Editorial

Pathologic tumor response to neoadjuvant chemotherapy in gastroesophageal cancer: what does it mean?

Toshiyuki Kosuga, Daisuke Ichikawa, Eigo Otsuji

Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

Correspondence to: Daisuke Ichikawa, MD, PhD. Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto, 602-8566, Japan. Email: ichikawa@koto.kpu-m.ac.jp.

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Surgical resection of the primary tumor and regional lymph nodes is the most effective method to cure resectable gastroesophageal cancer; however, the cancer often recurs even after curative resection. Therefore, multimodal therapeutic protocols, such as perioperative chemotherapy or chemoradiotherapy, are increasingly employed to improve the treatment outcomes. Since the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated the survival benefits for patients with preoperative and postoperative chemotherapy with epirubicin, cisplatin and infused fluorouracil (ECF) when compared with surgery alone (1), perioperative chemotherapy is the recommended standard of care for resectable gastroesophageal cancer especially in Europe. However, despite the improvement of 13 percentage points in survival rate compared with surgery alone, 5-year overall survival (OS) rates for patients in the perioperative chemotherapy arm in the MAGIC trial remained at 36.3%. Given that a considerable number of patients relapse and die of their cancer even after current perioperative chemotherapy plus resection, identification of prognostic factors, such as pathologic response to chemotherapy or molecular biomarkers, is desired to develop more promising treatment strategies especially for patients at higher risk for recurrence. However, previously published studies in this field were all retrospective, usually performed with single-center nonrandomized cohorts, used a variety of different tumor regression grading (TRG) systems, and lacked a surgery-alone control group. Therefore, no prognostic marker is currently available beyond standard pathologic TNM staging for patients with gastroesophageal cancer who receive neoadjuvant treatment.

In a study recently published in *Journal of Clinical Oncology*, Smyth and colleagues aimed to identify independent prognostic factors with special emphasis on pathologic response and lymph node status after neoadjuvant chemotherapy for patients with resectable gastroesophageal cancer treated in the prospective randomized phase III trial (the MAGIC trial) (2). Representative blocks with primary tumor or complete pathologic response were chosen by local pathologists and were collected centrally. Three hundred thirty patients (171 from the surgery-alone arm, 159 from the chemotherapy-plus-surgery arm) had tissue available for TRG, representing 70% of patients who underwent surgery within the MAGIC trial. Pathologic regression was assessed by two independent pathologists using the Mandard TRG system as follows (3): TRG 1 (complete regression/fibrosis with no evidence of tumor cells), TRG 2 (fibrosis with scattered tumor cells), TRG 3 (fibrosis and tumor cells with dominant fibrosis), TRG 4 (fibrosis and tumor cells with a dominance of tumor cells), and TRG 5 (tumor without evidence of regression). As the survival of patients with TRG 1 and 2 was similar, the data set was dichotomized into two groups: TRG 1 or 2 (TRG 1–2) versus TRG 3, 4, or 5 (TRG 3–5). The 5-year OS rate for chemotherapy-treated patients with TRG 1–2 was 58.8%, whereas that for chemotherapy-treated patients with TRG 3–5 was 28.9%. Univariate analysis, including age, sex, performance status, site of primary tumor, TRG, and lymph node status, demonstrated that both pathologic response and lymph node status were significantly correlated with OS in chemotherapy-treated patients [TRG 3–5: hazard ratio (HR), 1.94; 95% CI, 1.11 to 3.39; P=0.021; lymph node metastases: HR, 3.63; 95%

CI, 1.88 to 7.00; P<0.001]. On the other hand, multivariate analysis, including TRG and lymph node status, performed in 110 patients for whom all clinical-pathologic information were available demonstrated that lymph node status, but not pathologic response, was the only independent predictor of OS in patients after neoadjuvant chemotherapy in the MAGIC trial (TRG 3–5: HR, 1.32; 95% CI, 0.69 to 2.52; P=0.411; lymph node metastases: HR, 3.36; 95% CI, 1.70 to 6.63; P<0.001).

Considering that a perioperative regimen of ECF decreased tumor size and stage, and hence, significantly improved OS in the MAGIC trial, how can we best explain the lack of prognostic significance of pathologic response on survival in this study? From a statistical point of view, the incidence of lymph node metastases was significantly higher in patients with TRG 3–5 than in those with TRG 1–2, and this correlation may be one of the responsible factors for the lower relevance of pathologic response in multivariate analysis. Although patients with TRG 1–2 in the primary tumor may have high T categories (ypT), the correlation between TRG and ypT was not shown in this study. However, prognostic impact of pathologic response in the primary tumor was not independent of pathologic lymph node status, which was the only independent predictor of survival in patients treated with chemotherapy. As there are no independent prognostic effects of pathologic response in the primary tumor, the survival benefits of perioperative chemotherapy in the MAGIC trial may be due to a high R0 resection rate resulting from down-sizing and down-staging of the tumor, and a good control of micrometastatic cancer cells beyond the extent of the surgical field. Indeed, in the MAGIC trial, cancer recurrence occurred less frequently at both local and distant sites in the chemotherapy-treated arm than in the surgery alone arm. As lymph node status was the only independent prognostic factor, adequate lymph node dissection is essential for accurate staging and prognosis prediction; however, D2 was actually performed in only 42.5% of the chemotherapy-treated patients in the MAGIC trial.

Currently, several systems have been designed for the assessment of pathologic tumor regression in the primary tumor, but it is contentious as to which system can accurately reflect chemotherapeutic effects and OS for patients with gastroesophageal cancer. In the study by Smyth *et al.*, the Mandard system was adopted for the assessment of TRG, which is the most widely used system in gastroesophageal cancer. However, they could not find the value of pathologic response in the primary tumor as an independent surrogate for the efficacy of neoadjuvant chemotherapy and survival outcomes. In the Mandard system, because only a representative block, including the main residual tumor, is chosen for the assessment, if the underlying cancer demonstrates heterogeneity of response to chemotherapy, then the assessment would be biased toward nonresponsive. Regarding another evaluation system for pathologic response, the Becker *et al.* system (which was designed specifically for assessment in chemotherapy-treated patients with gastric cancer) requires review of the entire tumor bed, which was not available for all MAGIC specimens (4). In the largest previous uncontrolled study analyzing prognostic factors for 850 patients neoadjuvantly treated for gastroesophageal cancer, pathologic response was graded according to the Becker *et al.* system; however, this study also demonstrated in multivariate analysis that ypTNM stage, R category, and complications, but not pathologic response, were independent prognostic factors (5). Taken together, regardless of the way of assessment, pathologic response in only the primary tumor cannot independently reflect chemotherapeutic effects or survival outcome. Pathologic response in metastatic lymph nodes or the correspondence between clinical and pathologic N stages may have some prognostic information; however, few studies have answered this question.

Smyth *et al.* also created a statistical model containing four groups of chemotherapy-treated patients: (A) ypN0 and TRG 1–2 (node-negative responders, n=15); (B) ypN+ and TRG 1–2 (node-positive responders, n=12); (C) ypN0 and TRG 3–5 (node-negative nonresponders, n=19); and (D) ypN+ and TRG 3–5 (node-positive nonresponders, n=64). The 5-year OS rates for groups A, B, C, and D were 66.0%, 50.0%, 71.8%, and 16.2%, respectively. Interestingly, at least for us, node-positive responders (group B) had survival outcomes superior to node-positive nonresponders (group D), although TRG had no independent prognostic impact in multivariate analysis. However, in this study, the majority of patients were categorized as nonresponders (75.5%), particularly node-positive nonresponders (58.2%). Therefore, an addition of radiation to neoadjuvant chemotherapy may increase local response rates, and improve survival outcome; however, a recently published meta-analysis did not demonstrate that neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy for the treatment of adenocarcinoma of the esophagus (6). However, node-positive nonresponders after preoperative ECF are candidates for postoperative therapies with a noncross-resistant chemotherapeutic

regimen because of their poor prognosis, and only future randomized trials can determine whether these high-risk patients benefit from treatment with a different regimen.

Molecular biomarker abnormalities as well as pathologic response may be important for tumor chemo-sensitivity, and serve as a stratification criterion for tailored postoperative treatment in future studies. In the study by Smyth *et al.*, the effects of several molecular abnormalities, such as mutations in *KRAS* (codons 12 and 13), *BRAF*, *PIK3CA* (exon 9 and 20) and expression of HER2, on pathologic response were examined using surgical resections. Interestingly, TRG 1–2 was not detected in any patients with a *KRAS*, *BRAF*, or *PIK3CA* mutation; however, none of these genes were individually statistically correlated with a pathologic response to ECF, probably due to the small proportion of patients with such mutations (6.4% for *KRAS*, 0.7% for *BRAF*, and 5% for *PIK3CA*, respectively). As the chemo-resistant effects of *RAS* or *PIK3CA* pathway activation have already been described in several malignancies (7-9), they may apply to gastroesophageal cancer. HER2 positive patients appeared less likely to have TRG 1–2 in this study, but this requires further verification, as well (10). Therefore, the above findings must be interpreted with caution, as resection specimens were already molecularly and biologically modified by preoperative chemotherapy. Considering heterogeneity of molecular abnormalities within each tumor, not only resection specimens, but also pre-treatment biopsy specimens should be employed for studies of tumor chemo-sensitivity.

According to the pivotal Phase III trials, the standard treatment for patients with stage II or III gastric cancer in Japan is D2 surgery followed by adjuvant chemotherapy with S1 (11), and D2 surgery followed by adjuvant chemotherapy with capecitabine and oxaliplatin in Korea (12). However, even in East Asia, neoadjuvant chemotherapy is considered as a promising treatment option in resectable advanced gastric cancer. Neoadjuvant chemotherapy has several advantages over postoperative adjuvant chemotherapy as follows: first, it potentially leads to down-sizing or down-staging of the tumor, and thus improves the R0 resection rate. Second, micrometastatic tumor cells are initially treated without delay. Third, high compliance is expected due to less toxicity prior to the morbidity of surgery. Fourth, chemotherapeutic agents are more efficiently delivered to tumors prior to surgical disruption of the vasculature. Fifth, it provides information for biological response to a particular chemotherapeutic regimen that may affect the choice of postoperative regimen. Now, a novel phase III trial (the PRODIGY trial: NCT01515748) is ongoing in Korea, in which patients with T2-3/N (+) or T4/N (any) are being randomized to three cycles of neoadjuvant chemotherapy with DOS (docetaxel, oxaliplatin, and S1) followed by D2 surgery, or surgery alone. In both arms, S1 is given for 1 year postoperatively. In the near future, depending of the results of this trial, neoadjuvant chemotherapy may become a standard treatment even in East Asia where D2 surgery is routinely performed.

In summary, the current study by Smyth *et al.* has clearly shown that lymph node metastasis, and not pathologic response to chemotherapy is the only independent predictor of survival after chemotherapy plus resection in patients with resectable gastroesophageal cancer. Therefore, post-treatment lymph node status reflects the extent of residual tumor burden, and hence, may serve as a reliable surrogate marker in the course of developing more promising perioperative adjuvant therapy. Furthermore, in addition to the best solution for patients with positive lymph nodes after neoadjuvant chemotherapy plus resection, the best menu of neoadjuvant therapy to exhibit the maximum effects against involved lymph nodes is eagerly awaited. Future prospective randomized trials to target patients with positive lymph nodes will meet our expectations, and surely give us better weapons to fight against resectable gastroesophageal cancer, which has room for further improvement of treatment outcomes.

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Footnote

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