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ORIGINAL ARTICLE

Neoadjuvant Chemotherapy Vs Neoadjuvant Chemoradiotherapy on the Number of Lymph Nodes in Patients with Gastric Cancer Undergoing Gastrectomy D2

AbdolhassanTalaiezadeh[1], Amin Bahreini[2], MasoudHedayat[3], Khalil Kazemnia[2]*

[1]Department of Surgery and Cancer Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[2]Department of Surgery, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[3]Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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Abstract

This is a retrospective clinical trial conducted in Ahvaz (Iran) by selecting the adenocarcinoma cases from 220 patients with gastric malignancy who had undergone gastrectomy, of which 42 patients undergoing neoadjuvant therapy were included in the study (five patients undergoing neoadjuvant chemoradiotherapy and 37 cases with neoadjuvant chemotherapy). The number of positive lymph nodes, negative margin, and death and survival rates of patients were compared in both groups. The mean age of neoadjuvant chemotherapy group and neoadjuvant chemoradiotherapy group didn't differ significantly. The number of lymph nodes extracted from the neoadjuvant chemotherapy group differed statistically from neoadjuvant chemoradiotherapy. But, the lymph node involved in the neoadjuvant chemotherapy group not differed from the neoadjuvant chemoradiotherapy group. No statistical differences between these two groups were found in margin involvement, general postoperative status, postoperative wounds, postoperative complications as well as in mortality rates.

Introduction:

Cancer diseases are one of the growing health system challenges (Ahn *et al.*, 2010; Papenfuss *et al.*, 2014; Ferlay *et al.*, 2015). Among which gastric cancer is a fundamental health problem. Despite the fact that the occurrence of gastric cancers has been significantly declined in recent decades, unfortunately, with one million new cases per year, it is still the fifth prevalent malignancy in the world. With more than 700,000 deaths annually, it is the third cause of cancer deaths for both the genders worldwide with the highest mortality rate reported in East Asia (14 per 100,000 in males and 8.9 per 100,000 in females)(Ferlay *et al.*, 2015). In Iran, it is the most common type of cancer in both genders and the most important cause of cancer deaths (Papenfuss *et al.*, 2014).

Nowadays, gastrectomy surgeries are increasingly carried out with minimal invasion. In the past years, according to post-surgical outcomes, the results of gastrectomy have improved the mortality and survival rates of the patients (Ahn *et al.*, 2010). However, the role of extensive lymphadenectomy has been controversial in the past decades, the fact of whether extensive lymphadenectomy helps in improving the disease is still unknown. In the Asian countries, extensive lymphadenectomy (D2) has been the standard method for the past two decades; while in Western countries, only limited lymphadenectomy (D1) has been common by the recent years (Ahn *et al.*, 2010).

When detected at an early stage, gastric cancer associates with long-term survival rate i.e., over 90%. Nevertheless, the long-term survival rate is significantly lower in locally advanced cases (Cunningham *et al.*, 2006; Washington, 2010). Multiple treatments, including chemotherapy, radiation therapy and the negative margins surgery (Ro) present the best treatment in advanced cases. The UK MAGIC (Ychou *et al.*, 2011) and French FNCLCC/FFCD trials (van Hagen *et al.*, 2012) both indicated the significant benefits of a lifetime in preoperative chemotherapy compared to surgery alone; however, there is no difference between the two groups in the postoperative rate of disease or mortality.

The CROSS trial (Fujitani *et al.*, 2007) shows the superiority of preoperative and postoperative chemotherapy over the surgery alone, as well as the fact that there is no significant difference in postoperative mortality rate between the two groups. Therefore,

*Corresponding Author: Khak89@gmail.com

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neoadjuvant approaches have been much more widely used in locally advanced gastric cancers and gastroesophageal junction (GEJ), in spite of the fact that there are still concerns that neoadjuvant treatment may increase the complications of surgery. Several groups have so far conducted detailed studies on the effect of neoadjuvant therapy on postoperative mortality and mortality rates in patients with gastric cancer and GEJ (Roukos, 2000; Li *et al*., 2011; Valenti *et al*., 2011; Fuentes *et al*., 2016).

The lymphadenectomy level is classified with the degree of lymph node resection as D1 to D4, respectively. The D1 method involves the resection of lymph nodes around the stomach that are directly attached to the stomach (pre-gastric lymph nodes, stations 1 to 6, N1 level). In D2, often the lymph nodes in the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9), spleen artery and vein (station 10 & 11) of the N2 levels are often resected. In addition, the D3 and D4 are the resections of stations 12 to 14 of N3 level and stations 15 and 16 of N4 level (Cuschieri *et al*., 1999).

Many studies such as the British Medical Research Council, Dutch and Italian gastric cancer trials have been conducted; they have compared the benefits of extensive lymphadenectomy with the limited lymphadenectomy in Western patients and these studies have been conducted in the form of random clinical trials (Hartgrink *et al*., 2004; Songun *et al*., 2010; Degiuli *et al*., 2014). In the beginning, although D2 lymphadenectomy was associated with significant morbidity and mortality, none of these trials showed a difference in overall survival (Hartgrink *et al*., 2004; Songun *et al*., 2010; Degiuli *et al*., 2014). However, the long-term follow-up in Dutch trials indicated the benefits of lymph nodes resection more (Hermans *et al*., 1993; Hartgrink *et al*., 2004; Degiuli *et al*., 2014). Since much progress was not made in the field of surgery as it was expected, the survival rate improvement in gastric cancer is still in need of new therapies. To achieve this goal, many multi-purpose studies were conducted. Therapeutic strategies, such as chemotherapy and neoadjuvant radiotherapy, as well as adjuvant chemotherapy in several trials with limited patients, were tested with promising results (Hartgrink *et al*., 2004). Further, the role of chemotherapy in the neoadjuvant treatment was investigated, which was begun in the Dutch FAMTX Trial and become an important part of the gastric cancer treatment (Mercer, 2004). The use of radiotherapy in the neoadjuvant form has also obtained more space over time. Attention to chemotherapy with targeted agents has been recently increased. Consequently, over last 15 years, major advances in the field of multiple treatments strategies have changed the clinical management of gastric cancer.

Following the same, the effectiveness of two methods of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy in patients with gastric cancer undergoing gastrectomy D2 is compared in our study.

Methodology:

The current study is a retrospective clinical trial. The study population consisted of patients with gastric cancer, underwent neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy followed by gastrectomy D2 in Imam Khomeini and Apadana Hospitals of Ahvaz from 2010 to 2017. Out of 220 patients with gastric malignancy who underwent gastrectomy in the abovementioned treatment centers, the adenocarcinoma cases were chosen (42 patients), of which 5 under neoadjuvant chemo-radiotherapy and 37 under neoadjuvant chemotherapy were included in the study.

The data collection tool was a checklist set based on the desired variables. The data collection method includes observation and reviewing the sources (patient records). In order to collect the data, the records included in the statistical society were specified and examined after retrieval and the required data were extracted. Data related to the patients were used without mentioning their name and profile and only for presenting the plan results in the form of number and figures. In the end, for data analysis, descriptive statistics were used to provide statistical indices (mean, percentage, and so on) and independent t-test was used if the variables were normal; the Mann-Whitney test was also used in the case of non-normal variables. The statistical significance level was considered 0.05 and the SPSS version 22 was used for analysis.

Results:

Among 42 patients included in the study, 37 (88.09%) were in the neoadjuvant chemotherapy group and five (11.91%) were in the neoadjuvant chemoradiotherapy group. The mean age of neoadjuvant chemotherapy group was equal to 63.00±10.93 years and the mean neoadjuvant chemoradiotherapy group equaled 59.20±15.84 years, which were not significantly different ($p>0.846$). Comparison of the number of the extracted lymph nodes between the two groups showed that their mean number in neoadjuvant chemotherapy group was 12.89±6.32 and the mean number in neoadjuvant chemoradiotherapy group was 7.00±2.34, which had a statistically significant difference ($p<0.017$). Furthermore, the comparison of the involved lymph nodes between the two groups indicated that the mean of neoadjuvant chemotherapy group was 1.94 ± 5.51 and the mean of neoadjuvant chemoradiotherapy group was 1.2 ± 2.16, which had not a statistically significant difference ($p>0.445$). In the following, the comparison of the involved margin in the two groups indicated that 33 (89.2%) patients in the neoadjuvant chemotherapy group were non-interventional, while all patients (100%) had no conflict in the neoadjuvant chemoradiotherapy group, which revealed no statistically significant difference between the two groups ($p>0.697$). Comparison of general postoperative status between the two groups showed that 36 (97.3%) patients in the neoadjuvant chemotherapy

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group were in good condition (36%); while in the neoadjuvant chemoradiotherapy group, all patients (100%) were in good condition and no significant difference was found between the two groups (p>0.713). Comparing the postoperative wounds between the two groups showed that 34 patients (91.9%) in neoadjuvant chemotherapy group were in good condition, two patients (5.4%) in the condition of secretion from the wound site, and one patient (2.7%) were in Dehiscence condition; while in the neoadjuvant chemoradiotherapy group, all patients (100%) were in good condition, and no statistically significant difference was found between the two groups (p>0.514). Comparison of the postoperative specific complication between the two groups showed that in the neoadjuvant group, 6 (16.2%) patients had a specific condition, while in the neoadjuvant chemoradiotherapy group, three patients (60%) had a specific condition and there was no significant difference between the two groups (p>0.234). Finally, comparing the mortality rate between the two groups showed that mortality was seen in 14 patients (37.8%) in the neoadjuvant chemotherapy group and two (40%) patients in the neoadjuvant chemoradiotherapy group, which revealed no statistically significant difference (p>0.926).

Table-1: Patients characterizations in two group of Chemotherapy and Chemoradiotherapy

Variable	Group	Min	Max	Mean±SD	p-value
Age	Chemoth.	35	84	63±10.93	>0.846
	Chemoradioth.	31	69	59.20±15.84	
Extracted lymph nodes	Chemoth.	2	31	12.89±6.32	<0.017
	Chemoradioth.	5	10	7±2.34	
Involved lymph node	Chemoth.	0	31	1.94±5.51	>0.445
	Chemoradioth.	0	5	1.2±2.16	

Discussion:

As presented in the results section, in the final analysis, while the comparison of mean, clean margin, involved margin, general postoperative status, postoperative wound, postoperative mortality and specific complications between the two groups of chemotherapy and chemoradiotherapy, the calculated "p" values were not statistically significant. However, in comparing the number of the taken lymph nodes between the two groups of chemotherapy and chemoradiotherapy, the "p" value was calculated to be statistically significant (p<0.017); which indicate that the number of positive lymph nodes in the neoadjuvant chemoradiotherapy group was less than that in the neoadjuvant chemotherapy group. Thus, this result offers us that chemoradiotherapy is better to approach for treating patients.

Fuentes *et al.* (2016) examined the effects of neoadjuvant therapy (NAT) on postoperative complications of gastric adenocarcinoma and gastroesophageal junction (GEJ). In their study, no difference was seen in the morbidity or mortality rates between the groups; while the patients undergoing initial surgery had more complications than that of the patients under NAT (Mercer, 2004). Téoule *et al.* (2015) examined 135 patients with resectable gastric cancer, the effect of neoadjuvant chemotherapy on postoperative complications was examined. Postoperative complications were calculated 46.7% in Chemo. patients and 41.9% in Surg. patients with no statistical difference. Ito *et al.* (2015) reported in the Chemo. group, wound infection (23.3 Vs. 3.8%; p<0.002) and duodenal stump (13.3 Vs. 1.9%; p<0.022) were significantly higher.

Schuhmacher *et al.* (2010) examined chemotherapy just before the surgery in a phase III trial with accurate preoperative staging and surgery guidelines. Patients with locally advanced gastric adenocarcinoma or esophago-gastric junction stage III were randomly divided into two groups of chemotherapy before surgery or surgery alone. Total 52.8% of patients had tumors in the proximal gastric region; the surgical alone group had more lymphatic metastases than neoadjuvant group (76.5% Vs. 61.4%; p> 0.18). Postoperative complications were higher in the neo-adjuvant group (27.1% Vs. 16.2%; p>0.9) Chang *et al.* (2016).

In these two studies, it has been stated that the rate of complications associated with neoadjuvant chemotherapy treatment was higher than the surgery alone strategy. However, we have examined the two methods of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy and observed no significant differences in the postoperative wound, postoperative specific complication, postoperative general status, and mortality. Kim *et al.* (2015) assessed the efficacy of neoadjuvant chemotherapy (NACRT) on locally advanced gastric cancer resection (LAGC), the overall results of them expressed the benefits of neoadjuvant radiotherapy; while in our study, the number of patients treated with this method is lower and further investigation with larger sample sizes is needed.

The minimum lifespan in expired patients in the neoadjuvant chemotherapy group was 6 months and the maximum lifespan was 36 months. The minimum lifespan in expired patients in the neoadjuvant chemoradiotherapy group was 12 months and the maximum lifespan was 24 months. The mean life span in the expired patients in the neoadjuvant chemotherapy group was lower than that of neoadjuvant chemoradiotherapy group.

Conclusively, our data indicated that the number of lymph node in the chemoradiotherapy group was significantly less than chemotherapy group so chemoradiotherapy could be referred as a better approach for treating patients. Given the restrictions of this study, further studies with larger sample sizes and longer follow-ups are recommended.

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