

Postoperative Adjuvant Radiotherapy for Patients with Gastric Adenocarcinoma

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In gastric adenocarcinoma, high rates of loco-regional recurrences have been reported even after complete resection, and various studies have been tried to find the role of postoperative adjuvant therapy. Among them, Intergroup O116 trial was a landmark trial, and demonstrated the definite survival benefit in adjuvant chemoradiotherapy, compared with surgery alone. However, the INT O116 trial had major limitation for global acceptance of the INT O116 regimen as an adjuvant treatment modality because of the limited lymph node dissection. Lately, several randomized studies that were performed to patients with D2-dissected gastric cancer were published. This review summarizes the data about patterns of failure after surgical resection and the earlier prospective studies, including INT O116 study. Author will introduce the latest studies, including ARTIST trial and discuss whether external beam radiotherapy should be applied to patients receiving extended lymph node dissection and adjuvant chemotherapy.

Key Words: Stomach neoplasms; Radiotherapy; Adjuvant

Introduction

The postoperative adjuvant radiotherapy (RT) has been rarely applied to patients with gastric cancer, especially in Eastern country, such as Korea and Japan. The relatively underestimated role of RT in resected gastric cancer mainly comes from the undoubted role of surgery with extended lymph node dissection, the higher metastatic risk than that of loco-regional recurrence after radical surgery and the exaggerated concern of radiation complication. However, even after complete resection, high rates of loco-regional recurrences have been reported,⁽¹⁻¹⁰⁾ and RT combined with chemotherapy have decreased the loco-regional failure and improved the overall survival in some retrospective studies for unresectable or

residual disease after surgery.^(11,12)

After the introduction of the Gastrointestinal Cancer Intergroup Trial (INT 0116), the largest phase III trial to compare surgery alone versus postoperative chemoradiotherapy (CRT),⁽¹³⁾ the adjuvant RT combined with chemotherapy has attracted increasing attention and a series of prospective studies have been published, including Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial.⁽¹⁴⁾ However, the INT 0116 trial had a major limitation for global acceptance of the INT 0116 regimen as an adjuvant treatment modality. The limited lymph node dissection (D0 or D1), which was considered as suboptimal surgical resection in Eastern country, was performed in 90% of enrolled patients of the INT 0116 trial. Therefore, the investigation of the efficacy of postoperative CRT in patients with gastric cancer with curative resection and extended D2 lymph node dissection is increasingly important.

This review summarizes the data about patterns of failure after surgical resection and the earlier prospective studies, including INT 0116 study. The author will introduce the latest studies, including ARTIST trial, and discuss the role of adjuvant RT, which is performed in addition to surgery and chemotherapy in patients with

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gastric adenocarcinoma.

Patterns of Failure after Surgical Resection

There are several data (Table 1) analyzing the patterns of failure after curative resection, and they could be divided into three groups according to the purpose of analysis. The autopsy data showed the final results of disease failure, (1-3) re-operation data focused to the patients with potentially high risk for recurrence, (4,5) The clinical data (6-10) showed recurrence, which could be detected with clinical examination and imaging studies during the follow-up period. These patterns of failure data need to be interpreted with caution due to different definition of recurrence, different tumor stage and different surgical extension, especially the extent of lymph node dissection.

With the extended lymph node dissection, such as D2 dissection, local recurrence rate can be decreased and the relative rate of liver

metastasis or peritoneal seeding can be increased. (9,10) However, loco-regional recurrence developed in many patients after surgical resection and the percentage of loco-regional recurrence without liver metastasis or peritoneal seeding was as high as 20%.

Prospective Randomized Studies for Adjuvant Radiotherapy

The purpose of adjuvant RT is to improve loco-regional control, and combined CRT is a logical postoperative adjuvant treatment for gastric cancer. When combined CRT is applied, 5-fluorouracil (5-FU) is most commonly used chemotherapeutic agent for the radio-sensitization effect. The earlier prospective randomized studies before INT 0116 trial were shown in Table 2. Dent et al. (15) randomly assigned 142 patients, according to the disease status, and there was no difference in survival between the concurrent CRT and control groups in either patient cohort. Another study by Moertel et al. (16) randomly assigned 62 patients with poor prognosis gastric carcinoma to receive concurrent CRT or observation. The 5-year survival rate for patients randomized to treatment was 23%, and for those randomized to no treatment, 4% ($P < 0.05$). However, when analyzed according to actual treatment received, the difference was not significant because of small patient numbers. The British Stomach Cancer Group compared the results of surgery alone, adjuvant RT and adjuvant chemotherapy. (17) There was no survival advantage for those patients receiving either adjuvant therapy compared to those undergoing surgery alone, but the loco-regional failure rate was lowest in patient with the adjuvant RT group.

Overall, it is difficult to make conclusion from these studies be-

Table 1. Patterns of failure after surgical resection

Recurrence sites	Clinical (6-10)	Reoperation (4,5)	Autopsy (1-3)
Loco-regional	19~45%	69%	80~93%
Peritoneal seeding	23~44%	42%	30~50%
Distant metastasis	35~52%	23%	49%
Loco-regional failure			
Gastric bed	21%	55%	52~68%
Anastomosis/stump	6~25%	27%	54~60%
Abdominal/stab wound	-	5%	-
Lymph nodes	8~13%	43%	52%

Table 2. Prospective randomized studies – before INT 0116 trial

Study	Stage	Group	Patient number	Treatment RT/CTx	Survival	P-value
Dent et al. (15)	T1~3, N1~2, M0	Control	31	-	No difference	NS
		CCRT	35	20 Gy/5-FU		
	T4 or M1	Control	26	-		
		CCRT	26	20 Gy/5-FU		
Moertel et al. (16)	LN (+), T4	Control	23	-	5-yr SR 4%	<0.05
		CCRT	39	37.5 Gy/5-FU		
		CTx	24	Thiotepa		
BSCG (17)	Stage II~IVA	Control	145	-	5-yr SR 20%	NS
		RT	153	45 Gy		
		CTx	138	5-FU, ADR, MMC		

RT = radiotherapy; CTx = chemotherapy; CCRT = concurrent chemoradiotherapy; 5-FU = 5-fluorouracil; NS = not-significant; LN = lymph node; SR = survival rate; BSCG = British Stomach Cancer Group; ADR = Adriamycin; MMC = mitomycin-C.

cause of their heterogeneous cohort, small number of patients, failure to standardize surgery and suboptimal dose of RT and 5-FU. Therefore, the INT 0116 trial was very interesting and demonstrated a definite survival benefit with the CRT group in 3-year overall survival rates of 50% and 41% for the postoperatively treated and surgery-alone groups, respectively.(13) According to the updated data with a more than 10-year median follow-up, overall survival and relapse-free survival data demonstrate continued strong benefit from postoperative CRT and the reduction of loco-regional failure may account for the majority of overall relapse reduction.(18) However, only 10% of patients underwent D2 resection and this questioned whether the survival benefit seen in INT 0116 trial was simply compensatory for suboptimal surgery and whether CRT would still be required for patients receiving a D2 resection. In this trial, when subgroup analysis was performed in the D2 resected patients and the overall survival was compared according to treatment arm, and there was no difference between the two groups. However, because the numbers were only 34 and 20 patients in the adjuvant and observation groups, respectively, it was difficult to draw any conclusion.

Postoperative Chemoradiotherapy in D2-dissected Gastric Cancer

Although some Western randomized studies(19,20) showed negative results of extended lymph node dissection, several historical data and recent studies(21–24) reported that extended (D2) lymph node dissection leads to better results than limited (D1) lymph node dissection in loco-regional recurrence or overall survival. In addition, gastrectomy with D2 lymph node dissection has become a

standard surgical procedure for patient with gastric cancer. Until now, there have been many studies to find adjuvant effect of RT, chemotherapy or CRT after surgery. However, randomized studies done to patient cohort with D2-dissected gastric cancer is uncommon, and lately, a few randomized studies that were performed to patients with extended lymph node dissection were published. According to ACTS-GC and CLASSIC trials,(25,26) adjuvant chemotherapy after curative D2 gastrectomy improved 3-year overall survival and disease-free survival compared with surgery only, and should be considered as a treatment option for patients with operable gastric cancer. In this point, we need to discuss whether there is an additional role of adjuvant RT to patients receiving extended lymph node dissection and adjuvant chemotherapy.

Table 3 shows several gastric cancer studies, which were performed to patients with D2 gastrectomy. Kim et al.(27) reported observational study that showed an advantage in overall survival in patients who underwent a D2 lymph node dissection plus postoperative CRT (INT-0116 scheme) compared with those who underwent D2 lymph node dissection alone. In this observational study, when patterns of failure were analyzed, adjuvant CRT significantly decreased the regional lymph node recurrence rates, and there was no difference in distant metastasis between the two cohorts. Dikken et al.(28) retrospectively compared survival and recurrence patterns in patients from the Dutch Gastric Cancer Group Trial that randomly assigned patients between D1 and D2 lymph node dissection. They concluded that after D1 surgery, the addition of postoperative CRT had a major impact on local recurrence in resectable gastric cancer, and there was no additional effect of adjuvant CRT after D2 surgery.

We know that a prospective randomized trial can provide

Table 3. Gastric cancer studies performed to patients with D2 gastrectomy

Study	Stage	Group	Patient number	Treatment RT/CTx	Survival	P-value
Kim et al.(27)	II~IVA	Control	446	-	MS 63 mo	0.02
		CCRT	544	45 Gy/FL	95 mo	
Dikken et al.(28)	-	Control	325	-	2-yr LRR 13%	0.84
		CCRT	25	45 Gy/FL, XP	12%	
ARTIST(14)	IB~IVA	CTx	228	XP	3-yr DFS 74.2%	0.08
		CCRT	230	45 Gy/XP	78.2%	
Zhu et al.(29)	IB~IVA	CTx	175	FL	MS 48 mo	0.12
		CCRT	205	45 Gy/FL	58 mo	

RT = radiotherapy; CTx = chemotherapy; CCRT = concurrent chemoradiotherapy; FL = fluorouracil, leukovorin; MS = median survival; XP = capecitabine, cisplatin; LRR = local recurrence rate; ARTIST = Adjuvant Chemoradiation Therapy in Stomach Cancer; DFS = disease-free survival.

definite answers to the question whether postoperative RT has a clinical benefit over surgery with extended lymph node dissection and adjuvant chemotherapy. Currently, three such studies aim to answer this question. First, the ARTIST trial(14) randomly assigned 458 patients to chemotherapy arm and CRT arm. The conclusion of ARTIST trial was that the addition of RT to chemotherapy did not significantly reduce recurrence, except lymph node positive patients, and a subsequent trial (ARTIST-II) in patients with lymph node positive gastric cancer is planned. Interestingly, Zhu et al.(29) recently reported on a similar trial conducted in a Chinese population. They used intensity-modulated radiotherapy (IMRT) as RT technique and observed a significant difference in disease-free survival not only in patients with positive nodes, but in the whole population. In the third study (CRITICS), patients will receive neo-adjuvant chemotherapy, followed by D2 lymphadenectomy, and will be randomly assigned to the three additional courses of chemotherapy or CRT.

From these studies, which were performed to the patients with D2-dissected gastric cancer, we can summarize that the addition of RT to surgery and chemotherapy did improve disease-free survival, even though there were no influence on the overall survival. Because the improvement in disease-free survival mainly came from the radiation effect decreasing regional lymph node recurrence, when the subgroup of patients with pathologic lymph node metastasis were analyzed, patients randomly assigned to the CRT arm experienced superior disease-free survival, compared with those who received chemotherapy alone in the ARTIST trial. In the author's personal experience, the role of RT was to decrease the recurrence of regional lymph nodes (mainly Group 3 lymph nodes including some Group 2 lymph nodes), which could not be dissected even with extended lymph node dissection. Therefore, adjuvant RT should be considered to the patients with D2-dissected gastric cancer with pathologically positive lymph node metastasis, especially to those with advanced N stage. This opinion might be supported by the study(30) that analyzed patterns of regional recurrence after curative gastrectomy and D2 lymph node dissection in patients with stage III (N3) gastric cancer. According to this study, the most prevalent nodal recurrence in patients with advanced gastric cancer was in the nodal basin outside the D2 dissection field.

Conclusions

From the INT-0116 study, we could get the conclusion that the adjuvant CRT demonstrated survival benefit to the patients with

sub-optimally resected gastric cancer. When extended lymph node dissection was done, adjuvant chemotherapy improved survival compared with surgery only. Whether or not postoperative RT has a clinical benefit over surgery with extended lymph node dissection and adjuvant chemotherapy is still under investigation. However, ARTIST trial showed that an addition of RT made an improvement in disease-free survival in patients with pathologic lymph node metastasis, and lead to the assumption that the patients with gastric cancer benefit more from CRT than chemotherapy, as more advanced their cancers are. In addition, further investigation to find the highly selected patients who can be beneficial from adjuvant RT will be followed by ARTIST-II trial.

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