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EDITORIAL – GASTROINTESTINAL ONCOLOGY

Treatment of Oligometastatic Esophagogastric Cancer: A Spark of Light at the End of the Tunnel

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The treatment of esophagogastric cancer has notably improved during the last decades. In the absence of distant metastasis, 5-year survival rates of about 50% can be achieved by using a multimodal treatment concept.[1,2] Unfortunately, the majority of patients are not eligible for surgery due to the presence of distant metastasis at diagnosis, and up to 50% experience disease recurrence after treatment with curative intent.[3]

Previously, involvement of distant metastasis was considered to be a generalized state of widespread disease with a very poor prognosis, in clear contrast to the status of patients without any evidence of metastatic involvement. These patients have therefore generally been treated with palliative intent consisting of either best supportive care or palliative chemotherapy.

However, during recent decades, the proposed hypothesis has been that the difference between localized and systemic spread of cancer may not be that uncompromising. The concept of oligometastatic disease emerged, a transitional stage between local and metastatic cancer, representing patients with a single metastasis or only few metastases to a single organ.[4]

Although the exact definition and treatment of oligometastasis remains controversial, for several types of cancer consensus has been reached that patients with oligometastatic disease should be treated differently from those with obvious widespread metastatic disease.[5] However, due to the generally aggressive biologic behavior of esophagogastric cancer, the role of treating oligometastatic disease in this case remains controversial, and available literature is limited.

To date, some small retrospective non-randomized studies have suggested that surgical treatment or stereotactic body radiotherapy for oligometastatic esophagogastric cancer may be prognostically advantageous.[6] However, the majority of currently available studies are limited in application due to the heterogeneity of treatment methods within studies and also because the majority focused on patients who underwent local treatment and did not include patients who underwent systemic therapy.

In this issue of the *Annals of Surgical Oncology*, Kroese and colleagues present the results of an excellent cohort study that compared overall survival after local treatment (i.e., metastasectomy or stereotactic body radiation therapy), local treatment with systemic therapy, and systemic therapy only for oligometastatic esophagogastric cancer.[7] The study included 85 carefully selected patients with synchronous or metachronous oligometastatic esophagogastric cancer. Oligometastatic cancer included one organ or one extra-regional lymph node station with three or fewer lesions. Local treatment combined with systemic therapy was associated with a favorable overall survival (median, 35 months) and independently associated with better overall survival than for patients who underwent local treatment alone (median, 17 months) or systemic therapy alone (median, 16 months).

This study is an important next step in evaluating treatment strategies for oligometastatic esophagogastric cancer and confirms that metastatic disease is not necessarily inoperable for some carefully selected patients. Of special interest is the improved overall survival after combined local and systemic therapy compared with that of local or systemic treatment alone. The underlying theory

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may be that systemic therapy can aid in eliminating micrometastatic spread, which may improve disease control when combined with effective local therapy to treat the remaining macroscopic distant disease. An alternative hypothesis for the improved overall survival, however, may be explained by the selection of patients whose tumors demonstrated favorable biologic behavior that responded well to chemotherapy and who therefore were considered for local treatment. In this context, patients with limited metastatic disease in the AIO-FLOT3 trial received chemotherapy first with the aim to identify patients likely to benefit from additional local treatment (i.e., surgery) after evaluation of treatment response.

This study also demonstrated a favorable survival for patients who proceeded to local treatment. However, an evident limitation to determination of the real benefit from combined treatment in the study under discussion and the results of the AIO-FLOT3 trial is the lack of randomization. Regardless, the potential for improved survival outcomes with combined systemic and local treatment for oligometastatic esophagogastric cancer is of significant interest and supports further research in this context.

Another important aspect in this discussion is the lack of a uniform definition of oligometastasis in esophagogastric cancer. Without a clear definition, applicability and generalizability of studies evaluating treatment of oligometastatic cancer remain challenging. In a recent article in the *European Journal of Cancer,* the OligoMetastasis in Esophago-gastric Cancer (OMEC) group addresses this topic with a comprehensive consensus process to develop definitions for oligometastatic oesophagogastric cancer.[8] The process included 47 multidisciplinary tumor boards across Europe and achieved consensus on the definition of oligometastatic disease at diagnosis (1 to 2 metastases in the liver, lung, retroperitoneal lymph nodes, adrenal gland, soft tissue, or bone) and the definition of oligometastatic disease at follow-up evaluation (median systemic therapy of 18 weeks when no progression or progression in size only of the oligometastatic lesion is observed). Although the group to date has not reached consensus on treatment strategies for oligometastatic disease, this a crucial starting point for the applicability and generalizability of future studies and trials analyzing the treatment of oligometastatic esophagogastric cancer.

In conclusion, some patients have demonstrated the potential for long-term disease control with a much brighter future than conventionally thought for metastatic esophagogastric cancer. Especially when local and systemic treatment are feasible, the reported long-term survival is encouraging. Such treatment strategies for oligometastatic esophagogastric cancer currently are further explored in ongoing randomized controlled trials.[9–11] Nevertheless, the current available literature is limited and does not facilitate definite conclusions as to how these patients should be treated. Until definite conclusions are reached, the importance of an experienced multidisciplinary team to tailor treatment for patients with oligometastatic esophagogastric cancer cannot be understated.

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