J Gastric Cancer. 2023 Jan;23(1):194-206
https://doi.org/10.5230/jgc.2023.23.e1
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Review Article

Role of Adjuvant Radiotherapy in Gastric Cancer

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Received: Oct 13, 2022
Revised: Nov 7, 2022
Accepted: Nov 15, 2022
Published online: Dec 6, 2022

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Funding
This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Education (NRF-2022R1C1C1005415).

Conflict of Interest
The outcomes and data of the systematic review and meta-analysis used in this review were based on the results of a previous systematic review conducted by the Korean Gastric Cancer Association according to the new version of Korean Practice Guideline for Gastric Cancer, which was participated by

ABSTRACT

Although continuous improvement in the treatment outcome of localized gastric cancer has been achieved through early screening, diagnosis, and treatment and the active application of surgery and adjuvant chemotherapy, the necessity of adjuvant radiotherapy (RT) remains controversial. In this review, based on the results of two recently published randomized phase III studies (Adjuvant Chemoradiation Therapy In Stomach Cancer 2 and ChemoRadiotherapy after Induction chemoTherapy of Cancer in the Stomach) and a meta-analysis of six randomized trials including these two studies, the role of adjuvant RT in gastric cancer was evaluated and discussed, especially in patients who underwent curative gastrectomy with D2 lymphadenectomy. This article also reported the possible indications for adjuvant RT in the current clinical situation and in future research to enable patient-specific treatments according to the risk of recurrence.

Keywords: Gastric cancer; Radiotherapy, adjuvant; Treatment efficacy; Recurrence

INTRODUCTION

Gastric cancer (GC) ranks fifth in terms of incidence and fourth in terms of mortality worldwide [1] and remains the fourth most commonly diagnosed cancer in Korea [2]. Fortunately, the incidence of GC is continuously declining, and the age-standardized incidence rate also decreased by 30.5% between 1990 and 2019 worldwide [3]. In a recent study on the epidemiology of GC in Korea, the age-standardized incidence rate per 100,000 population significantly decreased from 34.0 in 2011 to 29.6 in 2019 [4]. Despite reports of a major decline in the incidence of GC, recent studies have suggested an increase in incidence among the younger age groups of less than 50 years [5]. Additionally, although the diagnosis rate of early-stage GC, which can be cured with endoscopic intervention or minimally invasive surgery alone, is increasing with the active implementation of national screening programs, including the use of upper gastrointestinal endoscopy [6], patients diagnosed with advanced-stage GC still account for a significant proportion (50%–60%), especially in Western countries [7,8].

In patients with locally advanced-stage GC who have undergone curative surgical resection, locoregional recurrence (LRR) is not negligible, although distant metastasis is the main

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the author. No potential conflict of interest relevant to this article was reported.

cause of treatment failure [9]. Extensive and complex lymphatic clearance is difficult to perform, and micrometastases through abundant, multi-directional, and complex lymphatic networks in the mucosal and submucosal layers can occur in the early stages of the disease [10]. Therefore, several studies have been conducted to improve the cure rate by reducing the risk of LRR through radiotherapy (RT) before or after curative surgery in patients with locally advanced-stage GC [11-15].

However, these studies were conducted in various target populations, geographic regions, and ethnic groups and used different surgical methods, RT techniques, chemotherapy applications, and/or regimens in the control group; hence, various results have been reported, making it difficult to interpret the overall outcomes. In this study, we aimed to review the advances in RT techniques for GC, compare the results of studies evaluating the role of adjuvant RT, and discuss the role of RT in the current standard surgical and systemic management of GC and the potential groups that can benefit from adjuvant or neoadjuvant RT by conducting clinical studies in the future.

TECHNICAL ADVANCEMENT OF RT IN GC

With the recent development of RT technology, its application in the oncological field is increasing, especially in areas where its use is extremely limited. Advancements in RT techniques have decreased the risk of side effects in normal organs when the same dose is delivered to the tumor, or facilitated the possible delivery of a higher total radiation dose while maintaining the risk of side effects in normal organs; therefore, these RT techniques are attracting attention, particularly for upper abdominal malignancies including GC, which develop close to the normal organs that are sensitive to RT, such as the liver, gastrointestinal tract, kidneys, and pancreas.

With regard to the application of RT as treatment for GC, the parallel-opposite technique using anteroposterior-posteroanterior (AP-PA) beams was mainly used until the early 2000s (**Fig. 1A**), including the Adjuvant Chemoradiation Therapy In Stomach Cancer (ARTIST) trial [14]. The AP-PA treatment planning technique does not consider the inhomogeneity of the human body and the resulting difference in radiation attenuation; therefore, the accuracy of the actual radiation dose distribution is limited. Hence, it is difficult to predict the exact radiation dose exposure and possible side effects in normal organs.

The application of computed tomography (CT) to RT planning has resulted in various developments not only in terms of calculating the radiation dose distribution in voxel units of tumor and normal organ volumes but also in terms of determining and combining various beam directions (**Fig. 1B**). Three-dimensional conformal radiotherapy (3D-CRT) treatment planning makes it possible to obtain the dose-volume histograms of tumors and normal organs and to predict the possibility of tumor control (tumor control probability) and side effects in normal organs (normal tissue complication probability). The radiation dose was increased while minimizing the risk of side effects. However, even after CT planning-based RT and 3D-CRT became more common, the AP-PA technique was frequently used in adjuvant RT for GC, especially when the remaining areas of the stomach were included as the target of RT. This is because the target area of RT is extremely large, and the volume of radiation exposure to the surrounding liver and kidneys inevitably increases when using multi-directional RT. The ARTIST-II study was performed using the 3D-CRT technique [11].

https://doi.org/10.5230/jgc.2023.23.e1

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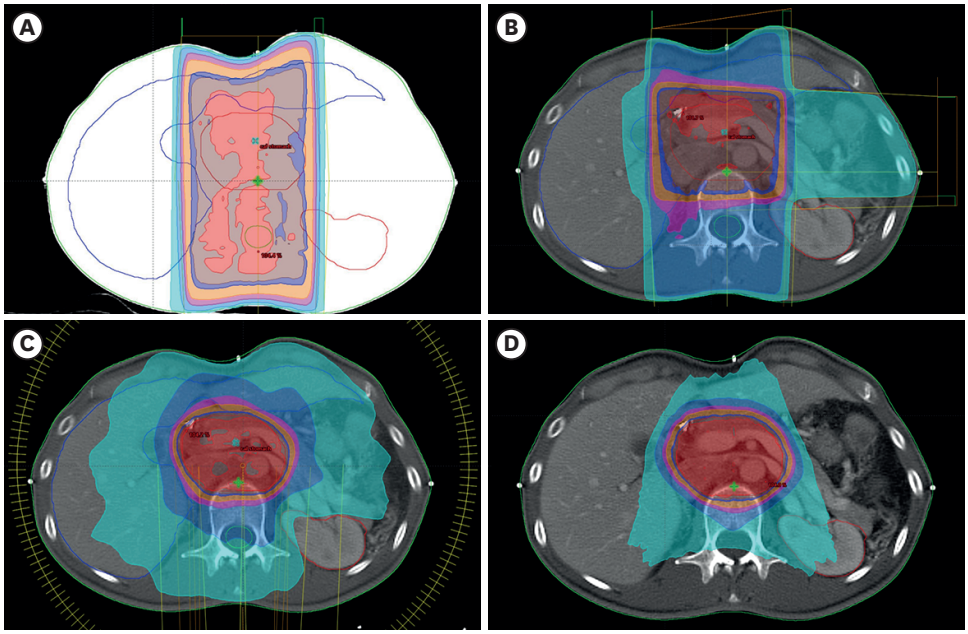

Fig. 1. Technical advancements in RT for gastric cancer. (A) The treatment planning of parallel opposite technique using anteroposterior-posteroanterior beams based on the dose distribution did not take into account the inhomogeneity of the human body. (B) Three-dimensional conformal RT planning using computed tomography made it possible calculate the radiation dose distribution in voxel units of tumor and normal organ volumes in the inhomogeneous human body and allowed the beams to radiate from various directions. (C) Intensity-modulated RT is a treatment method that delivers precise radiation to the tumor while minimizing radiation exposure to the surrounding normal organs by changing the position of the multi-leaf collimator with a width of 3–5 mm mounted on the radiation treatment machine, in real time and in multiple beam directions. (D) Particle beam RT showed highly conformal dose distribution from its unique characteristic called the "Bragg peak," which emits most of the radiation dose to a specific point determined according to the specific energy.
RT = radiotherapy.

Intensity-modulated radiotherapy (IMRT) is a type of CT planning-based RT similar to 3D-CRT, which enables the delivery of a precise radiation dose to the tumor while minimizing the radiation exposure to the surrounding normal organs (**Fig. 1C**). Meanwhile, 3D-CRT planning is used to determine the best dose distribution through a trial, and error process by the treatment planner, which enables a more favorable dose distribution through computer-based inverse treatment planning. This minimizes the radiation dose to the surrounding normal organs while delivering the required radiation dose to the tumor in voxel units such as a mosaic through a multi-leaf collimator. Based on these clear dosimetric advantages and insurance coverage for solid types of cancer, including GC, it has been the mainstay of RT in Korea since 2015 [16]. The ChemoRadiotherapy after Induction chemoTherapy of Cancer in the Stomach (CRITICS) trial was allowed to use either 3D-CRT or IMRT techniques to ensure a homogeneous dose delivery in the target area [17].

Recently, particle beam RT, including protons and heavy particles, has been commonly used for the treatment of gastrointestinal tumors and hepatocellular carcinoma [18]. The construction and use of proton and carbon-ion beam therapy centers are also increasing worldwide [19]. The proton beam RT uses a hydrogen nucleus, and its unique characteristic (the Bragg peak) enables the emission of most of the radiation dose to a specific point, which is determined according to the specific energy. This allows the delivery of an intensive radiation dose to the target tumor site and minimizes radiation exposure to the surrounding organs (**Fig. 1D**). The clinical application of proton beam RT in GC is extremely rare and is

https://doi.org/10.5230/jgc.2023.23.e1

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expected to show superior clinical outcomes owing to its ability to deliver a more precise, higher, and safer dose compared with IMRT, where the risk of gastrointestinal toxicities still remains, in patients with retroperitoneal lymph node (LN) recurrence or oligometastatic disease [20,21].

To ensure the accurate delivery of RT, the changes in the size, shape, and position of tumors as well as normal organs should be continuously monitored, which could change every day during the actual treatment delivery [22]. The latest RT machines are equipped with devices that can obtain images, including X-rays, cone-beam CT, or magnetic resonance, which can ensure the accurate delivery of radiation by reflecting the changes immediately before or during RT. Through accurate, high-precision image-guided RT, the side effects can be minimized, while tumor control is maximized in various oncologic fields.

DEFINITION OF THE GENERAL TARGET OF ADJUVANT RT FOR GC

The target of adjuvant RT is defined based on the postoperative recurrence pattern, especially that of LRR [23]. Although several studies have evaluated the pattern of tumor recurrence after curative surgery in GC patients, the pattern varied widely depending on the extent of the disease, geographic region, and adjuvant treatment used [24]. In particular, attention should be paid to the extent of lymphadenectomy, which largely affects the rates and patterns of LRR [25-28].

As shown in **Table 1**, the pattern and rate of LRR (10%–20%) after radical GC resection, including D2 resection and adjuvant treatment, are lower than those of distant metastasis, including peritoneal metastasis, in recent studies [26,28-34].

The target of adjuvant RT was defined as the potential area of local recurrence according to the location of the primary tumor, depth of invasion, and status of the resection margin. In general, RT for GC targets the tumor bed, remnant stomach, resection and/or anastomosis site, duodenal stump, and regional LNs. In patients with T4b stage, which is defined as

Table 1. Patterns of gastric cancer recurrence after curative resection

Study	Design	Year	Geographic region	Stage	No	Operation	Adjuvant treatment	Local*	Regional*	Peritoneal metastasis*	Hematogenous metastasis*
Smalley et al. [32]	RCT	2012	U.S.	≥T3 or N+	227	D0–1	Not used	8.0%	39.0%		18.0%
					282	D0–1	CCRT	2.0%	22.0%		16.0%
Songun et al. [30]	RCT	2010	Dutch	I–III	380	D1	Not used	21.6%	19.2%	34.2%	
					330	D2	Not used	12.1%	13.0%	29.7%	
Conrad et al. [33]	Retrospective	2016	Canada	≥T3 or N+	197	N.D.	CCRT	7.1%		28.9%	
Sakuramoto et al. [29]	RCT	2007	Japan	≥T2 or N+	530	R0/D2	Not used	2.8%	8.7%	15.8%	11.3%
					529	R0/D2	Chemotherapy	1.3%	5.1%	11.2%	10.2%
Bang et al. [31]	RCT	2012	Korea	≥T2 or N+	515	R0/D2	Not used	8.5%		10.9%	15.1%
					520	R0/D2	Chemotherapy	4.0%		9.0%	9.4%
Yu et al. [28]	RCT	2015	Korea	≥T2 or N+	228	R0/D2	Chemotherapy	4.8%	12.7%	16.2%	8.3%
					230	R0/D2	CCRT	4.8%	6.5%	16.1%	7.0%
Chang et al. [26]	Retrospective	2012	Korea	III	382	R0/D2	Chemotherapy	9.7%	27.5%	40.6%	23.8%
Pachaury et al. [34]	Retrospective	2022	India	N3	196	R0/D2	Chemotherapy or CCRT	All LRR 21.9% LRR only 10.7%		30.6%	20.9%

RCT = randomized controlled trial; CCRT = concurrent chemoradiotherapy; N.D. = not documented; LRR = locoregional recurrence.
*Cases of local and regional, peritoneal and regional, or peritoneal and hematogenous recurrence were reported together without distinction, were summed up, and presented in this table.

https://doi.org/10.5230/jgc.2023.23.e1

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infiltration of the surrounding organs, the tumor bed should be included as an RT target volume. The resection and/or anastomosis site could be included if the resection margin was not sufficient. The need to include the remnant stomach remains controversial, but recent domestic studies have reported that the risk of recurrence in this area is extremely low (1%–2%) after complete resection, even if it is not included in the target of adjuvant RT [26,28,35]. Additionally, the ARTIST and retrospective single-institutional Korean studies [26,28] showed that the most common sites of LRR after D2 lymphadenectomy were the para-aortic (LN station Nos. 16a2 and 16b1, and the upper part of 16b2), celiac (No. 9), hepatoduodenal (No. 12), retropancreatic (No. 13), and superior mesenteric vessels (No. 14). Based on the results of these studies, adjuvant RT generally included the secondary and tertiary LN stations after the perigastric LNs (**Fig. 2**, RT field of ARTIST-II); the potential IMRT plan and dose distribution according to this area are shown in **Fig. 3**.

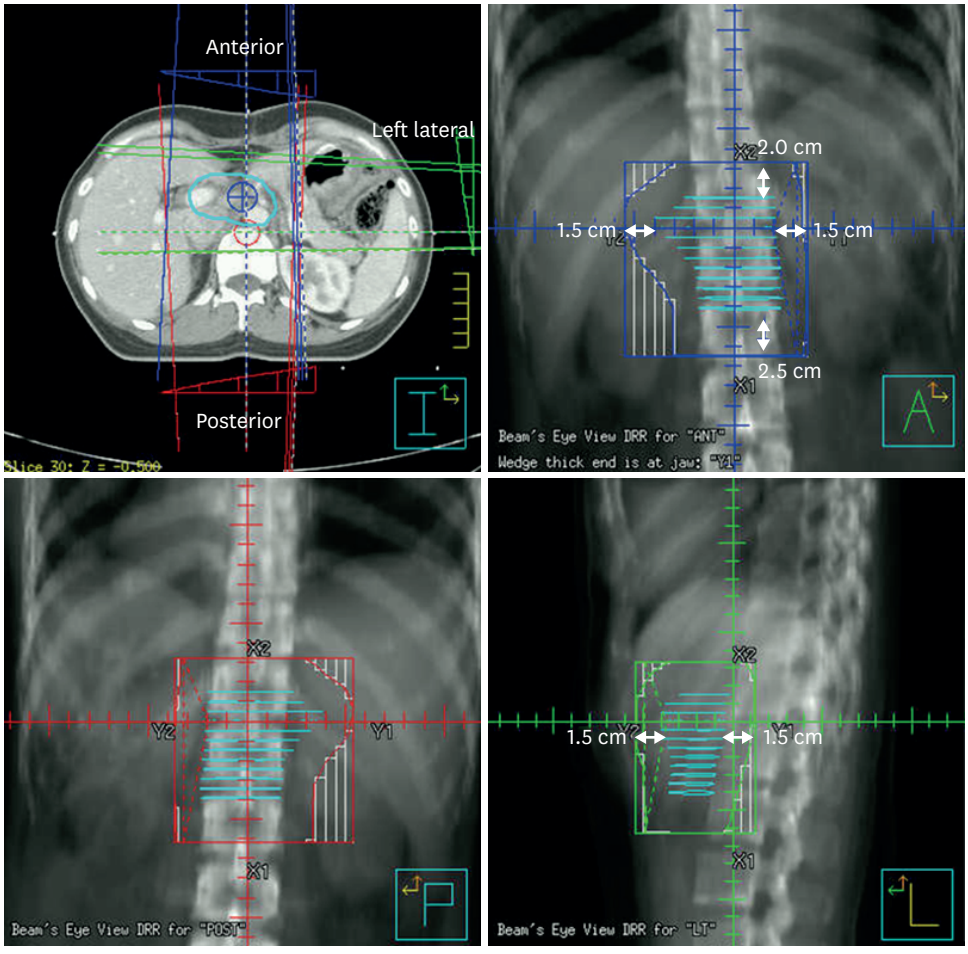

Fig. 2. Target definition and 3D-CRT planning recommended in the ARTIST-II trial. Based on the results of locoregional failure studies, secondary and tertiary lymphatic nodes including para-aortic (No. 16a2 to 16b1), celiac (No. 9), hepatoduodenal (No. 12), retropancreatic (No. 13), and superior mesenteric vessel (No. 14) were chosen as RT targets.
3D-CRT = three-dimensional conformal radiotherapy; ARTIST = Adjuvant Chemoradiation Therapy In Stomach Cancer; RT = radiotherapy.

https://doi.org/10.5230/jgc.2023.23.e1

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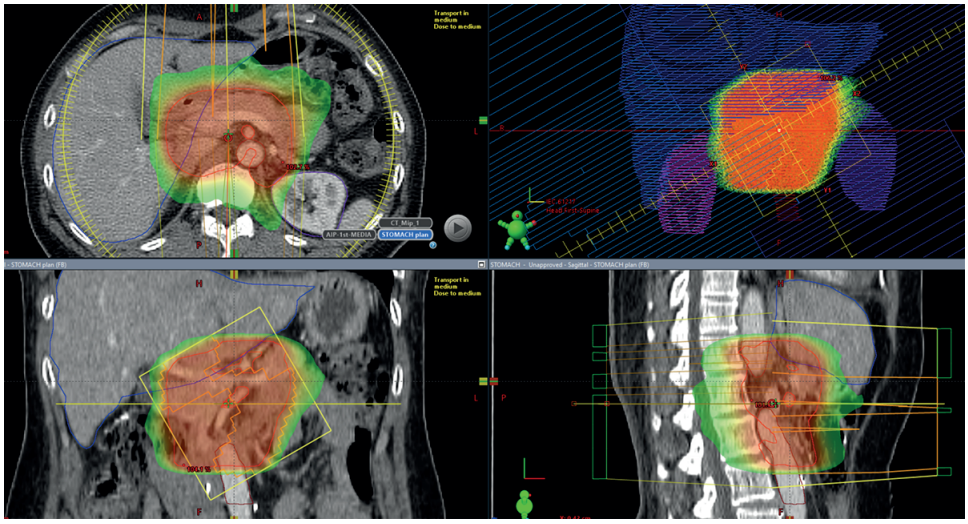

Fig. 3. Potential dose distribution of IMRT planning for targets recommended in ARTIST-II trial. It shows conformal dose distribution by controlling the radiation dose in voxel units through various beam directions and MLC position changes.
IMRT = intensity-modulated radiotherapy; ARTIST = Adjuvant Chemoradiation Therapy In Stomach Cancer; MLC = multileaf collimator.

ADJUVANT RT IN LESS THAN D2-RESECTED GC

The standard surgical management for localized GC is subtotal or total gastrectomy with D2 lymphadenectomy [36,37], although the oncological benefit of D2 over less than D2 lymphadenectomy remains unclear, which is restricted by the high morbidity and mortality rates due to the involvement of inexperienced surgeons, especially in Western countries [38]. The extent of D2 lymphadenectomy, as suggested in the Japanese guidelines, was defined as the resection of the secondary LN tier (LN stations No. 8–12) with perigastric LNs around the primary tumor, although a slight difference was found depending on the location of the primary tumor [39].

In the Dutch Gastric Cancer Trial (DGCT), the outcomes of D1 and D2 lymphadenectomy in GC were compared; D2 resection was associated with lower LRR and GC-related mortality, while D2 resection was closely associated with significantly higher postoperative mortality and morbidity rates [31]. In a randomized trial conducted by the Italian Gastric Cancer study group, D2 lymphadenectomy resulted in a marginally significant improvement in the disease-specific survival of patients with pathologic T2–4 and LN metastasis (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.36–1.06; P=0.078) [27]. According to a recent systematic review of retrospective studies, D2 lymphadenectomy with pancreas and spleen preservation has improved the survival outcomes of GC patients with higher T- and N-stage disease [40].

Therefore, D2 resection alone is not sufficient for managing GC, especially for locally advanced-stage disease. As discussed in the previous section, secondary LN tiers are the most common site of LRR in the para-aortic area and should be one of the targets of adjuvant RT. Based on this theoretical background, adjuvant RT can improve the treatment outcomes by lowering the LRR rate for patients with locally advanced-stage GC who underwent less than D2 resection.

In GC patients who have undergone less than D2 resection, adjuvant RT with concurrent chemotherapy (CRT) is generally recommended to improve the oncologic outcomes,

https://doi.org/10.5230/jgc.2023.23.e1

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including the local control rates [36,37]. Intergroup Study 0116 (INT-0116), a randomized phase III study conducted under the leadership of the Southwest Oncology Group published in 2001, confirmed the superiority of surgery with adjuvant CRT in improving the recurrence-free survival and overall survival (OS) rates compared with surgery alone [15]. Although D2 lymphadenectomy was recommended in the INT-0116 trial, D1 or less resection was performed in >90% of enrolled patients. Additionally, the beneficial effect of adjuvant CRT was detected in the subgroup that underwent D2 lymphadenectomy but not in the subgroup that underwent D2 lymphadenectomy [32].

A previous study compared the outcomes between patients enrolled in phase I–II studies evaluating the efficacy of intensified adjuvant CRT from the DGCT and those who did not receive conventional adjuvant treatment from the DGCT D1 and 2 lymphadenectomy study; results showed that adjuvant CRT decreased the LRR (2% vs. 8%, P=0.001) in patients who underwent D1 resection, whereas no significant difference was observed in patients who underwent D2 resection. Additionally, adjuvant CRT significantly improved the outcomes by reducing the LRR rate (6% vs. 26%; HR, 5.36; P=0.02) or increasing the 2-year OS rate (66% vs. 29%; HR, 2.91; P=0.002) in patients who underwent R1 (microscopically residual disease) resection compared with that in patients who underwent surgery alone [25].

ADJUVANT RT IN D2-RESECTED GC

Despite the results of the INT-119 trial, additional trials comparing adjuvant CRT with adjuvant chemotherapy have been conducted owing to the possibility that the benefit of reducing potential regional LN recurrence through adjuvant CRT may be attenuated during D2 resection.

The ARTIST trial was a phase III randomized trial conducted in a single Korean tertiary institution that compared the efficacy of adjuvant CRT with that of chemotherapy alone in patients with locally advanced GC who underwent complete resection with D2 lymphadenectomy. Although this trial reported a definite beneficial effect on the local control rate of the adjuvant CRT group (6.5% vs. 12.7%) [28], it failed to confirm the superiority of CRT in terms of disease-free survival (DFS), which was the primary endpoint of all enrolled patients [14]. Contrary to the main objective, the planned events were not reached after a median follow-up of >50 months (227 planned events, 127 actual events), and 60% of the patients in each arm included those with early-stage GC. The beneficial effect of adjuvant CRT was only observed when the patients with LN metastasis (estimated HR, 0.69; 95% CI, 0.47–1.00; P=0.05) were included, suggesting the need for a subsequent study on these patients.

The ARTIST-II trial, which compared the efficacy of two adjuvant chemotherapy regimens (S-1 [S-1 arm] and S-1 plus oxaliplatin [SOX arm]) and CRT (S-1 plus oxaliplatin and S-1 and RT [SOXRT arm]) in patients with D2-resected, stage II or III, node-positive GC, was conducted at multiple centers in Korea. Although this study was discontinued earlier than its original completion date, the results of the e interim analysis were sufficient to reach the endpoint. In this study, adjuvant CRT reduced the risk of recurrence compared with adjuvant S-1 monotherapy, although a significant P-value was not reached (HR, 0.724; 95% CI, 0.507–1.032; P=0.074). Compared with adjuvant doublet chemotherapy (TS-1 plus oxaliplatin), adjuvant CRT did not show any clinical benefit (HR, 0.971; 95% CI, 0.663–1.421; P=0.879). In terms of complications or quality of life, no significant differences were found according to the adjuvant treatment regimen used.

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In the CRITICS trial, a randomized phase III study conducted in Western countries, adjuvant CRT failed to show superior oncologic outcomes compared with adjuvant chemotherapy in D2-resected gastric or esophagogastric adenocarcinoma patients after neoadjuvant chemotherapy (HR from the stratified analysis, 1.01; 95% CI, 0.84–1.22; P=0.90) [12]. By contrast, adjuvant CRT showed significantly worse OS outcomes compared with chemotherapy alone in the post hoc per-protocol analysis (adjusted HR, 1.62; 95% CI, 1.24–2.12; P=0.0004) of patients who received adjuvant treatment [41]. In addition, the adjuvant CRT group showed significantly worse physical functioning and increased severity of dysphagia after treatment.

A previous meta-analysis of six randomized trials with similar designs was performed to compare the efficacy of adjuvant CRT with that of adjuvant chemotherapy alone in patients with complete D2-resected GC [11,12,14,28,41-46], including the abovementioned two recent studies, based on the results of a systematic review conducted according to the new version of the Korean Practice Guidelines for Gastric Cancer [47]. The overall detailed process and progress of the systematic review and meta-analysis of these guidelines will be published in another article; moreover, the full supporting data addressing the key question, "Could adjuvant concurrent chemoradiation improve the treatment outcomes compared with adjuvant chemotherapy alone in patients with pathological stage II or III who underwent curative gastrectomy with D2 lymph node dissection?", which is consistent with the topic discussed in this review, will be published separately in this journal [47]. A summary of the six randomized controlled trials evaluating the efficacy of adjuvant CRT in addition to adjuvant chemotherapy in patients with completely D2-resected GC included in this meta-analysis is presented in **Table 2**.

Table 2. Summary of 6 randomized controlled trials included in the meta-analysis

Study (yr)	Patients	Geographic region	Intervention/ Comparator	OS	DFS	LRR	Toxicities
Park et al. (2021) [11]	Curatively D2-resected stage II–III, node-positive GC (n=546)	Korea	CRT (SOXRT, n=183), CA (SOX, n=181), CA (S-1, n=182)	Not reported	At 3 years: CRT (SOXRT, 72.8%), CA (SOX, 74.3%), CA (S-1, 64.8%)	Not reported	All toxicities: CRT (SOXRT, 60%), CA (SOX, 70%), CA (S-1, 69%)
Cats et al. (2016) [12]	Stage IB–IVA resectable gastric or GE AD after perioperative chemotherapy and surgery (n=788)	Netherlands, Sweden, Denmark	CRT (XPRT, n=395), CA (EXP or EXO, n=393)	At 5 years: CRT (40%), CA (42%)	At 5 years: CRT (38%), CA (39%)	CRT: 11.2% (27/241), CA: 15.0% (35/233)	Gr ≥3 toxicities: XPRT: 45% (111/245), EXP or EXO: 57% (135/233)
Lee et al. (2012) [14]	Curatively D2-resected stage IB–IVA GC (n=788)	Korea	CRT (XPRT, n=230), CA (XP, n=228)	At 5 years: CRT (75%), CA (73%)	At 3 years: XPRT (78.2%), XP (74.2%)	CRT: 6.5% (15/230), CA: 12.7% (29/228)	Treatment modification: XPRT: 35% (80/230), XP: 52% (119/228)
Kim et al. (2012) [43]	Curatively D2-resected stage II–IVA GC (n=90)	Korea	CRT (FLRT, n=46), CA (FL, n=44)	At 5 years: CRT (65.2%), CA (54.6%)	At 5 years: CRT (60.9%), CA (50.0%)	CRT: 10.9% (5/46), CA: 23.3% (7/30)	Hematologic and GI toxicities: CRT 19.6% and 17.4% (8/46), FL 25% and 11.4% (5/44)
Zhu et al. (2012) [44]	Curatively D2-resected stage II–IVA GC (n=351)	China	CRT (FLRT, n=186), CA (FL, n=165)	At 5 years: CRT (48.4%), CA (41.8%)	At 5 years: CRT (45.2%), CA (35.8%)	CRT:15.6% (29/186), CA: 24.2% (40/165)	GI toxicities: CRT: 5.9% (11/186), CA: 0.0% (0/165)
Kwon et al. (2010) [42]	Curatively D2-resected stage II–IVA GC (n=61)	Korea	CRT (XRT, n=31), CA (FP, n=30)	At 5 years: CRT (70.1%), CA (70.0%)	At 5 years: CRT (76.7%), CA (59.1%)	CRT: 12.9% (4/31), CA: 23.3% (7/30)	GI toxicities: CRT: 9.7% (3/31), CA: 13.3% (4/30)

OS = overall survival; DFS = disease-free survival; LRR = locoregional recurrence; GC = gastric cancer; CRT = chemoradiotherapy; SOXRT = S-1 plus oxaliplatin and S-1 and radiotherapy; CA = chemotherapy alone; SOX = S-1 plus oxaliplatin; GE AD = gastro-oesophageal adenocarcinoma; XPRT = capecitabine plus cisplatin with radiotherapy; EXP or EXO = epirubicin + cisplatin or oxaliplatin + capecitabine; XP = capecitabine plus cisplatin; FLRT = fluorouracil plus leucovorin with radiotherapy; FL = fluorouracil plus leucovorin GI = gastrointestinal.

https://doi.org/10.5230/jgc.2023.23.e1

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This meta-analysis showed that the addition of adjuvant CRT can significantly reduce the LRR compared with chemotherapy alone (HR, 0.62; 95% CI, 0.48–0.81; P=0.0004), although all studies analyzed only patients with GC who underwent complete gastrectomy with D2 resection. Contrary to the general concerns, no significant difference was observed in the incidence of grade 3 toxicities or higher between the two groups (HR, 0.85; 95% CI, 0.63–1.13; P=0.26). Although adjuvant CRT showed superior outcomes compared with adjuvant chemotherapy alone in terms of DFS (HR, 0.85; 95% CI, 0.713–0.98; P=0.03) in the analysis conducted in all patients, this difference was not significant when platinum-based combination chemotherapy was administered (HR, 0.91; 95% CI, 0.78–1.07; P=0.24). Interestingly, adjuvant CRT in combination with adjuvant platinum-based combination chemotherapy had no beneficial effects, thus suggesting that the same pattern was observed in a recently published ARTIST-II trial conducted in patients with more advanced-stage disease with LN metastases [11]. The addition of adjuvant CRT did not improve the OS in patients treated with adjuvant chemotherapy alone (HR, 0.96; 95% CI, 0.81–1.14; P=0.58) or in patients treated with platinum-based combination chemotherapy (HR, 1.03; 95% CI, 0.87–1.23; P=0.70).

According to the outcomes of the above 2 large-scale multicenter studies and/or meta-analyses, adjuvant RT cannot be recommended in patients who underwent GC after complete gastrectomy with D2 resection, at least when adjuvant platinum-based combination chemotherapy is administered.

POTENTIAL APPLICATION OF ADJUVANT RT IN GC

Considering the outcomes of recent studies, the role of adjuvant RT in patients with GC who underwent complete gastrectomy with D2 resection, the standard surgical modality for advanced-stage GC in Korea, is not considered significant, especially in patients who received adjuvant platinum-based combination chemotherapy. Therefore, adjuvant RT is not currently recommended in this patient group.

In patients who underwent micro- or macroscopically incomplete resection of localized GC, which is not generally indicated in clinical trials, and/or less than D2 resection of GC, adjuvant CRT before or after standard chemotherapy may still be considered as part of adjuvant treatment, based on the results of INT-0116 [15]. However, this treatment should not be included as part of the standard treatment, owing to the lack of sufficiently validated research. Efforts to identify a subgroup whose main recurrence pattern is LRR and the use of adjuvant RT to improve the cure rate should be continuously implemented. Our group has conducted several studies in this aspect and suggested that the addition of adjuvant CRT is particularly effective in patients with complete D2-resected GC who do not have preoperative sarcopenia [48], have a non-mesenchymal subtype [49], are older than 45 years at diagnosis [50], and have an adequate absolute lymphocyte count prior to surgery [51].

The classification of cancer has recently changed and is determined based on molecular characteristics, including human epidermal growth factor receptor 2 overexpression, mismatch repair deficiency, microsatellite instability, and Epstein-Barr virus infection status [52,53]. Additionally, these characteristics are strongly related to the effects of chemotherapy, immunotherapy, and RT [54-56]. Hence, future studies should continue the application of RT as a tailored adjuvant treatment, according to the molecular characteristics of patients with GC.

https://doi.org/10.5230/jgc.2023.23.e1

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CONCLUSION

In GC, early diagnosis and minimally invasive treatment through screening programs are being established, and treatment outcomes have greatly improved. The development of surgical techniques and chemotherapy before and after surgery has played an important role in these improvements. Although RT is a major locoregional modality in the field of oncology, it is effective in many types of malignancies. However, several randomized trials have confirmed that the benefit of adjuvant RT in GC patients who underwent complete resection, including D2 lymphadenectomy and (neo-)adjuvant chemotherapy, is largely limited. Therefore, adjuvant RT should only be considered in patients with locally advanced-stage tumors that have not been completely resected or those who have undergone less than D2 lymphadenectomy. In addition, continuous efforts, including molecular characterization, are required for personalized management of GC.

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