



## Evaluation of Clinical Response to Neoadjuvant Chemoradiotherapy and its Comparison with Postoperative Pathologic Response in Patients with Esophageal Cancer in “5<sup>th</sup> December” Hospital in Gorgan

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### ABSTRACT

Esophageal cancer is an invasive disease, and various treatments have been proposed to improve the survival of patients with it. In this study, the results of clinical response to neoadjuvant chemoradiotherapy in patients were evaluated and then these results were compared with the postoperative pathological responses. This cross-sectional and descriptive-analytic study was performed on 60 resection able esophageal cancer patients who were referred to educational hospitals from April 2011 to 2017. The response to treatment of these patients before and after neoadjuvant chemoradiotherapy was evaluated using CT and EUS and compared with pathologic changes after surgery. Of the 60 patients who underwent endosonography and CT scan before neoadjuvant, 11 patients were at stage A2 (18.3%), 13 at stage B2 (21.7%), 15 at stage A3 (25%), 11 at stage B3 (18.3%), and 10 at stage C3 (16.7%). After neo-adjuvant surgery and pathology-based surgery, 24 (40%) responded fully to treatment. 32 patients (53.3%) had partial response and stage decrease, following 9 at stage 1 (4 stage A1, 5 stage B1), 19 at stage 2 (10 at stage A2, 9 at stage B2), 4 at stage 3 (2 at stage A3, 2 at stage B3), and 4 patients (6.6%) did not have any changes in the stage of the disease and did not respond to treatment. In this study, from patients undergoing chemoradiotherapy, 40% received complete pathologic response to treatment with satisfactory results and acceptable complications, and further consideration and evaluation is recommended in this regard.

**Keywords:** Esophageal Cancer, Neoadjuvant Chemoradiotherapy, Pathologic Response, Gorgan

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### INTRODUCTION

Esophageal cancer is one of the most common cancers with high mortality and Iran is a high-risk region with a prevalence of 5-6%. It usually represents at the advanced stage of the disease,

therefore half of the patients are fully advanced when diagnosed and 30-40% of them have detectable far away metastasis [1]. Although primary treatment for esophageal cancer is a surgical procedure, but due to its low survival, non-surgical methods are proposed. Low survival of esophageal cancer in single-cure surgical procedure and the need for an effective non-surgical intervention led to the development of chemotherapy regimens' patterns [4]. The results

of chemoradiotherapy and the subsequent surgical procedure versus solo surgical procedure, indicates high benefits of this technique [3, 5] and currently the most promising strategy for improving prognosis and progression of esophageal cancer, is chemoradiotherapy (CRT) and subsequent surgery [5]. Preoperative CRT leads to a reduction in the size of tumor and increases the amount of complete resection and furthermore improves local tumor control and prevention of far away metastasis [9, 13, 14]. Neoadjuvant therapy primarily involves chemotherapy, radiotherapy, or a combination of both. Despite nearly three decades of study, decisions of esophageal cancer remains controversial, but many studies support preoperative chemotherapy in comparison of surgery alone [20]. Therefore, there is no question of whether induction therapy is appropriate in an advanced local cancer or not. Although these evidences is not clear about the priority of preoperative chemoradiotherapy versus chemotherapy alone [7]. Our aim in this study was to evaluate the response to treatment of esophageal cancer patients before and after the neoadjuvant chemoradiotherapy with the aid of CT and EUS, and comparing the results with pathologic changes after surgery [21].

#### MATERIALS AND METHODS

This cross-sectional and descriptive-analytic study was performed on 60 resection able esophageal cancer patients who were referred to educational hospitals from April 2011 to 2017. All patients with esophageal cancer without metastasis which undergone chemotherapy and esophagostomy were included in the study. Sampling was done by enumeration method. According to available records during the years of study, 60 esophageal cancer patients were eligible to participate in this study. The inclusion criteria were patients with resection able esophageal cancer undergoing neoadjuvant chemoradiotherapy. Surgical operations were carried out by the thorax surgeon, in educational hospitals of "5<sup>th</sup> December". Exclusion criteria were patients who did not receive neoadjuvant chemoradiotherapy. Patients were categorized according to age and sex and at the beginning of the study; Staging was performed by CT scan and EUS for patients. Six weeks after the completion of radiotherapy, the patients underwent surgery and the clinical stage before chemoradiotherapy was evaluated and

compared with the postoperative pathological stage. The response to the treatment included full response to treatment (or complete tumor loss). The collected data were analyzed by SPSS software (version 24) after encoding and logging. To describe the data, mean, standard deviation, frequency, percentage, table and graph were used.

#### RESULTS

Of all patients with esophageal cancer who referred to "5<sup>th</sup> December" Medical Education Center in 2011-2017 and underwent various evaluations including endosonography, CT scan and biopsy-pathology, 60 patients with neoadjuvant therapy and subsequent surgery without metastasis were included in the study. In terms of gender, 37 (67.7%) participants were women and 23 (38.3%) participants were men. The mean age of the patients was 57.1 years when the first evaluations were performed and the standard deviation of their age was 14.4 years. The number of patients less than 60 years of age was 33 (55%) and the number of patients of 60 years and older was 27 (45%). In aspect of cancer type, among 60 patients, 57 (95%) had SCC and 3 (5%) had adenocarcinoma. In the case of esophageal involvement site, 32 cases (53.3%) had middle involvement, 26 (43.3%) had lower esophagus involvement, and 2 cases (3.3%) had upper esophagus involvement. The duration of the involvement and the onset of symptoms was less than 6 months in 28 patients (46.7%) and in 32 patients (53.3%) was 6 months and more. The mean duration of the disease in the subjects was 6.7 months and the standard deviation was 5.1 months. In the case of surgical procedure types, 32 (51.7%) cases had transhiatal surgery, 25 cases (41.7%) were operated by McConne method, and 4 cases (6.7%) by Ivor Lewis method. Of the 60 patients who underwent endosonography and CT scan before neo-adjuvant, 11 patients were at stage A2 (18.3%), 13 at stage B2 (21.7%), 15 at stage A3 (25%), 11 at stage B3 (18.3%), and 10 at stage C3 (16.7%). After neo-adjuvant surgery and pathology-based surgery, 24 (40%) patients responded fully to treatment. 32 patients (53.3%) had partial response and stage decrease, following 9 at stage 1 (4 stage A1, 5 stage B1), 19 at stage 2 (10 at stage A2, 9 at stage B2), 4 at stage 3 (2 at stage A3, 2 at stage B3), and 4 patients (6.6%) did not have any changes in the stage of the disease and did not respond to treatment. The results showed no significant correlation between tumor

involvement area and response to neoadjuvant chemoradiotherapy (Table 1).

**Table 1: Frequency distribution of CR cases in the subjects studied, by the tumor involvement site**

Tumor site	Non & partial response		Complete response		P Value
	Count	Percent	Count	Percent	
Middle	16	50%	16	50%	0.16
Lower	19	73.1%	7	26.9%	
Upper	1	50%	1	50%	
<b>Total</b>	<b>36</b>	<b>60</b>	<b>24</b>	<b>40%</b>	

The results of examining the frequency distribution of CR cases in the subjects, by the pre-neoadjuvant stage of the disease, showed no significant correlation between the pre-neoadjuvant stage of the disease and the response to neoadjuvant chemoradiotherapy (Table 2).

**Table 2: Frequency distribution of CR cases in the subjects studied, by the pre-neoadjuvant stage of the disease.**

Stage	Non & partial response		Complete response		P Value
	Count	percent	Count	percent	
A2	6	54.5%	5	45.5%	0.82
B2	7	53.8%	6	46.2%	
A3	12	80%	3	20%	
B3	6	54.5%	5	45.5%	
C3	5	50%	5	50%	
<b>Total</b>	<b>36</b>	<b>60%</b>	<b>24</b>	<b>40%</b>	

**Table 3: Frequency distribution of CR cases in the subjects studied, by the T values of Tumors**

Tumor T Value	Non & partial response		Complete response		P-Value
	Count	percent	Count	percent	
T1	2	100%	0	0%	0.08
T2	5	33.3%	10	66.7%	
T3	20	69%	9	31%	
T4	9	64.3%	5	35.7%	
<b>Total</b>	<b>36</b>	<b>60%</b>	<b>24</b>	<b>40%</b>	

**Table 4: Frequency distribution of CR cases in the subjects studied, by the N values of Tumors**

Tumor T Value	Non & partial response		Complete response		P-Value
	Count	percent	Count	percent	
N0	14	56%	11	44%	0.96
N1	10	66.7%	5	33.3%	
N2	11	64.7%	6	35.3%	
N3	1	33.3%	2	66.7%	
<b>Total</b>	<b>36</b>	<b>60%</b>	<b>24</b>	<b>40%</b>	

The results of examining the frequency distribution of CR cases in T values of tumors showed that there was no significant correlation between T values of tumors and response to neoadjuvant chemoradiotherapy (Table 3).

The results of examining the frequency distribution of CR cases in N values of tumors showed that there was no significant correlation between N values of tumors and response to neoadjuvant chemoradiotherapy (Table 4).

### DISCUSSION AND CONCLUSION

The aim of this study was to evaluate the response to neoadjuvant chemoradiotherapy and compare it with postoperative pathology. Of all the subjects, full response to treatment was seen in 24 (40%) patients. In this study as the type of esophageal cancer, from 60 patients, 57 had SCC meaning 95% and 3 patients had adenocarcinoma meaning 5%, so SCC had significantly higher prevalence than adenocarcinoma. North of Iran is the riskiest region of esophageal cancer from Central Asia to the north of China, and 90% of cases of esophageal cancer in this area are SCC. Baquet CR et al. [13], indicated in their study that the majority of the 20th and 1960s, 90% of esophageal tumors included SCC, but after two decades, the prevalence of adenocarcinoma in the Western countries increased and has reached more than 60%. In this study, there was no significant correlation between type of cancer and the response to neoadjuvant chemoradiotherapy due to the small number of adenocarcinoma samples (p = 0.15), and the comparison of these two types of cancer for the response rate to neoadjuvant therapy was not statistically possible. Other studies have shown that SCC patients responded better to therapy than adenocarcinoma cases. In this study, in terms of gender segregation of esophageal cancer, from 60 patients, 37 (67.7%) were women and 23 cases (38.3%) were men, and the prevalence of the disease was higher in women. Hurc et al. [17] indicated in his study that the incidence of adenocarcinoma in whites is 5 times more common than blacks and in men is 8 times more common than women; Although it is rising in women. A significant increase was seen in the incidence rate in individuals aged 45-65 years, with a 4.87 per 100,000 white man and a 0.68 per 100,000 white women. In the study of Tabatabaei et al. [18], which included mostly SCC patients, from 53 patients 30 were men (57%) and 23 were

women (43%), which is close to our results and associated with the above studies with absence of gender differences in countries with high prevalence of esophageal cancer. The results of this study showed that there is no significant correlation between sex and response to neoadjuvant chemoradiotherapy ( $P = 0.52$ ), which was consistent with other studies in this field. The mean age of the patients was 57.13 years, which was close to the mean age of the patients in Tabatabaei's study, which was  $55.2 \pm 10.3$ , but less than Adam's [10] study, which had the mean age of 60 years. The mean age of women was 56.25 and the mean age of men was 58.45. The prevalence of esophageal cancer under the age of 30 was very low, equal to 2%, and also at the age of more than 80 was low too, equal to 4%, and majority of patients equal to 52% were in the 50's and 60's. The results of this study showed that there was no significant correlation between age and response to neoadjuvant chemoradiotherapy ( $P = 0.34$ ). Also there was no difference in age in response to treatment in other studies. Area of involvement of 32 cases (53%) was the middle part of the esophagus, 26 (43%) was the lower esophagus and two cases (3%) had upper esophagus involvement. According to John RS and colleagues, the prevalence of SCC in the middle and the prevalence of adenocarcinoma in the lower part is higher, and the present study was consistent with that study, and most patients with SCC had middle site involvement, and of the three adenocarcinomas two cases had lower esophagus involvement and one had middle esophagus involvement. There was no significant correlation between tumor involvement site and response to neoadjuvant chemoradiotherapy ( $P = 0.16$ ) due to the low number of upper esophageal cancer cases, and their comparison for the response rate to neoadjuvant therapy was not statistically possible. However, other studies showed that patients with upper esophageal cancer had lower response to therapy comparing with median and lower sites. According to the type of surgical procedure, 32 cases (53%) with transhiatal surgery, 25 (42%) surgical procedures with McCone method and 3 cases (5%) by Ivor Lewis method. In a study by A Kutup *et al.* [19], trans thoracic esophagostomy (TTE) compared with trans hiatal esophagostomy (THE) performed on advanced esophageal cancers, it was indicated that TTE has more R0 resection rate (removal of the tumor without excess margins), longer survival and more lymph nodes and less mortality compared with THE,

although these were not considered in this study. The results of this study showed that there is no significant relationship between pre-Neoadjuvant Stage and response to neoadjuvant chemoradiotherapy ( $P = 0.82$ ). In Karapetyan *et al.* [2], of which about 70% of patients had adenocarcinoma, 28% of patients responded fully to treatment, 14% did not have any change and 58% had a stage decline, which is less responsive to treatment than the present study, and it can be declared that SCC has a better response to neoadjuvant treatment compared to adenocarcinoma. Also, in the study of P.Van Hagan *et al.*, of which 75% of patients had adenocarcinoma, 29% had complete pathologic response to treatment, which was still less responsive to treatment than the present study (However, the type and duration of chemoradiotherapy have not been compared in these studies). However, in the study of Y u-suotang *et al.* [20] on SCC patients, the neoadjuvant-surgery group had 57% complete response to treatment, and in Si Yeol Song *et al.* [21], 66% of patients had complete pathologic response, which was more than our study.

#### Overall Conclusion

In this study, patients undergoing chemoradiotherapy had 40% complete pathologic response to treatment. This response rate was lower compared to the articles mentioned in the thesis. The total pathologic response reported in valid textbooks, which meta-analyzed various articles, is 25%, which is less than the pathologic response calculated in our study.

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