Does Chemoradiation Benefit Patients With Gastric Cancer Managed Without Surgery?

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Curative-intent treatment for gastric cancer requires surgical resection with a subtotal or total gastrectomy and regional lymph node dissection, except for in carcinoma in situ or T1a tumors, select cases of which can be managed with endoscopic therapy. Phase III randomized trials published more than a decade ago established 2 standard-of-care approaches for the management of locally advanced gastric cancer. The UK MAGIC trial showed a survival benefit with perioperative chemotherapy consisting of epirubicin/cisplatin/fluorouracil (ECF) compared with surgery alone,¹ and the Intergroup 0116 trial showed a survival benefit with postoperative chemoradiation (CRT) to 45 Gy and concurrent fluorouracil and leucovorin.²

More recently, the CRITICS trial compared these treatment strategies. In patients who received preoperative chemotherapy and adequate surgery, no survival benefit was seen with postoperative CRT compared with postoperative chemotherapy.³ Treatment strategies further evolved after the FLOT4-AIO trial was presented at the 2017 ASCO Annual Meeting. Perioperative ECF was compared with perioperative FLOT (docetaxel/oxaliplatin/fluorouracil/leucovorin), with median overall survival (OS) improving from 35 to 50 months with FLOT.⁴ Thus, perioperative FLOT has emerged as a standard treatment approach for gastric cancer.

Although these and other phase III trials define the optimal management of resectable gastric cancer,¹⁻⁶ data are lacking to guide treatment for the large percentage of patients who do not undergo surgery. An analysis of the National Cancer Database (NCDB), which included >45,000 patients with stage IA–IIIC gastric adenocarcinoma diagnosed between 2004 and 2013, showed that 39% of patients did not receive curative-intent surgery.⁷ Factors independently associated with lack of surgery included type of insurance (not private or Medicare), treatment at a nonacademic hospital, residing in a small urban population or area with low median income, older age, and higher Charlson-Deyo score. Thus, the population of patients with gastric cancer managed without surgery includes those who face challenges regarding access to care, elderly patients, or those with medical comorbidities. Studies evaluating the optimal nonsurgical management of gastric cancer can improve outcomes for these patients.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gastric Cancer recommend CRT or palliative management for patients with gastric cancer who are not surgical candidates.⁸ Data in support of CRT using modern techniques are limited to small, single-arm, phase II studies, including one from China in which 36 patients received 2 cycles of docetaxel/cisplatin/fluorouracil before and after intensity-modulated radiation therapy (IMRT) to 50.4 Gy with concurrent docetaxel.⁹ In this study, 36% of patients experienced a clinical complete response (CR) with this approach.

In the absence of larger studies or randomized data, Li et al analyzed the NCDB to compare survival for patients with localized gastric cancer treated with chemotherapy or CRT, without surgery. In their article, elsewhere in this issue, they describe their cohort of nearly 4,800 patients with nonmetastatic gastric adenocarcinoma diagnosed between 2004 and 2015. Patients with in situ or T1a disease were excluded, as were those who received any type of gastric surgery. Using multivariate analysis and propensity score-matched analysis, an OS benefit was seen with concurrent CRT or sequential chemotherapy and radiation therapy (RT) compared with chemotherapy alone.

The survival benefit Li et al observed with the addition of RT was modest (median OS, 12.3 vs 11.3 months for chemotherapy). RT was delivered to a median dose of 45 Gy, and those who received <45 Gy had decreased survival, suggesting that a palliative dose

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of radiation was less effective at impacting outcomes. In addition, RT was delivered with concurrent chemotherapy in nearly two-thirds of patients and sequentially for the remaining third. Thus, the heterogeneity of the treatment regimen could dilute the impact of RT on patient outcomes, and it is possible that a greater benefit with RT would be seen in the setting of definitive-intent radiation doses and/or concurrent chemotherapy. Furthermore, on subset analysis, the survival benefit persisted in patients with stage I–II disease but was not significant in those with stage III disease. This result is probably because patients with stage III disease are at higher risk for metastatic progression and are less likely to benefit from locoregional therapy.

CRT can be potentially curative for patients with esophageal cancer, yet studies evaluating definitive CRT in gastric cancer are lacking. Phase II studies of preoperative RT for gastric adenocarcinoma have shown promising pathologic CR rates similar to those seen in patients with esophageal adenocarcinoma.^{10,11} In the RTOG 9904 study, patients received 2 cycles of induction chemotherapy followed by CRT to 45 Gy, with concurrent fluorouracil and paclitaxel. A pathologic CR was achieved in 26% of patients, with improved survival in these patients.¹¹

The ongoing phase III TOPGEAR trial is evaluating the addition of preoperative CRT to perioperative chemotherapy in a randomized setting.¹² If pathologic response and outcomes are improved with neoadjuvant CRT, results would support the consideration of CRT in the management of nonsurgical patients as well.

Retrospective large data set analyses have their inherent limitations, the most relevant being the lack of information regarding treatment intent. Nonetheless, the study by Li et al highlights the fact that a large fraction of patients with gastric cancer do not receive surgery, and that the optimal management of these patients should be better studied. Certainly, RT can provide a palliative benefit, including control of bleeding or improvement of obstructive symptoms. This analysis of the NCDB suggests that RT may improve survival outcomes for patients with unresected gastric cancer and that consideration should be given to incorporating local therapy with RT into future clinical trials for patients with unresectable gastric cancer.

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