

Results of combination chemotherapy and radiation therapy in non-metastatic gastric cancer in Yazd – Iran

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Abstract

BACKGROUND: Gastric cancer is the first cause of cancer death in Iran. Most of the patients are diagnosed in advanced stages and survival rate is low. The aim of this study was to evaluate the survival rate of patients with gastric and gastroesophageal junction adenocarcinoma receiving combination chemotherapy and radiation therapy in Iran. **MATERIALS AND METHODS:** This study was conducted on 53 patients with gastric or gastroesophageal junction adenocarcinoma referring to Shahid Ramezanzadeh Radiation Oncology Center between 2004 and 2010. All patients underwent surgical operation, chemotherapy, and radiotherapy. Data contained in patients' records were extracted and follow-up was conducted through telephone contacts. To analyze the data, Kaplan Meier curves, and SPSS software were employed. **RESULTS:** Seventeen (32.1%) patients were female and 36 (67.9%) were male. Mean age was 58.32 years. In 14 patients (26.9%) no lymph node was resected or reported by the pathologist. In 29 patients (54.7%) one to six lymph nodes were found, and in 10 patients (18.9%) seven lymph nodes or more were detected. In two patients, (3.77%) more than 15 lymph nodes were resected. Surgical staging was impossible for 16 patients (30.2%). Mean survival was 50.9 months and median survival was 51 months. 3, 5 and 7 year survival rates were 73%, 36%, and 18% respectively. None of the variables had a significant relation to survival. **CONCLUSIONS:** Despite inadequate surgery, the survival rate in our study is one of the best one reported in our country. We think this advantage may be due to poly drug chemotherapy and sequential radiation therapy.

Key Words: Chemotherapy, gastric cancer, radiation therapy, survival

Introduction

Gastric cancer (GC) is one of the common malignancies world-wide with nearly 900,000 new cases diagnosed annually.^[1] It is the second leading cause of cancer-related deaths world-wide.^[2] In Iran, the incidence is around 7300 cases per year, being the most common cancer in men. GC is the first cause of cancer death in both sexes in Iran and the disease in most patients is diagnosed in advanced stages.^[3] 5 year survival rate in most studies in Iran is less than 25%.^[3-5] Although, surgery is the cornerstone of treatment; however, there are many controversies about extension of surgery especially extension of lymphadenectomy. On the other hands different opinions exist around the value of adjuvant and neoadjuvant therapies.^[6-10] This study was performed to evaluate the survival rate of patients with gastric adenocarcinoma and gastroesophageal junction and quality of surgical resection and efficacy of adjuvant therapies. Limitation of the project: (a) The number of the patients referred to our center was limited. (b) Most of the referred patients were initially managed in different private clinics; therefore, it was difficult to obtain full information on the previous history and the other necessary data. (c) Regarding the above two limitations added to scarcity of financial resources we were not able to design a randomized clinical trial study.

Methods

Among the patients referred to our center for radiation therapy after curative intent surgery and/or chemotherapy between 2004 and 2010 all those with documented

pathology of adenocarcinoma of stomach or gastrointestinal junction and pathologic T stages T2 b, T3 and T4 (according to American Joint Committee on Cancer Staging of GC 2002) and/or positive lymph node were enrolled in the study. The treatment modality was clearly explained to the patients and their families and medical consent forms were obtained from the patients. The patients had neither distant metastases, nor any previous history of cancer. Data contained in the patients' records were extracted and follow-up was conducted through periodic visits and telephone contacts. Through coordination with The Health Center of Province, data on mortality demographics of patients was obtained; however, information regarding other provinces was gathered through telephone contacts. In patients receiving their chemotherapy in other centers, we contacted their physicians to get information on the patients' chemotherapy regimens; however, such data could not be obtained for nine of them. Radiation therapy was performed after two dimensional simulation with oral and intravenous contrast by 9 mV X-ray photon with two parallel apposed anterior-posterior/posterior-anterior fields. Whenever the linear accelerator of this center didn't work for any reasons the patients were treated with the cobalt 60 machine. Treating field encompassed tumor bed, residue of the stomach, and lymph nodes of celiac, paraaortic and splenic and liver hilum. For three patients Mayo clinic regimen (5Fluorouracil[5FU] and Leucovorin), along with concurrent radiation therapy was employed. 21 patients had received an Epirubicin based regimen, 19 had received Taxane based regimen, and for 9 of them the regimen type was unknown.

Statistical analysis

In this study survival rate was assessed using the Kaplan-Meier curves employing Log Rank model and SPSS 15 software. Survival was estimated from the day of starting treatment. The relation between variable and survival rate was evaluated.

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Results

Between 2004 and 2010, 53 patients were enrolled in this study. A total of 17 (32.1%) were female and 36 (67.9%) were male. Mean age was 58.32 years. Computed tomography (CT) scanning was performed prior to radiation therapy for those patients who had not undergone such a procedure previously. For 28 (52.8%) patients total gastrectomy was performed and 25 (47.2%) patients underwent subtotal gastrectomy. Surgical margins were positive in 17 (32.1%) patients. A total of 10 patients had received neoadjuvant chemotherapy and in all of them the Epirubicin-based regimen was used and in one of them (10%) surgical margin was positive. In 14 (26.9%), of cases no lymph node was resected by the surgeon or reported by the pathologist. In 29 patients, (54.7%) one to six lymph nodes were found, and in 10 patients (18.9%) seven lymph nodes or more were found but only in two patients (3.77%) more than fifteen lymph nodes were resected or evaluated. With these limitations, surgical staging of patients was impossible for 16 patients (30.2%). The other stagings included: Stage I b (15.1%), stage II (26.4%), stage III a (22.6%), stage III b (3.8%) and stage IV (non-metastatic) (1.9%). Chemotherapy regimens were 5FU-based, Taxane-based and Epirubicin-based in 5.7%, 35.8%, and 39.6% respectively. In 18.9% of patients type of chemotherapy regimen was unknown. We summarized the characteristics of the patients in Table 1. Mean survival was 50.9 months (CI 95%; 43.11-58.69) and median survival was 51 months (CI 95%; 40.45-61.54). 3, 5 and 7 year survival rates were 73%, 36%, and 18% respectively [Figure 1]. Mean disease free survival was 42.26 months (CI 95%; 33.96-50.55) [Figure 2]. None of the variables such as stage, age, sex, type of surgery, positive surgical margins, type of complementary treatment and the number of resected lymph nodes did not have any significant relation to survival.

Discussion

The incidence of GC has increased in Iran in the past decades in contrast to Japan and Western countries.^[11] The survival rate of GC patients in Iran is lower than in Japan and Western countries. It may be due to late diagnosis and

nonexistence of national programs for screening of high-risk patients. On the other hand, less effective treatments may be another cause.

Although surgery is the cornerstone of treatment, extent of surgery is different in Japan and South Eastern Asian Countries, European Countries, and USA. In Japan, a D2 lymph node dissection is the standard surgical procedure because of its acceptable safety profile and superior treatment outcome.^[8] D2 lymph node dissection is an extended lymphadenectomy, entailing removal of nodes along the hepatic, left gastric, celiac, and splenic arteries as well as those in the splenic hilum.^[12] In Europe, two large controlled trials performed by The British Medical Research Council Trial and Dutch Gastric Cancer

Table 1: Characteristics of the patients

Characteristics	No.	%
Sex		
Male	36	67.9
Female	17	32.1
Age		
≤60	26	49.1
>60	27	50.9
Type of surgery		
Total gastrectomy	28	52.8
Subtotal gastrectomy	25	47.2
Surgical margins		
Positive	17	32.1
Negative	36	67.9
Resected LN		
None	14	26.9
1-6	29	54.7
≥7	10	18.9
Stage of disease		
Unknown	16	30.2
Ib	8	15.1
II	14	26.4
IIIa	12	22.6
IIIb	2	3.8
IV	1	1.9

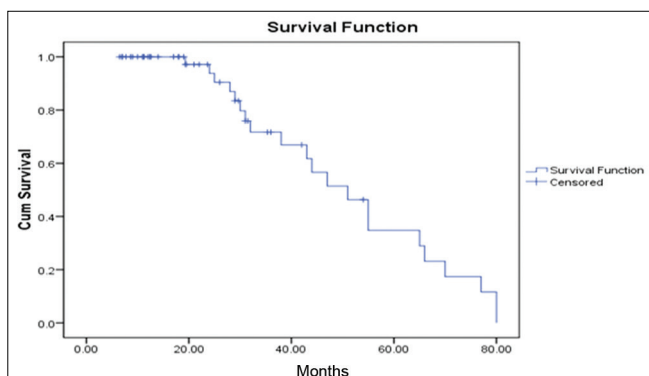


Figure 1: Overall survival

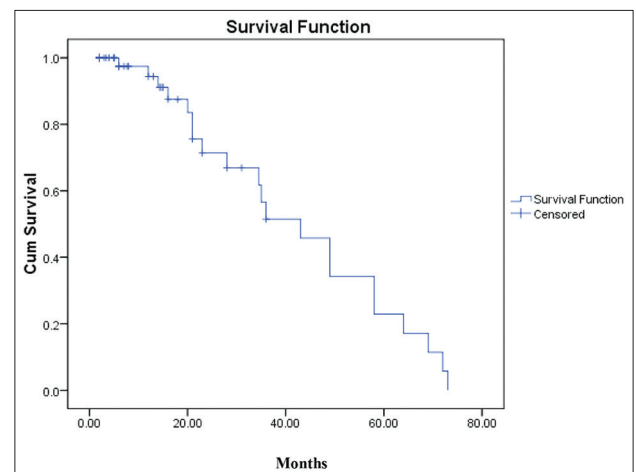


Figure 2: Disease free survival

Group could not prove any survival benefit for D2 lymphadenectomy versus D1.^[8] The most important reason was increasing post-operative mortality after D2 dissection. D1 lymphadenectomy refers to a limited dissection of only the perigastric lymph nodes.^[12] On the other hands in Japan, because of good results in D2 resected patients and safety of this procedure, a clinical trial comparing D1 versus D2 would be considered unethical today.^[13] After final analysis, the results of Dutch trial patients with N2 disease (metastasized to 7-15 lymph nodes) showed a survival benefit over D2 resection; however; it is impossible to determine N2 patients preoperatively. According to this trial, there is no difference in survival after 11 years whether less than 15 lymph nodes, between 15 and 25 lymph nodes, or more than 25 lymph nodes were harvested.^[14] In contrast using multivariable Cox regression models in USA showed that removal of more than 25 lymph nodes improved overall survival and disease free survival compared with patients who had fewer lymph nodes resected.^[2] In our study there was no significant survival difference between patients for whom no lymph node, 1-6 lymph nodes and 7 or more lymph nodes were harvested ($P = 0.997$).

Adequate lymph node sampling is essential for accurate staging. According to the American Joint Committee on Cancer Staging of GC 2010, more than 15 lymph nodes are essential for staging.^[15] In our study, only two patients (3.77%) had undergone adequate lymph node dissection. In 14 (26.9%) of cases no lymph node was reported and therefore there is strong possibility that we underestimated the real stages of the patients. In three previous studies, positive surgical margins showed negative effect on survival.^[16-18] In none of those three studies radiation therapy was employed. Two other studies showed that the effect of positive margin disappears in advanced stages^[19] and it was important in lymph node negative patients.^[20] In our study, although mean survival was 46.7 months in margin positive patients and 51.52 months in the negative group, the difference was not significant. ($P = 0.646$).

Even after curative surgery, there is a noticeable risk of local, regional and distant recurrence. Loco-regional failure rates range from 38% to 93% and distant failure rates of 22%-52% reported in various studies, clearly indicate the need for adjunctive therapies beyond surgery.^[9] For decreasing locoregional and distant metastasis, Southwest Oncology Group Intergroup study (SWOG 9008/INT-0116) trial was performed. In this study post-operative 5FU based concurrent chemoradiation therapy was employed and median overall survival increased from 27 months in the surgery only group to 36 months in the other group (surgery and chemoradiation) and median relapse free was 19 months in the surgery only group versus 30 months in another group.^[7] In this study only 10% of patients underwent a D2 dissection, 36% had a D1 dissection and 54% underwent less than D1 lymphadenectomy. Then, the question was

raised about whether or not chemoradiation would only decrease loco-regional recurrence in patients who underwent an inadequate lymph node dissection. In a subset analysis in this trial, there was no evidence that the benefit of adjuvant treatment was different based on the extent of lymphadenectomy.^[21] A large non-randomized trial conducted on 544 patients who underwent D2 dissection in South Korea and received concurrent 5FU-based chemoradiation showed exactly results similar to the INT-0116 trial compared with 446 patients who only underwent D2 dissection. The study showed a significant increase of disease free survival in the chemoradiation group. In USA a study that used multivariable Cox regression models for assessing independent prognostic factors affecting overall survival and disease-specific survival confirmed that survival benefit of adjuvant radiation therapy following gastrectomy persists in patients who had undergone extended lymphadenectomy.^[2]

Patterns of relapse analyses from the INT-0116 trial suggested that the survival benefit was achieved secondary to a reduction in locoregional relapse rates and not to distant metastases. Therefore, using more effective chemotherapy regimens seems necessary for decreasing the rate of distant metastasis. Although previous studies did not show any significant benefit of adding a post-operative chemotherapy with mitomycin, 5FU and cytarabine to serosa negative patients after D2 dissection in Japan, an oral fluoropyrimidine, S-1, improved overall survival in stage II and III patients Adjuvant Chemotherapy Trial of TS-1 for GC.^[22] Magic trial showed that chemotherapy improves survival of patients with resectable tumors. In this trial three courses of chemotherapy with Epirubicin, Cisplatin and 5FU preoperatively and three courses of the same regimen post operatively increased overall survival and disease free survival. 5 year survival rate increased from 23% in the surgery alone group to 36% in the chemotherapy group. These days the variations of this regimen that substituted Cisplatin with a less toxic drug in the same family, Oxaliplatin and 5Fluorouracil with its oral precursor Capecitabine are very advocated. Combination of Docetaxel, Cisplatin and 5FU (DCF) is an effective regimen in treating unresectable, metastatic or locally recurrent gastric tumors. Induction chemotherapy with Docetaxel and Cisplatin and then concurrent chemoradiation with these two drugs followed by surgery in esophageal squamous cell carcinoma (SCC) and adenocarcinoma in a Phase II trial showed promising results.^[23] Vuidez *et al.*, used neoadjuvant Docetaxel, Oxaliplatin and Capecitabine concurrently with radiotherapy and showed that 68.4% of the patients had a major response to therapy.^[24] In our study, 35.8%, and 39.6% of patient received Taxane-based (mostly DCF) and Epirubicin based

Table 2: Comparing five year survival of our patient to three other studies

Study	Five year survival rates in chemoradiation /chemotherapy group
INT 0116	43%
Magic trial	36%
ACTS-GS	72%
Our study	36%

chemotherapy respectively. All of them received sequential radiation therapy. However, there is no survival rate difference between the two groups. Median overall survival and 5 year survival were 51 months and 36% respectively. 5 year survival in our study is similar to Magic trial and worse than INT 0116 that showed 43% 5 year survival. However, as to our knowledge, it is the best survival rate for GC patients so far reported in our country. We compared 5 year survival rates of this study with three famous studies from USA, Europe and Japan in Table 2. It seems that multiple drugs chemotherapy with such agents as Docetaxel, Oxaliplatin, Epirubicin with Fluoropyrimidines, and sequential radiation therapy improve the survival even in patients undergoing inadequate surgical procedures.

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