NEOADJUVANT CHEMORADIOTHERAPY IN TREATMENT OF RESECTABLE CARCINOMA ESOPHAGUS- TOLERABILITY AND TOXICITIES

A dissertation submitted to

the Tamilnadu Dr. M.G.R. Medical University, Chennai,

in partial fulfilment of the requirements for the award of the degree of

DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY

April 2017

CERTIFICATE

This is to certify that this dissertation titled "**NEOADJUVANT CHEMORADIOTHERAPY IN TREATMENT OF RESECTABLE CARCINOMA ESOPHAGUS- TOLERABILITY AND TOXICITIES"** is a bonafide record of the work done by **DR. MUTHIAH.K**, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of his postgraduate study for the degree of M.D. (Branch IX–Radiotherapy) from 2014-2017 under my direct guidance and supervision.

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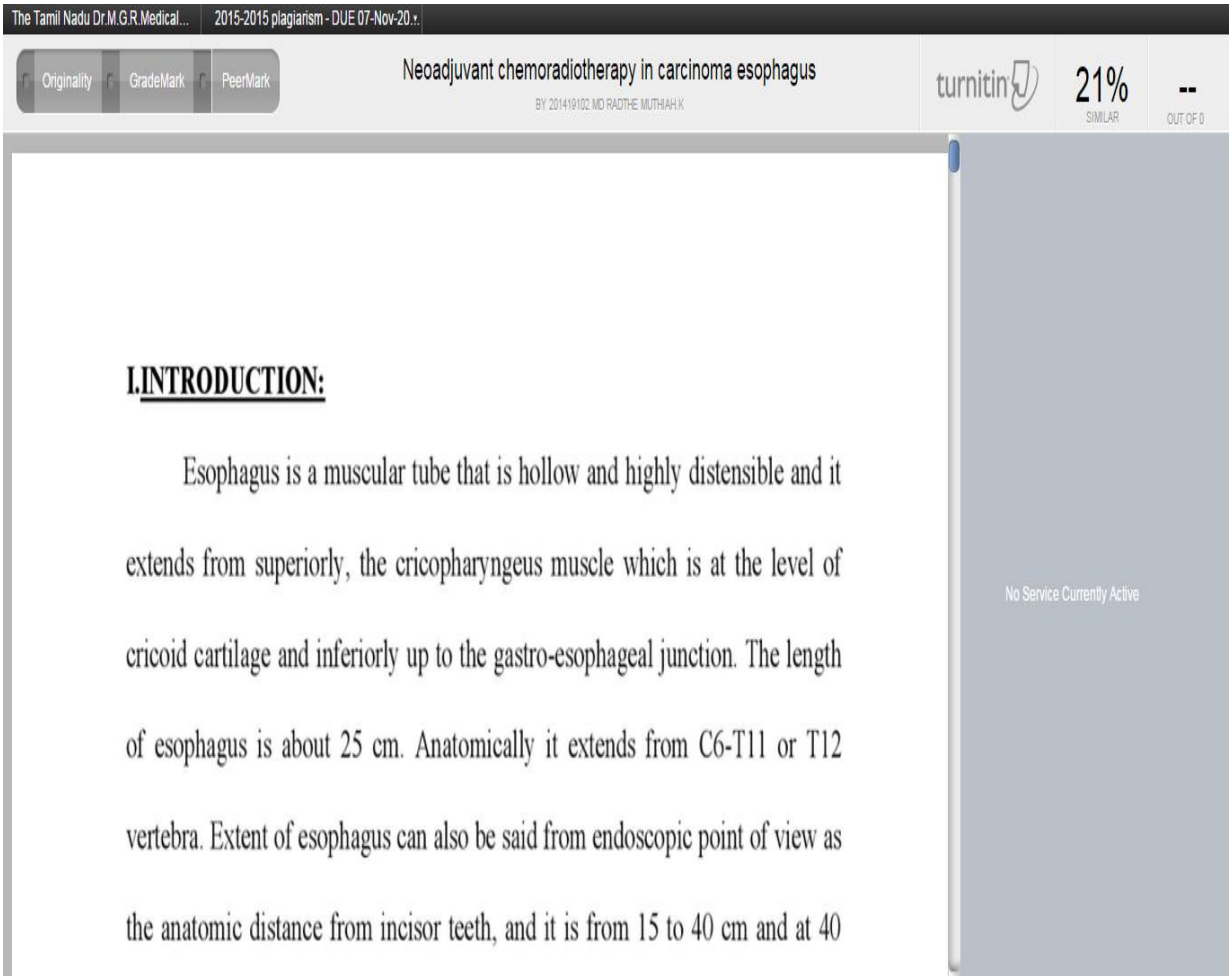

I.INTRODUCTION:

Esophagus is a muscular tube that is hollow and highly distensible and it extends from superiorly, the cricopharyngeus muscle which is at the level of cricoid cartilage and inferiorly up to the gastro-esophageal junction. The length of esophagus is about 25 cm. Anatomically it extends from C6-T11 or T12 vertebra. Extent of esophagus can also be said from endoscopic point of view as the anatomic distance from incisor teeth, and it is from 15 to 40 cm and at 40

PREFACE

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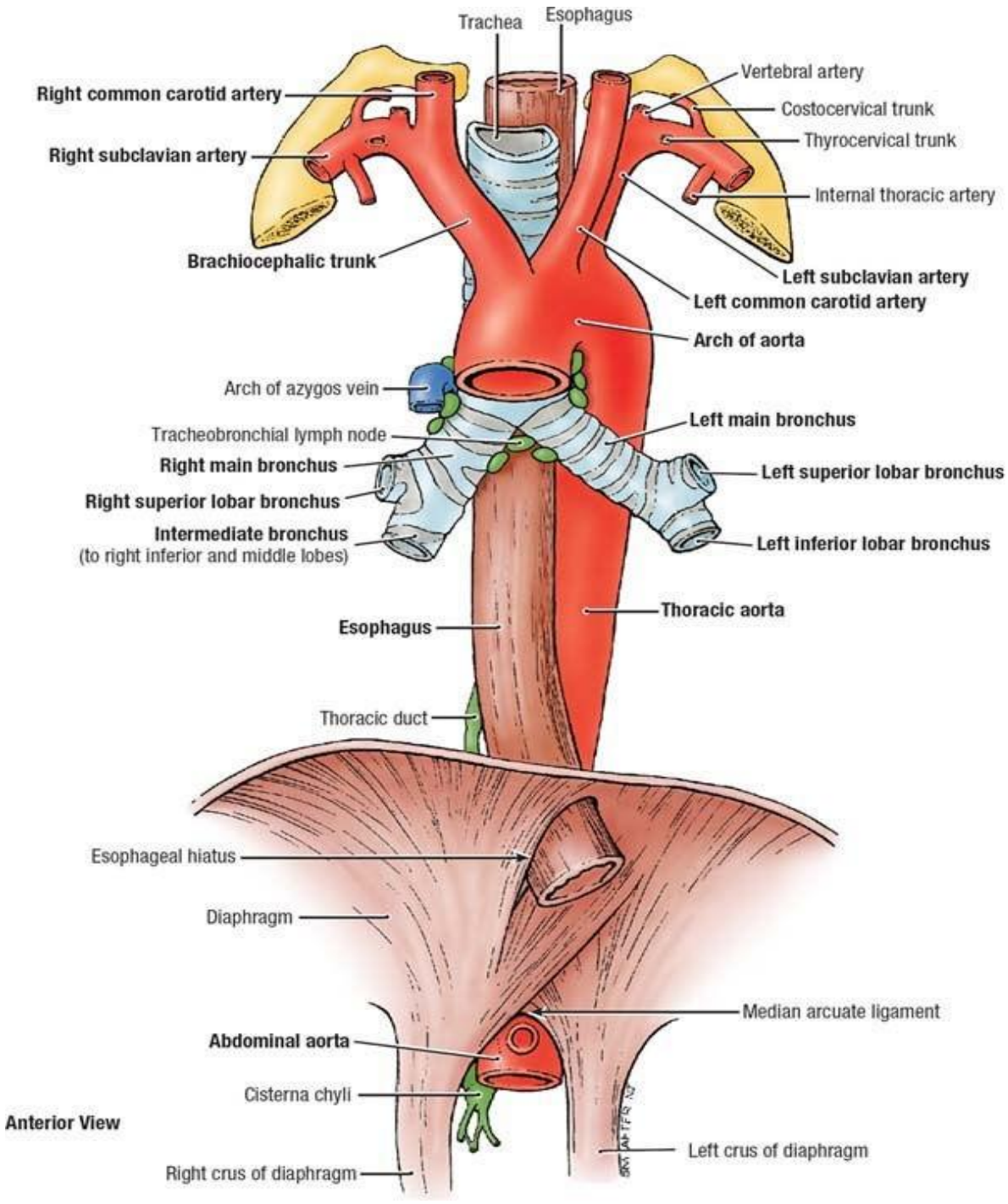
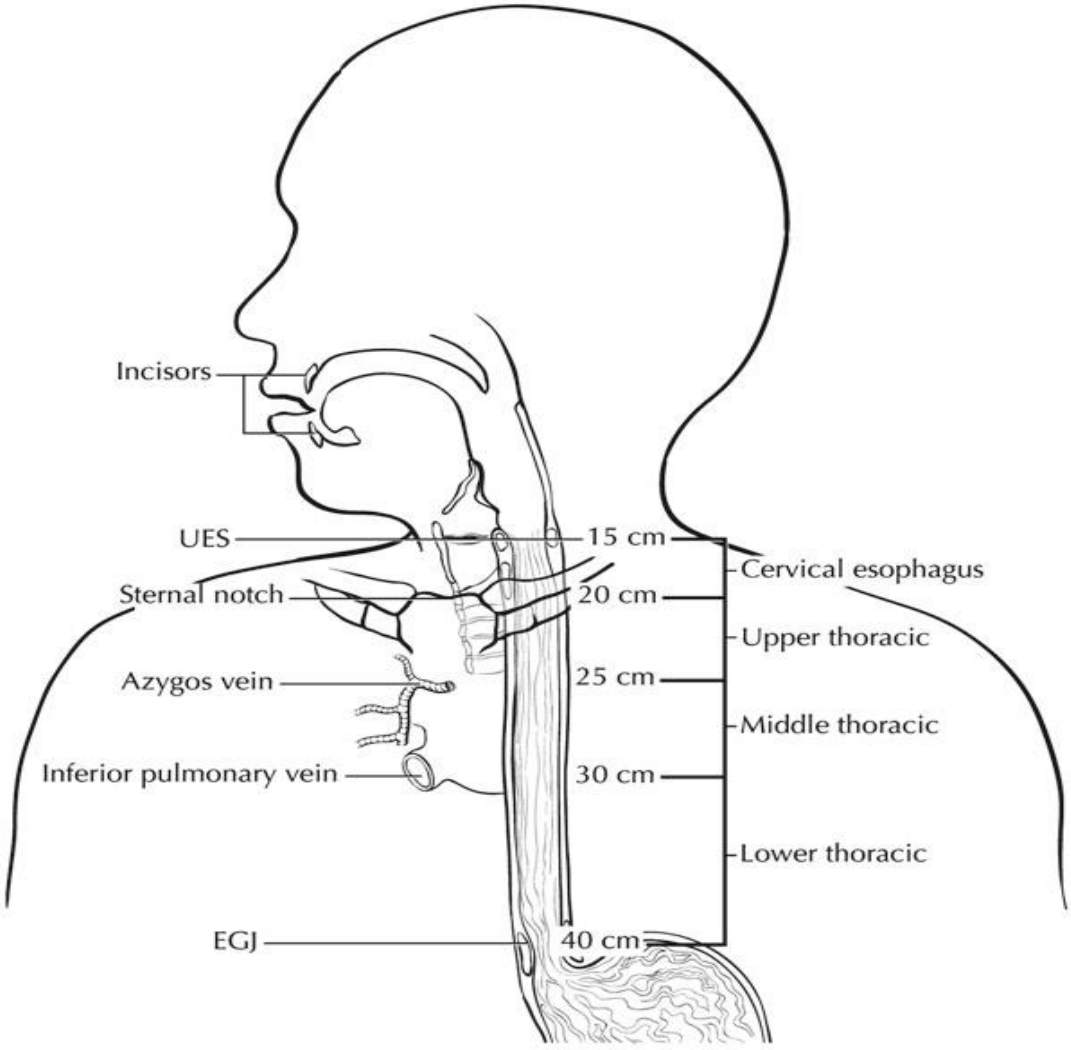
Along the course of esophagus there are three constrictions- proximally at the level of cricoid cartilage, and in midway at the anterior crossing of the left atrium and left main bronchus along the side of aortic arch and distally at the level where esophagus is entering in to the diaphragm (at T10 level). Esophagus has two physiologic sphincters. Upper esophageal sphincter is formed by the 3 cm segment at the level of superior border, formed by cricopharyngeus muscle and the lower esophageal sphincter (LES) is 2 to 4 cm segment which is at the level of diaphragm just proximal to the anatomic gastro-esophageal junction. There is no anatomic landmark that helps in delineating the intervening musculature from these high pressure regions.

AJCC Classification:

The esophagus is divided into four regions by the most recent American Joint Committee on Cancer (AJCC) [1]: Cervical, Upper thoracic, Mid thoracic and Lower thoracic esophagus.



Anatomically the borders of cervical esophagus which lies in the neck are formed superiorly by the hypopharynx and inferiorly by the thoracic inlet which is present at the level of sternal notch. Endoscopically it extends from 15-20 cm. CT wise the cervical portion is considered to be the esophageal wall thickening which begins above sternal notch. It extends from C7-T3 vertebra.



The borders of upper thoracic esophagus are formed by thoracic inlet superiorly and inferiorly by lower border azygos vein. Great veins, trachea, arch vessels and surround it anteriorly and it is related to the vertebra posteriorly. CT

location is from sternal notch till azygos vein inferiorly. Endoscopic extension is from 20-25 cm from incisor and from D3-D5 vertebra.

The extension of middle thoracic esophagus is from D5 to D8 vertebra, bordered by lower border of azygos vein superiorly and the inferior pulmonary veins forms the lower limit and identified by CT with the same structures as landmark. On the left it is related to the descending thoracic aorta. It is related anteriorly to the pulmonary hilum, and posteriorly to the vertebra and it is sandwiched between them. Endoscopic extension is from 25 to 30 cm from incisors.

The lower thoracic esophagus is superiorly bordered by the inferior pulmonary veins and inferiorly by the stomach. It includes the Gastro-esophageal junction. Anteriorly it is related to the pericardium and posteriorly to the vertebra. It is related on the left to the descending thoracic aorta. The intra abdominal portion of esophagus is variable. Endoscopically it extends from 30 to 40 cm from incisors. Vertebral level corresponding to lower thoracic esophagus is from D8-D11 vertebra. One more important landmark endoscopically is the carina which is at 25 cm from esophagus.

SIEWERT's CLASSIFICATION:

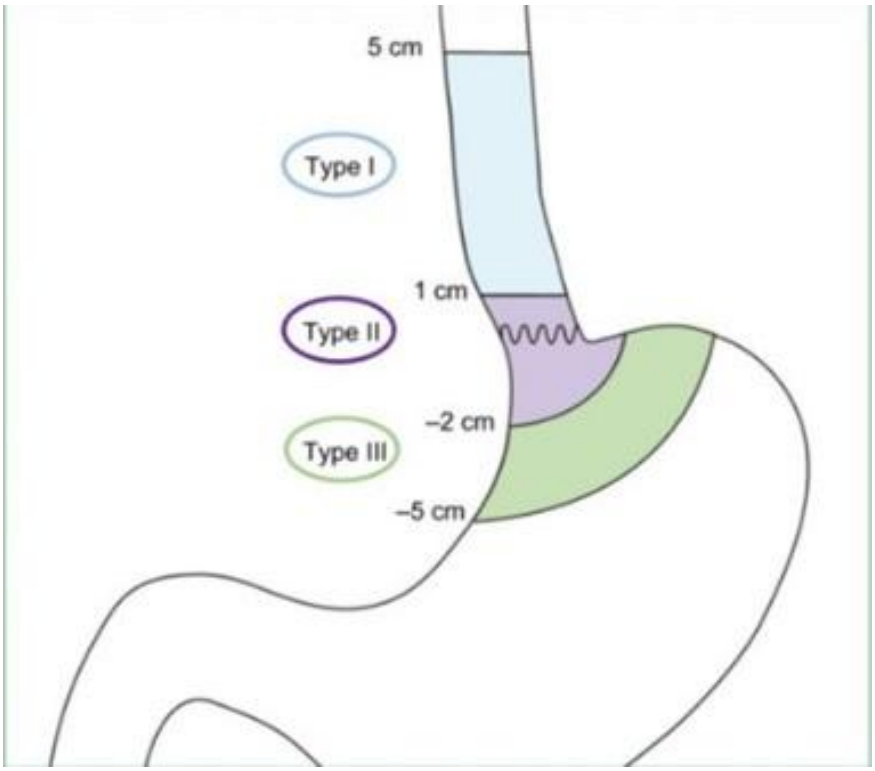
The main area of contention is the arbitrary portion of esophagus, which is the distal 5 cm of esophagus and 5 cm of proximal stomach [2]. Cancers with an epicentre in stomach and which is located more than 5 cm below the gastro-esophageal junction or tumors which are present within 5 cm of gastro-

esophageal junction but not extending to the OG junction or esophagus are considered to be primary gastric carcinomas.

Type I: Tumor located >1cm up to 5 cm above the gastro-esophageal junction.

Type II: Tumor located 1 cm cephalad and 2 cm caudad to the gastro-esophageal junction.

Type III:Tumor located greater than 2 cm to less than 5 cm below OG junction.



ESOPHAGEAL WALL:

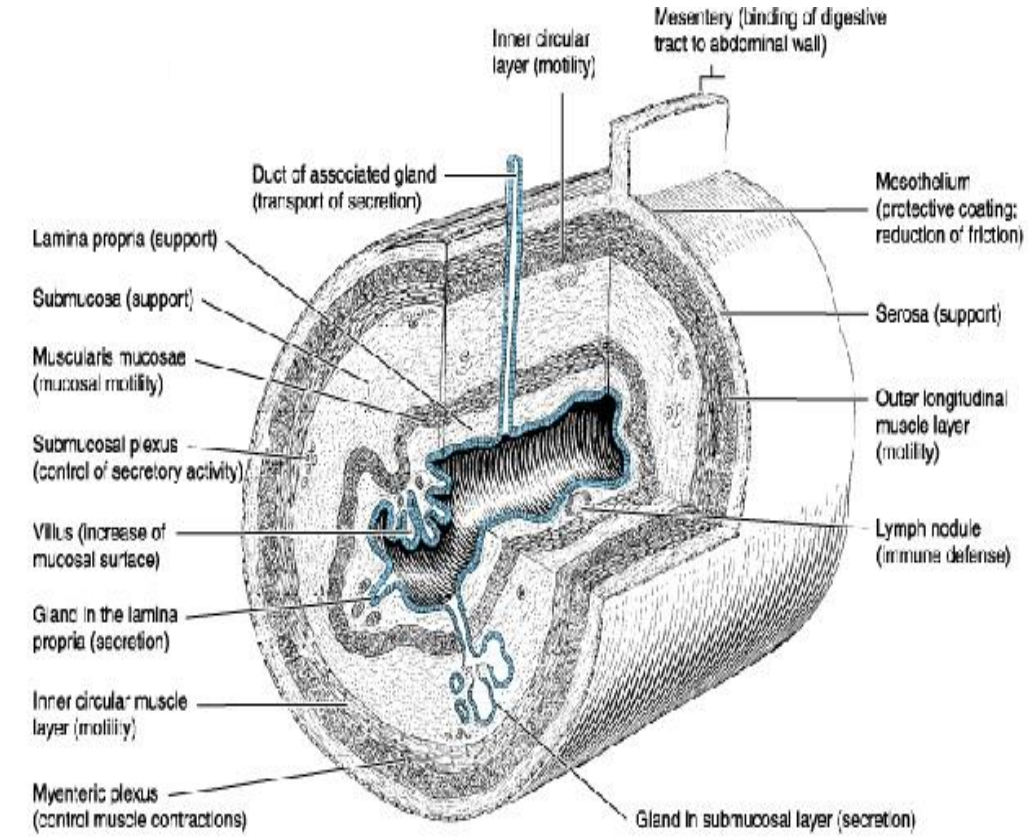
Esophagus is composed of mucosa, submucosa, muscularis propria and adventitia and it is devoid of serosa.

Mucosal layer is made up of epithelium, lamina propria and muscularis mucosa. The further subdivision of mucosal layers are: M1(epithelium), Lamina propria forms the M2 layer, Muscularis mucosa is called the M3 layer. Mature squamous cells forms the epithelial layer which is overlying basal cells. 10-15% of mucosal thickness is contributed by the basal layer and it contains reserve cells which has great proliferative potential. Lamina propria is the non-epithelial portion of mucosa. It contains leucocytes and vascular tissues which forms areolar connective tissue of lamina propria. Finger like extensions that extend into epithelial layer from lamina propria are called as papillae. Muscularis mucosa contains smooth muscle bundles oriented longitudinally and it is a very delicate layer.

Submucosa, just lies below mucosa and it is formed by a layer of loose connective tissue which contains a rich network of lymphatics, submucosal glands, meissner's plexus and blood vessels. Squamous epithelium lined ducts connect the submucosal glands to the lumen. These glands are scattered along the entire esophagus but these glands are more concentrated in upper and lower esophagus. The esophagus is lubricated by the mucin containing fluid secretions from this gland.

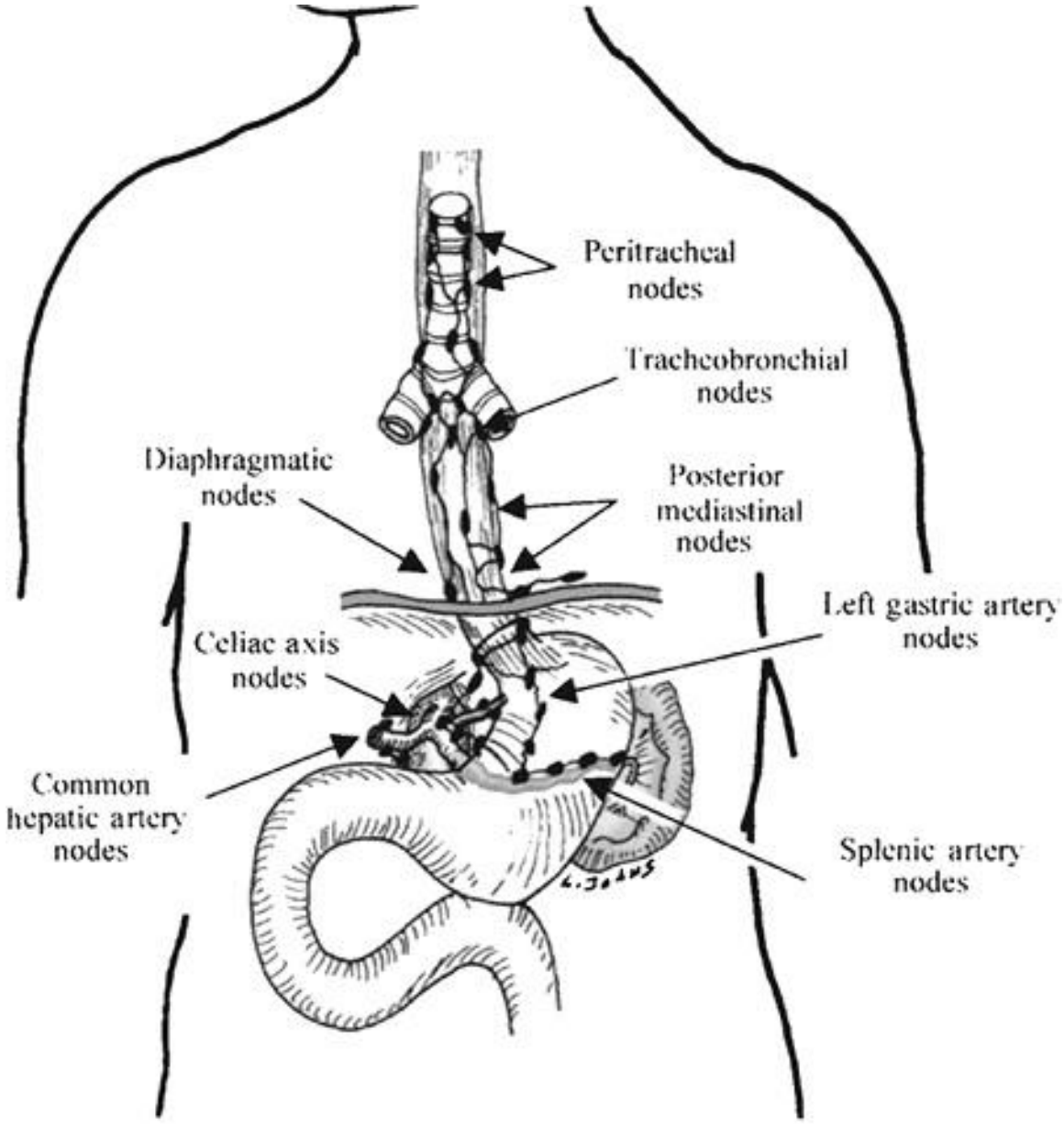
Muscularis mucosa contains outer longitudinal and inner circular smooth muscle layers with myentric plexus (Auerbach plexus) intervening between the two layers. The muscularis propria also contains striated muscle fibres from cricopharyngeus muscle for about the proximal 6-8 cm.

The esophagus is devoid of serosal coat in contrast to the rest of gastrointestinal tract, but contains adventitia (periesophageal connective tissue). As it is devoid of serosal layer there is high chance of extra esophageal spread of carcinoma. The adventitial layer directly lies on the muscularis propria.



Lymphatic Drainage:

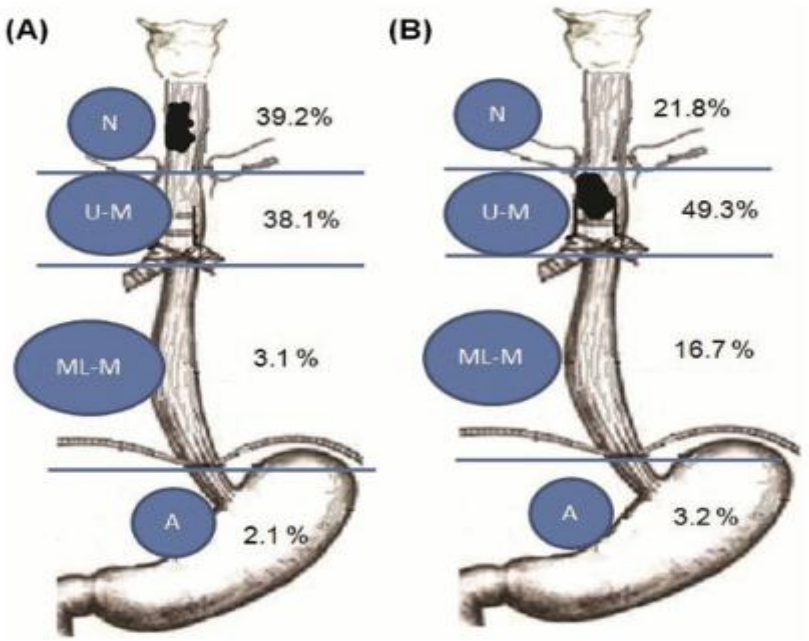
The esophagus has a rich network of lymphatics. The Lymphatic drainage in esophagus is longitudinal and intramural[3]. Lymphatic channels are present in lamina propria but the lymphatic network is concentrated in submucosa. Early in the course of disease there are lymphatic metastases from superficial cancers through these lymphatic channels.



Regional lymph nodes extend from periesophageal cervical nodes to celiac nodes [4]. Tumors of the cervical and upper thoracic esophagus drain into cervical and superior mediastinal nodes. Middle third drains both proximally and distally and drains into paratracheal, hilar, subcarinal, periesophageal and precarinal nodes. Lower third drains in lower mediastinum and celiac nodal plexus. Due to extensive submucosal lymphatic network, skip metastasis are common.

LYMPH NODE DRAINAGE IN PERCENTAGE: [5]

ESOPHAGUS PARTS	CERVICAL NODES	MEDIASTINAL NODES	ABDOMINAL NODES
CERVICAL	14.2	11.1	2.8
UPPER THORACIC	8	85.2	31.9
MIDDLE THORACIC	6.2	50.7	6.6
LOWER THORACIC	5.2	66	92.7



A study conducted by China that assessed CT based Lymph nodal involvement in **Cervical (A) and upper thoracic esophageal cancer (B)** ,
ML-M-Middle-lower mediastinum, N-Neck, A-Abdomen, U-M-Upper mediastinum

1).ESOPHAGEAL CANCER EPIDEMIOLOGY:

MMTR DATA: (MADRAS METROPOLITAN TUMOR REGISTRY)-TRENDS OF ESPHAGEAL CANCER

The MMTR Crude Incidence Rates (CIR) and Age Standardised Rates (ASR) for men and women per 1 lakh population are mentioned below which shows changing trends in incidence of esophageal cancer over the period of three decades from 1980-2013.

Esophagus cancer	**1982-1986**	**1987-1991**	**1992-1996**	**1997-2001**	**2002-2006**	**2007-2011**	**2012-2013**
Men: CIR / 100,000	4.5	6.5	6.2	7.3	6.9	6.3	4.5
Men: ASR / 100,000	6.6	9.3	8.3	9.1	8.0	6.7	4.5
Women: CIR / 100,000	3.8	4.6	4.6	4.7	4.2	3.9	3.5
Women: ASR / 100,000	5.4	6.4	5.9	5.7	4.7	4.1	3.3

The crude incidence rate and age standardised rate is more in men as compared to women and CIR per 1,00,000 population has shown an increasing trend 1980-2000 and it then there was gradual fall in the rates. The CIR and ASR rates of esophagus cancer in the world, India and Chennai are mentioned below:

Regions	Male			Female		
	No. of Cases	CIR	ASR	No. of Cases	CIR	ASR
World	323008	9.1	9.0	132776	3.8	3.1
More Developed Region	67748	11.2	6.4	18396	2.9	1.2
Less Developed Region	255260	8.6	10.1	114380	4.0	4.1
India	27152	4.2	5.4	14622	2.4	2.8
Chennai(2012-13)	210	4.5	4.5	164	3.5	3.3

CRUDE INCIDENCE RATE: (CIR)

Crude incidence rate is defined as the number of new cases occurring in an area due to a disease in a given time period. It is usually presented as the annual incidence rate and it is mentioned as the number of cases per 100,000 of a defined study population.

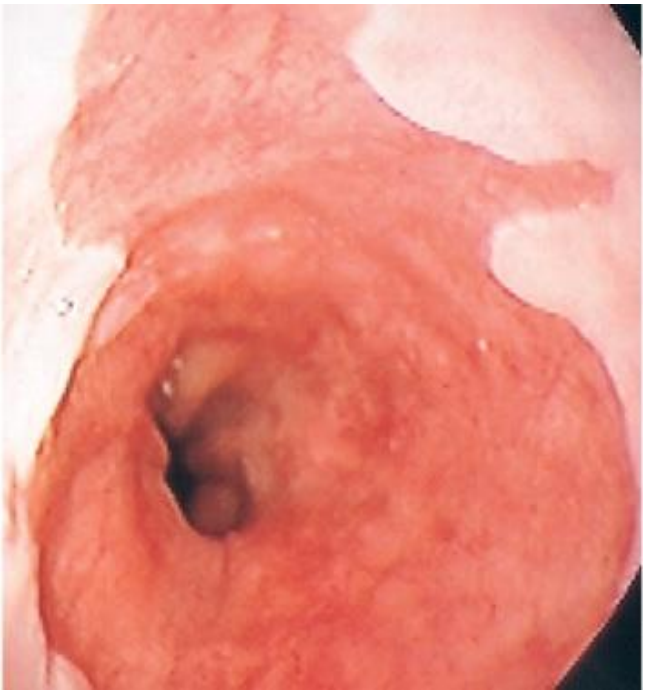
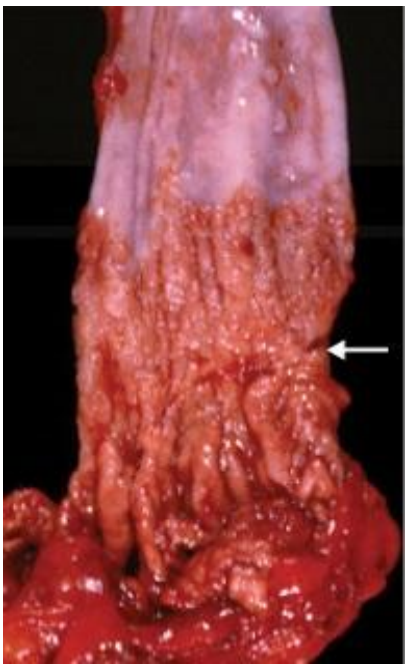
AGE STANDARDISED RATE: (ASR)

This is the crude rate which would have occurred if the age specific rates of a study population had operated in a reference population known as a ‘standard

population'. The same standard population is used for all rates to be compared. The number in each age group in the standard population is used as a weighting system in the standardisation process. The age standardised rate is calculated as the sum of the crude age specific rates multiplied by the respective proportions represented in the standard population, giving a 'weighted mean' (the ASR). In practise it is usual to calculate ASRs with age specific rates in 5 year age bands and European or world population proportions as the standard.

2).ETIOLOGY OF CANCER ESOPHAGUS:

Alcohol and tobacco is found to be associated with 80-90% of carcinoma. There are reports that have described the relative risk of esophageal cancer by the amount of alcohol and tobacco consumed, with a relative risk of 155:1 when consuming >30 g/day of tobacco along with 121 g/day of alcohol [6]. The main risk factor for the development of esophageal carcinoma is Barett's esophagus. It is a condition in which the normal squamous epithelium is replaced by metaplastic columnar epithelium. The most significant risk factor for Barret's esophagus is severe and long standing GERD (GastroEsophageal Reflux Disease), which may lead to adenocarcinoma.

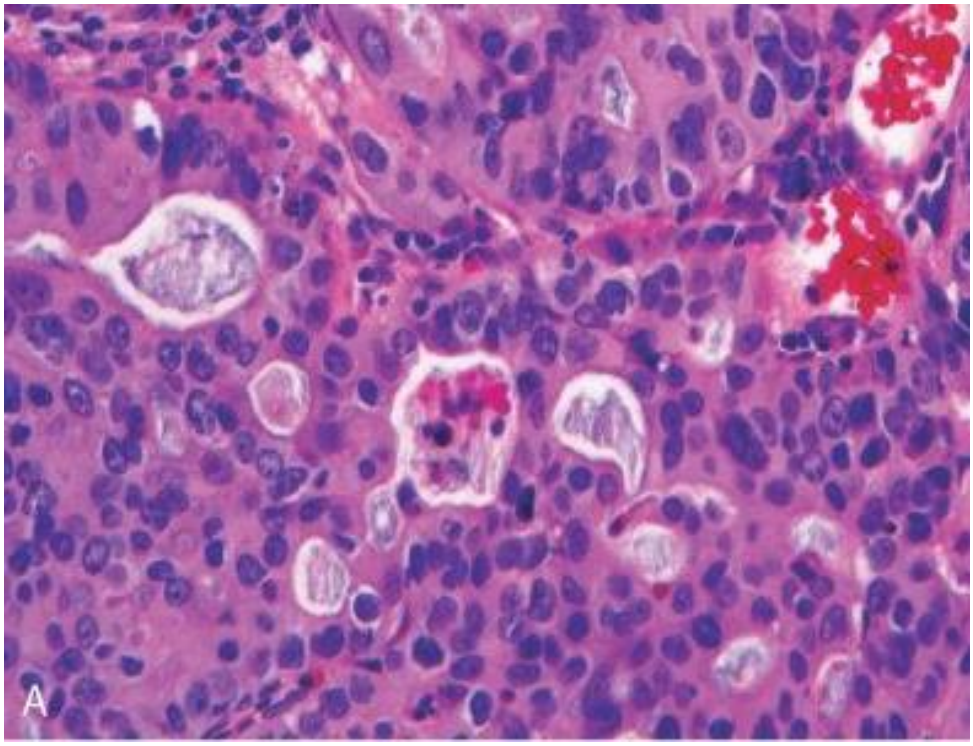
A.  B. 

A. Endoscopic view which shows red velvety GI-type mucosa extending from the GE orifice. B. Granular zone of Barrett esophagus (*arrow*).

Long standing severe reflux have 44-fold risk of developing adenocarcinoma [7]. Other factors associated with Barret's esophagus are age, hiatal hernia size and male gender. The length of Barret's esophagus is found to be associated with adenocarcinoma esophagus.

Radiofrequency ablation has become the preferred treatment for patients with Barret's esophagus and High grade dysplasia. Alternative strategies include cryoablation or photodynamic therapy (PDT). Surgical resection is reserved for patients with High grade dysplasia and characteristics that are unfavourable for non surgical therapy like nodualrity or long segment.

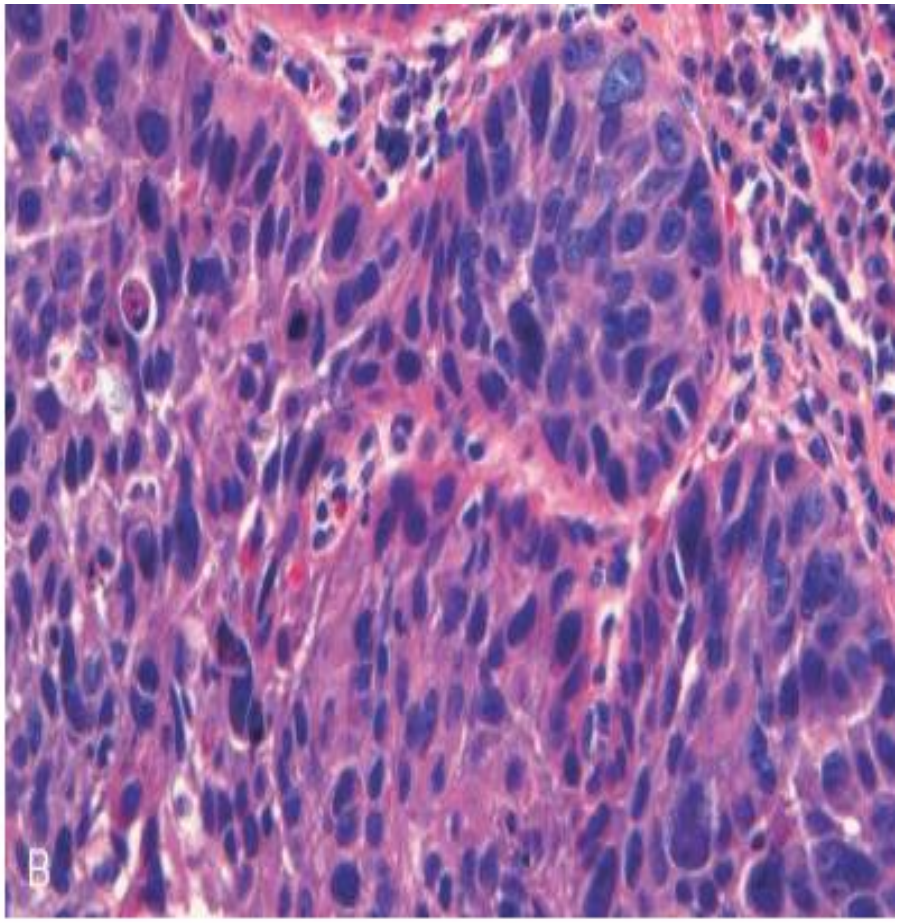
Obesity has been linked to a threefold to fourfold risk of adenocarcinoma, possibly due to increased risk of reflux [8]. Middle aged patient with Barrett's esophagus has 10-15% risk of developing esophageal adenocarcinoma during his or her lifetime.



A. Esophageal adenocarcinoma showing back to back glands

For patients with low grade dysplasia or metaplasia, proton pump inhibitors or histamine receptor antagonists are used to control the reflux. Smokers appear to have twofold to threefold greater risk for developing esophageal adenocarcinoma than non-smokers. The relative risk of esophageal adenocarcinoma persists to three decades following smoking cessation, in

contrast to a significant decline in similar patients with squamous cell carcinoma.



B.SQUAMOUS CELL CARCINOMA OF ESOPHAGUS

In very rare cases genetic causes may be involved in pathogenesis of esophageal cancer. Genetic abnormalities in squamous cell carcinoma include p53 mutations and allelic lossess of 3p and 9q and also cycclin D1 and EGFR (Epidermal Growth factor Receptor) amplification [9]. These mutations can cause cell hyperplasia, low and high grade dysplasia and ultimately squamous cell carcinoma. In contrast adenocarcinoma is associatd with overexpression of p53, allelic loss at 17p, 5q and 13 q and amplification and overexpression of

EGFR and HER-2 (Human epidermal growth factor receptor), leading to stepwise development of Barret's esophagus and ultimately adenocarcinoma.

3).FREQUENCY OF METASTASES BY ANATOMIC LOCATION:

LOCATION OF METASTASIS	PERECENTAGE
LYMPH NODES	73
LUNG	52
LIVER	47
ADRENALS	20

A review which showed the incidence of metastases to lymph node and the depth of penetration revealed that the lymph nodal metastases incidence for T1 lesions is 14-21%, and that for T2 lesions it increases to 38-60% [10,11]. At autopsy, lymph nodal metastases are found in around 70% patients.

According AJCC R-status, age and histologic subtype were independent prognostic factors of survival, but grade of tumor or the location of carcinoma was not [12]. But these data only considered patients treated with surgery alone and it did not apply to patients treated with chemotherapy or radiotherapy. In a study which considered patients who underwent surgical resection as primary treatment length of tumor adversely affected survival with 5-yr survival rates of 77%, 48%, 38%, 23% for tumor lengths of 1,2,3 or> 3 cm respectively. But length was not prognostic if patients were N+, M+. Mayo clinic conducted a study which concluded that the factors that affected prognosis included T and N

status, tumor grade, age >76 years, extracapsular lymphnodal extension and the absence of chemotherapy and radiotherapy as treatment modality [13]. Deep ulceration of tumor, sinus tract formation and fistula formation are considered to be other factors associated with poor prognosis.

Further the most significant risk factor for failure is positive margins which have been associated with long term outcome. An Intergroup study evaluating chemotherapy preceding and following esophagectomy concluded that the survival was same in patients undergoing R1 resection (positive microscopic margins) and R2 resection (gross residual disease) and only patients undergoing R0 resection (negative margins) which showed benefit in long term disease free survival. [14]

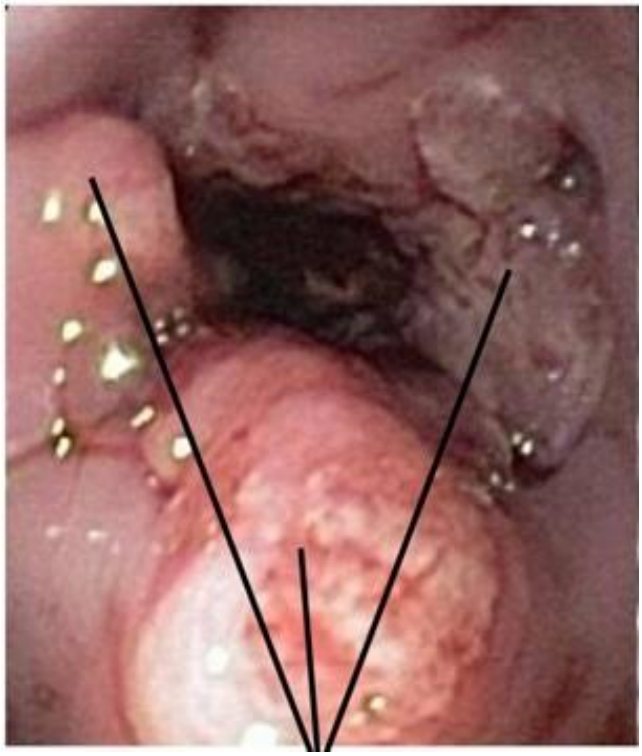
4).CLINICAL PRESENTATION:

Patients with esophageal carcinoma most commonly present with complaints of dysphagia and weight loss. In more than 90% patients, dysphagia will be the presenting complaint. In general for esophageal cancer the symptoms often begin 3 to 4 months before the diagnosis of malignancy and patient generally gives history of progressive dysphagia. Another common presentation with 40%-70% patients come to the hospital is with weight loss. The other presenting symptoms are odynophagia (20%) [15], dull retrosternal pain which may be due to invasion of mediastinal structures, bone pain which signifies bone metatstases and cough and hemoptysis due to paratracheal nodal involvement and lung metastasis. The least common presentations are

pneumonia due to tracheoesophageal fistula or exsanguinating hemorrhage due to aortic invasion. If celiac axis node is involved, patient can present with abdominal pain or back pain.

5).DIAGNOSIS:

On presentation of patient to the hospital, a thorough history including the alcohol, smoking and tobacco history, symptoms of long standing reflux disease should be taken. Patient should be examined thoroughly including oral cavity, oropharynx and Indirect laryngoscopy examination as there has been high incidence of field cancerisation in the upper airway and head and neck. Careful examination of the neck to be done to know the presence of any cervical nodes. Basic blood counts and Biochemical investigations to be done. Then patient should undergo Upper Gastrointestinal endoscopy to know the exact upper and lower location of lesion and to make a histological diagnosis and to know the gastroesophageal junction location. Bronchoscopy is done to evaluate for tracheal invasion in patients with proximal malignancies. Computed Tomography scan of the Chest and upper abdomen should be done to identify metastases of disease to upper abdominal nodes, liver and adrenals. Computed Tomography scan (CT) predicts respectability in only 65% to 85% cases. In 65% cases CT accurately predicts Tumor (T) stage and in 50% to 70% cases it predicts the nodal involvement. [16,17]

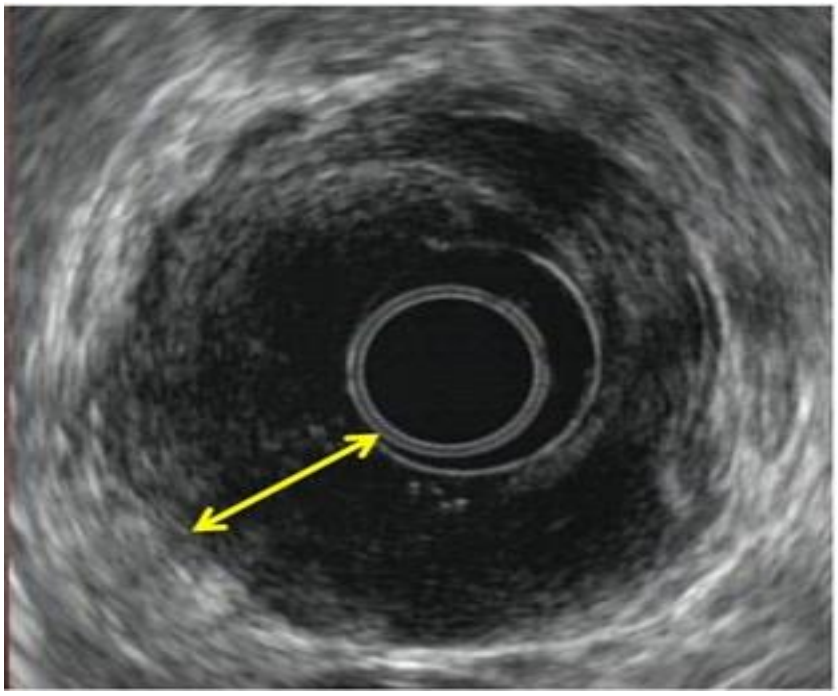


Circumferential Esophageal Carcinoma- Black arrows- Endosocopic view

Endoscopic Ultrasound (EUS) has more accuracy rates to predict T stage (85% to 90%) and 75% to 80% accuracy rates for nodal metastases. [18]

The role of PET (Positron emission Tomography) in esophaus cancer is mainly to assess the response to treatment. The addition of PET scan to Computed Tomography (CT) improves the accuracy of detecting Stage III disease in 23% and in 18% Stage IV disease [19, 20]. If patients have locoregionally advanced disease CT wise PET will detect metastases to distant sites in 20% of patients but in detecting nodal disease PET scan has lower accuracy.

Recent data suggest that PET responders have significantly better outcomes than those who did not respond to treatment. [21]



Cancer invading the inner layers of esophagus- EUS view of the endoscopic picture

And also PET can be used to know the treatment response early in the course of treatment.

6).<u>DEFINITION OF TNM STAGING:</u>

Tx-Primary tumor cannot be assessed.

T0-No evidence of primary tumor.

Tis-High grade dysplasia(Includes all non invasive neoplastic epithelia that was formerly called carcinoma in situ)

T1a-Tumor invades lamina propria or muscularis mucosa(M1 or M2)

T1b-Tumor invades submucosa.

T2-Invades muscularis propria

T3-Invades adventitia,

T4a-Resectable tumor invading pleura, pericardium or diaphragm.

T4b-Unresectable tumor involving other adjacent structures such as vertebral body, aorta, trachea etc.

NODAL STAGING:

Nx-Regional lymph nodes cannot be assessed

N0-No lymph nodes.

N1-Involvement of 1-2 regional nodes.

N2-Involvement of 3-6 regional lymphnodes.

N3-Regional nodes >6

Number of nodes must be recorded for total number of regional nodes sampled and total number reported with metastases.

DISTANT METASTASES: (M)

M0-No metastases

M1- Distant metastases.

STAGE GROUPING FOR SQUAMOUS CELL CARCINOMA:

Stage	T	N	M	Location	G
0	Tis(HGD)	0	0	Any	1
IA	T1	N0	M0	Any	1
IB	T1 T2-3	N0 N0	M0 M0	Any Lower	2-3 1
IIA	T2-3 T2-3	N0 N0	M0 M0	Upper,Middle Lower	1 2-3
IIB	T2-3 T1-2	N0 N1	M0 M0	Upper,Middle Any	2-3 Any
IIIA	T1-2 T3 T4a	N2 N1 N0	M0 M0 M0	Any Any Any	Any Any Any
IIIB	T3	N2	M0	Any	Any
IIIC		N1-2 Any N3	M0 M0 M0	Any Any Any	Any Any Any
IV	Any	Any	M1	Any	Any

STAGE GROUPING FOR ADENOCARCINOMA:

Stage	T	N	M	G
0	Tis(HGD)	0	0	1
IA	T1	N0	M0	1-2
IB	T1 T2	N0 N0	M0 M0	3 1-2
IIA	T2	N0	M0	3
IIB	T3 T1-2	N0 N1	M0 M0	Any Any
IIIA	T1-2 T3 T4a	N2 N1 N0	M0 M0 M0	Any Any Any
IIIB	T3	N2	M0	Any
IIIC		N1-2 Any N3	M0 M0 M0	Any Any Any
IV	Any	Any	M1	Any

7).TREATMENT FOR CARCINOMA ESOPHAGUS WITH REVIEW OF LITERATURE:

SURGERY ALONE:

Surgical resection is the primary modality of management in carcinoma esophagus. Even though with more recent advances in techniques in surgery the results of surgery as single modality in carcinoma esophagus is very poor. Moertel published the results of carcinoma esophagus treated with surgery alone after reviewing 18 series, with a total of 4109 patients. He found a 5-year overall survival rate of 9.6% (range from 3%-20%). Sun et al found that of 474 operable patients, 44.5% were found to have Lymph node positivity at the time of surgery and he concluded that lymph node positivity had a poor survival when compared to node negative patients when treated with surgery alone. The entire group had overall survival of 31%, with 13% 5 yr Overall survival for patients with positive nodes and 44% 5 yr Overall survival for node negative patients. [22,23]

During surgery the number of lymph nodes to be removed still remains unclear and recently published SEER data showed at least 23 lymph nodes to be removed and a recent study suggests 18 lymph nodes to be removed.

The surgical approaches used for Carcinoma esophagus are: Ivor-Lewis procedure(Trans thoracic approach) or Trans Hiatal approach. But there is no

significant evidence to show that one technique is superior to others. However there is more morbidity associated with transhiatal approach. [24]

Esophagectomy was considered to be the standard of care for high grade dysplasia and superficial cancers. However due to the surgical morbidity and mortality minimally invasive esophagectomy (MIE) and endoscopic treatment have been considered to be better options for High grade dysplasia patients.

RADIATION ONLY:

For patients treated with radiation only the results are very poor with 2 year survival rate of 7-10% and 5 year survival rate of only 5% . There are no trials comparing radiation only versus surgery alone. A meta analysis of patients who were treated with radiation alone for carcinoma esophagus which included a total of 8400 patients found that overall survival at 1 year was 18%, 2 years was 8% and 5 years was 6% [25]. Stage wise survival rate for 5 years for patients treated with radiation alone was reported by a study conducted by Okawa et al. The entire group had a 5 year overall survival of 9% and for stages I,II,III and IV the 5 year survival were 20%, 10%, 3% & 0% respectively. [26]

PREOPERATIVE RADIATION VERSUS SURGERY ALONE:

Multiple studies have demonstrated benefits of preoperative radiation. Wang et al [27] randomized 206 patients to surgery alone versus 40 Gy radiation in 2 Gy per fraction delivered preoperatively. No significant survival benefit was seen with radiation alone.

Meta analysis from esophageal cancer collaborative group which included 5 studies with more than 1000 patients. [28] With a median follow up of 9 years overall reduction in risk of death was 11% in favour of preoperative radiation arm, with a absolute survival benefit of 4% in preoperative radiation arm which was not statistically significant. So it is concluded that there may be improvement in local control with preoperative radiation but there is no survival benefit.

CHEMORADIATION VS RADIATION:

The landmark trial which compared chemoradiation versus radiation was RTOG 85-01. [29] It randomized patients into two arms: Chemoradiation arm with 50 Gy along with cisplatin and 5-Fluorouracil and Radiation only arm to receive a Total dose of 64 Gy. There was a significant difference in median survival in chemoradiation arm 12.5 months versus 8.9 months in radiation only arm and 2 year survival rate of 38% vs 10% in favour of chemoradiation arm. Distant metastases at 2 years reduced from 26% to 12% and local recurrence decreased from 24% to 16% in favour of chemoradiation arm. The patients in RT arm were transferred to chemoRT arm as there was significant survival difference and further study was stopped. A update showed 5 year overall survival rate being 26% vs 0%. As for as the toxicities were concerned rates of acute toxicity, hematologic toxicity and fistula formation were more with concurrent chemoradiation when compared to radiation arm.

PREOPERATIVE CHEMORADIATION VERSUS PREOPERATIVE CHEMOTHERAPY:

The POET trial, [30] which randomized patients into two arms, the patients in one arm were randomized to receive Cisplatin/ 5-FU based chemotherapy only and other arm received same induction chemotherapy followed by concurrent chemoradiation with 30 Gy radiation and Cisplatin/Etoposide chemotherapy. The study had poor accrual and was stopped earlier. However the study concluded that preoperative concurrent chemoradiation had higher N0 rates (64% vs 37%) and pathological complete response rates (16% vs 2%) and higher local control rates (76% vs 59%) and improved 3 year overall survival (47% vs 28%). So the study concluded that preoperative chemoradiation had significantly better overall survival rates.

CHEMORADIATION VERSUS CHEMORADIATION FOLLOWED BY SURGERY:

A French study [31] which included 445 patients, with squamous and adenocarcinoma of esophagus which were clinically resectable randomized patients to either chemoradiation arm versus chemoradiation followed by surgery arm. The chemotherapy given in both arms were cisplatin and 5-FU. Radiation given was 45 Gy over 4.5 weeks and the patiuents who had partial response(259 patients) were further randomized to surgery or additional chemoradiation with cisplatin and 5-FU. The 2 year overall survival was 67% vs 57% in favour of surgery arm. However death rates were 9% with surgery

arm and 1% in chemoradiation arm. So the conclusion of the study was surgery in responding patients did not improve survival.

Another German study [32] which included 172 patients treated initially with induction chemotherapy which included etoposide, 5-FU, leucovorin, and cisplatin for 3 cycles and after which patients were randomized to either further chemoradiation followed by surgery vs only chemoradiation alone concluded that surgery does not improve overall survival and only improves local control of tumor and also those patients who did not respond to induction chemotherapy might benefit from surgery and patient should be treated according to apt tumor response and hospital morbidity was higher in the surgery arm of about 11%.

ROLE OF BRACHYTHERAPY

The role of brachytherapy in treatment of carcinoma esophagus is mainly in advanved or recurrent disease or patients with luminal obstruction. The indications for brachytherapy in esophageal cancer are for tumor obstruction causing dysphagia and after external beam radiotherapy for tumor remission for boost treatment. Intraluminal brachytherapy alone will not be useful in achieving tumor remission, so the most common treatment is starting with external beam radiotherapy to reduce the tumor burden and adding brachytherapy as a boost. In seleceted cases to achieve rapid symptom relief from advanced esophageal lesions brachytherapy is used to initially before external beam radiotherapy.

CRITERIA FOR PATIENTS TO BE TREATED WITH CARCINOMA ESOPHAGUS:

- Patients with mid and lower thoracic adeno- or squamous cancers.
- With no evidence of intra-abdominal disease.
- Lower extent of tumor should be 2 cm above the GE junction.
- Normal chest x-ray with no evidence of disease.
- Lymph nodes should not be palpable.
- Normal ultrasound of the abdomen.
- Patients not fit for chemotherapy
- Non resectable esophageal carcinoma patients
- No tracheal or bronchial involvement.
- No Cervical or upper thoracic esophagus location.
- No skip lesions

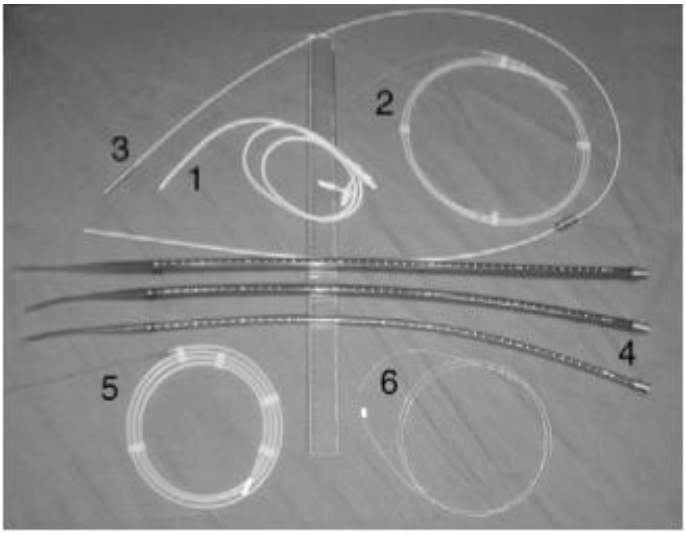
Few studies which show the benefit of brachytherapy are:

1.Radiotherapy Department, Galliera Hospital, Genoa, Italy: Twenty eight patients with previously untreated oesophageal carcinoma without distant metastases were divided into two groups: Group A consisted of 18 pts. treated with conventional external radiotherapy only. Another group of 10 pts. (Group B) received treatment with external beam irradiation with further high dose rate intraluminal brachytherapy up to a dose of 4-12 Gy delivered in 2-3 sessions of 4 Gy (one session a week). All patients were evaluated clinically, radiologically

and endoscopically every 3 months. At the end of treatment there was a marked difference in relief of dysphagia (39% in Group A vs. 90% in Group B), local control (56.7% in Group A vs. 100% in Group B) and time to progression of dysphagia (20.8 weeks in Group A vs. 67.7 weeks in Group B). No marked difference was observed in overall survival. In both groups the complication rate were low and major complications were observed in pts. treated with external radiotherapy alone (two fistulas). The association of external beam and intraluminal radiotherapy can have a better local control of the disease, improvement in quality of life of patients.

2.In the multi-centre analysis by Okawa et al., which analysed results of definitive radiotherapy for superficial esophageal cancers in Japan showed a slightly higher 2- year local control rate for patients treated with external beam radiation with intraluminal brachytherapy (90%) than in patients who were treated with external beam RT alone (77%) The primary aim of brachytherapy is to relieve dyaphagia and improve quality of life from obstructive lesions.

The intent of treatment decides the total dose and fractionation in intraluminal brachytherapy. The preferred method of treatment is HDR brachytherapy. For patients who are treated with curative intent after a dose of 50 Gy external beam therapy 1 or 2 applications of brachytherapy with 5 to 6 Gy per fraction is generally considered with one week apart.



The applicators used in Intraluminal brachytherapy for esophagus shown in the above image are,

1. Naso gastric tube used as applicator.

2. Bronchial applicator with 6 mm diameter.

3.Connector.

4.Esophagus bougie applicators with 10 mm, 13 mm and 15 mm diameterand the tube as a source carrier should be inserted into the esophagus bougie applicators.

5. Guide wire.

6.Radiographic marker wire.

The diameter of the applicators used are at least 10 mm and the dose is generally specified at 5 mm tissue depth. Brachytherapy is used in treatment of patients who are treated with radiation alone and not medically fit for

chemotherapy. Brachytherapy is not routinely used concurrently with chemotherapy as there are high incidence of stricture and fistulas. 2 weeks interval should be given between completion of external beam radiation and initiation of brachytherapy for the acute reactions of external beam radiation to subside. In a palliative setting the total dose of brachyterapy given was 15-25 Gy at 10 mm from the source axis and it is delivered in single fraction per week for 3-4 weeks. And smaller diameter applicators are generally used. Brachytherapy in either curative or palliative setting is just to improve the quality of life of patients and not in improving survival. Though with these advantages brachytherapy is used minimally as there are high rates of complications like stenosis, fistula and perforation.

ONLY SURGERY VERSUS CHEMORADIATION FOLLOWED BY SURGERY:

The trimodality treatment involving neoadjuvant chemoradiation followed by surgery is being investigated for more than 20 years in patients with carcinoma esophagus to improve the survival by addressing the substantial local failure rates and distant metastatic failure rates.

In many studies, the most commonly used chemotherapy drugs are 5-Fluorouracil and Cisplatin concurrent with radiation as these drug combination has been showed to be beneficial when added to definitive radiation in RTOG 8501 trial.

Chemoradiotherapy with 5-Fluorouracil/ cisplatin with or without surgery have been analysed in number of randomized trials to know the benefits of these regimens. Now there is much interest in using or developing new chemotherapeutic regimens, which may reduce the treatment related toxicity or improve the disease free survival and overall survival. Most of these trials were underpowered, and the results conflicting. The studies by Walsh et al, Tepper et al and Urba et al [33] are notable studies. On comparing the median survival and overall survival, for the combined therapy group versus surgery, there was no statistically significant difference in the Urba study, the 3-year overall survival in combined therapy group versus surgery group was 30% vs 16% respectively. In the Walsh and Tepper studies demonstrated statistically significant survival improvement, this difference was consistent with the long-term survival benefit seen in Urba study. Also in Urba study locoregional failure rates were 19% *vs* 42% in favour of neoadjuvant chemoradiotherapy group, whereas the number of patients with distant metastases (60% vs 65%) in both the groups did not differ. A Meta-analysis which included 1209 patients from nine trials done by Gebski et al. showed a benefit for neoadjuvant chemoradiotherapy followed by surgery compared with surgery alone. There was 13% reduction in mortality at 2 years with the use of neoadjuvant chemoradiotherapy. The hazard ratio for death by any cause was 0.81 (95% CI, 0.70 to 0.93). The recent large trial which showed benefit of neoadjuvant chemoradiotherapy is by CROSS trial done at Netherlands. [34]

CROSS GROUP STUDY:

A recently published large RCT of 368 patients, the CROSS Group study(March 2004-December 2008), randomly assigned patients with cancers in the esophagogastric junction or esophagus, 23% (84 patients) who had squamous- cell carcinoma and adenocarcinoma was the histology in majority of patients 75% (275 patients), and in 2% (7 patients) histology was large-cell undifferentiated carcinoma. All were resectable tumors and they were randomized either to receive surgery alone or radiotherapy (41.4 Gy in 23 fractions, 5 days per week) concurrent with weekly administration of paclitaxel (50 mg per square meter of body-surface area) and carboplatin (doses titrated to achieve an area under the curve of 2 mg per milliliter per minute) for 5 weeks, followed by surgery. The median overall survival was 49.4 months versus 24 months in the chemoradiotherapy followed by surgery group and surgery alone group respectively. In neoadjuvant chemoradiotherapy followed by surgery group the overall survival was significantly better (hazard ratio, 0.657; 95% confidence interval, 0.495 to 0.871; P=0.003).

They concluded that neoadjuvant chemoradiotherapy improved overall survival in patients with potentially curable esophageal or esophagogastric-junction cancer and it was associated with acceptable toxicities.

Cross update: (in August 2015)

After median followup for surviving patients of 84.1 months, median overall survival was 48.6 months vs 24 months for patients treated with neoadjuvant chemoradiotherapy followed by surgery group and in the surgery alone group respectively. Median overall survuival for patients with squamous cell carcinoma was 81.6 months vs 21.1 monthsin the neoadjuvant chemoradiotherapy followed and surgery group and surgery alone group respectively. For patients with adneocarcinomas, it was 43.2 months vs 27.1 months in favour of the neoadjuvant chemoradiotherapy followed by surgery group .

Wang et al in a meta-analysis of twelve randomized controlled trials concluded that surgery following neoadjuvant chemoradiotherapy was associated with significantly improved 1-year, 3-year and 5-year survival rates compared with surgery alone. RR = 0.86, 95 % CI = 0.74-0.98, P = 0.03 for 1 year survival, RR = 0.82, 95 % CI = 0.73-0.92, P = 0.0007 for 3-year survival and 5-year survival RR = 0.83, 95 % CI = 0.72-0.96, P = 0.01 in favour of neoadjuvant chemoradiation. A subgroup analysis was done which showed that this survival advantage is not associated with sequential chemotherapy but only with concurrent chemoradiotherapy. For squamous cell carcinomas 3-year and 5-year survival outcomes were improved with neoadjuvant chemoradiotherapy. There was no increase in postoperative mortality for patients treated with

neoadjuvant chemoradiation (RR = 1.56, 95 % CI = 0.97-2.50, P = 0.07) and morbidity (RR = 0.97, 95 % CI = 0.86-1.09, P = 0.56).

II.RADIOTHERAPY AND TECHNIQUES:

The knowledge of anatomy, extent of disease, nodal involvement and radiobiologic principles are necessary for delivery of radiation therapy. Further a radiation oncologist should consider methods to reduce the treatment related toxicities. Also the radiation dose to the adjacent vital organs like heart and lungs should be with acceptable limits. So it is necessary to reduce the normal structures dose to the utmost without compromising the primary tumor dose and dose to the draining lymph nodes. This is mainly done by simulation, Dose volume histograms and simulation. The patients can be treated by either conventional or conformal therapy.

In conventional therapy, barium swallow and esophagoscopy is done to identify the primary tumor which is the target volume. The target volume should include a proximal margin of 5 cm and 3 cm margin distally. The margins laterally should be in a such a way that it surrounds the soft tissue surrounding the esophageal wall which is usually 6 cm or if the adjavent nodes are included it is 8 cm. [35] In elderly patients, the upper and lower margins can be reduced to limit the acute radiation reaction severity. The main constrain for the delivery of homogenous dose distribution to esophagus are the anatomical factors like spinal cord, lung,anterio-postreror diameters and the heart. The changing position of esophagus during its course along with contour

of body variation, mostly leads to the plane of treatment to be inclined rather than parallel to couch. The dose to the lungs and spinal cord should be kept to the minimum.

The primary tumor and bilateral supraclavicular lymphnodes should be included in treatment of cervical and upper third esophagus lesions. For distal esophagus lesions celiac axis nodes to be included. For treating cervical primaries, patient is placed supine and ideally treated with a three field technique, two anterior oblique and a posterior. But, as the primary tumor is rarely related to midline, AP/PA (anteroposterior/posteroanterior) fields are used upto a dose of 39.6 to 41.4 Gy followed by using a right or left opposed oblique pair fields upto a dose of 50.4 Gy. A electron field up to a depth of 2 to 3 cm is added to supraclavicular fossa to bring a total dose of 50.4 Gy as this technique will not include the supraclavicular fossa. For mid and lower esophageal tumors generally a four field technique is preferred with anteroposterior/posteroanterior (AP/PA) fields and and opposed lateral fields.

DEFINITION OF VOLUMES:

It is necessary to properly delineate the target volumes in definition of the radiation fields. The Gross Tumor Volume (GTV) include the lower and upper limit of malignancy based on distance from incisors as described by the gastroenterologist. The extents should be visualised on CT scan by the help of anatomical landmarks like GE junction at 40 cm from incisors and carina which is situated at 25 cm from incisors. Endoscopic ultrasound is the most reliable

test and it is also useful to assess the depth of tumor which helps in defining GTV. The main advantage of Endoscopic ultrasound is that it can detect lymphnodes that is not seen in CT or PET imaging. On defining the margins, on analysis of 66 resection specimens [36] in a prospective analysis showed that in squamous cell carcinomas placement of 3 cm margin proximally and distally would cover 94% of microscopic disease extension and in gastroesophageal junction carcinoma a 3 cm proximal margin and 5 cm distal margin covers 100% and 94% subclinical spread respectively. As esophagus has rich submucosal network of lymphatics the placement of upper and lower margins is a matter of debate.

Most of the contemporary radiation trials used upper and lower margins of 3 to 5 cm and a radial margin of 2 cm.

The general guidelines for CTV (Clinical Target Volume) are explained below:

1. For Cervical and upper thoracic esophagus lesions, superiorly CTV should include supraclavicular and lower cervical nodal basins and inferiorly up to the subcarinal lymph nodes and it should also include the upper paraesophageal lymph nodes.
2. For middle thoracic esophagus carcinomas, it is individual decision according to the clinical scenario and it should include paraesophgeal mediastial lymph nodes coverage. [37]
3. For Lower esophageal lesions, it should include the subcarinal region nodes superiorly and inferiorly to include the celiac lymph nodal basins/

common hepatic artery and left gastric nodes.

For the treatment of thoracic esophageal malignancy or OG junction tumors there are many beam orientations, which are,

- Initial AP/PA approach followed by anterio-posterior/ RPO (Right posterior oblique)/Left posterior oblique (LPO) fields with or without boost
- Three field technique (AP/PA with left lateral or oblique fields)
- Anterio-posterior/ Postero-anterior alone approach.
- Initial AP/PA followed by Right anterior oblique (RAO)/LPO) fields with or without boost.

The approach which is most preferred for treatment is AP/PA/RAO/LPO with boost which is given by using laterally oriented beams.

Field design for adenocarcinoma of esophagus deserves a special mention though it is similar to the lower thoracic squamous cell carcinoma. For all patients periesophageal lymph nodes are generally included. As there is correlation between the lymph nodal involvement and depth of penetration of tumour i.e T stage, and because gastroesophageal junction tumours usually present in more advanced stage, celiac lymph nodal basins are generally included for tumors in the lower esophagus and OG junction tumours. Studies done by Erlangen et al shows some specific considerations. [38] They are

- Nodal spread is predicted by lymphovascular invasion.

- Tumors which has proximal extension beyond the Z line, and in type II and type III tumours which has more distal spread there is an increasing evidence of involvement of paraesophageal lymph nodes.

Estimated nodal incidence cut-off of 20% for inclusion has special considerations which are:

- CTV should include the lower paraesophageal, left gastric artery nodes , lesser curvature and paracardial nodes
- A nodal spread of more than 20% to left and right gastroepiploic, splenic hilar regions, celiac trunk, greater curvature is predicted by the presence of lymphovascular invasion.
- The greater curvature, splenic artery ,splenic hilar, gastroepiploic, , common hepatic artery and celiac trunk should be included in T3/T4 disease. Left gastroepiploic, greater curvature and celiac nodes should also be included in high grade tumors.
- Splenic hilar, splenic artery and also nodes along greater curvature should also be included for large and deeply penetrating tumors.

Tumour extending more than 1.5cm beyond the Z line and those extending above diaphragm should include midesophageal nodes up to carina. It should be borne in mind, that such extensive field will lead to potential side effects and hence the fields should be decided based on individual build and anatomy of the patient.

RADIATION DOSE:

The dose of radiation used in treatment of carcinoma esophagus in radical chemoradiation is 50 to 50.4 Gy. Several randomized trials have been conducted to analyse the significance of dose escalation if radiation in treatment of carcinoma esophagus. A contemporary analysis of national cancer database for radiation dose escalating in esophageal cancer between years 2004-2012 which included a total of 6854 patients [39], in which 55.7% received 50-50.4 Gy RT and the remaining received >50.4 Gy radiation. Dose analyses were done dividing patients into groups: 50-50.4, 51-54, 55-60, >60 Gy. On analysis it should no appreciable difference in overall survival in any group compared to 50-50.4 Gy group. Rather on dose escalation there were significant toxicities. Further INT 0123 study [40, 41] which compared combined modality therapy using high dose (64.8 Gy) versus 50.4 Gy Radiation therapy concurrent with 5-Fluorouracil and Cisplatin chemotherapy in both arms. It analysed the locoregional control, survival and toxicity. The median follow up time was 16.4 months. No significant difference in median survival between high dose and standard dode radiation arms, 13 vs 18.1 months respectively. No differences in locoregional failure (56% vs 52%) but there were 11 deaths related to treatment in high dose arm compared to the standard dose arm. So it concluded that there was no increase in overall survival and locoregional control in high dose arm.

According to NCCN (National Comprehensive Cancer Network) guidelines, for preoperative radiation a dose range of 41.4 to 50.4 Gy is

generally recommended. For patients, in whom surgery is not possible due to contraindications, and who receive radical radiation or chemoradiation should receive 50 to 50.4 Gy doses delivered in 1.8-2 Gy per fraction. For radiation given postoperatively, the dose ranges should be 45-50.4 Gy.

Intensity Modulated Radiotherapy (IMRT):

IMRT is done using MLCs to define the beam intensity, independently at different regions of the incident beam, thereby producing the desired dose distribution uniformally, or deliberate non uniformal dose distribution within the target volume. The position of the leaves can be modified in time with a fixed or a moving gantry. IMRT can be delivered by means of:

- Dose compensation
- Multiple static fields
- Step and Shoot technique
- Dynamic MLC
- Tomotherapy

In the Step and shoot technique, the sequence of static beams are used with the beam switched off between changes in position. In the dynamic MLC, there is automatic sequence of beam segments without stopping treatments. Other methods like tomotherapy involves intensity modulated rotational delivery with the help of fan beams. Forward planned or Segmental IMRT, involves simple tissue compensation

with the beams eye view of PTV and the subsegments are shaped with different MLC to create a uniformal dose distribution. Inverse planning requires dose to the PTV, CTV, OARs in terms of dose volume constraints, optimization of fluence, and 3D dose planning. Careful quality assurance is must in assuring the accuracy of the beam. Dose delivery is verified throughout the course of treatment by using radiographic films or EPIDs. Accurate patient positioning, target volume delineation, reduction of organ and patient movements especially respiration, validates the use of safe and precise IMRT dose delivery. IMRT modulates the intensity of the beam and the geometric conformation, so that, it delivers complex dose distributions with the help of forward and inverse planning. Plans can be produced with concave shapes, and hence critical structures like spinal cord, etc can be spared better, thereby reducing the late toxicities of treatment. However, integral dose is higher, which is a drawback with IMRT, and hence increases the risk of development of second malignancies. IMRT with steep dose gradients, can lead to under dosage of tumour if margins are close and organ movements are present. It is difficult to produce evidence of benefit for this new technology, until, wide randomized controlled trials are done to prove its superiority. Furthermore, the unwanted late effects of treatment cannot be predicted, and hence true efficacy of the treatment and to arrive at its therapeutic ratio, is delayed.

ORGANS AT RISK (OAR):

Oragns at risk as defined by ICRU (International Commission on Radiological units) are the normal tissues which are adjacent to the tumor site which is included in radiation fields and might cause loss or impaired function of the organ. So planning must be done to avoid normal tissue toxicity in addition to delineating tumor tissues. The OAR's in treatment of carcinoma esophagus are Spinal cord, heart and lungs.

TOLERANCE DOSE OF SPINAL CORD:

The point dose to spinal cord should be less than 45 Gy to avoid toxicities. The toxicity due to increased dose to spinal cord presents as Myelopathy and irreversible paralysis. The spinal cord is contoured and a 5 mm margin to create the planning organ at risk volume (PRV).

TOLERANCE DOSE TO LUNG:

The lung is contoured in a such a way that volume of lung recieveing 20 Gy should be less than 30% (V20 <30%) and

TD 5/5: 45 Gy (1/3), 30 Gy(2/3), 1750 cGy(3/3)

TD 50/5: 65 Gy(1/3), 45 Gy(2/3), 2450 cGy (3/3)

TOLERANCE DOSE TO HEART:

The mean dose of heart should be kept less than 26 to 30 Gy and volume receiving 30 Gy should be less than 46%.

TD 5/5: 60 Gy (1/3), 45 Gy (2/3), 40 Gy (3/3)

TD 50/5: 70 Gy(1/3), 55 Gy(2/3), 50 Gy (3/3)

TD 5/5- gives an estimate of about 5% of probability for a given side effect to appear 5 years after treatment.

TD 50/5- gives an estimate of about 50% of probability for a given side effect to appear 5 years after treatment.

Postoperative complications:

- Pulmonary complications
- Cardiac morbidity
- Leak at anastomotic sites
- Recurrent laryngeal nerve paralysis
- Stricture formation (14-27%)

Radiation induced Toxicity:

Acute Toxicities:

- Esophagitis
- Dysphagia
- Neutropenia
- Thrombocytopenia
- Epidermiditis

- Fatigue
- Weight loss
- Nausea
- Vomiting

Some of the life threatening complications in addition to above are Perforation of esophagus, which presents with retro-sternal pain, fever, thready pulse, shock, hemorrhage, [42] etc. The addition of chemotherapy increases the risk of side effects mentioned above, at least increasing in about 50-70% of patients. In fact, the risk of grade 3 toxicity increases to about 44% compared to 25% with radiation therapy alone. Grade 4 toxicity is shown to be 20% with concurrent chemoradiation in contrast to 3% with radiation therapy alone. [43,44]The percentage is less, because the number of patients with such toxicities may not survive the same.

Late Toxicities:

The most common late effects associated with radiotherapy are stenosis and stricture formation. Dysphagia associated with stenosis and stricture occurs in about 10-15% of patient, and can be relieved by Savary-Gilliard dilatation, 42 as a temporary basis. Usually three to four dilatations will be required. RTOG

trial showed that long term side effects especially Grade 3 toxicity are nearly equal with both concurrent chemoradiation and radiation therapy (29% vs 23%). However grade IV toxicities were more with concurrent chemoradiation arm (23%) than radiation arm (3%).

Radiation pneumonitis:

One of the most common under reported complications is Radiation pneumonitis. It can range from minimally symptomatic to fatal disease. The most common presenting features are non productive cough, dyspnea, respiratory distress, etc; which occurs mostly after two to six months of radiation therapy. Some of the most common predictive markers to assess lung toxicities are V20 > 30 percent, mean lung dose of more than 20 Gy, V5 of more than 42%, or an absolute V5 of more than 3000 sq.cm. [45]

In a study from MD Anderson Cancer Centre [46], 110 patients received preoperative chemoradiation, the absolute lung dose, mean lung dose and the effective dose receiving less than or equal to 5Gy were calculated which proved to predict the risk of developing postoperative pulmonary complications. In this study pulmonary complications postoperatively was present in 18%, and higher rates were seen when the V10 values were more than or equal to 40% (35% vs 8%) and V15 values of more than or equal to 30% (33% vs 11%). The study concluded that reduction of irradiated volume of lung led to reduced postoperative pulmonary complications. The increase in pulmonary complications postoperatively like pneumonitis, acute respiratory distress

syndrome, when V10 value was more than 40% suggest that postoperative pulmonary complications are predicted by volume of remaining or undamaged lung tissue. In other words, patients with smaller lung volume to begin with will experience higher rates of postoperative pulmonary complications. [47] Postoperative complications are also higher in patients with less fuctional reserve. Hence, it is essential to calculate total lung volume in addition to dose volume histogram.

Radiation induced cardiac toxicity:

Radiation induced cardiac toxicity involves injury to numerous structures like pericardium, which manifests as effusion or pericarditis, coronary arteries, heart muscle fibres, cardiac valves, or nerve and conduction defects. Radiation mainly leads to fibrosis or small vessel injury. Classic radiation tolerance values i.e TD 5/5 for the heart is about 60 Gy when the irradiated volume is less than or equal to 25%. Similarly, TD 5/5 is 45 Gy when the irradiated volume is about 65%. The mechanism that leads to cardiac injury especially in esophageal cancer is poorly defined. Historically, treated patients with Hodgkin's disease who received more than 40 Gy led to increased cardiac morbidity and mortality. [48,49]. Roughly, V30 of more than 46% predicts an increased risk of having pericardial effusion leading to increased cardiac morbidity. Also, there was reports stating that increased V20 dose to left ventricle led to decrease in ejection fraction, and thereby functioning of the heart. [45]

III.ORIGIN OF PROPOSAL:

Esophageal cancer constitutes 6% of all GI malignancies with high prevelance in Asian population of approximately 800 per 1,00,000 population. In Cancer Institute in past 5 years there were approximately 480 cases of esophagus registered with a male preponderance of 1.6:1. Unfortunately disease is asymptomatic in early stages and most of the patients present in and are diagnosed in late stages. Historically, surgical resection was the standard treatment modality for localized carcinoma of the esophagus, with cure rates reported in the range of 10% to 20%.On literature search for patients who were treated with surgery alone the local recurrence rates has been 32-45%when treated with surgery alone and for radiation therapy alone the local recurrence rates are very poor which is up to 77%. Neoadjuvant chemoradiation appears to be a promising option for advanced esopahageal cancers, it has contributed to tumor shrinkage, leading to higher resectability and longer survivals. The weight of the evidence from multiple phase II trials, has underpowered phase III trials and meta-analyses has suggested that this is an appropriate treatment choice. A recently published randomized control trial (RCT) addressing this issue (CROSS Group study) and a Meta- Analysis has proven a high progression free survival and overall survival in this treatment approach. The standard of care for operable patients with carcinoma esophagus who are fit is tri-modality approach using neoadjuvant chemoradiation followed by surgery.

In India malignancy of esophagus is emerging as a most common cancer. With new diagnoses in more than 480,000 patients annually, esophageal cancer is the eighth most common cancer worldwide. It is a highly lethal disease, causing more than 400,000 deaths per year. Esophageal cancer is emerging as a common cancer in India. (Malken et al) Squamous cell carcinoma of the esophagus is the third leading cancer in men and fourth leading cancer in women in India.

Carcinoma esophagus is ranked fifth among males and sixth among females accounting for 6.4% of all male cancers and 3.5% of all female cancers in the Chennai Hospital Cancer Registry (HCR). SCC was the predominant histology in up to 70% and adenocarcinoma accounting for 10.7% of the cases. Radiation therapy either alone or in combination with chemotherapy has been the main modality of treatment.

Despite advances in cancer therapy, esophageal cancer remains one of the least treatment- responsive malignancies. Less than $1/5^{th}$ of the cases presenting at Cancer Institute received cancer directed treatments, the 5-year overall survival by actuarial method for patients treated. But the advent of neoadjuvant chemoradiation has increased the disease free survival and progression free survival in patients with resectable carcinoma esophagus with good tolerability and accepatable toxicities.

IV.AIM OF THE STUDY:

To study the safety and efficacy of Neoadjuvant chemoradiation (41.4 Gy of radiation concurrent with five cycles of Carboplatin and Paclitaxel chemotherappy) in terms of compliance to therapy and number of cycles of chemotherapy given concurrent with radiotherapy and pancytopenia requiring pend in radiation and Granulocyte-Colony Stimulating Factor (G-CSF) support, in patients with resectable carcinoma of the mid and lower esophagus (Both squamous and adenocarcinomas)

V.MATERIALS AND METHODS:

Eligibility criteria:

a. Histologically proven resectable carcinoma (Squamous and Adenocarcinoma) of the middle and/or lower third of esophagus
b. Cancers deemed resectable clinically (T2-T4aN0-1M0)
c. The length of the tumor should be less than or equal to 8 cm and width of the tumor should be less than or equal to 5 cm.
d. The upper border of the malignancy should start 3 cm beloe the esophageal sphincter.
e. Patients with gastric tumors proximally but only with minimal invasion are excluded from the study.

Inclusion and exclusion criteria:

a. Informed Consent
b. ECOG performance status 0-1
c. Age<65 years
d. Absolute neutrophil count > 1,200/mm^3, WBC > 4,000/mm^3, Platelet count 150,000/mm^3
e. INR ≤ 1.5 Patients on therapeutic anticoagulant for unrelated medical condition such as atrial fibrillation or anti-thrombocyte treatment allowed provided treatment can be withheld for operation
f. Total serum bilirubin ≤ 1.5 mg/dL , Alkaline phosphatase < 2.5 times upper limit of normal (ULN), SGOT < 1.5 times ULN

g. Serum creatinine normal, BUN normal

h. Not pregnant or nursing

i. No history of severe congestive heart failure or severe pulmonary disease. Patients who are status post-revascularization procedures with satisfactory cardiac function are eligible, No acute myocardial infarction within the past 6 months

j. No significant history of a medical problem or co-morbidity (e.g., severe congestive heart failure or active ischemic heart disease) that would preclude a major thoracic surgery

k. No concurrent second malignancy requiring systemic therapy

l. No psychiatric or addictive disorders or other conditions that would preclude the patient from meeting the study requirements

All consecutive eligible patients of resectable carcinoma of the mid and lower thoracic esophagus registered at the Institute was offered the protocol of Neoadjuvant CRT.

CHEMOTHERAPY:

The Neoadjuvant CRT schedule administered will be as follows: Paclitaxel at a dose of 50 mg per square meter of body-surface area and Carboplatin targeted at an area under the curve of 2 mg per milliliter per minute(AUC-2) given intravenously on days 1,8,15,22 and 29.

Details of Chemotherapy:

Intravenous Paclitaxel and carboplatin weekly

- Day 1:i.v Paclitaxel 50 mg/m^2 IV over 3 hours.
- Day 1:i.v carboplatin AUC 2 IV over 1 hour

Absolute dose of Carboplatin = [target AUC] x (GFR + 25).

GFR = [((140 – age) x 1.23 x body weight) / serum creatinin X (0.85 (female) or 1.00 (male))]

Anti Emetic Regime:

- Inj.Dexamethasone 8 mg IVOD X Day 1
- Inj.Palensetron 0.4 mg IV OD X Day 1

Before the patients are planned for a subsequent cycle of chemotherapy, they are required to have an ANC (Absolute Neutrophil Count) of more than or equal to 1500 cells per cubic millimetre, a platelet count of more than or equal to 100,000 cells per cubic millimeter, and a creatinine levelof 1.2 mg per deciliter or less

- GCSF Support shall be decided by the treating physician

If the chemotherapy is associated with hematologic side effects, treatment is modified which includes delay in chemotherapy cycle, reducing the dose of chemotherapy, and by adding G-CSF Granulocyte-Colony Stimulating Factor). There is no dose modification if there is neutropenia or leukopenia without fever. For cases with grade 3 or 4 peripheral neuropathy, a creatinine level more

than 1.2 mg per deciliter, or a calculated creatinine clearance being less than 50 ml per minute, there is postponement of treatment.

If the treatment is delayed for two weeks patient is removed from the study.

Dose of paclitaxel shall be reduced (85%) if there is grade 2 peripheral neuropathy. Patients who requires discontinuation of protocol treatment due to Paclitaxel-related toxic effect shall receive intravenous therapy, with carboplatin alone.

RADIATION:

FRACTIONATION SCHEDULE:

Patient will receive a daily fraction of 1.8 Gy, 5 fractions a week to a total dose of 41.4 Gy given in 23 fractions, starting the first day of the first cycle of chemotherapy. 3D conformal technique was used to deliver radiation in all patients. The position of patient was supine position and orthogonal laser beams were used to assess the reproducibility.

SIMULATION PROCEDURE:

Before starting radiation a plain Computed Tomography scan is done from the level of mastoid process upto the level of L1 vertebra, with 3.5 or 5 mm slice thickness in supine position.

DEFINITIONS OF TARGET VOLUMES AND CRITICAL

STRUCTURES:

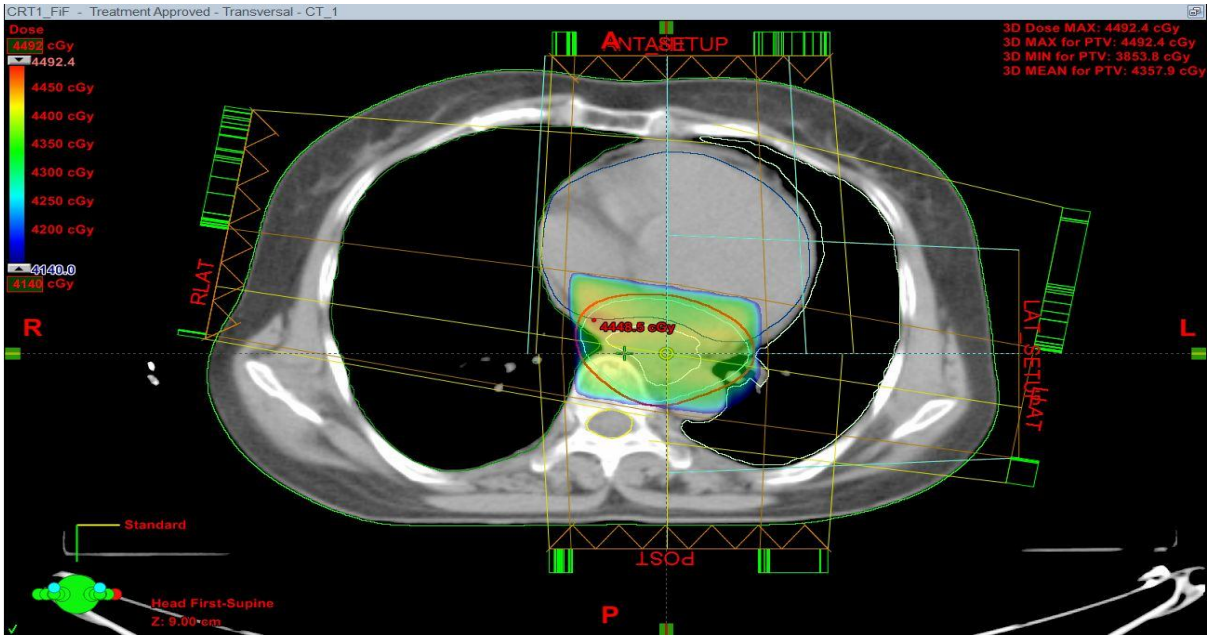
In each CT slice the primary tumor with the enlarged regional nodes is taken as

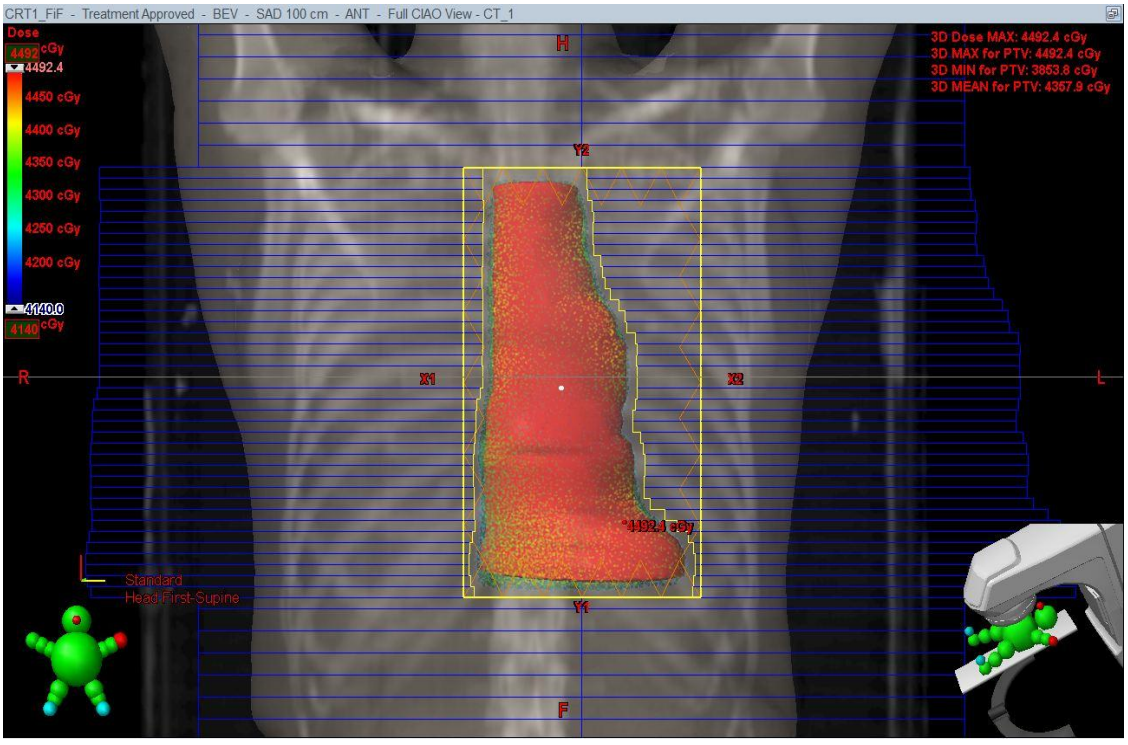
the GTV (Gross Tumor Volume) and drawn . The findings of physical examination, endoscopy, computed tomography scan of the thorax and upper abdomen will be taken in to account to determine the GTV. The PTV (Planning Target Volume) will be proximal margin of 4 cm and distal margin of 4 cm will be considered and a distal margin of 3 cm will be considered if the tumor has extended in to stomach. To compensate for set up variations and fro tumor motion and to include the area of subclinical involvement a radial margin of 1.5 cm is given.

The heart and both the lungs were contoured. The borders of the heart are, cranial border should exclude great vessels as much as possible and should include apex of both atria, and the infundibulum of the right ventricle. The lowest part of the left ventricle's inferior wall which is distinguishable from the liver is taken as the caudal border. To know the dose received by spinal cord the spinal canal should be contoured.

The planning of patient with dose color wash treated with conformal therapy to a Total dose of 41 Gy is shown below


CRT1_FiF - Treatment Approved - Transversal - CT_1
Dose
4492 cGy
4492.4
4400 cGy
4300 cGy
4140.0
4140 cGy
ANTA_SETUP
RLAT
LAT_SETUP
4427.2 cGy
R
L
P
SOd
Z: 8.50 cm
CRT1_FiF - Treatment Approved - BEV - SAD 100 cm - ANT - Full CIAO View - CT_1
3D Dose MAX: 4492.4 cGy
3D MAX for PTV: 4492.4 cGy
3D MIN for PTV: 3863.8 cGy
3D MEAN for PTV: 4357.9 cGy
H
Y2
R
X1
X2
L
4492.4 cGy
Y1
F
Standard
Head First-Supine
CRT1_FiF - Treatment Approved - Frontal - CT_1
H
R
RLAT
ANTA_SETUP
4479.4 cGy
LAT_SETUP
L
F
Y: -0.85 cm
CRT1_FiF - Treatment Approved - Sagittal - CT_1
H
P
POST
LLAT
LAT_SETUP
4477.7 cGy
RLAT
ANTA_SETUP
A
F
X: 1.37 cm





BEAMS EYE VIEW OF A TREATMENT PLAN

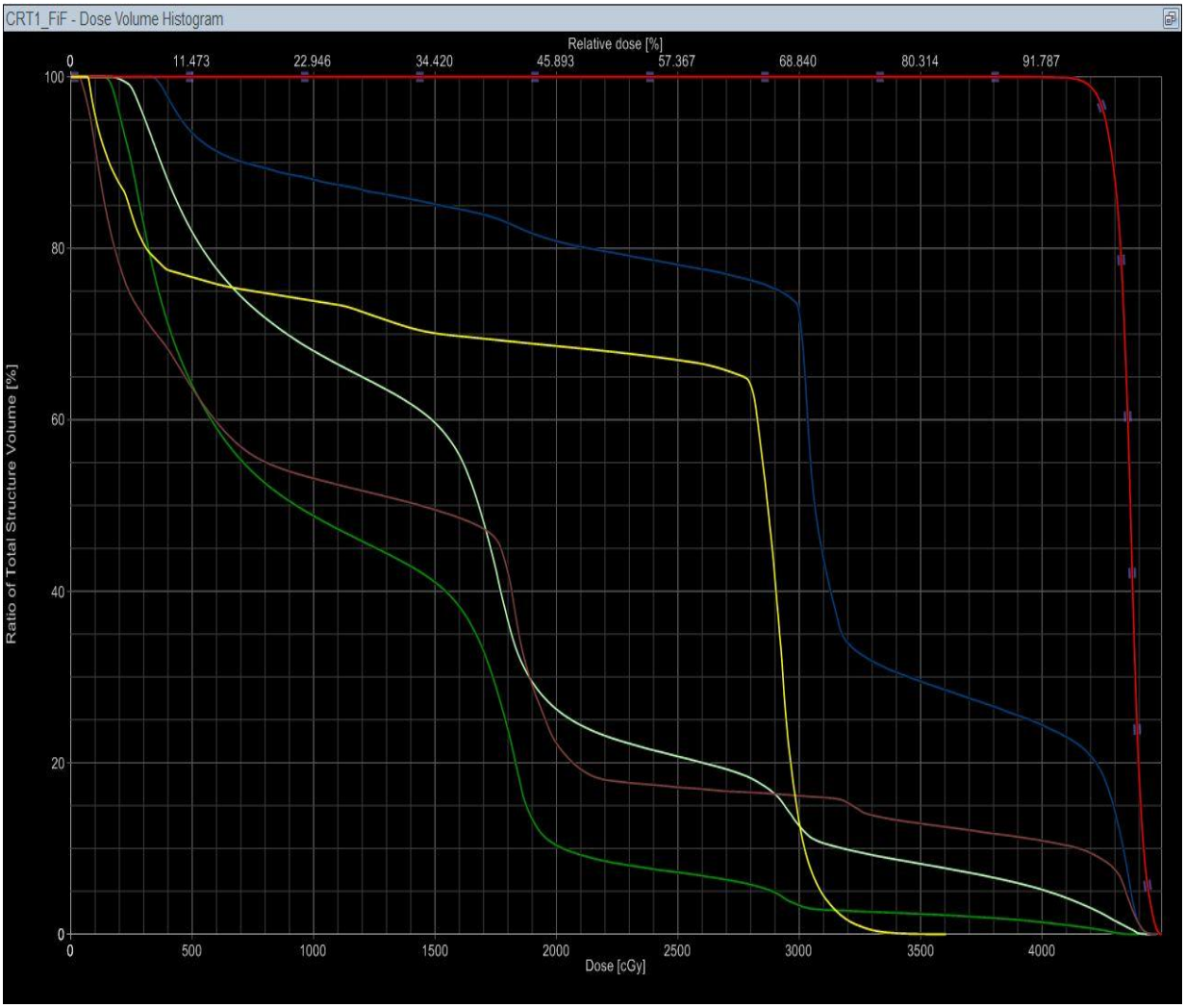
RADIATION TECHNIQUE:

Multiple field technique is used to deliver radiation. A combination of anterior/posterior, oblique or lateral field is used to deliver treatment. To ensure proper shape of treatment fields MLC's (Multi Leaf Collimators) are used. All patients will undergo a 3D planning. To ensure optimal normal tissue sparing and optimal coverage of target volume Beams-eye-view (BEV) displays will be used.

Dose-Volume-Histograms (DVH's) are mainly obtained to know the normal tissue damage. Normal tissue tolerance DVH's of the spinal cord, the heart and both lungs will be obtained for all patients. DVH's may also help to select the most appropriate treatment plan. Optimal sparing of both the lungs and V20 <30 Gy for both the lungs are ensured. Volume of both the lungs will be limited by field shaping and by using Beams-Eye-View planning so as to minimize the risks for severe pneumonia for the patients treated. The dose to spinal cord is always kept less than 45 Gy.

Megavoltage equipment is used to deliver radiation therapy and energies more than or equal to 6 MV are used. To shape the irradiation portal according to the PTV (planning target volume) multileaf collimators will be used.

DOSE VOLUME HISTOGRAM (DVH) OF A PLAN:



DOSE SPECIFICATION:

The prescription dose will be specified at the ICRU 50/62 reference point, which will be the isocenter for most patients. 1.8 Gy will be the daily prescription dose at the ICRU reference point and the entire planning target volume (PTV) should encompass the 95% isodose. The maximum to the PTV

should not exceed by >7% of the prescription dose. Treatment verification portal images was done at the beginning of each week.

The patients will then be taken up for surgery after completion of chemoradiotherapy as early as possible (eight weeks prefreably). The toxic effects of chemotherapy and radiotherapy were monitored in patients closely. Common Terminology Criteria for Adverse Events CTCAE 4.0 and Radiation Therapy Oncology Group (RTOG) criteria are used to grade toxicities, mentioned as below.

RTOG TOXICITY CRITERIA:

Grade 0-5

Grade 0-Normal

Grade 5-Death

Leukpenia:

Toxicity Grade	White Blood Cell Count (cells/mm3)
1	3000-less than 4000
2	2000-less than 3000
3	1000-less than 2000
4	Less than 1000

Thrombocytopenia:

Toxicity grade	Platelet count(cells/mm3)
1	75000-less than 1 lakh
2	50000-less than 75000
3	25000-less than 50000
4	Less than 25000 or spontaneous bleeding

PNEUMONITIS: (ACUTE)

Grade 1	Mild symptoms like dry cough and dyspnea on exertion
Grade 2	Persistent cough requiring narcotics/antitussives; dyspnea with effort but not at rest
Grade 3	Severe cough requiring antitussives, dyspnea at rest, Radiological changes of patchy pneumonitis, might require steroids or oxygen.
Grade 4	Severe respiratory compromise requiring assisted ventilation.

PNEUMONITIS: (LATE)

Grade 1	Mild symptoms like dry cough with mild changes radiologically
Grade 2	Moderate symptoms like fibrosis and pneumonitis. Presents

	with severe cough, patchy radiological changes and fever
Grade 3	Severe fibrosis, Dense radiological changes
Grade 4	Severe respiratory insufficiency, continuous assisted ventilation with oxygen.

CTCAE 4.02 Grading:

Adverse Event	1	2	3	4	5
Hypokalemia (mmol/L)	3-3.5 Asymptomatic	3-3.5 Symptomatic; intervention required	2.5-3	<2.5; life threatening complications	Death
Hyponatremia (mmol/L)	<lab lower limit-130	-	<130-120	<120; life threatening complications	Death
Vomiting	1-2 episodes in 24 hours (5 minutes gap between episodes)	3-5 episodes in 24 hours (5 minutes gap between episodes)	>=6 episode requiring hospitilisation. TPN or tube feeding	life threatening complication; urgent intervention required	Death

SURGERY:

The surgical technique which was performed was either a transhiatal esophagectomy or transthoracic esophagectomy (also known as Ivor-Lewis procedure) with a two-field lymph-node dissection. For restoring the continuity of the digestive tract, cervical anastomosis using a gastric tube will be the preferred technique. The patients will be monitored for serious adverse events including the duration of hospital stay and the pathological response will be assessed for pathological complete primary and nodal response as response to concurrent chemoradiation given.

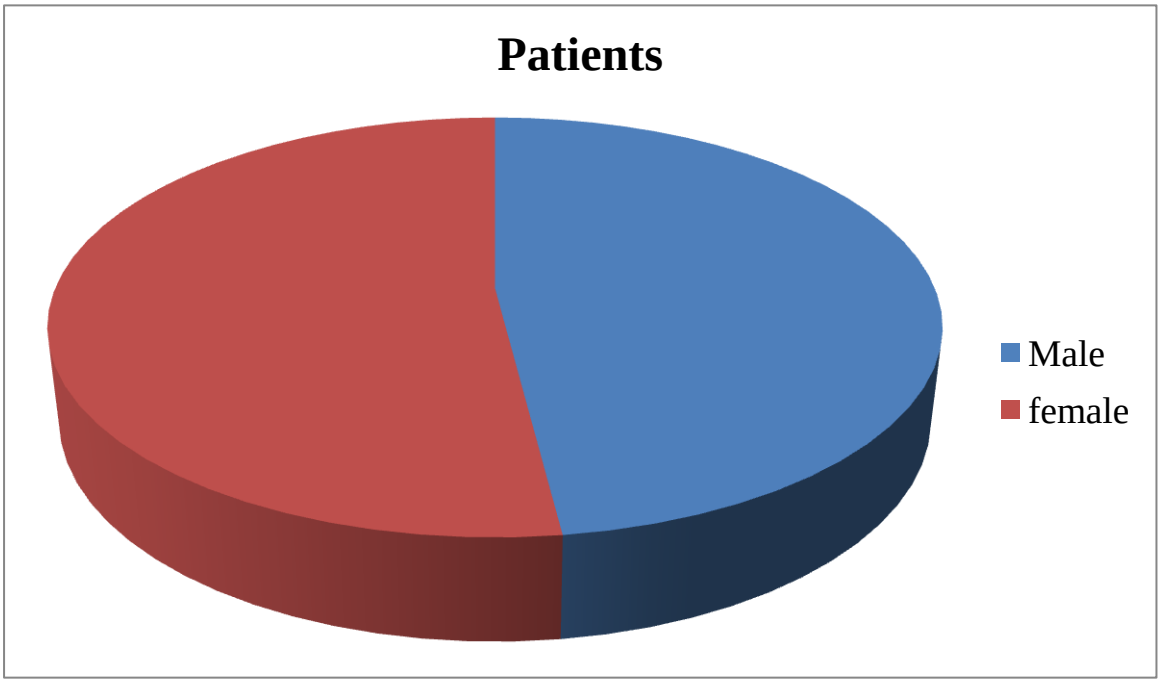
PATIENT CHARACTERISTICS:

All patients before randomizing to Neoadjuvant chemoradiation underwent Routine blood investigations which includes Hemoglobin, Total count, Platelet count, Coagulation profile, Blood Urea, Serum creatinine, Serum Bilrubin, Serum alkaline phosphate levels, Coagulation profile and Blood sugar , Upper Gastrointestinal endoscopy to assess the upper and lower extent of the disease and for histological diagnosis, Chest x-ray, Ultrasound scan of the abdomen, Computed Tomography scan of the Chest including upper abdomen to assess the approximate thickness of lesion and to assess the operability. Once the lesion is considered to be operable patients were planned for neoadjuvant chemoradiation

From July 2013 to July 2016, 28 patients with carcinoma esophagus who had resectable disease were considered eligible for Neoadjuvant chemoradiation

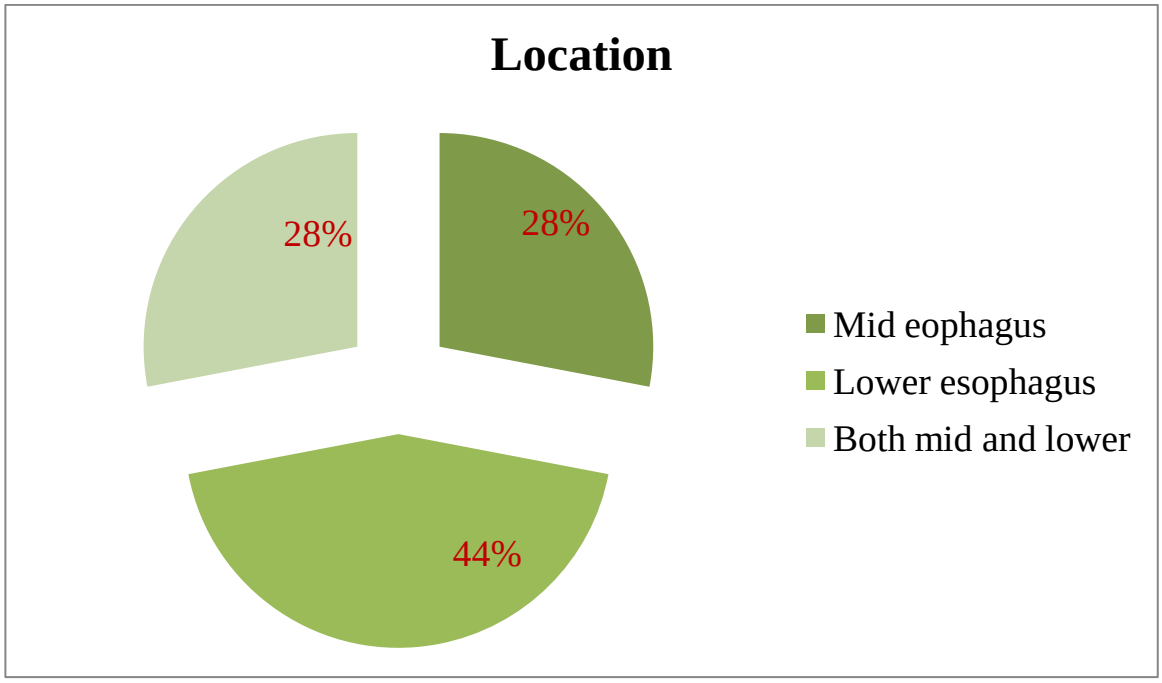
followed by reassessment for surgery. Out of the 28 only 25 (89%) patients underwent surgery post neoadjuvant chemoradiation. The remaining 3 patients defaulted post chemoradiation for treatment. The remaining 3 patients were not included in the analysis.

In the remaining 25 patients, 12 were males and 13 patients were females with Male: Female ratio of 1:1.1. The median age of the patients studied was 49 years (ranging from 31-66 years).

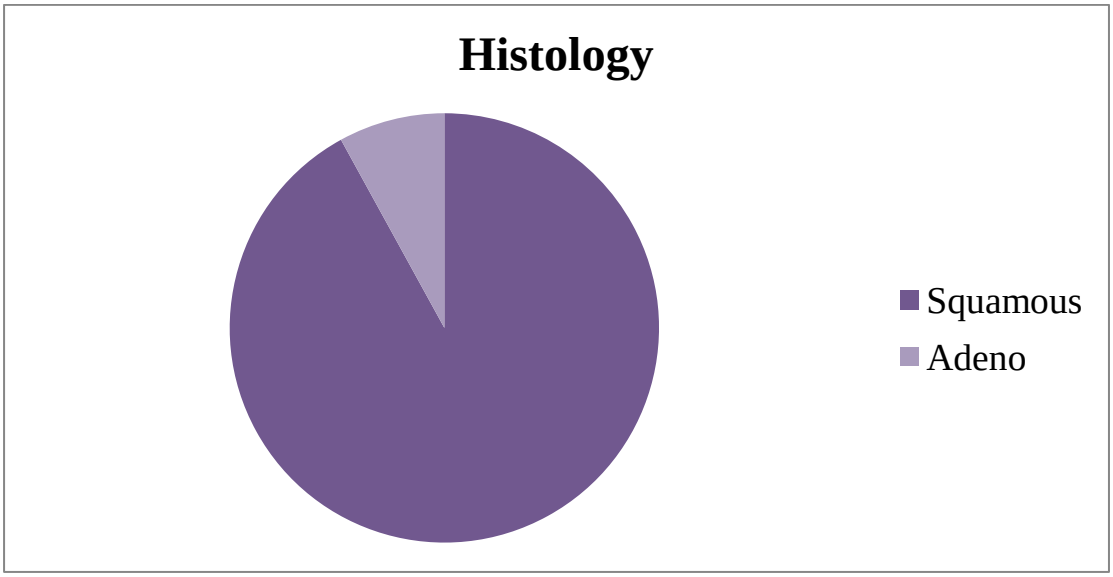


The location of malignancy in esophagus, 28% (7 patients) had lesion in mid thoracic esophagus (25-30 cm) and 44% (11 patients) had disease only in lower esophagus (30-40 cm) and the remaining 28% (7 patients) had disease both in mid and lower esophagus but the length was not exceeding 8 cm. Out of the patients with lower thoracic esophagus lesion 87.5% had esophago gastric junction involvement with cardia of stomach involvement in 1 patient. All

patients were started on first cycle chemotherapy, Paclitaxel and carboplatin with radiation on the same day at a fractionation of 180 cGy per day.



Out of the 25 patients, 92% (23 patients) had histological diagnosis of squamous cell carcinoma and remaining 2 patients had Adenocarcinoma



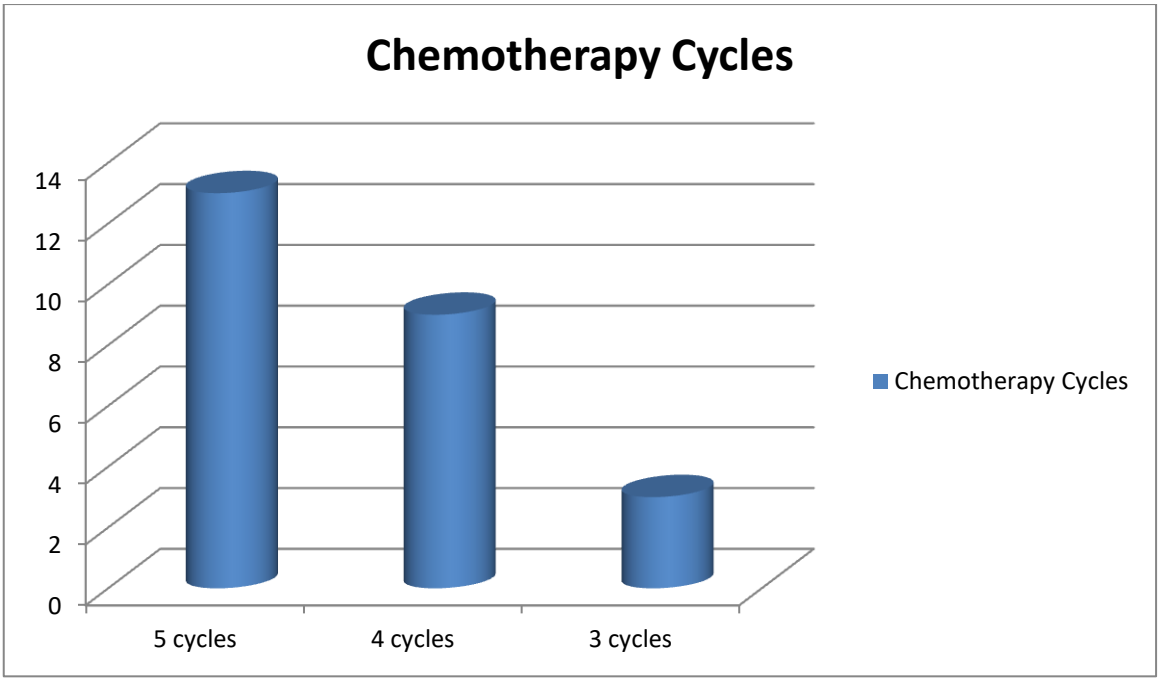
All patients were of Performance status 0-1 according to ECOG Performance status score, with PS-0 being fully active and PS-1 being unable to carry out heavy physical work. The patients were reassessed after chemoradiation at 4 weeks and repat CT scan and Upper Gastrointestinal scopy is done to know the status of disease in patients. The patients were taken up for surgery preferably 6-8 weeks from the complete of neoadjuvant radiation. The postoperative complications and duration of hospital stay postoperatively are also assessed for patients.

VI.RESULTS:

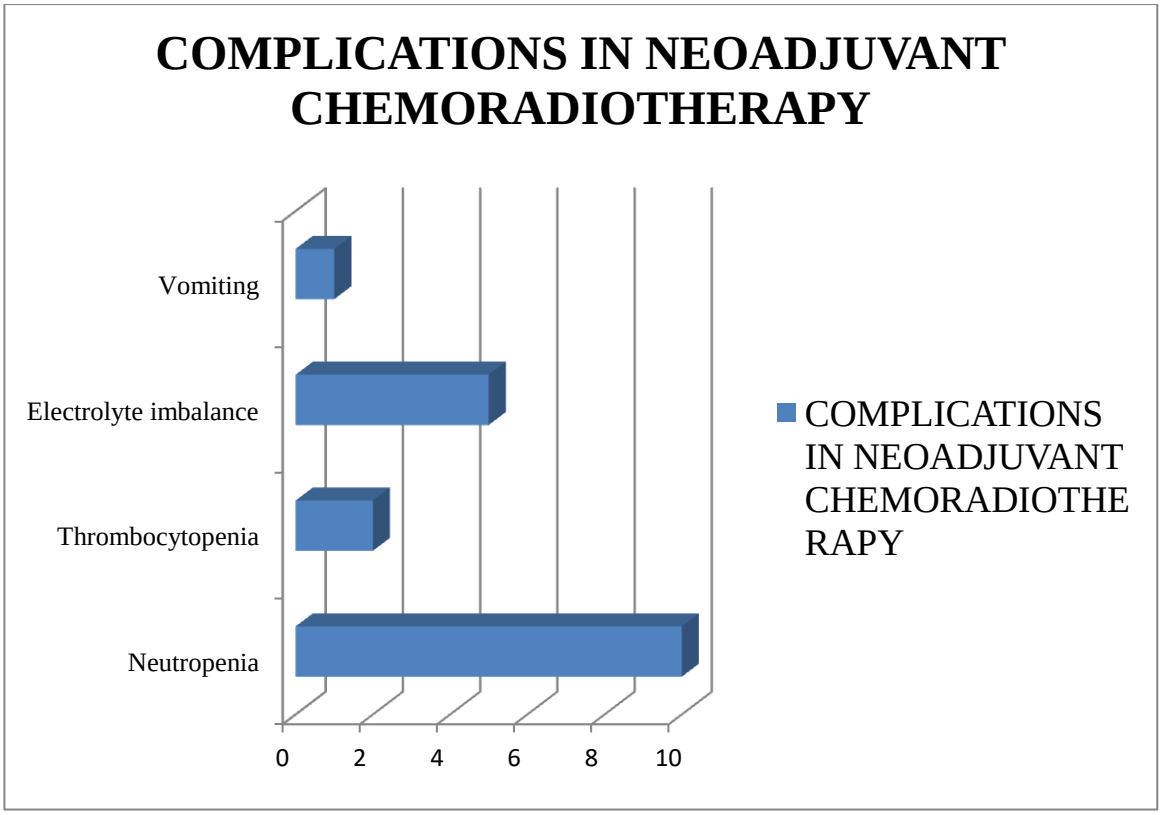
From July 2013 to July 2016, 28 patients with carcinoma esophagus who had resectable disease were considered eligible for Neoadjuvant chemoradiation followed by reassessment for surgery. Out of the 28 only 25 (89%) patients planned for surgery post neoadjuvant chemoradiation. The remaining 3 patients defaulted post chemoradiation for treatment. The remaining 3 patients were not included in the analysis.

The total median duration of chemoradiation is 36 days (ranging from 31 to 50 days).

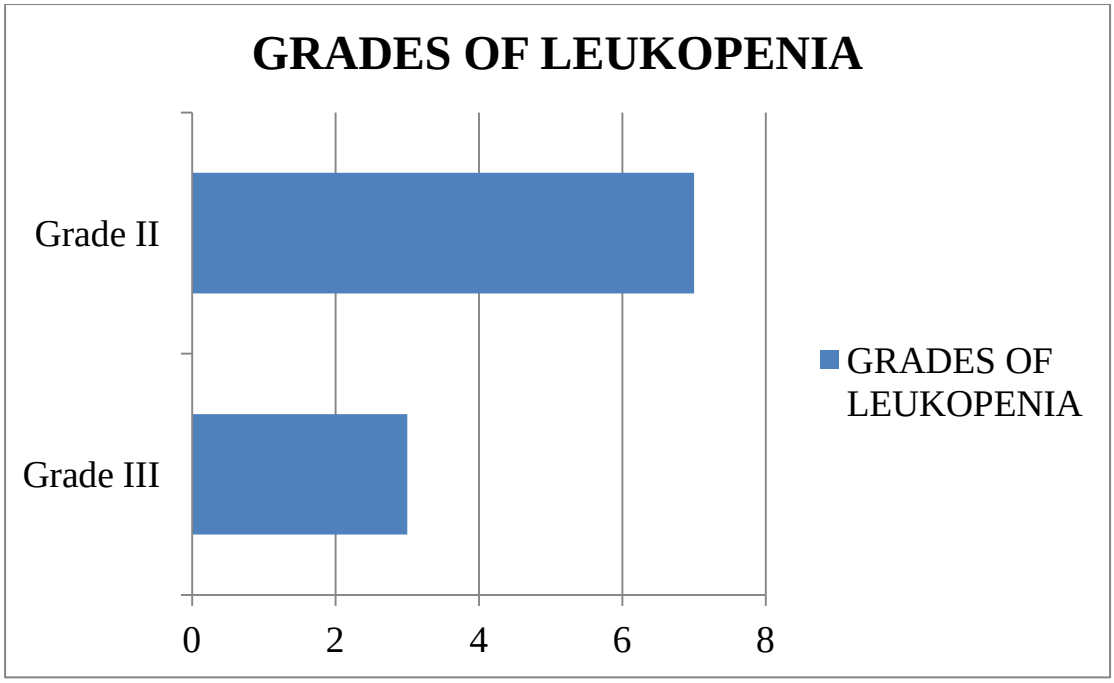
The patients were initially planned for 5 cycles chemotherapy but only 52% (13 patients) were able to complete all the 5 cycles of chemotherapy and 36% (9 patients) were able to complete only 4 cycles of chemotherapy and the remaining 3 patients (12%) received only 3 cycles of chemotherapy concurrent with radiation due to poor tolerance.



The toxicity of chemotherapy was assessed according to Common Terminology Criteria for Adverse Events CTCAE 4.0 and RTOG criteria. Treatment breaks during radiation was present in 9 (36%) patients with a median of 6.5 days (ranging from 4-10 days) for toxicities which are neutropenia requiring Granulocyte Colony Simulating Factor support, thrombocytopenia and electrolyte imbalance. Out of 25 patients, 32% (8 patients) had only neutropenia, 2 patient had thrombocytopenia and 2 patients had both neutropenia and electrolyte imbalance and 3 patients had only electrolyte imbalance and 1 patient had chemotherapy induced vomiting.



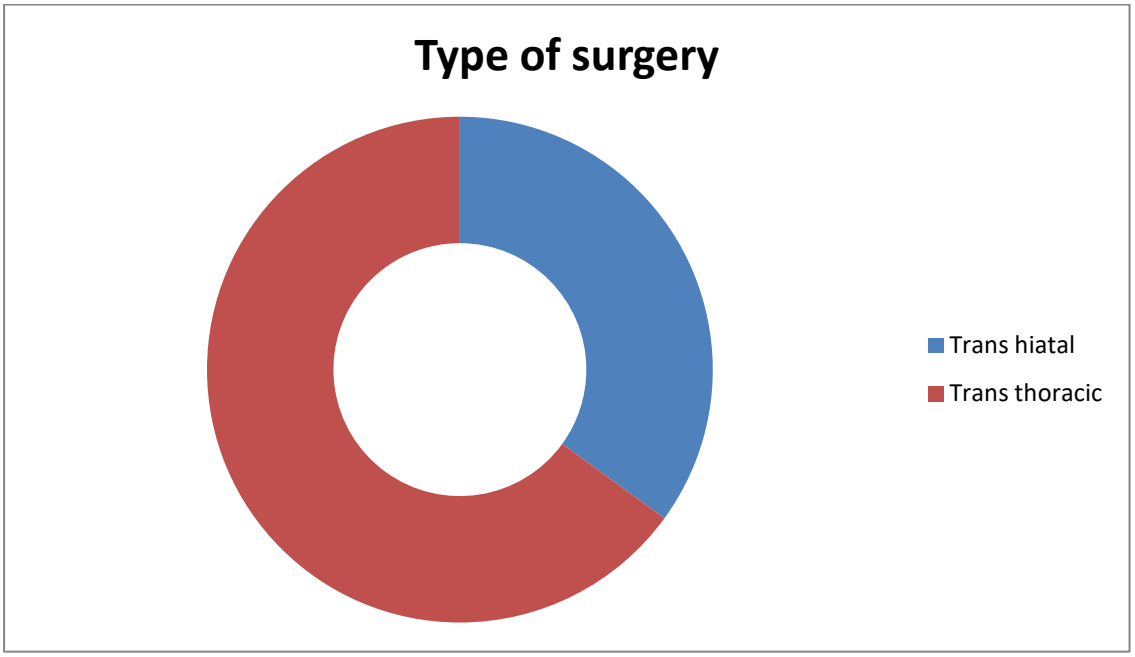
Out of the 10 patients who had neutropenia 3 patients had Grade III neutropenia and 1 among those developed febrile neutropenia with Nadir Total count of 1500 cells/mm3. The patients with Grade II neutropenia were 7 patients. Patients with no symptoms and no fever where continued on radiation and the Total WBC count was repeated daily.



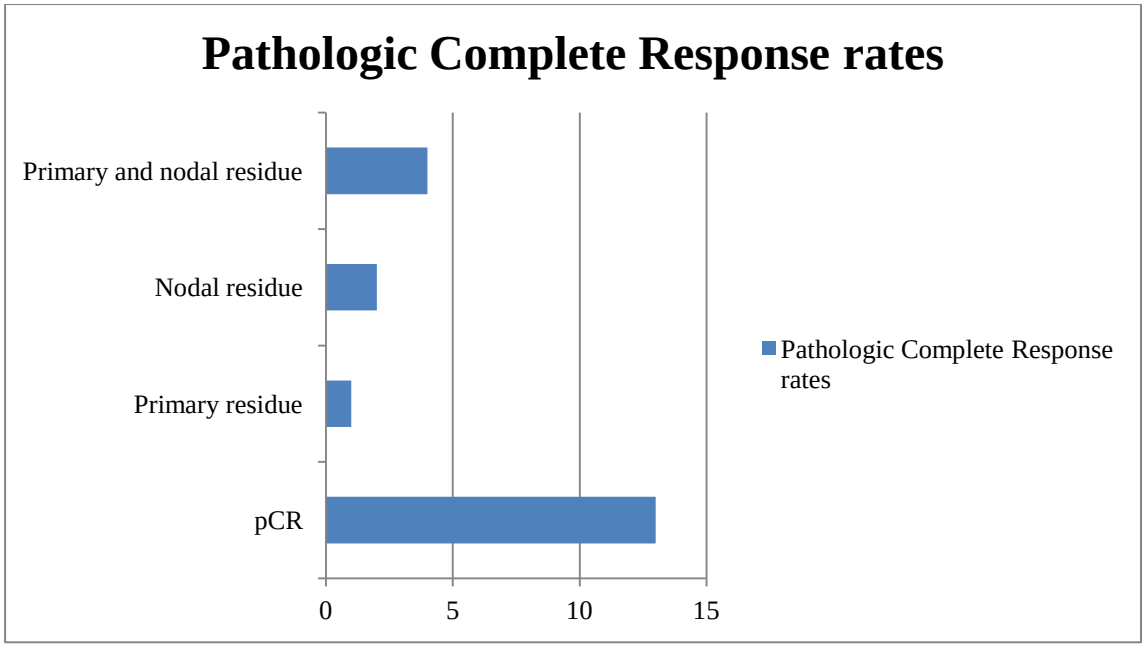
If the patient was symptomatic Radiation was pended and patient started on GCSF support. Post chemoradiation patients were seen after 4 weeks for reassessment and were taken up for surgery. The median duration from the end of chemoradiation to surgery was 62.5 days (ranging from 45 days to 108 days).

Post chemoradiation patient were assessed using repeat Upper gastrointestinal endoscopy and Computed Tomography scan of the chest and upper abdomen. Out of the 25 patients, only 20 patients (80%) underwent esophagectomy. In remaining patients, one patient progressed to have spine metastasis and one patient found to progressive disease with paraortic nodes during evaluation for surgery and in two patients surgery was abandoned as the tumor was adherent to retroperitoneal structures and due to adherent celiac plexus. And in one more patient palliative stenting was done as patient had signifivant residual disease in pre surgery evaluation. The remaining 20 patients

underwent either Transhiatal esophagectomy or transthoracic esophagectomy. Out of 20 patients, 7 patients(35%) underwent Transhiatal esophagectomy and remaining 65% underwent Transthoracic esophagectomy. Postoperative complications were assessed and the duration of stay, the pathological primary complete response rates were assessed postoperatively



65% patients had pathological complete response of primary and nodes and 1 patient had only residue of the primary and two patients had nodal residue and 4 patients (20%) had both primary and nodal residue. All patients who underwent esophagectomy had a R0 resection. There was no incidence of pneumonitis in any of these patients. The postoperative morbidity were not significant and in all the cases postoperative period was uneventful with a median postoperative stay in hospital of 17 days (Ranging from 14 to 22 days)



Out of the 20 cases who underwent surgery, 1 patient expired due to residual disease postchemoradiation and the survival after surgery in this patient was approximately 9 months. His pathological status was ypT2N1. 1 patient had metastatic disease to lung and the disease free survival in this patient is 8 months. The patients in whom surgery was abandoned (5 patients), are not alive and expired due to progressive disease. The remaining 18 patients (72%) are alive and are free of disease. The patient who had metastasis had residue post chemoradiation.

VII.DISCUSSION:

Treatment of carcinoma esophagus has been a great challenge for oncologist. About 80% patients present with advanced disease. Patients with esophageal carcinomas usually present late as usually in early stages they have vague symptoms like dyspepsia, bleeding, gastritis, vomiting and dysphagia and classic symptoms of dysphagia for solids present only late stages. The patients only report to outpatient department after they have near total dysphagia. When compared to other cancers the local control, disease free survival, progression free survival and overall survival at 2 years and 5 years are very less. Further on evaluation, patients present with unresectable tumors as there is high chance of skip metastasis and infiltration of adjacent vital structures like trachea and great vessels. Less than 10% patients only survive if treated with radiation alone at 5 years and overall survival benefit for patients treated with concurrent chemoradiation is 20-30%. One of the significant factors for survival is R0 resection. Since the results of surgery alone, radiation and chemoradiation are very poor and much efforts have been put in improving tumor respectability, long term locoregional control and overall survival.

Several phase III randomized studies have been done to compare chemoradiotherapy followed by surgery versus surgery alone. One landmark trial is the one conducted in Netherlands, the CROSS trial- Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone in patients with adenocarcinoma or squamous cell carcinoma of esophagus. It enrolled 366

patients from March 2004 for a period of 4 years, up to December 2008 in which 75% had adenocarcinoma and 23% squamous cell carcinoma and 180 people were randomized to neoadjuvant chemoradiotherapy followed by surgery arm and 188 patients to surgery only arm. Most tumors were in the lower esophagus. On comparison R0 resection rates in neoadjuvant chemoradiotherapy plus surgery arm which was 92% versus 69% in surgery only arm. Pathological nodal positivity was seen in 31% in neoadjuvant chemoradiation arm and 75% in the surgery only arm. The median overall survival was 49 months versus 24 months in the neoadjuvant chemoradiation arm followed by surgery arm and surgery alone arm respectively and histological factor was not prognostic factor for survival.

On assessing toxicities during chemoradiotherapy of any grade there was high incidence of fatigue in 67% and thromobocytopenia of 54% and neutropenia of 19% and vomiting of 25%.

In our institute based on the results of CROSS group study we started practising neoadjuvant chemoradiation in patients with resectable carcinoma esophagus. Earlier all patients were randomized to radical chemoradiation or radiation only arm based on fitness of the patient. The radical dose of radiation was 54 Gy RT with chemotherapy being weekly cisplatin (40 mg/m2) or 3 weekly cisplatin (70mg/m2). There was difficulty in randomizing patients with resectable carcinoma esophagus as nearly only 7-10% of patients per year present with operable disease and other patients present late with advanced

inoperable disease. In 2014 a total of 97 cases were registered with carcinoma esophagus in our institute, 47 cases were treated with radical chemoradiation with 54 Gy RT to the primary and nodal regions using conformal technique with 1.8 Gy to 2 Gy fraction a day concurrent with weekly (40 mg/m2) or 3 weekly cisplatin (70 mg/m2). 36 patients are treated with radical radiation only as they were older, had poor performance status and poor nutrition. Only 2 cases were randomized to Neoadjuvant chemoradiation in the year 2014. 3 patients were diagnosed with early stage disease and underwent direct surgery. Nearly 4 patients defaulted for treatment after evaluation and 7 patients defaulted during the course of treatment. In the 47 patients who were treated with radical chemoradiation only 10% (5 patients) were able to complete 5 cycles of weekly cisplatin concurrent with radiation. Other patients had significant toxicities in the form of grade II and III leukopenia and electrolyte imbalance in the form of hyponatremia and hypokalemia. Out of the 97 patients treated in the year 2014 only 44 patients were alive at the end of 2 years which is about 45%. Out of the 47 patients treated with radical chemoradiation only 28 patients are alive and only 13 patients are free of disease at the end of two years and the remaining patients has residue or metastatic disease. The patients treated with radiation alone have poor outcomes. Only 13 patients out of 38 treated with radical radiation in 2014 are alive which approximates to 30%. In view of significant toxicities there was poor compliance to treatment secondary to tolerance.

In this study we compared the tolerability and toxicity of neoadjuvant chemoradiation followed by surgery in resectable carcinoma esophagus patients with tumor in the mid and lower thoracic esophagus. All patients are treated with 5 cycles of Paclitaxel and carboplatin concurrent with 41.4 Gy radiation. All patients had better tolerability and the patients were able to undergo at least 3 cycles of chemotherapy with radiation. The toxicities which were seen were neutropenia, thrombocytopenia and electrolyte imbalance which were manageable in many as outpatient basis. The Grade III toxicity was seen in neutropenia and other all toxicities were Grade II. The treatment breaks during radiation was present in 9 (36%) patients with a median of 6.5 days (ranging from 4-10 days). And all patients completed chemoradiation with a median duration of 36 days and all patients completed chemoradiation and was reassessed for surgery after 4 weeks. The rates of R0 resection was 100%. The pathological complete response rates were higher post neoadjuvant chemoradiation with paclitaxel and carboplatin and 41 Gy RT. The neoadjuvant chemoradiation did not result in significant postoperative morbidity. There were no cases of radiation pneumonitis in the patients treated with neoadjuvant chemoradiation. The concept of neoadjuvant chemoradiotherapy was designed based on the CROSS group study in Netherlands. The rates of R0 and pathologically no residue signifies that the neoadjuvant chemoradiation substantially down stage the disease. The disease free survival and overall survival needs long follow up of patients and not mentioned in this study. The

main drawback of this study is it had very small sample size and it requires further prospective analysis with comparison with radical chemoradiation arm.

VIII.CONCLUSION:

The use of neoadjuvant chemoradiotherapy in treatment of carcinoma esophagus has improved the rates of resection and pathological complete response rates in resectable carcinoma esophagus. The neoadjuvant chemoradiotherapy with paclitaxel and carboplatin had acceptable adverse event rates. There is a lack of optimal data for use of paclitaxel and carboplatin chemotherapy with radical dose of 50 to 50.4 Gy radiation. With this high amount of pathological complete response rates, less toxicities and good compliance the use of Paclitaxel/Carboplatin chemotherapy concurrent with radiotherapy in treating inoperable tumors requires further prospective study.

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