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TOPIC HIGHLIGHT

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Postoperative adjuvant chemoradiotherapy in D2-dissected gastric cancer: Is radiotherapy necessary after D2-dissection?

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Abstract

Studies from the Far East have demonstrated that D2-dissection is superior to D0/1-dissection. The effect of postoperative chemoradiotherapy (CRT) after D2-dissection has not been accepted due to the lack of D2-dissection in Western countries, as well as the potential harmful effect of radiotherapy. In the current NCCN guideline, adjuvant chemotherapy alone is recommended in D2-dissected patients. However, three recent prospective randomized controlled trials in South Korea and China (ARTIST, NCC and Multicenter IMRT Trials) demonstrated that adjuvant CRT can be safely administered to D2-dissected patients with notable benefits. To identify the role of radiotherapy (RT) in the D2-dissected postoperative setting, clinical research attempts should include (1) identification of high-risk patients for loco-regional recurrence who might benefit from CRT; (2) modification of RT target volume based on the findings that failure patterns should be different after D1- and D2-dissection; and (3) integration of new RT techniques to decrease treatment-related toxicity. The present paper is a review of recent studies addressing these fields. Well-designed prospective randomized studies are needed to clearly define the role of adjuvant CRT in D2-dissected gastric cancer, however, future clinical studies should also focus on answering these questions.

Key words: Gastric cancer; D2-dissection; Recurrence; Radiotherapy; Chemotherapy

Core tip: The survival benefits of postoperative chemoradiotherapy (CRT) in gastric cancer with D0/1-dissection have been established in Western countries. However, in Eastern areas, where D2-dissection is the standard surgical procedure, most surgeons are skeptical about the benefit of CRT in D2-dissected patients, and CRT has not been examined in this setting in clinical trials. Here we aimed to provide a review of recent research and to suggest future directions regarding adjuvant CRT after D2-dissection.

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INTRODUCTION

During the past two decades, a multimodal treatment combining chemotherapy and chemoradiotherapy (CRT) has been investigated worldwide to prevent recurrence and improve survival in gastric cancer patients who underwent curative surgical resection[1]. Due to the lack of

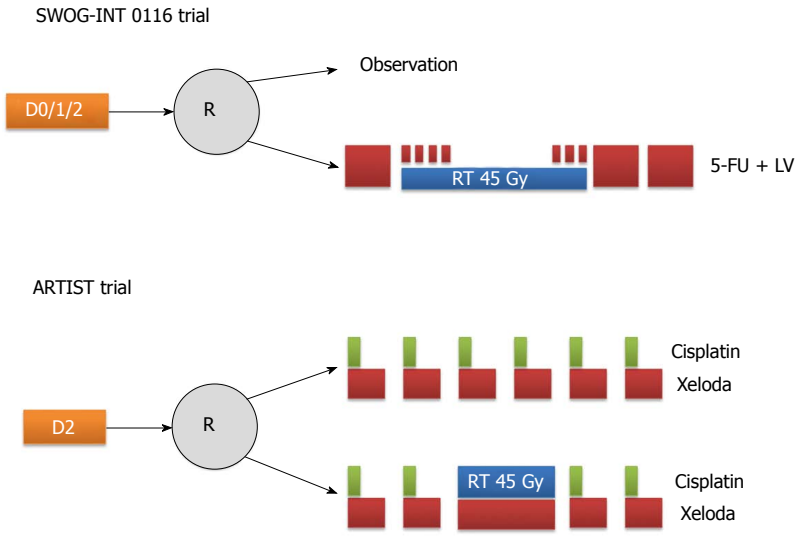

Figure 1 Treatment and randomization schemes of the SWOG/INT-0116 and ARTIST trials. 5-FU: 5-fluorouracil.

robust evidence as to which of the currently available approaches is better, there has been marked discrepancy in adjuvant treatment nationwide and worldwide. In the West, peri-operative intensive chemotherapy (MAGIC trial) and postoperative CRT (SWOG/INT-0116 trial) are recommended for resectable gastric cancer[2,3]. In the East, on the other hand, adjuvant chemotherapy after D2-dissection is considered the standard treatment (ACTS-GC and CLASSIC trials). Studies from the Far East have demonstrated that D2-dissection is superior to D0/1-dissection. The effect of postoperative CRT after D2-dissection has not been accepted due to the lack of D2-dissection in Western countries, as well as the potential harmful effect of radiotherapy[4,5]. However, three recent prospective randomized controlled trials in South Korea and China have demonstrated that adjuvant CRT can be safely administered to D2-dissected patients with notable benefts[6-8]. Currently, some important clinical questions still remain unanswered: (1) Does adjuvant CRT in D2-dissected patients provide similar benefit to that shown in the SWOG/INT-0116 trial (mostly D0/1-dissected patients)? (2) What is the incidence of loco-regional recurrences, which sometimes mimic metastatic peritoneal seeding or distant lymph nodes, after D2-dissection? (3) If CRT is considered as adjuvant treatment for D2-dissection felds, is it necessary to modify the traditional radiation feld, which was developed for D0/1-dissected fields? (4) Is radiation therapy still potentially harmful even with modern radiotherapy (RT) techniques and modifed RT felds in gastric cancer? and (5) Is there a subset of patients with specific characteristics who would benefit from adjuvant CRT after D2-dissection? This review discusses the current status of adjuvant CRT for gastric cancer patients undergoing D2-dissection, with updated data to provide a guide to the priorities on which investigators should focus on in future studies.

RATIONALE FOR ADJUVANT RADIOTHERAPY IN GASTRIC CANCER

High rates of local and regional recurrence have been shown in patients with gastric cancer treated with surgical resection. The reported rate of loco-regional recurrence ranges from 19%-45%, and reported loco-regional recurrence from re-operation or autopsy data is up to 90%[9-13]. Gunderson *et al*[14] suggested potential radiation portals based on the patterns of loco-regional failures in the re-operation group, leading investigators to verify the role of radiotherapy in preventing such recurrence[14-17].

The SWOG/INT-0116 trial, directly compared postoperative CRT with observation alone, and clearly showed the survival benefit of postoperative CRT in resected gastric cancer[3]. Even though the eligibility criteria included stage I B through IVM0 (AJCC 1988), most of the enrolled patients were at high risk for recurrence (T3/4, 69% and N^+, 85%). CRT consisted of 45 Gy of radiation with concurrent bolus 5-fuorouracil/leucovorin (FL) (Figure 1). RT-related gastrointestinal toxicity may have been severe, in that only 64% of patients completed the planned treatment. Nonetheless, three-year relapse-free survival and overall survival (OS) were signifcantly improved by adjuvant CRT in a median follow-up of five years, which led to its adoption as standard treatment in the United States. Since the publication of the SWOG/INT-0116 trial results, adjuvant CRT was found to be used more commonly in United States based on the SEER database analysis (33% in 1998-2001 *vs* 45% in 2002-2007, $P < 0.001$)[18]. The updated data after 10-y of follow up in SWOG/INT-0116, demonstrated a persistent benefit of adjuvant CRT[19]. The rate of loco-regional failure, but not distant relapse, was signifcantly decreased in the group treated with adjuvant CRT, suggesting that the improved OS by adjuvant CRT was mainly due to

the prevention of subclinical loco-regional diseases. The long-term toxicity, including secondary malignancies, appeared acceptable.

EXTENT OF LYMPH NODE DISSECTION

Could these findings lead to the adoption of adjuvant CRT for gastric cancer patients in Eastern countries? As only a minority of patients [54 (10%) of 552] in SWOG/INT-0116 underwent D2-dissection, an extremely conservative approach has been followed in Eastern areas, such as South Korea and Japan where D2-dissection has long been the standard[20]. Over the past few decades, whether the extent of lymph node dissection (D1 *vs* D2) favorably impacts survival outcome has been a controversial issue. Two prospective randomized controlled trials in the West addressed this controversial issue: thereafter, it took a long time to provide robust evidence that D2-dissection improves survival over D1-dissection when performed by well-trained surgeons with acceptable rates of postoperative mortality[21,22].

MRC trial

The Medical Research Council (MRC) in the United Kingdom randomized 400 patients to D1 resection or D2 resection[21]. The rates of postoperative morbidity and mortality were significantly higher in the D2 group (46% *vs* 28% and 13% *vs* 7%, respectively), which was due to splenectomy and distal pancreaticosplenectomy. In an update with a median follow-up time of 6.5 years, five-year survival rate following D2-dissection was not better than that following D1-dissection (33% *vs* 35%)[23].

Dutch trial

Another large prospective randomized controlled trial was conducted by the Dutch Gastric Cancer Group (DCGC) in the Netherlands, which randomized 711 patients to D1 or D2 dissection[22]. The Dutch trial by Bonenkamp *et al*[22] had a unique characteristic regarding quality control of surgical management compared to the MRC trial in that the participating surgeons were instructed by Japanese surgeons during the first four months. The results were similar to those in the MRC trial in that postoperative morbidity and mortality rates were higher; however five-year survival rate was not higher in the D2 group. The incidence of postoperative complications and death were 43% and 10% in the D2 group, and 25% and 4% in the D1 group. Even though an updated report with more than 10 years follow-up found that D2-dissection did not generate long-term survival benefits, the latest report after a follow-up of 15 years showed lower loco-regional recurrence and gastric cancer-related death in the D2-group[24,25]. Collectively, regardless of whether the patients were treated in the East or not, D2-dissection is now recommended for resectable gastric cancer patients if it is performed by well-trained surgeons in high-volume centers.

ADJUVANT CRT IN D2-DISSECTED GASTRIC CANCER

Only a few small prospective studies and several retrospective studies have explored the role of adjuvant CRT in D2-dissected gastric cancer[26-30]. Dikken *et al*[26], using a Dutch cohort, compared 91 patients who received adjuvant CRT in two phase Ⅰ/Ⅱ studies with 694 patients from the DCGC D1/D2 trial. In this study, the addition of CRT seemed to be beneficial in preventing local recurrence after D1-dissection, but not after D2-dissection. However, in the updated analysis of the SWOG/INT-0116 study with a 10-year follow-up, there was no evidence of lack of survival benefit in patients who had undergone the D2 level of resection. A retrospective study by Kim *et al*[27] in South Korea showed improved survival and lower regional recurrence by adding CRT, albeit in patients who underwent D2-dissection. The five-year survival rates were consistently longer in the adjuvant CRT group (n = 554) at stages Ⅱ, Ⅲ, and Ⅳ compared with those in the comparison group (n = 446). However, these data are based on unplanned subgroup analysis or nonrandomized observation studies with suitable controls (level Ⅲ).

RECENT TRIALS OF ADJUVANT CRT AFTER D2-DISSECTION

There has been no evidence directly comparing adjuvant chemotherapy, which is a standard treatment in Eastern countries for D2-dissected gastric cancer[28]. In 2012, the findings of three prospective randomized controlled trials were published, however, the results were inconclusive[6-8].

ARTIST trial, South Korea

The Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial, led by the same authors as the aforementioned observational study by Kim *et al*[7], was the first and largest prospective study to address the role of CRT as adjuvant treatment in D2-dissected gastric cancer[6]. This study randomly assigned 458 patients undergoing complete resection with D2-dissection to six cycles of adjuvant capecitabine with cisplatin (XP, n = 228) or 45 Gy of CRT with concurrent capecitabine following two cycles of XP and two additional cycles of XP (n = 230) (Figure 1). Over a median follow-up of 53 mo, no statistically significant difference in three-year disease-free survival (DFS) between the two groups (XP: 74% *vs* CRT: 78%, P = 0.0862) was found. However, this trial should not be interpreted as a negative result for adjuvant CRT in D2-dissection. Since the implementation of the nationwide cancer screening program in South Korea (GI endoscopic examination in individuals aged over 40 years every two years), a significant proportion of enrolled patients were stage Ⅰ/Ⅱ disease; therefore, the planned events were not reached at the time of final analysis. The unplanned subset analysis revealed that the combined modality sig-

Table 1 Major patient characteristics and results of phase Ⅲ trials of postoperative radiotherapy for gastric cancer

Ref.	*n*	Enrolled period	Median F/u (m)	pT3-4	pN$^+$	Ⅲ-Ⅳ	D2	OS	DFS/RFS	Remarks
SWOG/INT-0116[3]	556	91-98	60	70%	85%	NR	10%	3-yr: 50% *vs* 41% (P = 0.005)	3-yr: 48% *vs* 31% (P < 0.001)	Similar benefit in 10-yr follow-up data
ARTIST[6]	458	04-08	53	NR	86%	41%	100%	NR	3-yr: 78% *vs* 74% (P = 0.0862)	DFS benefit in N$^+$
NCC, South Korea[7]	90	02-06	87	63%	98%	100%	100%	5-yr: 65% *vs* 55% (P > 0.05)	5-yr: 61% *vs* 50% (P > 0.05)	LRRFS benefit (DFS benefit in stage Ⅲ)
IMRT, China[8]	351	03-08	43	NR	86%	71%	Majority	5-yr: 48% *vs* 42% (P = 0.122)	5-yr: 45% *vs* 36% (P = 0.029)	

F/u: Follow-up; PS: Performance status; NR: Not reported; OS: Overall survival; DFS/RFS: Disease-free survival/relapse-free survival; LRRFS: Loco-regional failure-free survival.

Table 2 Treatment parameters and toxicities in phase III studies of postoperative radiotherapy for gastric cancer

Ref.	Group	Concurrent chemo	RT planning	RT dose (Gy)	RT target	Severe toxicity	Completed planned treatment
SWOG/INT-0116[3]	CRT	5FU + LV	2D	45	Tumor bed, LN (Nos. 1-16)	G3$^+$, 41%, G4$^+$ 32% (GI, 33%)	64% (17 due to toxic effect)
ARTIST[6]	CT-CRT-CT	Capecitabine	2D or 3D	45	LN (Nos. 7-9 and 12-16)	Similar toxicity profile between the two groups (mostly well tolerated)	82% (5 due to toxic effect, but 1 during CRT)
NCC, South Korea[7]	CRT	5FU + LV	2D or 3D	45	Tumor bed, LN (Nos. 1-16)	G3$^+$ Hema; 20% *vs* 25%, G3$^+$ GI; 17% *vs* 11%	87% (2 due to toxic effect)
IMRT, China[8]	CRT	5FU + LV	IMRT	45	Tumor bed, LN (Nos. 1-16)	Similar toxicity profile between the two groups (mostly well tolerated)	91% (4 due to toxic effect)

RT: Radiotherapy; CRT: Chemo-radiotherapy; 5FU + LV: Fluorouracil and leucovorin; LN: Lymph node; GI: Gastrointestinal; Hema: Hematologic; IMRT: Intensity modulated radiotherapy.

nificantly improved the three-year DFS in node positive patients, supporting the hypothesis of this trial.

NCC trial, South Korea

The National Cancer Center (NCC) in South Korea conducted a single-institution phase Ⅲ trial in stage Ⅲ-Ⅳ gastric cancer patients who underwent R0 gastrectomy and D2-dissection[7]. A total of 90 patients were randomly assigned to the chemotherapy arm (FL, n = 44) or the CRT arm (INT-0116 scheme, n = 46). Unfortunately, this underpowered study was terminated early due to poor accrual (possibly why the ARTIST trial included 60% stage Ⅰ/Ⅱ patients). Although five-year DFS, which was the primary endpoint of this trial, was not significantly improved in the combined modality group which included RT, the five-year loco-regional recurrence-free survival (LRRFS, secondary endpoint) was significantly improved in the median follow-up of 87 mo.

Multicenter IMRT trial, China

In contrast to these two trials, a significant benefit in DFS, but not in OS, was shown in a Chinese multicenter randomized trial, in which patients with D2-dissection were randomly assigned to chemotherapy alone or intensity-modulated RT plus concurrent chemotherapy[8]. The chemotherapy consisted of the FL regimen in both groups. With a median follow-up of 43 mo, adjuvant CRT was associated with a significant reduction in the risk of recurrence (5-year DFS, 45% *vs* 36%), and with no significant survival advantage (5-year OS, 48% *vs* 42%). Not surprisingly, no difference in the rate of distant metastasis was noted between the two groups (24% *vs* 27%, P = 0.595), and loco-regional recurrences were less frequent in the adjuvant CRT group (15% *vs* 24%, P = 0.042).

DISCUSSION OF RECENT TRIALS

The results of three recent randomized controlled trials from South Korea and China comparing adjuvant chemotherapy and CRT, which included a total of 895 patients in the meta-analysis, showed no apparent survival benefit with the addition of RT (HR = 0.79, 95%CI: 0.61-1.03) during the 4-7 year follow-up period, but found significantly improved LRRFS (HR = 0.53, 95%CI: 0.32-0.87) and DFS (HR = 0.72, 95%CI: 0.59-0.89) in the CRT group (Table 1)[31]. When interpreting the findings of these trials, several important points should be considered. Firstly, although in the SWOG/INT-0116 trial, 41% of CRT patients experienced severe treatment-related toxicity, resulting in only 64% com-

Table 3 Description of lymph node station

LN station	Node location
1	LN at right paracardium
2	LN at left paracardium
3	LN along the lesser curvature
4	LN along the greater curvature
5	LN at suprapylorum
6	LN at infrapylorum
7	LN along the left gastric artery
8	LN along the common hepatic artery
9	LN around the celiac artery
10	LN at the splenic hilum
11	LN along the proximal splenic artery
12	LN in the hepatoduodenal ligament
12a	LN along the hepatic artery
12b	LN along the bile duct
12p	LN behind the portal vein
13	LN on the posterior surface of the pancreatic head
14	LN along the superior mesenteric vessels
15	LN along the middle colic vessels
16	LN around the abdominal aorta
16a	LN from the upper margin of the celiac trunk to the lower margin of the left renal vein
16b	LN from the upper margin of the left renal vein to the aortic bifurcation

LN: Lymph node.

pleted planned treatments, in 3 recent randomized trials, no increase in treatment-related toxicity was observed in the CRT group compared with the chemotherapy alone group; consequently, most patients (ARTIST 75%, NCC 87%, and China 91%) completed treatment as planned (Table 2). One plausible explanation for this is the application of modern RT techniques (IMRT or CT-based 3D-CRT) in recent trials rather than 2D-conventional RT in the SWOG/INT-0116 trial carried out in the 1990's and/or the modification of RT target volume in the ARTIST trial, which could reduce the irradiating bowel volume. Secondly, the patient population varied between the studies. The proportion of stage Ⅲ/Ⅳ disease, which could involve a high risk of loco-regional relapse, was 41% in the ARTIST trial, 71% in the Chinese trial, and 100% in the NCC trial. The positive results for DFS in the Chinese trial and subset (N^+) analysis of the ARTIST trial indicated that the use of adjuvant CRT for the entire population undergoing D2-dissection may be overtreatment, and, therefore, identification of the high-risk subgroup which would benefit most from CRT should be carried out.

LOCOREGIONAL RECURRENCE AFTER D2-DISSECTION: IMPLICATIONS FOR POSTOPERATIVE RT

In Eastern countries including South Korea and Japan, D2-dissection with low morbidity and mortality is believed to contribute to rare loco-regional recurrence and a high OS rate[32]. However, actual reported rates of local/regional recurrence after D2-dissection range from 19%-33%[12,25,27]. The largest retrospective study from South Korea analyzed the failure patterns of 2328 patients who underwent D2-dissection, and reported 19% of loco-regional recurrence as a single pattern and 33% as a combined pattern[12]. Another retrospective study from Korea reported 22% of loco-regional failure in 446 patients who did not receive adjuvant RT[27]. In the Dutch D1/D2 trial from DCGC, a similar rate of loco-regional recurrence was noted in 331 patients in the D2 group (local 12% and regional 13%)[25]. It should be noted that these studies included entire patient populations from stage Ⅰ to stage Ⅳ (M0) disease. One possible explanation for under-reporting of loco-regional recurrence included lack of attention due to distant spread and difficulty in determining loco-regional failure using current imaging modalities. The intra-abdominal location of regional lymph nodes (LNs) could make recurrence less likely to be detected as the first failure pattern compared with other organs.

In the present authors' opinion, the identification of a high-risk subgroup for loco-regional recurrence among D2-dissected patients is essential and of higher priority than assessing the efficacy of regular application of adjuvant CRT in all D2-dissected gastric cancer patients. The subgroup analysis in the ACTS-GC trial from Japan may provide a clue to identifying patients who are most likely to benefit from adjuvant CRT[33]. The pivotal Japanese ACTS-GC study demonstrated the survival advantage of postoperative S-1 chemotherapy over observation[4]. Subgroup analysis of 5-year OS in this study showed that insufficient survival benefit of S-1 was observed in N3a (HR = 0.779, 95%CI: 0.534-1.138) and N3b stages (HR = 0.927, 95%CI: 0.477-1.799), in contrast to clear efficacy in N0-N2 stages, which may indicate room for improvement in the application of RT in these patients at high risk for loco-regional recurrence. In Korea, the report by Chang *et al*[34] revealed an interesting finding that N3 patients are at substantial risk of regional recurrence as well as peritoneal seeding and distant spread despite D2 dissection and adjuvant chemotherapy. The report also demonstrated that the most frequent locations of regional recurrence were in the nodal stations outside the D2-dissection field (12p-16), which are classified as distant metastasis (M1 node) according to the 7th edition of the AJCC classification system, but as regional node according to the Japanese Classification of Gastric Carcinoma (JCGC) criteria (Table 3)[35].

RT TARGET VOLUME COULD BE MODIFIED IN D2-DISSECTED GASTRIC CANCER

The RT target volume has varied in the studies of adjuvant RT[36]. In the SWOG/INT-0116 trial, the field of radiation included the tumor bed and 2 cm beyond the proximal and distal margins of resection, and regional nodes (perigastric, celiac, local para-aortic, splenic, hepa-

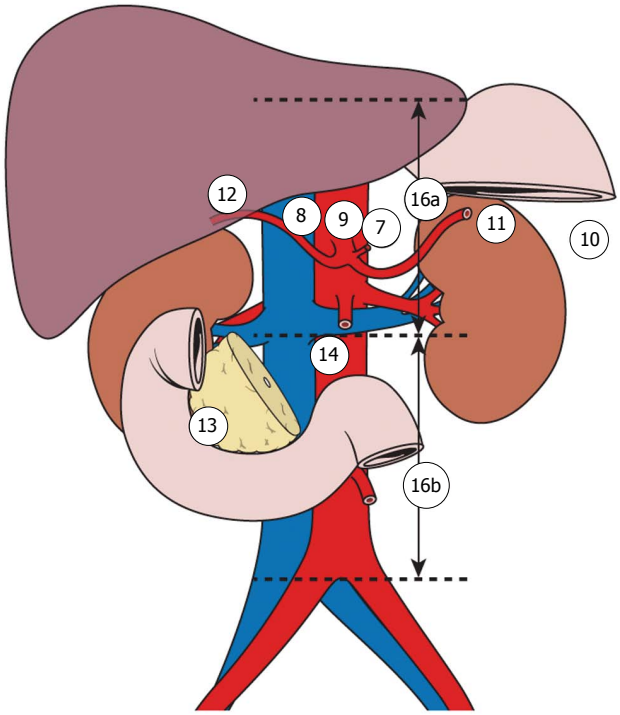

Figure 2 Schematic diagram of lymph node station. LN: Lymph node; 7: LN along the left gastric artery; 8: LN along the common hepatic artery; 9: LN around the celiac artery; 10: LN at the splenic hilum; 11: LN along the proximal splenic artery; 12: LN in the hepatoduodenal ligament; 13: LN on the posterior surface of the pancreatic head; 14: LN along the superior mesenteric vessels; 16a: LN from the upper margin of the celiac trunk to the lower margin of the left renal vein; 16b: LN from the upper margin of the left renal vein to the aortic bifurcation.

toduodenal, and pancreaticoduodenal LNs)[3,14]. This field was defined based on patterns of failure after D0/1 dissection in a Western population, which might be the representative failure pattern of suboptimal surgical resection. On the other hand, in the ARTIST trial, the RT target volume did not include LNs in the splenic hilum (No. 10), LNs along the proximal splenic artery (No. 11), perigastric LNs (Nos. 1-6) and tumor bed, based on their previous study analyzing patterns of failure after D2-dissection (Figure 2)[6,37].

Coupled with a retrospective central review by one GI radiologist, Chang *et al*[34] investigated patterns of LN recurrence after D2 dissection for 382 patients with stage Ⅲ (N3) disease. The most prevalent regional recurrence was LNs around the abdominal aorta from the upper margin of the celiac trunk to the lower margin of the aortic bifurcation (Nos. 16a and 16b), followed by hepatoduodenal LNs (No. 12), LNs along superior mesenteric vessels (No. 14), retropancreatic LNs (No. 13), and celiac LNs (No. 9). These results provide consistent evidence that RT target volume in D2-dissected patients can exclude perigastric LNs (Nos. 1-6), and splenic LNs (Nos. 10-11). Since the development of severe gastrointestinal complications is mostly attributed to the extent of the RT target volume in gastric cancer, understanding the specific location of loco-regional recurrence after D2-dissection could potentially allow more effective RT strategies. A subsequent report by Yoon *et al*[38] demonstrated RT target volume delineation based on CT-guided vascular structure using the data from 91 patients who had LN recurrence from their previous study.

CURRENT TRIALS

Well-designed prospective randomized studies with adequate statistical power are needed to clearly define the role of adjuvant CRT in D2-dissected gastric cancer. The ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach (CRITICS) trial is currently randomizing patients undergoing preoperative ECF followed by $D1^{+}$ dissection (Nos. 1-9 and 11) to postoperative ECF alone or 45 Gy of CRT with concurrent capecitabine plus cisplatin, and comparing the efficacy of the MAGIC trial regimen which showed the survival benefit of a perioperative approach combined with intensive chemotherapy (ECF; epirubicin, capecitabine, and cisplatin) with those of the SWOG/INT-0116 trial[39]. The ARTIST Ⅱ trial plans to accrue LN positive patients using a 2-by-2 factorial design of chemotherapy agents (S-1 *vs* capecitabine plus oxaliplatin) and treatment modality (chemotherapy alone *vs* CRT).

CONCLUSION

Current treatment guidelines of adjuvant CRT for D2-dissected gastric cancer are based on low-level evidence due to a paucity of prospective studies and a near total absence of phase Ⅲ multicenter randomized trials. Recent prospective randomized trials from South Korea and China demonstrated that the addition of RT to chemotherapy could prevent loco-regional recurrence and, furthermore, improve DFS in selected patients even after D2-dissection. Considerable rates of loco-regional recurrence have been reported after D2-dissection and the most prevalent locations of recurrence are found in the nodal basin outside the D2-dissection field. Whether modification of RT target volume and/or new RT techniques can reduce GI toxicity without compromising the oncologic outcomes is a clinically relevant question. Identification of high-risk patients for loco-regional recurrence is crucial. Because D2-dissection has been recently recommended as the standard surgical method worldwide, data on the influence of clinical results is now available from both Eastern and Western studies. Future statistically robust prospective studies are strongly warranted to further investigate the role of CRT in the field of D2-dissection.

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