



## Capecitabine with radiation is an effective adjuvant therapy in gastric cancers

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Author contributions: Tham CK, Choo SP, Poon DYH, Toh HC, Ong SYK, Wang MLC and Foo KF designed the research; Tan SH analyzed the data; Tham CK and Choo SP wrote the paper.

Supported by National Cancer Centre Singapore

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Received: July 14, 2009 Revised: December 23, 2009

Accepted: December 30, 2009

Published online: August 7, 2010

tients (64.8%) had advanced stage III and IV disease (with no distant metastasis). All except 4 patients had D2 gastrectomy. Twenty one patients (19.4%) had positive surgical resection margins. Thirty three patients received XRT compared with 52 who had 5FU-RT and 23 who received chemotherapy alone. For the patients in the chemotherapy-only group, all had fluoropyrimidine-based therapy, with added cisplatin in 7 patients and epirubicin in 2 patients. Median recurrence-free survival was longer for the XRT group (52 mo) compared to the 5FU-RT (35 mo) and chemotherapy-only groups (25 mo) ( $P = 0.48$ ). The patients in the XRT group achieved similar median overall survival (53 mo) as the 5FU-RT (54 mo) and the chemotherapy-only groups (44 mo) ( $P = 0.5$ ).

**CONCLUSION:** Capecitabine with concurrent radiation was as effective as concurrent 5FU with radiation or fluoropyrimidine-based chemotherapy alone when used as adjuvant treatment in patients with gastric cancers.

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### Abstract

**AIM:** To analyze the outcome of patients who received concurrent capecitabine (Xeloda) and radiation (XRT) compared to the established concurrent 5-fluorouracil (5-FU) with radiation (5FU-RT) and fluoropyrimidine-based chemotherapy alone as adjuvant treatment in gastric cancers.

**METHODS:** All patients with gastric cancers who received adjuvant treatment at the National Cancer Centre Singapore between 1996 and 2006 were reviewed. Treatment outcomes of patients who received XRT were compared with those who had 5FU-RT or chemotherapy alone as adjuvant therapy for gastric cancers.

**RESULTS:** A total of 108 patients were reviewed. Median age at diagnosis was 60. The majority of the pa-

**Key words:** Capecitabine; Radiation; Gastric cancer; Adjuvant chemotherapy

**Peer reviewers:** Piero Marco Fisichella, MD, Assistant Professor of Surgery, Medical Director, Swallowing Center, Loyola University Medical Center, Department of Surgery, Stritch School of Medicine, 2160 South First Avenue, Room 3226, Maywood, IL 60153, United States; Dr. Takehiro Okabayashi, Department of Surgery, Kochi Medical School, Kohasu-Okochi, Nankoku-City, 783-8505, Japan

Tham CK, Choo SP, Poon DYH, Toh HC, Ong SYK, Tan SH, Wang MLC, Foo KF. Capecitabine with radiation is an effective adjuvant therapy in gastric cancers. *World J Gastroenterol* 2010; 16(29): 3709-3715 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i29/3709.htm> DOI: <http://dx.doi.org/10.3748/wjg.v16.i29.3709>

## INTRODUCTION

Surgery is the curative treatment for gastric cancer. However, the outcome of large T3-T4 tumors and those with lymph node involvement remains poor after surgical resection alone with high risk of local and distant recurrence<sup>[1]</sup>. Many attempts had been made to improve the prognosis of resected gastric cancers. These include postoperative adjuvant chemotherapy with or without radiation and perioperative chemotherapy.

Adjuvant therapy in gastric cancer is a field of ongoing active research. The different modalities in the adjuvant setting include chemoradiation and chemotherapy alone. There is currently no randomized phase III trial that directly compared these various modalities. Hence, the optimal adjuvant therapy in gastric cancer remains to be determined.

Capecitabine (Xeloda), an oral fluoropyrimidine, was shown to have equivalent efficacy to continuous-infusional 5-fluorouracil (5-FU) in several phase III trials in metastatic gastric cancers. The REAL-2 study compared capecitabine or 5-FU in combination with cisplatin and oxaliplatin and showed no differences in response rates or survival between all the 4 combination regimens<sup>[2]</sup>. The ML 17032 trial comparing the combination of capecitabine with cisplatin to 5-FU with cisplatin showed that capecitabine and cisplatin had a better response rate (41% *vs* 29%) and overall survival (10.5 mo *vs* 9.3 mo)<sup>[3]</sup>. Because of the convenient oral administration of capecitabine, its use in the adjuvant setting is an attractive option to explore. In fact, capecitabine with concurrent radiation as an adjuvant or neoadjuvant treatment in resected gastric cancer and other gastrointestinal malignancies, particularly rectal cancer, has been explored in several studies<sup>[4-6]</sup>. These studies demonstrated that capecitabine with concurrent radiation was feasible with manageable toxicities. However, the regimen has never been compared with the more established concurrent 5-FU and radiation (5FU-RT) or adjuvant chemotherapy alone.

Hence, in this study, we aimed to analyze the outcome of patients who received adjuvant concurrent capecitabine and radiation (XRT) compared to those who received concurrent FU-RT or fluoropyrimidine-based chemotherapy alone in the adjuvant setting in gastric cancers.

## MATERIALS AND METHODS

All patients diagnosed with gastric cancer who received adjuvant treatment at National Cancer Center Singapore from 1996 to 2007 were reviewed. Clinical information was collected retrospectively and included age, gender, performance status, *Helicobacter pylori* status, surgical outcome, tumor histology, carcinoembryonic antigen, baseline hematologic and biochemical parameters, recurrence and survival data.

The patients were divided into 3 groups based on the adjuvant treatment received. These included 5FU-RT, XRT and chemotherapy alone for analysis. The patients in the XRT group received 825 mg/m<sup>2</sup> capecitabine daily with concurrent radiation followed by capecitabine 2000 mg/m<sup>2</sup>

every 3 wk for 6 cycles. Patients in the 5FU-RT group received chemoradiation which consisted of 5 cycles of 5-FU 400 mg/m<sup>2</sup> plus leucovorin (20 mg/m<sup>2</sup>) given every 28 d with 2 cycles given concurrently with radiation. The total radiation dose in both the XRT and 5FU-RT groups was 45 Gy delivered over a period of 5 wk. The patients in the chemotherapy-only group received fluoropyrimidine-based chemotherapy.

The patients receiving XRT were compared with those who had 5FU-RT and fluoropyrimidine-based chemotherapy in terms of recurrence-free survival and overall survival. We also compared the patients who received radiation as part of their adjuvant therapy to those who received chemotherapy alone.

Comparison of the median age at baseline between treatment groups was done using the Mann-Whitney *U* test. Other baseline characteristics, such as gender, performance status, stage and grade, as shown in Table 1, were performed using Fisher's exact test.

Recurrence-free survival duration was calculated from the date of diagnosis to the date of recurrence or death (whichever occurred first) or last follow-up. Overall survival duration was calculated from the date of diagnosis to the date of death or last follow-up. The Kaplan-Meier method was used to estimate and plot the recurrence-free survival and overall survival curves for the 3 treatment groups. The log-rank test was used to test if the survival function for the treatment groups were statistically different at the 5% significance level.

For recurrence-free survival and overall survival, the Cox proportional hazards model was used to estimate the crude and age-adjusted hazard ratios between treatment groups using the XRT arm as the reference treatment. Age at diagnosis was included in multivariate Cox regression analyses to estimate the adjusted hazard ratios. Subgroup analysis of the recurrence-free survival and overall survival hazard ratios between the chemotherapy-only group and chemoradiotherapy (XRT or 5FU-RT) were performed using the Cox proportional hazard model for patients with a positive surgical margin, Stage 3 or 4, and positive nodes, respectively.

### Statistical analysis

The Cox proportional hazards model and log-rank test were also used to estimate the hazard ratios to assess if any of the baseline characteristics were associated with recurrence-free survival and overall survival in each of the 3 treatment groups. Normality of the variables in the Cox model was assessed using a Q-Q plot and proportionality assumption of the Cox model was assessed using the Schoenfeld test.

Two-sided *P*-values of less than 5% were considered as statistically significant. The software used for the analyses was STATA version 9.1.

## RESULTS

A total of 108 patients had received adjuvant therapy for gastric cancer at our institution in the specified period. Median follow-up duration was 23 mo.

Table 1 Patient characteristics *n* (%)

	All patients ( <i>n</i> = 108)	XRT ( <i>n</i> = 33)	5FU-RT ( <i>n</i> = 52)	Chemo alone ( <i>n</i> = 23)	<i>P</i> -value <sup>1</sup> for XRT <i>vs</i>	
					5FU-RT	Chemo alone
Age (yr)						
Median	60	64	57	56	0.003 <sup>2</sup>	0.03 <sup>2</sup>
Inter-quartile range	49.5-66.0	57.7-68.8	48.0-63.7	49.3-65.7		
Gender						
Male	65 (60.2)	22 (66.7)	30 (57.7)	13 (56.5)	0.5	0.6
Female	43 (39.8)	11 (33.3)	22 (42.3)	10 (43.5)		
ECOG						
0	6 (5.6)	1 (3.0)	3 (5.8)	2 (8.7)	1.0	0.6
1	102 (94.4)	32 (97.0)	49 (94.2)	21 (91.3)		
<i>Helicobacter pylori</i> status						
Yes	36 (53.7)	16 (66.7)	15 (50.0)	5 (38.5)	0.3	0.2
No	31 (46.3)	8 (33.3)	15 (50.0)	8 (61.5)		
Surgical margins						
Positive	21 (19.4)	4 (12.1)	14 (26.9)	3 (13.0)	0.2	1.0
Negative	87 (80.6)	29 (87.9)	38 (73.1)	20 (87.0)		
Stage						
1 or 2	38 (35.2)	12 (36.4)	14 (26.9)	12 (52.2)	0.5	0.3
3 or 4	70 (64.8)	21 (63.6)	38 (73.1)	11 (47.8)		
Grade						
1 or 2	31 (28.7)	12 (36.4)	12 (23.1)	7 (30.4)	0.2	0.8
3	77 (71.3)	21 (63.6)	40 (76.9)	16 (69.6)		
Albumin						
< 30	12 (13.3)	4 (12.9)	4 (10.0)	4 (21.1)	0.7	0.5
≥ 30	78 (86.7)	27 (87.1)	36 (90.0)	15 (78.9)		
CEA						
Normal	50 (90.9)	17 (89.5)	24 (92.3)	9 (90.0)	1.0	1.0
High	5 (9.1)	2 (10.5)	2 (7.7)	1 (10.0)		
Hemoglobin						
< 10	26 (25.7)	8 (24.2)	14 (29.2)	4 (20.0)	0.8	1.0
≥ 10	75 (74.3)	25 (75.8)	34 (70.8)	16 (80.0)		

<sup>1</sup>All *P*-values calculated using Fisher's exact test unless otherwise stated; <sup>2</sup>*P*-value calculated using the Mann-Whitney *U* test. XRT: Capecitabine + radiation; 5FU-RT: 5-fluorouracil + radiation; ECOG: Eastern Cooperative Oncology Group status; CEA: Carcinoembryonic antigen.

Thirty-three of these patients received XRT, 52 received 5FU-RT and 23 received fluoropyrimidine-based chemotherapy. Of the patients who received chemotherapy alone, 11 had capecitabine alone, 6 had ECF (epirubicin, cisplatin and 5-FU), 4 had XELOX (capecitabine and oxaliplatin) and 2 had 5-FU alone. Ninety-one percent of the patients in the XRT group, 89% in the 5FU-RT and 91% in the chemotherapy-only group completed the full course of adjuvant treatment.

The characteristics of these patients are shown in Table 1. Median age at diagnosis was 60 years. Sixty-five percent of the patients had advanced stage III and IV (with no distant metastasis) disease. All except 4 patients had D2 gastrectomy (2 in the XRT group, 2 in the chemotherapy-only group). Twenty-one of these patients (19.4%) had positive surgical resection margins (14 in the 5FU-RT group, 4 in the XRT group and 3 in the chemotherapy-only group). The only significant difference in characteristics among the 3 groups of patients was median age, with the median age of the patients in the XRT group being greater than that of the other 2 groups.

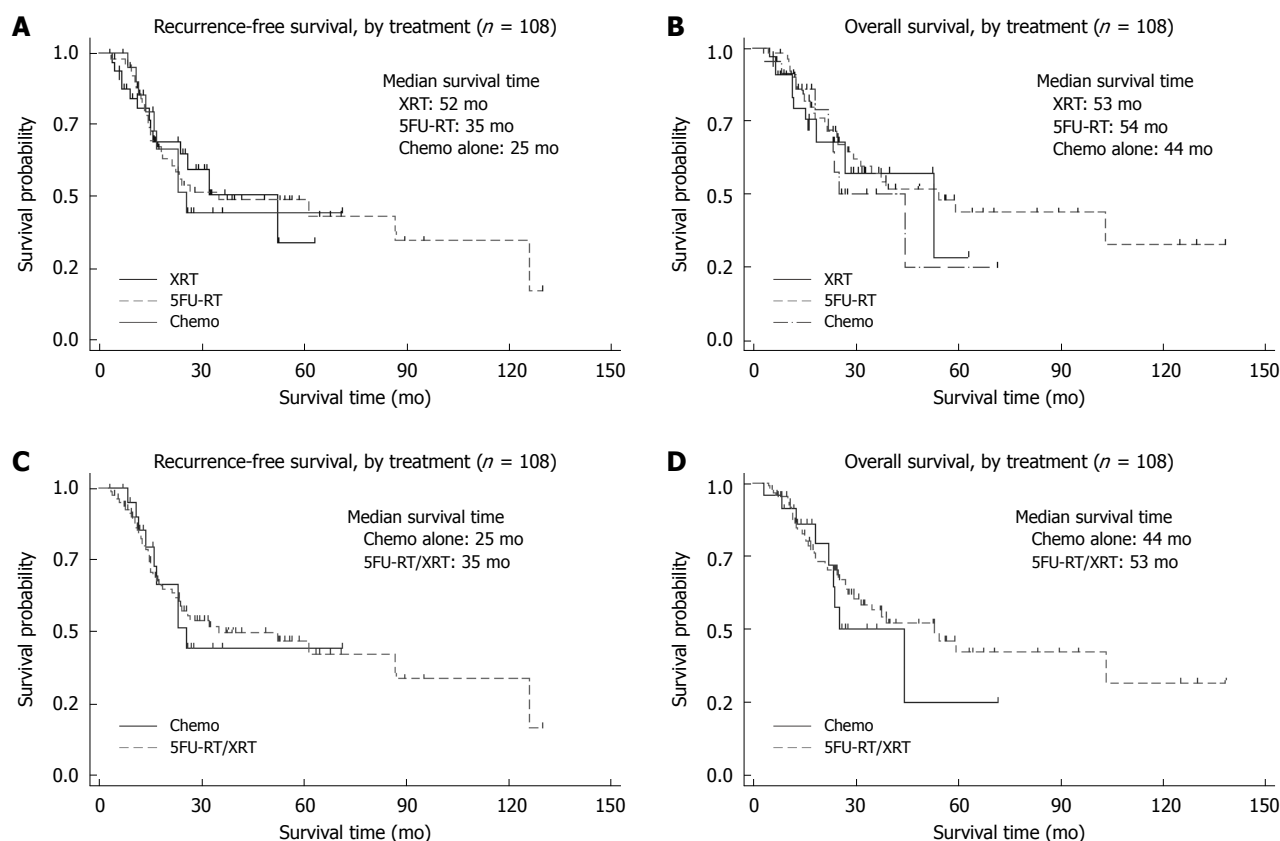
Median recurrence-free survival was longer for the XRT group (52 mo) compared with the 5FU-RT (35 mo) and chemotherapy-only groups (25 mo). However, the recurrence-free survival curves between the 3 groups were not statistically significant (*P* = 0.5, Figure 1A, Table 2).

Patients with positive surgical margins were found to have a significantly poorer recurrence-free survival in both the XRT and 5FU-RT groups but not in the chemotherapy-only group (Table 3).

The overall survival times of the patients in the 3 treatment groups were not statistically different (*P* = 0.5), with the median overall survival of the patients in the XRT group at 53 mo, the 5FU-RT group at 54 mo and the chemotherapy-only group at 44 mo (Figure 1B). Patients with positive surgical margins were found to have poorer survival across all the treatment groups (Table 3).

When comparing patients who received radiation as part of their adjuvant therapy to those who received chemotherapy alone, there was no statistical difference in recurrence-free survival and overall survival between these 2 groups of patients (Figure 1C and D). Subgroup analyses of patients with positive surgical margins, lymph node positive and T3 or T4 disease did not show a statistically difference in survival between patients who received radiation as part of their adjuvant therapy and those who did not (Table 4).

Treatment was generally well tolerated in the 3 treatment groups. In total only 6 patients (5%) had grade 3 or 4 toxicities, 4 in the 5FU-RT group, one in the XRT group and one in the chemotherapy-only group. Diarrhea was the most common grade 3 or 4 adverse effect. One



**Figure 1 Kaplan-Meier estimates.** A: Recurrence-free survival of capecitabine + radiation (XRT), 5-fluorouracil + radiation (5FU-RT) and chemotherapy alone; B: Overall Survival of XRT, 5FU-RT and chemotherapy alone; C: Recurrence-free survival of RT-containing regimen vs chemotherapy alone; D: Overall survival of RT-containing regimen vs chemotherapy alone.

**Table 2 Recurrence-free survival and overall survival analysis**

Variable	Categories/units	n	HR (95% CI)	P-value
Recurrence-free survival				
Treatment	XRT	108	1	
	5FU-RT		1.00 (0.508-1.959)	1.0
	Chemo only		1.05 (0.448-2.462)	0.9
Treatment	XRT	108	1	
	5FU-RT		0.97 <sup>1</sup> (0.477-1.966)	0.9
	Chemo only		1.03 <sup>1</sup> (0.433-2.444)	0.9
Overall survival				
Treatment	XRT	108	1	
	5FU-RT		0.83 (0.411-1.681)	0.6
	Chemo only		1.13 (0.474-2.677)	0.8
Treatment	XRT	108	1	
	5FU-RT		0.89 <sup>1</sup> (0.428-1.856)	0.8
	Chemo only		1.19 <sup>1</sup> (0.494-2.882)	0.7

<sup>1</sup>Age-adjusted hazard ratio (HR). XRT: Capecitabine + radiation; 5FU-RT: 5-fluorouracil + radiation.

patient in the XRT group had acute myocardial infarction during the therapy period. There was one death from non-neutropenic sepsis during the adjuvant treatment in the 5FU-RT group.

## DISCUSSION

Our study showed that XRT was as effective as 5FU-RT and fluoropyrimidine-based chemotherapy when given

as adjuvant treatment for locally advanced gastric cancer. XRT had comparable recurrence-free and overall survival with the other 2 adjuvant regimens.

The Intergroup-0116 study has established the role of adjuvant chemoradiation for resected locally advanced gastric cancer in the United States. Compared to surgery alone, the addition of chemoradiation after resection leads to an increased local control (30 mo *vs* 19 mo,  $P = 0.001$ ) and better median overall survival (36 mo *vs* 27 mo,  $P = 0.005$ )<sup>[7]</sup>. In our study, the median overall survival for patients receiving XRT or 5FU-RT was 53 and 54 mo, respectively. This outcome when compared to the Intergroup trial is encouraging as 66% of patients in our study population had T3 or T4 disease and 86% had lymph node-positive disease, similar to the study population in the Intergroup study (68% and 85%, respectively). This difference could be explained by the differences in surgical techniques. All except 2 of our patients underwent D2 gastrectomies compared to only 10% in the Intergroup study. This may suggest that the adjuvant treatment could be a measure to compensate for inadequate surgical treatment. Nevertheless, the extent of lymph node dissection remains an ongoing debate with trials from the Dutch Gastric Cancer Group<sup>[8]</sup> and Medical Research Council<sup>[9]</sup> showing a lack of survival benefit of D2 over D1 lymph node dissection. However, the role of adjuvant chemoradiation in D2-resected gastric cancer had been studied in a Korean prospective non-randomized trial involving 544 patients receiving postoperative 5FU-

Table 3 Recurrence-free survival and overall survival analysis

Variable	Categories/units	Chemo alone		5FU-RT		XRT	
		HR (95% CI)	P-value <sup>1</sup>	HR (95% CI)	P-value <sup>1</sup>	HR (95% CI)	P-value <sup>1</sup>
Recurrence-free survival							
ECOG	0	1	0.9	1	1.0	E/N = 0/1	0.5
	1	0.92 (0.115-7.422)		1.01 (0.238-4.326)		NE	
Gender	Male	1	0.9	1	0.2	1	0.5
	Female	0.91 (0.244-3.419)		1.58 (0.727-3.436)		0.65 (0.198-2.163)	
Surgical margins	Positive	1	0.5	1	< 0.001	1	0.03
	Negative	0.51 (0.059-4.351)		0.16 (0.070-0.384)		0.27 (0.081-0.918)	
Stage	1 or 2	1	0.1	1	0.2	1	0.06
	3 or 4	2.92 (0.724-11.773)		1.86 (0.749-4.633)		3.87 (0.853-17.586)	
Grade of tumor	1, 2	1	0.3	1	0.09	1	0.3
	3	2.17 (0.444-10.636)		2.44 (0.836-7.099)		1.94 (0.515-7.288)	
Overall survival							
ECOG	0	1	0.8	1	0.9	E/N = 0/1	0.4
	1	0.78 (0.096-6.366)		0.95 (0.220-4.069)		NE	
Gender	Male	1	1.0	1	0.2	8/22	0.7
	Female	1.02 (0.253-4.148)		1.63 (0.740-3.598)		0.78 (0.234-2.597)	
Surgical margins	Positive	1	0.004	1	< 0.001	4/4	0.02
	Negative	0.10 (0.013-0.700)		0.26 (0.113-0.603)		0.25 (0.071-0.901)	
Stage	1 or 2	1	0.2	1	0.1	2/12	0.06
	3 or 4	2.59 (0.646-10.412)		2.08 (0.778-5.557)		3.80 (0.829-17.397)	
Grade of tumor	1, 2	1	0.4	1	0.06	3/12	0.4
	3	2.04 (0.418-9.944)		3.04 (0.903-10.239)		1.83 (0.482-6.980)	

<sup>1</sup>P -values were calculated using the Log-rank test. 5FU-RT: 5-fluorouracil + radiation; XRT: Capecitabine + radiation; ECOG: Eastern Cooperative Oncology Group status; E/N: Number of events/number of patients in the group; NE: Not estimable; HR: Hazard ratio.

Table 4 Subgroup analysis for overall and recurrence-free survival

Subgroup	Variable	Categories/units	n	Overall survival		Recurrence-free survival	
				HR (95% CI)	P-value	HR (95% CI)	P-value
Surgical margins = positive	Treatment	Chemo alone	21	1		1	
		5FU-RT/XRT		0.47 (0.100-2.191)	0.3	1.58 (0.206-12.154)	0.7
Stage T3/4	Treatment	Chemo alone	66	1		1	
		5FU-RT/XRT		0.65 (0.294-1.454)	0.3	0.78 (0.352-1.709)	0.5
Node positive	Treatment	Chemo alone	94	1		1	
		5FU-RT/XRT		0.92 (0.404-2.081)	0.8	1.10 (0.489-2.482)	0.8

5FU-RT: 5-fluorouracil + radiation; XRT: Capecitabine + radiation; HR: Hazard ratio.

radiation. This trial demonstrated significantly longer overall survival in the chemoradiation group compared to the surgery alone group (95.3 mo *vs* 62.6 mo,  $P = 0.02$ )<sup>[10]</sup>. Hence, there appears to be a role of adjuvant concurrent chemoradiation even in the setting of optimal surgical resection of gastric cancer.

Continuous infusion 5-FU was preferred over 5-FU bolus infusion in most of the gastrointestinal malignancies, especially colorectal cancer, and was also found to be more effective than the bolus 5-FU<sup>[11,12]</sup>. Continuous 5-FU infusion with radiation was used extensively in the neoadjuvant and adjuvant treatment of rectal cancer<sup>[13,14]</sup>. Oral capecitabine, in the metastatic and adjuvant setting, has been shown to be as effective as continuous 5-FU in gastrointestinal malignancies<sup>[2,12,15,16]</sup>. The ease of oral administration of capecitabine compared with the continuous infusion of 5-FU, which requires the placement of a central venous catheter, makes the use of capecitabine concurrent with radiotherapy an attractive option. Our

results, albeit retrospective, showed an equivalent survival between XRT and 5FU-RT. Hence, XRT could be a reasonable alternative to 5FU-RT as adjuvant treatment in resected stomach cancer. Several phase I / II studies have already explored the addition of capecitabine with concurrent radiation<sup>[4,5]</sup> in adjuvant stomach cancer and shown it to be safe and tolerable.

Our analysis has shown that there was no survival difference between those who had radiation as part of their adjuvant therapy compared to those who did not. Even in patients with a positive surgical margin, the addition of radiation did not appear to significantly improve survival compared to adjuvant chemotherapy alone. The role of adjuvant chemotherapy had been studied in many phase III Western trials but the results were inconsistent in showing a survival benefit of adjuvant chemotherapy over surgery alone<sup>[17-20]</sup>. Meta-analyses of these trials suggest a potential absolute increase in 5-year survival of 2% to 4% with adjuvant chemotherapy in resected gastric



cancer<sup>[21,22]</sup>. The Asian adjuvant trials had demonstrated more favorable results with a recent Japanese study on adjuvant S1 in resected stage II or III gastric cancer showing a significantly higher 3-year overall survival rate in the S1 group compared to the observation arm (80.1% *vs* 70.1%,  $P = 0.003$ )<sup>[23]</sup>. Hence, fluoropyrimidine-based chemotherapy may have a role in adjuvant treatment. However, there is currently no phase III trial that compared adjuvant chemoradiation and chemotherapy alone. Our study has shown that there is no survival difference between adjuvant chemoradiation and chemotherapy, suggesting that adjuvant chemotherapy alone may be a reasonable option of adjuvant therapy in resected gastric cancer. A study involving capecitabine alone for adjuvant therapy in gastric cancer will be an interesting follow-up study.

In conclusion, XRT as an adjuvant therapy in resected gastric cancer can achieve similar outcomes to that of 5FU-RT or chemotherapy. The result from our hypothesis-generating study provides the basis for a further prospective study in evaluating the role of radiation with concurrent capecitabine as adjuvant therapy in resected gastric cancers.

## COMMENTS

### Background

Gastric cancer is a major cause of cancer deaths in the world. The outcome of large gastric tumors and those with lymph node involvement remains poor after surgical resection. The optimal adjuvant therapy after surgical resection remains to be determined.

### Research frontiers

The most common strategies in the adjuvant treatment of gastric cancers include fluoropyrimidine-based chemotherapy with or without radiation. The introduction of capecitabine has largely replaced continuous-infusion 5-fluorouracil (5-FU) owing to its ease of administration. However, its efficacy is not proven in randomized phase III trials involving gastric cancers. In this retrospective review study, the authors examined the role of capecitabine with radiation and compared its efficacy to the 5-FU with radiation regimen and fluoropyrimidine-based chemotherapy alone.

### Innovations and breakthroughs

This study showed that capecitabine with concurrent radiation was as effective as 5-FU with radiation or fluoropyrimidine-based chemotherapy alone without radiation when given as adjuvant treatment for locally advanced gastric cancer.

### Applications

This hypothesis-generating study will provide the platform for a larger randomized study to be conducted using capecitabine as one of the study regimens in adjuvant gastric cancer trials.

### Terminology

Capecitabine and 5-FU are fluoropyrimidine-based chemotherapy commonly used in the treatment of gastrointestinal cancers.

### Peer review

This is a retrospective clinical study that looked at the effects of chemoradiation therapy by using capecitabine in patients undergoing gastric surgery for gastric cancer. The results are well presented and the discussion is well organized. The conclusions are supported by the data and the tables contain appropriate information.

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S- Editor Wang YR L- Editor Cant MR E- Editor Lin YP