EDITORIAL

The Real Estate of Gastric Cancer Induction Therapy: Location Versus Intrinsic Molecular Architecture

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Midstage gastric cancer, although deemed resectable, imparts considerable survival hazards as a result of postoperative disease recurrence. Although local and regional disease control are frequently, but not always, feasible via R0 resection and extended lymphadenectomy, operative treatment cannot affect the extraregional recurrence risks that specifically result from hematogenous (visceral) and transserosal (peritoneal) progression. Several approaches to perioperative adjuvant therapy of gastric cancer have shown benefits in postoperative survival, including postoperative chemoradiation, postoperative systemic chemotherapy, postoperative intraperitoneal chemotherapy, and perioperative systemic chemotherapy.^{1–5} Despite, or perhaps because of, these variable approaches, we have no single standard of adjuvant therapy as of today. Preoperative induction therapy is of particular interest, as it can diminish the disease extent resulting in greater R0 rates; it also provides response assessment with affiliated prognostic implications, as major primary tumor responses have been associated with superior survival.^{6,7} In the current issue of *Annals of Surgical Oncology*, Reim et al.⁸ present data from a high-volume center's longstanding experience with preoperative chemotherapy of gastric cancer. Postoperative outcomes are superb and confirm the center's preeminent status of excellence. The specific findings suggest that adenocarcinomas of the esophagogastric junction (AEG) were more likely to respond to preoperative therapy than gastric cancers of the remainder of the stomach (GC). The authors conclude that this may help identify patients who benefit from preoperative therapy. Data from a large patient cohort such as that reported by Reim et al. deserve to be carefully analyzed and assessed

for their impact on the discussion regarding preoperative adjuvant therapy, even when based on a retrospective analysis. What can we learn from this experience, and are the findings sufficient to answer questions we have in our current approach to midstage gastric cancer?

Location of the primary tumor within the stomach has long been known to carry prognostic information; resection of proximal cancers of equal pathologic stage has resulted in lower survival than distal lesions.^{9,10} Should intragastric location now also be considered as predictor for the likelihood of induction therapy response or benefit, perhaps to the extent of not offering GC lesions preoperative cytotoxic therapy? We are not so certain about the latter aspect. Increasing evidence suggests that we can consider gastric cancer a spectrum of different diseases on the basis of identifiable molecular genetic mechanisms with variable biologic behavior and degrees of therapeutic susceptibility.^{11–13} In light of the complexity of molecular and biologic mechanisms at work, it almost appears too crude to be able to classify gastric cancers within merely two anatomic location groups and expect the response rates to follow suit. In the data presented, lesions in the GC cohort were more frequently advanced (by T category), poorly differentiated, and of nonintestinal type; somewhat surprisingly, more than 20 % of patients overall underwent resection despite M1 disease extent. Does the combination of these adverse prognostic factors within the GC group explain the lesser response rate compared to the AEG cohort, and is the intragastric location therefore a mere surrogate for this unfavorable constellation? For example, the phenotypic Lauren classification, a useful prognostic parameter, has also been linked to induction cytotoxic therapy responses, with complete response rates of 53 % for intestinal and 28 % for nonintestinal tumor.¹⁴

How do the Munich data compare to other studies that have helped establish a role for chemotherapy for gastric cancer, irrespective of the intragastric tumor location?

The MAGIC trial did show a clear overall survival benefit to perioperative (primarily preoperative) ECF therapy, although only around 25 % of patients with AEG were part of that study.⁵ Even postoperative chemoradiotherapy has demonstrated treatment-related benefits throughout various gastric cancer location subgroups, with approximately 20 % of patients in the Intergroup trial diagnosed with cardia lesions.¹ We would be reluctant to abandon the MAGIC strategy at this stage on the basis of the data provided, or apply the approach selectively on the basis of intragastric location. In the series of Reim et al., only 27 of 551 patients received ECF, and seven different chemotherapy combinations were administered over 20 years, albeit all platinum containing. It is unclear how long the preoperative therapy was administered, but heterogeneity is suspected. Previously, the Munich group has made significant contributions regarding the metabolic response to induction therapy as predictor of subsequent histopathologic response and improved survival.^{14,15} This has spawned an approach as applied in the MUNICON trial, in which patients with no metabolic response after 14 days of induction therapy would undergo resection rather than prolonged chemotherapy.¹⁶ How many patients in the current series underwent metabolic response assessment with which results, and how many received abbreviated therapy? Is the primary tumor histopathologic response under these conditions an appropriate surrogate for the “MAGIC-type” chemotherapy benefit, or is there a survival benefit to patients via extraregional micrometastasis control even when the local tumor shows little response to the treatment administered preoperatively?

We interpret the implications of this study and the data provided in three ways. Firstly, the authors confirm that responses to induction therapy, especially complete pathologic responses, are linked to superior survival results, as demonstrated earlier.^{6,7} In addition, responses appear to be associated with stage, at least for AEG lesions. Searching for predictive governors of response, therefore, has become an important therapeutic planning objective, not only for gastric cancer. We believe that these governors are identifiable through molecular pharmacogenomic analyses of the primary tumors (or within the germline), and that these results will provide sufficient predictive detail to individualize preoperative therapy to the point of maximum response achievement in the future. If we were to gamble, we would expect intragastric location to fall off the predictive formula as a result of the emergence of intratumoral molecular parameters of cytotoxic agent sensitivity or genetic polymorphisms of regulatory gene products.^{17,18} Secondly, the fact that the GC primaries were less likely to respond than AEG cancers should not be interpreted to mean that the GC patients saw no benefit and the AEG patients did; it just appears that the benefit may have been

greater in the AEG patients. In neither group is the response rate such to rest our feathers on. Therefore, thirdly, the study supports the perceived need for protocol-based efforts with more specific treatment approaches, rather than routine or indiscriminant use of a certain therapy regimen. Irrespective of whether intragastric location or (more likely) molecular architecture guide this process of navigating the gastric cancer estate in the future, the dream of appropriately individualizing therapy for gastric cancer can become a reality.

REFERENCES

1. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725–30.
2. Neri B, Cini G, Andreoli F, et al. Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow-up. *Br J Cancer*. 2001;84:878–80.
3. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol*. 2011;29:4387–93.
4. Yu W, Whang I, Suh I, Averbach A, Chang D, Sugarbaker PH. Prospective randomized trial of early postoperative intraperitoneal chemotherapy as an adjuvant to resectable gastric cancer. *Ann Surg*. 1998;228:347–54.
5. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
6. Lowy AM, Mansfield PF, Leach SD, Pazdur R, Dumas P, Ajani JA. Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer. *Ann Surg*. 1999;229:303–8.
7. Mansour JC, Tang L, Shah M, et al. Does graded histologic response after neoadjuvant chemotherapy predict survival for completely resected gastric cancer? *Ann Surg Oncol*. 2007;14:3412–8.
8. Reim D, Gertler R, Novotny A, et al. Adenocarcinomas of the esophagogastric junction are more likely to respond to preoperative chemotherapy than distal gastric cancer. *Ann Surg Oncol*. doi: 10.1245/s10434-011-2147-8.
9. Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the “different disease” hypothesis. *Cancer*. 2000;88:921–32.
10. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large U.S.-population database. *J Clin Oncol*. 2005;23:7114–24.
11. Kim B, Bang S, Lee S, et al. Expression profiling and subtype-specific expression of stomach cancer. *Cancer Res*. 2003;63:8248–55.
12. Tay ST, Leong SH, Yu K, et al. A combined comparative genomic hybridization and expression microarray analysis of gastric cancer reveals novel molecular subtypes. *Cancer Res*. 2003;63:3309–16.
13. Tan IB, Ivanova T, Lim KH, et al. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology*. 2011;141:476–85.

14. Ott K, Fink U, Becker K, et al. Prediction of response to pre-operative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. *J Clin Oncol.* 2003; 21:4604–10.
15. Ott K, Herrmann K, Lordick F, et al. Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study. *Clin Cancer Res.* 2008;14:2012–8.
16. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol.* 2007;8:797–805.
17. Baek SK, Kim SY, Lee JJ, Kim YW, Yoon HJ, Cho KS. Increased ERCC expression correlates with improved outcome of patients treated with cisplatin as an adjuvant therapy for curatively resected gastric cancer. *Cancer Res Treat.* 2006;38:19–24.
18. Keam B, Im SA, Han SW, et al. Modified FOLFOX-6 chemotherapy in advanced gastric cancer: results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. *BMC Cancer.* 2008;8:148.