Review Article

Outcome of secondary gastrectomy for stage IV gastroesophageal adenocarcinoma after induction-chemotherapy

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Abstract: Stage IV gastric cancer represents a therapeutic challenge in gastric cancer treatment. Despite initiation of screening programs almost a quarter of the patients still present with metastatic disease. As palliative chemotherapy and best supportive care concepts were standards in the past, new therapeutical concepts are emerging over the recent years. Advancements in surgical therapy for metastatic gastric cancer revealed promising results over the past 5 years. However the only prospective trial on palliative gastrectomy for metastatic disease could not confirm the promising retrospective data. Therefore multimodal treatment concepts incorporating preoperative chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC) and intraperitoneal (IP) chemotherapy have led to improved response rates requiring reevaluation of conversion surgery. This review summarizes the most promising results from retrospective studies published in the recent past and presents an outlook of ongoing clinical trials.

Keywords: Gastric cancer; stomach cancer; metastatic; chemotherapy; surgery

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Introduction

Despite decreasing incidence, gastric cancer is a common malignancy and demonstrates one of the highest mortality rates among gastrointestinal malignancies. The highest prevalence can be found in Eastern Asian countries like Korea, Japan and China (1). Due to the lack of national screening programs in Western countries a high percentage of patients are presented to surgical oncologists in metastasized stages. A recent analysis from Southern German centers demonstrated that almost a quarter of all patients demonstrate metastases at the time of diagnosis (2). Gastric cancer metastases can be predominantly found in the peritoneum (35–51%), the liver (23–39%), distant lymph nodes (38–57%), lung (9%) and bones (3–8%) (3). Whereas palliative care was applied to these patients in the past without surgical consideration, recent reports revealed promising results when these patients were submitted to surgical resection. These retrospective evaluations demonstrated heterogeneous results and were not able to reveal a significant improvement in terms of overall survival when compared to conservative treatments such as palliative chemotherapy. On the other hand, a recent meta-analysis was able to reveal superiority of surgical resection in the metastasized setting (4). This systematic review demonstrated that median survival reached up to 15 months in the resected group compared to 7 months in the non-surgically treated group. Further, the authors revealed no statistically proven between-study heterogeneity in metastasized patients. The authors also investigated on the effect of additional chemotherapy after surgical resection and were able to demonstrate a significant survival benefit in a subgroup analysis. However the authors did not state if they also respected preoperative chemotherapy

for their analysis (4). Nonetheless these results appear difficult to evaluate, because many different clinical settings were investigated (liver metastasis, peritoneal seeding, bulky lymphatic disease). This may be related to the fact that stage IV gastric cancer was differently characterized in the sixth and seventh UICC definitions (5). Whereas cancer invading adjacent organs together with additional lymph node metastasis or N3 disease was defined as stage IV cancer in the sixth UICC edition, stage IV is defined as proven metastatic gastric cancer only in the seventh edition (6). So far there is only one randomized controlled trial investigating on the role of palliative gastrectomy for non-curative cancer. This Japanese/Korean trial randomized 175 patients to either undergo surgery followed by palliative gastrectomy or to undergo chemotherapy only. However, there was no survival benefit for patients undergoing surgical resection ahead of chemotherapy, so that gastrectomy followed by chemotherapy cannot be recommended for patients suffering from gastric cancer with a single-non-curative factor (7).

Preoperative chemotherapy was originally introduced in order to downsize primarily non-resectable tumors. Results from several randomized controlled trials led to the introduction of standardized neoadjuvant or perioperative chemotherapy for locally advanced gastric cancer (8-11). In recent years several reports revealed that there is a considerate amount of patients almost completely responding to chemotherapy in the metastasized situation rendering curative situations possible, especially since new therapeutic regimens were introduced in clinical practice [Neo-5-FU, leucovorin, oxaliplatin and docetaxel (FLOT), FLOT, etc.] (12,13). This review describes the most recent developments for patients undergoing chemotherapy followed by so called conversion surgery in the metastasized situation and gives an outlook into future developments for this challenging clinical setting.

Peritoneal carcinomatosis, positive cytology

Peritoneal seeding on gastric cancer represents a challenging situation. However numerous analyses were published over the recent years providing important insights for further trials and treatment. Here we review the most promising data on multimodal treatment of patients with peritoneal malignancy without distant metastases.

Positive cytology upon resection is related to decreased overall survival rates and results in almost as poor prognosis as proven peritoneal carcinomatosis. A retrospective study by Aizawa *et al.* investigated on the outcome of patients undergoing chemotherapy for positive cytology and without proven distant metastasis (14). In this analysis 47 patients underwent chemotherapy consisting either of S1/PLF or S1/PLF/docetaxel or 5-FU/cisplatin/paclitaxel after diagnosis of positive cytology. Fifty percent converted to negative cytology in a repeated laparoscopy and a complete resection was possible in 50% of the patients. Interestingly in 20% of the patients an initially negative cytology turned positive upon resection. R0-resection resulted in a significantly improved median survival (30 *vs.* 15 months, P=0.03). Recurrence preferably occurred via lymphatic and venous tumor cell distribution. Despite the promising results for overall survival there was no statistically proven improvement for relapse-free survival (P=0.11). Another interesting analysis by Lorenzen *et al.* demonstrated that cytology conversion occurred in 37% of the cases after neoadjuvant chemotherapy with PLF which was related to improved median overall survival (15). However, 25% of the patients progressed to positive cytology which almost halved overall median survival. The authors therefore concluded that neoadjuvant treatment may be a risky strategy for cytology negative patients.

A prospective phase II study was performed in 25 patients with proven peritoneal seeding or positive cytology by Fujiwara *et al.* (16). Here, patients received neoadjuvant intraperitoneal (IP) chemotherapy consisting of mitomycin C and cisplatin followed by systemic chemotherapy consisting of two cycles of docetaxel, 5-FU and cisplatin. After neoadjuvant treatment, patients underwent another staging laparoscopy and were resected when no macroscopically detectable tumor lesion were found. The resection rate was 88%. Only three patients progressed to an unresectable stage. A major response according to the RECIST criteria was detected in 59% of the patients and 56% of the patients turned out to be negative for peritoneal seeding and cytology upon the second staging laparoscopy. The median overall survival for all patients was 16.7 months. Negative cytology and absence of peritoneal seeding after the neoadjuvant treatment turned out to be significantly related to overall survival with median overall-survival times of 27.1 months. Morbidity and chemotherapy associated toxicity was acceptable in this phase II study.

Okabe *et al.* retrospectively evaluated patients undergoing combined S1/cisplatin-chemotherapy for peritoneal malignancy proven by laparoscopy (17). Response of the peritoneal lesions was investigated in 41 patients. Chemotherapy was applied for two cycles and response

was evaluated according to the RECIST criteria and secondary staging laparoscopy and oncologic gastrectomy was performed. A response rate of 46% was achieved in this cohort and surgical resection was considered feasible in 78% of the patients upon secondary laparoscopy. A complete resection without any proof of residual disease was achieved in 69% of the cases. The median overall survival was 20.4 months and the 3-year survival rate accounted for up to 36%. Those patients undergoing curative resections (R0) demonstrated a median overall survival of 43 months and a 3-year survival rate of 58%. The curability was mainly associated with the grade of peritoneal dissemination which was limited peritoneal seeding adjacent to the stomach (P1) or limited seeding to the distant peritoneum (P2) whereas scattered peritoneal dissemination was unfavourable for achieving a R0 resection in this analysis.

A similar retrospective analysis was performed by Yonemura *et al*. in 2006 (18). Here 61 patients undergoing therapy for gastric cancer with peritoneal seeding were investigated. Patients received neoadjuvant IP-chemotherapy with docetaxel and carboplatin followed by systemic chemotherapy with methotrexate and 5-FU. In 32% of the patients a conversion to negative cytology could be detected. However curative resection was possible in only 20% of all cases, which was related to an improved overall survival time of 20 months compared to 14 months in the non-curative situation. A follow-up study published in 2012 by Yonemura *et al*. reported on 96 patients undergoing two cycles of so called bidirectional chemotherapy consisting of IP chemotherapy with cisplatin and taxotere and oral S1 (NIPS) were subjected to surgery when paraaortic lymph node involvement and distant metastasis were ruled out upon re-staging (19). After calculating the peritoneal carcinomatosis index (PCI) by exploratory laparoscopy patients underwent oncologic gastrectomy together with peritonectomy. Sixty nine percent of the patients conversed to negative cytology after NIPS. Eighty five percent of the patients underwent resection and a completeness of cytoreduction score (CC). CC-0 was achieved in almost 71% of the cases which was related to a significantly improved median survival time (21.1 months for CC-0 *vs.* 8.4 months for CC-1 and higher). Interestingly, patients with a PCI of ≤6 survived longer compared to patients with higher PCIs and histopathologic response. This study is the only one published applying the validated PCI and CC-scoring system proposed by Coccolini (20).

A phase II study evaluating the safety and efficacy of neoadjuvant IP chemotherapy followed by systemic chemotherapy was conducted by Imano *et al*. (21). Upon diagnosis of peritoneal seeding patients received a single dose intraperitoneal chemotherapy with paclitaxel followed by five cycles of systemic chemotherapy consisting of S1+ paclitaxel. Patients underwent secondary staging laparoscopy in case of measurable response as defined by RECIST. Sixty five percent of the enrolled patients revealed response and were transferred to surgery, which consisted of radical D2 gastrectomy and R0 resection was feasible in 97% of the cases. Patients undergoing surgical resection demonstrated significantly longer median survival compared to those patients who were ineligible for resection (29.7 *vs.* 14.7 months). Interestingly, over 20% of the patients, who underwent surgery survived more than 5 years, whereas none of the patients undergoing chemotherapy reached an overall survival of 60 months.

Kitayama *et al.* presented another prospective phase II study of patients undergoing neoadjuvant IP chemotherapy combined with S1 chemotherapy (22). Here 64 patients were enrolled after confirmation of peritoneal seeding by staging laparoscopy. Paclitaxel was administered through an IP port system repeatedly and cytology turned negative in 78% of the cases. However, the number of chemotherapy cycles was not restricted and most patients underwent secondary laparoscopy when RECIST-compliant response was detected. Surgery was considered when distant metastasis were ruled out, cytology turned negative and when peritoneal nodules were reduced or at least non-progressive. Postoperative IP and systemic chemotherapy was continued until progression. Finally 34 patients (53%) were eligible for surgery and R0 resection was achieved in 65% of the cases. Morbidity was comparable to published results and no perioperative mortality occurred. Patients undergoing resection demonstrated significantly longer median survival time (26 *vs.* 12 months). Interestingly, there was no significant survival difference between R0 and R1/R2 resections.

Hepatic metastases

The incidence of synchronous liver metastases in gastric cancer patients was reported to be 2–10% (23). Published data on conversion surgery for patients with synchronous hepatic metastasis is scarce. A recent review by Kodera *et al.* reviewed the results from 17 published articles investigating the role of surgery in gastric cancer liver metastases. The article summarizes data from 515 patients undergoing hepatic resections for gastric cancer metastasis. Surgical

morbidity and mortality accounted for 19–47% and 1.1% respectively. The 5-year survival rates ranged between 0–37% with a median survival time of 9–38 months for all cases. The authors concluded that surgical options should be considered in case of solitary nodules, restriction to one liver lobe, tumor size of less than 5 cm and abundance of further distant metastases. However, it was also noted that the role of perioperative chemotherapy has not yet been evaluated sufficiently. Here we report of recently published retrospective series investigating the role of conversion surgery in hepatic metastases.

A recently published study by Li *et al.* (24) investigated on the outcomes of 49 patients undergoing chemotherapy for synchronous hepatic gastric cancer metastases (HGCM). All subjects underwent chemotherapy consisting of three cycles of paclitaxel/capecitabine before undergoing RECIST-compliant response evaluation. Fifty percent of the patients received D2 gastrectomy together with hepatic resection. Median overall survival was significantly longer for surgically treated patients (20.5 *vs.* 9.1 months). Interestingly survival was worsened after hepatic resection compared to those patients undergoing gastrectomy only (16.3 *vs.* 30 months). This study however had several limitations. The treatment decision was taken by individual MDT evaluation. This is also reflected by the fact that patients were taken to surgery more frequently when response was detected in the CT scans. Further the authors do not state on R0-resection rates and why hepatic resections were not performed in 50% of the cases. Another Chinese analysis (25) investigated the outcomes of perioperative chemotherapy followed by surgery in synchronous liver metastases. Here 114 patients underwent chemotherapy with S1/cisplatin or docetaxel/cisplatin/5-FU (DCF). Seventeen percent of the patients underwent surgery when a potentially curative resection was considered feasible. Surgical resection was related to improved median survival time compared to those patients undergoing chemotherapy only (22.3 *vs.* 5.5 months). The only study undertaken in a controlled setting was published by Li *et al.* (26). This phase I study reports on two cycles of preoperative chemotherapy according to the DCF regimen followed by oncologic gastrectomy and metastasectomy followed by another two cycles of DCF. Only four patients (50%) underwent resection. Due to the limited sample size the authors did not include a comparative analysis between resected and non-resected patients. However, survival appeared to be longer in patients undergoing resection.

Conclusively, data on conversion surgery remains scarce for patients suffering from synchronous hepatic metastases from gastric cancer. From an evidence based point of view conversion surgery cannot be recommended. However, repetitive evaluation and follow-up by a multidisciplinary team appears to be mandatory to identify patients potentially benefitting from combined gastrectomy and metastasectomy.

Multiple locations

In the recent literature several publications exist reporting on the outcomes of different metastatic settings such as bulky lymph nodes, T4b gastric cancer and combined peritoneal metastasis. Here we review the most important publications demonstrating potential benefits for conversion surgery.

A Japanese retrospective analysis reports on the outcomes of 28 patients undergoing systemic chemotherapy for synchronously metastasized gastric cancer (27). The authors included patients with tumors infiltrating adjacent organs (pT4b), involvement of distant lymph-nodes, but also distant metastases to liver and peritoneum. Chemotherapy was not standardized in this series and many different regimens were applied but usually included S1. Surgery was considered individually by multidisciplinary team review upon RECIST-compliant response and technical resectability. Thirty two percent of the patients revealed pT4b cancers, whereas the other patients demonstrated true M1 disease. R0 resection was realized in almost 93% of the patients without perioperative mortality. Almost all patients received S1-based adjuvant chemotherapy. Median survival time after surgical resection was 37 months and the 5-year survival rate was 34%. Another prospective phase II study was published by Satoh *et al.* (28) prospectively investigating 51 patients with gastric cancer staged either cT4N+, cN3, cM1 (hepatic or peritoneal) or positive peritoneal washing cytology. All patients received S1+ cisplatin for two cycles and resectability was re-evaluated. Single incurable factors were found in 47% of the patients and multiple factors in 53% in the preoperative work-up. Eighty six percent of the patients were transferred to surgery and R0 resection was achieved in 59% of the cases. The median survival was 19.2 months. R0 resection and positive cytology as the only incurable factor ahead of therapy were associated with improved overall survival. Although the data seem to be promising it has to be taken into account that only 56% of the patients having undergone surgical resection turned out to be true stage IV gastric cancers, leading to the notion that

there was a considerate amount of over-staging (44%) in the preoperative workup. Another retrospective comparative analysis reports on 34 patients with clinical stage IV gastric cancer undergoing preoperative chemotherapy with either docetaxel/S1 or cisplatin/S1 or docetaxel/cisplatin/S1 (29). Chemotherapy was not standardized and surgery was considered, when RECIST-compliant response criteria were detected. Almost 59% of the patients were transferred to surgery. R0 resections were achieved in 75% of the cases which was related to improved survival rates. This study should be considered with great care because of a strong selection bias from an evidence based point of view. The positive selection of responding patients may have severely confounded the outcome. Fukuchi and colleagues retrospectively investigated the outcomes of conversion surgery in 40 patients (30). Non-curative factors were pT4b cancer, peritoneal seeding, positive cytology, hepatic or distant metastasis. Patients with at least one of those factors underwent systemic chemotherapy with S1/cisplatin or S1/paclitaxel (n=151). Patients were evaluated for response every 8 weeks and considered for conversion surgery when curative surgery appeared to be feasible. Twenty six percent of the patients finally underwent conversion surgery. In 80% of those patients R0 resection was achieved and median survival time of resected patients was 53 months with a 5-year overall survival rate of 43% compared to patients undergoing chemotherapy only (median survival 14 months, 5-year survival rate 1%). There was no significant difference in overall survival among resected patients regarding the chemotherapeutic regimen. Survival was significantly related to only one non-curative factor and R0-resection. The only retrospective analysis investigating this challenging oncologic setting in the Western hemisphere was published by Novotny *et al.* (31). In this analysis 58 patients underwent conversion surgery after induction chemotherapy with cisplatin/5-FU/leucovorin for either distant lymphatic, hepatic, peritoneal or distant metastases. Decision for surgery was undertaken according to clinical response upon multidisciplinary team review. R0 resection accounted for almost 33% of the patients and was related to improved median survival compared to those patients with residual disease (72 *vs.* 12 months). Remarkably, there was a high amount (23%) of long-term survivors (>36 months). This analysis has some important implications, because no comparable series was published in the Western hemisphere. In contrast to the Japanese and Korean experiences the amount of cardia cancers was considerably higher.

Future developments

Despite some promising data regarding conversion therapy on a retrospective scale, prospective randomized controlled trials are almost inexistent. However, several trials have been initiated in various countries in order to generate prospective and reliable data. All trials described here were accessed via the WHO International Trials Platform as of November 2015.

The so called GASTRIPEC trial (NCT02158988) investigates the role of perioperative chemotherapy (epirubicin/oxaliplatin/capecitabine or cisplatin/capecitabine/trastuzumab) followed by cytoreductive surgery (CRS) in limited peritoneal carcinomatosis with or without intraoperative HIPEC (mitomycin C/cisplatin) followed by postoperative chemotherapy. Data will become available by 2020.

A phase II multicentric exploratory single cohort trial in Spain investigates the efficacy of a combined systemic (5-FU) and intraperitoneal (docetaxel/cisplatin) chemotherapy followed by CRS and HIPEC (mytomicin C/Adriamycin) combined with intraoperative systemic 5-FU/leucovorine followed by adjuvant chemotherapy (DCF) in case of complete cytoreduction (CC-0). The primary outcome measure is disease free survival (NCT01342653).

A phase II study from China assesses the R0 resection rate after staging laparoscopy in patients with a PCI <20 [PCI according to Coccolini (20)] undergoing subsequent HIPEC (paclitaxel) followed by three cycles of systemic chemotherapy (paclitaxel/S1) followed by surgical exploration and CRS (if PCI <20) followed by HIPEC and three cycles of systemic chemotherapy (paclitaxel/S1) in order to determine the optimal protocol for conversion therapy in patients with advanced gastric cancer and peritoneal metastasis (NCT02549911).

In China, a new chemotherapeutic regimen (S1/paclitaxel/Apatinib) ahead of surgery investigates the conversion rate in unresectable gastric cancer for any of the following conditions: technically unresectable cancer, paraaortic lymph node metastasis, non-extensive metastasis to liver (not more than three metastatic lesions), limited peritoneal metastasis (cytology positive or limited peritoneal seeding) or Krukenberg tumors followed by adjuvant chemotherapy (three cycles S1/Apatinib). The primary endpoint is the R0 resection rate (NCT02529878).

A Japanese phase II trial assesses the outcome of neoadjuvant docetaxel/cisplatin/S1 in patients with

paraaortic lymph node metastasis proven by CT-scan. The endpoint is the histopathologic response rate after surgery (JPRN-UMIN000006036). The same chemotherapeutic regimen is currently undergoing investigation in a similar phase II trial with the condition of peritoneal seeding (JPRN-UMIN000004932) and bulky lymph node disease (JPRN-UMIN000003052).

In Korea another phase II trial investigates the safety and efficacy of capecitabine/oxalitplatin/lapatinib in patients with limited liver metastases (maximum number 2–5 or maximal diameter <5 cm) and exclusion of distant metastases in HER2 positive gastric cancer (NCT02015169). A similar trial is currently being conducted in China. Here patients with potentially resectable liver metases and HER2-positivitiy without any other metastases are enrolled to receive preoperative chemotherapy consisting of capecitabine/oxaliplatin and trastuzumab ahead of surgery. The primary endpoint is progression free survival (NCT02380131).

An interesting phase III study (NCT02578368) is about to be initiated in Germany investigating the outcomes of conversion surgery in previously untreated patients with limited metastatic disease, defined as single potentially resectable metastatic lesion (i.e., liver metastasis, localized peritoneal seeding, solitary lung metastasis). Here, patients undergo four cycles of 5-FU, leucovorin, oxaliplatin and docetaxel (FLOT). Patients without disease progression will be randomized to receive additional chemotherapy (4–8 cycles of FLOT) or surgical resection followed by subsequent chemotherapy (4–8 cycles of FLOT). The primary endpoint is overall survival. However, results will not become available before 2021.

Conclusively there are several interesting trials generating data on a prospective scale. However, the highest effective therapeutic regimen has not been conclusively defined yet. Further, there is a predominance of Eastern Asian studies which leads to the notion that results from those trials may not be adopted by Western oncologists. Nonetheless potent new drugs may be able to provide a therapeutic advantage for metastasized gastric cancer patients in the future.

Conclusions

Metastatic gastric cancer represents a therapeutic challenge. The presented analyses and mostly retrospective data demonstrate a considerate risk of bias. Almost all of the studies described here originate from Japan, Korea or China, which leads to the notion that Western patients may not benefit from the procedures described here. However, results appear to be promising and could possibly lead to improved survival in this challenging setting, but so far there is no clear evidence which of the approaches discussed here is the most effective. The role of neoadjuvant intraperitoneal chemotherapy for peritoneal seeding has not been evaluated in any phase III trial yet. Further, systematic neoadjuvant chemotherapy has not yet been standardized but the existing data support the notion that S1-cisplatin combined with docetaxel or paclitaxel might be effective regimens in this setting. Neoadjuvant regimens such as PLF, ECF or FLOT have not been evaluated yet as much as the possible influence of HER2-inhibitors. Currently running trials include neoadjuvant intraperitoneal chemotherapy in their setup, but conclusive data is not yet available for clinical practice. A possible role of neoadjuvant HIPEC will have to be finally evaluated in a prospective setting. Response evaluation represents another major problem. It has not yet been properly defined when and how patients should undergo conversion surgery. In peritoneal malignancy, repeated staging laparoscopy appears to be reliable. Here the PCI can be clearly defined and resection might be performed if the cutoff point has not been surpassed yet. The role of surgery in patients with distant metastasis undergoing “neoadjuvant” chemotherapy is unclear from an evidence based point pf view. Response prediction according to RECIST-criteria appears to be unreliable. Nonetheless prospectively randomized trials are urgently needed to introduce conversion surgery in a generally applicable setting. Until then multidisciplinary reevaluation of responding patients is considered to be of utmost importance in order to identify patients who may possibly benefit from conversion surgery.

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Footnote

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