Original Article

Postoperative chemoradiation in patients with localized gastric adenocarcinoma: Single center experience

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Abstract

BACKGROUND: 5-Flourouracil (FU)-based chemotherapy (CT) and concurrent 45 Gy radiotherapy (RT) is one of the standard postoperative approaches currently used in gastric carcinoma. The high toxicity rates of this treatment leads to interruption of treatment in the majority of patients. In our study, we investigated the rates of toxicity and treatment discontinuation observed during postoperative FU-based chemoradiotherapy (CRT); retrospectively evaluated the effect of CRT and the other prognostic factors on local and distant control and survival. **PATIENTS AND METHODS:** A total of 160 patients consisting of 97 total and 63 subtotal gastrectomy receiving postoperative CRT, have been studied retrospectively. **RESULTS**: Patients who had to discontinue the treatment for a median of 6 (range, 3–13) days experienced toxicity during treatment at a rate of 43%. During the 21 (range, 4–68) months of follow-up local recurrences were observed in 8 (5%) patients and distant recurrences were observed in 41 (25.6%) patients. While the 1–3 year overall survival (OS) rates were 75% and 42%, 13-year disease-free survival (DFS) rates were 63% and 42%, respectively. In the univariate analysis for OS and DFS demonstrated statistical significance for below those 60 years of age, D1–D2 dissection type, negative surgical margin, early treatment beginning, the absence of invasion, and early stage disease. D1D2 dissection type, early treatment begining, age below 60 years and early stage disease significantly improve OS and DFS in multivarite analysis. **CONCLUSIONS:** Survival is worse in patients older than 60 years, had late treatment begining, advanced stage and D0 dissection.

Key words: Gastric carcinoma, postoperative chemoradiotherapy, 5-flourouracil

Introduction

The main treatment modality in gastric carcinoma is radical surgery. However, the rates of local metastasis in the tumor bed and regional lymph nodes as well as distant metastasis via hematogenous or peritoneal pathways are high in the postoperative period and the survival rates decline.[1] Various CT regimens used to prevent the invasion and improve the poor survival rates provide small but statistically significant clinical benefit.[2,3]

Postoperative CT has become the standard treatment in gastric carcinoma particularly in the United States (US) after it has been proved that CT (FU and leucovorin-FA) and concurrent 45 Gy RT which has been incorporated into surgery with the INT 0116-SWOG 0008 study provides survival benefit.[4]

Similar to as practiced in the US, postoperative CRT has become the standard treatment modality also in our country. The biggest disadvantage of this treatment, despite its survival benefits, is its quietly high toxicity rates.

In our study, we investigated the rates of toxicity and treatment discontinuation observed during postoperative FU based CRT; and retrospectively evaluated the effect of this and other prognostic factors on local and distant control and survival.

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Patients and Methods

Patient selection

Patients below 80 years of age and classified as ECOG 1–2 referred during January 2001 to December, 2007

to our center, for postoperative therapy, 97 with total and 63 with subtotal gastrectomy, a total of 160 patients that received postoperative CRT were evaluated retrospectively. Median age of the patients was 55 (range, 25–76). Patient characteristics revealed that 72.5% of the patients were male and the tumors were mostly localized in the antrum [Table 1]. The tumor was located in the antrum in 76, in the corpus in 55, in the cardia in 26, and as linitis plastica in 3 other patients.

Lung X-rays, abdominal and pelvic CT-scanning, biochemical analysis and whole blood counts were performed in all cases and staging was done according to the American Joint Committee for Cancer Staging System (AJCC) 1997 and informed consent was taken.

Treatment

In patients staged as IB–IV M0 disease with an indication for postoperative CRT, a CT regimen with FU 425 mg/m^2/day + leucovorin 20 mg/m^2 for five days was started in 160 patients within a median of 36 days (range, 16–75). The second course of CT was given for four days with the same doses, 28 days later following the first day of RT. The third course of CT was given during the last three days of RT again at same doses.

After RT, same agents were used as adjuvant therapy for three months. The adjuvant CT course differed between 1 and 3 courses depending on the toxicity. CT was performed for a total median of 5 (range, 4–6) courses. Fifteen patients could have only received one course of CT; of which 2 patients due to grade I hematologic toxicity; 12 patients with grade II hematologic toxicity and one patient with grade III hematologic toxicity. Forty-five patients could have only received two courses of CT caused by toxicity of which 12 patients with grade I, 12 patients with grade II, and 9 patients with grade III hematologic toxicities. Twelve other patients decided not to continue their therapies with their own will. CT in other four patients had to be discontinued after three courses of which two patients with grade II hematologic and two other patients with Gr III hematologic toxicity. Ninety-two (59.8%) patients have successfully completed the adjuvant therapy. The CT was interrupted in 15.6% of the patients who received CT median 40 days (range, 7–115) after the surgery. The median duration of therapy interruption was 8 days (range, 4–13).

RT was performed with a Co60 source or 6 MV photon beams, comprising the tumor bed and perigastric, celiac, suprapancreatic, pancreatoduodenal, portahepatic, and proximal para-aortic lymph nodes with 180 cGy/fr, median 45 Gy (range, 39.6–52.2). While doses (range, 36–52.2) with a median of 45 Gy were administered in RT, dosing was ceased at 36 Gy in one patient due to dehiscence of the incision. RT course had to be discontinued in one patient with Gr III hematologic and Gr I gastrointestinal toxicities at 3780 cGy, in one other patient with Gr III hematologic and Gr II gastrointestinal toxicities at 4140 cGy and in a fourth patient with Gr II

Table 1: Patient characteristics

Patient characteristics	n	(%)
Gender		
Male	116	72.5
Female	44	27.5
Age		
Median	55	
Range	25–76	
Type of Surgery		
Total gastrectomy	97	60.6
Subtotal gastrectomy	63	39.4
Tumor localization		
Antrum	76	47.5
Corpus	55	34.4
Cardia	26	16.2
Linitis plastica	3	1.9
Pathology		
Adenocarcinoma	95	59.4
Signet ring cell carcinoma	43	26.9
Mucinous carcinoma	11	6.9
Indifferentiated	4	2.5
Tubular adenocarcinoma	5	3.1
Papillary adenocarcinoma	2	1.2
Type of dissection		
D0	51	31.9
D1	69	43.1
D2	40	25
Surgical margin		
Positive	33	20.6
Negative	127	79.4
Grade		
Gr I	10	6.2
Gr II	50	31.2
Gr III	78	48.8
Unknown	22	13.8
T-stage		
T1	9	5.6
T2	29	18.1
T3	111	69.4
T4	11	6.9
Lymph node		
0	13	8.1
1–3	47	31.5
4	82	55
NX	12	7.5

Table 1: Patient characteristics (Contd.)

Patient characteristics	n	(%)
Stage		
IB	13	8.1
II	22	13.7
IIIA	54	33.8
IIIB	35	21.9
IV	24	15
Unknown	12	7.5
Surgery-chemotherapy interval (days)		
Median	40	
Range	7-115	
Total RT dose (Gy)		
Median	45	
Range	36–52.2	
Treatment break		
Yes	23	15.4
No	126	84.6
Treatment break (days)		
Median	6	
Range	3–13	
Follow-up (months)		
Median	21	
Range	5–81	

Table 2: Grades of acute toxicity during chemoradiotherapy

Grades	Gastrointestinal n (%)	Hematologic n (%)
G1	6 (3.7)	15 (9.4)
G2	6 (3.7)	28 (17.5)
G3	1 (0.6)	13 (8.1)

Table 3: Details of relapse

Site of relapse	n	(%)
Local	8	5
Distant	41	25.6
Peritoneum	14	8.8
Bone	2	1.2
Liver	13	8.2
Liver + peritoneum	1	0.6
Liver + bone	1	0.6
Liver + lung	1	0.6
Lung	3	1.8
Lung + peritoneum	2	1.2
Lung + bone + brain	1	0.6
Brain	2	1.2
Supraclavicular lymph node	1	0.6

hematologic and Gr II gastrointestinal toxicities at 4320 cGy. One hundred fifty six (97.5%) patients successfully completed the concomitant CRT courses. However, the dosing was increased to 52 Gy in one patient due to positive surgical margin. All patients were treated using two opposing fields in a conventional method. The tumor bed and remaining gastric portion were marked in all patients with 3 cm margins. In patients with total gastrectomy, preoperative CT and pathology reports were taken into account for the determination of the tumor bed. Simulation with oral barium contrast and I.V. contrast was performed to establish the RT field and kidney protection was ensured.

The acute toxicities seen during and after therapy enlisted in the files were determined according to Radiation Therapy Oncology Group (RTOG), Acute Radiation Morbidity Scoring Criteria. None of the patients needed to quit therapy, yet in 24 (15%) patients it had to be interrupted and in these patients supportive therapies were given to provide the completion of therapy. However, in 68 (42.5%) patients their therapy had to be discontinued.

Follow-up

Patient's follow-up was carried up for the first 2 years with an interval of 3 months and than for every 6 months with clinical examination, a complete blood count, liver function tests, and thorax and abdomen CT scanning when clinically indicated.

Statistical methods: Kaplan–Meier survival analysis was used for survival analyses and Log Rank test was used for comparing survival data. For multiple evaluations, Cox-regression test was used. A P value < 0.05 was considered significant. Statistical analyses and graphics were performed by using SPSS 11.0 software.

Result

Toxicity

When the treatment related toxicities were assessed from patient's records and their clinical complaint; it was noted that 13 patients (8%) experienced gastrointestinal toxicity, whereas 56 patients (35%) experienced hematological toxicities [Table 2]. It was observed that both toxicities were mostly grade II. Evaluation of total duration of treatment and treatment interruptions revealed that treatment of 24 (15%) patients had to be interrupted for a median of 6 days (range, 3–13).

Recurrences: During the 21 (range, 5–81) months of follow-up, local and distant recurrences were observed in 8 (5%) and 41 (25.6%) patients, respectively [Table 3]. Among eight patients with local recurrences, only one patient had positive surgical margin, whereas seven had negative surgical margins and all local recurrenses were observed within the radiation fields. Four cases had

undergone D0 resection, while two had D1 and two had D2 resection.

Among the patients with recurrences, subtotal gastrectomy was performed in five and total gastrectomy in three patients. None of the recurrences were Gr I, whereas five were Gr II and three were Gr III. The most common sites of metastasis among 41 patients with metastasized disease were the peritoneum and liver. Ten of the patients with distant metastasis had positive surgical margins and 31 had negative surgical margins; it was observed that 12 patients had undergone D0, 15 patients D1 and 14 patients D2 resections. The 13 subtotal and 28 total gastrectomy cases were studied by grades, and it was observed that 4 patients were Gr I, 10 patients were Gr II, and 27 patients were Gr III. No factors were found to be prominent in terms of the features searched in local recurrences, whereas Gr III histology was observed most commonly in patients with distant metastasis.

Survival

During the follow-up period, 90 (56.2%) patients died and 70 patients (43.8%) were still alive. The median duration of OS was 25 (±4.23) and median DFS was 20 (±4.67) months and the 1–3 years OS rates were 75% and 42%, 1–3 years DFS rates were 63% and 42% [Figures 1 and 2].

In the evaluation of 1 and 3 year DFS and OS values in the univariate analysis according to the probable prognostic factors, the following results are obtained:

The factors as age below 60 years (P = 0.001) (P = 0.001), early stage; IB (P = 0.002) (P = 0.003), negative surgical margin (P = 0.022) (P = 0.015), early treatment begining (P = 0.045) (P = 0.047), the absence of invasion (P =0.038) (P = 0.033), and D1-2 dissection type (P =0.014) (P =0.019) yields a better statistically significant DFS and OS [Table 4].

But, N stage (P = 0.056) (P = 0.058), gender (P = 0.420) (P = 0.496), pathology (P =0.114) (P =0.102), type of surgery (P = 0.081) (P =0.106), location of the tumor (P = 0.291) (P =0.194), the number of lymph nodes taken out during operation (P =0.163) (P = 0.164), tumor grade (P = 0.991) (P = 0.915), interruption of therapy (P = 0.729) (P = 0.760) were not found to be associated with better statistically significant DFS and OS curves.

Table 4: Survivals in the univariate analysis according to the possible prognostic factors

	Survival (%)					
	Disease-free survival			Overall survival		
Prognostic factors	1-year	3-year	*P*-value	1-year	3-year	*P*-value
Age						
Below 60	75	50		86	50	
Above 60	44	30	0.001	63	29	0.001
Stage						
IB	92	85		92		
II	64	59		73	59	
IIIA	70	41		80	42	
IIIB	49	24		63	23	
IV	46	11	0.002	71	11	0.003
Surgical margin						
Positive	51	25		64	25	
Negative	66	46	0.022	78	46	0.015
Time to start the treatment						
0-20 days	64	46		79	46	
20-40 days	70	50		79	48	
40-60 days	59	31		76	33	
Above 60 days	44	27	0.047	56	27	0.0045
Present of invasion						
Yes	58	37		59	38	
No	82	60	0.038	70	37	0.033
Dissection type						
D0	55	33		72	34	
D1	75	51		81	51	
D2	52	34	0.014	67	34	0.019

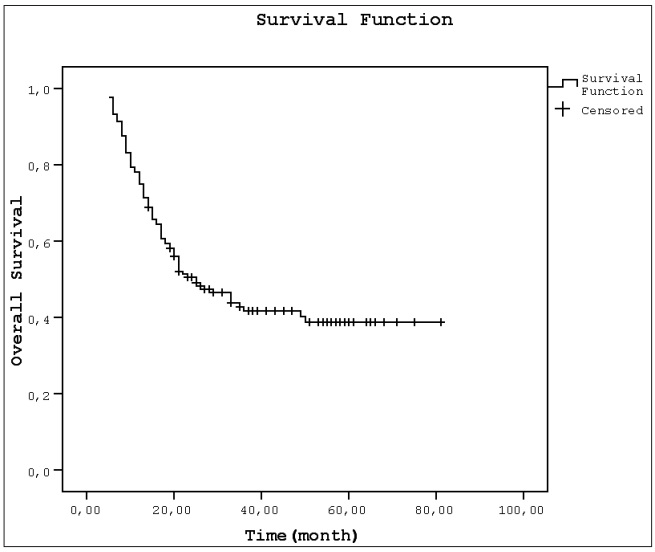

Figure 1: Overall survival rate

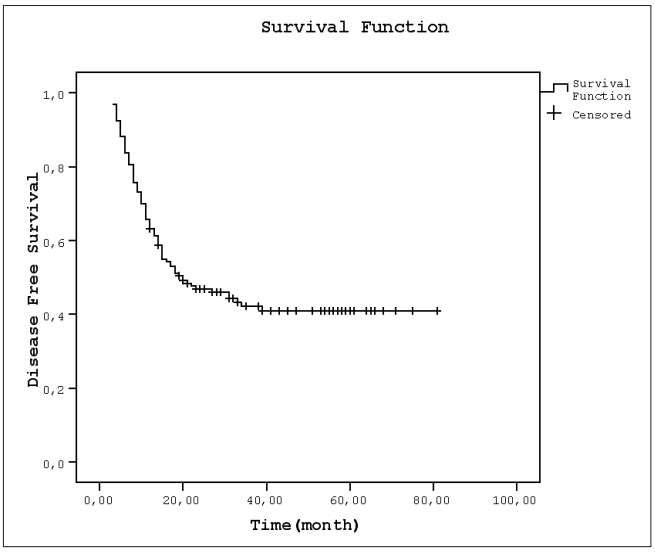

Figure 2: Disease-free survival rate

Table 5: Comparison of patient characteristics and treatment results between the MacDonald's study and the present study

	MacDonald	The present study
Number of patients	281	160
Median age	60 (25 - 87)	55 (25 - 76)
Gender (male) (%)	72	72.5
T-stage (%)		
T1-2	31	23.7
T3	62	69.4
T4	8	6.9
N-stage (%)		
0	14	7.4
1-3	42	31.5
>4	43	55
Tumor localization (%)		
Antrum	53	47.5
Corpus	24	34.4
Cardia	21	16.2
Linitis plastica	2	1.9
Time from surgery to chemotherapy in days (range)	27 - 48	7 - 115
Time from surgery to radiotherapy in days (range)	50 -76	35 - 145
Treatment interruption (%)	34	15.4
Protocol treatment completed (%)	64	57.5
Grade 3-4 gastrointestinal toxicity (%)	33	13
Grade 3-4 hematologic toxicity (%)	54	35
Local relapse (%)	19	5
Distant metastases (%)	33	25.6
Median overall survival (months)	36	25

In the multivariate analysis of these prognostic factors, we found that age older than 60 years ($P = 0.002$) ($P = 0.002$) , D0 dissection type ($P = 0.004$) ($P = 0.014$), late treatment beginning ($P = 0.020$) ($P = 0.035$), and advanced stage ($P = 0.007$) ($P = 0.008$) were related to decreased OS and DFS.

Discussion

Postoperative CRT that has been demonstrated to be effective in gastric carcinoma in the INT 0116-SWOG 0008 study, has become a treatment standard in this area. This treatment has become the treatment standard

in our country also however, the excess toxicity in this treatment poses a problem which is tried to be reduced with dose modifications and oral agents.[5,6] No marked difference has been determined between these.[7] In our study, we found lower rates of toxicity and treatment interruption compared with the latter study [Table 5].

The fact that there were older patients up to the age of 87 years in the INT 0116 and people's acquired resistance maintained against poor living conditions that they experience in our developing country might be the cause of the lower rates of toxicity found in our study.

However, despite the lower rates of toxicity and relapse, our study showed lower survival rates. It is always difficult to evaluate toxicity in a retrospective study and the rates of toxicity presented here, particularly the gastro-intestinal toxicity is probably underestimated.

While the median OS rate was 36 months and 3-year OS rate was 50% in INT 0116, these parameters were found to be 25 months and 41.6% in our study, respectively. In the analysis of the univariate analysis of patient characteristics in INT 0116 and our study with the aim of explaining this difference in survival rates, it was incidentally noted that tumors were located relatively more in the corpus in our study, as the location, and that had worse survival compared to the other locations, although not statistically significant. Similarly, no survival differences were determined between the N3 stage which is observed more commonly in our study and the remaining N stages.

Factors that might influence survival including sex, grade, the number of involved lymph nodes, pathology, and tumor localization did not differ statistically significantly; however, patients with early stage, negative surgical margin, D1–2 type of dissection, time to start the treatment and patients older than 60 had significantly better prognosis. In terms of the benefit of treatment interruption for survival, it was observed that those with interruption of the treatment had better survival, but this finding did not reach a statistical significance. In multivariate analysis, the four factors influencing both OS and DFS rates are advanced age, stage, D0 dissection type and late treatment beginning that reduce survival rates. In our study, such factors as the age of patients (median 55), existence of only a small portion of younger patients, 40% of the total group consisting the advanced stage disease like stage IIIB and IV; moreover, the time between surgery and chemotherapy reaching a maximum of 115 days as well as the time between surgery and radiotherapy reaching a maximum of 145 days, which consequently restricts the early therapy initiation may explain the moderate results of the therapy. Discontinuing or quitting the treatment caused by toxicity decreases the chance of administering adjuvant CT to patients following the CRT. In our study, only a median of two courses (range, 1–3) of adjuvant CT could be administered to patients after concurrent CRT.

Although it has been stated in the literature that inadequate administration of adjuvant CT reduces locoregional control, this has not been proved in our study.[8]

It has been suggested that the type of dissection influences survival and the best results were obtained in patients treated with D2 dissection and CRT.[9] In addition, it should also be kept in mind that postoperative mortality among patients with D2 dissection is higher in patients from European descent.[10,11] The comparison of D1 and D2 dissection with D0 (in 31.9% of the patients) dissection in our study showed differences neither in DFS nor in OS. Moreover, no difference has been found between dissection types D1 and D2 either. The timing of CRT in gastric carcinoma is still unclear. It is not known whether preoperative or postoperative CRT is better.[12] Studies on preoperative CRT are still in the phase II stage. Randomized studies which would be performed with this postoperative approach shall help us determining the optimum time of CRT.

Administration of the RT mostly under conventional conditions is another cause of this excess toxicity. Use of the three-dimensional (3D) conformal method is important in reducing this toxicity.[13-16] Hence, the dose received by critical organs might be reduced enabling a reduction in toxicity and thus a more regular treatment program. The use of conventional RT during the administration of treatments evidently was the cause of relatively higher rates of toxicity in our study. This toxicity will be reduced with 3D conformal treatment. Currently, particularly in the US postoperative CRT is incorporated into the routine while the other countries use different accepted standards.

In Western Europe, the standard treatment modality is also CT consisting of prepostoperative epirubicine + cisplatin + fluorouracil.[17] This treatment regimen reduces both tumor size and increases progression free survival (PFS) and OS.

In Southeastern Asia, however, another treatment standard, i.e., an oral fluoropyrimidine S-1, is used effectively in the adjuvant treatment of gastric carcinoma following a D2 dissection.[18]

Today, it is not feasible to determine which one is more

ideal since the accepted standards cannot be compared. Further randomized studies on this issue shall enlighten this question.

Consequently, adherence to treatment has become difficult with the current standard approach in gastric carcinoma. Interruptions are frequently required to improve the performance of the patients and help completing the treatment.

Novel treatment approaches are needed in patients above 60, had late treatment beginning, advanced stage and D0 dissection with worse prognosis. New randomized studies on this issue shall help determining the optimal treatment in gastric carcinoma.

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