Editorial

Chemotherapy versus chemoradiotherapy following surgery and neoadjuvant chemotherapy for resectable gastric cancer (CRITICS): an editorial

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Gastric cancer is a malignancy with a strong global distribution, being more common in Asian countries like Japan and South Korea. As such, treatment algorithms differ significantly between the Eastern countries and Western. According to the Japanese Gastric Cancer Guidelines, neoadjuvant therapy is not utilized, even for advanced stage cancers (1). On the contrary, the National Comprehensive Cancer Network Guidelines for gastric cancer recommends perioperative chemotherapy for patients with T2 or greater disease (2). This recommendation was predicated by results of the MAGIC trial, wherein perioperative chemotherapy conferred a survival benefit over surgery alone in resectable gastric cancer (3). The criticism of this trial by some, however, was in the surgical technique, which often did not employ routine use of D1+ or D2 lymphadenectomy. Approximately 40% of each group, perioperative chemotherapy or surgery, underwent a D2 lymphadenectomy. Additionally, the chemotherapy regimen was associated with significant toxicity, with less than 50% completing perioperative chemotherapy as designed, or even initiating adjuvant chemotherapy following surgery (3). Some argue that the utility of perioperative chemotherapy therefore was used to overcome the inadequacy of surgical resection. Nonetheless, this trial established perioperative chemotherapy as standard of care in US and Western countries.

The multicenter Western trial INT-0116 established adjuvant radiation as a modality that conferred survival benefit following curative surgical resection (4). This showed a median survival of 36 months in the chemoradiotherapy group, as opposed to 27 months in the surgery—only group, P=0.005. An updated analysis showed persistent benefit with a more than ten-year follow-up (5). However, this trial was also limited by poor surgical technique; of 552 patients, only 10 percent underwent formal D2 dissection. Most, 54%, underwent D0 dissection (4). A similar argument arose which proposed that adjuvant chemoradiotherapy was utilized to overcome the survival disadvantage imparted by inadequate surgery.

The CRITICS trial, therefore, sought to understand the role of adjuvant radiation following neoadjuvant chemotherapy as well as improved surgical outcome (6). In this Dutch study, 788 patients were randomly assigned 1:1 to receive either the same neoadjuvant chemotherapy regimen or radiochemotherapy following surgical resection and neoadjuvant chemotherapy. Unlike the INT-0116 trial, the majority (90% in the chemotherapy group, 87% in the radiochemotherapy group) underwent D1+ lymph node dissections during surgery. A similar proportion of each group were able to complete treatment as intended by trial design: 46% in the chemotherapy group and 50% in the chemoradiotherapy group. With over 5-year median follow-up, overall survival and event free survival did not significantly differ between the two groups. The authors concluded that adjuvant chemoradiotherapy did not confer a survival benefit over chemotherapy in patients undergoing neoadjuvant chemotherapy and surgical resection.

This trial is similar to the ARTIST trial in that the study

population had undergone adequate lymphadenectomy during surgery; in ARTIST, groups were then randomized to either six cycles of capecitabine and cisplatin, or two cycles of adjuvant chemotherapy followed by chemoradiotherapy and then an additional two cycles of chemotherapy (6). No significant difference was seen in either disease free survival or overall survival between groups. A notable difference between ARTIST and CRITICS, however, is that CRITICS incorporated the neoadjuvant approach prior to initiation of chemoradiation.

In an era where newer chemotherapy regimens such as FLOT (docetaxel, oxaliplatin, fluorouracil/leucovorin) (7) have become available and have demonstrated better tolerance and greater efficacy than the cisplatin based regimens, the question of whether adjuvant radiation therapy is beneficial in the setting of these highly effective chemotherapy regimens remains. The premise of radiation is to cover the nodal drainage basin at risk and often the proximal or distal margin, depending on the location of the primary tumor. Since surgical technique has become standardized, to include a D1+ or modified D2 lymphadenectomy, inadequate lymphadenectomy has become less common (8). Utilization of radiation to overcome the effect of inadequate lymphadenectomy therefore is much less of an indication. With positive margins following surgery, radiation may be beneficial, but this would constitute the minority of patients. Given the poor tolerance of adjuvant radiation (50% completed treatment as designed in the CRITICS trial), and the lack of understanding of its benefit in those undergoing neoadjuvant chemotherapy and optimal surgery, it would seem the benefit of adjuvant radiotherapy is imparted only to those with positive margins or inadequate lymphadenectomy.

The role of neoadjuvant radiation is also relatively unexplored. Several small studies have been published which show that neoadjuvant radiation is well tolerated and may lead to improved locoregional control (9,10). This may be a beneficial modality in patients with locally advanced, T4 disease and in those with bulky lymph nodes; however, further study is needed to elucidate the true survival benefit of neoadjuvant radiation in this group.

Understanding the CRITICS trial in the context of other trials and clinical practice remains confusing, without clear indication regarding what the optimal multidisciplinary approach should be. However, the optimal surgical strategy has clearly been shown to include D1+/D2 lymphadenectomy, and the optimal oncologic strategy has clearly been shown to include neoadjuvant chemotherapy. What remains to be determined, and what is not answered by any of the adjuvant radiation trials, is whether radiation confers a survival benefit in this group of patients. In those who have undergone neoadjuvant chemotherapy, with good response, optimal surgery with negative margins and D1+/D2 lymphadenectomy, radiation may not confer any survival benefit and may be a source of toxicity. However, only future trials evaluating radiation in those who have undergone modern, effective chemotherapy, with optimal surgery, can answer this question.

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