



Radiation Schedules for Palliation in Carcinoma Esophagus

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This study was undertaken to compare the three different radiation schedules for their efficacy in symptom relief, dysphagia free survival and radiation morbidity (if any), in carcinoma oesophagus. A total of 116 inoperable patients were prospectively randomized to three different arms of radiation. Arm-A received external beam radiation (EBRT) to a dose of 30Gy/10 #/2 weeks along with two sessions of intraluminal brachytherapy (ILBT), 600cGy each, one week apart, after a gap of two weeks from EBRT. Arm-B received only EBRT to a dose of 30Gy/10 #/2 weeks. Arm-C received EBRT to a dose of 20Gy/5#/1week without brachytherapy. The age of the patients ranged from 30 - 70 years. Improvement in dysphagia was seen in 76% of patients in Arm-A, 56% in Arm-B & 54% in Arm-C at 1 month. The dysphagia progression free survival was 10.6+0.6 months in Arm-A, 9.8+0.8 months in Arm-B and 9.9+0.6 months in Arm-C respectively. Grade 1 & 2 acute radiation toxicity was seen in 50% of patients in Arm-A, 55% patients in Arm-B & 30% patients in Arm-C. It is concluded that all the three radiation schedules achieved good palliation with similar dysphagia free survival.

Key words

Carcinoma esophagus, Radiation, Palliation, ILBT

Introduction

Carcinoma esophagus is the seventh most common cancer worldwide(1). Worldwide incidence varies from 2.5 to 5.0 per 100,000 in men and 1.5 to 2.5 per 100,000 in women(2). Unfortunately, about 60-70% of these patients are undernourished and already in advanced stage of disease at presentation(3). The 5-year survival rates are only between 10-20%. So the main objective of treatment in these patients is only palliative, to relieve dysphagia with minimum morbidity and with better quality of life.

Radiotherapy remains the mainstay in palliation of carcinoma esophagus with certain distinct advantages over other modalities. Radiotherapy is cost-effective, produces fewer complications, can be given on an outdoor basis, and is readily acceptable to most of the patients. Radiotherapy can be given as external beam, intraluminal brachytherapy or both in combination. Owing to the anatomy and location of esophagus it is extremely difficult to deliver sufficient dose of radiation

to esophagus alone without affecting the neighboring vital structures except with brachytherapy.

Our study was designed to evaluate the different EBRT schedules with or without brachytherapy in that subset of patients who are considered for palliation only.

Material and Methods

Between June 2002 to June 2005, 116 patients with advanced, inoperable carcinoma esophagus attending the outpatient services of the department of radiotherapy were prospectively considered eligible for the study on the basis of the following selection criteria such as; biopsy proven squamous cell carcinoma, tumor more than or equal to 5 cm in length on endoscopy and/or barium swallow, surgically inoperable disease, age; 17 to 70 years, Karnofsky performance score > 50 and no prior malignancy in the past 5 years. Tippet's random number table was used for randomization of patients in three arms. Informed written consent was taken from all patients.

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All the patients initially were examined clinically and routine base line investigations were done and recorded for each patient viz. a hemogram, biochemical profile including liver function tests, renal function tests and a chest X-ray. Site, length and type of growth were confirmed by barium swallow/endoscopy. An ultrasound of the abdomen was done to rule out any metastasis in liver and in coeliac group of lymph nodes. After a complete investigation of the patients, they were planned according to the treatment scheme as; Arm-A: 30Gy/10#/2weeks EBRT followed by 2 weeks gap and ILBT 600cGy per session x 2 one week apart, Arm-B: 30Gy/10#/2weeks and Arm-C: 20Gy/5#/1 week EBRT only.

External Beam Radiotherapy

The patients were planned on a simulator and following barium swallow examination, fields were marked and checked under fluoroscopic vision or on taking an x-ray. The fields used were a pair of parallel opposed AP-PA fields so as to cover the tumor adequately along with safety margin of 5 cm proximally and distally and 2-3 cm laterally. Radiotherapy was delivered with megavoltage photon beams either on Co-60 teletherapy unit or a 6 MV linear accelerator.

Intraluminal Brachytherapy

ILBT treatment was given on out patient basis and patients were taken up for endoscopy and esophageal bougie insertion. A mouth gag was placed inside the mouth; a stainless steel guide wire was inserted through the endoscope. After that the endoscope and the mouth gag were withdrawn leaving the guide wire in situ across the tumor site in the esophagus.

A Pagliero-Rowland type of selection bougie was used for treatment. The guide wire was gradually withdrawn and the facemask firmly strapped over the mouth of the patient. It was ensured that the mask of the bougie was placed at such a length such that the total treating length was at least 1-2 cm below the lower limit of the original lesion.

Treatment Planning

The patient with the bougie in situ was then wheeled into the simulator room where after placing the dummy pellets inside the applicator; orthogonal antero-posterior and lateral x-ray were taken. Planning was done using the PLATO treatment planning system. Dose was prescribed at 1 cm from the central source axis.

After completion of the treatment schedule, all patients were on regular follow up. The schedule for the same was as every fortnightly for one month, monthly for three months and quarterly for six months. At every visit patient underwent a complete clinical examination for the assessment of symptom relief, radiation morbidity. Barium swallow and endoscopic examination was done at three monthly intervals. Statistical analysis was done at a median follow-up of nine months (range, 3-34 months).

Assessment of dysphagia relief was done using WHO grading(4). Acute and late radiation morbidity was assessed using the EORTC/RTOG criteria (5).

Results

Most of patients in all the arms were seen in 5th-7th decades. Mean age of the patients in Arm-A was 58 years, in Arm-B it was 56 years and in Arm-C mean age was 54 years as shown in Table 1. The incidence of disease was almost twice among males as compared to females (1.8:1). Most of the patients (57.8%), in the three arms had lesion in middle one-third, followed by lower one-third (31%). All the patients had biopsy proven squamous cell carcinoma, the commonest was squamous cell carcinoma NOS (50%). Keratinizing type was seen in 28.4% of patients. The endoscope was not negotiable in 71% of patients at the time of presentation, due to the advance stage of disease.

Table 1. Patient characteristics

Characteristics	Arm- A	Arm- B	Arm- C
Age			
Mean	58	56	54
Sex			
Male	21	21	22
Female	17	19	16
Location of lesion			
Upper 1/3	8	7	8
Middle 1/3	20	17	20
Lower 1/3	10	16	10
Histology			
SCC -Keratinizing	15	8	10
SCC -Non Keratinizing	8	9	8
SCC -NOS	15	23	20
Endoscopic status			
Negotiable	18	12	8
Not negotiable	20	28	30

Symptom Relief

At 1 month, 76% of patients in Arm-A had shown improvement in dysphagia while 18% did not show improvement and 6 % patients were lost to follow-up. In Arm-B 59% patients had shown improvement in dysphagia while 33.3% did not show improvement, 5.7 % patients were lost to follow-



up. In Arm-C, 54% had shown improvement in dysphagia while 32% did not show improvement while 14% lost to follow-up.

Improvement in Mean Dysphagia Grade

When the percentage improvement in mean dysphagia grade as a function of time was studied; it was found out that it peaked to maximum at 1 month in all the three arms. Out of all three arms, Arm-A had maximum improvement of 36.7%, followed by Arm-B 28.6%. After 1 month there was no further improvement in dysphagia in all the three arms. At 6 months, improvement in mean dysphagia grade in Arm-A was 21%, in Arm-B it was 15.6%; while in Arm-C it was only 14.2%. The percentage improvement in mean dysphagia grade in various arms with time duration after radiotherapy was as shown in Table-2.

TABLE -2. Improvement in Mean Dysphagia Grade

TREATMENT ARM	15 DAYS	1 MONTH	3 MONTHS	6 MONTHS
Arm A	28.6%	36.7%	24.5%	21.0%
Arm B	26.5%	28.6%	22.3%	15.6%
Arm C	17.8%	27.9%	18.3%	14.2%
Total	24.3%	31.0%	21.7%	16.9%

Barium/endoscopy Response

On barium swallow / endoscopic assessment; at 3 months of interval in Arm-A 68.8% of patients had shown improvement while 32.2% had stable disease. In Arm-B 61.2% had improvement and 39.8% were with stable disease. In Arm-C, only 45.6% patients had improvement. At six months, 53.8% of patients in Arm-A had improvement and 26.6% had stable disease. In Arm-B results were 33.6% and 24.6% respectively. In Arm-C only 22.6% of patients had improvement, while 16.9% had stable disease. The arm wise distribution was as shown in Table-3.

Table -3. Barium / Endoscopic response

Treatment Arms	3 Month		6 Months	
	Improvement	Stable disease	Improvement	Stable disease
A	26(68.8%)	15(39.2%)	20(53.8%)	9(26.6%)
B	24(61.2%)	16(39.8%)	13(33.6%)	10(24.6%)
C	17(45.6%)	16(41.2%)	9(22.6%)	6(16.9%)

Complications

Tracheo-esophageal fistula formation was seen in one patient in Arm-C at 3 months and one patient in Arm-B at 6 months. Most of the patients had only grade 1&2 radiation toxicity. The toxicity score are as shown in Table 4.

Additional procedures to restore feeding

Additional procedures to restore feeding (in form of naso-gastric tube insertion, endoscopic dilatation/

Table -4. Radiation toxicity

Toxicity score		Arm	Arm	Arm	Total
		A	B	C	
1 mo	0	4	8	7	19
	1	12	9	7	28
	2	5	1	1	4
3 mo	0	5	5	7	16
	1	1	6	5	18
	2	3	4	0	7
6 mo	0	3	2	2	7
	1	4	3	2	9
	2	1	2	2	5

Table 5a. Additional procedures to restore nutrition

Procedures	Treatment Arms			
	A	B	C	Total
At 3 months				
RT insertions		2	4	6
Endoscopic dilatation	4	4	3	11
Endoscopic Stenting			1	1
Feeding jejunostomy		1	2	3
Total	4	7	10	21

Table 5b. Additional procedures to restore nutrition

Procedures	Treatment Arms			
	A	B	C	Total
At 6 months				
RT insertions	2	4	6	12
Endoscopic dilatation	4	3	1	8
Endoscopic Stenting	2	1		3
Feeding jejunostomy		2	2	4
Total	8	10	8	26

stenting or feeding jejunostomy) were required in 4 patients at 3 months and 8 patients at 6 months in Arm-A. In Arm-B, 7 patients at 3 months and 10 patients at 6 months needed additional procedures. In Arm-C, 10 patients at 3 months and 8 patients at 6 months needed additional procedures.

Dysphagia Progression Free Survival

The follow up of the patients ranged from 3 months to 34 months. Applying Kaplan Meier analysis, mean dysphagia progression free survival was as; Arm-A: 10.6 0.6 months, Arm-B: 9.8 0.8 months and Arm-C: 9.9 0.6 months respectively. The difference in three arms was not significant by Log rank analysis ($p = 0.26$)

Discussion

For a long time, surgical procedures were done to relieve dysphagia; however studies have shown that the relief of dysphagia is similar with both the modalities radiotherapy and surgery. Above all radiotherapy is a noninvasive procedure with minimal morbidity and mortality and it also control disease progression for quite a few months, hence radiotherapy is a better modality for palliation in carcinoma esophagus.

Table - 6. Studies with Combination of EBRT & ILBT

Author	Year	Regimen	Response (OR)	Median Survival (mo)
Dawe's et al ¹⁰	1989	30Gy EBRT +10Gy ILBT	-	19
Agarwal et al ¹¹	1992	20-50 Gy EBRT +10 Gy ILBT	92%	-
Kohek et al ¹²	1995	30Gy EBRT + 12.4Gy ILBT	96%	9
Schraube et al ¹³	1997	44GyEBRT +17.5Gy ILBT	97%	9
Datta et al ¹⁴	1998	35 Gy EBRT + 12 Gy ILBT	49%	8
Hujala et al ¹⁵	2002	40Gy EBRT +10GyILBT	40%	-
PRESENT STUDY	2005	30 Gy EBRT + 12 Gy ILBT	76%	10

Abbreviations – EBRT, external beam radiation therapy; ILBT, intraluminal brachytherapy and OR, overall response.

Many studies have been done with hypofractionation in squamous cell carcinoma at other sites for palliation. In our experience, with a dose of 20 Gy /5#/1 week good palliation was noticed, 54% patients had shown relief of symptom at one month after radiotherapy. Albertson *et al* (7) evaluated palliative effect of radiotherapy for esophageal cancer with a dose of 40-45 Gy at a rate of 2 Gy/#. About 45% of patients experienced relief of dysphagia within 2 months of radiotherapy. Although the symptomatic relief is comparable to the present study but it has added advantage of short over all treatment time. By the time acute reactions develop treatment is

already over so patient need not stay for longer time in the hospital.

Rathi *et al*(8) in their study have evaluated swallowing performance after giving 40Gy/4 weeks as palliative EBRT with overall response rate of about 80%. In our study with the radiation dose of 30Gy/10#, 56% patients had shown relief of dysphagia at one month after EBRT. So only one study has been reported in literature by Kelsen *et al* (9), where 20Gy/5#/1wk has been used in carcinoma esophagus in advanced stage with palliative intent they, also reported median survival of 9 months which is comparable to the present study.

During the recent years some trials have been conducted where chemotherapy has been added to radiation to improve treatment outcome however such combined modalities cannot be applied to all patients due to advanced stage of the disease, poor nutritional status, old age, poor KPS and other comorbid conditions not allowing extensive treatment. So, for these advanced stage patients radiotherapy is still the treatment of choice.

Some of the studies done using combination of EBRT and ILBT for palliation are shown in Table 6. It can be seen that various authors have used different dose schedules; but in most of them the median survival is only 9 months. Although there is no difference in overall survival but symptoms relief is definitely better with combined EBRT and ILBT. In the present study, with combination of EBRT and ILBT, symptom relief was seen in 76% of the patients at 1 month after radiotherapy, which is in the range of response reported in various studies (Table 6). EBRT in combination with ILBT gives better palliation and less complication than either of these used alone. Initial EBRT causes rapid shrinkage of tumor so that ILBT can be done with ease. ILBT delivers high dose locally so good local control can be achieved with limited complications. High dose rate (HDR) ILBT has further advantage that treatment is quick and therefore discomfort from having esophageal bougie in place for a long period is avoided.

Only grade1 & grade 2 radiation morbidity (RTOG grades) was seen in 40.3% of the patients in acute phase (3 months) and 22.6% patients in chronic phase (6months) in all the arms in toto. The fistula formation was there in only 2 patients, one each in Arm-B and Arm-C. The ulceration and stricture formation which required



additional procedures (like Ryle's tube insertion / stenting / feeding jejunostomy) were there in 31.5% of the patients in Arm-A and 42.5% in Arm-B and 47.3% of the patients in Arm-C respectively (Tables 5a & 5b). All of these patients had local disease on endoscopy. In combined EBRT and ILBT intervention was required due to stricture formation and in other two arms it was due to disease progression. Similar results are reported in various series in which palliative doses of radiotherapy were given. Datta *et al*(14) reported morbidity in the form of ulcers, strictures and fistulae were observed in 9%, 7% and 5% of patients treated with low dose as compared to 8%, 8% and 13% in those with high dose respectively. Sharma *et al*(16) found that 12 Gy in 2 fractions (6Gy per fraction) in advanced carcinoma esophagus gives dysphagia free survival of about 10 months. Overall complication rate was 30% with strictures seen in 15%, ulceration in 10% and fistula in 5%.

Conclusion

Carcinoma of esophagus is an extremely discouraging disease to treat as most patients present in advanced stage and in poor general condition when curative options are limited. Treatment is by palliative intent in most cases. Role of radiotherapy is well established for palliation of symptoms in carcinoma esophagus. Any of the three radiation schedules achieve good palliation with minimal morbidity.

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