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ORIGINAL RESEARCH

Outcomes of Definitive Chemoradiotherapy for Cervical and Upper Thoracic Esophageal Cancers: a Single-Institution Experience of a Rare Cancer

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Abstract

Purpose Upper esophageal carcinomas are uncommon but confer a poor prognosis. However, there is scarcity of data regarding outcomes of definitive chemoradiotherapy for cervical and upper thoracic esophageal squamous cell carcinoma in Iran.

Methods In this retrospective cohort study, we analyzed data of patients with squamous cell carcinoma of cervical and upper thoracic esophagus (at 16 to 25 cm from incisors) treated by definitive chemoradiotherapy in our institution between 2007 and 2015. The primary outcome was overall survival and secondary endpoints were predictors of overall survival.

Results From 2007 to 2015, 40 patients were entered to final analysis. The mean age of patients was 59.7 ± 14.3 (range 24–85 years). Sixteen (40%) were node-positive. The median follow-up time was 15.3 months. Twenty-seven patients (67.5%) died during post treatment period. Thirty-five percent and 25% of patients suffered from local and distant recurrences, respectively. The actuarial median overall survival was 19.2 (CI 95% 14.2–24.2) months. The 1- and 2-year overall survival rates were 76 and 38%, respectively. The overall survival was higher among patients who were younger than 50 years, of female gender, had stage II tumor, grades I to II, who received induction chemotherapy, and whom treated with doses < 60 Gy. However, none of the differences was statistically significant.

Conclusions Cervical and upper thoracic esophageal squamous cell carcinomas are associated with bad outcome. Studies with bigger sample sizes are required to define best treatment strategies.

Keywords Chemoradiotherapy · Esophageal neoplasms · Gastrointestinal cancer · Iran · Survival

Introduction

In contrast to middle and lower third esophageal cancer which have a high incidence rate in northern Iran (> 100 per 100.000), incidence of cervical and upper thoracic esophageal cancer seems to be rare in the region as well as other parts of the world [1]. Upper esophageal cancer (UEC) behaves aggressively and is often diagnosed in locally advanced stages [2]. It can easily invade surrounding anatomical structures such as cricoid and thyroid cartilages. Because of rich lymphatic drainage of this part of the esophagus, most patients come with cervical lymphatic metastases as well [3]. Historically, most patients with UEC used to be treated by surgery which included pharyngo-laryngo-esophagectomy (PLE) and gastric pull-up [4, 5]. Because of significant morbidity of surgical resection, definitive chemoradiation (DCRT) was adopted in treatment of upper esophageal cancers and has become the standard modality recommended by most experts [6]. The usual recommended dose of radiotherapy is 50.4 gray (Gy) in 1.8-Gy fractions and mostly, platinum-based chemotherapy is used concomitantly as a radio-sensitizing agent [7]. Although concurrent chemoradiotherapy (CRT) has the advantage of lower morbidity and mortality compared to surgery, its loco-regional tumor control and overall survival rate

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is still poor [3]. The aim of this study was to evaluate outcomes (including overall survival and disease-free survival) and prognostic factors of upper esophageal carcinoma treated by DCRT at the Iran Cancer Institute in 2007–2015.

Materials and Methods

Patients and Study Design

In this study, we retrospectively reviewed biopsy-proven locally advanced cervical and upper thoracic esophageal cancer (clinical T3–T4 or clinical-node positive) patients who were treated by definitive chemoradiotherapy at our institute, between 2007 and 2015. Patients were identified from Iran Cancer Institute database and tumor registry. Patients recruited to our study had no distant organ metastasis based on pan CT scan and no history of prior radiotherapy or chemotherapy. Our study was reviewed and approved by the institutional review board and ethics committee to be in agreement with World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, (www.wma.net). Patients routinely provide informed consent at the time of admission to our cancer institution to share their disease information for future investigations.

Clinical Staging and Treatment

Staging was done based on endoscopy, EUS, and CT scan image data according to the 7th edition of American Joint Committee on Cancer guideline for esophageal cancer staging [8]. Cervical esophageal cancer was defined as tumors located between cricopharyngeal muscle and thoracic inlet (from 16 to 20 cm of incisors on endoscopy), whereas upper thoracic esophageal cancers was defined as tumors arising from 21 to 25 cm from incisors. All patients were evaluated by a surgeon and a radiation oncologist before planning for a definitive chemoradiotherapy. Patient immobilization, simulation, and treatment planning were performed according to our department policy for 3D conformal radiotherapy. Target volume delineation was done by radiation oncologist based on endoscopy, EUS, and CT scan image data. Patients were treated by 50 to 66 Gy in 1.8–2-Gy fractions, five fractions per week over 5–7 weeks. All patients received concurrent chemotherapy. The chemotherapy agents were cisplatin, 5-flourouracil, carboplatin, paclitaxel, and oral capecitabine.

Follow-up

Patients were visited weekly during RT. Follow-up visit were done 1 month after the completion of treatment, then every 3 months within the first 2 years, every 6 months for years 3 to 5, and annually thereafter. The visit consisted of disclosure of patient's new complaints and appropriate physical examination. Additional diagnostic tests including endoscopy and computed tomography (CT) scan of the neck, thorax, and abdomen were requested as clinically indicated.

Statistical Analysis

We analyzed data using the Statistical Package for Social Sciences software (SPSS version 20.0, IBM Corporation, Chicago, IL, USA). Kaplan-Meier survival analysis was used for calculating overall survival (OS) and disease-free survival (DFS) rate. These rates were presented with confidence interval (CI) 95%. Cox proportional hazards model and log-rank test were used to determine any significant predictors of OS. Level of significance was placed at $p < 0.05$.

Results

Patients' Characteristics

From 2007 to 2015, 40 patients with accessible and complete medical records were entered to final analysis that all were followed up for at least 1 month after completion of chemoradiotherapy. The mean age of patients was 59.7 ± 14.3 (range 24–85 years). Median distance from incisors was 19 ± 3.75 cm. Sixteen (40%) were node-positive. The primary characteristics have been presented in Table 1.

Treatment Characteristics

Median radiotherapy duration was 40.5 days (mean = 39.5 ± 7.9, range 22–63 days). Fifty-seven percent (23 persons) had longer treatment time than expected duration with a median 4.8 day difference (range 1–25). Median radiotherapy dose was 50.4 Gy (mean = 50.4 ± 4.9 Gy, range 40–66). About

Table 1 Baseline characteristics

Male to female ratio		17:23
Age group	< 50	8 (20%)
	51–65	17 (42.5%)
	> 65	15 (37.5%)
Distance from incisors	≤ 20	24 (60%)
	21–25	16 (40%)
Grade	I	10 (25%)
	II	9 (22.5%)
	III	6 (15%)
	Non-specified	15 (37.5%)
Stage	II	5 (12.5%)
	III	22 (55%)
	Non-specified	13 (32.5%)

12.5% of patients received induction chemotherapy before definitive chemoradiation. All received concurrent chemotherapy and the most common regimen was cisplatin plus 5-flourouracil (40%) followed by weekly cisplatin alone at second rank (25%).

Outcomes

The median follow-up time in our cohort was 27.8 months. Twenty-seven patients (67.5%) died during post treatment period. During follow-up period, 14 (35%) and 10 (25%) patients suffered from local and distant recurrences, respectively. The 1-, 2-, and 3-year overall survival rates were 76% (CI 95% = 63–89), 38% (CI 95% = 20–56), and 16% (CI 95% = 3–29), respectively (Fig. 1). The actuarial median overall survival was 19.2 (mean = 24.6, CI 95% for median 14.2–24.2) months. The 1-, 2-, and 3-year disease-free survival rates were 63, 31, and 7%, respectively (Fig. 2). The actuarial median disease-free survival (DFS) rate was 13.9 (mean = 17.9, CI 95% for median 9.9–17.8) months. As shown in Table 2, the overall survival was higher among patients with fewer than 50 years of age, female gender, stage II tumor, and well to moderately differentiated squamous cell carcinoma. The overall survival was also higher among individuals who received induction chemotherapy or who treated with doses lower than 60 Gy. However, none of the differences was statistically significant.

Discussion

Cancers at cervical site of the esophagus account for approximately 5% of all esophageal cancers and historically, it was managed by surgery that could be cervical or total esophagectomy. This type of resection often required a laryngopharyngectomy procedure that leave patients with high morbidity and substantially reduced quality of life. Previous investigations showed that patients surviving after esophagectomy had persistent problems of physical functioning and never regained their former quality of life [9, 10]. Thus, more recent literature showed that cervical and upper thoracic esophageal cancer can be safely managed by other approaches requiring no or more limited surgical procedures including definitive CRT, neoadjuvant CRT followed by surgical resection, or surgical resection followed by adjuvant RT [11, 12]. Notwithstanding, in the majority of the cancer centers, definitive chemoradiation is preferred over surgery because with similar survival rates, it is possible to preserve patients' voice and normal swallowing mechanism [13, 14].

Although there is a high incidence of esophageal cancer in Iran [1], there is not enough data on outcomes of definitive chemoradiotherapy for this type of cancer especially those located in cervical and upper thoracic parts. In this study, 1- and 2-year overall survival (OS) rates were 76 and 38%, respectively. These rates are so disappointing but do agree with those of other studies in other parts of the world. For example, in Huang et al., 2- and 5-year overall survival rates were 31 and 13%, respectively [11]. In the thoracic esophagus, Ishikura reported median survival of 21 months and 5-year OS rate of 29% [15]. Based on earlier studies, long-term survivals occurred only in one out of four patients with upper esophageal cancers [16]. By introduction of newer radiation techniques such as intensity-modulated radiation therapy

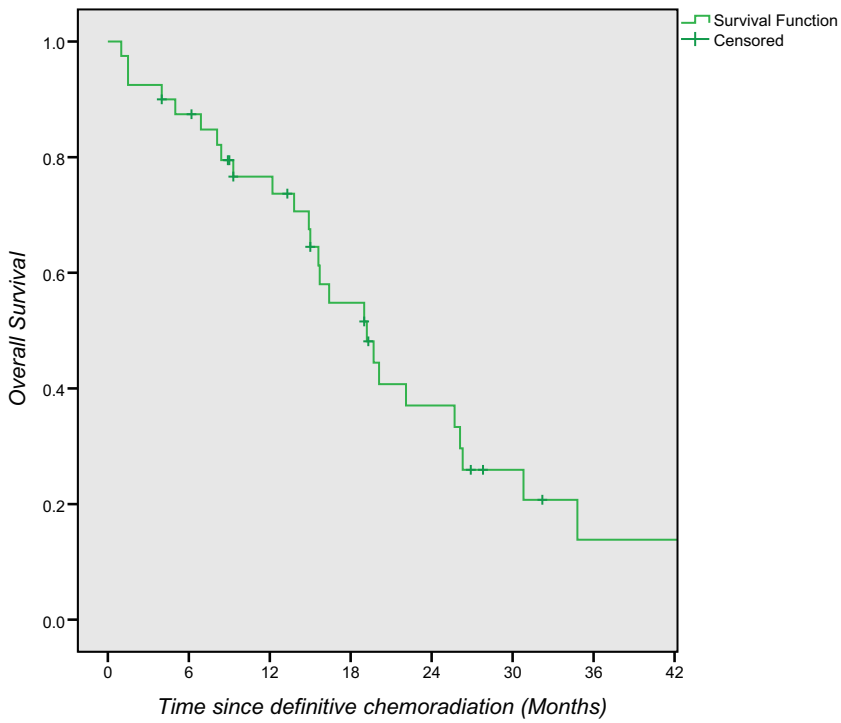

Fig. 1 Actuarial overall survival rate

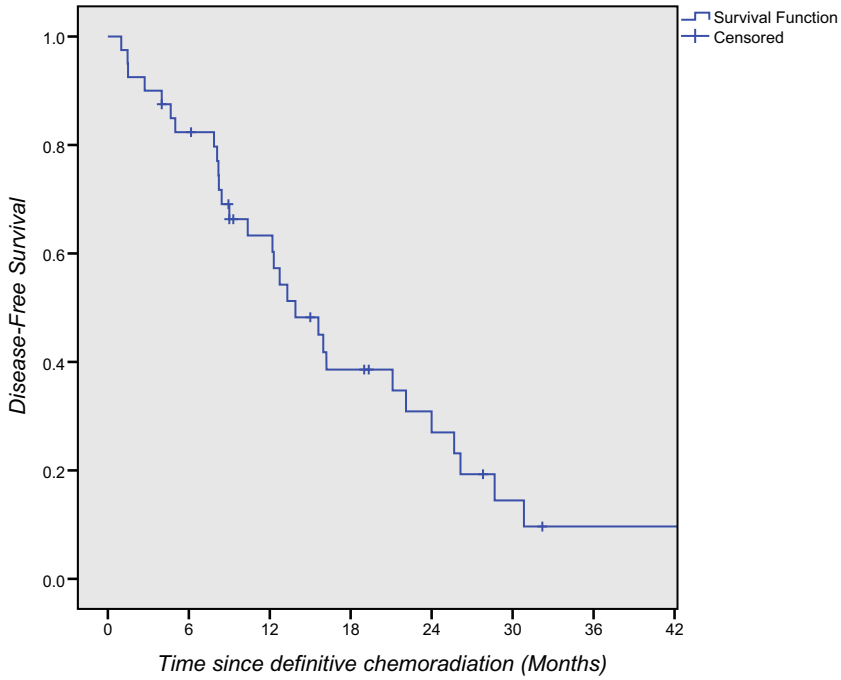

Fig. 2 Actuarial disease-free survival

(IMRT) and adopting newer chemotherapy agents, newer studies report higher survival rates about 46% at 2 years [5]. Albeit, in cohorts consisting of mostly early lesions, 5-year OS rates reach to 55% [17]. This outcome is much worse than adjacent head and neck cancers arising in the hypopharynx. In this area, survival curves reach a plateau state after 2 years but in esophageal cancer, the curve continuously declines [18]. Keeping in mind that real cause is still unknown, some explanations have been proposed for this bad outcome. Most patients present with locally advanced disease. The impaired nutritional status due to long-term dysphagia makes treatment intolerable for many patients. There are technical problems in irradiation of upper esophageal tumors including irregular target shape (e.g., different thickness of the neck and upper thorax), proximity to the spinal cord, and uncertainty about microscopic spread of the disease for elective irradiation. In our institution, in particular, there are some extra reasons to explain such poor outcomes. *First*, surgery (PLE) is not a welcomed option for patients with failure of treatment or recurrence because its complications are relatively unmanageable; it confers high morbidity considering our nursing care while in the first place, a large proportion of patients are not good medical candidates for surgery. *Second*, although providing a surgical nutritional access like jejunostomy is recommended in patients with moderate to severe dysphagia, most of our patients started treatment without it. However, due to large numbers of patients who are referring to our high-burden institution with limited number of hospital beds, patients should wait a long time for admission to surgery ward. Thus, radiotherapy would be postponed for a significant matter of time. *Third*, patients usually come from remote locations with poor socioeconomic status. They are visited with advanced disease and very poor nutritional status. They cannot afford appropriate foods even if they do not suffer from severe dysphagia. *Fourth*, due to machine overload and subsequent unexpected breakdowns, and irregular patients' attendance due to transportation or medical problems, the overall treatment duration was longer than expected in more than half of patients. It is a somehow rule in radiation oncology that treatment lengthening is associated with the adverse outcome because of repopulation of tumor cells especially in tumors like SCC that has accelerated proliferation [19–21]. Unfortunately, due to limited sample size, we could not effectively analyze the impact of

Table 2 Predictors of overall survival

		OS (month)	Significance
Age group (years)	50 or less	36.0	0.087
	51–65	19.1	
	Over 65	17.3	
Sex	Male	19	0.568
	Female	21.4	
Distance from incisors	15–20	20.2	0.402
	21–25	20.3	
Stage	2	24.0	0.510
	3	18.75	
Grade	I/II	19.9	0.640
	III	15.8	
Induction chemo	Yes	25.8	0.108
	No	19.2	
RT dose (Gy)	< 60	20.5	0.555
	60 or more	17.4	

treatment delays on the ultimate disease outcomes. *Fifth*, due to very limited number of positron emission tomography (PET) facilities, we could not perform such diagnostic modality for better staging, evaluation for response to treatment, and delineating radiation target volumes. So our treatment may be not as accurate as needed. There is hope that by implementing PET imaging for better visualization of microscopic distribution of the disease and adopting newer radiation techniques and more effective chemotherapeutic drugs, we may improve outcomes by more accurate treatment.

We assessed the prognostic value of some factors in our study that showed borderline significance in previous studies. As mentioned in the "Results" section, many factors affected trends toward better survival including gender, age, TNM stage, histologic grade, and radiation total dose. We observed that radiation doses equal or higher than 60 Gy were associated with a trend toward inferior survival. Interestingly, this conclusion was made by the investigators of INT0123 study. In that trial, total dose of 64.8 Gy compared to 50.4 Gy did not improve survival or loco-regional control rate [22]. Age is another controversial prognostic factor. Although in some studies older patients had unexplained better survival, in our study, the contrary was true. In other words, patients younger than 50 years survived longer. Patients who received induction chemotherapy experienced a trend toward superior survival. There are some explanations for this relationship. Induction chemotherapy may alleviate patients' nutrition by downsizing tumor obstructing the esophageal lumen. Micrometastatic disease will be confronted earlier. Radiotherapy volumes may become smaller after tumor downsizing by chemotherapy. These two factors may improve tolerance for chemoradiotherapy which is the main treatment.

Our study suffered from some limitations. *First*, we only managed to analyze data belonging to 40 patients during 8 years. This little sample size combined with relatively short follow-up duration attenuated the power to find significant differences or weak prognostic factors. *Second*, we collected information regarding the patients who underwent chemoradiation over an 8-year period. Despite advances in diagnostic and treatment modalities in this duration that might impact the outcome, due to the rarity of cervical and upper thoracic esophageal cancer, we had to lengthen the study accrual period to achieve an appropriate size of patients. *Second*, the retrospective design of our study limits the interpretation of observed trends. For example, induction chemotherapy increased survival. But there is a possibility that only patients with better performance who better tolerates treatment, who are expected to survive longer, received induction chemotherapy. *Third*, we could not evaluate the function of preserved organ by omitting PLE, quality of life in survivors, and also acute or late side effects such as irradiation-induced vocal cord palsy, mucositis, hypothyroidism, dermatitis, and pharyngitis. *Fourth*, our staging work-up was not complete in all patients. Prior to 2012, performing upper endosonography was not a routine diagnostic procedure in our institution due to very limited facility and skilled gastroenterologists.

Compliance with Ethical Standards

Our study was reviewed and approved by the institutional review board and ethics committee to be in agreement with World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, (www.wma.net). Patients provide informed consent at the time of admission to our cancer institution to share their disease information for future investigations.

Conflict of Interest The authors declare that they have no conflict of interest.

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