

Is postoperative chemoradiotherapy benefit to D2-resected gastric cancer?

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In *Journal of Clinical Oncology*, Park *et al.* report the final results of a phase III trial (ARTIST) examining whether the addition of radiotherapy to adjuvant chemotherapy improved disease-free survival (DFS) in patients with D2-resected gastric cancer (1). In 2002, Lee and his colleagues reported the initial analysis of the ARTIST trial (2), which was the only one randomized phase III trial in the world so far performed in Asian patients undergoing D2 lymph node dissection comparing the efficacy of capecitabine plus cisplatin (XP) versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy (XPRT). The 3-year DFS showed no statistically significant difference (74% for XP *vs.* 78% for XPRT; $P=0.0862$), and as a result, chemoradiotherapy (CRT) in addition to adjuvant chemotherapy was not recommended in patients with gastric cancer underwent D2 surgery. With a median follow-up time of 7 years, the overall survival (OS) results was presented to update showing that both DFS and OS remained similar between two treatment arms. However, significant increased DFS and OS were presented in patients with intestinal-type and node-positive gastric cancer.

Although the ARTIST trial reached a negative result, there were a number of issues could not be ignored in this study.

First, early stage tumors accounted for appropriately 60% of all patients, leading to a low rate of disease recurrences. Thus, the role of adjuvant CRT would be much weakened. Meanwhile, events were too few to reach statistical significance.

Second, in Asia, particularly in Japan and South Korea, D2 dissection has been the standard of care for gastric

cancer. In the ARTIST trial, the median number of total lymph nodes achieved 40, resulting in a favorable 5-year OS of 73–75% in two arms. Data from a large US population database also indicated the more accurate lymph node dissection was performed, the lower locoregional recurrence and better survival rate can be achieved (3). While, D2 dissection is not undertaken popularly out of East Asia. Even in China, given the many differences between centers or institutions in the volume, patient populations, surgical practices and training, postoperative nursing experience, lymph node identified and examined pathologically, it is uneasy to standardize and generalize the D2 dissection. Thus, choose of optimal adjuvant setting for gastric cancer patients in our country should be based on the individual characteristics and quality of surgery.

Third, the results of the ARTIST trial suggested a significant lower locoregional recurrence CRT group (12.7% for XP *vs.* 6.5% for XPRT; $P=0.03$) in all patients, and even lower in node-positive patients (14.5% for XP *vs.* 6.4% for XPRT; $P=0.009$) (4). Therefore, CRT should be considered as one of the main modalities used to reduce locoregional recurrences even after D2 dissection. But finding those patients who would benefit most from adjuvant CRT is of important concern because the locoregional recurrence rate is not high and additional radiotherapy may induce more acute or late toxicities or the second primary tumor. Although this study suggested that patients with Borrmann type 3 or 4, intestinal type Lauren classification, lymphovascular invasion or lymph node metastasis showed greater locoregional recurrence free survival benefit from XPRT than XP, further investigation

is required to be determined the indication for adjuvant CRT.

Finally, the target delineation in postoperative radiotherapy for gastric cancer following D2 dissection has not been established, since the failure patterns after D2 dissection were different from those who underwent D0 or D1 dissection. Hoon *et al.*, also from South Korea, reported that most metastatic lymph node occurred at the first recurrence were outside the D2 dissection field. The most commonly involved first recurrent lymph nodes were No. 16a (lymph nodes around the abdominal aortal for the upper margin of the celiac trunk to the lower margin of the left renal vein), accounting for more than 58% of 91 patients with first regional recurrence in stage III, N3 gastric cancer. However, definition of the target volume in ARTIST trial was somewhat similar to INT 0116 except for the exclusion of the remnant stomach (5). Hence, how to delineate an accurate and optimal radiation target for patients with D2 dissection was still a question we should answer in the future.

In a word, adjuvant CRT significantly improved locoregional control in D2-resected gastric cancer patients, as well as favorable DFS in patients with positive lymph nodes and intestinal type. The target volume might concentrate to the areas in the second or the third stations of the lymphatic drainage defined by Japanese Gastric Cancer Association in its old version of definition. At present, the ARTIST-II trial is ongoing and we are looking forward to the results.

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Footnote

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