Editorial Commentary

Perioperative adjuvant, RESOLVE, toward new standards for locally advanced gastric cancer

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Introduction

Gastric cancer is the fifth most common cancer worldwide and the third leading cause of cancer mortality (1). Along with the advances in surgical and medical oncology, several new standard therapies have been established for locally advanced gastric cancer in Europe and Asia. RESOLVE is a well-designed phase 3 randomized trial (RCT) to compare three groups in cT4aN+ or cT4bNany gastric or gastro-esophageal junction adenocarcinoma undergoing D2 gastrectomy (2). In RESOLVE, perioperative S-1 and oxaliplatin (SOX) was superior to adjuvant capecitabine and oxaliplatin (CapOx); and adjuvant-SOX was not inferior to adjuvant-CapOx by comparing 3-year disease-free survival. The hazard ratios (HRs) of perioperative-SOX and adjuvant-SOX *vs.* adjuvant-CapOx were 0.77 and 0.86, respectively. The effectiveness is similar to the recent RCTs, FLOT4 in German (3) and JACCRO GC-07 in Japan (4), evaluating perioperative fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) and adjuvant S-1 plus docetaxel (SD), respectively.

Adjuvant therapy for locally advanced gastric cancer

In RCTs to evaluate perioperative chemotherapy, it is difficult to secure whether the baseline prognostic factors are well balanced between the arms considering the inaccurate clinical staging. In JCOG1302A to evaluate accuracy of clinical diagnosis, the positive predictive value and the sensitivity for pathological stage III gastric cancer were 43.6% and 87.8% respectively (5). Primary tumors are mostly visible by combined endoscopy and CT, but small lymph node metastases are so difficult to be identified. TNM stages have been updated properly based on the worlds' large data; however, tumor size is not included in gastric cancer staging. Tumor size is known as an independent prognostic factor associated with pT and pN stages (6), and it can be estimated by endoscopy and CT. In SAMIT, factorial RCT for UFT *vs.* S-1 and sequential paclitaxel, sT4a–b and sN0–2 cases, staged at surgery, were included (7). The randomization was stratified including tumor size (<8 *vs.* ≥8 cm) and cN stage, so the four groups were well randomized as confirmed by the pathological stages. In RESOLVE, cT and cN were well balanced, but pT and pN were slightly discrepant between adjuvant-SOX and adjuvant-CapOx groups; pT4 and pN3 ratios in SOX group were both 6% lower than those of CapOx group. In future gastric cancer trials, especially for perioperative RCT, tumor size should be included in stratifying factors for appropriate randomization.

By subgroup analysis in RESOLVE, the efficacy is almost consistent in most groups; however, perioperative-SOX was more effective for females than males. The HRs in female and male groups were 0.49 and 0.88, respectively with a P value 0.04 for interaction. Conversely in CLASSIC trial, the HRs of adjuvant-CapOx *vs.* surgery in female and male groups were 0.83 and 0.49, respectively (8). Also, in meta-analysis for CLASSIC and ACTS-GC, HRs of adjuvant

vs. surgery in female and male groups were 0.80 and 0.64, respectively; also there was an interaction for BMI (9). In these trials, adverse events among the groups were similar, but postoperative weight loss and BMI were not identified. Weight loss after gastrectomy is inevitable and associated with compliance of adjuvant chemotherapy and patients' prognosis (10,11). The latter Korean study found that one month after surgery, weight loss rates were higher in female and adjuvant groups. Considering surgical burden and compliance of adjuvant, perioperative adjuvant could be suitable and more effective for female and low BMI patients which must be increased in the aging society like Japan.

D2 gastrectomy is a standard for resectable gastric cancer with relatively high surgical burden and complications, especially in extensive TN or in frail patients. In JCOG trials for gastric cancer with bulky and/or para-aortic lymph node metastases; preoperative chemotherapy + D3 gastrectomy was shown to be favorable, and might be effective except for tumors with metastases to both areas (12,13). In these studies, staging laparoscopy, M0, and peritoneal lavage cytology, negative, were mandatory in the inclusion criteria. In these high-risk patients, accurate staging is necessary for appropriate therapies.

To move forward

Perioperative chemotherapy has not been standardized in Asia, and it will be so in the near future. Recently, immunotherapy, nivolumab, has been approved for the adjuvant treatment of esophageal or gastroesophageal junction cancer in the world. In addition to the nutritional status, immunity is associated with cancer growth and the effectiveness of treatment (14). We need to move forward to a new system to evaluate the clinical tumor stage, patients' status of nutrition and immunity. Combining BMI and estimated weight loss is important for clinical decision-making. In parallel with ongoing new RCTs, meta-analyses are needed to evaluate the clinical biomarkers using these large RCTs' individual patient data.

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Footnote

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