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Assessment of the Efficacy of External Beam Radiotherapy Followed By Intraluminal Brachytherapy in Palliation of Dysphagia in Patients with Carcinoma Oesophagus.

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Abstract: *The management of locally advanced carcinoma oesophagus is challenging.Various modalities of treatment are available for palliation of dysphagia, but there is no consensus regarding the best method. Studies have shown combination of high dose-rate brachytherapy (HDRBT) and External Beam Radiation Therapy (EBRT) is superior to HDRBT alone for the palliation of oesophageal cancer. Our study aim is to assess efficacy of external beam radiotherapy 30Gy followed by intraluminal Brachytherapy 16Gy (8Gy per fraction).A total 30 adult subjects (both male and females) of aged ≥ 18, years were for in this study, conducted in department of Radiation oncology, Madras medical college.Between October 2016 to September 2017, 30 patients who met the criteria of the protocol were recruited. The duration of radiation therapy was 5 weeks.The response rate observed 73.3%.this single arm prospective study showed that a combination of external beam radiation therapy and high dose rate Intraluminal brachytherapy can produce acceptable rates of dysphagia relief with little complications.*

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I. Introduction

Oesophageal carcinoma accounts for approximately 1% of all malignancy and 6% of all gastrointestinal malignancy, Fatality rates are high. It is the sixth most common cause of death. In India it is the sixth most common cancer in male and eight most common among female[1]. Oesophageal carcinoma is usually presents as locally advanced and metastatic having a considerable decline in health-related quality of life (HRQoL) with poor prognosis[2]. In more than 50% of cases with an advanced stage disease not suitable to surgery.Dysphagia is the most common and clinically relevant symptom. The main objective of treatment remains palliation of dysphagia. Various palliative treatment modalities have been used as an attempt to relieve dysphagia and improve patient quality of life until death.[3,4]. Treatment options include surgical, laser treatment, stent placement, photodynamic therapy, bypass surgery, chemotherapy, external beam radiation therapy (EBRT) and brachytherapy. The main aim of treatment for patients with locally advanced and metastatic oesophageal cancer remains continuing oral intake until death. Recently published guidelines by the European Society of Gastrointestinal Endoscopy (ESGE), European Society of Radiotherapy and Oncology (ESTRO), European Society for Medical Oncology (ESMO)[5] strongly recommend brachytherapy with palliative purpose as a valid alternative to stenting in patients with dysphagia and longer life expectancy. Despite this strong recommendation, brachytherapy is underused and infrequently considered for the management of malignant dysphagia, possibly because of the unawareness of its usefulness[6]. In many centres good palliation has been achieved with combination of external beam radiation with brachytherapy[7]

II. Material &Methods

This prospective study was carried out on patients of Department of Radiation oncology at Madras Medical College, Chennai, Tamil nadu, India.A total 30adult subjects (both male and females) of aged ≥ 18, years were for in this study.

Inclusion Criteria:

1. endoscopic and biopsy proven carcinoma of oesophagus, either squamous cell carcinoma or adenocarcinoma.
2. lesion of thoracic oesophagus but not involving the cardia of stomach.
3. locoregionally advanced disease not amenable to curative treatment.

4. metastatic disease when the predominant symptom was dysphagia.
5. informed consent singed prior to the study.

Exclusion Criteria:
1. patients with tracheoesophageal fistula
2. patients with stricture oesophagus
3. patientssuitable for curative treatment with either surgery or chemoradiation disease within 2cm of the cricopharynx.
4. disease involving gastroesophageal junction
5. perforation or massive oesophageal bleeding
6. previous treatment for oesophageal cancer (chemotherapy, radio therapy, laser therapy)
7. pregnant women
8. evidence of synchronous lung primary

Sample Size: 30 patients

Investigation Details:
1. Complete history and physical examination
2. upper gastrointestinal endoscopy
3. biopsy of primary tumour
4. fibreoptic bronchoscopy
5. grading of dysphagia by modified takita's dysphagia scoring

Takita's dysphagia grading

Grade	
Grade I	Able to eat normally
Grade II	Require liquid with meals
Grade III	Able to take only semisolid foods
Grade IV	Able to take only liquids
Grade V	Able to swallow saliva but not liquid
Grade VI	Complete dysphagia

Laboratory studies
1. complete blood count with differential count
2. serum sodium,
3. Serum potassium,
4. Blood glucose,
5. blood urea,
6. serum creatinine

Radiographic studies
1. chest x-ray
2. contrast enhanced CT scan of thorax and abdomen

Patient preparation
1. All patients were persuaded to quit smoking and alcohol
2. Nasogastric tube placement before the initiation of treatment
3. Patients were educated about the expected adverse effect like skin desquamation and odynophagia and how to tackle the day to day problems associated with it.

Treatment
Patients were treated both inpatient and out patients
External beam radiotherapy

Target volume
primary tumour with 2cm clearance in superior- inferior and circumferential aspects.

Portals
Patients are treated in opposing anterior and posterior portals daily with patients in supine position.

Physical factors –
1. cobalt 60 teletherapy unit
2. SSD 80 Cm

Dose fractionation
1. Total dose of 30 Gy in 10 fractions, 3Gy each fraction
2. In all patients' treatment was started on a Monday, 5 days a week for 2 weeks.

Dose prescription
Target dose was prescribed at midplane level between the anterior and posterior portals.

Treatment verification
Treatment portals were verified by simulation films

Intraluminal brachytherapy
Timing of delivery–
1. Intraluminal brachytherapy was delivered in two fractions separated by 1 week apart.
2. The first fraction was delivered approximately 1 week after last fraction of EBRT

Dose
1. HDR brachytherapy using ^{60}CO.
2. Dose of 16 Gy was delivered in two fractions, 8Gy each, spaced 1 week apart
3. target dose to be prescribed at 1 cm from source axis of the applicator.
4. The active length of application was tumour extent plus 1 cm on cranial and caudal ends

Applicator
Nasogastric tube was used as brachytherapy applicator in all patients.

Treatment planning:
1. Planning CT were taken with dummy in situ.
2. Superior and inferior extent of the tumour as evident by pre-treatment evaluation was marked and CT taken with dummy in situ
3. Treatment plan was evaluated with the help of isodose curves and 3-D dose distribution by treatment planning system

Anticipated toxicities:
1. Radiation induced esophagitis was expected and its timing with dose and severity were noted. Sucralfate was used in the management as indicated
2. Epilation and various degrees of skin reaction were expected in treated area
3. Oesophageal bleeding and hematemesis were anticipated
4. Possible late effects include stricture formation

Supportive care:
1. Adequate caloric intake was encouraged
2. Analgesics and sucralfate were prescribed for the management of odynophagia

Criteria for discontinuation of treatment
1. Patients refusal to continue study participation
2. Occurrence of unacceptable toxicity necessitating major modification of treatment. In this event, follow up continues according to protocol

Toxicity reporting
The revised RTOG grade was used to score acute radiation (<90days) toxicities associated with this protocol.

Patient assessment:
Complete history taking and physical examination were done prior to starting the treatment. Patients were seen daily during the treatment and complaints were attended to. Physical examination, body weight, hemogram, renal function and toxicity evaluation were done every week during radiotherapy

Response criteria:

In all patients' pre-treatment swallowing status was scored using modified takita's dysphagia scoring system on the first day of external beam radiotherapy, after completion of treatment, dysphagia was again evaluated 4 weeks after second fraction of brachytherapy

Evaluation after treatment

Monthly for first 6 months, every 2months for next 6 months and every 3 months and thereafter.
CT thorax and abdomen and endoscopy in first follow up.

Analysis of plan:

Dysphagia score assessment before and at 4 weeks after treatment using modified takita's dysphagia scoring system
systemic and acute radiation effects were scored using the radiation therapy oncology group (RTOG) acute toxicity criteria

Data Analysis:

The primary endpoint of the study was the comparison of the pre-treatment and post treatment dysphagia scores. Dysphagia scores were assessed before treatment and at 4 weeks after treatment using singed ranks test . Systemic and acute radiation effects were scored using the Radiation Therapy Oncology Group (RTOG) Acute toxicity criteria.

III. Result

STUDY POPULATION:

Between October 2016 to September 2017, 30 patients who met the criteria of the protocol were recruited. The duration of radiation therapy was 5 weeks. All patients received therapy as per protocol.

Age:

The median age of the study population was 58 years

Table 1

Age group (years)	Number of patients
31 – 40	3
41 – 50	9
51 – 60	12
61 – 70	6

Sex

18 (60%) patients were males and 12 (40%) patients were female

Table 2

Sex	Number of patients	Percentage
Male	18	60%
Female	12	40%

Performance status

3 (10%) patients had a performance status of ECOG 1, 16 (53.3%) had performance status of ECOG 2 and 11 (36.6%) had performance status of ECOG3

Table 3

Performance status	Number of patients	Percentage
1	3	10%
2	16	53.4%
3	11	36.6%

Presenting symptoms

Majority of the patients 24(80%) out of 30 had dysphagia as the presenting symptom while in others odynophagia was the presenting symptoms.

Table 5

Presenting symptoms	Number of patients	Percentage
Dysphagia	24	80%
Odynophagia	6	20%

Tumour characteristics:

16.6% tumour were in upper 1/3rd of thoracic oesophagus, 53.4% in middle 1/3rd and 30% in the lower 1/3rd of thoracic oesophagus.

Table 6

Location in thoracic oesophagus	Number of patients	Percentage
Upper 1/3rd oesophagus	5	16.6%
Middle 1/3rd oesophagus	16	53.4%
Lower 1/3rd oesophagus	9	30%

Histopathology:

Table 7

Histopathology	Number of patients	Percentage
Squamous cell carcinoma	24	80%
Adenocarcinoma	6	20%

80% of the patients had squamous cell carcinoma while 20% had adenocarcinoma.

T stage

70% of patients had T3 while 16.4% had T4a and 13.3% had T4b

Table 8

T stage	Number of patients	Percentage
T3	21	70%
T4a	5	16.4%
T4b	4	13.3%

OUTCOME ANALYSIS

Overall response

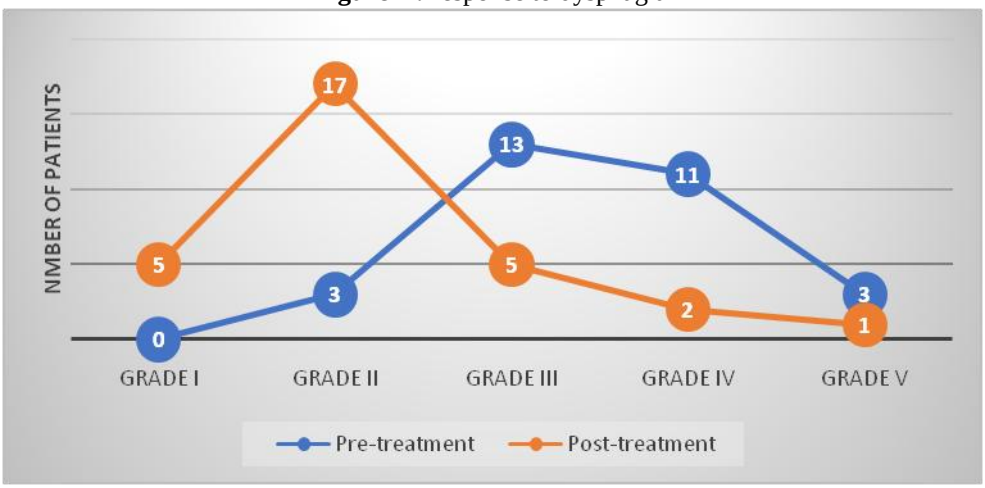
At 4 weeks after HDR brachytherapy the median dysphagia score improved from a **median of 3 to 2** Dysphagia had improved and swallowing had become easier in **22 patients** 7 patients maintained their pre-treatment swallowing status while 1 patients had worsening of dysphagia.

Eight patients with no improvement in dysphagia one had stricture formation confirmed by endoscopy.

Table 9

Dysphagia score	Pre-treatment	Post-treatment
Grade I	0	5
Grade II	3	17
Grade III	13	5
Grade IV	11	2
Grade V	3	1

Figure 1 . Response to dysphagia



No patients had normal swallowing before treatment while five patients had normal swallowing after treatment.

Response According To Patient Characteristics
Gender

Table 10

Gender	Number of patients treated	Number of patients with dysphagia improvement
Male	18	14
Female	12	8

14 male patients had improvement in dysphagia while of the 8 femalepatient had improvement in dysphagia.

Performance status

Table 11

Performance status	Number of patients	Number of patients with dysphagia improvement
1	3	3
2	16	12
3	11	7

3 Out of 3 (100%)patients with performance status of ECOG 1, 12 out of 16 (75%) patients with ECOG 2 and 7 out of 11 (63%) patients with performance status of ECOG 3 had improvement in dysphagia.

Response according to tumour characteristics:
Location in thoracic oesophagus:

Table 12

Location in thoracic oesophagus	Number of patients	Number of patients with dysphagia improvement
Upper 1/3rd oesophagus	5	4
Middle 1/3rd oesophagus	16	15
Lower 1/3rd oesophagus	9	3

4 Out 5 (80%) of patients with tumour in upper 1/3rd, 15 out of 16 (93%) patients with tumour in middle 1/3rd and 3 of 9 (33%) patients with tumours in lower 1/3rd of the oesophagus had improvement in dysphagia.

Histology

Table 13

Histopathology	Number of patients	Number of patients with dysphagia improvement
Squamous cell carcinoma	24	19
Adenocarcinoma	6	3

19 Out 24 (86.3%) of patients with squamous cell carcinoma and 3 out 6 (50%) of patients with adenocarcinoma had improvement in dysphagia.

Tumour size

Table 14

T stage	Number of patients	Number of patients with dysphagia improvement
T3	21	18
T4a	5	3
T4b	4	1

Figure 2 Response according to location

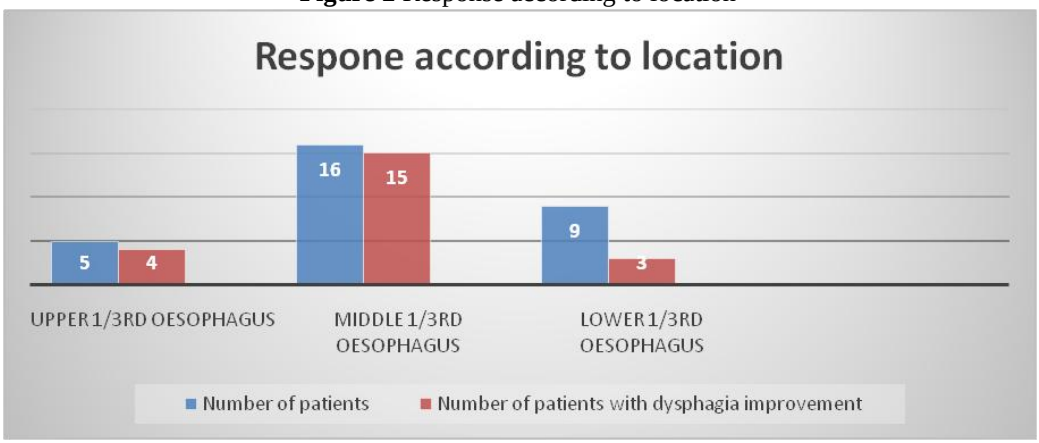
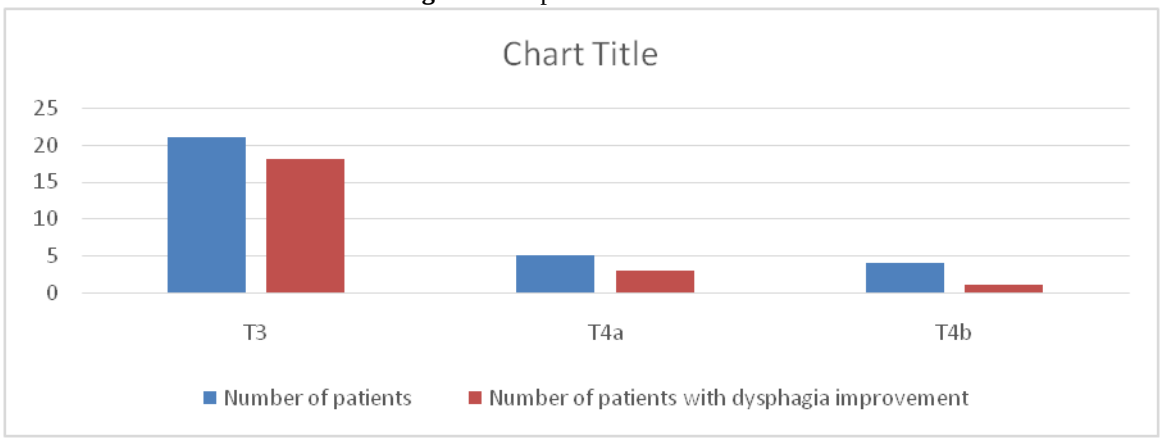


Figure 3 Response to tumour size



18 Out 21 (85%) patients with T3 tumour, 3 out 5(60%) of patients with T4a and 1 out of T4b had improvement.

Complications

One had stricture formation, 13 patients developed Grade 1 esophagitis, 8 patients developed Grade 2 esophagitis, 1 patients developed Grade 3 esophagitis

Serial dilation was attempted in one patient with stricture and was successful.

One Patients had feeding jejunostomy.

Recurrence of dysphagia

12 out of 22 (54.4%) had dysphagia free survival, 10 out 22(45.6%) had a recurrence of dysphagia. In all the patients there was progressive growth of residual tumour as seen by endoscopy.Further follow up is needed to evaluate the number of recurrence of dysphagia, the time for recurrence and overall survival.

IV. Discussion

At presentation most of the patients with carcinoma oesophagus have locally advanced disease or metastatic disease. Most cases surgeries are not feasible.Majority of the patient presenting with locoregionally advanced or metastatic disease, the most important goal of the treatment is to improve dysphagia rapidly with minimal or no hospital stay, and to maintain the ability to swallow during life thus improving the Quality of life.

Various modalities have been tried to achieve palliation of dysphagia. Radiotherapy has been successfully used for palliation of dysphagia. External beam radiotherapy, intraluminal brachytherapy or in combination is used

Hietet al[8] reported 92% success rate for dilatation and demonstrate safety for peroral dilatation for obstructing oesophageal cancer. David Fleischer et al[9] Symptomatic patients with dysphagia treated in palliative intent were treated endoscopically with the Nd:YAG laser. Photodynamic therapy is another method to relive dysphagia. Overall efficacy of photodynamic therapy is comparable to Nd:YAG thermal ablation..

Palliation of dysphagia due to oesophageal cancer by placement of peroral stents has been performed over 100 years but not safe and effective until late 1950s[83]. But most of these technique does not provide substantial relief of dysphagia.

Radiotherapy is one of the three conventional arms used for treatment of carcinomaoesophagus; radiation not only provide palliation of dysphagia but also decrease the recurrence by their action on primary site; radiotherapy is cheap compared to endoscopic procedures. Brachytherapy is one of the techniques in radiotherapy

Various combinations of external beam radiation and intraluminal brachytherapy has been tried. In a study conducted at Tata memorial Hospital Mumbai[9] palliative schedule of 16 Gy in 2 fractions HDR ILBT and 30 Gy in 10 fraction EBRT was compared with HDR ILBT alone in patients with locally advanced oesophageal carcinoma. Among 148 analysed 74 were found to be eligible for study. The median OS was 9 months with 1-year OS of 27%, the median duration of dysphagia relief was 3 months. Overall 47% had improvement in dysphagia score. 37% had dysphagia free survival. There was improvement in weight in 39%. 62.1% had residual disease. 27% had stricture, 5% had bleeding and 5% had fistulae formation. Study concluded that intraluminal brachytherapy is an effective mode of palliation of dysphagia.

In a study conducted by International atomic energy agency (IAEA) Rosenblatt et al[10] 219 patients were randomized to receive 16 Gy in 2 fractions of intraluminal brachytherapy prescribed at 1 cm from source centre, then patients randomized to EBRT received 30 Gy in 10 fractions or observed. Median follow-up was

seven months, with a median Overall Survival of 6 months and an 18% survival rate at 1 year. DRE was significantly improved with combined therapy, for an absolute benefit of +18% at 200 days from randomization. In analyses, scores for dysphagia, odynophagia, chest pain, regurgitation and performance status were all significantly improved. In contrast, weight, toxicities and overall survival were not different between study arms.

Present study:

In present study eternal beam radiation was delivered to a dose of 30Gy in 10 fractions and HDR brachytherapy was used to deliver 16 Gy in 2 fractions. The response rate observed 73.3%, which is similar tometaanlaysis done by fuccio et al. toxicity rates are higher compared to other similar studies sarbani et al Tata memorial hospital, Rosenblatt et al International atomic energy agency. Most common toxicity was esophagitis. Long term followup is needed to assess the progression free survival and overall survival in present study.
The following table shows a comparison between the present study and other similar studies

Comparison with similar studies

Table 15

AUTHOR	REGIMEN	RESPONSE
Agarwal et al	20 – 50 Gy EBRT + 10 Gy ILRT	92%
Kohek et al	30 Gy EBRT + 12.4 Gy ILRT	96%
Schraube et al	44 Gy EBRT + 17.5 Gy ILRT	97%
Datta et al	35GyEBRT + 12 Gy ILRT	49%
Hujala et al	40GyEBRT +10 Gy ILRT	40%
Yadav et al	30GyEBRT + 12 Gy ILRT	76%
Rosenblatt et al	16GyILRT + 30 Gy EBRT	82.7%
Sarbani et al	16GyILRT + 30 Gy EBRT	47.3%
Present study	30GyEBRT + 16Gy ILRT	73.3%

Comparison of toxicities

Table 16

STUDIES	REGIMEN	OVERALL COMPLICATIOS	STRICTURE	FISTULAE
Sharma et al	12 Gy ILRT + 30 Gy EBRT	30%	15%	5%
Sur et al	16 Gy ILRT + 30 Gy EBRT	16%	13%	3%
Rosenblatt et al	16 Gy ILRT + 30 Gy EBRT	34%	27%	5%
Sarbani et al	16 Gy ILRT + 30 Gy EBRT	40%	27%	4%
Our study	30 Gy EBRT + 16 Gy ILRT	65%	5%	5%

As can been seen there are difference in the response rates between the various studies. However, the difference in the study designs and the difference in patient population among the various studies emphasize the need for well-designed prospective randomized controlled trail to identify the optimal radiotherapy schedule in the palliative treatment of carcinoma of oesophagus.

In summary radiotherapy is an important treatment modality in the palliation of dysphagia of oesophageal carcinoma and can achieve good and durable palliation. However, the optimal radiotherapy schedule remains to be determined. Other endoscopic methods of palliation can be used to supplement radiotherapy and can used in the setting progressive disease in spite of radiation.

V. Conclusion

In conclusion, this single arm prospective study showed that a combination of external beam radiation therapy and high dose rate Intraluminal brachytherapy can produce acceptable rates of dysphagia relief with little complications. Long term follow-up is needed to assess the duration of palliation and incidence of late complication.

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