2, ≥2 metastatic nodules, primary tumor ≥ T3, Tumor diameter > 3 cm |
| Kinoshita 201523  | Retrospective | 256          | Solitary: 168 (66%), 2 nodules: 44, 3 nodules: 18, ≥4 nodules: 26 | 31                      | Not identified     |
| Guner 201624      | Retrospective | 98           | Solitary: 74 (67%), 2 nodules: 15, ≥3 nodules: 11 | 30                      | Not identified     |
| Tatsubayashi 201725 | Retrospective | 28           | Solitary: 20 (71%), 2 nodules: 7, ≥3 nodules: 1 | 32                      | Not identified     |

MRI, magnetic resonance imaging; RFA, radiofrequency ablation.

### 4 | PERITONEAL METASTASIS

Peritoneal metastasis is considered to occur from cancer cells that are shed from the serosal surface or disseminated during surgical...
manipulation. As meticulous systematic lymphadenectomy has been the standard in cancer surgery for a long time in Japan, locoregional recurrences, especially recurrences to regional lymph nodes that should have been resected, have been considered regrettable and are actually infrequent. Thus, in Japan and Korea, the pattern of recurrence after curative surgery has long been peritoneal dissemination. In addition, there are patients who suffer from peritoneal disease at their first clinical visit, especially among patients with linittis plastica type cancer. Peritoneal deposits are whitish nodules typically seen in the omentum, fatty pads of the transverse colon, mesocolon and peritoneal surfaces adjacent to the stomach. They will eventually spread to all parts of the abdomen, constitute stone-hard nodules, and result in obstruction of the bowel, ureter and biliary tract, causing feeding problems, ileus, hydronephrosis, and jaundice. Massive ascites is another problem observed in a certain subset of patients with peritoneal disease.

In gastric cancer, peritoneal metastases have been deemed incurable even if only a few nodules are found at the time of laparotomy. Furthermore, presence of free cancer cells in the peritoneal cavity detected by cytological examination of the peritoneal washes predicts recurrences as peritoneal carcinomatosis with a high positive predictive value. These characteristics prompted several surgeons to carry out staging laparoscopy for selected patients and in clinical trials to accurately stage patients and avoid futile laparotomy. In addition, as a result of the peculiar pharmacokinetics of systemically delivered anticancer drugs in the peritoneal cavity and lack of lesions that are measurable by imaging studies, peritoneal disease has not been eligible in phase II studies for new drugs in which overall response rates were often used as a surrogate end-point. Taken together, this resulted in paucity of treatment options with evidence for this particular type of metastatic gastric cancer.

Cytological examination of the peritoneal washes obtained at laparotomy or laparoscopy is a useful means of detecting peritoneal disease before a metastatic nodule grows to be macroscopically detectable. Presence of cancer cells, termed CY1, denotes poor prognosis, and CY1 is regarded as equivalent to M1 and P1 (presence of visible peritoneal metastasis) in the Japanese Classification of Gastric Carcinoma. Thus, patients with CY1 status fall into the stage IV category. After some pilot studies, Ishigami et al. conducted successive staged surgery for patients with CY1 cancer in the absence of other non-curative factors. Nevertheless, when the CY1 status is diagnosed at the time of staging laparoscopy, surgery could be postponed and chemotherapy delivered as an initial treatment, so that only patients who responded and were converted to CY0 status at the second staging laparoscopy could be selected to proceed to gastrectomy. Treatments such as i.p. chemotherapy and hyperthermic i.p. effusion chemotherapy (HIPEC) could add further impact, and some clinical trials exploring preoperative HIPEC by the laparoscopic approach and HIPEC at the time of gastrectomy have been conducted for the CY1 population.

Gastrectomy is far less likely to be conducted for patients with macroscopic peritoneal metastasis. Gastrectomy accompanied by total peritonectomy followed by HIPEC has been theoretically proposed as the ideal mode of treatment. Cytoreductive surgery and HIPEC remain to be widely explored for malignancies derived from the peritoneal mesothelioma, appendiceal mucinous neoplasms, and peritoneal metastases of colorectal and ovarian origin, but several researchers decided not to further pursue this approach for gastric cancer because of uncertainty in efficacy despite the high morbidity. It is not practical to expect further exposure to anticancer agents after the classical combination of total peritonectomy followed by HIPEC because of serious adhesions.

However, benefits of i.p. administration of anticancer drugs in terms of pharmacokinetic advantages of higher intratumoral concentrations and less systemic toxicity remain attractive. Randomized trials that explored i.p. chemotherapy in various settings are listed in Table 3. A single i.p. delivery of cisplatin on the day of surgery combined with further systemic chemotherapy did not confer any survival benefit over surgery alone when given in the postoperative adjuvant setting among serosa-positive CY0 patients. Although this result was highly disappointing, repeated i.p. doses of paclitaxel in ovarian cancer aroused interest in the subsequent generation of surgeons. An in vivo model of peritoneal dissemination implied efficacy of paclitaxel given i.p. compared with the same drug given i.v. Pharmacokinetic study of paclitaxel delivered i.p. to patients with malignant ascites showed that the concentration of paclitaxel in the ascites was >2000-fold that of the plasma at 3 hours after the dosage. Safety of i.p. dosage of paclitaxel, once questioned in cases of ovarian resection with colorectal resection and anastomosis, was confirmed in a trial in which i.p. paclitaxel was given immediately after gastrectomy. However, survival benefit of a short series of i.p. doses of paclitaxel prior to the evidence-based systemic treatment was not proven for gastric cancer patients with risk factors for recurrence as peritoneal carcinomatosis (Table 3). This was considered attributable to the lack of systemic effect of single-agent chemotherapy because of the extremely poor transition of i.p. delivered paclitaxel to the plasma.

After some pilot studies, Ishigami et al. conducted successive phase I and phase II trials to establish a combination of S-1, i.e.
TABLE 3  Outcome of patients registered for three prospective randomized trials exploring I.p. chemotherapy for gastric cancer and one randomized trial for ovarian cancer

| Study          | Setting                     | No. of cases (IP vs others) | Eligibility | IP regimen | Control | No. of administrations | Primary endpoint | Hazard ratio (IP vs others) | P-value |
|----------------|-----------------------------|-----------------------------|-------------|-------------|---------|-------------------------|------------------|---------------------------|---------|
| Gastric cancer | Postoperative adjuvant      | 135 vs 133                  | cT4, CY0    | CDDP IP at surgery, 5FU + CDDP, UFT | Surgery alone | Once on the day of surgery | 5-year OS 62.0% (53.7-70.2) | Not reported | .482 |
| INPACT51       | Advanced/metastatic         | 39 vs 44                    | Limis plastica, CY1, P1 etc. | PTX IP | PTX IV | 7 times including the day of surgery | MST 42.3 mo vs 37.7 mo | 1.16 (0.64-2.09) | .628 |
| PHOENIX-GC52   | Advanced/metastatic         | 114 vs 50                   | P1          | S-1 + PTX IV + PTX IP | S-1 + CDDP | Not limited | MST 17.7 mo vs 15.2 mo | 0.72 (0.49-1.04) | .08 |
| Ovarian cancer | Advanced/metastatic         | 205 vs 210                  | Stage III, with no residual mass >1 cm | PTX IV + PTX IP + CDDP IP | Paclitaxel IV + CDDP IV | 6 cycles | MST 65.6 mo vs 49.7 mo | 0.75 (0.58-0.97) | .03 |

These trials suggest importance of repeated exposure and combination with systemic chemotherapy. In the PHOENIX-GC trial, patients were allocated in a 2:1 method.

Figures in parentheses denote 95% confidence interval.

IP, Intra Peritoneal chemotherapy; mo, months; MST, median survival time; OS, overall survival; PTX, paclitaxel.
greater detail compared with the previous version\(^2\) (Figure 2). Queries regarding patients with minimal numbers of metastases in various metastatic categories are led to relevant clinical questions that are answered in the Q&A section of the guidelines by referring to the currently available evidence, as has been described in this review.

6  |  CONCLUSIONS

Surgery could play a part in multimodality treatment for stage IV gastric cancer. It may have a decisive role after neoadjuvant chemotherapy in highly selected cohorts of patients. In other cases, surgery could take on a role of adjuvant treatment in the form of conversion surgery when exceptional responses to chemotherapy are observed. Although the role of surgery cannot be denied, further prospective studies will be needed to establish more explicit indications for surgical treatments in each category of stage IV disease.

DISCLOSURE

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