Commentary

Impact of pathologic tumor response in the treatment of gastric cancer

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The treatment of gastric cancer in the U.S. and Europe has largely been affected by trials demonstrating improved survival with perioperative treatment with chemotherapy. As such, assessing the pathologic tumor response to such treatment may provide important information as to the efficacy of neoadjuvant treatment, and several systems have been established to grade the pathologic response. Currently, however, no defined treatment strategy exists for how to treat patients post-operatively with poor tumor response. The question remains: should patients with a poor tumor response to neoadjuvant therapy undergo a different adjuvant therapy strategy?

The treatment of gastric cancer has undergone significant evolution and now mirrors strong geographic preferences. Treatment paradigms in Eastern countries, such as South Korea, Japan and China favor surgery up front, even for advanced cancer (1). Contrary to this approach, the U.S. and Europe favor administration of neoadjuvant chemotherapy for all advanced cancers (T2 disease or greater), driven largely by the results of the MAGIC trial, which found a survival benefit when patients received perioperative chemotherapy (2). In this trial, 503 patients were randomly assigned to perioperative treatment with epirubicin, cisplatin and 5-fluorouracil versus surgery alone; the perioperative chemotherapy arm demonstrated improved overall and progression free survival (2). Critics of the MAGIC trial often emphasize the suboptimal surgery performed, with low rates of D2 lymphadenectomy in the two arms; additionally, only approximately 40% of patients completed all six planned chemotherapy cycles. Nonetheless, this study was pivotal in establishing a new algorithm of care, as conveyed by comprehensive cancer care guidelines, such as the US National Comprehensive Care Guidelines for cancer (NCCN) (3).

Because neoadjuvant therapy has been adopted widely in the US and Europe, effects of chemotherapy on the tumor, as seen radiographically and, more recently, pathologically, have been reported. In a recent study published in the *Journal of Clinical Oncology*, 330 patients from the MAGIC trial (171 from surgery alone and 159 from the perioperative chemotherapy arm) were evaluated for tumor regression grade (TRG), lymph node status and survival (4). TRG can be reported using a number of grading schemes; however, the premise remains similar, whereby evidence of fibrosis or estimated percentage of residual tumor is used to grade a tumor's response to neoadjuvant therapy (5). The authors used the Mandard system and dichotomized the group into responders, TRG 1 and 2, and non-responders, TRG 3, 4 and 5 (4,6). Median survival was not reached for the chemotherapy-treated TRG 1 and 2 patients, and 5-year overall survival was significantly improved over the TRG 3, 4, and 5 group, P=0.02. However, in multivariable analysis including lymph node status and TRG, only lymph node metastases independently predicted overall survival (4).

Importantly, the same concern regarding surgical adequacy is raised in this cohort, with only half of patients with >15 lymph nodes dissected, a number recommended by the NCCN clinical practice guidelines (3). Additionally, this study reports the TRG as measured independently by two pathologists; the interobserver agreement was not strong, kappa =0.64, which increased to 0.7 when considering the dichotomized groups. For clarity, a kappa of 1.0 would demonstrate 100% agreement. This suggests that there is some variability within the assessment of the grade, even when considering two larger groupings.

Smaller, single institution studies have been performed, evaluating the prognostic impact of histologic grading following neoadjuvant chemotherapy. A total of 168 patients treated at Memorial Sloan-Kettering Cancer Center underwent neoadjuvant chemotherapy followed by gastrectomy and D2 lymphadenectomy, with splenic preservation when possible (7). Although a histologic response ≥50% demonstrated improved disease specific survival on univariate analysis, this did not retain significance when considering factors such as perineural or vascular invasion or presence of positive lymph nodes, again confirming the poor prognosis of positive lymph nodes following neoadjuvant chemotherapy (7). Additionally, only a small percentage of patients were observed to have significant histologic response, with two thirds of patients showing a response <20%.

Several other studies have also demonstrated similar findings, with low percentages of patients demonstrating significant pathologic response, with few viable cancer cells remaining (8,9). TRG was found to be predictive of survival in patients treated with perioperative etoposide, doxorubicin, and cisplatin, although tumor size and lymphatic invasion had a stronger impact (8); in patients treated with epirubicin, cisplatin, 5-fluorouracil chemotherapy, only completion of perioperative chemotherapy was found to be independently predictive of survival (9). Our own investigation into this question also did not find that TRG was an independent predictor of survival; however, post-therapy positive lymph nodes were associated with worse survival (10).

Intuitively, a poor TRG, or little regression in the pathologic specimen, would suggest ineffective neoadjuvant treatment. This would lend support to changing the chemotherapy regimen given in an adjuvant fashion. However, this paradigm of treatment has not been adopted, likely because the trials showing efficacy of perioperative chemotherapy were designed to include the same chemotherapy regimen pre and post-surgery. The recommendation to continue with adjuvant chemotherapy notwithstanding, a third of patients may not go on to receive any adjuvant therapy (11). Some will receive lower doses of the prescribed regimen or perhaps a regimen with omission of a particular agent. Administration of adjuvant therapy, however, strongly contributes to the survival benefit of perioperative chemotherapy (11). For those in robust conditions following neoadjuvant chemotherapy and optimal surgical resection with a modified D2 lymphadenectomy and adequate lymph node retrieval, the question remains: what is the optimal treatment strategy for them?

This is a question that would be best answered in the context of a clinical trial. Because previous trial designs have not allowed for the possibility of changing to alternate treatment strategies in the post-operative course, a design in which a poor TRG found on final pathology allows for changing adjuvant therapy to a regimen not given neoadjuvantly seems optimal. Despite this, advanced disease with lymphovascular invasion would suggest that even with neoadjuvant treatment and optimal surgery, an aggressive gastric cancer has a natural history that defies currently available treatment.

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Footnote

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