INTENSITY-MODULATED RADIATION THERAPY IN THE DEFINITIVE TREATMENT FOR CERVICAL AND UPPER-THORACIC ESOPHAGEAL CANCER: CLINICAL OUTCOME AND ACUTE TOXICITY

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SUMMARY

Objectives: To evaluate patient's characteristics and treatment outcomes of concurrent chemoradiation therapy with intensity modulated radiation therapy technique in upper third esophageal cancer patients. Subjects and methods: A descriptive perspective study on 32 upper third esophageal cancer patients treated by concurrent chemoradiation therapy with intensity-modulated radiation therapy using simultanous intergrated technique in Department of Radiation Oncology, 108 Military Central Hospital from 2014 to June 2018. Results: Diseases were mainly seen in men, aged 40 - 59 years old. Most of the patients were in late stage. 100% histopathology was squamous cell cancer with 50% of moderately differentiation. Radiation schedules were 66 Gy/30fx and 60 Gy/28fx in 25% and 75%, respectively. Chemo regimens were cisplatin 75 mg/m^2 and fluorouracil 750 mg/m^2 every 28 days. Full dose chemotherapy was given in 71.9%. Complete and partial response was seen in 56.2% and 34.4% of patients. The 6-month, 1-year, 2-year overall survival rate was 77.6%, 66.3% and 51.6%, respectively. Common toxicities were low hematological toxicity, esophagitis (90.6%) and dermatis (56.2%). Most of them were in grade 1, 2. Conclusions: Concurrent chemoradiation with intensity-modulated radiation therapy technique in upper third esophageal cancer patients had promising results and good tolerence.

** Keywords: Upper third esophageal cancer; Concurrent chemoradiotherapy; Intensity-modulated radiation therapy.*

INTRODUCTION

Esophageal cancer ranks seventh in terms of incidence (572,000 new cases) and sixth in mortality overall (509,000 deaths). The latter signifies that esophageal cancer will be responsible for an estimated 1 in every 20 cancer deaths in 2018 [1]. Cervical esophageal cancer is relatively uncommon, representing 4.4% of all esophageal cancers [2]. The prognosis of cervical and upper thoracic esophageal cancer is very poor, owing to late presentation, treatment toxicity and the moderate to high risk of local, regional and distant failure. Due to the unique anatomical position between the lower border of the cricoid cartilage and the thoracic esophagus inlet, the cervical and upper thoracic esophageal carcinoma easily and frequently invades upwards to the hypopharynx and downwards to the thoracic esophagus [3].

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It is difficult to perform surgery in these patients and such surgeries tend to result in a loss of normal body funtion as a result of the complicated anatomical location of the tumor, the presence of ambient abundant blood vessels and the distribution of nerves.

In these cases, chemoradiotherapy (CRT) is considered to be a standard treatment with several reports showing that CRT provides comparable survival to surgical resection [4]. Recently, intensity - modulated radiotherapy (IMRT) can provide excellent dose coverage and conformity to the target volume while minimizing excessive dose to normal organs compared to 3D conformal radiotherapy (3D - CRT) [5]. However, data on patients with cervical and upper thoracic esophagus cancer treated with IMRT and concurrent chemotherapy are rare. The purpose of this study is: *To evaluate the efficacy of IMRT combined with chemotherapy through a retrospective analysis of the clinical outcome of our cohort.*

SUBJECTS AND METHODS

1. Subjects.

**Inclusion criteria:*

Between January 2014 and June 2018, we respectively reviewed 32 patients diagnosed with cervical or upper thoracic esophagus. All patients were pathologically confirmed esophageal squamous cell carcinoma (SCC) without distant metastasis and who received definitive chemoradiotherapy with IMRT technique at Department of Radiation Oncology, 108 Military Central Hospital. Patients were 18 - 75 years old with Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2. Patients were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC 2010) staging system.

2. Methods.

** Radiotherapy:*

Patients immobilization, simulation, and treatment planning were performed according to standard protocols for patients with esophageal carcinoma receiving conformal radiotherapy [6]. All patients received IMRT with 6 - 8 MV photon beams. The gross tumor volume of the primary lession was defined using diagnostic imaging such as a barium contrast study, CT and PET/CT imaging. The clinical target volume of the primary lesion was defined as the gross tumor volume primary with 2 cm of craniocaudal margin on the esophageal wall, 0.5 cm margin in the lateral direction was used. The clinical target volume of the node lesion was defined as the involved lymph node with a 0.5 cm margin in every direction. The clinical target volume for the prophylactic area was from the cervical node of level III to mediastinal node. The planning target volume primary/node/ prophylactic was defined as clinical target volume primary/node/prophylactic with a 0.5 - 1.5 cm margin, considering the extent of internal organ motion. IMRT - simultaneous intergrated boost (SIB) were used in our study. A total prescription dose of 60 - 66 Gy was delivered to both planning target volume primary and planning target volume node. For planning target volume prophylactic was received 50.4 Gy (1.8 Gy/fraction).

** Chemotherapy:*

The following chemotherapeutic agents were used: Cisplatin 75 mg/m^2 D1 + 5 - FU 750 mg/m^2 D1-4 at weeks 1, 5, 9 and 13. All patients received a total of four cycles.

** Suspension and withdrawal:*

Radiotherapy was withheld for any patient with ≥ grade 3 esophagitis/ pneumonitis/skin reaction or ≥ grade 2 laryngeal reactions. Therapy was resumed when the toxicity had resolved to ≤ grade 2 (or to ≤ grade 1 for a laryngeal reaction). If the duration of discontinuation was more than 2 weeks, radiotherapy was canceled. Chemotherapy was not administered during radiation breaks. Concurrent chemotherapy was delayed for patients with ≥ grade 3 toxicities until the toxicities were resolved. If the delay was ≥ 2 weeks, if the discontinuation of radiotherapy was ≥ 1 week, or if weight loss was ≥ 10%, the second round of concurrent chemotherapy was canceled.

** Criteria for response and toxicity:*

CT of the neck, chest, abdomen and barium esophagogram as well as esophagoscopy were repeated before and after treatment. PET/CT and EUS were recommended before CRT and after the last treatment. According to the Response Evaluation Criteria for Solid Tumors (version 1.1), the response criteria for a complete response were normal barium esophagogram, normal CT, no visible tumor by esophagoscopy and negative biopsies if performed. For a partial response, the criteria were greater than 50% regression of tumor volume as evaluated by CT or greater than 50% reduction of intraesophageal tumor extension as assessed by barium swallow and esophagoscopy. For no change, the criteria were less than 50% regression of tumor extension and no evidence of tumor progression. Acute side effects were classifed according to CTCAE 4.0. Late effects were classifed according to the RTOG/EORTC.

** Statistical analysis:*

Statistical analysis were performed using SPSS version 16.0. Chi-squared test assessed measures of association in frequency tables and the t-test evaluated the equality of population distributions. Survival analysis was done using Kaplan-Meier methodology. Overall survival (OS) referred to the time interval between initial diagnosis to death from any cause, with censorship based on particular follow-up times.

RESULTS

1. Patients' characteristics.

Table 1: Patients' characteristics (n = 32).

Age	53.75 ± 6.9 (39 - 67)		Pathology SCC	32	100%
Male	31	96.9%	PS		
Female	01	3.1%	0	09	28.1%
Symptoms			1	23	71.9%
Dysphagia	32	100%	T stage		
Chest pain	11	34.4%	3	19	59.4%

Cervical node	08	25.0%	4a	11	34.4%
Hoarseness	05	15.6%	4b	02	6.2%
Weight loss	28	87.5%	N stage		
Pathological grade			0	01	3.1%
Grade 1	02	6.2%	1	14	43.8%
Grade 2	16	50%	2	14	43.8%
Grade 3	14	43.8%	3	03	9.3%
Radiotherapy dose (Gy)			TNM stage		
60 Gy/28	24	75.0%	IIIA	11	34.4%
66 Gy/30	08	25.0%	IIIB	07	21.8%
			IIIC	14	43.8%

The median age of the patients was 53 years old (range: 39 to 67 years old). Of the total 32 patients included in this study, there was only one female. At the time of presentation, 100% of the patients tolerated dysphagia, more than 85% of them lost their weight before treatment. According to the AJCC 7th edition, 100% of patients were in stage III disease and SCC, the highest rate was stage IIIC (43.8%) and pathological grade 2 (50%). 24 patients received radiation doses of 60 Gy and 8 patients received 66 Gy.

2. Dosimetric parameters in the IMRT planning.

Table 2: Dosimetric parameters related to radiotherapy in the IMRT planning.

Parameters organ at risks		
Spinal cord Dmax (Gy)	41.5 ± 24.5	Max ≤ 45
Mean lung dose (Gy)	9.72 ± 2.6	Mean ≤ 12
V20 lung (%)	19.76 ± 0.62	V20 ≤ 20
Mean heart dose (- Gy)	19.6 ± 12.9	Mean ≤ 30
V30 heart (%)	7.7 ± 13.3	V30 ≤ 30
Parameters treatment		
Tumor length		6.4 ± 2.64
GTV (cm^3)		37.01 ± 27.44
PTV60 - 66 volume		102.6 ± 40.2
PTV50.4 volume		508.04 ± 92.8
Number of fields		6.06 ± 0.98

A trend towards larger PTVs was observed and increased the number of fields radiation in IMRT plans. Interestingly, the analysis showed the exposure of normal tissue such as lung, heart, spinal cord at significantly low threshold and safely.

3. Treatment response.

Table 3:

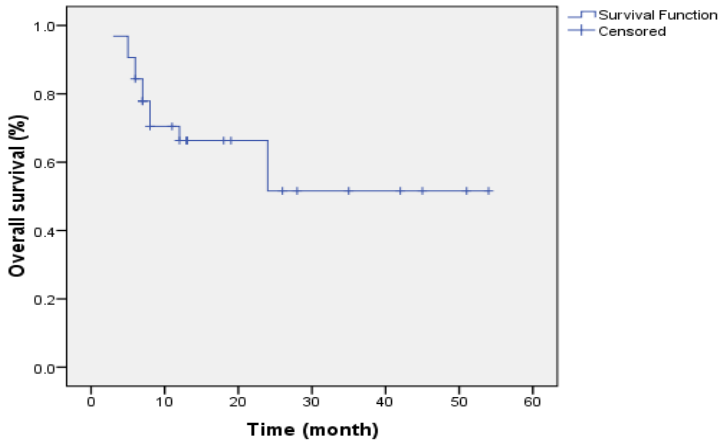
	Stable disease	Partial response	Complete response
Endoscopy	3 (9.4%)	9 (28.1%)	20 (62.5%)
CT	3 (9.4%)	11 (34.4%)	18 (56.2%)

Of the 32 patients treated with IMRT, after the initial response analysis, 18 patients were presented with a complete response, 11 patients with a partial response and 3 patients with stable disease, whereas none presented with progressive disease. The response rate (stable response, complete response + partial response) was 29/32 patients (90.6%).

4. Overall survival and some related factors.

Table 4:

Factor	OS 2 years	p value
TNM stage		
IIIA	87.5%	0.029
IIIB	71.4%	
IIIC	48.2%	
Response		
Complete response	72.9%	0.001
Partial response	31.8%	
SD	0%	



In our study, the 6-month OS, 1-year OS, 2-year OS were 77.6%, 66.3%, 51.6%, respectively. At the time of analysis, 13 patients had developed recurrence of any type. Among these patients, there were 4 patients with locoregional failure, 9 patients with distant metastasis to lung, liver. Importantly, there was statistically significant difference in the 2-year OS between some related factors such as TNM satge, treatment response ($p < 0.05$).

5. Acute toxicities.

Table 5: Acute toxicities related to radiotherapy.

Toxicities	Grade (%)			
	0	1	2	3 - 4
Nausea	34.4	56.2	9.4	0
Esophagitis	9.4	50.0	37.5	3.1
Skin reaction	43.8	34.4	18.8	3.1
Pneumonia	81.2	9.4	6.2	3.1
Myelo suppression	78.1	12.5	6.2	3.1

Acute toxicities during CRT were evaluated using CTCAE4.0. Only 1 patient with grade 3 myelosuppression and one case (3.%) that had grade 3 pneumonia were cured after treatment. The major complication was esophagitis and skin reaction grade 1 - 2. After a short follow-up period, late toxicities were unable to be reliably presented herein.

DISCUSSION

Carcinoma of the cervical and upper thoracic esophagus is uncommon. Most patients are not treated by surgery due to the involvement of mutilating resections, including pharyngo-laryngo-esophagectomy. Therefore, definitive CRT is the standard treatment modality recommended by the National Comprehensive Cancer Network (NCCN) [7]. Several different chemoradiation schedules and techniques were investigated, but no consensus has been reached regarding the optimal treatment for cervical and upper thoracic esophagus cancer. Using IMRT for cervical and upper thoracic esophageal cancer is believed to achieve excellent dose coverage and conformity of target volume coverage compared with that of 3D conformal radiotherapy. Therefore, we conducted the current study to evaluate IMRT technique in chemoradiotherapy for cervical and upper thoracic esophagus cancer.

We expected that the advantage in dose coverage of the PTV of IMRT would lead to improved local control compared to 3D conformal radiotherapy. However, in previous studies, there were not apparent difference in either locoregional control or PFS existed between the groups [8, 9, 10]. Interestingly, some recent reports of patients treated with both modalities showed advantages in terms of the clinical outcomes of IMRT [11, 12]. According to Ito et al (2017), IMRT had a significantly better 3-year OS than 3D conformal radiotherapy (81.6% vs. 57.2%; p = 5). Ito et al suggested 2 major reasons for this survival difference. The IMRT planning might minimize the high-dose area surrounding normal tissue, increasing the possibility of sufficient salvage treatment. Another reason was that the 2 groups were treated in different eras; hence, several biases can be correlated with the difference in the OS rates between the

2 groups. There was a difference in the rate of successful salvage treatment between the groups. In our study, using IMRT - SIB in concurrent CRT initially provided a good outcome about 1-year OS, 2-year OS were 66.3%, 51.6%, respectively.

Table 5: Results of radiotherapy for cervical esophagus cancer in previous reports.

Authors	Year	No. of patients	Irradiation method	Radiation dose, (Gy)	Chemotherapy rate	OS
Zhang et al [8]	2015	102	3D/IMRT	60	100%	3-y 39.3%
Cao et al [9]	2016	64	IMRT	64	34%	2-y 42.5%
Yang et al [10]	2016	78	3D/IMRT	60 - 70	28%	2-y 56.2%
Zenda et al [11]	2016	30	3D	60	100%	3-y 66.5%
Ito et al [12]	2017	80	3D/IMRT	60	100%	3-y 66.6%
		32	IMRT	60	100%	3-y 81.6%
Haefner et al [13]	2017	49	3D	55.4	100%	3-y 35.5%
		44	IMRT	55.4	100%	3-y 50.9%
Current study	2018	32	IMRT	60 - 66	100%	2-y 51.6%

Although there is still little debate that IMRT theoretically allows for safer dose-escalation. Dosimetric investigations have determined that advanced IMRT techniques provide numerical advantages over 3D CRT, but without outcome differences. This particularly applies to a reduction of high dose exposure to the OAR. We experienced no severe pulmonary toxicity using IMRT planning. Although IMRT planning would increase low dose exposure to the lung, leading to a potential increase in radiation pneumonitis, no grade 4 pulmonary toxicity developed in the present series; thus, we believe that pulmonary toxicity was acceptable in the IMRT radiotherapy.

The potential limitations of our study are the nature of a retrospective analysis, relatively small sample size and that it was a single institution experience.

CONCLUSION

We find that using IMRT in definitive CRT for cervical and upper esophageal cancer provided a good outcome and tolerable acute toxicities, with a two-year OS of 51.6%. IMRT is an excellent option for the treatment of patients with cervical and upper thoracic esophagus cancer.

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