



# REGATTA trial: its achievement and the issues unsolved

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In gastric cancer patients with distant metastases, the standard treatment is systematic chemotherapy that targets the circulating cancer cells throughout the body (1). As the life expectancy of such patients is very short, aggressive surgical treatments are considered unreasonable owing to the relatively high risk of postoperative morbidities that may delay chemotherapy. Several studies have shown that primary tumor excision improves the prognosis of these patients owing to favorable short-term outcomes after surgery as well as the reduction in tumor burden; hence, adjuvant chemotherapy becomes more amenable (2). However, whether removal of the primary cancer is beneficial for patients with distant metastases remains unclear.

The REGATTA trial was designed to address this issue. It was the first randomized controlled study to evaluate the role of palliative gastrectomy for advanced gastric cancer with a single non-curable factor (3). However, despite being well-designed as a multi-national multi-center study, it was terminated because of the futility of palliative gastrectomy. Palliative gastrectomy had previously been performed for symptom relief and better enteral nutrition, which are critical for good compliance with chemotherapy. For example, a previous retrospective study performed in Korea concluded that palliative gastrectomy in stage IV gastric cancer with one metastatic site may improve survival, although only by 1.5 months (4).

Two previous studies that evaluated the effect of primary tumor removal in cancer patients with distant metastasis included one of renal-cell carcinoma (5) and another

of colorectal cancer (6). The former study resembled the REGATTA trial, as it was a prospective comparison of patients who underwent surgery plus chemotherapy versus chemotherapy alone, while the latter study was a population-based propensity score-adjusted retrospective study. Both revealed that the removal of primary cancer can improve patients' overall survival.

By contrast, the REGATTA trial showed that the palliative gastrectomy did not affect the patients' survival at all. Moreover, the REGATTA administrators reported that palliative total gastrectomy (TG) was associated with worse overall survival in patients with upper-third lesions. Their findings indicated that the effect of palliative gastrectomy may vary according to the type of surgery. TG is known to have higher risks of postoperative complications than distal gastrectomy (DG) (7,8). According to a study by Lee *et al.* (7), the complication rate of TG was two times higher than that of DG; major complications can result in prolonged hospitalization or fasting, which may delay the administration of chemotherapy. However, since more than half of the enrolled patients in REGATTA trial underwent TG, their results may have been biased considering about 70% of gastric cancer surgeries in Korea and Japan are DG.

Another factor to consider regarding the results of the REGATTA trial is that the employed chemotherapy regimen was S-1 and cisplatin, which is quite common regimen for advanced gastric cancer in Japan (9). Administration of oral medications is heavily influenced by post-gastrectomy complications, which can delay chemotherapy and reduce therapeutic compliance.

Therefore, it is difficult to evaluate the effect of palliative gastrectomy itself. If the chemotherapeutic regimen had included intravenous drugs (e.g., 5-fluorouracil, docetaxel, paclitaxel, and irinotecan), treatment may have been less influenced by post-gastrectomy complications; in such a case, the aim of the study (i.e., the evaluation of the effects of palliative surgery) would not be undermined by its own protocol. Such result would also be strongly pertinent to patients in the western countries, where the standard chemotherapy regimens are administered intravenously (10).

Peritoneal seeding, hepatic metastasis, and para-aortic lymph node metastasis are three of the non-curable factors evaluated in the REGATTA trial. Because they are based on metastasis, they were considered similar, however, each may affect prognosis differently. The recently published study from Sweden reported that the patterns of metastasis in gastric cancer patients differ according to the location of the lesion (11); for example, peritoneal seeding causes seeding-ileus more frequently than the other two factors. Given that abdominal surgery carries the risk of postoperative ileus, patients with peritoneal seeding who were assigned to the surgery group may have been at a higher risk of developing ileus postoperatively than patients with other non-curable factors who were assigned to the chemotherapy-only group. Nevertheless, these three factors were grouped together in the REGATTA trial even though patients with peritoneal seeding were predominant. Subgroup analysis was impossible because the proportions of patient with hepatic metastasis and para-aortic lymph node metastasis were only 9.1% and 13.7%, respectively.

The differences in outcomes between countries cannot be ignored. Japan and Korea have the highest incidences of gastric cancer in the world; many studies on surgical skills, postoperative outcomes, and chemotherapy regimens have been conducted in these two countries. Physicians in both nations have tried to improve clinical outcomes. However, the detailed surgical procedures and the post-surgical managements inevitably differ between countries; such differences may impact the results of the REGATTA trial.

In conclusion, although the REGATTA trial had succeeded in unraveling the long standing clinical question about the role of palliative gastrectomy in stage IV gastric cancer, they also had several significant limitations that ought to be addressed in future studies. A common feature of these limitations is that subjects with different characteristics were included within a single cohort of stage IV gastric cancer patients. Additionally, the one of chemotherapeutics (S-1) was administered orally; this may

have negatively influenced the outcome in the gastrectomy group. Further studies with refined patient cohorts and diversification of the chemotherapy regimens are required in the future.

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