

## Characteristics and Survival Rate of Patients with Gastric and Gastroesophageal Junction Adenocarcinoma in Yazd, Iran

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### Abstract

**Background:** Gastric cancer is the leading cause of cancer deaths in Iran. Treatment for gastric adenocarcinoma varies worldwide. The aim of this study is to evaluate characteristics and survival rate of gastric and gastroesophageal junction adenocarcinoma in Yazd, Iran.

**Methods:** This study was conducted on 53 patients with gastric or gastroesophageal junction adenocarcinoma who referred to Shahid Ramezanzadeh Radiation Oncology Center between 2004 and 2010. All patients underwent surgery, chemotherapy and radiotherapy. Data from patients' records were extracted and follow up was conducted through telephone contacts. To analyze data, Kaplan Meier curves and SPSS software were employed.

**Results:** There were 17 (32.1%) female and 36 (67.9%) male patients. The mean age was 58.32 years. CT scans were performed preoperatively for 18 (34%) patients. In 14 (26.9%) patients no lymph node was resected or reported by the pathologist; in 29 (54.7%) patients one to six lymph nodes were found; and in 10 (18.9%) patients seven lymph nodes or more were detected. In 2 (3.77%) patients there were more than fifteen lymph nodes resected. Surgical staging was impossible for 16 (30.2%) patients. Mean survival was 50.9 months and median survival was 51 months. The survival rates were 73% for three years, 36% for five years and 18% for seven years. Among the variables only histologic grade had a significant relation to survival.

**Conclusion:** Preoperative staging procedures and surgical resections are inadequate in our province. Survival rates are acceptable and similar to Western countries. This finding may have been the result of the effectiveness of combination chemotherapy regimens and radiotherapy used in our patients.

**Keywords:** Stomach, Adenocarcinoma, Chemotherapy, Radiotherapy, Survival

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## Introduction

Adenocarcinoma of the stomach was the leading cause of cancer-related deaths worldwide through most of the 20<sup>th</sup> century. It currently ranks second to lung cancer with an estimated 875,000 new cases diagnosed annually worldwide.<sup>1</sup> One of the most striking epidemiological observations has been the increasing incidence of adenocarcinomas that involve the proximal stomach and distal esophagus.<sup>1</sup> Upper gastrointestinal cancers are the cause of 55% of all cancer-related deaths in Iran, with gastric cancer being the most common.<sup>2</sup> Unfortunately gastric cancer is diagnosed at an advanced stage and has a low survival rate in Iran; the five-year survival rate varies between 0.83%<sup>3</sup> to 22.6%<sup>4</sup> in different studies. Although surgical resection with adequate margins is the cornerstone of treatment, the extension of lymphadenectomy remains a subject of controversy. Because of high rates of recurrence after radical surgery resection, adjunctive therapies (perioperative chemotherapy, postoperative chemotherapy and postoperative chemoradiation) have been widely used. We have evaluated 53 patients with gastric and gastroesophageal junction adenocarcinomas and their survival rate.

## Materials and Methods

We selected patients with documented pathology of adenocarcinoma of the stomach or gastrointestinal junction who referred to our center for postoperative radiation therapy and/or chemotherapy from 2004-2010. In this study, we enrolled patients with the following pathologic T stages: T2b, T3 and T4 according to the American Joint Committee on Cancer Staging of Gastric Cancer 2002, and/or positive lymph nodes. Patients had no evidence of distant metastases, nor any previous history of cancer. Data contained in the patients' records were extracted and follow up conducted by periodic visits and telephone contacts. Though co-ordination with the Province Health Center, we obtained data regarding patients' death demographics, however information regarding other provinces was gathered through

telephone contacts. For patients receiving their chemotherapy in other centers we contacted their physicians to get information on their chemotherapy regimens, however such data could not be obtained for nine of whom couldn't obtain information. Radiation therapy was performed after two-dimensional simulation with oral and intravenous contrast, using a 9 mega voltage X-ray photon with two parallel opposed anterior-posterior/posterior-anterior fields. In all cases where the linear accelerator in our center was not functional, those patients were treated with a cobalt 60 machine. The treating field encompassed the tumor bed, gastric residue, as well as lymph nodes of the celiac, para-aortic spleen and liver hilum. Patients received radiation doses of 4500 to 5040 cGY. For three patients, the Mayo clinic regimen of 5-fluorouracil (5-FU), leucovorin and concurrent radiation therapy was employed. These patients received one course of chemotherapy before radiation, two courses concurrent with radiation and two courses post-radiation therapy. A total of 21 patients received an epirubicin-based regimen, 19 received a taxane-based regimen (six courses for most) and the regimen was unknown for 9 patients.

## Statistical analysis

This study assessed survival rate using the Kaplan-Meier curves that employed the Log Rank test model and SPSS 15 software. We evaluated the relation between variables and survival rate.

## Results

Between 2004 and 2010, 53 patients enrolled in our study. Of these, 17 (32.1%) were female and 35 (67.9%) were male. Patients' mean age was 58.32 years. We do not have endoscopic ultrasound (Eus) in Yazd, therefore only two patients underwent Eus in Tehran, Iran. Only 18 (34%) patients underwent preoperative CT scanning, despite the availability of facilities in Yazd; however 66% underwent abdominopelvic sonography. In 13 (24.5%), the tumor was located in the cardia. A total gastrectomy was performed for 28 (52.8%) patients whereas 25 (47.2%)

underwent subtotal gastrectomies. Surgical margins were positive in 17 (32.1%) patients. Neoadjuvant chemotherapy that consisted of an epirubicin-based regimen was administered to 10 patients, of which one (10%) had a positive surgical margin. Histological grading of the tumor was as follows: well differentiated for 13 (24.5%) patients, moderately differentiated in 17 (32.1%) patients and poorly differentiated in 23 (43.4%) patients. In 14 (26.9%) patients no lymph nodes were resected by the surgeon or reported by the pathologist. In 29 (54.7%), one to six lymph nodes were resected and in 10 (18.9%) patients, seven lymph nodes or more were detected. Only 2 (3.77%) patients had more than fifteen lymph nodes resected or evaluated. With these limitations surgical staging was impossible for 16 (30.2%) patients. Other stages included: Ib (15.4%), II (26.9%), IIIa (21.2%), IIIb (3.8%) and IV or non-metastatic T3N3 (1.9%). Due to the inadequacy of the lymph node resection, most stages might have been underestimated. Chemotherapy regimens consisted of: 5-FU-based (5.7%), taxane-based (35.8%) and epirubicin-based (39.6%). In 18.9% of patients, the chemotherapy regimen was unknown.

Mean survival was 50.9 months and median survival was 51 months. The three-year survival rate was 73%, five-year was 36% and the seven-year survival rate was 18% (Figure 1). Mean disease-free survival was 42.26 months (Figure 2). Among variables, only histological grade had a significant relation to survival. There was no significant relation to survival and stage, age,

sex, type of surgery, positive surgical margins, type of complementary treatment and number of resected lymph nodes.

### Discussion

Although the incidence of gastric cancer has decreased in the last three decades in Japan, the USA and Western Europe, it has increased in Iran.<sup>5</sup> Ardibil, in Northwestern Iran, has the highest incidence of gastric cancer. In this region, the cardia is the most frequent site of gastric cancer as seen in Western countries. However in other parts of Iran, such as our province, non-cardia tumors are more frequent.<sup>5</sup> In the current study, 75.5% of tumors were non-cardia. In a national study, the male to female ratio was 2.8:1, with the peak incidence observed in the age group over 60 years.<sup>6</sup> In this study, the male to female ratio was 2.11:1, with an equal incidence rate in patients younger or older than 60 years. The mean age in our study was similar to that reported by Pourhoseingholi et al.,<sup>7</sup> however it was less than reported by Zeraati et al.<sup>4</sup>

When gastric cancer is diagnosed, a triphasic CT with oral and intravenous contrast of the abdomen, chest, and pelvis is imperative. Multi-detector CT scan (MDCT) with thin-sliced multiplanar reconstruction (MPR) and water filling enables improved accuracy in preoperative gastric cancer staging.<sup>1,8</sup> Although there are five MDCT in our province, only 34% of patients had preoperative CT scans. Accurate preoperative staging assists with detection of metastases and prevents unnecessary laparotomy. Preoperative

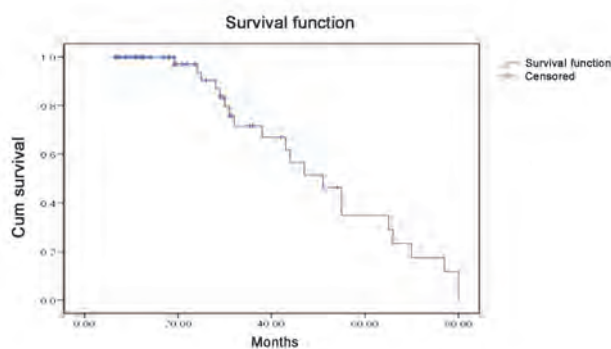


Figure 1. Overall survival.

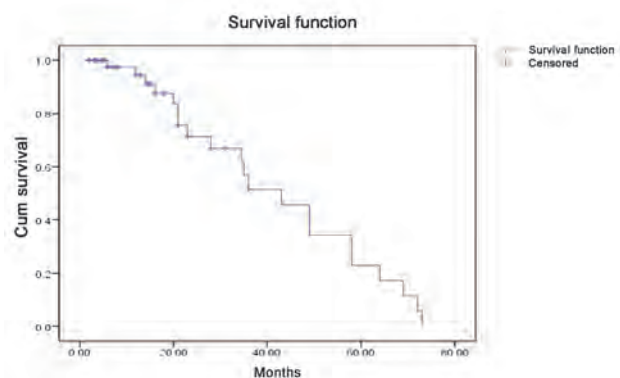


Figure 2. Disease-free survival.

staging can locally depict advanced patients for whom en bloc resection of tumors is not possible without neoadjuvant treatment and may decrease the numbers of surgeries with positive margins.

In the current study, 10 (18.9%) patients underwent neoadjuvant epirubicin-based chemotherapy; of these, the surgical margin was positive in one patient. However there were positive surgical margins in 37.2% of patients who did not receive neoadjuvant therapy. The presence of a positive surgical margin was a negative prognostic factor in previous studies. In our study, although the mean survival was 51.52 months for patients with negative surgical margins and 46.7 months in group with positive margins, this difference was not significant ( $P=0.646$ ).

Numerous controversies exist regarding the extension of lymphadenectomy that is necessary for treatment of gastric carcinoma. In Japan and other Southeastern Asian countries most surgeons believe extended lymphadenectomy (D2 and D3 versus D1) increases survival. A D1 LN dissection refers to a limited dissection of only the perigastric lymph nodes. D2 LN dissection is an extended LN dissection that entails removal of nodes along the hepatic, left gastric, celiac, and splenic arteries as well as those in the splenic hilum. D3 dissection is a super-extended LN dissection and has been used by some to describe a D2 lymphadenectomy plus the removal of nodes within the portahepatis and periaortic regions. Others use the term to denote a D2 LN dissection plus periaortic nodal dissection alone.<sup>9</sup> However, in Western countries D1 lymphadenectomy is more acceptable and has a staging rather than therapeutic role. For adequate staging at least 16 lymph nodes must be resected by the surgeon and evaluated by a pathologist. Unfortunately, in our study only 2 (3.77%) patients underwent adequate lymph node staging.

There are controversies that surround the role of adjuvant therapy in gastric adenocarcinoma. This therapy has been recommended in high-risk patients with T2b, T3 or T4 tumors according to previous AJCC staging at the time the current study was performed. Currently, it is recommended in T3, T4 and/or lymph node

positive patients. Adjuvant therapy is not uniformly administered in various parts of the world. In Japan, after extended lymphadenectomy of at least D2 dissection, S-1, an oral fluoropyrimidine was administered which increased overall three-year survival to 80.1%.<sup>1</sup> In the UK and other European countries perioperative chemotherapy with an epirubicin-based regimen and surgery have been used; this has increased five-year survival to 36%.<sup>10</sup> In the US, after surgery a 5-FU-based chemoradiation therapy is the standard of care for gastric adenocarcinoma, which has increased median overall survival from 27 to 36 months.<sup>11</sup>

Although previous studies have reported various survival rates for gastric cancer in Iran, the majority were epidemiological studies that did not evaluate treatment modalities and their role in gastric adenocarcinoma. Only three studies discussed the effects of treatment, of which two evaluated the efficacy of different chemotherapy regimens in locally advanced gastric adenocarcinoma.<sup>12,13</sup> In the third study Ahmadloo et al.<sup>14</sup> evaluated 58 patients over a ten-year period in Shiraz. All were surgically resected, non-metastatic gastric adenocarcinomas with serosal and/or nodal involvement, that had positive or close resection margins who received post-operative radiotherapy with a cobalt 60 machine. Only 14% received concurrent chemotherapy with 5-FU. On all patients, at least a D1 dissection was performed, however the mean number of resected lymph nodes was not reported. Only 2 (3.44%) had positive surgical margins. The local control rate was 42.5% and overall five-year survival rate was 29.3% with a mean of 15 months. Five-year survival was better in our study (36%), despite the employment of worse surgical procedures. This survival might be the result of the better radiotherapy machine (linear accelerator) used in this study and the use of more aggressive chemotherapy regimens. Although our results were worse than the Japanese study, however they were similar to the UK Magic trial. In comparison to the US INT 0116 trial,<sup>11</sup> our study showed better median survival (51 months vs.

36 months). However the five-year survival was less than the INT 0116 trial (36% vs. 43%). The lesser five-year survival in our study might be due to a shorter follow up of survivors in our study. In the INT 0116 trial most patients (54%) underwent inadequate lymphadenectomies and 5-FU-based chemoradiation therapy was administered. In the current study approximately 96% of patients had inadequate lymph node resection by surgeons and/or an insufficient attempt in finding resected lymph nodes by pathologists. However, in the current study most patients received more aggressive chemotherapy regimens than in the INT 0116 trial. If we consider equal radiation therapy techniques and effectiveness in both studies and worse surgical techniques in our study, the better median survival obtained in our study might be due to the most effectively performed chemotherapy.

Gastric cancer is one of the most important concerns of the health care system in Iran. Better preoperative staging, particularly with the availability of modern MDCT in most provinces and the use of neoadjuvant chemotherapy in advanced cases, may create better surgical outcomes. Additionally, appropriate use of taxane- or epirubicin-based chemotherapy regimens and radiation therapy in high risk patients such as T3, T4 and/or lymph node positive patients, those with inadequate lymphadenectomies (less than 16 evaluated lymph nodes), and/or patients with positive margins may contribute to better survival rates.

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