

RESEARCH ARTICLE

Neoadjuvant Chemoradiotherapy in Non-cardia Gastric Cancer Patients - Does it Improve Survival?

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Abstract

Background: Survival rates after resection of advanced gastric cancer are extremely poor. An increasing number of patients with gastric carcinomas (GC) are therefore being treated with preoperative chemotherapy. We evaluated 36 month survival rate of GC patients that were treated by adding a neoadjuvant chemoradiotherapy before gastrectomy. **Materials and Methods:** Patients with stage II or III gastric adenocarcinomas were enrolled. The patients divided into two groups: (A) Neoadjuvant group that received concurrent chemoradiation before surgery (4500cGy of radiation at 180cGy per day plus chemotherapy with cisplatin and 5-fluorouracil, in the first and the end four days of radiotherapy). Resection was attempted 5 to 6 weeks after end of chemoradiotherapy. (B) Adjuvant group that received concurrent chemo-radiation after surgical resection. **Results:** Two (16.7%) patients out of 12 patients treated with neoadjuvant chemo-radiotherapy and 5 (38.5%) out of 13 in the surgery group survived after 36 months. These rates were not significantly different with per protocol and intention-to-treat analysis. The median survival time of patients in group A and B were 13.4 and 21.6 months, respectively, again not significantly different. Survival was significantly greater in patients with well differentiated adenocarcinoma in group B than in group A ($p < 0.004$). **Conclusions:** According to this study we suggest surgery then chemoradiotherapy for patients with well differentiated gastric adenocarcinoma rather than other approaches. Additional studies with greater sample size and accurate matching relying on cancer molecular behavior are recommended.

Keywords: Gastric cancer - adenocarcinoma - neoadjuvant chemoradiotherapy - surgery - stomach

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Introduction

Although the incidence of gastric cancer has been declining steadily since the 1930s, it remains a main cause of cancer death and continues to be a major public health problem worldwide and also in Iran, especially in Northern parts (Sadighi et al., 2005; Ferlay et al., 2008; Jemal et al., 2010; Parkin et al., 2010; Roshanaei et al., 2011; Shafaghi et al., 2013). The disease is commonly diagnosed at an advanced stage and about two thirds of patients have locally advanced disease at initial diagnosis (Greenlee et al., 2000; Kundel et al., 2011). Overall 5-year survival rate approximates 20% and has undergone minimal change over the last decade (Garcia et al., 2008).

However, recently the treatment of gastric cancer has been rapidly evolving with the emergence of new cytotoxic drugs and molecular targeted agents that show promising response rate and disease progression-free survival (Saghier et al., 2013). Surgery is the primary treatment for gastric carcinoma (Degiuli et al., 2004; Patel and Kooby, 2011; Wang et al., 2011). Over the past two decades, efforts

have been made to improve surgical techniques such as adjuvant chemotherapy, preoperative chemotherapy (CT) and radiation. Thus multimodality approach clearly offers survival benefit over surgery alone and preoperative chemoradiation or postoperative adjuvant chemoradiation is widely practiced in major centers (Jiang and Ajani., 2010; Blank et al., 2014). In an effort to improve survival outcomes, adjuvant therapy regimens with chemotherapy and/or radiotherapy (RT) have been used (Mari et al., 2000; Janunger et al., 2002).

Unlike early stage gastric cancer where surgical resection is the only curative modality, treatment of advanced gastric cancer is difficult and the combination of surgical and adjuvant chemotherapy or radiation is required for better outcomes (Du et al., 2012). The surgical requirements for an eligible resection were surgery with curative intent and en bloc resection of the tumor with both macroscopically and microscopically negative margins (R0 resection). Preoperative chemoradiotherapy has the theoretical advantage of treating an untouched tumor (lack of treatment-induced resistance), with

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intact vascularization and without fibrotic remodeling of the tumor bed due to surgical trauma the presence of intact tumor vasculature and oxygenation may enhance responsiveness to radiotherapy (RT) and systemic therapy (Roth et al., 2003). This treatment approach may also sterilize the surgical field, potentially reducing the risk of local tumor dissemination at resection. These considerations might account for the higher response rates observed when systemic therapy is administered preoperatively. Trials of neoadjuvant radiotherapy or chemoradiotherapy compared to surgery alone have shown an overall survival (OS) advantage with preoperative treatment in patients with esophageal and gastric cardia adenocarcinomas (Pepek et al., 2013). Gastric cancer patients other than this area expected to experience an increase in survey compared with those receive surgery alone (Ott et al., 2003). The aim of this study was to examine feasibility and effectiveness of neoadjuvant chemoradiotherapy (CRT) for locally advanced non-cardia gastric cancer patients. In this study, we compared 36 month survival rate of GC patients that were treated by a neoadjuvant chemoradiotherapy before gastrectomy with postoperative Chemoradiotherapy.

Materials and Methods

Study design and criteria

In this study, the inclusion criteria were: age under 70 years; adenocarcinoma of non-cardia area (Intestinal type by Lauren classification); no evidence of distant metastases; WHO performance status 0 to 1; proven adenocarcinoma of the stomach (stage II and III using American Joint Committee on Cancer Staging Guideline 6th edition (Edge et al., 2010), karnofsky score more than 70; no prior gastric surgery; no previous chemotherapy or radiotherapy; no uncontrolled infection or cardiopulmonary disease; adequate renal and hepatic function; no previous or concurrent cancer except non-melanoma skin malignancy. Patients were excluded if initial plan designed for chemoradiation but they were found to have metastatic disease in pre-treatment work up.

This study protocol was confirmed by Ethics Committee of Gastrointestinal and Liver Diseases Research Center of Guilan University of Medical Sciences which was registered under IRCT 138901111155N7 at the Iranian Registry of Clinical Trials (www.irct.ir). All patients signed a written informed consent.

Besides staging by CT and chest x-ray, a general laparoscopic survey of the abdominal cavity and lesser sac with laparoscopic ultrasound of the liver was performed through three abdominal port sites before enrollment to the trial. Then the studied patients with negative laparoscopic findings (in stage II and III) were randomly assigned between two groups of: perioperative chemo radiotherapy followed by surgery (Neoadjuvant group) or post-operative chemo radiotherapy (adjuvant group).

Treatment protocols

Treatment protocol for group A (neoadjuvant) consist of concurrent chemo radiotherapy before surgery. External beam Radiotherapy was used by CO -60 unit 4500cGy

in 180cGy per day with parallel-opposed anteroposterior/posteroanterior (AP/PA) fields plus chemotherapy with cisplatin 20mg/m² intravenous (IV) over 1h and 5-fluorouracil 700mg/m² (IV) over 24h in the first and the end four days of radiotherapy was administered .The treatment protocol for group B (surgery) was included the surgery then administration of chemo-radiotherapy consisted of 5040cGy of radiation at 180cGy per day plus concurrent chemotherapy with 5FU 325mg/m² (IV- bolus) and leucovorin (30mg/m²) on the first four-day and the last three days of radiotherapy. Method of surgery was defined by the preference of team surgeon, tumor location and disease extension.

After completed surgery and chemoradiation in 2 groups, both of them received 3 or 4 cycles of chemotherapy that consist of epirubicin 50mg/m², cisplatin 60mg/m² and capecitabine 625mg/m²/bid for 14 days (ECX). For each chemotherapy session, the following criteria must be promised; WBC≥3500, Hb≥10mgr/dl, PLT≥100.000 and PMN≥1500. Besides liver and renal function tests should be in normal range; if creatinine clearance was 45-60 ml/min, cisplatin dosage was reduced by 50% and if creatinine clearance was less than 45, the administration of cisplatin was stopped . If CBC was not in the normal range, chemotherapy postponed for one week.

Statistical analysis

SPSS version 16 (SPSS Inc., Chicago, IL, USA) was used in all statistical procedures. Descriptive statistics and compared means were also used. Numerical data are expressed as (MEAN±SD). An independent two-tailed t-test was performed to compare survival within the groups. The survival analysis was performed using Kaplan-Meier estimates. All tests considered 2-tailed and P-value less than 0.05 considered significant. The Kaplan-Meier method was used to estimate 3-year survival with 95% confidence intervals (95%CI).

Results

Twenty-five patients were enrolled in our study. They included in two treatment groups of neoadjuvant chemoradiation then surgery (A), and surgery then adjuvant chemoradiation (B).The follow up time was 36 months. Laparoscopic ultrasound staging was used for all patients besides abdominopelvic and chest CT scan. Two

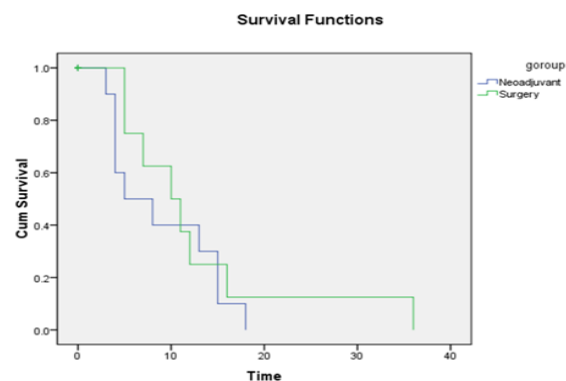


Figure 1. Kaplan-Meier Estimates for Patients' Survival

patients were died after surgery in group A. Three patients could not complete the treatment course in study group B.

The patient's descriptive data including age, gender, postoperative tumor categories, mean of involved and dissected lymph nodes and, histomorphological tumor classifications are given in Table 1. It compares these finding between two treatment groups.

Grade 3-4 Chemoradiotherapy related toxicity including hematologic and non-hematologic side effects is listed in Table 2. Two patients (16.7%) died following surgery as mentioned above. One patient (8%) in group A and three patients (23%) in group B suffered from neutropenic fever that were admitted and successfully treated by proper antibiotic administration.

By intention-to-treat analysis, out of 12 patients treated with neoadjuvant chemoradiotherapy, 2 patients (16.7%) and out of 13 patients in another group, 5 patients (38.5%) survived after 36 months, respectively. According to perprotocol analysis 20% and 50% of patients in groups A and B were survived after 36 month, respectively. According to both perprotocol analysis and Intention-to-treat analysis, the 3-year survival was not significantly different between two studied groups. The median survival time for A and B group was 13.4 (7.1-18.7) and 21.6 (13.8-29.5) months respectively that was not significantly different between two studied groups (p=0.169).

Furthermore there was not any statistically significant difference of survival according to T staging (p=0.673) and N staging (p=0.37) between two groups. While the mean survival time in patient with well differentiated tumor in neoadjuvant group was 8 months vs 33.6 months for

similar patients in another group (p<0.004). There was not any survival benefit according to primary site of tumor in the stomach.

Discussion

As gastric cancer has a poor prognosis, investigation of novel therapeutic strategies, such as neoadjuvant chemotherapy with or without radiation may be a reasonable approach to management of these patients. The largest and most recent publication INT-0116 trial (Macdonald regimen) provides data in support of adjuvant chemoradiotherapy following complete surgical resection, particularly since it used contemporary RT techniques and leucovorin-modulated 5-FU (Kundel et al., 2011). US Intergroup study INT-0116 randomly assigned 556 patients following potentially curative resection of gastric cancer to observation alone or adjuvant-combined chemoradiotherapy. These results changed the standard of care in the US following potentially curative resection of gastric cancer from observation alone to surgery followed by adjuvant combined chemoradiotherapy. A criticism of the intergroup trial was the limited extent of the surgical procedure in most cases. Although D2 lymph node dissection (removal of nodes along the hepatic, left gastric, celiac and splenic arteries, and in the splenic hilum) was recommended, it was only performed in 10 percent of cases, and 54 percent did not even have clearance of the D1 (perigastric) nodal regions. This noncompliance likely contributed to inferior survival and a 64 percent relapse rate in the surgery alone arm. A key obstacle to the adoption of the chemoradiation used in INT-0116 is the significant toxicity reported for this regimen, including treatment related deaths. This is of greater concern when such a reportedly toxic regimen is to be administered outside the relatively secured framework of a clinical trial and to be adopted into the routine practice (Wilke et al., 1989).

The application of neoadjuvant chemotherapy to the treatment of gastric adenocarcinoma was first reported by Wilke et al." who treated patients with locally advanced, unresectable tumors. Shortly thereafter, phase II trials were expanded to examine patients with potentially resectable disease there were some other reports about multiple aspects of this modality but a recently published meta-analysis showed that neoadjuvant chemotherapy followed by surgery was not associated with a higher rate of overall survival or complete resection (R0 resection). It does not increase treatment-related morbidity and mortality. This meta-analysis did not demonstrate a survival benefit for the combination of neoadjuvant chemotherapy and surgery (Liao et al., 2013).

Preoperative combined chemotherapy and RT is more commonly used for esophageal and EGJ cancers than for potentially resectable gastric adenocarcinomas. Review of the literature reveals limited data on neoadjuvant chemoradiotherapy for non cardia gastric carcinoma (Henning et al., 2000; Ott et al., 2003; Ajani et al., 2004; Klautke et al., 2004). Data extracting from these observations is very heterogeneous as wide range of radiation doses, limited number of patients, including

Table 1. Patient and Tumor Characteristics between Two Groups

Characteristics	A	B	Differences
Number of patients	12	13	---
Mean age	62.7	58.5	NS
F/M ratio	10-2	11-2	NS
Tumor grading			NS
1	4	5	
2	5	4	
3	3	4	
Tumor staging			NS
II	5	7	
III	7	6	
Site of tumor			
Fundus	3	5	NS
Body	7	6	
Antrum and pylorus	2	2	
Mean of dissected lymph nodes	10.42±3.28	5.79±9.5	NS
Mean nodal involvement	4.5±3.6	3.8±4.4	NS

*G1=Well differentiated, G2=moderately differentiated, G3=poor differentiated. NS= Not Significant

Table 2. Grade 3-4 Chemoradiotherapy-associated Toxicity

Toxicity	Group A	Group B
HematologicAnemia	4	4
Leukopenia	5	6
Thrombocytopenia	3	3
Non-hematologicGI	4	2
Hepatic	1	1
Dermatologic	4	4
Neurotoxic	1	2
Infection	1	3
Others	1	1

cardia type gastric cancer and absence of control group and also the data of survival benefit from these and other related studies are still controversial.

Klatutke et al (2004). reported a median survival and the 2-year survival rate 18 months and 42%, respectively, for the patients following R0 resections as compared to 10 months and 0% for the remaining patients ($p=0.035$). In our study the median survival of neoadjuvant group was 13.4 months and 3-year survival rate was 16.6% that were not significantly different with another group. If pathologic subtypes of gastric carcinoma was considered, the median survival of well differentiated carcinoma was better in adjuvant group than neoadjuvant group ($p=0.004$). Thus neoadjuvant therapy could not increase median survival time especially in well differentiated gastric carcinomas. Neoadjuvant chemotherapy is considered potentially to have several clinical benefits such as destroying micrometastases, and reduction in primary tumor size, an enhancement in treatment compliance, and an improvement in the chemo sensitivity (Matsuda et al., 2014).

Furthermore, the addition of radiation could improve local control. Therefore, we think that there were several clinical benefits of neoadjuvant chemoradiation in patients with gastric cancer, especially in stages II or III. In contrast, patients with this treatment modality did not have a better post surgical course as we expected due to theoretical supposed downstaging because two patients (16.6%) died after surgery in neoadjuvant group. In one study it was reported no 30-day or in-hospital mortality and postoperative morbidity was 19% (Ott et al., 2003). One question in this context is whether neoadjuvant treatment really can lead to the reduction in primary tumor size. We think, this high rate of downstaging might have been overestimated because by using EUS in the staging of gastric cancer in related studies, problems may be seen due to nearly low sensitivity of EUS especially in differentiating the T2 from the T3 category (Ott et al., 2003).

The overall toxicity of the neoadjuvant regimen was moderate, and, in particular hematologic toxicity was low. Anemia and thrombocytopenia grade 3 and 4 were not observed and leucopenia grade 3 was noted in 3 patients (25%). Grade 3 Leukopenia and thrombocytopenia were reported at 47.6% and 23.8% of patients by Klautke G, et al, respectively (2004). A major concern was neutropenic fever in one patient that he was acutely ill who need hospital admission and broad spectrum antibiotics administration. Neoadjuvant chemoradiotherapy may reduce the risk of local recurrence and may be particularly beneficial for patients with squamous cell carcinoma as these tumors are more radiosensitive. However, patients with gastric adenocarcinoma are more likely to relapse with distant disease, and therefore a systemic disease approach with chemotherapy is likely to be more beneficial than a purely localized treatment strategy for these patients. If radiotherapy is performed, modern approaches such as intensity-modulated radiotherapy and image guidance should be applied, as these methods reduce dose to organs at risk and provide a more homogenous coverage of

planning target volumes (Buerge et al., 2012). Nonetheless the recent advancement of technology, radiotherapy for gastric cancer is still challenging. Precise target and organ delineation and dose-volume calculation is evolving with three-dimensional conformal radiotherapy.

However, uncertainties arising from variations in stomach filling and respiratory motion still remain (Wysocka et al., 2010). On the other hand, several factors concur in determining outcome for locally advanced gastric cancer patients. Geographic origin of the patient seems to play a major role. It should be considered that other than histologic subtype (diffuse versus intestinal) there seems to be a series of polymorphisms of genes usually involved in cell interaction and migration that can explain a different metastatic pattern in resected patients that would define the survival. Further research on these determinants of metastatic spread could be used to select those patients who may benefit from this experimental treatment and those who may benefit from standard adjuvant or that gain no benefit at all (Bittoni et al., 2012). Also Coordination between the oncology and surgical team is of utmost importance (Lee et al., 2013). According to this study we suggest surgery then chemotherapy for patients with well differentiated gastric adenocarcinoma rather than other approaches. Other studies with more sample size and accurate matching relying on cancer molecular behavior was recommended.

In conclusion, although a number of neoadjuvant chemoradiotherapy trials in gastric cancer have been conducted and these early data seem encouraging, they have been conducted in highly selected patients. Randomized trials will ultimately be necessary to confirm its benefit. Inadequate numbers of patients and improper control groups have made much of these data inconclusive. Recent results from some of these trials have established a promising outcome. Preoperative strategies have been shown to be feasible and may result in better curative resections. Randomized trials are needed to assess the survival benefits. Advances in molecular biology as a new tool for the understanding of multiple aspects of gastric cancer should be mentioned in near future. Efforts at correlating cancer biology and clinical behavior are ongoing. Cancer genetics and biology may facilitate cancer treatment and newer drugs will be added to our medication list.

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