RESEARCH ARTICLE

Impact of Postoperative Chemoradiotherapy and Chemoradiotherapy Alone for Esophageal Cancer in North-West Iran

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Abstract

Background: To investigate the role of surgical treatment for locally advanced esophageal cancer, we compared the outcomes of chemoradiotheroy alone (CRT) to postoperative chemoradiotherapy (S/CRT), using, Regional Radiotherapy Center, database. Materials and Methods: This retrospective study was conducted in North-West of Iran, included of 255 consecutive patients with esophageal cancer. Eligible operable and non-operable, were treated with S/CRT and CRT respectively. Radiotherapy (RT) was delivered at 1.8-2 Gy/day for five consecutive days in a given week. Chemotherapy (CT) consisted of cisplatin and 5-fluorouracil. Results: From March 2006 to March 2011 255 patients: male/female 129/96, median age 68 (35-90), squamous/adeno 213/12, received CRT /S+CRT 166/59, median radiation dose 45±13.6Gy, Median survival 13.5 (11-15), overall survival (OS) One/ Two/Three 57/21/16%, Died/alive 158/97, Univariate analysis prognostic factors: age/stag/differentiation/dose of RT/fraction/treatment, Multivariate analysis predictor factor: dose of RT/fraction. Conclusions: Although this treatment offers some possibility for improvement of patients with esophageal cancer, there remains a significant need for development of new drug and new therapeutic approaches that can substantially impact survival.

Keywords: Definitive chemo radiotherapy - survival - esophageal cancer - postoperative chemo radiotherapy - Iran

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Introduction

Esophageal cancer is one of the leading causes of cancer-related mortality. In 2011, an estimated 17,000 cases of esophageal cancer will be diagnosed in the USA, with approximately 15,000 people dying from the disease (Siegel et al., 2011). The five-year OS of esophageal cancer in the north-west of Iran is 12% (Mirinezhad et al., 2012). The optimal treatment for resect able esophageal cancer remains unclear, despite the volume of clinical research that has attempted to determine the best therapy for this patient population (Malthaner et al., 2010). At least 60% of patients are unsuitable for surgical resection either due to the advanced stage or their comorbidity (Jun Jiang et al., 2012). Definitive chemoradiation as primary treatment modality is offered to esophageal cancer patients, as an alternative for patients considered medically unfit for surgery or having irresectable tumors (Smit et al., 2012). As a result of conflicting evidence, the choice of treatment modalities seems to depend on local practices. The aim of this study is to evaluate impact of S/CRT and CRT for esophageal cancer patients and Compare tow modality treatment.

Materials and Methods

Patients

From March 2006 to March 2011, 225 patients with esophageal cancer underwent CRT at the Department of Radiation Oncology, Tabriz Imam Reza (AS) medical University Hospital. We reviewed the medical records and collected the survival status by telephone contact of these patients. Some patients were excluded for the following reasons: loss of medical records, recurrent cancer, two or more primary malignancies, or incomplete RT dose. Almost all patients had surgery transthoracic method.

Concurrent chemoradiotherapy

Adjuvant therapy, consisting of concurrent chemo radiation was begun 2-3 week after surgery. They received two course of Cisplatine (100 mg/m^2 per day) and 5-fluoro-uracil (5-FU; 1000 mg/m^2 per day) for three consecutive days, beginning 1-5 week after with RT. RT was delivered at 1.8-2 Gy/day for five consecutive days in a given week. Patients with a stage IV of the disease only received a chemoradiation (≤30 Gy dose in 10 sessions) as a palliative treatment. Patients lay supine, with the tumor

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volume and surrounding nodes included within the RT field with longitudinal and lateral margins of 5 and 3 cm, respectively. The spinal cord dose was limited to 44 Gy.

Statistical analysis

Data analysis was carried out using the Statistical Package for the SPSS version 16.0. Descriptive analysis was done for demographic, pathology and clinical features. Results were expressed as means±standard deviation and percentage. Grouped data were expressed as the median (range) and non-parametric methods were used. Cumulative survival was calculated according to the life-table method of Kaplan and Meier, and differences in survival between groups of patients were analyzed with the Log-rank test. Separate queries were performed to analyze OS outcomes for all patients. OS was measured from diagnosis until death from any cause. Multivariate analyses using Cox proportional hazards survival regression analyses were performed to evaluate the influence of covariates on OS. $p<0.05$ was considered as statistically significant.

Results

There were 225 patients in this study, 166 (74%) of who were received CRT (median age 68 (35-90) years) and 59 (26%) patients undergo surgery followed by postoperative (chemo) radiotherapy (median age 58 (29-80) years). The mean age of the patients at diagnosis was 64±12.7 years (range, 29-90 years); 96 women (43%) and 129 males (57%). The most common tumor histology was SCC (95%), and most tumors (48%) were located in the lower thoracic region. The median radiation dose was 45±13.6Gy. The end of study 158 (69.8%) patients was died.

Survival

Median survival was 13.5 months (ranging 11–15 months). The 1-, 3- and 5-year OS of all 225 patients were 57, 21 and 16%, respectively. The 26 of 59 patients in S/CRT (44.1 percent) was alive, as compared with 42 of 166 patients in the CRT (25.3 percent). The 1-, 3- and 5-year survival rates in S/CRT were 75, 31 and 31% and those in CRT were 51%, 18% and 10%, respectively. On univariate analysis for identifying potential prognostic factors related to age at diagnosis ($p=0.006$), stag ($p<0.0001$), total dose of RT ($p\leq0.0001$). The median survival time for S/CRT was 24.8 months and that for CRT was 11.8 months.

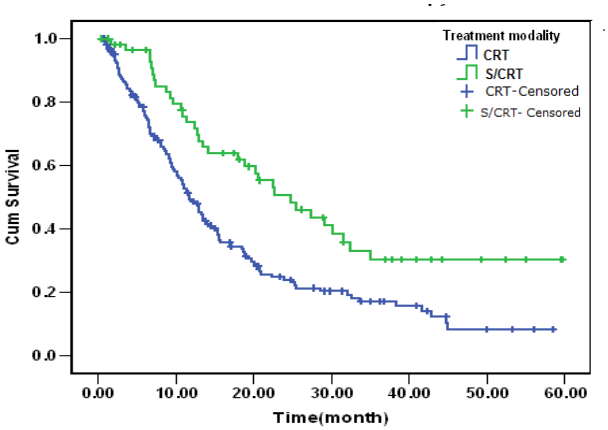

Figure 1. Kaplan-Meier Compare of Survival on Modalities Treatment are Shown S/CRT and CRT Alone

Table 1. Patient Characteristics (n=225)

Characteristic		S/CRT (N=59) No (%)	CRT (N=166) No (%)	Total (N=225) No (%)
Age years	<65	43 (72.9)	57 (34.3)	100 (44.4)
	≥65	16 (27.1)	109 (65.7)	125 (55.6)
Sex	Female	23 (39.0)	73 (44.0)	96 (42.7)
	Male	36 (61.0)	93 (56.0)	129 (57.3)
Tumor histology	SCC	54 (91.5)	159 (95.8)	213 (94.7)
	AC	5 (8.5)	7 (4.2)	12 (5.3)
Stage	II	26 (44.1)	1 (0.6)	27 (12.0)
	III	31 (52.5)	5 (3.0)	36 (16.0)
	IV	2 (3.4)	23 (13.9)	25 (11.1)
	Unknown	0 (0.0)	137 (82.5)	137 (60.9)
Tumor differentiation	Well	43 (72.9)	62 (37.3)	105 (46.7)
	Moderate	9 (15.3)	28 (16.9)	37 (16.4)
	Poor	2 (3.4)	6 (3.6)	8 (3.6)
	Unknown	5 (8.5)	70 (42.2)	75 (33.3)
Tumor location	Upper	3 (5.1)	26 (15.7)	29 (12.9)
	Middle	23 (39.0)	61 (36.7)	84 (37.3)
	Lower	31 (52.5)	78 (47.0)	109 (48.4)
	Unknown	2 (3.4)	1 (0.6)	3 (1.3)
Radiation therapy dose (Gy)				
	≤30	3 (5.1)	18 (10.8)	21 (9.3)
	31-50	32(54.2)	74 (44.6)	106(47.1)
	>50	24(40.7)	74 (44.6)	98(43.6)
Fraction group	<10	1 (1.7)	9 (5.4)	10 (4.4)
	10-25	34(57.6)	79 (47.6)	113(50.2)
	>25	24(40.7)	78 (47.0)	102(45.3)

*S/CRT=postoperative (chemo) radiotherapy. CRT=chemoradiotherapy alone

Table 2. Analysis of the 225 Patients Undergoing S/CRT and CRT

Characteristic		Survival rate% (year) 1	5	P value (Log-rank)	Hazard Ratio	P value (Cox Regression)
Age years	<65	65	23	0.006	R	0.578
	≥65	50	10		0.906	
Sex	Female	56	15	0.88	-	-
	Male	58	17		-	-
Tumor Histology	SCC	56	17	0.86	-	-
	AC	75	0		-	-
Stage	II	73	25	<0.001	R	0.316
	III	82	34		0.415	0.136
	IV	39	0		0.489	0.184
Tumor differentiation						
	Well	63	22	0.047	R	0.587
	Moderate	52	24		0.762	0.179
	Poor	63	0		0.861	0.554
Tumor location	Upper	38	10		-	-
	Middle	64	18	0.158	-	-
	Lower	57	17		-	-
Radiation therapy dose (Gy)						
	>50	70	18	<0.001	R	0
	31-50	53	18		0.108	0.001
	≤30	17	0		0.104	0
Fraction group	>25	70	14	<0.001	R	0.039
	10-25	47	15		2.156	0.296
	<10	37	0		3.243	0.014
Treatment	S/CRT	75	31	<0.001	R	0.939
	CRT	51	10		1.042	

*S/CRT=postoperative (chemo) radiotherapy. CRT=chemoradiotherapy alone

There was statistical significant in survival between the two groups (Log-rank chi-squared=12.63, df 1, p<0.0001) (Figure 1). Several prognostic factors (age, stage, total dose of RT, and treatment modality) were evaluated by Cox regression analysis procedure. On multivariate analysis, use of Radiation therapy dose ≤30 and 31-50 Gy were again associated with improved survival (HR=0.104, p<0.0001) and (HR=0.108, p=0.001) respectively. Fraction group <10 was associated with decreased survival (HR=3.24, p=0.014). There was no associated between two treatment groups (p=0.939) (Table 2).

Discussion

Surgery has been the standard of care for esophageal cancer for many years, although only 30-40% of patients have potentially operable disease at presentation (Ling Yeh et al., 2012). Definitive chemo radiotherapy may offer an alternative treatment in selected patients who are unsuitable for surgery. Neither postoperative radiotherapy nor chemotherapy alone provided a survival benefit after curative esophagectomy for esophageal squamous carcinoma. However, the optimum postoperative adjuvant therapy for esophageal cancer, especially for squamous cell carcinoma of the thoracic esophagus has not yet been established (Ling Yeh et al., 2012). The overall 3-year and 5-year survival rates were 21% and 16%, respectively, for patients with esophageal cancer in this study, which were poorer than the results reported by Byun and colleagues (Byun et al., 2011). We considered the reason was that the group of patients in our study had more cases of ESCC with advanced disease. The important finding of this study was that patients older than 65 years of age suffered relatively poor outcomes when compared with younger patients. This finding corresponds to Davies et al. (2010). Differentiation is considered to affect the prognosis of ESCC. Tumor with poor differentiation leads to a poor survival, while tumor with high and moderate differentiation had a better prognosis (Yuequan et al., 2010). We also observed that the grade of tumor differentiation influenced prognosis. In our study, univariate analyses showed that the grade of tumor differentiation was a prognostic factor. Our study also showed that overall 1-year and 5-year survival rates were significantly different in radiation dose groups. This has been demonstrated by many researchers (Gwynne et al., 2011; Semrau et al., 2012). In this study, univariate and multivariate analysis showed that patients received high dose radiation had significantly longer survival times than those with low dose radiation. Discussion of our study was limited by the no direct comparison between postoperative chemo-radiotherapy and chemo-radiotherapy alone is available. Among these previous studies, reported by Aghcheli et al showed the OS superiority of S/CRT over chemoradiation therapy alone (Aghcheli et al., 2011). This report corresponds to our study. Some studies expressed an opposing opinion. Some reports evaluated S/CRT compared with CRT. The 5-year OS were 90.0%, without significant differences between the S/CRT and the CRT groups in anal cancer (Berger et al., 2012). Yoon et al. (2010) found no improvement in survival with tow treatment arm in patients with esophageal AC. Another study revealed that OS without significant differences between postoperative radiotherapy vs. definitive radiotherapy alone in Tonsil Cancer (Ryool Koo et al., 2012). We considered the reason was that the group of patients in these studies had cases of anal cancer, esophageal AC and Tonsil Cancer respectively. IN conclusion, although this treatment offers some possibility for improvement of patients with esophageal cancer, there remains a significant need for development of new drug and new therapeutic approaches that can substantially impact survival.

Acknowledgements

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