

Multidisciplinary approach for the treatment of gastric cancer

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Gastric cancer remains a worldwide public health problem especially in Asia. Over the past decade, the pattern of gastric cancer has considerably changed. Despite declining rates of distal gastric cancer, a trend of significant increasing in the incidence of proximal gastric cancer has been observed in the United States, Europe and Asia (1,2). The histology, tumor biology and clinical course are quite different between the two types of the gastric cancer. For example, diffuse histologic pattern and aggressive clinical course are frequently seen in the proximal gastric cancer. Nonetheless, the management of these two types of gastric cancer remains the same in the current practice.

The management of gastric cancer has been evolving over the past two decades. Complete surgical resection remains the corner stone for the cure of localized early stage gastric cancer. Issues investigated and debated over the past 20 years have focused on the extent of lymphadenectomy (D1 *vs.* D2 dissection) with the goal of delivering an optimal cancer operation while limiting morbidity. Although D2 dissection has been the standard practice in Japan and most Asian countries, major Western studies, the "Dutch trial" (3,4) by Bonenkamp *et al.* and The British MRC ST01 trial (5), failed to show survival benefit of D2 dissection. These trials were criticized by poor quality control of participating surgeons. Despite these negative large randomized studies, most physicians consider that D2 dissection is advantageous due to more precise staging. This notion is supported by the stage migration phenomenon first reported by Bunt and colleagues in 1995 (6). Today, extended lymphadenectomy with pancreas and spleen preservation (known as "over-D1") is generally practiced at major centers in the United States.

Adjuvant chemoradiation with 5-fluorouracil (5-FU) and leucovorin has been the standard practice in the United

States for the past twenty years. INT-0116 is a phase III randomized trial in which 603 patients with resected adenocarcinoma of the stomach or gastroesophageal junction (stages IB-IVM0) were randomized to either observation or combined modality therapy consisting of five monthly cycles of bolus chemotherapy with 45 Gy radiotherapy concurrent with cycles 2 and 3 (7). Patients in the INT-116 trial represented a high-risk group and 85% of the patients in both arms had lymph node involvement. After a median follow-up of 5 years, 3-year relapse free survival rates (48% *vs.* 31%; $P < 0.001$), and hazard ratios for relapse (HR=1.52, 95% CI: 1.23-1.86) significantly favored adjuvant chemoradiotherapy. More significantly, OS rates (50% *vs.* 41%; $P = 0.005$), hazard ratio for death (HR=1.35, 95% CI: 1.09-1.66), and median OS (36 mo *vs.* 27 mo; $P = 0.0005$) were also significantly improved in the chemoradiation group. Outcome data in this trial was updated in January 2004 after a median follow-up of 7 years (8). The major endpoints of the trial: OS (HR=1.31, 95% CI: 1.08-1.61), DFS (1.52, 95% CI: 1.25-1.85) were unchanged from the initial analysis.

Postoperative radiotherapy is not commonly practiced in Japan and other Asian countries. Adjuvant chemotherapy trials in the US have been disappointing. Recently, Japanese adjuvant trial is most intriguing (9). A total of 1,059 patients with stage II or III gastric cancer who underwent D2 surgical resection were randomized to either observation or one year oral S-1 adjuvant therapy. S-1 (Taiho Pharmaceutical) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract) in a molar ratio of 1:0.4:1. The 3-year overall survival

was improved in the S-1 group (80.1% in S-1 group *vs.* 70.1% in the observation group; $P=0.003$). The toxicity profile was very favorable. Although S-1 may impact the clinical practice in Asian population, the results of this agent in Western population are rather disappointing as demonstrated in the First Line Advanced Gastric Cancer Study (FLAGS) (10). This may be due to biological differences between patient populations as to how the drug is metabolized.

Preoperative chemoradiation and perioperative chemotherapy provide benefit to down-stage the primary tumor and eliminate micrometastasis early on. In addition, the preoperative therapy is generally better tolerated. The most compelling evidence for perioperative chemotherapy is the phase III UK Medical Research Council Adjuvant Gastric (MAGIC) trial (11). A significantly better overall survival ($HR=0.75$; 95% CI: 0.60-0.93; $P=0.009$; 5 year survival rate of 36% *vs.* 23%) and progression free survival ($HR=0.66$; 95% CI: 0.53-0.81; $P<0.001$) was achieved in the perioperative group. The trial was criticized for its non-standardized surgery, potentially inaccurate preoperative staging due to the absence of laparoscopy, and a relatively poor outcome in the surgery alone group. The recent large phase III preoperative chemotherapy studies, MRC OEO2 and intergroup 8911, had complete different conclusions (12). However, these two studies population enrolled predominant esophageal cancer. In the OEO2 study, a total of 802 were randomized to either preoperative chemotherapy with 2 cycles of cisplatin and 5-FU followed by surgical resection or surgery alone. The study demonstrated a benefit of overall survival for the preoperative chemotherapy group with a 16% risk reduction ($HR=0.84$, 95% CI: 0.72-0.98; $P=0.03$). However, the intergroup 8911 did not support overall survival advantages.

Several neoadjuvant studies have demonstrated that complete pathological response (pCR) is indicative of better prognosis. Chemotherapy alone hardly achieves pCR. Preoperative chemoradiation generally produces approximately 25% pCR. Most recently, Van Hagen and co-workers published a randomized phase III study to compare preoperative chemoradiation followed by surgery to surgery alone (13). The study enrolled 368 patients that were treated with surgery alone or carboplatin and paclitaxel concurrent with radiotherapy followed by surgery. The median overall survival was 49.4 months in chemoradiation group and 24 months in surgery only group ($P=0.003$). A 29% pCR was achieved in the chemoradiation

group. The study demonstrated a superior survival benefit with combined modality.

Clinical data demonstrated that multidisciplinary approach is usually required to achieve maximum clinical benefit. The current Chinese guidelines by Ji *et al.* has included the most updated and comprehensive information in diagnose and treatment of gastric cancer. The guidelines clearly endorse multidisciplinary approach in managing this disease. The guidelines will provide a standard practice in Chinese Oncology arena and minimize practice variations. Importantly, such guidelines put a step forward to bring Chinese patient population into international clinical trials, which will certainly offer a tremendous opportunity to further understand tumor biology, pharmacogenetics and epidemiological aspects of gastric cancer.

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