ASSESSMENT OF THE EFFICACY OF EXTERNAL BEAM RADIOTHERAPY FOLLOWED BY INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF DYSPHAGIA IN PATIENTS WITH CARCINOMA ESOPHAGUS

A SINGLE ARM PROSPECTIVE STUDY

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RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
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CERTIFICATE

This is to certify that **Dr.INGERSAL N** has been a Post Graduate MD Student during the period from MAY 2015 to MAY 2018 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled **"ASSESSMENT OF THE EFFICACY OF EXTERNAL BEAM RADIOTHERAPY FOLLOWED BY INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF DYSPHAGIA IN PATIENTS WITH CARCINOMA ESOPHAGUS''**is a bonafide work done by him during the study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination.

DEAN

Madras Medical College &

Rajiv Gandhi Government General Hospital,

Chennai-03

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Prof.Dr. N.V.Kalaiyarasi, MDRT, DCH,

Professor and Head, Department of Radiotherapy,

Madras Medical College &

Rajiv Gandhi Government General Hospital,

Chennai-03

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The dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical UNIVERSITY towards the fulfilment for the award of M.D. Degree (Branch IX) in Radiotherapy

Place: Chennai

Date:

Dr Ingersal N

M.D Radiotherapy

Post Graduate student

Department of Radiotherapy

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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].Most of the centres use single fraction of intraluminal brachytherapy, equally good palliation has been achieved with combination of external beam radiation with brachytherapy[7].

ANATOMY

The development of the oesophagus begins in the 3rd week of gestation. Steps involved are initial formation of the gut tube, molecular regulation of the gut tube, differentiation of the endoderm (the lining of the oesophagus), and derivation of the muscular layers from the mesoderm. Growth of the oesophagus continues at a slow pace after morphologic changes stops. Swallowing first appears at the 14th week and is established by the end of the 4th month of gestation[8]

The oesophagus is a two-layered mucosa-lined muscular tube. Lies in the posterior mediastinum. It commences at the base of the pharynx at C6 and terminates in the abdomen, where it joins the cardia of the stomach at T11. its average length is 25- to 30-cm. Relative to incisor the cervical oesophagus begins as a midline structure that deviates slightly to the left and passes through the neck into the thoracic inlet. At the level of the carina, it deviates to the right. Then slightly deviated to the left as it enters the diaphragm through the oesophageal hiatus at the level of the 11th thoracic vertebra. In the neck and upper thorax, the oesophagus is secured between the vertebral column, posteriorly, and the trachea, anteriorly. Thoracic oesophagus lies anterior to the heart and pericardium at the

level of carina[9]. Microscopically, the oesophageal wall is composed of four layers: mucosa, submucosa, muscularis propria and adventitia. The oesophagus has no serosa, this allows oesophageal cancers to spread more easily and makes them harder to treat surgically [10]

Cervical Oesophagus lies in the neck, bordered superiorly by the hypopharynx and inferiorly by the thoracic inlet. length of the cervical oesophagus from

incisors are from 15 to 20 cm.

Upper Thoracic Oesophagus is bordered superiorly by thoracic inlet and inferiorly by the lower border of the azygos vein. Measures 20 to 25 cm from incisors.

Middle Thoracic Oesophagus is bordered superiorly by the lower border of the azygos vein and inferiorly by the inferior pulmonary veins. It is sandwiched between the pulmonary hilum ant descending thoracic aorta on the left, and vertebrae posteriorly; on the right, it lies freely on the pleura. measures 25 to 30 cm from incisor.

Lower Thoracic Oesophagus is bordered superiorly by the inferior pulmonary veins and inferiorly by the stomach, includes the oesophagogastric junction (OGJ). Measures 30 to 40 cm from incisor endoscopically.

The arbitrary 10-cm segment encompassing the distal 5 cm of the oesophagus and proximal 5 cm of the stomach, with the EGJ in the middle, is an area of

contention. Cancers arising from 5cm of distal oesophagus and 5cm proximal of the stomach are variably staged as oesophageal or gastric cancers, depending on orientation of the treating physician[11]

Regional lymph node

The lymphatic drainage of the oesophagus is extensive, consists of two interconnecting lymphatic plexuses arising from the submucosa and muscularis layers. The submucosal lymphatics drains into the plexus that runs longitudinally in the oesophageal wall. In the upper two thirds lymphatic flow is upward, in the distal third flows downward.

Specific regional lymph nodes are as follows

Table 1

Cervical oesophagus

Scalene
Internal jugular
Upper and lower cervical
Periesophageal
Supraclavicular

Upper, middle and lower thoracic oesophagus

Upper periesophageal
Subcarinal
Lower periesophageal
oesophagogastric junction
Lower oesophageal
Diaphragmatic
Pericardial
Left gastric and celiac[6]

PATHOLOGY

Two morphologic variants comprise majority of oesophageal cancers: adenocarcinoma and squamous cell carcinoma.

Squamous cell carcinoma is common worldwide, but in Western countries adenocarcinoma is on the rise. squamous cell carcinoma of esophagus mostly occurs over age 45 and affects males four times more frequently than females[11].

Squamous cell carcinoma begins as an insitu lesion termed as **squamous dysplasia.** Early lesions appear as small, gray-white, plaque-like thickenings.

Advanced tumours are polypoid or exophytic and protrude into and obstruct the lumen. Some tumours may be ulcerative or diffusely infiltrative lesions. The molecular pathogenesis is incompletely defined, but loss of several tumour suppressor genes p53 and p16/INK4a are involved[12].

Adenocarcinoma of the oesophagus typically arises from Barrett oesophagus and long-standing gastroesophageal reflux disease. Incidence varies 60-fold worldwide, highest in developed Western countries. Occurs through stepwise acquisition of genetic and epigenetic changes. Initially appearing as flat or raised patches in intact mucosa, may develop to large masses to about 5cms. Tumours most commonly produce mucin and form glands often with intestinal-type morphology; less frequently are diffusely infiltrative signet-ring cells and in rare cases, small poorly differentiated cells (like small-cell carcinoma of the lung[13].

Adenoid cystic carcinomas are rare, with an incidence about 0.75%.mucoepidermoid tumors (adenosquamous carcinomas) are more aggressive and have poor prognosis. Small-cell carcinoma is similar to small-cell carcinoma of the lung[14]l **Leiomyosarcomas** are more common. 25% of patients with this tumor present with metastases.These tumors have interlacing bundles of spindle-shaped cells.Prognosis is favorable than that of squamous cell carcinoma[15].

Kaposi's sarcoma occurs with acquired immune deficiency syndrome[16]. **Malignant melanomas** are rare and can occur as a primary esophageal tumor or

as a metastasis.often lesions are usually large and often covered by intact squamous mucosa with focal areas of ulceration.Spread is usually submucosal[17.]

Lymphoma comprises approximately 1% of esophageal malignancies. Esophageal involvement are typically secondary to extension from other sites[18].

Etiologic factors and predisposing conditions

Tobacco&Alcohol

90% of squamous cell carcinoma of the esophagus attributed to tobacco and alcohol use. tobacco and alcohol use are independent risk factors, highest risk of developing esophageal cancer with heavy use of both agents. cigarette smoking is a risk factor for development of Barrett's oesophagus. ICMR data indicate a high incidence of tobacco-related cancers in the north-eastern region. The proportion of tobacco-related cancers is highest in Assam and Meghalaya[19]. Alcohol is a major risk factor for development of squamous cell carcinoma of oesophagus in western world, dose response relationship exists between alcohol ingested and development of squamous cell carcinoma. The mechanism of how tobacco and alcohol in combination lead to increased risk of oesophageal cancer has been extensively studied. Alcohol can damage DNA by decreasing metabolic activity and promoting oxidation [20,21,23]

Diet and Nutrition

Deficiencies of few nutrients and dietary components like Vitamin A, C, E, selenium, carotenoids have been associated with increased risk of oesophageal carcinoma[24]. Consumption of hot beverages is a risk factor for oesophageal carcinoma. Diets enriched with animal products was significantly associated with the development of oesophageal carcinoma. diets high in fibres, polyunsaturated fatty acids and vitamin D are protective of developing oesophageal carcinoma[25].

GERD – Gastroesophageal Reflux Disease

Reflux is a Strongest risk factor for development of adenocarcinoma esophagus[26]. Chronic reflux is associated with Barret's Oesophagus, reflux can cause dysplasia initially low grade and progress to high grade and finally turn malignant, mechanism of malignancy is like barrette's oesophagus. Increased frequency, severity and chronicity of reflux symptoms are associated with increased risk of adenocarcinoma esophagus[27].

Barrett's Oesophagus

Squamous cells of distal oesophagus are replaced by columnar cells with mucin producing goblet cells. On upper gastrointestinal endoscopy mucosa appears salmon colour. Intestinal metaplasia confirmed by histologic examination of biopsy specimens is required for the diagnosis of Barrett's oesophagus [27]. The absolute risk to develop adenocarcinoma is estimated to be 0.12% to 0.33%.

Diagnosis of Barrett's oesophagus confers 40- to 125- fold higher risk progressing to oesophageal carcinoma. Barrett's oesophagus has 11.3 relative risk of developing adenocarcinoma. Progression from intestinal metaplasia to dysplasia in Barrett's oesophagus signifies an unequivocal neoplastic change associated with the potential for malignant degeneration [29]. American board of gastroenterologist suggest periodic surveillance in patients Barrett's oesophagus and shown that control of reflux symptoms can decrease the incidence of carcinoma. Experienced pathologist is necessary to distinguish from low grade and high-grade dysplasia in case of low grade dysplasia chemoprevention may disrupt carcinogenesis. Barrett's oesophagus has shown to express COX-2. so, both selective and nonselective COX-2 inhibitors can be used for chemoprevention[30]. Ongoing ASPECT trail is evaluating role of aspirin and esomeprazole on progression of dysplasia in barrettes oesophagus.

Plummer Vinson / Patterson Kelly Syndrome:

Characterised by classical triad of iron deficiency anaemia, glossitis and oesophageal webs[30.] Dysphagia can be improved by iron supplementation. Alimentary tract mucosa rapidly loses iron-dependent enzymes due to its high cell turnover, which is speculated to cause mucosa degeneration and web formation. About 10% with this syndrome develop hypopharyngeal or oesophageal epidermoid carcinoma [32]. Carcinogenesis in Plummer Vinson

syndrome is due to chronic irritation of injured mucosa by food particle and nutritional deficiency, but exact mechanism not fully understood.

Caustic injury

Squamous cell carcinomas may develop in lye strictures after 40 to 50 years of caustic injury. Majority of them occur in middle third of esophagus[33]. Patients with caustic injuries are often diagnosed late because strictures can mask malignancy. Chronic mucosal irritation and injury by food particle can cause dysplasia and turn to malignancy.

Achalasia

It is an idiopathic oesophageal motility disorder characterised by incomplete relaxation of lower oesophageal sphincter and absence peristalsis of the body of oesophagus. Squamous cell carcinomas occur in mid oesophagus due to prolonged irritation from retained foods. Often diagnosed very late [34]. There is 16 to 20-fold increase in squamous cell carcinoma in mid oesophagus. Neoplasm is due to chronic irritation of retained food particle due incomplete relaxation of oesophageal sphincter.

Tylosis

Focal nonepidermolytic palmoplantar keratoderma is characterised by hyperkeratosis of palms, soles and oesophageal papilloma. he frequency of the disorder in the general population is not known [35]. Diagnosis of tylosis with oesophageal cancer is made based on a positive family history, clinical features, including focal palmar and plantar hyperkeratosis and oesophageal lesions and mutations in RHBDF2. They are at a high risk of developing oesophageal carcinoma[36].

Helicobacter pylori infection:

H.pylori has negative correlation with development of adeno carcinoma. cagA+ strains along with chronic atrophic gastritis have shown to be protective against development of adeno carcinoma, but not with squamous cell carcinoma. some studies have shown presence of H.pylori infection along with chronic atrophic gastritis can predispose to squamous cell carcinoma due to production of nitrosamines which is a carcinogenic agent.

Human papilloma virus

Human Papilloma Virus infection may contribute to the pathogenesis of oesophageal squamous cell carcinomas in high incidence area[37]. High incidence area includes china and south Africa, studies in these regions have shown one third of oesophageal carcinoma are due to HPV infection. HPV encodes two main

oncogenic protein E6 and E7. E6 is responsible for late carcinogenesis and E7 is responsible for early carcinogenesis. Carcinogenesis in HPV infection is due to inhibition of p53 and Rb gene.

Prior aerodigestive tract malignancy:

10% chance of oesophageal carcinoma in prior oropharyngeal malignancy or lung carcinoma, but there has been a discordance with p53 gene mutation.

Natural History:

At presentation majority of the patients have regionally advanced or disseminated cancer due to the lack of a serosal envelope, rich submucosal lymphatic network of oesophagus that provide a favourable milieu for extensive local infiltration by tumour and lymph node involvement. Lungs, liver and bone at the most common sites of distant spread. In upper and middle third oesophageal carcinomas which are squamous locoregional recurrence is common whereas in patients with lesions of lower third which are adenocarcinomas, distant recurrence is more common.

Molecular characteristics

TP53 gene mutation are present in 80% of oesophageal cancers. The mutations for squamous tumours, which are AT base pairs, are different from the mutations seen in adenocarcinomas.

Squamous cell carcinoma is preceded by squamous dysplasia, whereas adenocarcinoma is preceded by intestinal metaplasia of the normal squamous

epithelium of the oesophagus or Barrett oesophagus. EGFR is commonly overexpressed in early-stage oesophageal cancer, and overexpression correlates with a poor prognosis. Overexpression is also associated with recurrent disease and decreased overall survival in patients undergoing curative resection. cyclin D1 overexpression causes cyclin D1 dysregulation, mutations in cyclin D1, mutations in Fbx4, induces mutation in E3 ligase for cyclin D1, thereby preventing degradation of cyclin D1 in the cytoplasm and reimportation into the nucleus, where it exerts its oncogenic effects. p16 mutation via promoter hypermethylation, point mutation, or allelic deletion. Loss of heterozygosity of 9p21, the locus for both p16 and p15, has been demonstrated with high frequency of adenocarcinoma. loss of 13q, locus of the Rb gene resides, is found in 50% of patient's adenocarcinoma and squamous cell carcinoma. aberrant expression of telomerase is seen oesophageal cancers. Loss of E-cadherin, a cell–cell adhesion molecule, associated catenin p120 catenin and p120ctn disrupt cell–cell interactions, which results in tumour progression. SOX2, on chromosome 3q induces squamous cell growth, this may have implications in the therapy of squamous cell carcinoma. GATA6, a transcriptional factor, has been reported to be overexpressed in adenocarcinoma.

Clinical presentation

Most common symptoms are dysphagia and weight loss. Dysphagia is seen in more than 90% regardless of tumour location, initially present for solids and

slowly progress to liquids, occurs when lumen of oesophagus narrows to 13mm. Palliation of this single symptom will impact the quality of life of the patient. Few patients have odynophagia (painful swallowing). Other symptoms include dull retrosternal pain due to invasion of mediastinal structures, bone pain secondary to bone metastasis, cough and hoarseness secondary to recurrent laryngeal nerve involvement. Cervical or supra clavicular lymphadenopathy.

Diagnosis:

Oesophageal Endoscopy and Biopsy can diagnose oesophageal carcinomas with 100% accuracy. History of tobacco use, alcohol use, symptomatic reflux, diagnosis of Barrett's oesophagus are the predisposing factors.

Oesophagogastroscopy allows precise evaluation of the extent of oesophageal and gastric involvement and the location of the tumour from the incisors. Upper endoscopy reveals skip lesions or second primaries as well as presence of Barrett's oesophagus.

In Endoscopy, dilatation of a stenotic lesion provides relief from dysphagia temporarily. Bronchoscopy rules out invasion of membranous trachea and tracheoesophageal fistula. Bone scan yield is very low and is not a part of routine investigation unless symptoms are present.

CT Scan of chest, abdomen and pelvis is a must for the initial evaluation of the extent of the disease. CT is highly accurate 100% in detecting lung and liver

metastases and suggesting peritoneal carcinomatosis. Not ideal for T staging, as CT misses small T1 and T2 tumours since individual layers of tumour wall are not defined.

EUS endoscopic ultrasonography and EUS guided FNAC are invaluable tools for pre-treatment staging of ca oesophagus. Many studies support that EUS is superior to CT in T and N staging. EUS is highly operator dependant to procure adequate images and correct interpretation and is limited in defining superficial lesions as T1 or T2. So miniprobe high frequency sonographic catheters that are passed through the standard endoscope are now being used to get very accurate results. New generation thin calibre endoscopes that can be passed over a guidewire can traverse almost all obstructing lesions thus EUS allows proper staging[37].

Recently **FDG PET** flurodeoxyglucose positron emission tomography is being widely applied in the management of Ca oesophagus. In Regional lymph node assessment accuracy falls in between CT and EUS. In distant metastasis assessment FDG PET is superior to CT.FDG PET evaluates response to chemotherapy and radiotherapy[38,39].

Prognostic factors

Stage at diagnosis is the most important prognostic factor: Depth of invasion is the most important factor for nodal and distant spread. Tumour volume is prognostically important Lymphovascular invasion is a poor prognostic factor.

Among patient related factors; Age of patients per se is not a significant prognostic factor; Performance status determines the feasibility of curative therapy for patients with non-metastatic disease. Deep ulceration, sinus tract formation, and fistula have poor outcome.

Diagnostic or treatment related factors include; Incomplete pathologic response to preoperative chemotherapy or chemoradiotherapy is a poor prognostic factor. patients undergoing R1 resection have good prognosis compared to R2 resection or patients not undergoing surgery at all.

STAGING OESOPHAGEAL CARCINOMA

AJCC TNM STAGING seventh edition

Table 2

PRIMARY TUMOR

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	High-grade dysplasia
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa.
T1a	Tumour invades lamina propria or muscularis Mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades adventitia
T4	Tumour invades adjacent structures
T4a	tumour invading pleura, pericardium, or diaphragm
T4b	Unrespectable tumour invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

REGIONAL LYMPHNODE

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes

DISTANT METASTASIS

M0	No distant metastasis
M1	Distant metastasis

CLASSIFICATION OF STAGING FOR OESOPHAGEAL CANCER

SQUAMOUS CELL CARCINOMA

Table 3

GROUP	T	N	M	GRADE	TUMOR LOCATION
0	Tis	N0	M0	1	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T1-2	N0	M0	1, X	Upper, Middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, Middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

ADENOCARCINOMA

Table 4

GROUP	T	N	M	GRADE
0	Tis	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

TREATMENT OVERVIEW OF ESOPHAGEAL CANCER

OPERABILITY: Treatment recommendations are dependent on tumour stage and the general condition of the patient. In early lesions, endoscopic mucosal resection provides a good specimen for histopathological assessment. Laparoscopy is indicated if abdominal tumour spread is suspected, and can also identify tumour extension on the gastric part of the tumour for junctional adenocarcinomas, identify comorbidities (e.g. cirrhosis), and be used for placement of a feeding tube if required.

Age, comorbidities, nutritional status and cardiopulmonary capacity should be considered before surgery, and patient is assessed by an experienced anaesthetist. Consultation of cardiologists and dietitians, a treadmill test and spirometry can provide valuable information. For older patients (aged >75 years), geriatric assessment might be helpful before initiating therapy.

Treatment recommendations

Multidisciplinary assessment is required for treatment planning, the multidisciplinary team should have expertise in pathology, radiology, endoscopy, medical oncology, radiotherapy, surgery, nursing, dietetics, and other relevant specialists such as laryngologists, physiotherapists, and social workers. Treatment plan depend on tumour stage, subsite, histology of the tumour, performance status, and comorbidity.

Multidisciplinary team meetings can provide an opportunity to follow up treatment results and to discuss recruitment of patients for research studies.

Curative treatment

Only 20% of patients at the time of presentation are localised to oesophagus and 80% have either locally advanced or distant metastasis

Treatment of premalignant and T1 disease

High grade dysplasia is a powerful predictor for invasive carcinoma. Superficial tumours confined only to mucosa have little risk of lymph node metastasis. Studies have shown endoscopic resection followed by careful surveillance with endoscopy at 3 to 6-month interval is necessary [40].

Endoscopic treatments

Endoscopic techniques, such as radiofrequency ablation, endoscopic mucosal resection, and endoscopic submucosal dissection, are increasingly used for curative treatment of early oesophageal. Most studies support ablation therapies in early oesophageal squamous cell carcinomas[41]. Endoscopic mucosal resection combined with radiofrequency ablation can prevent cancer progression in patients with lesion confined to mucosa, and are increasingly also used in patients with low-grade dysplasia, even if multifocal. Endoscopic removal for patients with early (T1) oesophageal cancer has increased during the past few years [42]. Superficial oesophageal cancer can be successfully removed by endoscopic

submucosal dissection in 90% of patients. Main complication is 3–8% risk of stenosis, which can be managed with endoscopic dilatation. Compared with endoscopic mucosal resection, endoscopic submucosal dissection offers a higher rate of complete resection. These organ-sparing procedures offer substantial quality of life benefits compared with esophagectomy, and clinical guidelines recommend endoscopic mucosal resection or endoscopic submucosal dissection rather than surgery for T1a oesophageal adenocarcinoma. However, 5% risk of lymph node metastasis exists in intramucosal (T1a) cancer and a 17% risk in submucosal cancer (T1b). Moreover, endoscopic therapy is associated with an increased risk of local tumour recurrence compared with surgery. Thus, in patients with superficial submucosal infiltration (T1b) esophagectomy optimises the prognosis, whereas in patients unfit for surgery or definite chemoradiotherapy, endoscopic resection is a good alternative[44,45].

Treatment of localized disease

Surgery has been treatment of choice for patients with locally advanced carcinoma of oesophagus. Recent trails have shown benefits of neoadjuvant therapies to surgery alone. Multimodality treatment that includes surgery is standard of care for resectable disease.

Surgical approaches

Trans hiatal esophagectomy – first laparoscopic approach is done to rule out disseminated disease, then midline incision and mobilization of viscera, left cervical inscion made for exploration of cervical oesophagus, two field lymph node dissection followed by en block resection of tumour and cervical anastomosis done[46]. Advantage of this procedure is avoidance of thoracotomy incision thereby reducing pulmonary complications. Disadvantage are poor visualization of thoracic oesophagus, anastomotic leak, and possibility of recurrent laryngeal nerve damage.

Trans thoracic esophagectomy – most common and standard surgical approach, right thoracotomy usually done for better visualization of upper, middle and lower thoracic oesophagus

Ivor Lewis procedure involves right thoracotomy and laparotomy followed by two field lymph node dissection and enblock resection for middle and distal oesophageal tumours

Mc kewon (or) three-hole procedure involves right thoracotomy, laparotomy, and cervical approach followed by two (or) three field lymph node dissection and enblock resection of tumour. other approaches are left thoracotomy and left thoracoabdominal.

Extended esophagectomy is an attempt to improve locoregional control and decrease poor survival. It is a radical approach with concept of enbloc resection primary tumour followed by systematic lymph node dissection of cervical, thoracic, and abdominal basins [48,49]. From available data and evidence extended thoracotomy improves staging and local control but no data on survival benefit is available.

Whether thoracotomy or non-thoracotomy technique is used, postoperative survival is similar, approximately 20% to 25%. This has been underscored most graphically by Muller and associates through metaanalysis to compare overall post esophagectomy survival by techniques and showed no significant difference between them. Better patient selection plays an important role in improved outcome. Steyerberg and colleagues have proposed a simple scale based on important comorbidities, age, neoadjuvant therapies, and esophagectomy volume at the treating hospital that divides patients into groups with predicted 30-day mortality of under 4% to approximately 20%. It is also expected that more accurate preoperative staging with PET scanning and oesophageal ultrasound could improve surgical outcome by removing some patients who have existing gross metastatic disease.

Adjuvant therapies

Preoperative chemotherapy nearly 75% of oesophageal cancer are locally advanced at the time of presentation, poor survival is seen with surgery alone due

to local and systemic recurrence. Benefits of induction chemotherapy are potential downstaging of the tumour, improving resectability, eradication of potential micrometastaasis, relief of dysphagia, and for decision of postsurgical chemotherapy after pathological assessment, disadvantages are development of chemotherapy resistance and delay in surgery. About six trails shows that preoperative chemotherapy improves R0 resection rates but no overall survival benefit.

Kelsen et al. compared the efficacy of preoperative chemotherapy with preoperative radiation. This phase III study indicated that Radiation and Chemotherapy led to almost identical outcomes, resection and operative morbidity and mortality.

Postoperative chemotherapy- With available data from Japanese Oncology Group adjuvant chemotherapy provides survival benefit in patients who had R0 resection and N1 disease.

Preoperative or postoperative radiation – with available data preoperative or postoperative radiation alone will not decrease local failure or improve survival

Preoperative chemoradiation trimodality therapy involving prechemoradiotherapy followed by surgery has led to increase in 3-year survival rates prolongation of median disease-free survival. In CROSS trial 366 patients with locally advanced oesophageal carcinoma were randomized to receive either neoadjuvant chemoradiation with 41.4 Gy and carboplatin / paclitaxel followed

by surgical resection versus surgical resection alone in this trial, median survival was effectively doubled by the addition of chemoradiation (49.4 vs 24 months, P 5 .003). Improved survival was seen in both adenocarcinoma and SCC, although the magnitude was slightly greater in SCC. The R0 resection was 93% in the chemoradiation arm, compared with 69% in the surgery alone arm (P<.001). Despite concerns that a lower radiation dose combined with carboplatin and paclitaxel may not be as effective, the pathologic complete response (pCR) rate was 29%. The pCR rate and survival in the CROSS trial is comparable to most previous trials and retrospective reviews. In addition, no significant difference in perioperative complications was seen between treatment arms. now with the publication of the CROSS trial, the standard of care for patients with locally advanced but medically resectable adenocarcinoma of the oesophagus is now preoperative chemoradiation.

Geh et al analysed factors responsible for pathological complete response after preoperative chemoradiation, about 26 trails were analysed, overall pathological control rate was 24% and increased with increase in radiation dose. Response rate also increased with use of 5-FU based chemotherapy. Some studies suggest that cascade of signalling gene are involved in outcome p13, p53, EGFR, Hypoxia inducible factor-1 and other mRNA signatures.

Posttreatment imaging with PET-CT have been studied in response assessment, some studies have shown 63% sensitivity and 55% specificity.

Definitive chemoradiation-

In patients not planning to undergo surgery due to comorbidities or patient's choice, combined chemoradiation can be used based on RTOG 85-01 and INT 0123. In the landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial in which patients were randomized to receive either 64Gy at 2 Gy/d or chemoradiation, all patients who received radiation alone were all dead of disease by 3 years.6,7 Shi and colleagues reported a 33% 5-year survival rate with the use of late course accelerated fractionation to a total dose of 68.4 Gy[55,56]. In INT0123 trail 236 patients were randomized to receive either 64.8Gy or lower dose of 50.4Gy. there was no significant difference in median survival (13.0 months vs 18.1 months), 2-year survival (31% vs 40%), or local/regional failure and/or local/regional persistence of disease (56% vs 52%) between the high-dose and standard-dose arms. at this point, based on results of the INT 0123 trial, the standard dose of external beam radiation remains 50.4 Gy[57].

Toxicities with chemoradiation:

Toxicities depend on the total dose and use of chemotherapy. Most patients develop esophagitis during 2 -3rd week of radiation, but resolve within 3 weeks after radiation. Most of information about toxicities of radiation comes from studies involving radiation alone such as RTOG 85-01, a dose of about 64 Gy of radiation alone was given. Patients experienced toxicities in form of esophagitis

and strictures. About 25% developed grade 3 toxicity and about 3% developed grade 4 toxicity. Long term toxicities were about 20%.

Stricture was common among patients who received both chemotherapy and radiation. Total percentage of stricture in patients receiving both chemotherapy and radiation are high up to 40%. Incidence of stricture decreases with advancement in treatment techniques. Benign strictures required dilation and malignant stricture require intubation.

Higher incidence of fistulae is associated with both chemoradiation and intraluminal brachytherapy boost. RTOG 92-07 trail showed that about 17% developed fistulae on receiving brachytherapy boost.

Pericarditis and pneumonitis is about 5%. Earlier trail with chemotherapy oxaliplatin and 5FU showed decreased lung function. Techniques such as IMRT can reduce dose to heart and lung.

Brachytherapy boost: Brachytherapy can be delivered by low- or high-dose rates. The primary isotope is Iridium 192 (Ir-192), which is usually prescribed to treat to 1 cm from the source. Chemoradiation plus brachytherapy was tested prospectively by the RTOG Trial 9207. A total of 75 patients with cancers of the thoracic oesophagus (92% squamous cell, 8% adenocarcinoma) received the RTOG 8501 50-Gy chemoradiation regimen followed by a boost during cycle 3 of chemotherapy with either low-dose-rate or high dose-rate intraluminal brachytherapy. The complete response rate was 73%. With a median follow-up

of only 11 months, local failure as the first site of failure was 27%. Acute toxicities were high [58,59]. If chemoradiation is used (defined as 5-fluorouracil [5-FU]–based chemotherapy plus 45–50 Gy), the recommended doses of brachytherapy are 10 Gy in 2 weekly fractions of 5 Gy each for high-dose rate and 20 Gy in a single fraction at 4 to 10 Gy/h for low-dose rate[60].

Palliation of dysphagia-

Most of the patients present at locally advanced stage or metastatic disease. Since most of the patients live no longer than 6 months, aim of palliative treatment is to relief dysphagia with minimal hospital stay. Modes of palliation of dysphagia are Endoscopically delivered (bougie dilatation) rigid pulsion dilators (Savary-Gilliard) or balloon dilators, chemical energy (alcohol injection), thermal energy (Nd-YAG laser, argon beam coagulation, photodynamic therapy), self-expanding metal stents (SEMS), radiotherapy and chemotherapy, palliative resection, bypass surgery and nutrition.

RADIOBIOLOGY OF BRACHYTHERAPY

Ionizing radiations X-rays & gamma-rays, biological effect produced depend on the dose rate of total dose received. Reducing the dose rate decreases the biological effectiveness,decreasing the dose rate increases the dose needed for the same level of effect. The number of factors can contribute to the dose rate or dose fractionation effect, depending on the conditions and cell or tissue system

involved. Biological factors that affect the responses of normal and tumour tissues in fractionated

4 Rs form the basis for radiobiology of radiotherapy are defined as

- repair,
- reassortment (redistribution),
- repopulation
- reoxygenation.

Brachytherapy was first started with use of radium as source, due its toxicities such as deposition over bones, low safety profile and significant hazard to worker source such as cobalt-60, iridium-192, cesium-137, iodine125 are used. Initially preloading technique was used now we have moved to era of after loading technique. After loading can be done either by manual after load or remote afterload. Based on the dose rate brachytherapy is classified as

- low dose rate (0.4 -2 Gy),
- medium dose rate (2- 12Gy),
- high dose rate (>12Gy).

Advantage of HDR Brachytherapy are:

- Dose optimization,
- No requirement for hospitalization,
- Low thromboembolism risk,

- Short treatment time,
- Patient feels more comfortable,
- Better protection from radiation,
- Less applicator movement.

Disadvantages are:

- Serious risk in case of machine failure,
- Less experience compared to LDR
- Expensive equipment
- No possibility of correcting position during treatment,
- more treatment cost compared to LDR.

The major radiobiological difference between HDR and LDR brachytherapy is in relation to sublethal damage(SLD) repair. This repair causes the shapes of survival curves to change. Survival curves for some tumour cells is linear and have an initial negative slope. survival curves for late-reacting normal tissue cell exhibit a larger shoulder at low doses which represents a greater potential for repair of sublethal damage. A brachytherapy uses this concept. Using multiple fractions of radiation, each of small size, allows more repair of the normal tissue compared with that of some cancer cells. There is essentially a “window of opportunity” whereby treatment at dose/fraction below the crossover point of the two survival curves results in more killing of tumour than normal tissue cells, and this is the reason we fractionate. It should be noted that this crossover

point will be highly tumour- and normal tissue-specific, which is why the optimal dose/fraction is not the same for all clinical situations.

At least 6 hours should be allowed between fractions if this repair to occur. Irradiating continuously at LDR allows sufficient time during the treatment for repair to occur. Empirical methods such as the NSD (nominal standard dose), TDF (time-dose factor), or a dose reduction factor of 0.6 have been used in the past to convert HDR doses to LDR equivalent doses. The L-Q mathematical calculations are may not be practical on a day-to-day basis. The L-Q equation does not consider the proliferation of tumour cells. This factor is small if the treatments are performed over a short duration.

Inverse dose rate effect plays a key role in LDR brachytherapy. When the dose rate is decreased cell killing is increased this knowns as inverse dose rate effect. When dose rate is reduced, cell is frozen in G2 phase known as "G2 Block'', G2M phase is most radiosensitive phase and cell do not progress in cell cycle causing shallow survival curve.

Therapeutic ratio is achieved over a dose rate of about 0.25Gy to 0.8Gy this range belongs to the LDR region. Biological effect of radiation also varies with the position of source in the target volume, this is the reason for excellent results with LDR brachytherapy compared to HDR. In HDR a dose range of about 100 to 500 Gy/hr is given at one centimetre. Number of fractions in HDR determine the clinical efficacy of HDR brachytherapy. A HDR 4 fraction can

improve therapeutic ratio by 4% compared to 3 fractions and 5 fraction yields another 4% improvement in therapeutic ratio.

LITERATURE

REVIEW

LITERATURE REVIEW

Palliative treatment

Palliative treatment is to maintain swallowing during life and to avoid serious complications. Individualised treatment is based on tumour stage, medical condition and performance status of the patient. Palliative care is best started early during illness and across multiple-care settings While palliative care refers to an approach to care focused on symptom management and improving quality of life, palliative medicine is used to describe the medical specialty focused on providing palliative care. Palliative care is provided by an interdisciplinary team including physicians, nurses, social workers, pharmacists, psychologists. Palliative care teams not only treat the patient but also attend to the needs of the family, understanding that family can include any person the patient identifies as part of their support network. With focused symptom management and clear goals of care, patients living with oesophageal cancer can improve their quality of life and maximize valuable time with friends, family, and loved ones.

Palliative Modalities

Table 5

Surgery
Radiation Therapy • External Beam Radiotherapy • Intraluminal Brachytherapy
Chemotherapy
Endoscopic Techniques
Stent placement
Laser Therapy
Photodynamic therapy
Dilatation
Nutritional support
Nasoentric Feeding Tube
Feeding Gastrostomy
Feeding Jejunostomy

Stent placement

Stents are inexpensive, and were used for palliation of malignant oesophagobronchial fistulas. Initial stents used for palliation of malignant dysphagia were rigid stents, which continued to be used in some countries. Rigid plastic oesophageal prostheses are placed endoscopically. These devices have fixed internal and external diameters. The stent diameters are fixed and relatively large, so large-bore dilation is required. They are associated with high rates of perforation, migration and obstruction and poor relief from dysphagia and high mortality during the procedure [61].

Self-expanding metal stents decreased the rate of such complications and increased the ease of insertion and improved relief of dysphagia up to 95%Other advantages are ease of insertion, reduced sedation, and more stent flexibility. Disadvantages include tumour ingrowth, high cost acute and late complications like stent migration, obstruction, fistulisation, chest pain[62]. Tracheoesophageal fistula closure is obtained with covered stent. The incorporation of β-emitting agents and cytotoxic agents in oesophageal stents may increase their efficacy, particularly in the prevention of tumour overgrowth at both ends of the stent [63].

Laser Therapy

Laser recanalization helps patients to swallow better. Nd YAG lasers are ideal. Nd: YAG works by emission of an invisible light beam (wavelength 1064 nm) delivered via a quartz fibre housed within a Teflon sheath and passed through the

working channel of a standard or therapeutic endoscope [64]. The goal is to vaporise enough malignant tissue to restore luminal patency. Most reports found it required 2 to 4 treatment sessions to achieve the desired goal. However, using a retrograde approach, Pietrafitta and Mitty have reported achievement of luminal patency in 1.6 and 1 session, respectively [65]. Recanalization is achieved in 90% of the patients and they can swallow solids. While laser therapy can be applied with some degree of effectiveness to any lesion in any region of the oesophagus, lesions deemed most conducive to successful treatment tend to be shorter lesions, usually less than 6 cm or on a surgical anastomosis, in the straight part of the middle third of the oesophagus, and exophytic, mucosal lesions[66]. Nd: YAG has no side effects and gives good palliation of dysphagia. Downside is the cost and availability of equipment and operator's technical expertise.

Photodynamic Therapy:

Photodynamic Therapy can be performed in the outpatient setting and may be repeated and/or be used along with other therapies, such as surgery, radiation, or chemotherapy.

Porfimer (Photofrin) is the only photosensitising agent approved for treatment of oesophageal Carcinoma. PDT uses a photosensitising agent in combination with endoscopic nonthermal laser exposure to cause optimal tissue ablation. Photodynamic Therapy with Porfimer produces singlet oxygen and has a direct toxic effect on malignant cells causing tumour necrosis. Patients are discharged

home 2 to 3 hours post procedure with instructions to maintain a liquid diet for 24 to 48 hours and then to progressively advance the consistency of the diet. Patients also need to be advised to avoid sunlight and other sources of ultraviolet light [67].

PDT provides significant palliation from dysphagia and technically more easier than Nd: YAG laser. PDT should not be performed in patients with acute porphyria, poor kidney or liver function, thrombosis of main blood vessels, leukopenia, thrombocytopenia, and terminal tumour stage [68]. Side effects are chest pain, fever, pleural effusion and post-treatment esophagitis which resolves in many patients over weeks except a few who develop strictures. Within 72 hours after injection porfimer is cleared from a variety of tissues except in skin, liver, spleen. Skin photosensitivity may last for 4 to 6 weeks. Sunscreens do not block visible light and thus are ineffective.

Dilatation

Dysphagia to solids occurs when oesophagus lumen decreases to 13 mm from the normal 25mm.Dilatation is used for benign tumours and not recommended for dilatation or use of wire guided polyvinyl bougies. Repeat dilatation in 1-2 weeks.

Surgical palliation-

Surgical intervention may still play a beneficial role in some patients with oesophageal carcinoma who present with acute perforation, pulmonary

complications from fistulae, or dysphagia unresponsive to endoscopic or other less invasive means, assuming they are acceptable operative candidates with a reasonable predicted survival. Surgical procedures include palliative esophagectomy, palliative bypass surgery, feeding jejunotomy and gastrostomy. Only in exceptional circumstances primary resection can be performed as a palliative procedure. Techniques that bypass oesophageal tumour are Retrosternal reversed gastric tube bypass with cervical anastomosis, Retrosternal gastric conduit bypass with total oesophageal exclusion, Intrathoracic gastric bypass with exclusion of the thoracic esophagus proximal to the tumor and distal drainage into a loop of jejunum, Intrathoracic jejunal Roux-en-Y bypass [69][70][71]. while these operations are creative and can have excellent palliative results, typical morbidity and mortality rates remain too high to justify their use over current less invasive measures.

Chemotherapy

Chemotherapy is appropriate for patients with disseminated oesophageal carcinoma to palliate dysphagia with a favourable QoL, provided the patient's performance status is good. Combination regimes of cisplatin and 5-FU are mostly used to increase survival in both squamous and adeno carcinomas. Phase 3 randomized trials have shown that capecitabine and oxaliplatin have the potential to replace cisplatin and 5-FU[72]. There is good response with acceptable toxicity. Intratumorally cisplatin permits local drug administration while

minimising systemic toxicity. Touchefeu et al[73] retrospectively compared the efficacy of chemotherapy and self-expanding metal stent in a total of 69 patients having inoperable esophageal carcinoma with progressively worsening dysphagia, dysphagia scores improved by 1 point in 67% of patients in chemotherapy group vs. 93% in the stent group. Using chemotherapy alone for palliation of dysphagia is not a feasible option, given its toxicity profile and the availability of more efficient methods of palliation.

Radiotherapy-

Both external beam radiation and intraluminal brachytherapy has been used for palliation of dysphagia. External beam radiation and intraluminal brachytherapy has been used in various combinations. Bleeding can be effectively controlled by hypo fractionated radiation. Brachytherapy has been effective method of palliation of dysphagia when used alone or in combination with external beam therapy. Studies comparing stent insertion to brachytherapy have shown long term dysphagia relief with brachytherapy.

Planning technique of External Beam Radiotherapy:

Site and extent of tumour are determined by endoscopy, CT and barium swallow. Definition of tumour volume to be targeted is chosen to allow a margin of 3cm superior and inferior to the tumour. CT simulation is done for planning.

For patients with growth in upper third oesophagus patient lies in supine position with cervical spine parallel to the couch top, for growth in middle and lower third oesophagus patients lie in supine position with arms above. If patient is kyphotic or frail this may not be possible.

In case of conventional planning antero-posterior simulator films are taken after patient has swallowed barium. This shows the length and width of target volume. Lateral films are taken to determine the depth of target volume. The depth and width of target volume are transferred onto the simulator film outline. Position of spinal cord is marked at each level. In case of palliation patient treated in supine position with arms by their side.

For CT based planning, patient is immobilized, tattoos are made anteriorly over the sternum and laterally in the mid axillary line for laser alignment. Contrast CT are taken. Oral contrasts delineate oesophagus and stomach. The target volume, spinal cord, lungs are outlined on each CT slice. Tumour extent is localised. Additional CT scan during quiet respiration are taken to check tumour moments during respiration and to account PTV.

Field arrangements in two-dimensional planning aims to treat homogeneously and to avoid spinal cord. Since treatment planes are non-coplanar dosimetry is complex. For middle and lower oesophageal tumour two phase treatment is given. This ensures exclusion of posterior mediastinum. In three field techniques one anterior and two posterior oblique fields are used, for upper third growth one

anterior open field and two anterior oblique wedged fields are used. Compensation for neck curvature are provided by aluminium alloy compensators.

Three dimensional localisation of target volume is accompanied by provisional dose description to the target volume and limiting dose to spinal cord, lungs and heart. Dose conformity can be achieved using alloy blocks or multileaf collimeter. Intensity modulated beams maybe used to produce an optimised dose distribution. Three-dimensional treatment planning provides conformal dose distribution while considering body contour and tissue density.

IMRT uses CT based planning but differs from 3D conformal radiation by delivery of radiation in multiple small fields varying in size, shape and intensity. In dynamic IMRT leaves move in and out of the radiation path during treatment. In step and shoot IMRT leaves change the radiation shape when beam is off. IMRT uses inverse planning in which dose is prescribed to target volumes and computer software designs the treatment field. One of the disadvantages of IMRT is integral dose. IMRT requires precise planning otherwise leads to geographical miss.

Dose constraint organ should always be maintained while planning. Spinal cord should be limited to 45 Gy. Conventional planning APPA approach can minimise dose to lung but not to heart. Lung constraints are V20 < 20%, mean lung dose of < 18 Gy. Total cardiac dose should be less than 40 Gy and < 50% can receive 25 Gy. 4D CT or breath hold technique used to reduce significant dose to heart.

In case of kidney receiving dose, it should be < 20 Gy. Nuclear Medicine renal studies can be done to assess renal function in case of anticipated dose to kidney.

Based on Minysky et al study which randomised patients to receive 64.8 Gy versus 50.4 Gy both receiving chemotherapy, there was no significant difference between two-year overall survival and locoregional failure. Based on these data, standard dose to oesophageal ca is 50.4 Gy at 1,8 Gy per fraction in case of definitive and adjuvant setting. 45 to 50 Gy in case of neoadjuvant setting.

Brachytherapy

Brachytherapy has been used in carcinoma of oesophagus for both curative and palliative purpose. It has been used alone in case of early stage carcinoma or along with external beam radiation as a boost, along with other modalities for palliation. Advantages of brachytherapy is its inverse square law, allowing decreased dose to normal tissue and dose escalation to tumour.

For definitive treatment with external beam radiation concurrent chemotherapy can be given but should not be given concurrently with brachytherapy. Brachytherapy is usually started two to three weeks after completion of concurrent chemoradiation.

Keyes et al found that adding brachytherapy after external beam radiation increased pathological control rate. Brachytherapy is planned with 1 to2 cm of proximal and distal margin clearance.

Selection criteria for intraluminal brachytherapy

Good candidate-

- Primary tumour less than 10cm
- No lymph node or systemic metastasis
- Thoracic oesophageal location
- Confined to oesophageal wall

Poor candidates-

- Extra oesophageal extension
- Tumour more than 10 cm
- Regional lymphadenopathy
- Tumour involving OG junction or cardia

Contraindications

- Fistulae
- Cervical oesophagus in location
- Complete stenosis which cannot be bypass.

Bronchoscopy is performed before brachytherapy planning to rule out presences of fistulae, bronchoscopic evidence of fistulae is a contraindication for brachytherapy[75.] cervical oesophagus is situated close to trachea and can cause fistulae post radiation[76].

Brachytherapy can be given with LDR, MDR and HDR. Nowadays most of the centres use HDR[77]. there are different types of applicators used based on diameter ranging from 1.7mm to 20mm. applicators are catheters that allows treatments in various cylindrically shaped PTVs. Variation in construction of applicators depend on anatomic situations. In a wide oesophageal lumen large applicators are used, in case of narrow lumen small diameter applicators are used.

For completely obstructed lumen of oesophagus large bougies can be used to mechanically dilate the lumen followed by careful application of the applicator, for such lesion application should be done by experienced person because there is a significant risk of perforation or bleeding from oesophagus. Applicators with largest diameters should be used. Balloon applicators can be used to achieve large diameter, such are Japanese applicator, Blackmore applicator and even sengstaken tube can be modified. Balloon can be filled with contrast to achieve a separation of 10mm from centre of source.

Application is performed under endoscopic or fluoroscopic guidance. Patients fast on morning of treatment, fluids given intravenously, local anaesthesia given to facilitate endoscope or applicator. Goal of application is always to use largest diameter applicator to prevent eccentric position of applicator, under dosing to tumour and over dose to normal structures. Application is performed in dedicated brachytherapy room. Vagolytics or sedation is given

prior to application. Oropharynx and hypopharynx are palpated by fingers to assess the applicability. When is into the oesophagus. The proximal and distal end of the tumour are noted. The distances in cm from the teeth are noted and compared to the results of pre-therapeutic examinations. A flexible guide wire with twice the length of endoscope is passed through the biopsy channel and placed far beyond the distal tumour. The endoscope is then withdrawn over the guide wire which remains in place.in fluoroscopic assisted application, applicator is introduced into oesophagus with help of two fingers placed over oropharynx, applicators is safely passed through resistance. To avoid bleeding or perforation never push through resistance. After its placement distance from tip to incisors are noted, now inner source tube can be passed. If difficulty in present in application Seldinger technique can be used. A guide wire which is twice the length of applicator is introduce through gastric tube, then gastric tube is removed, followed by which applicator is introduced carefully and finally guide wire is removed. Proximal al and distal ends of tumours are marked on patient's skin with radio opaque marker to delineate the extend of tumour. In small diameter applicators it can be passed through nose with patient on sitting position.

In supine position, two orthogonal X ray films are taken to check the applicator is in the correct position. The position of the applicator on the radiographs is carefully checked and compare with pre-treatment barium swallow, carina,

vertebral bodies, aortic notch as anatomical landmark. The tip of the applicator should reach several centimetres beyond the distal end of the visible tumour. Entire PTV should be covered adequately. In 2D planning the dose prescription point is usually taken at an arbitrary distance. This distance is based on the applicator surface, usually 5 to 8 mm from applicator. It can be related to the source axis in the case of small diameter applicators, usually 10mm. This arbitrary distance is to prevent obliteration of the lumen in palliative treatments and tumour control in curative intent. Thus, the whole oesophageal wall should be included, which is possible in small flat lesions using large diameter applicators, whereas in a palliative treatment some distance into the obliterating part of the tumour will be sufficient. The Depth of the Planning Target Volume (PTD) can only be delineated precisely using CT or MRI at the time of application with the applicator in place. Dose can be prescribed at a single point at a certain depth in central plane or at several points at distances along the source tract in stepping source afterload. The dose distribution around a line source with constant linear activity over the source length results in a cigar shaped treated volume. In stepping source dwell position and time can be changed according to anatomical location of tumour to obtain a cylindrical shape adapted to differences in target depth along the active source length, more dose in the macroscopic stenotic tumour, less dose in the proximal and distal adjacent tissue. when small diameter applicators are used, doses are prescribed and reported at a reference point 10 mm from the

source axis. A reference point at 5 mm from the applicator surface or at 5 mm tissue depth is chosen. Taking these different reference points, the reported reference doses and the dose gradients including the applicator/lumen surface doses vary significantly.

According to the recommendations of ICRU 58 (1997) the reference depth for reporting is specified in the central plane at 10 mm from the source axis for small applicators. However, this recommendation is only related to the source and not to the individual application and the individual anatomy in the patient. The ABS Consensus guidelines recommend prescribing the dose always at 10 mm from the mid source position, the Japanese guidelines recommend prescribing and reporting always at 5 mm from the applicator surface.

AIMS & OBJECTIVE

Aims and Objectives

Primary Objectives:

To assess the dysphagia scores before and after radiotherapy (External beam radiotherapy and Intraluminal Brachytherapy.

Secondary Objective:

To evaluate the toxicities

Study Centre: Dept. Of Radiotherapy, Barnard Institute of Radiology and Oncology, Madras Medical College, Chennai-03.

Duration of the Study: one year.

Study Design: Single arm prospective study

The study was reviewed and approved by the Institutional Ethical Committee

MATERIALS AND METHOD

Methodology (Material & Methods):

Inclusion Criteria:

- endoscopic and biopsy proven carcinoma of oesophagus, either squamous cell carcinoma or adenocarcinoma.
- lesion of thoracic oesophagus but not involving the cardia of stomach.
- locoregionally advanced disease not amenable to curative treatment.
- metastatic disease when the predominant symptom was dysphagia.
- informed consent singed prior to the study.

Exclusion Criteria:

- patients with tracheoesophageal fistula
- patients with stricture oesophagus
- patients suitable for curative treatment with either surgery or chemoradiation
- disease within 2cm of the cricopharynx
- disease involving gastroesophageal junction
- perforation or massive oesophageal bleeding
- previous treatment for oesophageal cancer (chemotherapy, radio therapy, laser therapy)

- pregnant women
- evidence of synchronous lung primary

Sample Size: 30 patients

Investigation Details:

- Complete history and physical examination
- upper gastrointestinal endoscopy
- biopsy of primary tumour
- fibreoptic bronchoscopy
- grading of dysphagia by **MODIFIED TAKITA'S DYSPHAGIA SCORE**

Takita's dysphagia grading

Table 6

GRADE	
GRADE I	ABLE TO EAT NORMALLY
GRADE II	REQUIRES LIQUID WITH MEALS
GRADE III	ABLE TO TAKE ONLY SEMISOLID FOOD
GRADE IV	ABLE TO TAKE ONLY LIQUIDS
GRADE V	ABLE TO SWALLOW SALIVA BUT NOT LIQUIDS
GRADE VI	COMPLTE DYSPHAGIA

LABORATORY STUDIES

- complete blood count with differential count
- serum sodium,
- Serum potassium,
- Blood glucose,
- blood urea,
- serum creatinine

RADIOGRAPHIC STUDIES

- XRAY CHEST
- contrast enhanced CT scan of thorax and abdomen

PATIENTS PREPARATION

- All patients were persuaded to quit smoking and alcohol
- Nasogastric tube placement before the initiation of treatment
- 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 RADIATION THERAPY

TARGET VOLUME

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

PORTAL

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

PHYSICAL FACTORS –

- cobalt 60 teletherapy unit

- SSD 80 Cm

DOSE FRACTIONATION

- Total dose of 30 Gy in 10 fractions, 3Gy each fraction
- 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.

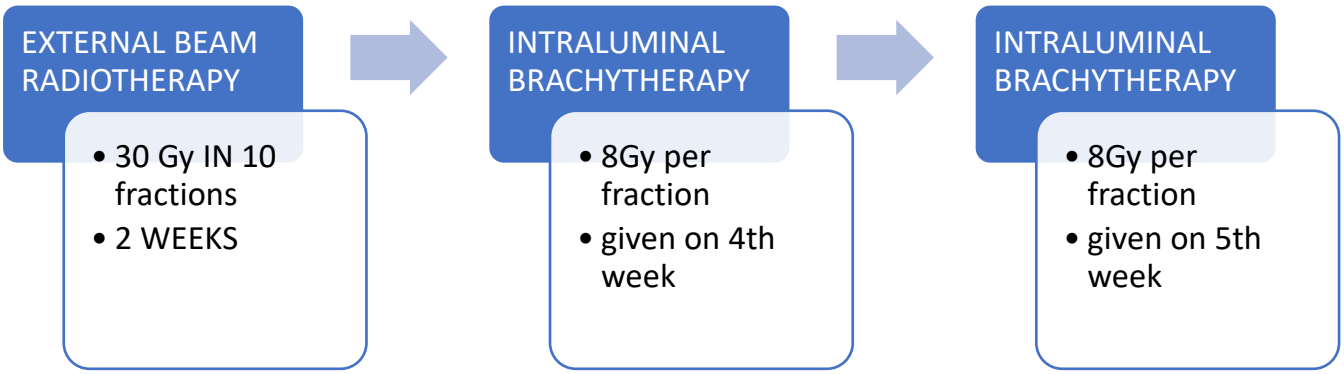
TREATMENT VERIFICATION

Treatment portals were verified by simulation films

INTRALUMINAL BRACHYTHERAPY

TIMING OF DELIVERY –

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



DOSE

- HDR brachytherapy using ^{60}CO.
- Dose of 16 Gy was delivered in two fractions, 8Gy each, spaced 1 week apart
- target dose to be prescribed at 1 cm from source axis of the applicator.
- 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:

- Planning CT were taken with dummy in situ.
- Superior and inferior extent of the tumour as evident by pre-treatment evaluation was marked and CT taken with dummy in situ

- Treatment plan was evaluated with the help of isodose curves and 3-D dose distribution by treatment planning system

ANTICIPATED TOXICITIES:

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

SUPPORTIVE CARE:

- Adequate caloric intake was encouraged
- Analgesics and sucralfate were prescribed for the management of odynophagia

CRITERIA FOR DISCONTINUATION OF TREATMENT

- Patients refusal to continue study participation
- 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.

RESULTS

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 7

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

Figure 1 Age group of study population

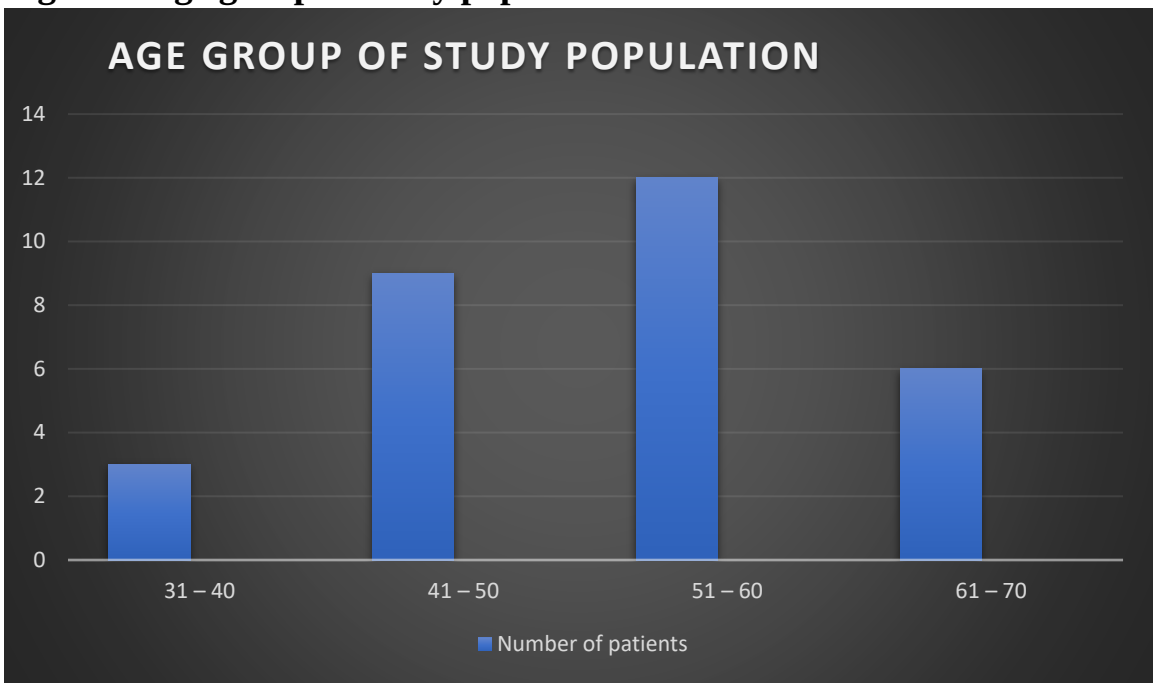
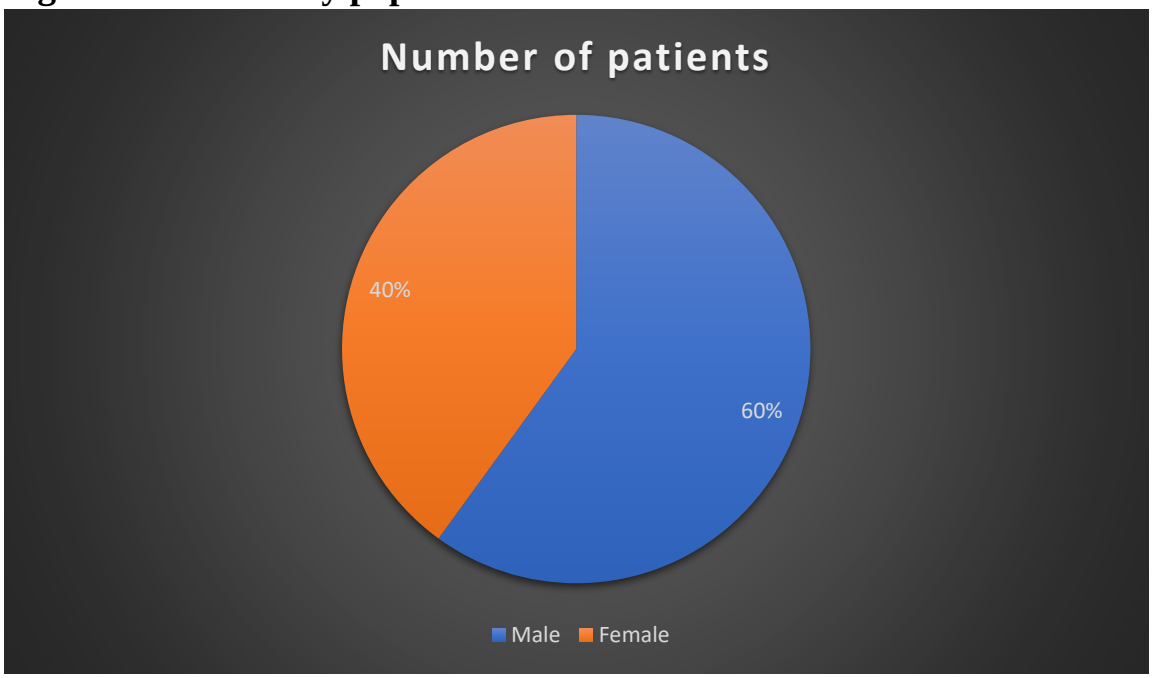


Figure 2 Sex of study population



Sex

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

Table 8

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 9

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

Figure 3 performance status of study population

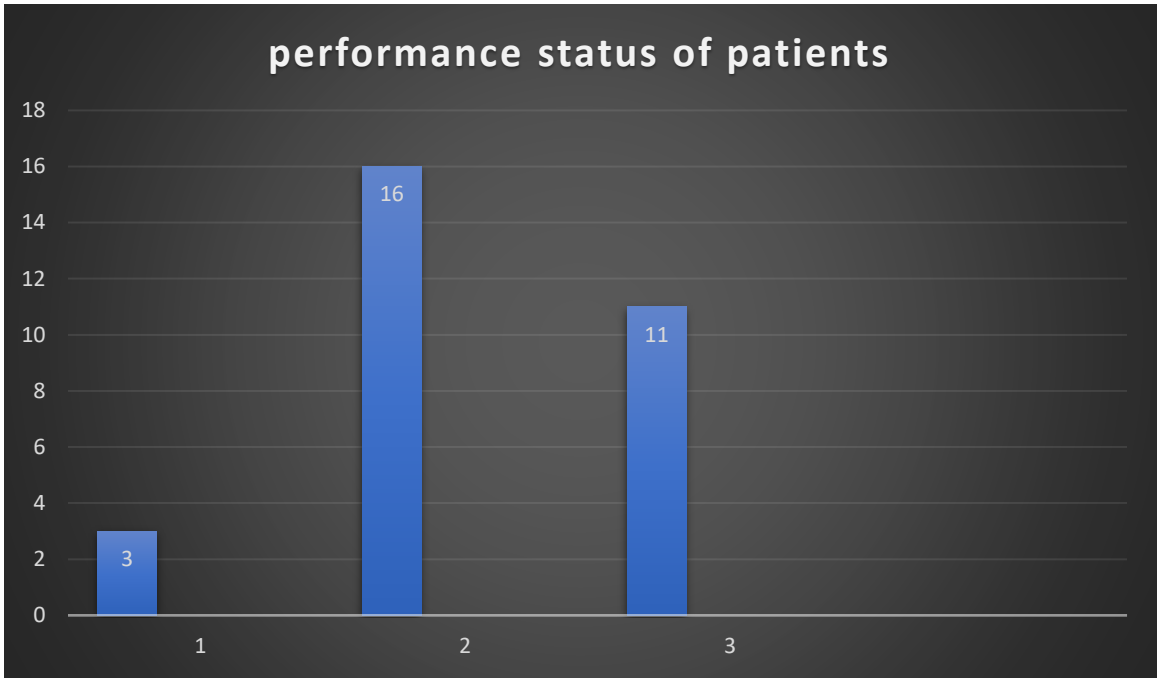
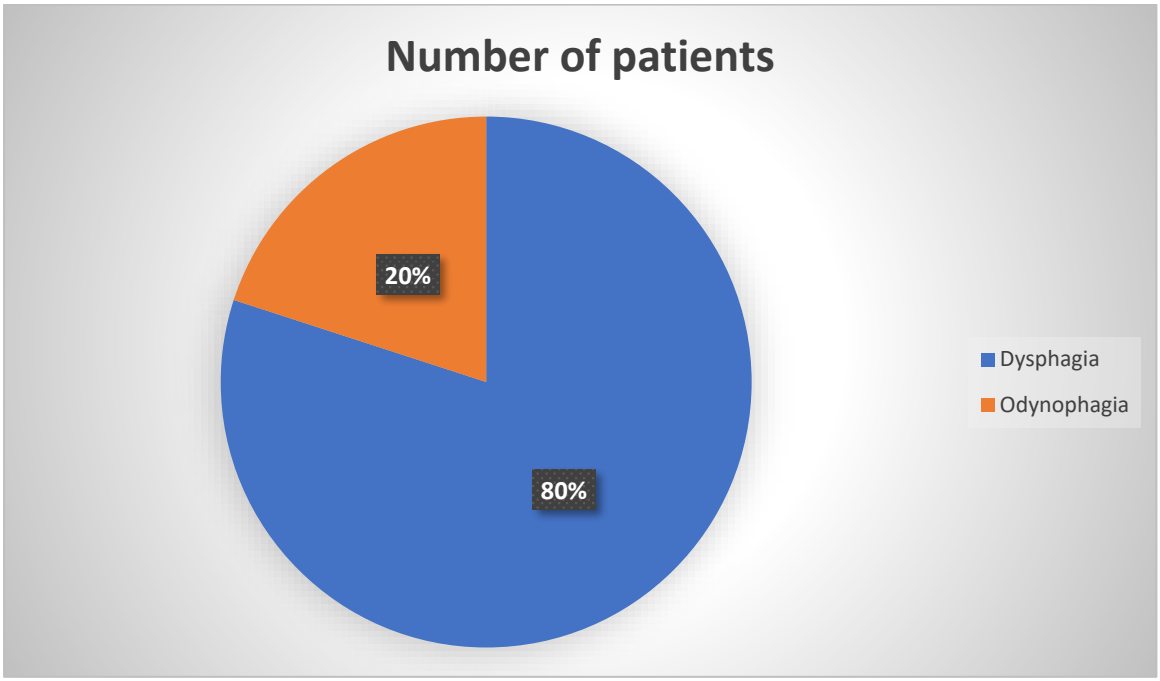


Figure 4 Presenting symptoms in patient



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 9

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 10

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%

Figure 5 Location of primary tumour

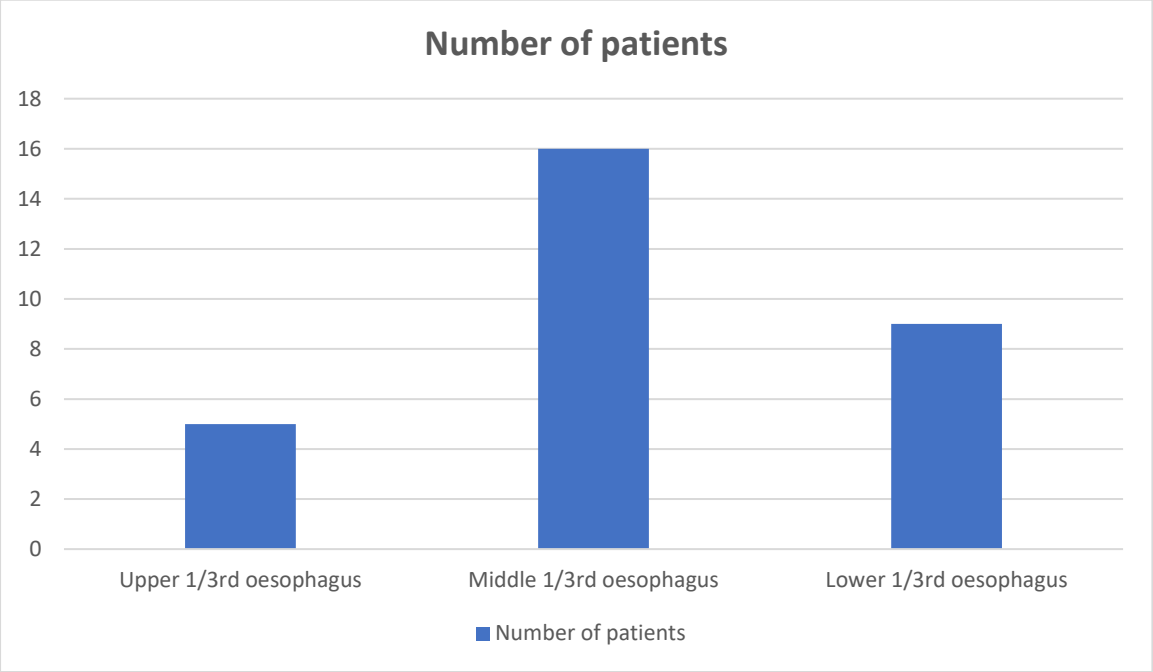
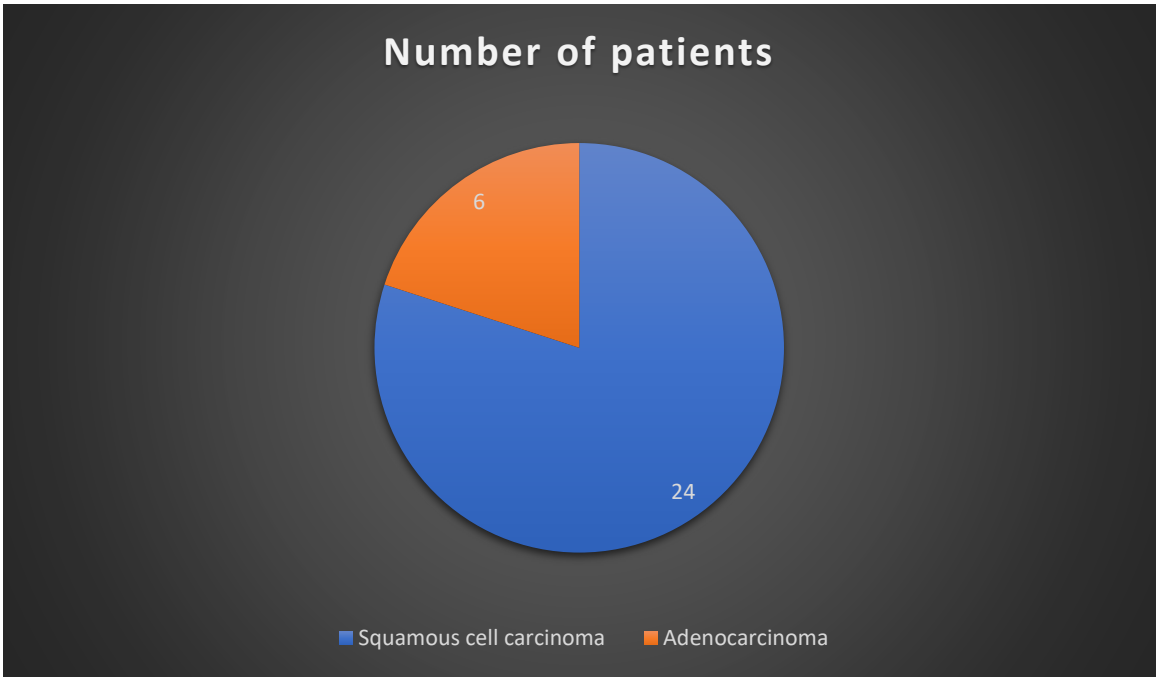


Figure 6 Histopathology



Histopathology:

Table 11

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 12

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

N stage

Table 13

N stage	Number patients	Percentage
N0	0	-
N1	2	6.6%
N2	18	60%
N3	10	33.4%

6.6% of patients had N1 Disease, 60% patients had N2 Disease and 33.4% patients had N3 disease.

M stage

17 (56.6%) patients had no evidence of metastatic disease while 13 (43.4%)patients had metastatic disease.

Table 14

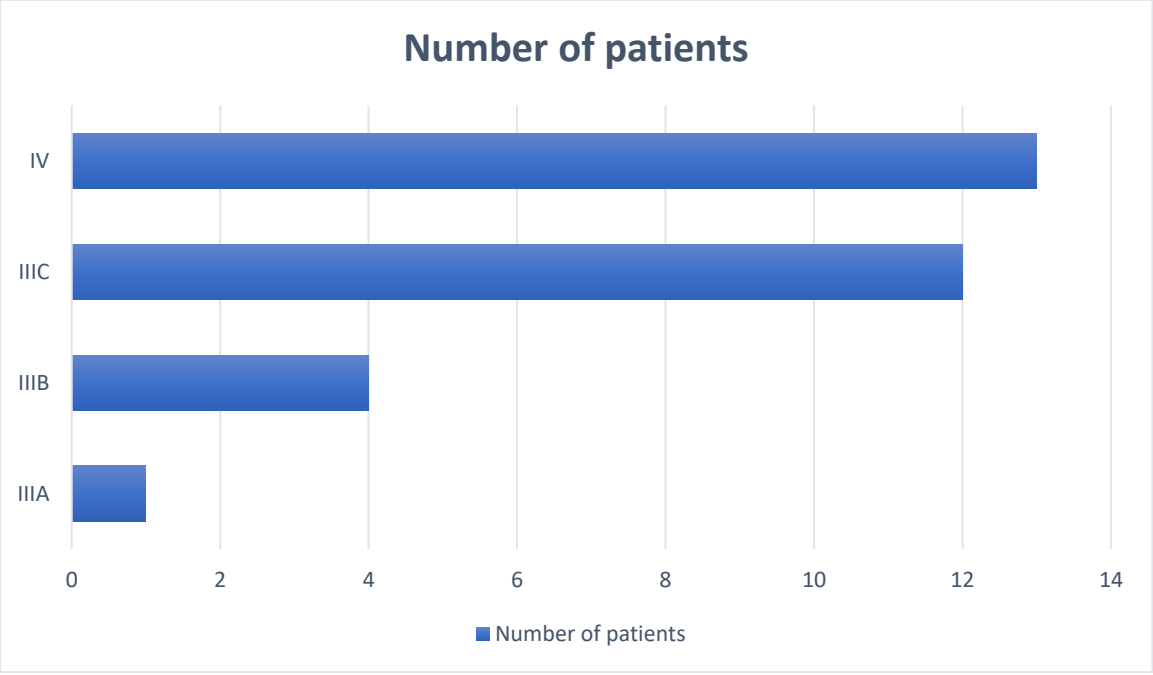
M stage	Number of patients	Percentage
M0	17	56.6%
M1	13	43.4%

Stage grouping

Table 15

Stage grouping	Number of patients	Percentage
IIIA	1	3%
IIIB	4	13.3%
IIIC	12	40%
IV	13	43%

Figure 7 Stage grouping



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 16

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 8 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 17

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-female patient had improvement in dysphagia.

Performance status

Table 18

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 18

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 19

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 20

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

Figure 9 Response according to location

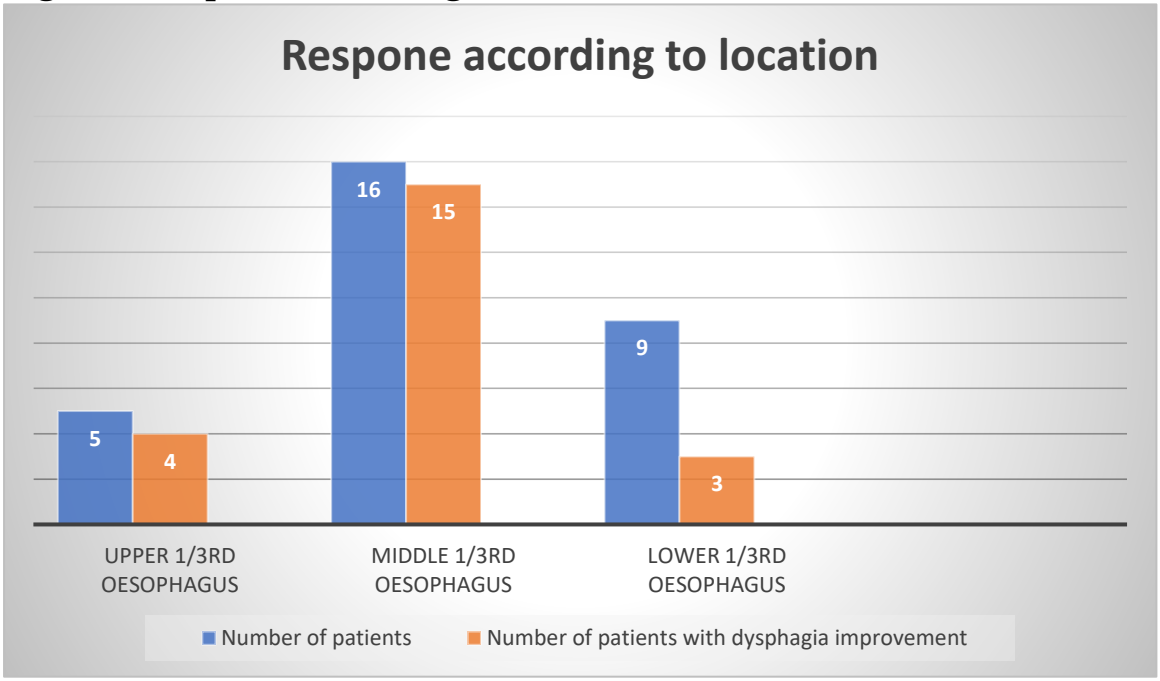
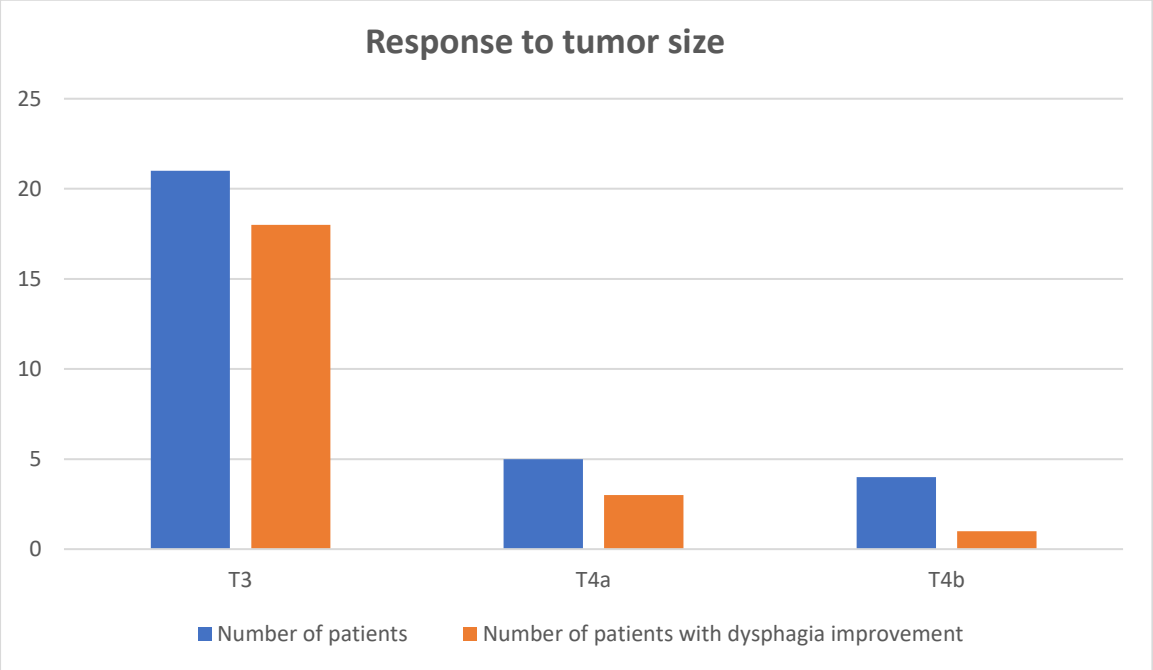


Figure 10 Response to tumour size



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.

Table 21

Acute toxicity – esophagitis

ESOPHAGITIS	NUMBER OF PATIENTS
Grade 0	7
Grade 1	13
Grade 2	8
Grade 3	1
Grade 4	1
Grade 5	0

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.

Figure 11

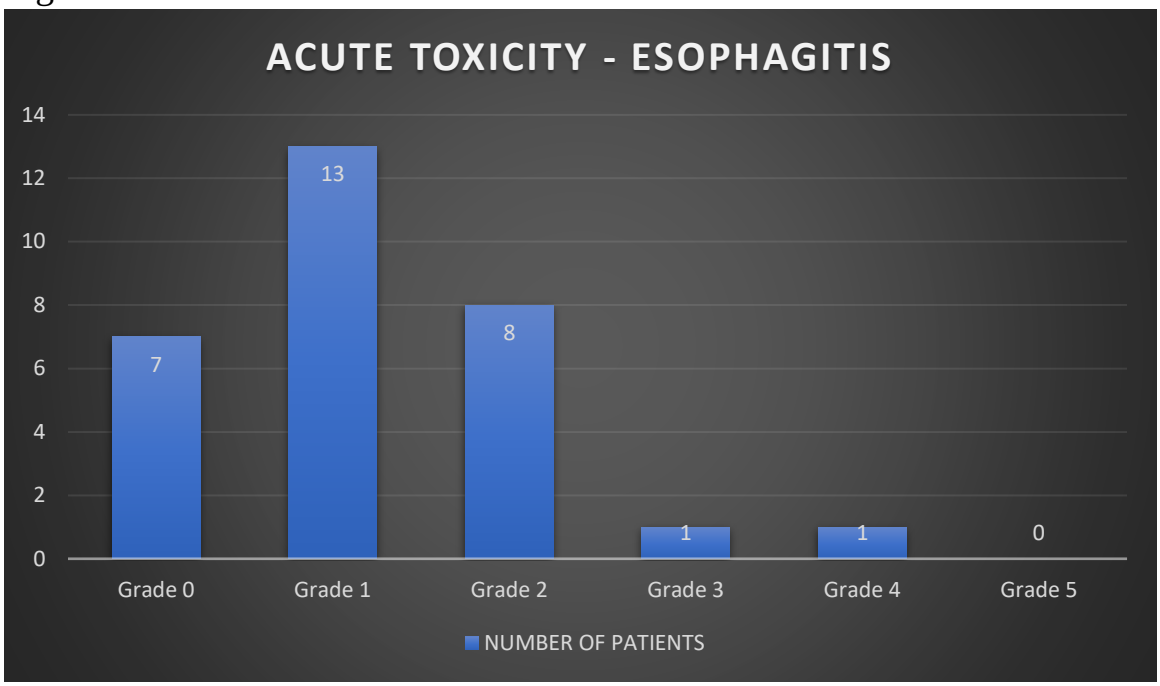


Figure 12

X-ray simulation of 73-year-old male patient, squamous cell carcinoma, lower 1/3rd oesophagus.

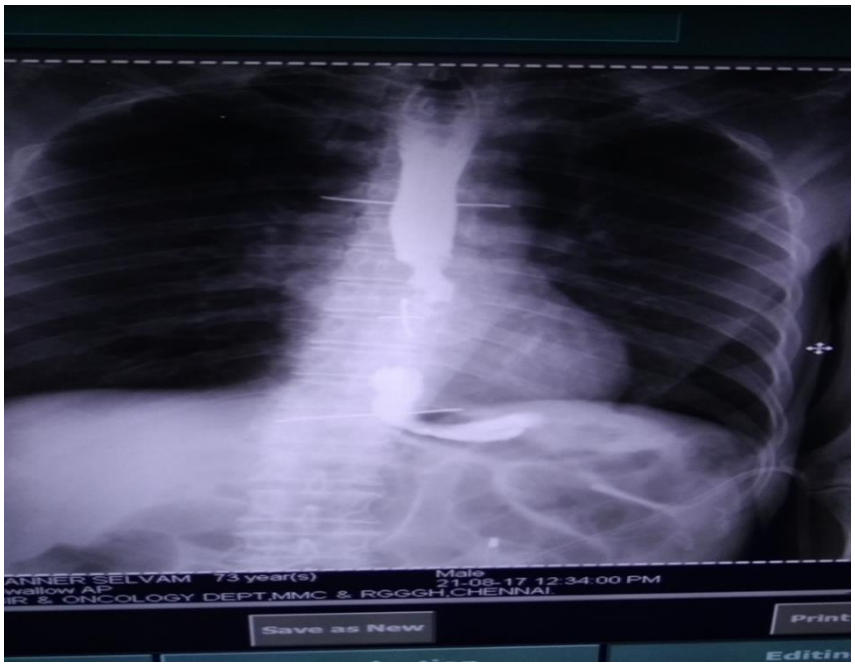


Figure 13

AP view of ILRT planning

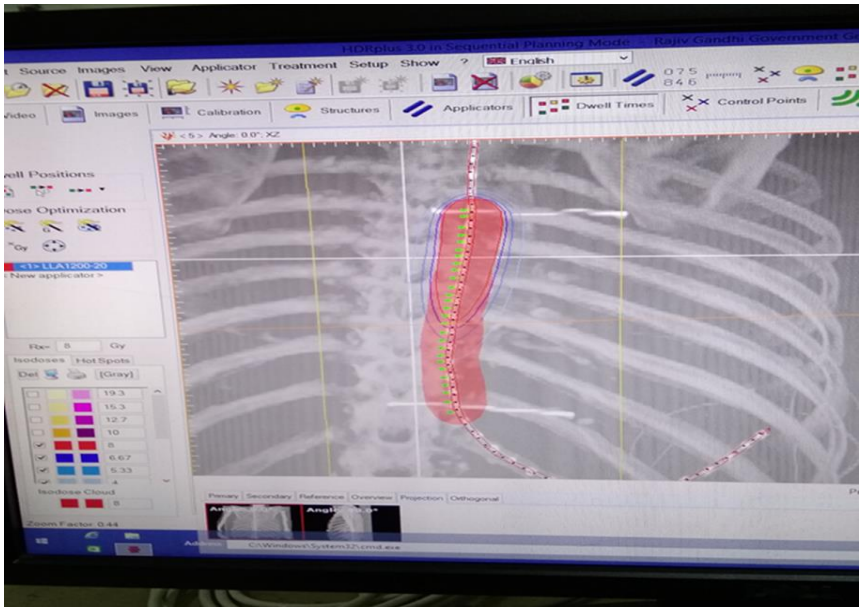


Figure 14- Lateral view of ILRT planning

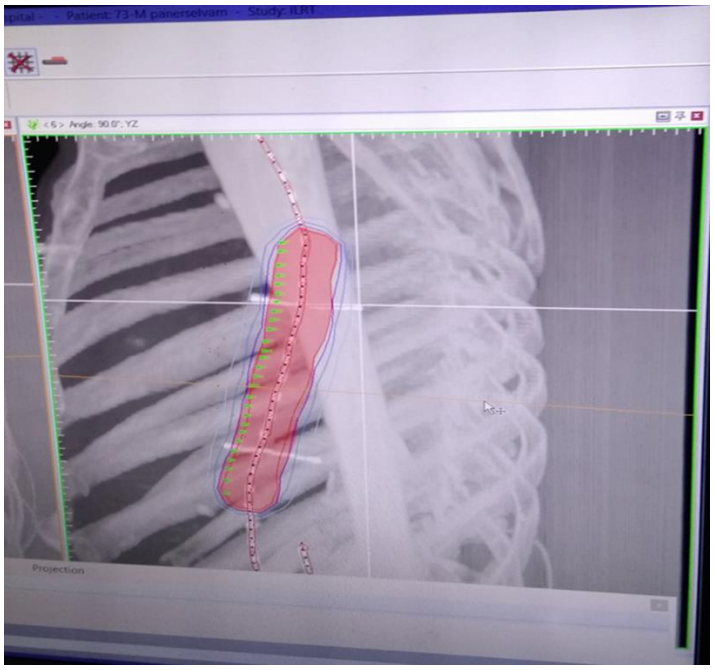
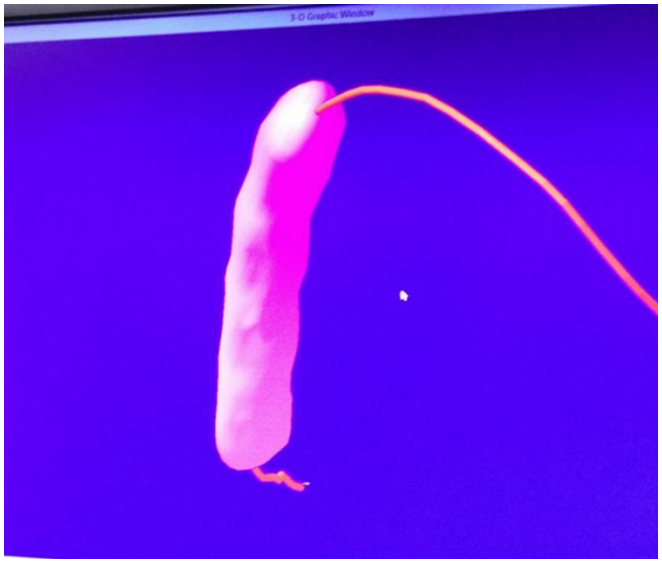


Figure 15 3D dose distribution in ILRT



DISCUSSION

DISCUSSION

At presentation most of the patients with carcinoma oesophagus have locally advanced disease or metastatic disease. Despite improvements in diagnostic modality, advance treatment methods, prognosis remains poor. Surgery is the cornerstone of treatment of oesophageal carcinoma, but only 10% of patients are resect able. With resection alone 20% to 25% 5year survival is achieved, but surgical mortality and prognosis remain unchanged. With advent of multidisciplinary approach in combination with radiation and chemotherapy an attempt to improve survival is made. The principle behind multimodality therapy is that providing chemotherapy and radiation simultaneously is to improve both locoregional and systemic control.

Most of the patients present at advanced stage and are not eligible for curative treatment, palliation becomes a necessity. Late occurrence of dysphagia in this patient population is due to lack of serosal lining for oesophagus, allowing for unimpeded radial distension and swallowing despite progressive tumour growth. As a result, dysphagia does not occur until the cancer occupies >80% of the oesophageal circumference. Further patients have tendency to modify their diets for a long time before seeking medical attention. Thus, most of the patients with oesophageal cancer present with locally advance, un resect able and metastatic disease.

In 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.

Dysphagia may progress rapidly due to tumour obstructing the lumen and due to loss of appetite. Patient may not be able to swallow solids and liquids make them nutritionally compromised and prone to infection. Obstruction can also cause regurgitation of food and cause aspiration leading to aspiration pneumonitis. So long term palliation of dysphagia is the goal. Dysphagia means difficulty in swallowing, clinically means difficulty in passage of solids and liquid bolus through the lumen of oesophagus and stomach. The average patient has had a recognizable dysphagia for at least three to six months before seeking medical care. Salilorrea or excessive salivation is regularly associated with oesophageal lumen obstruction, regurgitation of this foamy mucus with frequent spiting is common complain. Increased accumulatio of this fluid also increases the risk of aspiration leading to aspiration pneumonia. The presence of chest pain at initial presentation is also a poor prognostic sign.

Various modalities have been tried each with moderate to high success, to achieve palliation of dysphagia. These modalities include endoscopic dilation, stenting, laser therapy, photodynamic therapy, radiotherapy and chemotherapy. Among

the various procedures stenting produces high rates of palliation but for short duration compared with other modalities.

Radiotherapy has been successfully used for palliation of dysphagia. External beam radiotherapy, intraluminal brachytherapy or in combination is used. In case of external beam radiation alone with hypofractionation have better outcome with median survival of 9 months.

Hiet et al[78] reported 92% success rate for dilatation and demonstrate safety for peroral dilatation for obstructing oesophageal cancer. Forty-six patients were admitted with diagnosis of Squamous Cell Carcinoma of Oesophagus between January 1977 and December 1981. 39 (85%) patients were dilated an average of 27 times. A Maloney dilator, Eder-Puestow dilator, Hurst dilator were used. Thirty-five of the 39 patients dilated (90%) noted improvement in swallowing following dilation, allowing resumption of soft or regular diet. Failure of dilation occurred in four patients: three patients who refused further dilation and were treated with an indwelling feeding tube, and one patient who died during dilation. Those 35 patients who responded to dilation continued oral intake until shortly before death or the advent of a complication that required the placement of the prosthesis. Although adequate lumen diameter can be restored recurrent restenosis occurs within days to few weeks, this was shown by frequent dilatation. An oesophageal prosthesis can further alleviate symptoms in patients whom dilation fails. Because prosthesis placement is associated with a relatively high

rate of complications, it should be reserved for patients with advanced refractory disease or tracheo-oesophageal fistula, for whom no other palliative alternatives exist[79]. When short term response fails, physician needs to start planning and educating patients with newer approach.

David Fleischer et al[80] Symptomatic patients with dysphagia treated in palliative intent were treated endoscopically with the Nd:YAG laser. Five patients aged 49 to 64 years, with tumours ranging in length from 5 to 11 cm, were treated. Significant clinical, endoscopic and radiographic improvements were noted in all patients. No major side effects were encountered. But results are short term.

Ell and colleagues[81] reported results of laser therapy in 816 patients with oesophageal carcinoma with success rate of 83%, perforation rate of 2.1% and procedure related mortality of 1%. A more recent multicentre trial produced perforation rate of 7%[82]. This same study revealed only 50% of patients improving at least one dysphagia grade and 25% with no change. Mean survival time following thermal laser ablation is similar to other ablations[83].

Photodynamic therapy is another method to relive dysphagia. Overall efficacy of photodynamic therapy is comparable to Nd:YAG thermal ablation. PDT is technically easier, less operator depended and less painful than laser in patients under conscious sedation. The time to palliation failure of one month was comparable for PDT and thermal ablation therapy using laser. The cost using PDT is high due to porfimer sodium plus two endoscopies and hospital observation to

manage the possible short-term side effects. as with Nd:YAG laser therapy, repeat treatment is required approximately every month, a not so satisfactory r\frequency for an expensive palliative therapy in a patient with advanced carcinoma and short survival.

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] . there is a developing consensus that oesophageal obstruction due to either fibrosis from radiation or residual recurrent neoplasm is best managed by dilatation followed by peroral stent placement84. Oesophageal stent provide palliation and survival time similar to laser and other techniques designed to relive dysphagia. In prospective trail loizou et al[85] reported that long term improvement in swallowing was present only in 50% of 34 adenocarcinoma treated by lase but occurred in 92% of 20 patients treated with stent. The perforation rate of peroral stent is less than 5% and mortality is nearly zero. Once metal stents are placed they are difficult to remove or reposition. Tumour overgrowth, repositioning and slipping of stent are significant problems. Cost effectiveness is also a consideration due to high cost of metallic stent.

Radiation therapy is the most commonly used palliative treatment in patients with carcinoma oesophagus. Traditionally external beam radiation therapy was the choose modality for unresectable, locally advanced disease and other procedures such as stenting were used as supplements or recurrent cases where radiation was

not possible. There are several reasons for this: radiotherapy is one of the three conventional arms used for treatment of carcinoma oesophagus; 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. Another mode of radiation delivery is brachytherapy, with the advent of high dose rate brachytherapy like ^{192}Ir enabled radiation oncologist to deliver short treatment time from very close to tumour without violating normal tissue constraints.

Various combinations of external beam radiation and intraluminal brachytherapy has been tried.

Casper et al retrospectively analysed group of 127 patients with oesophageal carcinoma treated with external beam radiation with different dose levels. It was found that 70.5% of patients showed improvement in dysphagia and 54% remained palliated with respected to food passage until their death. The median disease-free interval and overall survival of patients treated with a relatively low dose were 2.5 and 4.8 months, compared to 10.1 and 8.3 months respectively, for patients treated with high doses.

Datta et al compared two different schedules in inoperable carcinoma of oesophagus. External beam radiation composed of group L 55 patients receiving low dose of 35 Gy in 15 fractions, while high dose group H received 50 Gy in 25 fractions. Both group received high dose rate intraluminal brachytherapy of 12

Gy in two fractions a week apart. Relief of dysphagia was 49% in group L and 75% in group H.

Rathi et al in their study have evaluated swallowing performance after giving 40Gy as palliative external beam radiation over 4 weeks response rate was about 80%.

HDR brachy alone was tried as mean of achieving good dysphagia relief with short treatment duration in patients with short life expectancy.

Sur et al compared 18 Gy in 3 fractions to 176 Gy in 2 fractions. The dysphagia free survival for whole group was 7.1 months. They conclude there was no significant difference in dysphagia relief between two fractions and intraluminal brachytherapy alone is an effective method of palliation.

Skowronek et al treated patients with unresectable, locally advanced oesophageal cancer with HDR brachytherapy. All patients received a total dose of 22.5 Gy in three fractions. Remission of dysphagia and other clinical and radiological factors were assessed in the first month post treatment. They concluded that HDR brachytherapy allowed for improvement of dysphagia in most patients.

Sharma et al treated fifty-eight patients with unresectable, locally advanced oesophageal cancer with HDR brachytherapy with or without irradiation. The mid-third of the oesophagus involved in 38 patients, four with metastatic disease, and four with second primary oesophageal lesions and twenty-one with recurrent

tumours. Thirty-eight patients (65%) received intraluminal brachytherapy alone. 20 patients (35%) received a combination of external and intraluminal radiation therapy. 0All patients received 2 fractions of HDR intraluminal brachytherapy 1 week apart with 6 Gy per fraction at 1 cm off axis. Overall improvement in swallowing status was seen in 48%, and 41% maintained pre-treatment swallowing status. Median dysphagia-free survival was 10 months. Overall complication rates were 30%, with stricture seen in 9 patients, tracheo-oesophageal fistula in 3 patients and ulceration in 6. Complication rates were higher in the post-treatment group than in the previously untreated group. The median overall survival for the entire group was 7 months. Median survival was better, although not significantly, for the previously untreated cohort: 7.8 months vs. 6 months for the post-treatment group. They concluded HDR ILRT achieved good palliation with acceptable complication in advanced and recurrent oesophageal tumours.

While brachytherapy alone may alleviate dysphagia in patients with a life expectancy of 1-3 months, addition of external beam radiation may prolong the duration of relief of dysphagia, external g=beam radiation can be delivered before or after intraluminal brachytherapy.

Sur et al conducted a trail in which HDR intraluminal brachytherapy of 16 Gy in 2 fractions was given to all patients. Following treatment, patients were randomized to receive no further treatment in group A or receive 30 Gy of

external beam radiation in 10 fractions. Patients were followed for 1 year. They concluded that from the preliminary analysis, adding External beam radiation to intraluminal brachytherapy does not improve disease free survival.

Agarwal et al treated seventy patients who were unsuitable for surgery with combined external beam radiotherapy 20 to 50 Gy in 5 to 20 fractions over a period of 1 to 4 weeks, followed by intraluminal brachytherapy in sixty-six patients with PDR after loading. Dysphagia was relived in 65 patients although 39 patients subsequently need repeated dilatation.

Kohek et al[90] conducted study on unresectable, locally advanced oesophageal cancer with brachytherapy and external beam irradiation. Durable palliation of dysphagia occurred in 96% of patients.

In a study conducted by Yadav et al[91] 116 patients who were inoperable were prospectively randomized to three different arms of radiation. Arm A received EBRT 30Gy in 10 fractions followed by ILRT of 12 Gy in two fractions, Arm B received 30 Gy in 10 fractions of EBRT alone. Arm C received 20 Gy in 5 fractions EBRT alone. Improvement of dysphagia was seen in 76% of patients in arm A, 56% in arm B and 54% in arm C at one month.

In a study conducted by Rajeev atri at PGIMS Rohtak patients were retrospectively analysed, 30 patients who underwent curative chemoradiation of external beam radiation of 40 Gy in 2 Gy per fraction followed by 15 Gy in 3 fraction 5Gy per fraction Intraluminal Brachytherapy Boost, were compared with

patients who received external beam radiation only of 60 Gy. Complete response was 37% in arm A and 23% in arm B. overall survival was similar. The author concluded that adding brachytherapy does not improve survival but provides dysphagia relief.

Metanalysis of prospective studies on palliation of dysphagia by intraluminal brachytherapy done fuccio et al in University of Bologna, Italy. In this analysis studies which included at least 20 patients were analysed. Systematic review to examine efficacy and safety in treatment was done. Six studies were included with 623 patients. Disease free survival and adverse effect were analysed. Results were DFS at the end of one month was 86.9%, at end of 3 month was 67.2%, at the end of 6 months was 47.4% and at the end of 1 year was 29.4%. complications were 22.3% and death during treatment was .3%. analysis concluded that brachytherapy is a safe and effective method for palliation of dysphagia.

In a study conducted at Tata memorial Hospital Mumbai 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 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 OS 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 to metaanlaysis 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 follow up 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 22

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 23

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.

CONCLUSION

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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APPENDIX

APPENDIX I

TABLES

1	Specific regional lymph node
2	TNM classification
3	Staging of Squamous cell carcinoma
4	Staging of adenocarcinoma
5	Palliative modalities
6	Modified Takita's dysphagia scoring
7	Age of study population
8	Performance status of study population
9	Presenting symptoms
10	Tumour characteristics
11	Histopathology
12	T staging
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17	Response of tumour – gender
18	Response of tumour – location
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21	Acute toxicity - esophagitis
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APPENDIX 2

FIGURES

1	Age of population
2	Sex of study population
3	Performance status of study population
4	Presenting symptom
5	Location of primary tumour
6	Histopathology
7	Stage grouping
8	Response to dysphagia
9	Reponses according to location
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11	Acute toxicity - esophagitis
12	X-ray simulation
13	AP view of ILRT planning dose distribution
14	Lateral view of ILRT planning dose distribution
15	3D dose distribution

APPENDIX 3

GRTOG ACUTE RADIATION MORBIDITY CRITERIA

Grade	0	1	2	3	4	5
SKIN	No symptoms	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate oedema	Confluent, moist desquamation other than skin folds, pitting oedema	Ulceration, haemorrhage, necrosis	death directly related to radiation effects
Oesophagus	No symptoms	Mild dysphagia or odynophagia, Topical anaesthetics or NSAIDs, Soft diet	Moderate dysphagia or odynophagia, Narcotic analgesics, Puree or liquid diet	Severe dysphagia or odynophagia, Dehydration or weigh loss >15%, IV fluids.	Complete obstruction, ulceration, perforation, fistula	Death directly related to radiation effects

RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEME.

Grade	0	1	2	3	4	5
Skin	no symptoms	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration	death directly related to radiation effects

Oesophagus	no symptoms,	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis / perforation fistula	death directly related to radiation effects

ANNEXURES

ANNEXURE 1

INFORMATION TO PARTICIPANTS

Title: ASSESSMENT OF THE EFFICACY OF EXTERNAL BEAM RADIOTHERAPY FOLLOWED BY INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF DYSPHAGIA IN PATIENTS WITH CARCINOMA ESOPHAGUS

Name of Participant:
Name of the Principal(co – investigator) : DR.INGERSAL N
Name of the institution : Department of radiotherapy, RGGGH, MMC.

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?
Esophageal carcinoma constitutes 4.1% of all cancer cases in the Indian population.
They are usually associated with poor prognosis owing to late presentation with advanced disease (which is seen in 60 - 70% of cases)
For such cases, curative options are limited and the main objective of treatment becomes palliation of dysphagia. Palliation also aims at diminishing pain & bleeding, as well as improving the patient's well-being. more than 50% of esophageal cancers are inoperable at presentation due to locally advanced or metastatic disease or severe comorbidities patients restoration of the ability to eat is only possible therapy
since most patient survive no longer 6 months aim is palliative treatment to relive dysphagia rapidly with minimal or no hospital stay and to maintain the ability of swallowing during life thus improving or maintain quality of life. To assess dysphagia before and after externalbeam radiotherapy 30gy followed by 2# 8gy intraluminal brachytherapy.

- To assess efficacy of external beam radiotherapy and intraluminal brachytherapy in palliation of dysphagia in carcinoma esophagus , We have obtained permission from the Institutional Ethics Committee.

The study design
Single arm prospective study

Study Procedures
The study involves assessment of dysphagia before and after external beam radiation and intraluminal brachytherapy. Blood investigation barium swallow will be done before and after radiation , These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.
You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator — Signature of Participant

Date — Date

ANNEXURE 2

INFORMED CONSENT FORM

TITLE OF THE STUDY **ASSESSMENT OF THE EFFICACY OF EXTERNAL BEAM RADIOTHERAPY FOLLOWED BY INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF DYSPHAGIA IN PATIENTS WITH CARCINOMA ESOPHAGUS**

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) : **DR. INGERSAL N**

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising myfree power of choice, hereby give my consent to be included as a participant in "ASSESSMENT OF THE EFFICACY OF EXTERNAL BEAM RADIOTHERAPY FOLLOWED BY INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF DYSPHAGIA IN PATIENTS WITH CARCINOMA ESOPHAGUS"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *****
8. I have not participated in any research study within the past 12month(s). *****
9. I agree to under go complete blood count, renal and liver function test, chest x ray, barium swallow, CT scan of the thorax
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)
Name _____ Signature_____ Date_____
Name and Signature of impartial witness (required for illiterate patients):
Name _____ Signature_____ Date_____
Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent
Name _____ Signature_____ Date_____

ஆராய்ச்சிதகவல் தாள்

ஆராய்ச்சியின் பெயர்:
வெளி மற்றும் உள்கதிர்வீச்சு பயன்படுத்தி உணவுக்குழாய் புற்றுநோய் விழுங்கற்கேடு மதிப்பீடு

ஆராய்ச்சியாளர் பெயர்: DR. இங்கர்சால் ந

பங்கேற்பாளர் பெயர்**:**

சென்னை இராஜீவ்காந்தி அரசு பொதுமருத்துவமனைக்கு வரும் உணவுக்குழாய் நோயாளியிகளிடம் கதிர்வீச்சுசிகிச்சை பற்றிய ஆராய்ச்சி.
உணவுக்குழாய் முற்றியபுற்றுநோய்க்கு பலவகையான கதிர்வீச்சுசிகிச்சை முறைகள் உள்ளன அதன் தொடர்பாக ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.
நீங்களும் இந்தஆராய்ச்சியில் பங்கேற்கவிரும்புகிறோம்.
இந்தஆராய்ச்சியில் கதிர்வீச்சுசிகிச்சை (உள் மற்றும் வெளி கதிர்வீச்சு) அளித்து சில சிறப்புபரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்
முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.
இந்தசிறப்புபரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மைபற்றியும் ஆராய்ச்சியின் போதுஅல்லதுஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

_____
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ஆராய்ச்சியாளர் கையொப்பம்:

பங்கேற்பாளர்கையொப்பம்:
தேதி:

ஆராய்ச்சிஒப்புதல் கடிதம்

பெயர்: தேதி:

வயது: உள்/புற நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண்:

ஆராய்ச்சியின் பெயர்:

வெளி மற்றும் உள்கதிர்வீச்சு பயன்படுத்தி புற்றுநோய் உணவுக்குழாய் விழுங்கற்கேடு மதிப்பீடு

ஆராய்ச்சியாளர் பெயர்: DR. இங்கர்சால் ந

பங்கேற்பாளர் பெயர்:

சென்னை இராஜீவ்காந்தி அரசு பொதுமருத்துவமனைக்கு வரும் உணவுக்குழாய் நோயாளியிகளிடம் கதிர்வீச்சுசிகிச்சை பற்றிய ஆராய்ச்சி.

உணவுக்குழாய் முற்றியபுற்றுநோய்க்கு பலவகையான கதிர்வீச்சுசிகிச்சை முறைகள் உள்ளன அதன் தொடர்பாக ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்தஆராய்ச்சியில் பங்கேற்கவிரும்புகிறோம். இந்தஆராய்ச்சியில் கதிர்வீச்சுசிகிச்சை (உள் மற்றும் வெளி கதிர்வீச்சு) அளித்து சில சிறப்புபரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்தசிறப்புபரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மைபற்றியும் ஆராய்ச்சியின் போதுஅல்லதுஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

_____ _____

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர்கையொப்பம்தேதி:

தேதி:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301A
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Ingersal.N.
Post Graduate in MD Radiotherapy
Madras Medical College
Chennai 600 003

Dear Dr.Ingersal.N.,

The Institutional Ethics Committee has considered your request and approved your study titled **"ASSESSMENT OF THE EFFICACY OF EXTERNAL BEAM RADIOTHERAPY FOLLOWED BY INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF DYSPHAGIA IN PATIENTS WITH CARCINOMA ESOPHAGUS" NO. 12102016.**

The following members of Ethics Committee were present in the meeting hold on **04.10.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.K.Ramasubramanian,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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https://clinicaltrials.gov/ct2/show/NCT00665197

Instances where selected sources appear:

9

CERTIFICATE – II

This is to certify that this Dissertation work titled **"ASSESSMENT OF THE EFFICACY OF EXTERNAL BEAM RADIOTHERAPY FOLLOWED BY INTRALUMINAL BRACHYTHERAPY IN PALLIATION OF DYSPHAGIA IN PATIENTS WITH CARCINOMA ESOPHAGUS"** of the candidate **Dr.INGERSAL N** with registration Number **201519003** for the award of **M.D. Degree** in the branch of **RADIOTHERAPY**.

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S.NO	AGE	SEX	LOCATION	HISTOLOGY	T-STAGE	N-STAGE	M-STAGE	STAGE-GRO	PRE TREAT	POST TREA	TOXICITY GRADE	
1	52	MALE	MIDDLE	SQUAMOU	T3	N3	M0	IIIC	4	2	1	
2	42	MALE	MIDDLE	SQUAMOU	T3	N2	M1	IV	3	2	2	
3	58	MALE	UPPER	SQUAMOU	T3	N3	M0	IIIC	4	2	1	
4	39	FEMALE	MIDDLE	SQUAMOU	T3	N2	M1	IV	2	1	0	
5	45	MALE	LOWER	ADENO	T3	N3	M0	IIIC	4	2	1	
6	35	FEMALE	UPPER	SQUAMOU	T4	N2	M1	IV	4	3	3	
7	53	FEMALE	MIDDLE	SQUAMOU	T3	N3	M0	IIIC	3	2	2	
8	39	MALE	MIDDLE	SQUAMOU	T3	N2	M1	IV	2	1	0	
9	65	FEMALE	UPPER	SQUAMOU	T3	N2	M1	IV	4	3	1	
10	46	MALE	MIDDLE	SQUAMOU	T3	N2	M0	IIIB	3	2	1	
11	54	FEMALE	LOWER	ADENO	T3	N2	M1	IV	3	2	1	
12	43	MALE	MIDDLE	SQUAMOU	T3	N2	M0	IIIB	5	3	2	
13	62	MALE	LOWER	ADENO	T4	N3	M0	IIIC	4	3	2	
14	44	FEMALE	MIDDLE	SQUAMOU	T4	N2	M1	IV	2	1	0	
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16	69	FEMALE	LOWER	SQUAMOU	T4	N2	M1	IV	4	2	1	
17	56	MALE	MIDDLE	SQUAMOU	T3	N3	M0	IIIC	4	4	2	
18	48	MALE	MIDDLE	SQUAMOU	T3	N2	M1	IV	3	1	0	
19	65	MALE	LOWER	ADENO	T4	N2	M0	IIIC	4	2	1	
20	55	MALE	LOWER	SQUAMOU	T3	N3	M1	IV	3	2	1	
21	68	FEMALE	MIDDLE	SQUAMOU	T3	N1	M0	IIIA	5	5	4	
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23	58	FEMALE	MIDDLE	SQUAMOU	T3	N3	M0	IIIC	3	2	0	
24	52	MALE	LOWER	SQUAMOU	T3	N2	M0	IV	4	2	2	
25	59	FEMALE	MIDDLE	SQUAMOU	T4	N3	M1	IV	3	2	2	
26	70	MALE	UPPER	SQUAMOU	T3	N1	M1	IV	3	2	1	
27	55	MALE	MIDDLE	SQUAMOU	T4	N2	M0	IIIC	4	1	0	
28	48	MALE	LOWER	ADENO	T4	N3	M0	IIIC	3	2	1	
29	59	FEMALE	UPPER	SQUAMOU	T3	N2	M0	IIIB	5	2	2	
30	58	MALE	MIDDLE	SQUAMOU	T3	N2	M1	IV	3	3	1	