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Effect of Adjuvant Chemoradiotherapy on Survival of Gastric Cancer Patients: Single Center Experience from the Southeast Region of Turkey

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Authors' contributions

This work was carried out in collaboration between all authors. Author FK designed the study. Author CUA wrote the protocol and wrote the first draft of the manuscript. Authors MG, FS and IS managed the literature searches. Authors FO, OO, NA and GY have done the statistical analysis and all authors read and approved the final manuscript.

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ABSTRACT

Background/Aim: Gastric cancer causes the second highest number of cancer related deaths. The purpose of this study is to evaluate the survival of patients who are T3, T4, lymph node positive postoperatively and have undergone adjuvant chemoradiotherapy (CRT). We also examined the toxicities of CRT.

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Materials and Methods: Included in this retrospective study were one hundred six, stage IIA, IIB, IIIA, IIIB and IIIC gastric cancer patients undergoing adjuvant chemoradiotherapy after four weeks of surgery presenting at our hospital between 2009 and 2013. Statistical analysis was done with the SPSS (version 19) programme and survival analysis was done by using the Kaplan-Meier method.

Results: The median follow-up of patients was 25 months (range; 7-38). There were local recurrences in 25.9% (n=22) of patients and liver metastasis in 20% (n=17), lung metastasis in 16.5% (n=14) and peritoneal metastasis in 5.9% (n=5). There were no recurrences in 31.8% (n=27) of patients. The median disease free survival (DFS) of the patients was 11 months (8.4-13.5) and overall surival (OS) was 29 months (24.3-33.6).

Conclusion: Survival rates were found to be lower than expected, this could be due to ongoing dietary habits and the low socioeconomic status of the patients. Toxicities were manageable.

Keywords: Gastric cancer; locally advanced; chemoradiotherapy; adjuvant therapy.

1. INTRODUCTION

Gastric cancer is the fourth most commonly seen cancer worldwide and is ranked second among cancer related deaths. Although early diagnosis is the goal with these patients, mortality is still high. Incidence of gastric cancer is higher in middle age and in men. The male/female ratio is 2/1. Gastric cancer incidence increases after the sixth decade but it can also appear earlier, for instance in hereditary types [1-3]. Gastric cancer is more commonly seen in countries such as Japan, Korea and Colombia. The effect of environmental factors and nutrition on gastric cancer has been investigated for many years. Although the etiologic agent in gastric cancer is not definite, diet has been shown to be an important factor. Gastric carcinogenesis involves the interaction of an etiologic agent (in most gastric cancers, Helicobacter pylori), the host characteristics and the external environment [4]. It has been shown that helicobacter pylori infection, a diet rich in carbohydrates and fats, pickles, high amounts of salt consumption, foods containing nitrites and salted meat and fish products increase gastric cancer risks, while milk, fresh vegetables and vitamin C decrease its risk [4]. Excluding very few countries, its prognosis is rather poor and the 5-year survival rate is approximately 20% [5,6].

Gastric cancer is classified into two types; the first one is the intestinal type, developed often in consequence of a sequence of precursor lesions, and the latter is the diffuse type, often associated with familial distribution and developed in the stomach following chronic inflammation.

Surgery with adjuvant chemoradiotherapy (CRT) which is the only curable modality is still the current treatment choice. However, adverse effects are rather common during adjuvant therapies due to the intensity of the treatment [1,2]. In patients with lymph node metastases, relapse and death rates in recurrent cancer are 70% and 80%, respectively. Recurrence is inevitable even in patients with R0 resection and D1 and D2 dissection. Intergroup - 0116 (INT-0116) studies carried out in the USA have shown that postoperative CRT increases survival. Adjuvant CRT is the standard treatment method in resectable gastric adenocarcinoma in the USA and many Western countries [7-9].

In gastric cancer, the curative treatment method is surgery. The chance to heal is possible only with curative surgical resection [10,11]. Our purpose in this study is to determine survival rates of 106 postoperative T3, T4, node (+) patients undergoing adjuvant CRT and the toxicities of CRT in the southeast region of Turkey.

2. MATERIALS AND METHODS

Patients with pathologically-proved adeno-carcinoma (100 patients) and six with other histologies, who had undergone surgery for resectable disease and who had taken adjuvant CRT, presenting at our hospital between 2009 and 2013, were retrospectively screened. Informed consent of the patients and the local ethics committee approval were taken. Patients staged from IIA to IIIC according to AJCC 7th edition were included in the study. Patients without peritoneal dissemination and metastasis in Positron Emission Scintigraphy (PET-CT), Magnetic Resonance Imaging (MRI) and Thorax-upper-lower abdomen Computerised Tomography (CT) and who had undergone partial/total gastrectomy and lymph node dissection were included in the study. Patients

with another known cancer, patients without postoperative follow-up or who received preoperative treatment were excluded. The patients' characteristics and the treatment protocols were summarized in Tables 1 and 2.

Table 1. Patient characteristics

Characteristics	N (%)
Total	106
Female	37 (35%)
Male	69 (65%)
Age	
Median	61
Range	27-82
Tumor localization	
Cardia	2 (1.8%)
Corpus	29 (27.2%)
Antrum	60 (56.6%)
Gastroesophageal	3 (2.8%)
Linitis plastica	12 (11.6%)
Tumor Grade	
Moderately differentiated	36 (34%)
Poorly differentiated	63 (59%)
Mixed	7 (7%)
Pathology	
Adenocarcinoma	100 (94.5%)
Other	6 (5.5%)
Pathologic T stage	
T3	69 (65%)
T4	37 (35%)
Pathologic N stage	
N0	13 (12.2%)
N1	33 (31.1%)
N2	42 (39.6%)
N3	18 (16.9%)
Stage	
2A	13 (12%)
2B	20 (18%)
3A	19 (17%)
3B	17 (16%)
3C	37 (34%)

(T: tumor, N: lymph node)

Postoperatively, depending on the localization and stage of the tumor, perigastric lymph nodes, celiac lymph nodes, peripancreatic, suprapancreatic lymph nodes, hepatic portal, splenic hilus, pancreaticoduodenal, periesophageal, mediastinal lymph nodes and clip areas were included in the treatment area in gastric radiotherapy. Margins including gastric bed, regional lymph nodes and two cm above and below the anastomosis line were included within the CTV (clinical target volume) area. In cardia tumors, inferior paraesophageal lymph nodes were included within the CTV area. Critical organs were identified as the kidneys, medulla spinalis, liver, heart, lungs and the spleen. 6MV and 18MV X rays were used in physical planning. The patients were treated with a D-2300CD high energy (LINAC) device which is a 3D conformal treatment device. The treatment dose administered was the standard 45 Gy (1.8 Gy/fx/day) on the tumor and regional lymph nodes and clip areas. Chemotherapy protocols added to radiotherapy were FUFA de Gramont and Mac Donald protocols according to NCCN guidelines [10,11]. 5-FU (bolus) 425 mg/m^2 IV was pushed daily on days 1-5 and leucovorin 20 mg/m^2 IV was pushed on days 1-5 at cycles 1, 3 and 4 (before and after radiation), cycled every 28 days. For cycle 2 (with radiation), 5-FU 400 mg/m^2 IV was pushed daily on days 1-4 and 31-33, leucovorin 20 mg/m^2 IV was pushed daily on days 1-4 and 31-33 (35 day cycle) was used [11]. The second regimen used is leucovorin 400 mg/m^2 IV on days 1 and 15 or days 1, 2, 15 and 16 with 5-FU 400 mg/m^2 IV pushed on days 1 and 15 or days 1, 2, 15 and 16 and 5-FU 600 mg/m^2 IV continuous infusion over 22 hours daily on days 1, 2, 15 and 16 (cycled every 28 days and 1 cycle before and 2 cycles after CRT). This also included radiation with 5-FU 200-250 mg/m^2 IV continuous infusion over 24 hours daily on days 1-5 or 1-7 (weekly for 5 weeks) [10].

Data were evaluated by using SPSS version 19.0 for Windows (SPSS Inc., Chicago, USA) Statistical software. Categorical variables were calculated using counts and percentages, whereas continuous variables were summarized by mean and standard deviation (median and min-max when required). The Kaplan Meier method was applied to compare survival times between groups. Statistical significance was accepted as $P<0.05$ in all tests.

2.1 Relapse

The patients had follow up appointments every three months in the first two years and every 6 months after 2 years. Physical examinations, whole blood tests, tumour markers and renal and hepatic function tests were carried out at follow-up. Thorax, upper-lower abdomen CT was carried out in all patients every 6 months during the first two years. Patients with clinical symptoms underwent gastroscopy. During follow-up, controls were classified as local relapse, locoregional metastasis and distant organ metastasis. The definition of local relapse included anastomosis line, duodenal stump, tumor bed and residual stomach. Locoregional metastasis meant metastasis to the liver or other

extraperitoneal organs and peritoneal metastasis. Distant metastases were to the lungs, bones or the brain.

3. RESULTS

One hundred six postoperative patients with gastric cancer were included in the study (Table 1). Thirty-five percent of the patients (n=37) were female and 65% (n=69) were male. The median age was 61 years (27-82). The median follow-up was 25 months (7-38) (Table 1).

The diagnostic methods used were PET-CT in 27 patients, MRI in 5 patients and CT in 74 patients. Tumor characteristics and treatment protocols of the patients are shown in Tables 1 and 2. Of 106 patients, 13% (n=14) underwent partial gastrectomy and lymph node dissection and 87% (n=92) had total gastrectomy and lymph node dissection. Sixty-five percent of the patients (n=69) were T3, 35% (n=37) were T4. There were no lymph node metastases in 12% of the patients (n=13), while 88% (n=93) had lymph node metastases. Seventy-two percent of the patients (n=76) underwent D2 dissection and 28% (n=30) D1 dissection. Eighty-eight percent of the patients (n=94) had RO and 12% (n=12) had R1 resections.

Of 106 postoperative patients, 76% (n=81) received FUFA de Gramont, 23% (n=24) Mc Donald protocol and 1% (n=1) received cisplatin with radiotherapy.

Table 2. Treatment protocols

Characteristics	N (%)
Chemotherapy regimen	
FUFA de gramont (10)	81 (76 %)
Mac Donald (11)	24 (23 %)
Cisplatin	1 (1 %)
Operation type	
Subtotal gastrectomy	14 (13.2 %)
Total gastrectomy	92 (86.7 %)
Nodal dissection	
D1	30 (28.4 %)
D2	76 (71.6 %)
Resection	
R0	94 (88.7 %)
R1	12 (11.3 %)
Radiotherapy	45 Gy
Follow-up	4 years

(FUFA: 5-fluorouracile, folinic acid)

At onset of CRT, the mean weight of the patients with gastric cancer was 71.8±9.31 kg, while they weighed 69.3±8.98 kg after CRT. This difference in weight was not statistically significant.

3.1 Follow-up of Patients and Toxicity

During the treatment process, vomitting, diarrhea and grade 1 mucositis were seen in 106 (100%) patients in the first, second and third weeks of CRT. Diarrhea was seen in 16.9% of patients (n=18) and 4.7% (n=5) quit treatment in the first three weeks. In the fourth week, 5.9% of patients (n=6) had grade 2 gastrointestinal toxicity, 7.9% (n=8) had grade 3 oral mucositis, 8.9% (n=9) had neutropenia, and 7.5% of the patients (n=8) quit treatment due to neutropenia. In the fifth week, 29.03% of the patients (n=27) had grade 3 gastrointestinal toxicity, 5.6% (n=6) quit chemotherapy and only completed RT, and 1.8% (n=2) could not complete RT but continued with CT. Simultaneous radiochemotherapy was completed in 80.2% of patients (n=85). The percentage of patients who could not complete the treatment was 19.8 (n=21). There were no deaths during the treatment. Treatment induced late toxicity was not seen in post treatment controls and there were no cases with secondary malignancies in the second year.

3.2 Recurrence and Survival

The median follow-up period was 25 months. Survival analysis of 85 patients who had completed CRT was evaluated using the Kaplan-Meier statistical method. DFS period of the patients was 11 months (8.4-13.5) (Fig. 1). The median OS was 29 months (24.3-33.6) (Fig. 2). Local recurrences developed in 26% of patients (n=22) whose pathology was poorly differentiated carcinoma. Liver metastases developed in 20% of patients (n=17), lung metastases in 16.5% (n=14) and peritoneal metatases in 6 % (n=5). There were no recurrences in 32% of the patients (n=27) and a total of 85 patients completed the treatment. Multiple metastases developed simultaneously in patients with relapses.

4. DISCUSSION

Epidemiological studies show that gastric cancer is frequently seen in older patients and is fatal. The five-year survival rate is below 20% [12]. Diets containing carbohydrates and fats, pickles, salt consumption in large amounts, foods containing nitrites, salted meat and fish products increase the risk of gastric cancer [4]. Gastric cancer is frequently encountered in our region of

Turkey. Therefore, it is thought that high consumption of salted fish, salty cube cheese (tendency to eat all salty foods), tandoor bread, spicy hot foods and beverages are effective in the development of gastric cancer in this region.

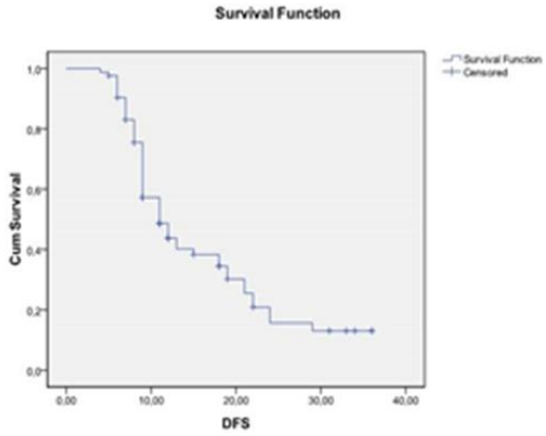

Fig. 1. DFS graph using Kaplan-Meier method

Patients are usually diagnosed at a locally advanced stage when serious invasion and lymph node metastases have occurred because gastric cancer is usually diagnosed late and survival of these patients is rather poor compared with those diagnosed with early stage gastric cancer. This study has evaluated the treatment protocols and consequently the survival of patients with locally advanced stage disease.

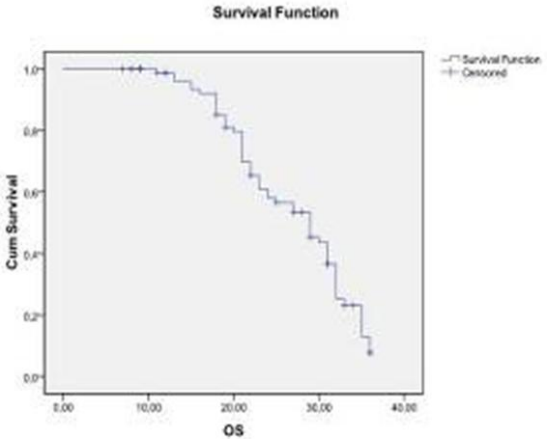

Fig. 2. OS graph using Kaplan-Meier method

The INT-0116 study has shown that simultaneously given adjuvant CRTs enhance survival. However, according to the INT-0116 study, adjuvant CRT is used as the standard treatment regimen in the USA in patients with operated gastric cancer [13,14]. In the U.S. Intergroup Southwest Oncology Group 9008/Intergroup 0116 Phase III study, the median follow-up was >6 years and with postoperative CRT, overall survival became 35 months versus 26 months (p=0,006), when compared with the surgery only arm [11,15].

In many Asian countries D2 lymph node dissection is applied as a standard approach despite its rather morbid course [16-18]. In the study of Medical Research Council (MRC) analysing morbidity and mortality of D1 and D2 lymph node dissection, morbidity and mortality rates were 28% and 6.5%, respectively, in the D1 arm and 46% and 13% in the D2 arm [19,20]. It is still controversial whether the morbidity in patients with D2 dissection is due to chemotherapy starting after the operation or due to the operation itself [16,17]. Chemotherapy of patients undergoing D2 lymph node dissection is controversial. In the Joint study, survival of patients receiving CRT following expanded D2 lymph node dissection, was increased and recurrences decreased [17,21]. Undoubtedly, the results of these two studies differ from each other when analysed regarding morbidity and mortality. However, D2 lymph node dissection is very controversial and is not carried out in some centers because of its high clinical mortality [17]. Furthermore, expanded lymph node dissection is still controversial in Western countries and to date a survival advantage has not been proved [13,14]. Both D1 and D2 lymph node dissections are carried out in our center and both groups receive standard CRT. The INT-0116 study does not involve a homogenous group with lymph node dissection and particularly decreasing number of D2 dissections. In our study, pathologic T3 and T4, node positive patients were included and a rather homogenous group of patients was involved. D2 dissections were carried out on 72% of our patients (n=76).

In a multicenter study on adjuvant gastric cancer, patients were given 3D conformal RT simultaneously with 5-FU therapy and 2 cycles of ECF following one cure of epirubicine, cisplatin and 5-FU (ECF). The 3-year overall survival of the patients was 62% [14]. Grade 3/4 neutropenia occurred in 66% of the patients. In another Korean study, expanded D2 lymph node dissection combined with adjuvant CRT resulted in a 5-year survival rate of 57% compared with 51% in the surgery only arm (p=0.02) and it was concluded that CRT administered following D2 lymph node dissection had a favorable effect on

the survival of patients [17]. In literature, it has been estimated that pre-operative evaluations of albumin and metastatic lymph node ratio should be performed to stratify the patients for risk analysis and prognosis [22].

Local recurrences occurred in 25.9% (n=22) and liver metastasis in 20% (n=17) of the patients who completed adjuvant CRT. This has unfavorably affected DFS. However, in our study, 85 patients completed treatment and the DFS of these patients was 11 months (8.4-13.5) and OS was 29 months (24.3-33.6). Due to grade 2 and grade 3 gastrointestinal toxicities, 30.1% of our patients (n=32) were started on alimentation fluids and supplemental therapies and there was no weight loss to interrupt treatment or lower chemotherapy dose during follow-up. In this research study carried out in the southeast region of Turkey, most of the patients were noted to present at locally advanced stage. The DFS and OS of the patients who completed adjuvant therapy were shorter than what literature states.

Our limitations were, only a small number of patients were included in the study and standard CRT protocols were used, but we wanted to emphasize the importance of dietary habits on the appearence and recurrence of gastric cancer in a specific region of Turkey. Additionally, we wanted to share our retrospective data for locally advanced gastric cancer patients.

5. CONCLUSION

In our study, survival rates were found to be lower than those found in the literature, this could be due to ongoing dietary habits and low socioeconomic status of the patients. Toxicities, however, were manageable. Environmental and personal factors such as a diet rich in salt play a role in the formation of gastric cancer. This could also affect patient prognosis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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