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Oligometastatic gastric cancer: an emerging clinical entity with distinct therapeutic implications

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Abstract: Gastric cancer (GC) remains responsible for a high burden worldwide being the third leading cause of cancer-related mortality. Most of patients present at an advanced stage at diagnosis and are thus candidate to standard chemotherapy resulting in median survival of less than 1 year. Oligometastatic gastric cancer is an increasingly recognized clinical entity characterized by limited metastatic spread that has been showing to benefit from aggressive multimodality strategies encompassing chemotherapy and surgery. The ongoing RENAISSANCE/AIO-FLOT5 (NCT02578368) phase III trial is aimed at evaluating if neoadjuvant chemotherapy followed by surgical resection of the primary tumour and metastases (if suitable) could become the new standard of care for oligometastatic GC. In the meantime, in addition to currently available clinical parameters, the emerging predictive/prognostic role of biomarkers such mismatch repair deficiency/microsatellite instability high status needs to be specifically addressed also in this subgroup of GC to assist in patient selection.

Keywords: advanced gastric cancer; neoadjuvant chemotherapy; oligometastases; surgery; metastasectomy.

Gastric cancer is still a major killer worldwide ranking third as leading cause of cancer-related mortality with 819.000 deaths in 2015 and a fatality-to-case ratio of 70%[1].

Two-thirds of patients develop advanced unresectable or metastatic disease at a some point during their clinical history. In this setting, platinum/fluoropyrimidine-based chemotherapy is the standard of care leading to a median overall survival (OS) of 9-11 months[2] in HER-2 negative disease, which extends to 14-16 months when trastuzumab is added to backbone chemotherapy in HER-2 positive cases[3]. Despite recent advances in the understanding of disease biology and drug development, advanced gastric cancer (AGC) remains an incurable disease[4]. In this scenario, growing evidence has suggested that a subset of carefully selected AGC with limited metastatic spread (so-called oligometastatic) exists that might achieve long-term disease control from a multimodality treatment strategy. In fact, although surgical resection of the primary tumour in stage IV disease has been recently discouraged by REGATTA study[5] and is not routinely recommended except for treating bleeding or obstruction, metastasectomies after neoadjuvant chemotherapy have gained interest following promising results from both clinical trials and real-world experience. In the last years, several lines of evidence have shown prolonged survival for selected patients undergoing liver and lung metastasectomies with promising 5-year OS of 27–37%[6-10] and 31-33%[11-12], respectively. Moreover, a meta-analysis of 16 studies including 1712 patients (of whom 378 patients treated with metastasectomy) reported increased OS at 1 (67%), 3 (32%), and 5 (25%) years for resection of metastases compared with other therapies (32%, 6% and 4%, respectively)[13]. Despite being quite encouraging, these results come from retrospective, uncontrolled and monocentric case series, enrolling mainly Asian patients, thus they have to be interpreted cautiously. In addition, administering neoadjuvant chemotherapy before an aggressive surgical approach could hopefully even result in better outcomes. Indeed, upfront treatment enables early administration of systemic treatment thereby preventing delays in chemotherapy delivery and thus maximizing the chance of benefit from systemic treatment. Still, it represents a tool for patient selection according to disease biology since it allows responsive patients to

proceed to surgery, while avoiding major risks associated to surgical procedure to less or non-responsive ones.

In a recent published article, Carmona-Bayonas and colleagues presented the results of a Spanish nationwide dataset regarding the real-world management of AGC[14]. The authors identified a subset of patients with oligometastatic disease, accounting for roughly 5% (n=92) of the whole population recorded over a decade. These patients showed a longer survival with multimodality strategy including neoadjuvant chemotherapy followed by surgical resection of metastases than without surgery (HR 0.34, 95%CI 0.06-0.80, p=0.021). The median OS was 16.7 months and the 3-year OS was 30.6%, with most of patients disease-free at that time point. This compares very favourably with median OS and 3-year OS from historical trials of fist-line chemotherapy in AGC, that are in the range of 9-11 months and <10%, respectively. Moreover, based on a survey jointly performed by EORTC-JCOG, the preferred option for both resectable synchronous and metachronous liver-only disease turned out to be preoperative chemotherapy followed by gastrectomy and hepatic resection (47.5% of Centres)[15]. Although commonly used in community practice, this approach requires confirmation in large prospective randomized trials to possibly build a new evidence-base standard of care for this clinical subset of AGC. In the AIO/FLOT3 trial, a three-arm, prospective, non-randomized phase II study, Al Batran et al. enrolled onto arm B 60 patients with limited metastatic gastric or gastroesophageal junction adenocarcinoma to receive 4 cycles of FLOT regimen (5-fluorouracil, oxaliplatin and docetaxel) followed by curative/life-prolonging intent surgery (primary tumour and metastases) if a R0 resection or at least a macroscopic complete metastasectomy was deemed feasible and 4 subsequent adjuvant FLOT cycles[16]. Patients in arm B had a single incurable site (e.g. liver with < 5 lesions, Krukenberg tumours, adrenal gland metastases) with or without retroperitoneal lymph nodes metastases, retroperitoneal lymph nodes metastases only, and no diffuse nor symptomatic nor clinically detectable peritoneal carcinomatosis. Arm A and arm C consisted of resectable and extensively metastatic tumours and were assigned to perioperative FLOT (4 cycles before and 4 cycles after surgery) and palliative FLOT, respectively. In arm B, 45% (27) of patients had only

retroperitoneal lymph nodes metastases, while 18.3% (11) had liver-only metastases. Among patients with limited metastatic spread, 36 (60%) went on to surgery with a median OS of 31.3 months, while patients who did not undergo surgery had median OS of 15.9 months. The median OS was higher in arm B (22.9 months) compared to arm C (10.7 months), while in arm A was not yet achieved. Despite the limitations pertaining to a non-randomized trial with a relatively small sample size, AIO/FLOT3 should be regarded as a proof of concept study which set the stage for confirmatory properly design phase III clinical trials, wherein standard first-line palliative chemotherapy is compared to a more aggressive treatment strategy including neoadjuvant chemotherapy and surgical resection of metastases. One such trial, the RENAISSANCE/AIO-FLOT5 (NCT02578368), is actively recruiting patients with the aim of answering all the open questions in this setting and the results are awaited in 2021.

Several issues need in fact to be addressed. First of all, the proper selection of AGC patients more likely to benefit from a combined approach is key to optimize treatment success, while sparing medical and surgical risks to the remaining. Although no standardized definition of oligometastatic GC exists, clinical criteria employed in the AIO studies provide us the reference on which building our clinical decision making. Moreover, younger age (≤ 70 years) patients with better performance status (ECOG PS 0-1), limited number of metastatic sites (< 3 sites), and limited number (≤ 5 lesions), favourable parenchymal location (unilobar) and small size of hepatic lesions have been proposed as positive prognostic factors in patients undergoing metastasectomies[6-13]. However, these findings require prospective validation and it is currently unknown whether they also apply to patients treated with preoperative chemotherapy. Secondly, novel biomarkers, other than clinical parameters, are emerging and might be useful in selecting the optimal candidates to a combined treatment strategy. In resectable GC, mismatch repair deficiency (MMRd) and microsatellite instability high (MSI-H) status have been shown to have a positive prognostic effect in patients treated with surgery alone and a negative predictive value in those who received perioperative chemotherapy[17]. Accordingly, recent evidence points to a positive prognostic role for MSI-H status in surgically treated stage IV AGC[18], though no data are available on the role of MSI status neither in

patients undergoing metastasectomy nor preoperative chemotherapy followed by metastasectomy. In the advance-disease setting, the potential predictive role of MSI status warrants further investigation particularly in light of the suggested benefit of oligometastatic GC from multimodality approach. Moreover, based on promising data on anti-PD1 nivolumab and pembrolizumab in heavily pretreated AGC[19-20], the incorporation of immune checkpoint inhibitors into conventional chemotherapy regimens is currently under investigation both for resectable and metastatic GC and would deserve a particular focus on oligometastatic disease. Indeed in these patients an improvement in anticancer activity might translate in a higher number of patients amenable to potentially curative or life-prolonging intent surgery.

Finally, specific mention also needs to be made to peritoneal carcinomatosis, which is one of the features conditioning the poorest prognosis and quality of life in AGC. Another aggressive multimodality treatment including cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (in addition to systemic treatment) has been tested in this setting. However, to date neither definitive nor convincing efficacy data have been produced, at the expense of increased toxicity with procedure-related morbidity and mortality in the range of 10%-55% and 3%-10%, respectively, in high-volume specialized centres[21]. Trial such as GASTRIPEC trial (NCT02158988) are underway to compare in a prospective randomized fashion cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery in properly selected AGC patients with peritoneal carcinomatosis.

In summary, the concept of “oligometastases” first proposed by Hellman and Weichselbaum in 1995[22] is increasingly showing to fit GC. Oligometastatic GC is indeed an emerging clinical entity with potentially distinct therapeutic implications that has no standard approach thus far. These patients seem to benefit from multimodality treatment strategies including neoadjuvant chemotherapy followed by surgical resection, resulting in intermediate survival outcomes between those of resectable and extensively metastatic GC (Figure 1). More interestingly, there is also hope to achieve not just long-term disease control but also curability at least in a proportion of them. Results of ongoing randomized phase III clinical trials are eagerly awaited

in order to clarify whether an aggressive multimodality approach could become a new standard of care in highly selected patients with oligometastatic GC.

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All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients.

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Figure 1. Treatment plan and survival outcomes according to clinical stage in gastric cancer.

	Locally advanced resectable	Oligometastatic	Metastatic
Clinical definition	T3-T4 and/or N+	M1 with one potentially resectable incurable site	M1 patients other than oligometastatic
Prevalence	30-40%	Unknown	40-50%
Treatment strategy	Perioperative FLOT	Neoadjuvant FLOT followed by surgery ± adjuvant FLOT	Platinum-fluoropyrimidine-based doublet or triplet
Median OS	50 months	31.3 months	9-11 months
3-year OS	57%	NA	< 10%