Original Research Article

Predictive factors of esophageal stricture after definitive chemoradiation therapy for esophageal carcinoma: A retrospective single institute study

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Abstract

Background: Esophageal cancer is the eighth most common cause of cancer. Chemoradiation is the well established approach for treatment of esophageal carcinoma. Radiation-induced esophageal stricture is one of the most common late complications of RT usually occurs 3–8 months after completion of RT. Esophageal stricture is often observed after radiation therapy despite good tumor response and hence the quality of life (QOL) suffered. The purpose of this to identify patient, tumor, and treatment factors that have a significant impact on the likelihood of developing esophageal stricture following definitive chemoradiation therapy (CRT) for esophageal/ gastroesophageal junction (GEJ) carcinoma. **Methods:** Retro one year audit of 40 patients with biopsy proven esophageal cancer who underwent definitive concurrent chemoradiationin Department of radiation oncology at Guru Gobind singh medical college and hospital. Barium swallow was performed for all patients within 3 months after completion of the radiation therapy and the esophageal stricture was evaluated. We then tried to establish the correlation between the stricture levels after radiation therapy. Time to stricture was defined as elapsed time from completion of RT to first dilatation. Prophylactic dilatations were not performed. Multiple patient, treatment, and tumor characteristics were evaluated in terms of risk for stenosis and was statistically evaluated. **Results:** Tumor location was significantly associated with stricture risk, with more superior tumors having higher rates of stricture. Patient age, sex, current or previous smoking history, alcohol use, stage group, RT technique, and the use of a dose above 54 Gy were not associated with stricture risk.**Conclusions:** Female sex, extent of circumference involved, site of the disease, severe esophagitis during radiotherapy are important factors predicting occurrence of post radiotherapy stricture in carcinoma esophagus.

Key Word: Carcinoma esophagus, Post-Radiation Stricture, Chemoradiation.

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INTRODUCTION

Esophageal cancer is the seventh most common cause of cancer, with 572,034 new cases and 508,585 deaths estimated worldwide in 2018, making it the sixth most common cause of death from cancer [1].The treatment of carcinoma esophagus with tri-modality approach includes surgery, chemotherapy and radiation, has become the standard of care in resectable, localized disease in patients who are medically fit and willing to go for surgery. However, in patients who do not undergo surgery, definitive chemoradiation is the standard of care[2,3,]The most common acute toxicity following chemoradiation for carcinoma esophagus include dysphagia, dehydration, mucositis, esophagitis, dermatitis, and fatigue. Radiation-induced esophageal stricture is one of the most common late complications of radiotherapy usually occurs 3–8 months after completion of radiotherapy. Other common

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late complication of chemoradiation therapy being fistula formation [4]. The molecular mechanisms involved in acute and delayed toxicity have still not been fully elucidated, although microvascular injury is reported to be involved in both the early and the late phases. Stricture of the esophagus seen after External Beam Radiotherapy is mainly characterized by fibrosis caused by progressive obliterative endarteritis, leading to ischemia of the esophageal wall. In addition to fibrosis, there is also an effect on muscle motor activity controlling swallowing through the upper segment of the esophagus[5,6]. Esophageal stricture is often observed after radiation therapy despite good tumor response and hence the quality of life (QOL) sufferedThe exact mechanism and also the risk factors associated with the development of esophageal stricture after treatment with chemoradiation in carcinoma esophagus have not been established.However, different anatomical sites of the disease, circumference of esophagus involved, length of esophagus involved,tumor stages, sex of the patient, acute toxicity in form of esophagitis during the chemoradiaton and other causative factors may have key roles in the pathogenesis of stricture formation and, therefore, need to be defined. The purpose of this to identify patient, tumor, and treatment factors that have a significant impact on the likelihood of developing esophagealstricture following definitive chemoradiation therapy (CRT) for esophageal/ gastroesophageal junction (GEJ) carcinoma.

MATERIAL AND METHODS

To identify patient, tumor, and treatment related factors having significant impact on the likelihood developing esophageal stricture following definitive chemoradiation therapy (CRT) for esophageal/ gastroesophageal junction (GEJ) carcinoma.Retro one year audit of 40 patients with biopsy proven esophageal cancer who underwent concurrent chemoradiation in Department of radiation oncology at Guru Gobind Singh medical college and hospital. All patients were treated using conventional technique with Co-60 teletherapy unit (Theatron).Barium swallow performed for all patients monthly after completion of the radiation therapy and the esophageal stricture evaluated. Time to stricture -defined as elapsed time from completion of RT to first dilatation. Prophylactic dilatations not performed.All procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 1983.Multiple patient, treatment, and tumor characteristics evaluated in terms of risk for stenosis and statistically evaluated.

RESULTS

Patient characteristics: The median age of the patients was 50 years (30-72 years). Out of the total 40 patients 62.5 per cent were males and 37.5 per cent were females. Majority of the patients belonged to rural background. Most of the patients (82.5 per cent) had grade 3 dysphagia at presentation. 32.5 per cent of the patients had more than 10 per cent weight loss at presentation. History of tobacco smoking was present in 17.5 per cent of the patients, 32.5 per cent of the patients had history of alcohol intake. 75 per cent of the patients had hot and spicy diet pattern (table 1). Most of the patients had locally advanced disease. Median length of tumour involvement of the oesophagus was 5.0 cm (range, 2.8-11.5). 62.5 per cent of the patients had 100 per cent circumferential involvement of the disease and 72.5 per cent had more than10 mm maximum thickness of the disease. 42.5 per cent of the patient had disease in middle one-third of esophagus 27.5 per cent in upper one-third and 30 per cent in lower one-third of the esophagus (table 2).

Table 1: Patient characteristics

Patient characteristics		Number of patients	Stenosis	
			Yes	No
1. Age	≤ 50	26(65%)	11	15
	>50	14(35%)	09	05
2. Sex	M	25(62.5%)	08	17
	F	15(37.5%)	12	03
3.Socioeconomic Status	Rural	33(82.5%)	16	17
	Urban	07(17.5%)	04	03
4.Grades Of Dysphagia	I		0	
	II		0	
	III	33(82.5%)	15	18
	IV	07(17.5%)	05	02
5. Weight Loss At Presentation	<10%	27(67.5%)	11	16
	>10%	13(32.5%)	09	04
6.Smoking	Yes	07(17.5%)	03	04
	No	33(82.5%)	17	16
7.Alcohol Intake	Yes	13(32.5%)	07	06
	No	27(67.5%)	13	14

8. Hot And Spicy Food Intake	Yes	30(75%)	17	13
	No	10(25%)	03	07
9. Hb	≤ 10g/dl	14(35%)	09	05
	>10g/dl	26(65%)	11	15

Table 2: Tumour characteristics

Tumour characteristics			Number of patients	Stenosis	
				Yes	No
1. Length of involved segment		≤ 5 cm	12(30%)	07	05
		>5 cm	28(70%)	13	15
2. Circumferential involvement		< 100%	5(12.5%)	01	04
		100%	35(87.5%)	29	06
3. Maximum thickness		≤10 mm	11(27.5%)	05	06
		>10 mm	29(72.5%)	15	14
4. Histopathology	Squamous cell carcinoma	W.D.	03(7.5%)	03	00
		M.D.	14(35%)	05	09
		P.D.	04(10%)	03	01
		NoS	18(45%)	09	09
	Adenocarcinoma		01(2.5%)	0	1
5. Regional lymph node involvement		N0	24(60%)	13	01
		N+	16(40%)	07	09
6.Site of disease		Upper 1/3	11(27.5%)	09	02
		Middle 1/3	17(42.5%)	09	08
		Lower 1/3	12(30%)	02	10

Table 3: Treatment characteristics

Treatment related factors		Number of patients	Stenosis	
			Yes	No
1. Treatment modality	Conventional	34(85%)	16	05
	Conformal	06(15%)	04	15
2. Duration of treatment	≤ 5.5 weeks	30(75%)	14	04
	>5.5 weeks	10(25%)	06	06
3. Type of concurrent chemotherapy	Taxane based	04(10%)	02	06
	Cisplatin	29(72.5%)	17	14
	Cisplatin +capecitabine	01(2.5%)	0	
	Capecitabine	01(2.5%)	0	
	No CCT	05(12.5%)	01	
4. Radiation dose	≤ 50 Gy-50.4Gy	09(22.5%)	04	01
	>50.4Gy	31(77.5%)	16	09
5. RTOG acute toxicity ,esophagitis	Grade 1	26(65%)	07	02
	Grade 2	11(27.5%)	10	08
	Grade 3	03(7.5%)	03	10
	Grade 4	00	00	

Treatment characteristics: Most of the patients (85 per cent) were treated using conventional technique. Median dose of radiotherapy delivered was 54 Gy (45-6 Gy) with 72.5 per cent of the patients receiving weekly cisplatin as the concurrent chemotherapy (table 3).Grade 1, 2 and grade 3 esophagitis occurred in 65 per cent, 27.5 per cent and 7.5 per cent of the patients respectively. Twenty out of forty patients developed stenosis within a median of six months (2-12 months) after completion of chemoradiation. Factors showing a significant correlation with post RT stenosis (table 4) were female sex (p-value, 0.003), 100% circumference involvement of the disease (p-value, 0.031), site of the disease (82% of the patients with disease in upper 1/3 and 53% in middle 1/3 and 16.6% in lower 1/3developing post RT stricture, p-value:0.007) and grade of esophagitis during chemoradiation (100% of the patients with grade 3 esophagitis,90% with grade 2 and 27% with grade1 esophagitis developing post RT stricture,p-value:0.0001). All the stenosis were evaluated endoscopically and by biopsy and only two were found to be positive for malignancy but were statistically insignificant due to small number of patient study population.

Table 4: Factors influencing occurrence of post radiotherapy stenosis

Characteristics		Number of patients	Stenosis		p-value
			Yes	No	
1. AGE	≤ 50	26(65%)	11	15	0.185
	>50	14(35%)	09	05	
2. SEX	M	25(62.5%)	08	17	0.003
	F	15(37.5%)	12	03	
3. Involvedcircumference	<100%	05(12.5%)	01	04	0.031
	100%	35(87.5%)	29	06	
4. Site of disease	Upper 1/3	11(27.5%)	09	02	0.007
	Middle 1/3	17(42.5%)	09	08	
	Lower 1/3	12(30%)	02	10	
5. Total length invovlved	<5 cm	28(70%)	07	05	0.49
	>5 cm	13(32.5%)	13	15	
6. Maximum thickness	≤10 mm	11(27.5%)	05	06	0.72
	>10mm	29(72.5%)	15	14	
7. Radiation dose	<50Gy-50.4Gy	09(22.5%)	07	06	1.000
	>50.4Gy	31(77.5%)	13	14	
8. RTOG acute toxicity,esophagitis	Grade 1	26(65%)	07	02	0.0001
	Grade 2	11(27.5%)	10	08	
	Grade 3	03(7.5%)	03	10	
	Grade 4	00	00		

DISCUSSION

Chemoradiotherapy (CRT) has an important role in the treatment of esophageal cancer in both the inoperable and the pre-operative settings. One of the most common late toxicity of Chemoradiation therapy in carcinoma esophagus is radiation induced esophageal stricture [4]. A knowledge and evaluation of the factors predicting the risk of developing Post radiation therapy esophageal stricture might be useful while treatment planning. If severe esophageal stenosis develops despite tumor regression by radiotherapy, patients will experience dysphagia, which will decrease their quality of life.Although detailed mechanisms of post Radiotherapy stricture formation has not been clarified yet but it may be caused by fibrosis or ishemic changes during the process of tumor reduction as a result of radiation. Seaman *et al* reported that patients with dysphagia after radiotherapy to the chest and neck show histologic evidence of fibrosis of the submucosa, and hyalinization of the smooth muscle layers of the esophagus. These processes probably include the accumulation of macrophages and increased local levels of proinflammatory. Proinflammatory cytokines induced by radiation, producing edema and fibrosis in the mucosal and submucosal layer that may secondarily affect the underlying muscles[7-10]. These processes may be much more pronounced in and around the shrinking tumors that respond well to radiotherapy. As a result, the involved circumference may show the most significant correlation with the severity of esophageal stenos is after radiotherapy[4,7]. There are very few reports stating the risk factors for esophageal stenosis post radiotherapy of esophageal carcinoma. In this study female sex (p-value,0.003) , 100% circumference involvement of the disease (p-value, 0.031) ,site of the disease (82% of the patients with disease in upper 1/3 and 53% in middle 1/3 and 16.6% in lower 1/3developing post RT stricture, p-value:0.007) and grade of esophagitis during chemoradiation (100% of the patients with grade 3 esophagitis,90% with grade 2 and 27% with grade1 esophagitis developing post RT stricture,p-value:0.0001) were the significant factors predicting the occurrence of post RT esophageal stricture after radiotherapy in esophageal carcinoma.In a study published in JCO in February 2017 by Natsuko Tsushita *et al*, obstructions before CRT, hypoalbuminemia and severe esophagitis during CRT are considered as risk factors of benign post RT stricture[11].L. Zamdborg *et al*, in their study also concluded that tumour location was significantly (P = 0.009) associated with stricture risk, with more superior tumours having higher rates of stricture[12].T stage, extent of involved circumference, and oesophageal wall thickness of the tumour region were useful predictive factors for acute oesophageal stenosis associated with tumour regression in radiotherapy by Atsumi *et al*[7]. Patients with more superior oesophageal tumours tend have higher rate of post radiotherapy stricturesEBRT dose did not appear to affect the estimated incidence of stricture. Dose escalation may be feasible in the inferior esophagus without affecting the rate of stricture. Prophylactic treatment should be established for esophageal carcinoma patients with risk factors of cicatricial stricture. The limitations of this study was its retro prospective nature and small sample size. More prospective trials with larger sample size are recommended for further investigating the factors

predicting the development of post radiation esophageal stricture in patients with carcinoma esophagus.

CONCLUSION

Female sex, extent of circumference involved, site of the disease, severe esophagitis during radiotherapy are important factors predicting occurrence of post radiotherapy stricture in carcinoma esophagus.

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