Current methods of treatment still have a small impact on the survival of patients with localized disease. Improved understanding of the underlying mutations seen in gastric cancer might suggest alternative treatments and ways to better select patients.

Despite a decrease in incidence, gastric cancer continues to be the third leading cause of cancer-related death worldwide.[1] For localized disease, surgery offers the best chance for cure. Despite surgery with curative intent, however, many patients experience recurrences, leading to dismal outcomes. With the goal of improving survival, neoadjuvant and adjuvant therapies have emerged. However, there are significant differences between countries and regions with regard to the management of localized gastric cancer. Dr. Chan and colleagues have provided an instructive article outlining current strategies used in the treatment of localized gastric cancer.[2] We should emphasize that for appropriate staging, a complete evaluation with computed tomography imaging, endoscopy with endoscopic ultrasound, and staging laparoscopy is recommended in all patients with localized disease.[3,4]

In Asia, adjuvant chemotherapy is the recommended treatment following a D2 gastrectomy,[5,6] while in Europe and Canada, perioperative chemotherapy is preferred for resectable disease.[7] Alternatively, in the United States, adjuvant chemoradiation has been popular, based on results from the Intergroup 0116 trial[8]; however, the addition of chemoradiation in this study seems to have compensated for the suboptimal surgery performed prior to study enrollment, raising questions about the role of chemoradiation after extensive lymph node dissection. Nevertheless, important limitations exist with regard to the application of results from one region to another: differences in population, in surgical approach, and in the biology of the disease have been recognized as barriers to the establishment of a consensus regarding the optimal treatment plan. One aspect of care that should be settled quickly is the adoption of D2 gastrectomy as the standard surgery for localized gastric cancer. While results from Western trials support alternate surgical approaches, D2 dissection increases the R0 resection rate and may improve survival in some selected node-positive patients.[9] The extent of lymphadenectomy contributes to the improved survival rates seen in Asian patients compared with Western patients.[5-8] But what is the best approach to adjunctive treatment? Adjuvant or neoadjuvant? A multidisciplinary approach with an experienced team should be the starting point when we treat patients with gastric cancer. Adjuvant chemotherapy is an acceptable treatment in Western patients who have undergone extensive nodal dissection, while chemoradiation should be reserved for patients who have had less than a D1 dissection (even though, by today’s standards, patients should not undergo less than a D1 dissection). The additional survival benefit of adjuvant chemoradiation in the setting of a D2 dissection has not been established; however, the Adjuvant Chemoradiation Therapy in Stomach Tumors (ARTIST) trial suggested that patients with node-positive disease might benefit from additional adjuvant chemoradiation.[10] The ARTIST-II trial will help clarify the benefit of this approach in node-positive disease (ClinicalTrials.gov identifier: NCT01761461). Recent results from the Chemoradiotherapy After Induction Chemotherapy in Cancer of the Stomach (CRITICS) trial showed no significant difference in overall survival between postoperative chemotherapy and chemoradiotherapy.[11] These results suggest that patient survival is similar regardless of postoperative chemotherapy or radiotherapy if adequate surgery was performed. The difficulty of delivering treatment in the adjuvant setting on account of postsurgical recovery makes the neoadjuvant approach reasonable, as therapy in this setting is more easily tolerated. Neoadjuvant strategies include preoperative chemotherapy and chemoradiation therapy. Neoadjuvant treatment has the advantage of tumor downstaging, resulting in improved surgical margins and reduced micrometastatic disease. Perioperative chemotherapy has been the standard practice in Western countries, based on the results of the MAGIC trial, yet only 40% of patients in this trial were able to complete the postoperative chemotherapy of the trial protocol due to increased toxicity and poor tolerance.[7] Should we therefore consider making preoperative therapy
standard? A three-step approach involving preoperative chemotherapy and chemoradiation has demonstrated a high R0 resection rate and pathologic complete response rate, which could translate to an improved survival benefit.[12-14] Additionally, locoregional recurrence rates are significantly decreased in patients who receive preoperative radiation. This suggests that preoperative therapy is feasible and may provide a survival benefit in patients with gastric cancer. Currently, the Australian Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR) trial (ClinicalTrials.gov identifier: NCT01924819) is evaluating preoperative chemoradiation, and the next phase II study (CRITICS II) will evaluate preoperative strategies, including chemoradiation; the results of these trials might change our current standard of care in the West.

Biologic-driven strategies have also been the subject of research, although the results have been rather disappointing in localized gastric cancer. Targeting the human epidermal growth factor receptor 2 (HER2) pathway with trastuzumab had positive results in the metastatic setting, and this approach might offer some promise in the neoadjuvant setting; however, phase III trials are needed to evaluate the targeting of HER2-amplified gastric cancer in this setting.

Current methods of treatment still have a small impact on the survival of patients with localized disease. Improved understanding of the underlying mutations seen in gastric cancer might suggest alternative treatments and ways to better select patients. The targeting of appropriate pathways and the introduction of immunotherapy have marked a new era in the treatment of solid tumors. The positive results seen with immunotherapy in other malignancies have led researchers to investigate immunotherapy in gastric cancer treatment. Trials of checkpoint inhibitors, alone or in combination with other immunomodulating agents, for the treatment of metastatic gastric cancer are currently ongoing (ClinicalTrials.gov identifier: NCT01928394). Preliminary results are promising[15] and provide a proof of concept that the addition of these checkpoint inhibitors in either the neoadjuvant or adjuvant setting may be able to reshape the future of the treatment of localized gastric cancer.

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