



## Original Article

# Evaluating the benefit of adjuvant radiotherapy after extensive lymph node dissection for gastric cancer: a single-institute retrospective study

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## ABSTRACT

**Objective:** This study aimed to evaluate whether adjuvant radiotherapy (RT) can improve the treatment outcome of patients with locally advanced gastric cancer who underwent extensive lymph node dissection (ELND). **Materials and Methods:** This retrospective study included patients with gastric cancer pathological stages IIA–IIIC at Taipei Tzu Chi Hospital between 2008 and 2015. Patients (a) aged >80 years, (b) with distant metastasis at diagnosis, (c) with coexisting malignancies, (d) who did not complete the prescribed RT course, and (e) who died 1 month after surgery were excluded. Among 420 patients diagnosed with gastric cancer, 98 were included. **Results:** The median follow-up was 24.5 months. Of 39 patients who underwent adjuvant RT, 38 also received adjuvant chemotherapy (CT). Of 59 patients who did not receive adjuvant RT, only 34 received adjuvant CT. ELND was performed in 67.3% of the patients. The 5-year overall survival (OS) rate was 40%. In the univariate analyses, adjuvant CT regimen, 5-fluorouracil + leucovorin, was associated with worst outcome, while TS-1 was associated with better survival outcome ( $P = 0.018$ ). The number of involved lymph nodes was strongly related to the OS and disease-free survival (DFS) ( $P < 0.001$ ). We tried using different numbers of involved lymph nodes as a cutoff point and found that adjuvant RT significantly improved both OS and DFS in patients whose involved lymph nodes were  $\geq 4$  (OS,  $P = 0.017$ ; DFS,  $P = 0.015$ ). In multivariate analyses, better DFS was associated with negative surgical margin ( $P = 0.04$ ), earlier disease stage ( $P = 0.001$ ), adjuvant radiotherapy ( $P = 0.045$ ), and adjuvant CT regimen TS-1 ( $P = 0.001$ ). **Conclusion:** Adjuvant RT could improve DFS of patients with locally advanced gastric cancer with or without ELND. When the number of involved lymph nodes is  $\geq 4$ , adjuvant RT is strongly suggested.

**KEYWORDS:** Adjuvant, Chemotherapy, Dissection, Gastric cancer, Radiotherapy

## INTRODUCTION

The standard treatment for locally advanced gastric cancer differs between Western countries and Asian countries. Perioperative chemotherapy (CT) [1] or postoperative chemoradiation (CRT) [2] are recommended for resectable gastric cancer in Europe and North America, while postoperative CT is the standard treatment according to the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer [3] and adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC) [4] trials in Asian countries. The different attitudes toward adding radiotherapy (RT) to the adjuvant treatment are partly related to the extent of lymph node dissection. The INT-0116 study [2], which was conducted in the US, was criticized mainly because only 10% of patients

received D2 dissections, while in Asian published studies, D2 dissection remained the mainstream surgical treatment for gastric cancer. Although the added value of postoperative chemoradiotherapy after a D2 dissection has been established in various studies [5,6], it remains unclear whether adjuvant CT or CRT is the best form of adjuvant therapy.

To answer the question, in 2012, the Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial


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[7] reported that the addition of RT to adjuvant CT did not significantly reduce recurrence after D2 dissection. However, in the large subgroup of node-positive patients (86.5%), postoperative chemoradiotherapy improved patients' outcome [8]. By contrast, the CT versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS) study claimed that postoperative chemoradiotherapy did not provide better survival outcomes compared with postoperative CT [9], which adjuvant treatment modality is optimal after D2 dissection remains inconclusive. This study aimed to review the treatment details and outcomes of patients with locally advanced gastric cancer at Taipei Tzu Chi Hospital, Taiwan.

## MATERIALS AND METHODS

### Patients

In this retrospective study, we included patients with pathologically confirmed gastric adenocarcinoma who underwent curative surgical resection at Taipei Tzu Chi Hospital from January 2008 to September 2015. Tumor staging was performed according to the AJCC/UICC TNM staging manual, 7<sup>th</sup> edition, and lesions staged as IIA–IIIC were included.

Patients (a) aged >80 years, (b) with distant metastasis at diagnosis, (c) with coexisting malignancies, (d) who did not complete the prescribed RT course, and (e) who died 1 month after surgery were excluded.

In the period of our study, 420 patients were diagnosed with gastric cancer at our hospital and 98 were selected for analysis based on the abovementioned criteria.

### Treatment regimen

#### Surgery

Patients who had curative and *en bloc* tumor resection were eligible for inclusion of our study. Due to the heterogeneity of the operative records, the exact lymphadenectomy D level cannot be specified. The median number of nodes examined after performing D2 lymphadenectomies at the National Cancer Center Hospital in Tokyo, Japan, and at Seoul National University Hospital in South Korea was >25–30 [10]. In a series of 367 patients with recurrent gastric adenocarcinoma from the Memorial Sloan Kettering Cancer Center, 81% of the patients had a D2 or more extensive lymphadenectomy and the median number of lymph nodes removed was 22 [11]. As an alternative to D2 dissection, extensive lymph node dissection (ELND) was defined as dissection of  $\geq 25$  nodes or more in our study.

#### Chemotherapy

Thirty-one patients in our study did not receive any CT. Meanwhile, 29 patients received high-dose fluorouracil and leucovorin-based CT[12] alone ( $n = 7$ ) or combined with oxaliplatin ( $n = 13$ ), carboplatin ( $n = 2$ ), or cisplatin ( $n = 7$ ). Oral TS-1 (tegafur + gimeracil + oteracil), 2 caps, PO, BID, was administered in 17 patients, while oral UFT (tegafur 100 mg and uracil 224 mg) 1 cap, PO, TID, was administered in 14 patients.

### Radiotherapy

The timing for adjuvant RT ranged from 2 to 6 weeks after the surgery. We used computerized tomography simulation and conformal treatment planning such as intensity-modulated radiation therapy (IMRT) or intensity-modulated arc therapy to deliver a lower dose of radiation to the organs at risk (e.g., heart, lungs, liver, kidneys, and small bowel). Patients were instructed to avoid taking heavy meal 3 h before simulation and treatment. They were treated in the supine position. Uncertainties from variations in stomach filling and respiratory motion were also considered. The clinical target volume (CTV) was individualized based on the extent and location of the primary tumor and involved lymph nodes and the type of surgery performed. The lymphatic drainage areas in the radiation fields included perigastric, celiac, splenic hilar, suprapancreatic, porta hepatis, pancreaticoduodenal, and local para-aortic nodes. In patients with tumors located at the gastroesophageal junction, paracardial and paraesophageal lymph nodes were included in the radiation fields, while pancreaticoduodenal region was not irradiated. The planning target volume consisted of the CTV with a 1-cm margin. The 45 Gy of radiation was delivered in 25 fractions, 5 days per week, to the tumor bed, regional nodes, and 2 cm beyond the proximal and distal margins of resection.

### Statistical methods

Overall survival (OS) was recorded from the date of radical surgery until death of any cause or last contact with the patient or any family member. Disease-free survival (DFS) was measured from the date of radical surgery to the date of the first disease recurrence. Locoregional recurrence was defined as recurrence at the anastomosis site, duodenal stump, tumor bed, remnant stomach, or regional lymph nodes within the RT field. Distant metastasis was defined as lymph node recurrence outside of the RT field, peritoneal seeding, liver metastasis, or metastasis to other extra-abdominal sites.

The Chi-square test and Student's *t*-test were used to compare the characteristics between with adjuvant RT group and without adjuvant RT group. The Kaplan–Meier method was used to estimate survival, while the log-rank test was used to determine significance. A Cox proportional-hazards model was used to estimate the prognostic factors for survival. SPSS software for Windows version 24.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Statistical significance was assumed when the *P* value fell below 0.05.

### Ethical approval

This study has been approved by the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation Institutional Review Board on Nov.,17, 2016 (IRB No. 05-X27-090). The constitution and operation of this review board are according to the guidelines of ICH-GCP. The informed patient consent was waived by the IRB.

## RESULTS

### Patients' characteristics

Patients' characteristics are shown in [Table 1]. Among the 98 patients in the study, 66 were men and their median

**Table 1: Patients' characteristics**

Characteristics	RT (n=39)	Without RT (n=59)	P
Gender			0.828
Male	27	39	
Female	12	20	
Age (years)			<0.001
Mean	55.62	67.46	
Range	28-76	30-80	
T classification			0.432
T1	1	0	
T2	1	5	
T3	23	42	
T4	14	12	
N classification			<0.001
N0	4	24	
N1	3	16	
N2	16	10	
N3	16	9	
Stage			0.003
2A	2	14	
2B	3	16	
3A	7	9	
3B	14	8	
3C	13	12	
ELND	32/39	34/59	0.012
Number of dissected LNs			0.001
Mean	38.49	28.08	
Range	16-90	3-57	
Number of involved LNs			<0.001
Mean	11.28	3.95	
Range	0-71	0-17	
Margin			0.399
R0	37	52	
R1/R2	2	7	
Chemotherapy regimen			<0.001
HDFL	26	3	
TS-1	3	14	
UFT	2	12	
Misc	7	0	
None	1	30	

ELND: Extensive lymph node dissection, HDFL: High-dose 5-FU/leucovorin, LNs: Lymph nodes, UFT: Uracil-Tegafur

age was 64 years (range: 28–80). Meanwhile, 66 patients underwent ELND. The median number of dissected nodes was 31 (range: 3–90). Seventy patients had regional nodal involvement and 9 had close or involved margins. Sixty-seven patients underwent adjuvant CT and 39 had adjuvant RT.

Patients who received adjuvant RT and those who did not receive adjuvant RT were compared. Of 39 patients who underwent adjuvant RT, only 38 received adjuvant CT. Of 59 patients who did not receive adjuvant RT, only 34 received adjuvant CT.

Those who underwent RT were significantly younger (55.62 vs. 67.46 years,  $P < 0.001$ ), with more involved lymph nodes (11.28 vs. 3.95,  $P < 0.001$ ), and with more advanced disease ( $P = 0.003$ ). The CT regimen in the RT group was mostly 5-fluorouracil (5-FU) + leucovorin

**Table 2: Univariate analysis**

Variable	Number of patients	Mean OS (months)	P	Mean DFS (months)	P
ELND			0.329		0.539
Yes	66	57.99		56.42	
No	32	47.26		48.57	
Adjuvant RT			0.528		0.662
Yes	39	43.96		42.36	
No	59	53.95		53.40	
Adjuvant Chemotherapy			0.023		0.018
No	31	43.65		41.10	
HDFL	29	32.10		28.95	
TS-1	17	83.45		83.39	
UFT	14	47.29		50.28	
Misc	7	65.65		65.19	
Margin			0.914		0.733
R0	89	54.86		54.02	
R1/R2	9	38.34		37.91	

OS: Overall survival, DFS: Disease-free survival, HDFL: High-dose 5-FU/leucovorin, ELND: Extensive lymph node dissection, RT: Radiotherapy, UFT: Uracil-Tegafur

(26 of 39), while more than half of the group without RT did not receive CT (30 of 59).

### Survival and relapse

The median follow-up was 24.5 months (range: 3–106 months). A total of 51 patients died; of them, 38 died due to disease recurrence (local, 8; regional, 11; and distant, 19), while 13 died due to other causes. Overall, the 5-year survival rate was 40% and the median OS was 44.7 months. The 5-year DFS rate was 40% and the median DFS was 39.1 months.

The prognostic factor for both OS and DFS identified in the univariate analysis is adjuvant CT [Table 2]. The regimen 5-FU + leucovorin was associated with worst outcome, while TS-1 was associated with better survival outcome. Whether patients had ELND or adjuvant RT did not show a significant difference.

As shown in [Table 3], in the multivariate analysis, better OS was associated with earlier disease stage ( $P = 0.003$ ), adjuvant RT ( $P = 0.058$ ), and adjuvant CT regimen TS-1 ( $P = 0.001$ ). Better DFS was associated with negative surgical margin ( $P = 0.04$ ), earlier disease stage ( $P = 0.001$ ), adjuvant RT ( $P = 0.045$ ), and adjuvant CT regimen TS-1 ( $P = 0.001$ ) or UFT ( $P = 0.034$ ).

To determine whether adjuvant CT or RT is indicated after ELND, we performed a multivariate analysis in this group of patients [Table 4]. Negative surgical margin ( $P = 0.013$ ), earlier disease stage ( $P = 0.002$ ), adjuvant RT ( $P = 0.009$ ), and adjuvant CT regimen TS-1 ( $P < 0.001$ ) or UFT ( $P = 0.04$ ) were associated with better OS. Better DFS was associated with negative surgical margin ( $P = 0.004$ ), earlier disease stage ( $P = 0.001$ ), adjuvant RT ( $P = 0.008$ ), and adjuvant CT regimen TS-1 ( $P < 0.001$ ).

We also observed that the number of involved lymph nodes was strongly related to the OS and DFS ( $P < 0.001$ ).

**Table 3: Prognostic factors based on multivariate analyses (n=98)**

Variable	OS		DFS	
	HR	P	HR	P
Age	1.006	0.664	1.004	0.78
Gender	1.07	0.854	0.952	0.887
Positive margin	2.593	0.144	3.764	0.04
Stage		0.003		0.001
IIB versus IIA	3.114	0.071	3.393	0.05
IIIA versus IIA	4.426	0.025	4.717	0.018
IIIB versus IIA	10.85	<0.001	10.810	<0.001
IIIC versus IIA	10.662	<0.001	14.311	<0.001
ELND	1.07	0.854	1.229	0.585
Adjuvant RT	0.29	0.058	0.279	0.045
Adjuvant CT		0.008		0.002
HDFL versus none	0.912	0.881	0.868	0.812
TS-1 versus none	0.142	0.001	0.124	0.001
UFT versus none	0.406	0.079	0.334	0.034
Misc versus none	0.189	0.158	0.152	0.108

ELND: Extensive lymph node dissection, HDFL: High-dose 5-FU/leucovorin, OS: Overall survival, DFS: Disease-free survival, HR: Hazard ratio, RT: Radiotherapy, CT: Computerized tomography, UFT: Uracil-Tegafur

**Table 4: Prognostic factors based on multivariate analyses in patients who underwent extensive lymph node dissection (n=66)**

Variable	OS		DFS	
	HR	P	HR	P
Age	1.022	0.294	1.025	0.246
Gender	0.63	0.353	0.884	0.792
Positive margin	10.891	0.013	13.538	0.004
Stage		0.002		0.001
IIB versus IIA	22.373	0.001	15.84	0.003
IIIA versus IIA	11.156	0.018	9.147	0.025
IIIB versus IIA	35.418	<0.001	40.142	<0.001
IIIC versus IIA	51.072	<0.001	52.775	<0.001
Adjuvant RT	0.017	0.009	0.016	0.008
Adjuvant CT		0.001		<0.001
HDFL versus none	4.804	0.232	5.262	0.24
TS-1 versus none	0.029	<0.001	0.03	<0.001
UFT versus none	0.193	0.04	0.308	0.109
Misc versus none	0.977	0.989	1.116	0.948

HDFL: High-dose 5-FU/leucovorin, OS: Overall survival, DFS: Disease-free survival, HR: Hazard ratio, RT: Radiotherapy, CT: Computerized tomography, UFT: Uracil-Tegafur

However, as there was considerable overlap between this factor and disease stage, we did not use it in the multivariate analyses. We tried using different numbers of involved lymph nodes as a cutoff point and found that adjuvant RT significantly improved both OS and DFS in patients whose number of involved lymph nodes were  $\geq 4$  (univariate analysis: OS,  $P = 0.017$ ; DFS,  $P = 0.015$ ). The process and results are presented in [Table 5].

## DISCUSSION

In the present retrospective study, patients who underwent adjuvant CT or RT were significantly younger, with more

lymph nodes dissected, and with more advanced disease. Simply put, the more advanced disease was treated more aggressively. Such an uneven distribution might explain why some treatment-related factors did not show statistical significance in the univariate analysis. However, it is noteworthy that oral TS-1 provided significantly better outcome even in such an uneven distribution. TS-1 is usually prescribed for locally advanced gastric cancer patients who have undergone a D2 dissection in Japan. Sakuramoto *et al.* demonstrated its survival benefit as an adjuvant treatment versus surgery alone [3]. In a systematic review, four studies supported that S-1 regimens slightly improve the OS (by less than an additional month) versus 5-FU-containing regimens [13].

Our multivariate analysis showed that adjuvant RT significantly improved DFS and TS-1 significantly improved both OS and DFS [Table 3]. Some previous randomized controlled trials (RCTs) showed similar outcomes favoring adjuvant RT. In INT-0116, surgery alone had significantly worse OS (HR = 1.35,  $P = 0.005$ ) and higher recurrence rate (HR = 1.52,  $P < 0.001$ ) than surgery followed by CRT. The role of adjuvant CRT after D2 dissection has also been established by several studies. A Korean retrospective study showed that the addition of adjuvant CRT was superior to surgery alone (95.3 months vs. 62.6 months,  $P = 0.02$ ) [5]. Jácome *et al.* also published a study showing that adjuvant CRT was associated with a lower risk of death in gastric cancer patients treated with D2 dissection [6]. With regard to the debates on adjuvant CT or CRT, Zhu *et al.* [14] compared adjuvant CRT with CT. The CRT arm showed better 5-year RFS (45.2% vs. 35.8%,  $P = 0.029$ ) and OS (48.4% vs. 41.8%,  $P = 0.122$ ), although the benefit on OS was not statistically significant.

On the contrary, the results of the ARTIST trial did not encourage the use of adjuvant RT. The 5-year OS of adjuvant CRT was similar to that of adjuvant CT alone (75% vs. 73%,  $P = 0.484$ ). The advantage of adding RT has been shown to provide better 3-year DFS (78.2% vs. 74.2%,  $P = 0.0862$ ) but diminished its association with 7-year DFS ( $P = 0.74$ ). Another Korean RCT reported that adjuvant CRT was not significantly better than adjuvant CT (5-year RFS: 45.2% vs. 35.8%,  $P = 0.029$ ; 5-year OS: 48.4% vs. 41.8%,  $P = 0.122$ ) [15].

However, in the following subgroup analysis [8] of node-positive patients in the ARTIST trial, postoperative chemoradiotherapy significantly lowered regional recurrence (23 in the CT arm; 5 in the CRT arm;  $P < 0.001$ ).

It is noteworthy that the RT technique used in the two Korean RCTs mentioned above was traditional AP-PA fields. Boda-Heggemann *et al.* [16] conducted a cohort study consisting of 27 patients treated with 3D-CRT with 5-FU and leucovorin and 33 patients treated with IMRT and capecitabine plus oxaliplatin. Patients in the IMRT group had a 30% absolute improvement in 2-year OS (67% vs. 37%;  $P = 0.0492$ ). It was possible that advanced RT could provide more benefits with more accurate radiation delivery and less adverse effects.

**Table 5: The effect of radiotherapy on different groups of patients with regional lymph nodes involved**

	The number of patients did not undergo RT	The number of patients underwent RT	P for OS	P for DFS
Involved LNs $\geq$ 2	31	34	0.139	0.128
Involved LNs $\geq$ 3	29	34	0.108	0.095
Involved LNs $\geq$ 4	23	31	0.017	0.091
Involved LNs $\geq$ 5	19	27	0.018	0.007
Involved LNs $\geq$ 6	17	24	0.031	0.011

The *P* was derived from a log-rank test comparing the RT group with the without-RT group. LNs: Lymph nodes, OS: Overall survival, DFS: Disease-free survival, RT: Radiotherapy

As a surrogate of D2 dissection, extensive LN dissection did not show a superior survival benefit in our multivariate analysis. This result indicates that the number of dissected LNs alone is probably not of significant importance. The nodal stations at risks need to be dissected thoroughly to achieve better locoregional control. The Dutch [17] and MRC [18] trials showed that D2 dissection was associated with increased postoperative mortality and morbidity and the survival outcome was not superior to D1 dissection. It is noteworthy that surgical morbidity and mortality rates for gastric adenocarcinoma are generally much higher in the United States than that in South Korea and Japan [10].

Nodal status is an important prognostic factor. Previous studies have proposed N-ratio, the ratio between metastatic and dissected lymph nodes, and the results showed that it is an independent prognostic factor for OS and DFS [19,20]. In the present study, we did not use the number of involved lymph nodes for multivariate analysis because it has already been included in the AJCC stage. To determine the patients who would benefit the most from adjuvant RT, we tried using different numbers of involved lymph nodes as a cutoff point. The univariate analysis result showed that in patients whose involved LNs were greater or equal to four, adjuvant RT significantly improved both OS (median: 46.8 vs. 14.27 months, *P* = 0.017) and DFS (median: 51.8 vs. 8.37 months, *P* = 0.015).

The major limitation of our retrospective study is the use of various treatment modalities with uneven patient distribution. Patients who underwent adjuvant CT or RT were significantly younger, with more lymph nodes dissected, and with more advanced diseases. Besides, due to the heterogeneity of the operative records, we used extensive LN dissection as the surrogate of D2 dissection and failed to show its locoregional control benefit.

## CONCLUSION

Our study indicates that adjuvant RT significantly improved DFS after gastrectomy with or without extensive LN dissection. When the number of involved LNs was  $\geq$ 4, adjuvant RT is strongly suggested for better locoregional control.

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## Conflicts of interest

There are no conflicts of interest.

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