RESEARCH ARTICLE

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Outcomes of Induction Chemotherapy Followed by Chemoradiotherapy Versus Chemoradiotherapy Alone in Esophageal Squamous Cell Carcinoma Induction chemotherapy in Esophageal Squamous Cell Carcinoma

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Abstract

Background: There is still no definite conclusion regarding the effect of Induction Chemotherapy (IC) combined with concurrent Chemoradiotherapy (CRT). Thus this study was aimed to assess outcomes of IC followed By CRT versus CRT alone in Esophageal Squamous Cell Carcinoma (ESCC). **Methods:** This multicenter retrospective study performed on 105 patients who underwent CRT and 73 patients who underwent IC+CRT, between January 2016 and December 2018. The primary endpoints were OS (from the date of treatment to the date of death or 3- years follow-Up). The toxicities of CRT were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). **Results:** one-year (73.8% vs. 53.2%) and 2-year (53.4% vs. 38.5%) OS rate of the IC+CRT group was significantly higher than that of the CRT group ($p < 0.05$). No statistically significant differences were observed between the IC+CRT group and the CRT group (31.5% vs. 27.4%) in terms of the 3-year OS rate ($p > 0.05$). In multivariate logistic regression, age<60 (OR: 1.48; CI 95% 1.02-1.97), clinical staging II (OR: 1.36; CI 95% 1.11-1.88), and the addition of IC (OR: 1.66; CI 95% 1.07-2.19) were independent prognostic factors that affected survival positively. **Conclusion:** Our data demonstrated that a combination of IC and CRT might be a promising treatment strategy to further improve OS in ESCC patients.

Keywords: Esophageal squamous cell carcinoma- induction chemotherapy- chemoradiotherapy- survival

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Introduction

Esophageal Cancer (EC), as the 8th most common cancer worldwide and the 2nd most common cancer of the digestive system [1, 2], is a lethal disease with an unsatisfactory prognosis, representing the 6th most common cause of cancer-related deaths [3]. The major pathological types of EC include adenocarcinoma and squamous cell carcinoma (SCC). Adenocarcinoma is commonly found in European and American countries, while the SCC is mainly found in Asian countries [4].

Early esophageal cancer is mostly treated by surgery. Moreover, surgical resection combined with the standard modality of treatment for neoadjuvant chemo radiotherapy (nCRT) is an important radical medical procedure for patients with operable esophageal squamous cell carcinoma (ESCC) [5, 6]. The randomized trials study identified nCRT followed by surgery, has demonstrated a 10%–15% improvement in long-term survival rate as compared with surgery alone [7, 8]. However, due to the lack of early clinical symptoms, more than 50% of newly diagnosed EC cases are diagnosed in the advanced stages, at which time patients often have lost the opportunity for surgery [9]. For these patients with locally advanced and unrespectable esophageal cancer, concurrent chemo radiotherapy is considered to be the main treatment [10].

In spite of this, the locoregional recurrence rate of EC patients is high and the survival rate is inappropriate. Thus, several intensified treatment modalities have been attempted to improve survival outcomes for patients with EC for instance induction chemotherapy (IC). In theory, the additional IC followed by CRT (IC+CRT) has potential benefits on better response rate, early eradication of micro metastases, increased tumor radio sensitivity because of tumor shrinkage, improve dysphagia and even prolonged overall survival (OS) [11]. Some researches have shown

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that patients treated with IC + CRT had a significantly higher OS and progression-free-survival than those in the CRT group, showing a superior survival advantage [12, 13]. However, other studies have reported that IC did not significantly improve OS, which may even reduce the dose intensity of CRT and increase postoperative mortality [14]. Therefore, the clinical efficacy of IC is still controversial.

Therefore, this study was aimed to investigated the outcomes of IC followed By CRT versus CRT alone In ESCC

Materials and Methods

Setting and Design

This is a multicenter retrospective study of collected data, conducted in firouzgar hospital,Tehran, approved by institutional review board of Iran University of Medical Sciences. We retrospectively studied 105 patients who underwent CRT and 73 patients who underwent IC+CRT, between January 2016 and December 2018. Criteria for inclusion were as follows: (1) histologically confirmed ESCC; (2) ECOG score 0-2 based on patients documents (3) no distant organ metastasis; (4) no anticancer therapy history; (5) no concomitant or previous malignancy history; (6) resectable or operable; and (8) complete and retrievable clinical data. In this study, patients who had considerable comorbidity e.g. uncontrolled diabetes, uncontrolled hypertension, history of ischemic heart disease, history of cerebrovascular accidents (CVA), presence of neuropathy grade 2 or higher, bone marrow failure (lymphopenia, leukopenia, and thrombocytopenia in the initial examination), heart failure (EF≤45%), kidney dysfunction (GFR<50 mg/ml) and liver dysfunction (AST/ALT≥3×ULN and Billt≥1.5×ULN), and those with incomplete information, were excluded.

Pretreatment Work-up

Pretreatment work-up included physical examination, standard laboratory tests, pulmonary function test, and also bone scans and positron emission tomography (PET) were performed selectively. Tumors were clinically staged by endoscope and ultrasonography, barium esophagography, and enhanced computed tomography (CT) according to the eighth TNM staging system of the American Joint Committee on Cancer.

Treatment

All patients received concurrent chemotherapy with weekly schedule of Carboplatin(AUC 2) + Paclitaxel (50mg/m^2) .Likewise, IC+CRT group underwent IC with one or two cycles carboplatin(AUC5-6) and paclitaxel(175mg/m^2) or FOLFOX regimen(modified 6). All patients underwent radiation (in IC group after 2-3 weeks of chemotherapy) therapy by three-dimensional conformal radiotherapy or intensity-modulated radiotherapy with 6-8 MV X-ray. The gross tumor volume (GTV) was referred to the primary tumor and positive lymph nodes (based on pre chemotherapy CT scan). The clinical target volume (CTV) was derived from GTV by prolonging the radiating coverage by 1 cm laterally and 5 cm both inferiorly and superiorly. CTV also comprised the regional lymphatic regions. The planning target volume (PTV) referred to the CTV with a 1-cm margin in all directions due to organ spontaneous and involuntary motions. The treatment plan and dose limits of organs at risk were based on the National Comprehensive Cancer Network version 1, 2020. A standard prescription dose of 50-50.4 Gy was delivered in 1.8-2.0 Gy fractions over 6-7 weeks.

Surgery

Patients were assessed before surgery using barium swallow radiography, CT scan of the chest and abdomen, esophagoscopy, and PET scan (when possible). Finally, all patients underwent surgery with an interval of 8-12 weeks after chemoradiation . The resected surgical specimen from all patients was examined to determine the degree of pathologic response based on the criteria described previously [15].

Endpoints and Follow-Up

The primary endpoints was OS (from the date of treatment to the date of death or 3- years follow-Up). Patients were followed up via physical examination, chest and abdominal CT, endoscopy with biopsies, and barium esophagography performed based on symptom. The toxicities of CRT were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Data collection

Baseline clinical and Tumor characteristics were obtained using a checklist. Several baseline characteristics including: age, sex, BMI, and smoking were collected. Other tumor characteristics including: histologic grade, ECOG performance status, clinical staging, Tumor location, dysphagia grade, resection achieved, and tumor regression grade (TRG) were collected.

Statistical analysis

Data were analyzed using descriptive statistics including mean ± standard deviation (SD), median, frequencies and percentages wherever applicable. Differences between subgroups were assessed using independent t-test for continuous and normally-distributed variables and chi-square test (or Fisher's exact test) for categorical variables. The survival curves were drawn using the Meier-Kaplan method and the Rank-Log test was performed to compare the survival rates. Factors associated with overall survival were assessed using univariable and multivariable logistic regression analyses. All basic variables were included in multivariate models when $p < 0.1$ was obtained in univariate analysis. Odds ratios (ORs) and 95% confidence Intervals (CIs) were calculated. A test was considered statistically significant if the probability value (P-value) was less than 0.05. All analyses were carried out using Stata software (version 14.1) (Stata Corp, College Station, TX, USA).

Ethics

The Research Ethics Committee at the Deputy of Research of Iran University of Medical Sciences approved the study protocol in November 2021. In addition,

individual personal information was kept confidential.

Results

Table 1 shows baseline clinical and tumor characteristics. Of 105 patients who underwent CRT, 69 (65.7%) were male, and the mean age was 62.12±9.38 years. Also, 19 (18.1%) patients had weight loss≥10, 63 (60.0%) had ECOG performance status 0-1, 88 (83.8%) had clinical staging III-IVA, 91 (86.7%) had dysphagia grade 0-1, and 77 (73.3%) had TRG 1. Of 73 patients whom underwent IC+CRT, 52 (71.2%) were male, and the mean age was 59.93±10.02 years. Also, 10 (13.7%) patients had weight loss≥10, 40 (54.8%) had ECOG performance status 0-1, 62 (84.9%) had clinical staging III-IVA, 64 (87.7%) had dysphagia grade 0-1, and 51 (69.9%) had TRG 1. Patient and disease-related characteristics were well balanced between the two treatment groups.

Moreover, 98.1% (103 patients) of CRT group was taken 6 course concurrent Chemoradiotherapy and 1.9% (2 patients) was taken 5 course. Also, 6 course of concurrent Chemoradiotherapy were given to the 94.5% (69 patients) of IC+CRT group and 5.5% (4 patients) were taken 5 course. In IC+CRT, 91.8% (67 patients) was taken 2 course CI and 8.2% (6 patients) was taken 1 course.

The incidences of grade 3-4 toxicities are reported in Table 2. There were no significant differences in the occurrence of hematological toxicity and non-hematological toxicities between the two groups.

The median follow-up time was 25 months (4-36 months) for the IC+CRT group and 23 months (3-36 months) for the CRT group, respectively. The 1-year, 2-year, and 3-year OS for the CRT group were 53.2%, 38.5%, and 27.4%. For the IC+CRT group, 1-year, 2-year, 3-year OS were 73.8%, 53.4%, and 31.5%, respectively (Figure 1). Likewise, 1-year (73.8% vs. 53.2%) and 2-year (53.4% vs. 38.5%) OS rate of the IC+CRT group was significantly higher than that of the CRT group ($p < 0.05$). No statistically significant differences were observed between the IC+CRT group and the CRT group (31.5% vs. 27.4%) in terms of the 3-year OS rate ($p > 0.05$).

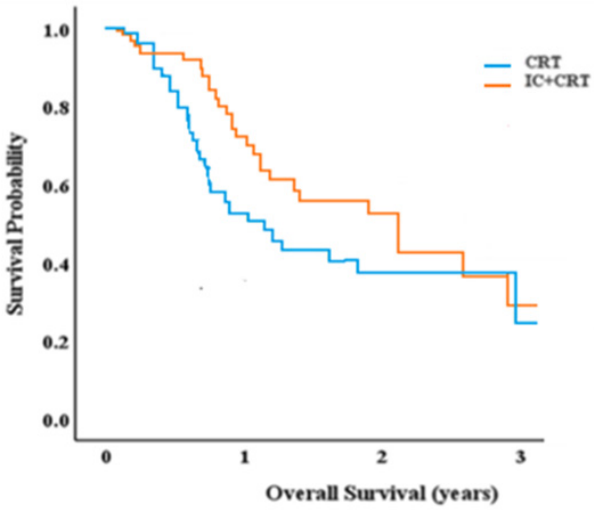

Figure 1. OS of Patients for IC + CRT Group and CRT Group

For the entire group, univariate analysis indicated that sex, smoking, weight loss before treatment, performance status, tumor location, histologic grade, T stage , N stage, dysphagia grade, resection achieved, and Histopathological response rate did not affect OS significantly Table 3. Statistically significant factors or those approaching significance ($P < 0.1$) in the univariate analysis were subsequently included in the multivariate analysis, which showed that age<60 (OR: 1.48; CI 95% 1.02-1.97), clinical staging II (OR: 1.36; CI 95% 1.11-1.88), and the addition of IC (OR: 1.66; CI 95% 1.07-

Table 1. Baseline Clinical and Tumor Characteristics

Variables	IC+CRT (N=73)	CRT (N=105)	P-value
Age (years)	59.93±10.02	62.12±9.38	0.138**
Sex (male %)	52 (71.2)	69 (65.7)	0.437*
BMI<18.5	7 (9.6)	15 (14.3)	0.349*
Weight loss≥10	10 (13.7)	19 (18.1)	0.434*
Smoking	41 (56.2)	82 (78.1)	0.001*
Histologic grade			
Gx/G1/G2	62 (84.9)	86 (81.9)	0.593*
G3	11 (15.1)	19 (18.1)	
ECOG performance status			
0	33 (45.2)	42 (40.0)	0.488*
1-2	40 (54.8)	63 (60.0)	
T stage			
T1-2	17 (23.3)	27 (25.7)	0.712*
T3-4	56 (76.7)	78 (74.3)	
N stage			
N0	10 (13.7)	18 (17.1)	0.534*
N1	63 (86.3)	87 (82.9)	
Clinical staging			
II	11 (15.1)	17 (16.2)	0.839*
III-IVA	62 (84.9)	88 (83.8)	
Tumor location			
Upper	39 (53.4)	52 (49.5)	
Middle	26 (35.6)	46 (43.8)	0.409*
Lower	8 (11.0)	7 (6.7)	
Dysphagia grade			
0/1	64 (87.7)	91 (86.7)	0.274*
2	5 (6.8)	12 (11.4)	
3	4 (5.5)	2 (1.9)	
Resection achieved			
R0	67 (91.8)	91 (86.7)	0.287*
R1	6 (8.2)	14 (13.3)	
Histopathological response rate			
TRG 0	20 (27.4)	19 (18.1)	0.125*
TRG 1	51(69.9)	77(73.3)	
TRG 2	2 (2.7)	9 (8.6)	

IC, Induction Chemotherapy; BMI, body mass index; CRT, Chemoradiotherapy, TRG, Tumor regression grade; ECOG, Eastern Cooperative Oncology Group; **, independent t-test ; *, chi square

Table 2. Treatment-Related Toxicity

Event of grade ≥3	IC+CRT (N=73)	CRT (N=105)	P-value
Hematological toxicity			
Anemia	1 (1.4)	1 (1.0)	0.794*
Leukopenia	15 (20.5)	16 (15.2)	0.358*
Neutropenia	14 (19.2)	14 (14.3)	0.292*
Thrombocytopenia	12 (16.4)	10 (10.5)	0.167*
Non-hematological toxicity			
Nausea/vomiting	7 (9.6)	8 (7.6)	0.641*
Diarrhea	3 (4.1)	4 (3.8)	0.920*
Radiation Esophagitis	4(5.5)	5 (4.8)	0.830*
Radiation Pneumonitis	4 (5.5)	4 (3.8)	0.596*
Skin toxicity	11 (15.1)	19 (18.1)	0.595*
Weight loss	5 (6.8)	9 (8.6)	0.674*
Fatigue	17 (23.3)	20 (19.1)	0.492*
ALT/AST	2 (2.7)	3 (2.9)	0.964*

IC, Induction Chemotherapy; CRT, Chemoradiotherapy, AST, Aspartate transaminase; ALT, Alanine transaminase; *, chi square

2.19) were independent prognostic factors that affected survival positively.

Discussion

In addition to traditional surgery, radiotherapy, and chemotherapy, immunotherapy and targeted therapy have been applied in the clinical practices to treat EC, but concurrent CRT is a gold standard treatment for EC patients. There is still no definite conclusion regarding the effect of IC combined with concurrent CRT. Thus this study was aimed to assess outcomes of IC followed By CRT versus CRT alone In ESCC.

We observed that patients who received IC plus CRT had a significant one and two year survival advantage over patients receiving CRT alone. In our study, the IC-CRT group had a higher 1-year and 2-year OS rate over that of the CRT group, but 3-year OS rate between the two groups was similar. Some possible reasons may explain this result. For example, the additional IC might facilitate the elimination of occult micro metastasis for the patients with well response to Chemoradiotherapy, whereas it might not carry out a positive impact for poorly responding patients and seemed to have limited benefits in long-term survival. In accordance with our findings, Luo et al. illustrated that the median OS (26.0 vs. 22.0 months) and 3-year OS (30.6% vs. 25.9%) of patients treated with IC + CRT were significantly higher than those of the CRT group [12]. A randomized clinical trial in Japan compared patients undergoing transit surgery or CRT after docetaxel plus cisplatin and 5-fluorouracil (DCF) induction chemotherapy with patients underwent CRT alone and indicated that OS of IC is superior to CRT alone [16]. Lu et al. illustrated that additional IC for EC patients treated with neoadjuvant CRT followed by esophagectomy was associated with a higher 5-year OS rate (90.5% vs. 48.1%, p = 0.015) compared to CRT alone [17]. The result of systematic review and meta-analysis done by Wang et al., showing that the IC-CRT group had a higher 1-year OS rate over that of the CCRT group, but 2- and 3-year OS rate between the two groups was similar [18].

The document supporting administration of IC before neoadjuvant CRT in EC is controversial. Conversely, Heta and colleagues investigated retrospectively 119 EC patients who underwent IC before neoadjuvant CRT and reported that the addition of IC had not effect on OS [19]. Ajani and coworkers conducted a randomized clinical trial to assess IC followed by neoadjuvant CRT versus neoadjuvant CRT. They found that the addition of IC did not prolong the OS [20]. In another randomized clinical

Table 3. Multivariate Regression Analysis to Identify Predictors for Survival

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age<60	1.76 (1.11-2.12)	0.006	1.48 (1.02-1.97)	0.037
Male	1.37 (0.65-2.96)	0.304	-	-
Smoking	1.03 (0.32-1.46)	0.948	-	-
BMI>18.5	1.41 (0.45-2.51)	0.274	-	-
Weight loss<10	0.94 (0.37-2.05)	0.802	-	-
Histologic grade (Gx/G1/G2 vs. G3)	1.31 (0.77-2.94)	0.409	-	-
ECOG performance status (0 vs. 1-2)	0.92 (0.87-1.73)	0.673	-	-
T stage (T1-2 vs. T3-4)	1.57 (0.72-1.88)	0.425	-	-
N stage (N0 vs. N1)	1.32 (0.98-1.75)	0.327	-	-
Clinical staging (II vs. III-IVA)	1.47 (1.08-2.17)	0.001	1.36 (1.11-1.88)	0.006
Tumor location (Lower/Middle vs. Upper)	1.17 (0.26-1.32)	0.668	-	-
Dysphagia grade (0-1 vs. 2-3)	0.93 (0.76-1.19)	0.555	-	
Resection achieved (R0 vs. R1)	1.20 (0.74-1.92)	0.339	-	-
Histopathological response rate (TRG 0 vs. TRG 1-2)	1.40 (0.93-2.22)	0.505	-	
Therapy regimen (IC+CRT vs. CRT)	1.82 (1.13-2.26)	0.001	1.66 (1.07-2.19)	0.004

IC, Induction Chemotherapy; BMI, body mass index; CRT, Chemoradiotherapy, TRG, Tumor regression grade; ECOG, Eastern Cooperative Oncology Group; *, logistic regression

trial, Doket et al. also found that the addition of IC before neoadjuvant CRT failed to better the OS [21]. There are several possible reasons for this variation. For instance, the majority of patients were esophageal adenocarcinoma in these studies, which is different from the histology of ESCC in current study. in the previous studies, there were few patients with T4 or stage IV disease. It has been reported that patients with T4 had an incidence of perforation of 14-23% during CRT. The addition of IC before CRT may decrease the risk of perforation by reducing the tumor volume before encountering severe esophagitis, which would benefit prolonged survival [21]. Akinori and colleagues indicated that IC for T4 esophageal cancer was efficient to resolve severe dysphagia [22]. Furthermore, 90% of the symptoms of dysphagia improved significantly after IC in the trial INT 0122 [23]. Therefore, IC might only be useful in some high-risk patients, like ESCC with T4 or stage IV disease.

Our results showed that age<60 (OR: 1.48; CI 95% 1.02-1.97), clinical staging II (OR: 1.36; CI 95% 1.11-1.88), and the addition of IC (OR: 1.66; CI 95% 1.07-2.19) were independent prognostic factors that affected survival positively. Luo et al. reported that the addition of IC was independent prognostic factor that affected survival positively [12]. The main limitation of this report is that it is a nonrandomized retrospective study. A larger randomized study with higher sample size is needed for definitive results.

In conclusion, our data demonstrated that a combination of IC and CRT might be a promising treatment strategy to further improve OS in ESCC patients. Furthermore, age<60, clinical staging II, and the addition of IC were independent prognostic factors that affected survival positively. The main limitation of this report is that it is a nonrandomized retrospective study. A larger randomized study with higher sample size is needed for definitive results.

Author Contribution Statement

All authors contributed equally in this study.

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Competing interests

The authors declare that there they have no conflicts of interest. In addition, the authors have no financial interest related to any aspect of the study.

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