Int J Cancer Manag. 2019 June; 12(6):e89003. doi: 10.5812/ijcm.89003.

Published online 2019 June 17. **Research Article**

Evaluation of Survival Rate and Non-Fetal Outcomes in Patients with Esophageal Cancer Under Treatment with Neoadjuvant Chemoradiotherapy Plus Additional Platinium-Based Chemotherapy from 2010 to 2016

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Received 2019 January 10; **Revised** 2019 June 03; **Accepted** 2019 June 08.

Abstract

Background: Esophageal cancer is an invasive lethal disease with a 10-year survival rate since diagnosis. About 45% of the tumor is completely removed by surgery, which has 5% mortality and 20% survival rate. In the locoregional stage, the use of neoadjuvant chemoradiotherapy and then surgery reduces recurrence and increases survival.
Objectives: This study was performed to investigate the effect of neoadjuvant chemoradiotherapy and the subsequent chemotherapy with platinum-based regimen on survival, recurrence, and response to treatment.
Methods: Planning a descriptive retrospective follow-up study, during 2010 to 2016, 44 patients with esophageal cancer, who received chemotherapy with 5-Fluorouracil + Oxaliplatin + Docetaxel before and after radiotherapy (45 - 50 Gray) accompanying by oral Capecitabin, were followed up. Five operable patients underwent surgery. Response to treatment and recurrence were evaluated by periodic endoscopic biopsy and imaging. To calculate the response rate to treatment, survival, and recurrence, the data were extracted and analyzed, using SPSS version 18. The categorized variables were compared, using Pearson's test. The survival curves were drawn, using the Kaplan Meier method and compared with the log-rank test.
Results: Among 44 patients with an average age of 61.5 $\pm$ 11.5 years, 88.6% had squamous cell carcinoma (SCC) and 11.4% had adenocarcinoma; surgery was performed for 5 patients, one of whom had severe complication leading to death and 54.5% had complete response as well as more survival rate. The patients suffering from SCC and middle segment tumors had more response rate. Also, recurrence was seen in 16 patients (36.4%), of whom 9.1% had local recurrence and 27.3% had metastatic recurrence. The mean survival rate was 38.87 months and 1-, 3-, and 5-year survival rate was %81.6, %47.6, and 39.6%, respectively. It was significantly more in middle esophageal segment and also tumors with complete response to treatment.
Conclusions: Regarding the results, this treatment approach increases overall and disease-free survival, and response to treatment and reduces locoregional recurrence even if no surgery is performed. This treatment is recommended as a definitive treatment for esophageal cancer without metastasis.

Keywords: Esophageal Cancer, Neoadjuvant Chemoradiotherapy, Survival, Platinium

1. Background

Esophageal cancer is an invasive lethal disease. It is the 8th most common cancer in the world with poor prognosis and a 5-year overall survival rate of about 3% to 30% (1, 2). Histologically, squamous cell carcinoma and adenocarcinoma are more seen in the esophagus. However, squamous cell carcinoma and adenocarcinoma are more prevalent in developing and developed countries, respectively (3). Despite the significantly-increasing incidence of adenocarcinoma in recent decades, squamous cell carcinoma is still the most common type of esophageal cancer (3). Since Iran is located on esophageal cancer belt, the prevalence of this cancer is relatively high in Iran with particularly on the Caspian Sea coast and Golestan province. Esophageal cancer is ranked 4th in women and 5th in men in terms of incidence, and 5th in terms of cancer-induced mortality (4). Advances in endoscopic diagnosis and the common use of such advanced technology in patients with gastrointestinal complaints in recent years have resulted in early detection of esophageal cancer and, thus, the possibility of its

complete surgical removal. Selecting the right treatment for patients depends on their condition and the accurate assessment of the disease stage. Surgery is the treatment of choice for esophageal cancer. However, about two-thirds of the patients cannot be surgically treated at the time of diagnosis (5). Neoadjuvant chemoradiotherapy (NCRT) is used as multimodality or trimodality method is the treatment of choice in patients without a satisfactory condition for surgery yet with the ability to tolerate chemoradiotherapy. However, those unable to tolerate both receive only palliative treatment, usually as radiotherapy (6, 7). NCRT is theoretically more beneficial than postoperative therapy (8). The combination of radiotherapy and chemotherapy reduces tumor implantation and decreases local and distant tumor metastasis. According to the National Comprehensive Cancer Network (NCCN) guideline, dual-drug combination of taxane-platinum is accepted as chemotherapy in NCRT; however, 5-Flouracil and Capecitabin are also therapeutically effective (9).

2. Objectives

Given the high and increasing incidence of cancers, the present study aimed at evaluating a new treatment approach, including neoadjuvant chemoradiotherapy plusa course of chemoradiotherapy after NCRT with Docetaxel, Oxaliplatin, Capecitabin (DOC) triple therapy in patients with esophageal cancer.

3. Methods

This was a descriptive retrospective study. The population included 44 patients out of 155 patients suffering from esophageal cancer that visited the Khatam-ol-Anbia Clinic in Yazd, Iran, between 2010 and 2016 and fulfilled the inclusion criteria and intended standard treatment approach that were sampled by census method. After physical examination, oesophagogastroscopy and biopsy, chest X ray, and abdominal CT scan were performed for the diagnosis of the type and metastases of tumor. The following patients were included in the study: patients with esophageal cancer that had not been previously treated (naïve) aged under 75 years, stage 2 - 3, SCC, receiving radiotherapy and/or chemotherapy.

If the patients were under 60 years and had the suitable conditions, they would undergo surgery.

Treatment protocol was chemotherapy with platinum-based regimen, containing 5-Fluorouracil (200 mg/m^2/continuous infusion), Oxaliplatin (85 mg/m^2), and Docetaxel (75 mg/m^2) for 3 to 4 sessions on a weekly basis followed by radiotherapy on esophagus and mediastinum with a high energy linear accelerator for an average of 25 to 28 sessions with a total dose of 45 to 50 Gray concurrently with oral consumption of Capecitabin (Xeloda); in the case of lymph node involvement, irradiation was performed on that area. After this NCRT, the patients obtained the specified regimen for 3 to 4 more sessions.

Patients with metastases, intolerance to treatment, inappropriate clinical conditions, or any contraindication, and those who did not receive the mentioned chemoradiotherapy regimen or those who only received palliative radiotherapy with tumor originated from stomach were excluded from the study. The required data, which included age, gender, tumor pathology, location (upper, middle, and lower), clinical stage (in case of endoscopic ultrasound), performing curative surgery or whose possible complications were extracted from patients' records or telephone interviews with them or their close relatives were recorded in a prepared form. Response to treatment (assessed by endoscopy and biopsy after chemoradiotherapy and surgery), survival duration after treatment with or without disease (characterized by serial endoscopy), and local recurrence or distant metastasis after treatment (diagnosed with endoscopy and biopsy and serial imaging) were also collected and calculated. Patients were examined every 6 months for survival, relapse, and complications of treatment. All cancers were confirmed histologically by endoscopy, biopsy, and pathological examination. Overall survival (duration of patient survival undergoing treatment until death or monthly data collection), 3-year survival rate (the rate of patients remaining alive 3 years after diagnosis), 5-year survival rate (the rate of patients remaining alive 5 years after diagnosis),complete pathologic response (no microscopic evidence of subsequent tumor after treatment), partial pathologic response (reduction in tumor cells with fibrosis after treatment), and no pathologic response (no reduction in tumor cells after treatment) were calculated. The pathologic response was measured, using the Mandard Tumor Regression Grading (TRG) (10). Based on the TRG criteria, the presence of fibrosis alone, the absence of cancer cells, the presence of fibrosis and very low number of cancer cells, the presence of fibrosis and cancer cells with majority of fibrosis, the presence of fibrosis and cancer cells with majority of cancer cells, and the presence of tumor tissue alone were scored 1 to 5, respectively. According to post-treatment pathologic responses, patients with a TRG score of 1 or 2 were placed in the complete pathologic response group, those with a TRG score of 3 or 4 in the partial pathologic response group, and those with a TRG score of 5 in the no pathologic response group. The collected data were analyzed by SPSS 18 software. Descriptive statistics including mean, median, and frequency were calculated, categorized, and compared, us-

ing Pearson, chi-Square, and t-tests. Survival curves were plotted, using Kaplan-Meier method and compared, using log-rank test. In all cases, P value < 0.05 was considered as statistically significant at 95% confidence interval. The Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran approved the present study under the code of IR.SSU.MEDICINE.REC.1394.387.

4. Results

A total of 155 patients with esophageal cancer visited Khatam-ol-Anbia Clinic in Yazd, Iran, and were referred, for radiotherapy, to the Shahid Ramezan Zadeh Radiotherapy Center from 2010 to 2016 (6 years), 44 of whom, including 22 women (50%) and 22 men (50%), were enrolled in the study. Among them, 18 patients (45%) were 60 years old or younger and 26 patients (55%) were 60 years old or older. The mean age of the patients was 61.5 $\pm$ 11.5 years. Thirty-nine patients (88.6%) had SCC and 5 patients (11.4%) had adenocarcinoma. The tumor was in the upper esophagus in 7 patients (15.5%), in the middle esophagus in 31 patients (70.5%), and in the lower esophagus in 6 patients (13.6%). Tumor was operable in 33 patients (75%) and inoperable in 11 patients (25%); however, in most operable cases (28 patients), patients were reluctant to undergo surgery or withdrew from operation on account of advanced age. Only 5 patients (11.4% of the total patients) underwent curative esophageal resection, out of whom 1 patient demised due to serious complication with the remaining patients exhibiting no significant complication.

In terms of pathologic response, 24 patients (54.5%) had complete pathologic response, 6 (13.6%) had partial pathologic response, and 9 (20.5%) had no pathologic response to treatment. There was no information on the rate of response to the treatment in 5 patients. Out of the 44 patients, 20 were alive (45.5%) and 18 (40.9%) had demised with no information on the remaining 6 patients (13.6%). The disease relapsed in 16 patients (36.4%) with 9.1% local relapse and 27.3% metastatic relapse. The relapse status was unknown in 6 patients (13.5%) and 15 patients (34.1%) had no relapse. Table 1 presents the results of the study regarding the frequency of different pathologic responses to treatment according to the study variables. Analysis of the results by chi-Square showed a significant difference between the frequency of pathologic response to treatment and surgery, so that the frequency of complete pathologic response in patients who were surgically treated was significantly more than those who were not surgically treated. As an important result, mortality was significantly higher in patient with no response to treatment (P < 0.0001). The middle esophageal tumors had significantly higher complete response rate, as well, unlike, lower segment tumors with significantly lower response rate (74.1% versus 16.7%).

As Table 2 shows, the difference between pathologic response and recurrence of disease is statistically significant. By omitting the no responders group, this difference was not significant between complete and partial responders. Also, metastasis was not different between responders and non-responders. Therefore, it can be concluded that the significant difference observed in the initial analysis was mostly due to local disease control in patients who responded appropriately to the treatment, meaning that response to treatment had no role in metastasis rate control.

The overall survival rate of patients was 31.35 to 46.38 months (38.87 months on average) at a 95% confidence interval. The median survival rate of patients was 15.96 to 56.04 months (36 months on average) at a 95% confidence interval. Survival rate was 19 months at 75th percentile. The 1-, 3-, and 5-year post-treatment patient survival rates were 81.6%, 47.6%, and 39.6%, respectively. Table 3 presents the mean survival of patients (in month) and 1-, 3-, and 5-year survival rates due to different study variables.

Analysis of the results showed a significant difference between the survival rates according to the tumor site, so that patients with the middle esophagus tumors survived for 34.70 to 52.33 months, which was longer than patients with upper and lower esophagus tumors. In addition, a significant difference existed in survival rate among different response groups. Survival was clearly higher in the group with complete response to treatment than the other two groups. In this group, the 1-, 3-, and 5-year survival rates were 95.2%, 70.8%, and 59%, respectively. In total, recurrence was not observed in 52.6% of patients at the end of 5 years. Survival was 56.2 $\pm$ 3.6 months in patients with no recurrence and complete pathologic response to treatment, but16.7 $\pm$ 5.5 months in patients with local relapse, and 34.5 $\pm$ 4.27 months in patients with metastasis. There was a significant difference between these 3 groups in survival (P = 0.001). In other words, the local disease was well restrained and improved, using this chemoradiotherapy in patients without any local relapse even in case of subsequent distant metastases.

5. Discussion

According to the results, the mean overall survival rate of patients treated with this approach was 38.87 months. The 1-, 3-, and 5-year survival rates were 81.6%, 47.6%, and 39.6%, respectively, with significantly increased in comparison with the survival and mortality rates of esophageal cancer in Iran (11-18). The median survival rate of patients with esophageal cancer in Golestan Province was reported

Table 1. Frequency of types of Pathologic Response to Treatment According to Study Variables

Variables	Response to Treatment			P-Value
	Complete Response	Partial Response	No Response	
Sex				0.428
Female	13 (59.1)	3 (13.6)	4 (18.2)	
Male	11 (50)	3 (13.6)	5 (22.7)	
Age (year)				0.952
60 ≥	14 (53.8)	2 (7.7)	6 (23.1)	
60 <	10 (55.6)	4 (22.2)	13 (16.7)	
Type of tumor				0.291
SCC	22 (56.4)	4 (10.3)	8 (20.5)	
Adenocarcinoma	2 (40)	2 (40)	1 (20)	
Location of tumor				0.120
Upper	20 (64.5)	2 (28.6)	1 (14.3)	
Middle	20 (64.5)	2 (6.5)	5 (16.1)	
Lower	1 (16.7)	2 (33.3)	3 (50)	
Surgical capability				0.220
Yes	20 (60.6)	4 (12.1)	7 (21.2)	
No	4 (36.4)	2 (18.2)	2 (18.2)	
Surgery				< 0.0001
Yes	4 (80)	1 (20)	0 (0)	
No	20 (58.8)	5 (14.7)	9 (26.5)	
Metastasis				0.786
Yes	8 (66.7)	4 (15.4)	7 (26.9)	
No	16 (57.7)	2 (16.7)	2 (16.7)	

Table 2. Frequency of Types of Pathologic Response to Treatment According to Recurrence

Recurrence	Response to Treatment				P-Value
	Complete Response	Partial Response	No Response	Missing	
No recurrence	13 (54.2)	2 (33.3)	-	-	< 0.0001
Local recurrence	3 (8.3)	2 (33.3)	-	-	
Metastatic recurrence	8 (33.3)	2 (33.3)	2 (22.2)	-	
Total	24 (54.4)	6 (13.6)	9 (20.5)	5 (11.5)	

11 months, with a 3-year survival rate of 14% (17). In another study in Golestan, the median survival rate of patients was 7 months with 5-year, 3-year, and 1-year survival rates of 0.8%, 6.5%, and 40.5%, respectively. Survival was associated with age, which disappeared after matching with treatment. Living in urban areas and not being of the Turkmen ethnicity were good prognostic factors (19). Malekzadeh et al. reported a 5-year survival rate of less than 10% (11). The distribution of people who received definite esophageal cancer treatments, whether surgical or non-surgical, differed in race and place of residence. However, with definitive treatment, the survival rate significantly increased. After the treatment, the 5- and 3-year survival rates were about 20% and 27%, respectively. The mortality rate was reported to be 48.8% in patients with no treatment, 10.1% in patients with surgery only, 5.6% in patients with surgery and radiotherapy, 6.8% in patients with surgery and chemoradiotherapy, and 13.2% in patients with chemoradiotherapy only. In this study, chemoradiotherapy was also an effective treatment, which markedly in-

Table 3. The Overall Survival Rate and 1-, 3-, and 5-Year Survival Rates Due to Study Variables

Variables	Survival Rate				P-Value
	Average Overall Survival (Month)	1 year Survival (Percent)	3 Year Survival (Percent)	5 Year Survival (Percent)	
Sex					0.601
Female	40.61	75	40.9	40.9	
Male	35.40	88.9	60.5	30.2	
Age (year)					0.427
60 ≥	30.26	81	38.9	38.9	
60 <	41.69	82.4	57.4	47.9	
Type of tumor					0.435
SCC	39.86	81.8	50.1	41.8	
Adenocarcinoma	24.4	60	40	40	
Location of tumor					0.023
Upper	27.66	83.3	33.3	33.3	
Middle	43.52	84.6	58.7	48.9	
Lower	18	50	16.7	16.7	
Surgical capability					0.275
Yes	40.94	80.6	49.5	49.5	
No	30.21	85.7	35.7	17.9	
Surgery					0.538
Yes	44.55	80	53.3	53.3	
No	37.8	78.8	47.4	37.9	
Metastasis					< 0001.0
Yes	50.99	95.5	70.8	59	
No	23.62	83.3	0	0	

creased the survival of patients. However, the therapeutic regimens used in this study were not mentioned (18). In another study, the 1-, 3-, and 5-year survival rates following radiotherapy were 42%, 11%, and 8%, respectively. In both of these studies, the survival rate of patients was lower than that of the present research even with treatment (16). These studies have been carried out in the northern part of Iran, more often on the Turkmen ethnicity, which itself is a factor for poor prognosis. In addition, treatment facilities and access to curative treatment in this area are much more limited than the present study area, which is considered a referral center. The mean survival rate in Ardabil, Iran, was 12.1 months, which was not related to age, gender, and tumor location. However, surgical treatment improved the survival of patients. Nevertheless, the selection of patients with a lower stage disease and without comorbidity and metastasis for surgery were identified to affect these results (15). In a meta-analysis, the 1-, 2-, 3-, and 5-year survival rates of esophageal cancer in Iran were 47%, 31%, 22%, and 12%, respectively, but the relationship between survival and treatment was not investigated (12). The mean survival rate of patients in Fars Province was 21.46 months (19). In foreign studies, the median survival rate of patients with esophageal cancer treated with chemoradiotherapy, often as neoadjuvant, ranged from 24 months to 29 months. This rate was 36 months in according with this study, which was higher than other studies (20-22). According to Schena et al. (19), the median survival rate of patients following NCRT was 42 months, almost twice as those who had not undergone surgery. Similar to this study, this number was 44.5 months after surgery in this research (20). The 5-year survival rate varied from 22% to 64.2% in the various studies, the least of which was 22% in those who did not undergo surgery (23). The highest 5-year survival rate (64.2%) was observed in a study with patients, who had undergone NCRT and surgery. There was a significant difference in the 5-year survival rate between stages 2 and 3 of the disease (33.1% versus 64.2%) (8). The overall 2- and 3-year survival

rates in various studies vary from 41% to 60% (22-24). This rate was 47.6% in our study and was approximately similar to studies, in which NCRT had been used as the sole treatment. Disease-free survival rates were different in various studies. It was 39.5% (25) and 42% (26) for 5-year survival and 49.2% (22), 53% (26), and 49.2% (8) for 3-year survival. Inpatients with complete pathologic response mean total survival was 47 months, 1-, 3- and 5-year disease-free survival rates were 95%, 73%, and 60%, respectively. These rates were higher in comparison with NCRT treatment alone or along with surgery. In a study on NCRT, the disease-free survival was 48 months and the 5-year survival rate was 62%, which is similar to the results obtained in the study (27). In studies that evaluated NCRT, this rate was 13.2% to 42% in the complete pathologic response and 48% to 60.5% in the partial pathological response (20, 21, 28-30). In a number of studies (22, 31), the complete and partial response were reported together from 80% to 93.4%. In most of these studies, NCRT was associated with esophageal resection surgery, whereas in our study, the complete and partial pathologic response rates were 54.5% and 13.6%, respectively. Contrary to expectations and previous studies, the rate of complete response was higher than that of partial response. However, the cases without treatment response were much lower (20.5%). In a number of studies, this figure was reported to be 0% in patients operated after NCRT (22). According to Anvari et al. (31), the total pathologic response to chemoradiotherapy was 6.7%, which was much less than the response to treatment in the study (32). As can be seen, the treatment applied in our study increased the complete pathologic response rate. The survival of patients with a complete pathologic response to treatment was 51 months on average, which was significantly higher than other patients. As was expected, this result is similar to studies that examined NCRT. In a systematic review on the effect of NCRT, Geh et al. (28) investigated 26 studies and concluded that the overall and disease-free survival of patients treated with NCRT increased with a complete response of 60%. In this study, the overall survival in the complete response group was greater than NCRT, but the disease-free survival had no significant difference with NCRT (33). In another study on NCRT in adenocarcinoma, the complete pathologic response rate was 19%, which was much lower than the complete pathologic response in adenocarcinoma that showed in this study (28). Therefore, it can be concluded that the treatment used in this study was more successful than NCRT in developing a complete pathologic response in adenocarcinoma. Similar to other studies, the incidence of local recurrence was very low (9.1%) (10, 26). This result demonstrates the effect of radiotherapy in local disease control in the field of therapy. The metastasis rate was 27.3% in patients receiving this treatment, which was higher than local relapse. This is indicative of the local control of patients through chemoradiotherapy and may also demonstrate the presence of micro-metastases at the time of diagnosis, which grows with the increased survival of patients leading to an increase in metastasis. The rate of metastatic relapse in those with a complete pathological response was 33.3%, approximately equal to those with a partial response (33.3%) or to metastasis in those without response to treatment (22.2%).

This study was performed to investigate the effect of NCRT and the subsequent chemotherapy with platinum-based regimen on survival, recurrence, and response to treatment .According to the results obtained and comparison of survival, response to treatment, and recurrence rates of patients participated in this study with the survival rate of patients with esophageal cancer in Iran, this platinum-based chemoradiotherapy regimen can be used as an effective approach for the treatment of patients with esophageal cancer. Despite the special role of surgery in the treatment of esophageal cancer as a definite curative treatment, the combination of surgery with NCRT can improve therapeutic outcomes. Also, it will remain a trustable treatment for the patients, who are not able to perform the surgery.

Acknowledgments

None declared.

Footnotes

Authors' Contribution: All of the authors had full access to the study data. They all involved in the study design (especially Mohsen Akhondi-Meybodi, and Hasan Ali Vahedian), data interpretation (especially Mohsen Akhondi-Meybodi and Fatemeh Mansouri) and writing of the manuscript (especially Fatemeh Mansouri and Mohsen Akhondi-Meybodi). All authors take the responsibility for data collection and confirm that the tests followed guidelines (especially Masoud Shabani and Hasan Ali Vahedian, Fatemeh Mansouri) and the results are valid. All authors read and approved the final manuscript.

Conflict of Interests: Authors declare that there is no conflict of interest.

Ethical Approval: This study has the ethical code number: IR.SSU.MEDICINE.REC.1394.387 that approved by Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Financial Disclosure: It was not declared by the authors.

Funding/Support: No funding.

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