RESEARCH ARTICLE

Adjuvant Radiotherapy for Gastric Carcinoma: 10 years Follow-up of 244 cases from a Single Institution

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Abstract

Background: Postoperative chemoradiotherapy (CRT) of gastric carcinoma improves survival among high-risk patients. This study was undertaken to analyse long-term survival probability and the impact of certain covariates on the survival outcome in affected individuals. Materials and Methods: Between January 2000 and December 2005, 244 patients with gastric cancer underwent adjuvant radiotherapy (RT) in our institution. Data were retrieved retrospectively from patient files and analysed with SPSS version 21.0. Results: A total of 244 cases, with a male to female ratio of 2.2:1, were enrolled in the study. The median age of the patients was 52 years (range, 20-78 years). Surgical margin status was positive or close in 72 (33%) out of 220 patients. Postoperative adjuvant RT dose was 46 Gy. Median follow-up was 99 months (range, 79-132 months) and 23 months (range, 2-155 months) for surviving patients and all patients, respectively. Actuarial overall survival (OS) probability for 1-, 3-, 5- and 10-year was 79%, 37%, 24% and 16%, respectively. Actuarial progression free survival (PFS) probability was 69%, 34%, 23% and 16% in the same consecutive order. AJCC Stage I-II disease, subtotal gastrectomy and adjuvant CRT were significantly associated with improved OS and PFS in multivariate analyses. Surgical margin status or lymph node dissection type were not prognostic for survival. Conclusions: Postoperative CRT should be considered for all patients with high risk of recurrence after gastrectomy. Beside well-known prognostic factors such as stage, lymph node status and concurrent chemotherapy, the type of gastrectomy was an important prognostic factor in our series. With our findings we add to the discussion on the definition of required surgical margin for subtotal gastrectomy. We consider that our observations in gastric cancer patients in our clinic can be useful in the future randomised trials to point the way to improved outcomes.

Keywords: Gastric cancer - chemoradiotherapy - adjuvant radiotherapy - surgery - prognosis

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Introduction

Gastric cancer is the fourth and fifth most common cancer in males and females respectively (Jemal et al., 2011). Despite its decreasing incidence, gastric cancer is the second most common cause of cancer related death worldwide (Jemal et al., 2011). The prevalence of the disease is generally at advanced stage and the mortality rate is high (Agboola, 1994; Gao et al., 2011; Jing et al., 2012; Wani M et al. 2012; Hajmanoochehri et al., 2013). Total or subtotal gastrectomy with limited (D1) or extended (D2) dissection is the recommended primary treatment (Songun et al., 2010; Czito et al., 2013). Although surgery is the most effective treatment modality, the sobering results with advanced stage disease have led to increasing efforts to improve outcomes by using adjuvant or neoadjuvant chemotherapy (CT) and/or radiotherapy (RT) (Cunningham et al., 2006; Macdonald et al., 2011; Czito et al., 2013). Although the positive impact of such therapies has become clearer over time, there remains no consensus as to the best approach. The controversies over the use of adjuvant therapies are mainly concentrated on whether or not adjuvant RT should be applied in addition to surgery and CT.

Our study reports the results of gastric cancer adjuvant treatment either with RT or chemoradiotherapy (CRT) in a single institution. It focuses in particular on the 10 years survival probability and on the impact of certain covariates on the survival outcome.

Materials and Methods

From January 2000 to December 2005, 244 patients with surgically resected gastric carcinoma were treated with adjuvant CRT or RT alone in our department. Patient characteristics and follow up data were collected from our hospital database and retrospectively analysed after institutional review board approval.

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Sixth American Joint Committee on Cancer Stage Classification (AJCC) system was used for staging. All patients underwent total or subtotal gastrectomy for gastric carcinoma. Lymph node dissection classification was done according to the Japanese Research Society for the Study of Gastric Cancer classification (de Aretxabala et al., 1987; Songun et al., 2010). D0 dissection was defined as no dissection or less than D1 dissection. Adjuvant CT consisted of one cycle of 5-Fluorouracil (5-FU) (425mg/m2 continuously during 4-5 days) and Leucovorin calcium (20mg/m2), followed one month later by RT given with concurrent 5-FU and leucovorin calcium (400mg/m2 and 20mg/m2 , respectively) on days 1 through 4, and on the last three days of RT or in a weekly schedule (5-FU 400mg/m2 and leucovorin calcium 20mg/m2 once per week). Two more cycles of CT (5-FU 425mg/m2 and leucovorin calcium 20mg/m2) were given at monthly intervals beginning one month after completion of CRT (Macdonald et al., 2001; Martoni et al., 1989; Vanhoefer et al., 1994; Takeda et al., 1995; Zhang et al., 2013).

Radiotherapy was delivered with a median dose of 4600 cGy in 180-200 cGy fractions. All patients were treated with a two-dimensional (2D) RT technique using anterior-posterior opposing fields. Simulation was performed in the supine position. The administration of oral contrast was used to visualize the site of anastomosis, the esophagus, gastric remnant and small intestine. Kidneys were visualized by use of IV contrast. The superior border of the RT field was above the left diaphragm, including the site of anastomosis with a 2 cm margin (approximately T10-11 vertebra level). The inferior border was L3-4 intervertebral border. Paraaortic lymphatics were included in the field by extending the inferior field below the L3 vertebra. At the level of T11-L1 vertebra, porta-hepatis lymphatics were included by extending the field 2 cm right lateral to the para-aortic field. Lateral borders were defined in order to include porta hepatis and gastric bed with shielding used to protect the kidneys (Figure 1).

Follow-up occurred at three-month intervals for the first two years, then at six-month intervals for five years, and yearly thereafter. Follow-up consisted of physical examination, complete blood count, liver-function testing, chest radiography, abdominal ultrasonography, endoscopy and computed tomography scanning as clinically indicated. Common Terminology Criteria v2.0 (Publish Date April 30, 1999) was used for adverse event reporting.

All events were measured from the time of diagnosis using the Kaplan-Meier method. Age, gender, haemoglobin (Hg) level at the beginning of RT, AJCC tumor stage, tumor size, tumor localisation, gastrectomy type, adjuvant treatment, chemotherapy schema, margin status, presence of perineural invasion, lymphovascular invasion or extracapsular extension (ECE) were evaluated as covariates in univariate analysis. The univariate effects of covariates on survival were investigated using the log-rank test. Factors found to influence prognosis on univariate analysis were subjected to multivariate analysis using Cox's proportional hazard regression model with backward selection, in order to determine independent predictors of survival. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. A 5% type-I error level was used to infer statistical significance. All calculations were performed using SPSS, version 21.0 (SPSS, Inc., Chicago, IL, USA).

Results

Two hundred and forty four patients with gastric cancer who underwent adjuvant RT or CRT were analysed in this study. Table 1 summarises patient and treatment characteristics of all 244 patients. The median age of the patients was 52 years (range, 20-78 years). Male to female ratio was 2.2:1. Pre-treatment Hg level was >12g/dL in 125 (51%) of the patients. The most common presenting symptoms in descending order of frequency included weight loss, abdominal pain, loss of appetite, bleeding and dysphagia. The majority of the patients (81%) presented with Stage III- IV disease. The antrum was the most frequent anatomical site involved (43%) and adenocarcinoma was the most common histopathological type (95%). The median tumour diameter was 5,4 cm (range, 0.4-14 cm). There was no significant difference between CRT and RT arms in terms of demographic or clinical characteristics.

A hundred patients (41%) underwent total gastrectomy while 144 (59%) underwent subtotal gastrectomy. D1-3 lymph node dissection was performed in majority of the patients (69%). The median number of the lymph nodes examined was 19 (range, 2-73) for all patients. All patients received adjuvant treatment (Figure 2). Adjuvant CRT

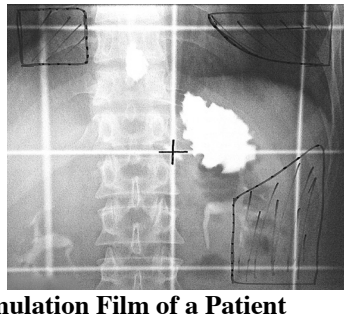

Figure 1. Simulation Film of a Patient

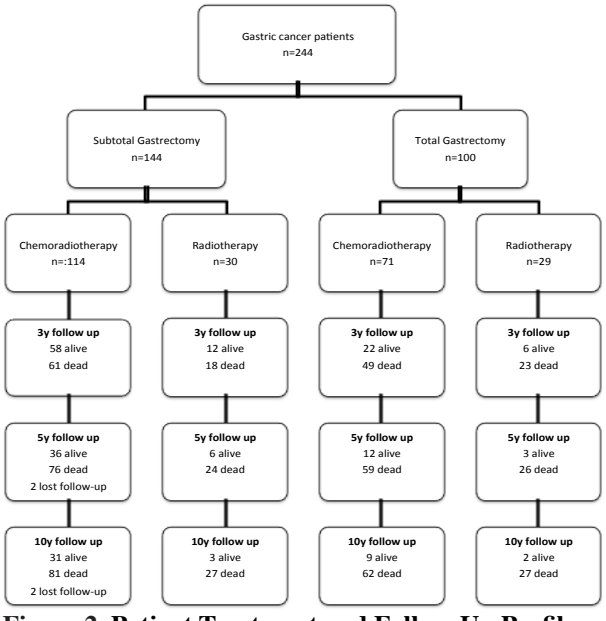

Figure 2. Patient Treatment and Follow-Up Profile

and RT alone was applied in 185 (76%) and 59 (24%) of the patients, respectively. Radiotherapy was delivered using Co60 (35%) or 6-15 MV x-rays (65%). Concurrent CT (5-FU 400mg/m^2; leucovorin calcium 20mg/m^2) was given on days 1 through 4, and on the last three days of RT or weekly during RT in 75 (40%) and 110 (69%) of all treatments, respectively. Of the 244 patients, 216 (88%) completed RT with at least 4500 cGy; 28 (11%) stopped treatment because of toxicity, technical problems or sociological factors (16 of those 28 received ≥4000 cGy).

The median follow-up was 23 months (range, 2-155 months). At the time of analysis, 43 patients were alive, with a median follow-up of 99 months (range, 79-132 months). Two patients were lost to follow-up after 4 years. Figure 3 shows actuarial overall survival (OS) and progression free survival (PFS) probability for all patients as computed by the Kaplan-Meier method. Actuarial OS probability for 1-, 3-, 5- and 10-year was 79%, 37%, 24% and 16%, respectively. Actuarial PFS probability was 69%, 34%, 23% and 16% in the same consecutive order.

Univariate analyses revealed that AJCC Stage I-II disease (OS, p<0.0001; PFS, p<0.0001), subtotal gastrectomy (OS, p=0.003; PFS, p=0.003), negative ECE status (OS, p=0.017; PFS, p=0.008) and adjuvant concurrent chemotherapy (OS, p=0.18; PFS, p=0.027) were predictive for prolonged survival. The effect of lymph node dissection type (D0-1 *vs*. D2-3) on survival was statistically insignificant (OS,p=0.084) or less powerful (PFS=0.005). Subgroup analyses revealed survival predictions in favour of subtotal gastrectomy for patients who received CRT (OS, p=0.008; PFS, p=0.007) as adjuvant treatment but not for those who received RT alone (OS, p=0.332; PFS, p=0.310). In subgroup analysis according to gastrectomy type, the effect of adjuvant treatment type (CRT *vs*. RT alone) on survival was statistically less powerful (Subtotal gastrectomy:

Table 1. Patient and Treatment Characteristics

Variables	Chemoradio-therapy n=185 (76%)	Radio-therapy n=59 (24%)	p value
Age			
<60	119 (49%)	34 (14%)	0.35
≥60	66 (27%)	25 (10%)	
Gender			
Female	55 (22%)	21 (9%)	0.39
Male	130 (53%)	38 (16%)	
Gastrectomy			
Subtotal	114 (47%)	30 (12%)	0.14
Total	71 (29%)	29 (12%)	
Lymph Node Dissection			
D0	52 (21%)	24 (10%)	0.18
D1	69 (28%)	19 (8%)	
D2-3	64 (26%)	16 (7%)	
Tumor Localisation			
Cardia	21 (9%)	9 (3%)	0.29
Body	53 (22%)	22 (9%)	
Antrum	83 (34%)	21 (9%)	
Unknown, n=35 (14%)			
Histopathology			
Adenocarcinoma	113 (46%)	41 (17%)	0.68
Mucinous adenocarcinoma	11 (4%)	2 (1%)	
Signet ring cell adenocarcinoma	51 (21%)	14 (6%)	
Neuroendocrine degeneration	7 (3%)	2 (1%)	
Others	3 (1%)	0 (0%)	
Tumor Status			
T1-2	20 (8%)	5 (2%)	0.65
T3-4	164 (67%)	52 (22%)	
Unreported, n=3 (1%)			
AJCC Stage (6th)			
I-II	36 (15%)	8 (3%)	0.34
III-IV	148 (61%)	49 (21%)	
Nodal Status			
Positive	162 (66%)	50 (21%)	0.8
Negative	22 (9%)	6 (2%)	
Unreported, n=4 (2%)			
Surgical margin			
Positive	20 (8%)	11 (5%)	0.18
Close	34 (14%)	7 (3%)	
Negative	115 (47%)	35 (14%)	
Unreported, n=22 (9%)			
Extracapsuler extension			
Positive	26 (11%)	7 (3%)	0.66
Negative	159 (65%)	52 (21%)	
Perineural Invasion			
Positive	66 (27%)	22 (9%)	0.82
Negative	119 (49%)	37 (15%)	
Lymphovascular Invasion			
Positive	73 (30%)	20 (8%)	0.44
Negative	112 (46%)	39 (16%)	

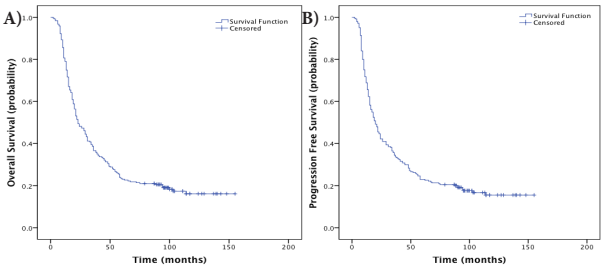

Figure 3. Actuarial Overall Survival (A) and Progression Free Survival (B) for All Patients

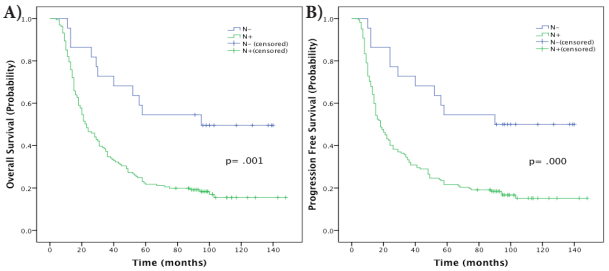

Figure 4. Actuarial Overall Survival (A) and Progression Free Survival (B) for Chemoradiotherapy Patients with Positive and for those with Negative Lymph Node Status

Table 2. Multivariate Analyses of the Association between Covariates and Survival

		Overall survival			Progression free survival		
		p value	HR	95% CI	p value	HR	95% CI
AJCC Stage	I-II *vs*. III-IV	<0.0001*	2.83	1.85-4.32	<0.0001*	2.8	1.82-4.30
Gastrectomy	Subtotal *vs*. Total	0.009*	1.46	1.10-1.94	0.010*	1.45	1.09-1.92
ECE	Positive *vs*. Negative	0.109	1.39	0.93-2.07	0.068	1.45	0.97-2.16
Adjuvant	CRT *vs*. RT	0.050*	1.38	1.00-1.90	0.051	1.38	0.10-1.90

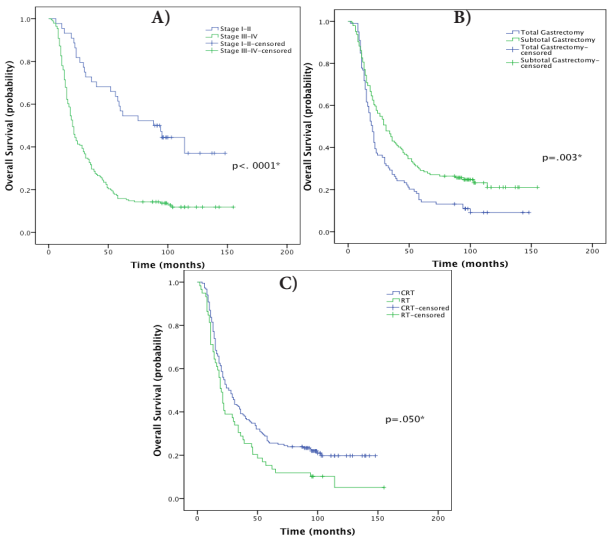

Figure 5. Actuarial Overall Survival for Patients with Stage I-II and for those Stage III-IV (A); for Patients with Total Gastrectomy and for those with Subtotal Gastrectomy (B); for Patients with Adjuvant Chemoradiotherapy (CRT) and for those with Adjuvant Radiotherapy (RT) Alone (C)

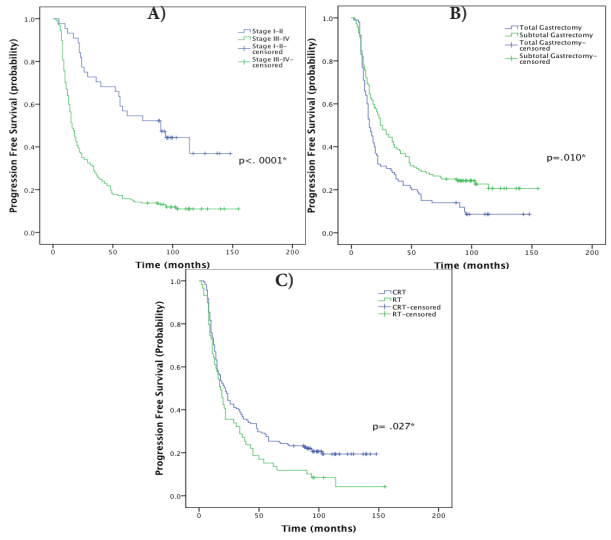

Figure 6. Actuarial Progression Free Survival for Patients with Stage I-II and for those Stage III-IV (A); for Patients with Total Gastrectomy and for those with Subtotal Gastrectomy (B); for Patients with Adjuvant Chemoradiotherapy (CRT) and for those with Adjuvant Radiotherapy (RT) Alone (C)

OS, p=0.058; PFS, p=0.068) or insignificant (Total gastrectomy: OS, p=0.339; PFS, p=0.487). Lymph node status was found to be predictive for survival in both RT (p=0.000)and CRT subgroups. Figure 4 shows actuarial survival curves for lymph node negative and positive patients who were treated with CRT.

Table 2 presents the results of the multivariate cox models for OS and PFS. AJCC Stage I-II disease, subtotal gastrectomy and adjuvant CRT were significantly associated with improved OS (Figure 5) and PFS (Figure 6) in multivariate analyses.

Acute gastrointestinal and haematological toxicity was observed in 26% and 8% of the patients respectively. Severe grade III fatigue was reported in 9% of all patients. Late grade III nephrological toxicity was observed in 2.8% in all patients. No grade IV-V toxicity was reported.

Discussion

Gastric cancer most commonly presents as late stage disease and as a result adjuvant treatment is frequently recommended before or after surgery (Macdonald et al., 2001; Cunningham et al., 2006; Smalley et al., 2012). The positive impact of adjuvant treatments has become clearer over time with two landmark trials (Cunningham et al., 2006; Smalley et al., 2012). Intergroup-0116 (INT-0116) was the first major randomised trial to show a survival advantage with adjuvant CRT over surgery alone in a Western population (Macdonald et al., 2001). The MAGIC trial demonstrated that the addition of perioperative CT (ECF; epirubicin, cisplatin, fluorouracil) to surgery improves survival in a Western population of gastric cancer patients (Cunningham et al., 2006). The INT-0116 and MAGIC trials were both heavily criticized due to insufficient lymph node dissection in a significant proportion of eligible patients (Kim et al., 2005; Ohri et al., 2013). As a result, adjuvant treatment is thought merely to correct for inadequate surgery in these trials inadequate surgery was shown as the reason of adjuvant treatment benefit in Western patients. However, Kim et al. (2005) confirmed the results of INT-0116 in a non-randomized trial on a population of D2-resected Eastern patients. In a recent meta-analyses by Ohri et al. (2013) it has been shown that adjuvant RT in resectable gastric cancer improves both OS and PFS by 20% in the published randomized trials. The ARTIST trial and data from a Chinese trial by Zhu, demonstrated a significant advantage in PFS of adjuvant CRT over adjuvant CT alone in an Eastern population (Lee et al., 2012; Zhu et al., 2012). The optimal adjuvant treatment of gastric cancer is still under debate. The Dutch, CRITICS trial and multinational TOPGEAR trial are ongoing trials that may provide more information on the role and timing of CRT in gastric cancer treatment.

To our knowledge, we present the largest retrospective series of gastric cancer patients treated with adjuvant RT from a single centre. We have nearly 100 months median follow-up for surviving patients. The early 2000s was a transitional period in our institution when we switched to concurrent CRT approaches in gastric cancer adjuvant treatment. At that time there was no clear consensus on what the optimal CT regime should be, nor on whether concurrent CT should even be given or not. Concurrent CT was given either with the INT-0116 schema or a weekly schema according to the expected treatment tolerability of the patient based on age, weight loss, blood tests and performance status (Martoni et al., 1989; Vanhoefer et al., 1994; Takeda et al., 1995; Macdonald et al., 2001; Zhang et al., 2013). The weekly 5FU regime of concurrent CRT was believed to be less toxic (Martoni et al., 1989; Vanhoefer et al., 1994; Takeda et al., 1995).

Our RT technique was 2D before 2005 due to our hospital facilities. A higher rate of acute gastrointestinal toxicity can be associated with this technique, which is

now no longer standard in our department. Late grade III nephrological toxicity was observed in 2.8% of all patients. Advanced RT techniques may enhance critical organ sparing and also may allow potential dose escalation of systemic agents.

In both univariate and multivariate analyses, stage of disease was the most important prognostic factor for survival. There was a slight improvement in survival with adjuvant CRT over RT alone. This survival advantage in favour of CRT disappeared after 5 years and the survival curves crossed after about 10 years. Our analyses of survival probability by patient subsets must be read with caution because of the retrospective nature of this study. Whether our observation of a slight survival benefit for patients with concurrent CT is reflective of a radiosensitizing effect or is a random observation of an unplanned analysis with heterogeneous performance status is unknown.

Our survival results demonstrated significant benefit for patients who underwent subtotal gastrectomy. No prospective randomized trials have definitely established optimal surgical therapy for gastric carcinoma. Larger lesions generally require total gastrectomy while smaller, body and antrum lesions maybe removed by subtotal gastrectomy. Surgeons usually perform total gastrectomy in order to achieve at least 5 cm surgical margin, which is considered a safe surgical margin for gastric cancer (Czito et al., 2013). In previously published series, 5-year survival rates of total and subtotal gastrectomy are 10-15% and 25-45%, respectively (Douglass 1985; ReMine et al., 1964; Serlin et al., 1977). It is not clear if this inferior survival of patients undergoing total gastrectomy is a reflection of unfavourably large lesions or due to the higher morbidity of the surgery. In our series, survival advantage for subtotal gastrectomy over total gastrectomy was seen to be independent from the tumor localisation and size. This survival advantage of subtotal gastrectomy was consistent in the CRT group but not in the RT alone group.

We also noted in our series that extended lymph node dissection was not predictive for improved survival. Extended lymph node dissection has been associated with improved outcomes for several decades in Eastern trials while Western surgeons observed high perioperative mortality associated with extended dissection (Hartgrink et al., 2004; Tamura et al. 2011). The recent 15-year follow-up update of the Dutch D1D2 trial indicated a significantly improved cancer-specific survival and local control in the D2 group compared to limited D1 surgery (Songun et al., 2010). However, there remains no consensus on optimal surgical approach for gastric cancer in Western patients (Van Cutsem et al., 2008).

In conclusion, our report presents the survival probability up to 10 years and the effects of different covariates on survival in a retrospective series of 244 gastric cancer patients treated with adjuvant RT or CRT from a single institution. We consider that our observations can be useful in future randomised trials focusing on key questions in improving combination therapy for these patients.

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