



Results of the REGATTA trial on surgical therapy of limited metastatic gastric cancer: open issues and future perspectives

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Gastric cancer (GC) is the third leading cause of cancer-related death worldwide (723,000 deaths, 8.8% of cancer associated mortality), with regional, etiological differences and the highest prevalence in Asia (1-3). In Western countries most of the patients are diagnosed in advanced stages (up to 80% stage IV) as the cancer remains often asymptomatic or presents with unspecific symptoms (4). Patients with stage III and IV GC have a poor prognosis with 5-year overall survival (OS) rates of 9.2–19.8% and 4.0%, respectively. Treatment in these stages is mainly in palliative intent (5). However, in Eastern countries active screening programs proved to be beneficial and higher percentages of patients are diagnosed in early stages, when treatment can be curative (6). The current standard therapy for early GC is gastrectomy and DII-lymphadenectomy, whereas locally advanced stages require a multimodality treatment approach including surgery combined with perioperative chemotherapy or chemo-radiotherapy (CRT) (5). The cornerstone of the treatment of advanced/metastatic GC remains chemotherapy; in addition, combinational strategies or monotherapy with targeted therapies against Her2 (ERBB2) or VEGFR2 (KDR) were recently introduced and proved to prolong OS (2,7,8). Furthermore molecular analysis of GC has led to new molecularly based GC classifications based on mutation status, gene copy-number changes, gene expression, and DNA methylation data (9,10). Of note, patient stratification to targeted agents or combinational therapies based on molecular signatures will become important as new

therapies like immunotherapy evolve but only subgroups of patients benefit from these novel treatment approaches. The prevalence of Her2 overexpression is only about 10% to 25% (11,12); thus, in the majority of patients chemotherapy and inhibition of angiogenesis or maybe in the future immunotherapeutic approaches are their only options. Therefore, identification of predictive biomarkers for patients' stratification is of utmost importance and should be the aim of future upcoming trials combining molecular testing and targeted therapy approaches.

Advanced stage GC patients experience often side effects from the local tumor growth. Major complications are bleeding, gastrointestinal obstruction or perforation (5). Therefore, palliative surgical approaches such as gastric resection and other non-resectional procedures for stage IV disease have been controversially discussed over the last years (5,13). Gastric resection or non-resectional approaches (e.g., gastric bypass) improved dramatically over time due to advances in peri- and postoperative management of patients and also improvements in patient selection (14). Another open question is the value of metastatic resection in very limited metastatic disease.

Improvements of oncological therapies and close interdisciplinary collaboration led in the recent years to an extension of surgical indications for metastatic disease in different entities. Currently, for esophageal and GC there is still an ongoing discussion on broadening of surgical indications. Mönig *et al.* emphasize the need to reevaluate the value of surgical resection in the frame of multimodal

therapeutic strategies even though the recent guidelines do not recommend surgery for local metastatic GC (15). Overall, different retrospective trials support the hypothesis that certain subgroups may benefit from surgical treatment of metastatic disease in addition to systemic treatment. Potentially systemic treatment can stratify patients into different prognostic groups according to response to systemic chemotherapy. In addition, the FLOT-3-trial could identify a subgroup of patients with metastatic disease with an intermediate prognosis (between localized and diffuse metastatic disease) that may potentially have a benefit from additional surgery. However the data have to be interpreted carefully as the trial is powered to identify a prognostic model for selecting patients treated with systemic chemotherapy and who may also be candidates for surgical intervention. The bi-modal concept has then to be validated in a future randomized trial identifying the optimal candidates for this interventional strategy (16). Prospective controlled trials have to proof if patients with limited metastatic GC benefit from metastasectomy.

The recent study by Fujitani *et al.* published in *Lancet Oncology* (17) addresses the highly relevant question whether gastrectomy in addition to chemotherapy improves survival for patients with advanced GC with a single non-curable factor. This question was addressed for the first time within a prospective randomized phase III clinical trial. This so-called reductive gastrectomy for advanced tumor in three Asian countries (REGATTA) trial was an open-label trial conducted at 44 sites in Japan, South Korea, and Singapore and included 175 patients aged 20 to 75 years, which were randomized between February 2008 and September 2013 to receive chemotherapy alone (n=86) or gastrectomy followed by chemotherapy (n=89). The single noncurable factor was defined as liver, peritoneal, or para-aortic lymph node metastasis. Chemotherapy consisted of oral S-1 at 80 mg/m²/d on days 1 to 21 and cisplatin at 60 mg/m² on day 8 of 5-week cycles. Gastrectomy was limited to D1 lymphadenectomy without resection of metastatic lesions. The primary endpoint was OS. Treatment groups were balanced with regard to baseline characteristics except for primary tumor location; middle-third tumors were more common in the chemotherapy group (57% *vs.* 34%), and upper-third tumors were more common in the surgery-plus-chemotherapy group (34% *vs.* 19%). Peritoneal metastasis was the most common non-curable factor in 75% of all patients. The study was closed for futility in September 2013. OS at 2 years was 31.7% [95% confidence interval (CI), 21.7–

42.2%] in the chemotherapy group *vs.* 25.1% (95% CI, 16.2–34.9%) in the gastrectomy-plus-chemotherapy group. Median OS was 16.6 months (95% CI, 13.7–19.8 months) *vs.* 14.3 months (95% CI, 11.8–16.3 months; hazard ratio =1.09, P=0.70). Grade 3 or 4 chemotherapy-related adverse events occurred more frequently in the gastrectomy-plus-chemotherapy group, including leukopenia (18% *vs.* 3%), anorexia (29% *vs.* 12%), nausea (15% *vs.* 5%), and hyponatremia (9% *vs.* 5%). One death considered related to treatment occurred in each group. The authors conclude that palliative surgery did not improve the OS of the included patients and that according to the REGATTA trial chemotherapy alone remains the standard of care for these patients (17). However some interesting finding could be observed and should be further investigated. Five patients were assigned to chemotherapy and showed during chemotherapy a disappearance of all noncurable factors and could afterwards undergo gastrectomy in curative attempt. These observations raise the question if conversion surgery could be a better strategy to identify patients more likely to benefit from surgery. In general this would necessitate a trial assessing patients receiving chemotherapy in the metastatic setting stratified to continuation chemotherapy versus surgery after achieving therapy response to chemotherapy.

Another ongoing clinical trial that will shed light on these open questions is the gastrectomy with metastasectomy plus systemic chemotherapy (GYMS) *vs.* systemic chemotherapy alone (SA) (GYMSSA) trial (18). The trial design includes a randomization to gastrectomy plus metastasectomy followed by systemic treatment versus systemic therapy alone; patient recruitment has been completed. The endpoint analysis is expected to show the effectiveness of tumor and metastases resection on OS and treatment associated adverse events. In contrast to the REGATTA trial the GYMSSA study aimed a complete resection including all metastatic sites and may therefore show a different result from REGATTA. Results are eagerly awaited.

Important prerequisites for the indication of surgical resection for oligometastatic GC in a multimodal setting are certainly an adequate clinical performance status, limited metastatic disease, that can be completely resected (or in the case of liver metastases ablated) and good response to chemotherapy. The ongoing RENAISSANCE/FLOT-5-trial (19) will clarify whether surgical resection in the frame of a perioperative chemotherapy concept can be superior for patients with oligometastatic GC compared to chemotherapy alone.

Analysis of debulking surgery for GC was unsuccessful,

except when it aimed for R0 resection (20) and therefore the concept of cytoreductive surgery (CRS) receives more attention. Thereby CRS attempts to reduce the neoplastic mass in a manner that other therapeutic strategies can be added such as hyperthermic intraperitoneal chemotherapy (HIPEC) (21). Further advantages of CRS are the reduction of the tumor mass (reduction of resistant cell clones, immunosuppression and metastatic spread), which leads to a better perfusion of the remaining malignant tissue and offers the chance for a better and more complete response to chemotherapy (22). Patient selection is crucial for these highly experimental multimodality therapy approaches which should be carried out by a multidisciplinary group of specialists (anesthesiologists, surgeons, and oncologists) in order to achieve better results and to reduce the high costs related to these procedures and relevant complications.

The results of the REGATTA trial show that the biological behavior of GC is unpredictable and that even oligo-metastatic disease cannot be generalized to one therapy concept. In summary, REGATTA does not completely exclude the possibility of gastrectomy in oligometastatic stages of GC but highlights the necessity of the optimal timing in the setting of a combined treatment approach. Furthermore a better characterization of the patient's prognosis and response to systemic treatment has to be established to identify the subgroups of patients with less aggressive tumor behavior and more likelihood to benefit from surgery. At the moment the GC population clinically still looks very heterogeneous and the probably to benefit from combined approaches including CRS and HIPEC cannot be easily predicted, if at all. This has to be investigated in future trials that will hopefully help to answer some of the unsolved issues. Furthermore, guidelines for treatment of patients with oligometastatic GC should be developed to improve and individualize therapy for this group of patients.

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Footnote

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