IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 10 Ser.2 (October. 2022), PP 03-31
www.iosrjournals.org

A comparative study of concurrent chemoradiation using oral capecitabine versus radiotherapy alone in the management of inoperable esophageal carcinoma in elderly patients.

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Abstract:
Introduction: *Esophageal cancer (EC) is the eighth most common cancer worldwide and the sixth leading cause of death from cancer.The Radiation Therapy Oncology Group (RTOG) trial 85-01 established the superiority of concurrentchemoradiationtherapy(CCRT) compared with radiotherapy (RT) alone in esophageal cancer patients.Capecitabine is an example of a rationally designed 5-FU pro-drug intended to mimic the continuous infusion of 5-FU while avoiding the complications and inconvenience associated with IV drug administration.Unfortunately so far, no standard treatment modality has been established for inoperable EC in elderly patients. Therefore, it is important to obtain a valid and better tolerated therapeutic choice particularly optimal CCRT/RT approaches for elderly patients with EC. Hence, the purpose of the present prospective, randomized study is to comparatively evaluate the tumour response and treatment related toxicities of CCRT using oral capecitabine versus RT alone to enable us to address the definitive treatment approach for inoperable EC patients in elderly population.*
Materials and method:*After obtaining the approval from the research ethics board of the institute, this Interventional prospective randomized double arm study was conducted from August 1st, 2018 to July31st, 2020.Total 60 patients with esophageal carcinoma were recruited in the study, 30 patients were recruited in the study arm and another 30 patients were in the control arm.Arm A (Study arm) patients were treated with two-dimensional external beam radiotherapy using Source axis distance(SAD) technique. The patients were given a total dose of 50 Gy in 25 fractions by conventional fractionation (5 days in a week) using TheratronTelecobalt machine.CCRT using oral capecitabine was given in a dose of 825 mg/ m2, twice daily after meal within 30 minutes for 7 days/week from Day 1 till the end of the treatment.Arm-B (Control arm) patients were given RT of same radiation technique, dose and fractionation alone as given in Arm –A. Chi square test and Kaplan-Meier survival curve were used in the study.*
Results: *Difference of early treatment response in both arms were statistically significant. More acute haematological toxicity was leucopenia followed by anaemia. Esophagitis and odynophagia were more common in study arm compared with control arm. Likewise,progression free survival was longer among patients in study arm compared to control arm.*
Conclusion*: In our study, patients treated with CCRT regime using oral capecitabine were associated with increased treatment response with increased acute manageable toxicities. Small sample size and the short follow up were the limitation of our study. Therefore, longer follow up with bigger sample size may be needed for drawing further conclusion.*
Keywords: *Esophageal cancer, concurrent chemoradiation, elderly, oral capecitabine.*

Date of Submission: 20-09-2022 Date of Acceptance: 05-10-2022

I. INTRODUCTION

The esophagus is a hollow, fibromuscular tube of about 25 cm long. It extends from lower border of cricoids cartilage at the level of vertebrae C7 to its opening at stomach. It runs vertically but inclines to the left from its origin to thoracic inlet and again from T7 to esophageal opening to the diaphragm. The esophago-gastric junction lies near the lower border of T11 vertebrae.[1]

Esophagus is frequently divided into cervical and thoracic esophagus. The American Joint Commitee on Cancer, further subdivided thoracic esophagus into upper thoracic, mid thoracic and lower thoracic esophagus.

The cervical esophagus begins at cricopharyngeal muscle (approximately C7 level or 15 cm from incisors) and extends to thoracic inlet at approximately to the level of T3. The thoracic esophagus extends approximately from T3 level to T10 or T11. Upper thoracic esophagus begins at thoracic inlet and ends by lower border of azygos vein extending approximately 20 cm to 25 cm from incisors. The mid and lower thoracic esophagus extends from lower border of azygos vein to inferior pulmonary vein and from inferior pulmonary vein to gastro-esophageal junction extending approximately 25 cm to 30cm and 30cm to 40cm from incisors.[2,3]

Normal esophagus is lined by squamous epithelium and the portion below diaphragm is lined by gastric type of mucosa without oxantic and peptic cells. The wall of esophagus consists of four layers; from within outwards are mucosa, submucosa, muscularispropria (inner circular and outer longitudinal muscle layer) and adventitia. Unlike most of the gastrointestinal tract, esophagus is not covered by serosa and only the abdominal portion of the esophagus is covered by peritoneum.[3,4]

There are two major types of esophageal carcinoma: squamous cell carcinoma (SCC) and adenocarcinoma. Squamous cell carcinoma is more evenly distributed through out the length of esophagus and adenocarcinoma is predominantly a disease of distal esophagus.[3]Approximately 80-90% of esophageal carcinoma are squamous and adenocarcinoma type, the former being the predominant form in developing countries. whereas adenocarcinoma is common in developed countries.4,5 Aroud 2-4% of esophageal cancer develops in patients with head and neck cancer as a second malignancy. Squamous cell carcinoma is common in thoracic esophagus and nearly all carcinoma of cardia are adenocarcinoma.[6,7]

Recent reports indicate that in western countries the incidence of SCC remains stable, while the adenocarcinoma has increased particularly in male. The increasing trends for esophageal and gastrocardia adenocarcinoma varied by age, being more pronounced among older male. The squamous cell carcinoma is three times higher in blacks.[7]

The causative and risk factors of adenocarcinoma are Barrett esophagus, gastroesophageal reflux disease (GERD), obesity, in most cases of adenocarcinoma and for squamous cell carcinoma are alcohol, tobacco, as well as dietary and environmental factors that causes chronic irritation and inflammation of the esophageal mucosa to cause esophageal cancer. Chronic and frequent reflux of gastric acids into the distal esophagus irritates that area and is considered to be as the primary factor underlying the most cases of esophageal adenocarcinoma. Several underlying predisposing conditions such tylosis, achalasia, esophagealdiverticulae and esophageal webs, Plummer- Vinson syndrome also increases the risk of developing esophageal cancer. Certain infections of esophagus such as human papilloma virus (HPV), H-pylori infection and occupational expouser to agents like chromium, nickel etc. may predispose to esophageal carcinoma. It is assumed that only esophageal cancer originating from high incidence geographic areas are associated with HPV infection, particularly with risk types 16 and 18.[9 ,10]

Higher intake of saturated fatty acids, smoked preserved foods, pickled and salty preserved foods, stale and fungai contaminated foods increases the risk of esophageal squamous cell carcinoma (ESCC). Diet containing nitrite and nitrosamines increases risk of squamous cell carcinoma of esophagus, while dietary antioxidants, especially folate, vitamin A, vitamin E, zinc and selenium could prevent the damage to the esophagus caused by oxidative stress, even if consumed in moderate amounts too. Dietary pattern rich in carbohydrate, dietary fibre and (n-3) polyunsaturated fatty acids (PUFA) along with high physical activity, low consumption of hot foods, beverages and fried meals reduces the risk of esophageal cancer.[6,10]

Squamous cell carcinoma expresses extensive local growth and has propensity to lymphatic spread. It can spread by direct infiltration, subepithelial extension, lymphatics and haematogenous spread. The lymphnode involvement depends on tumour size, stage, location and depth of penetration. For T1 lesion reported incidence is 14%, 21% in T2, and this may raise upto 38-68%. 'Skip lesion' may be found at distance away from the main tumour. For lower esophagus and gastroesophagealjunctional adenocarcinoma, approximately 70% of patients will have nodal metastasis at presentation. The distant metastasis is a result of haematogenous spread and can spread to liver, lung, pleura, adrenal gland, brain, bone and peritoneum. The venous involvement is found in 25% cases of submucosal carcinoma.[9,10]

. Esophageal cancer (EC) is the eighth most common cancer worldwide and the sixth leading cause of death from cancer.[3] EC accounts of about 6% of all gastrointestinal malignancies and 1% of all malignancy.[5]

The incidence of esophageal cancer varies considerably with geographic location and also, to some extent, among ethnic groups within a common area. Some of the highest rates occur in northern China and northern Iran, Zimbabwe and Turkenemia, where incidence exceeds 100 in 100000 individuals, in the U.S, the incidence is less than 5 per 100000, although rates are nearly quadriple for African Americans.10 Other areas where carcinoma of esophagus found high are in Southern-Eastern Africa and Eastern Asia; lowest rates observed in Western and Middle Africa and Central America in both males and females.[5] An 'Asian esophageal cancer belt , where the esophageal cancer is endemic extending from southern part of Caspian sea in the west to the northern China in the east and the residents involved in Iran.[11,12]

In India,approximately 47,000 new cases of esophgeal cancer are reported each year and reported deaths reach up to 42,000 each year.[13] According to a project report of the National Cancer Registry Programme:2012-2016, East Khasi Hills District has the highest age adjusted incidence rate (AARs) of esophageal carcinoma (71.2/100000) in males and (33/100000) in females, followed by Aizawl district(49.9/100000).14,15 In Manipur, esophageal cancer is the fourth most common cancer among male (3.5%) and in female 1.1%.[16]

Much regional variation exists in the incidence and pathology of esophageal cancer. It has been reported that in countries with higher human development index (HDI), there is a higher incidence of adenocarcinoma (AC) of the esophagus.13 For example, in the US, the incidence of adenocarcinoma of the esophagus has increased by over 400% over the past 25 years.5In contrast, in countries with low HDI, like India, there is a higher incidence of esophageal squamous cell carcinoma. The highest annual increase (10% per year) has been reported from the USA. Among the Asian countries, China and Singapore have alsoreported an increasing number of esophageal cancer.[13]

The AJCC has established a staging system for esophageal cancer that is based on the tumour- nodes-metastasis (TNM) system and is, in essence a pathological staging system. Only the depth of penetration is taken into account for the T- staging, not the length of the tumour, extent of involved circumference, or degree of lumen narrowing. Clinical staging takes into account the amount of disease that is present before treatment and is based on history, physical examination, biopsy, laboratory studies, endoscopic examination, and imaging such as endoscopic ultrasound (EUS), computed tomography (CT) scan PET scan. Pathological staging is based on the examination of the surgically resectedesophagus and lymph nodes. Spread to the celiac lymphnode is considered a site of distant metastasis, as are cervical nodes occurring with an esophageal primary elsewhere than in the cervical esophagus.[17,19]

Early esophageal cancer is usually asymptomatic. The commonest symptom encountered in esophageal cancer are painless progressive dysphagia from solid to liquid in >90% of patients, weight loss in 40-70% and regurgitation of foods. Ulcerated lesions sometimes presents with evidence of gastrointestinal bleeding, in the form of haematemesis, malena, or be found during work up for occult GI bleeding or iron deficiency anaemia. Advanced esophageal cancer can also cause bleeding but most of the patients present with dysphagia. Large intra luminal tumour presents with sensation of blockage or sticking of a swallowed food bolus in the throat. Symptoms of esophageal cancer commonly have a gradual onset. Weight loss is usually present. Weight loss and accompanying dysphagia is more common in squamous cell carcinoma. Nutritional status is an independent of treatment outcome and patients who are severly cachectic with more than 25% of body weight loss have a higher risk of morbidity and mortality. About 20% of patients experience odynophagia. Other presenting symptoms may include retrosternal pain,bone pain or hoarseness of voice. Hoarsenessof voice is late presenting symptom and is due to recurrent laryngeal nerve involvement. Cachexia is a less common symptom. [18,19]

The appropriate work up for a patient of esophageal carcinoma consists of asking complete history and thorough physical examinations, routine laboratory and biochemical tests, endoscopy and imaging. The diagnostic modalities at use are barium swallow, CT scan of thorax, upper gastrointestinal endoscopy and biopsy, transesophagealsonography or MRI. Many physician continue to order X-ray studies initially to evaluate patients with dysphagia. Endoscopy and endoscopy guided biopsy plays an important role and is the key diagnostic procedure of esophageal cancer. Examination of oral cavity, pharynx, larynx and trachea-broncheal tree are to be done while doing endoscopy because of second tumours in the headand neck and upper airways. Fine needle aspiration should be performed on any palpable cervical lymphnode to rule out extra thoracic spread of disease.[19,20]

The esophageal carcinoma has been long considered one of the deadliest malignancies. The outcome of adenocarcinoma of esophagus influenced by tumor stage, location, histiopathologic type at presentation as well as presence of co-morbid conditions such as barrett's mucosa, weight loss, dysphagia and other co-morbid disease. Adenocarcinoma has more advanced tumours and higher percentage of lymphnode invasion. In case of squamous cell carcinoma the outcome is mainly determined by age, the stage of cancer at presentation, tumour length and type of treatment. Long term survival is mainly reported in a fairly small proportion of cases whose disease is limited to mucosa and submucosa of esophagus and who receive appropriate treatment. Sex, race, socioeconomic status, and other etiologic factors of squamous cell carcinoma are also influence the prognosis of disease.[10,19]

The esophageal cancer has carried a bad prognosis inspite of major advances in cancer treatment. This has been attributed to the late presentation of patients with this disease and technical difficulties of an adequate surgical resection in the presence of advanced local and regional involvement. According to Pearson only 20% of patients present with truly localized diseae to the esophagus. [21,22]

There is a considerable controversy as to the ideal therapeutic approaches in the treatment of esophageal cancer. However, over the last few decades the treatment algoritham have changed considerably shifting from singal mode treatment to complex multimodal approaches. The therapeutic approaches in the

treatmet of esophageal cancer are surgical, nonsrgical or adjvent treatments. Primary treatment include surgery, radiation thrapy and chemoradiation. Radiotherapy may be in the form of preoperative(neoadjuvant) or postoperative radiation therapy (adjuvant) and chemotherapy also can be given as pre-operative or post operative chemotherapy or combined modality therapy. [23,24,25]

Till recently, surgery alone is considered to be the mainstay of treatment especially in operable cases of esophageal carcinoma for many years. Oesophagectomy remains the standard care for the treatment of early stage of esophageal cancer confined to esophagus.The two most common approaches for definitive resection are transthoracic oesophagectomy (Ivor-Lewis procedure) and transhiataloesophagectomy. The operative procedures are associated with higher rates of perioperative morbidity in patients and more in persons receiving transthoracic esophagectomy. Up till now, the operative superiority over chemo-radiotherapy has not been proven so far. Moreover surgery is associated with disappointing local failures and survival figures, and no clear-cut benefits by addition of surgery. [28,35 36,37]

Surgical resection is the main modality of treatment for localized esophageal cancer but recent population-based study showed that older patients have less intensive treatment ofesophageal cancer including surgery.[28,29] In addition, the literature states that patients over theage of 70 have relatively high rates of postoperative morbidity and mortality, and 75 years of age is often considered the age limit for surgery.[30,31]

The Radiation Therapy Oncology Group (RTOG) trial 85-01 established the superiority of CCRT compared with radiotherapy (RT) alone in esophageal cancer patients. However, the acute toxicity of this regimen was substantial: sixty-four percent of patients treated with CCRT experienced severe or life threatening side effects and only 23% of patients enrolled were aged over 70.[32,33] Several studies have reported the efficacy and toxicity in CCRT group elderly patients with inoperable oesophageal cancer, but the results were controversial.[34,35,36,37,38] In addition, the published reports are mainly on small series of patients, making it difficult to carry out reliable analysis. Therefore, we will review our institutional experience to evaluate the efficiency and safety of CCRT compared with RT alone in elderly thoracic esophageal cancer patients.[39,40,41,42] We defined an elderly population according to Social Security and Medicare regulations as persons aged 60 years or older.[58]

Capecitabine is an example of a rationally designed 5-FU pro-drug intended to mimicthe continuous infusion of 5-FU while avoiding the complications and inconvenienceassociated with IV drug administration. It is a fluoropyrimidinecarbamate that is convertedto the active 5-FU by the action of three enzymes: an esterase, a deaminase,[52]and a phosphorylase. In the third step, the enzyme thymidine phosphorylase (TP) converts 5`-deoxy-5-fluorouridine to 5-FU, which is released directly intotumor tissue.[55]This suggests that higher tumour concentrations of 5-FU might be expected, due to a higher production of active drug in the tumor tissue, thereby providing a favorable target-to-non-target ratio for toxicity. Tumor selectivity and conversion of capecitabine to active 5-FU within thetumor tissue have been confirmed in human samples that show a 3.2-fold higher concentration of 5-FU in tumor compared with normal tissue and a 21-fold higher tumor-to- plasma ratio. In comparison, when IV 5-FU is administered, either by bolus or continuousinfusion, the concentration of active drug in tumor is not higher than that in normal tissue .The greater levels of the TP enzyme in tumor tissue allow for targeted intra-tumouralrelease of 5-FU and subsequently less systemic toxicity compared with infusions of 5-FU. Formal patient preference studies suggest that oral capecitabine is preferred due to tolerability as well as route of administration.In general, there is less stomatitis and neutropeniawith capecitabine-containing regimens, with the trade-off of more HFS reactions and diarrhea.[55,56,57]

A majority of esophageal cancer patients presents with locally advanced disease at diagnosis. The appropriate management of these patients continues to be a matter of debate. Concurrent chemoradiotherapy is still viable option in majority of cases.The non-operative therapy offers an opportunity for cure without surgery related morbidity. Wide applicability of this treatment has led the investigators to study in wide range, methods to maximize therapeutic gain by combining radiation therapy with chemotherapy in esophageal cancer.[59,60,61]

Unfortunately so far, no standard treatment modality has been established for inoperableEC in elderly patients.Therefore,it is important to obtain a valid and better tolerated therapeutic choice particularly optimal CCRT/RT approaches for elderly patients with EC.[60,61,62]Hence, the purpose of the present prospective, randomized study is to comparatively evaluate the tumour response and treatment related toxicities of CCRT using oral capecitabineversus RT alone to enable us to address the definitive treatment approach for inoperable EC patients in elderly population.

II. REVIEW OF LITERATURE

Won E et al[19] focused on the management of older patients with localized EC, highlighting the role of comprehensive geriatric assessment to identify and better tailor treatment approaches in this patient population. They reviewed the literature and discussed the role of surgical resection and potential complications specific to an older patient. They reviewed the rationale of combined-modality treatment and the potential benefits of a CCRT-based approach in this patient population . CCRT could be used as primary treatment if functional status and comorbidities preclude surgery. Second, for patients with locally advanced tumors (T3 or higher or node positive), definitive CCRT was preferred, with consideration of upfront surgery for a selected subset of patients who are surgical candidates based on function, comorbidities, and life expectancy. Higher rates of clinical and pathological complete response were achieved with CRT. Preoperative chemotherapy was less preferred because it mandates surgical resection. Third, for squamous cell carcinoma, primary CRT was an accepted standard approach, with selective application of surgery for persistent disease. Fourth, carboplatin and paclitaxel could be considered as a preoperative and definitive CCRT regimen, given the low rates of toxicity and high rates of pCR demonstrated in the CROSS data.

Cooper JS et al[20] conducted this study to follow up effect of CCRT in treatment of EC. Patients under study had squamous cell or adenocarcinoma of the esophagus, T1-3 N0-1 M0, adequate renal and bone marrow reserve, and a Karnofsky score of at least 50. Interventions Combined modality therapy (n = 134): 50 Gy in 25 fractions over 5 weeks, plus cisplatinintravenously on the first day of weeks 1, 5, 8, and 11, and fluorouracil, 1 g/m2 per day by continuous infusion on the first 4 days of weeks 1, 5, 8, and 11. In the randomized study, combined therapy was compared with RT only (n = 62): 64 Gy in 32 fractions over 6.4 weeks. Combined therapy significantly increased overall survival compared with RT alone. In the randomized part of the trial, at 5 years of follow-up the overall survival for combined therapy was 26% (95% confidence interval [CI], 15%-37%) compared with 0% following RT. In the succeeding nonrandomized part, combined therapy produced a 5-year overall survival of 14% (95% CI, 6%-23%). Persistence of disease (despite therapy) was the most common mode of treatment failure; however, it was less common in the groups receiving combined therapy (34/130 [26%]) than in the group treated with RT only (23/62 [37%]). Severe acute toxic effects also were greater in the combined therapy groups. There were no significant differences in severe late toxic effects between the groups.

Ji Y et al[22] conducted this study to evaluate dose escalation with S-1 and RT in treatment of EC. RT was administered in 1.8 Gy fractions 5 times weekly to a total dose of 54 Gy. S-1 was administered on days 1–14 and 29–42 at the following dosages: 60, 70, and 80 mg/m^2/day. No grade 3 or 4 toxicity was observed in six patients treated at the 60 and 70 mg/m^2 dose levels. DLT was observed in four of six patients treated at the 80 mg/m^2 dose level. Two patients developed grade 3 esophagitis, one patient developed grade 3 esophagitis and pneumonitis, and one patient developed grade 3 thrombocytopaenia. Endoscopic complete response (CR) was observed in eight patients (66.7%). The median progression free survival (PFS) was 20 months and median overall survival was 29 months. The MTD of S-1 was 80 mg/m^2, and the recommended dose (RD) for phase II studies was 70 mg/m^2. This regimen was well tolerated and active in elderly patients with EC, meriting further investigation in phase II studies.

Zhao Q et al[23] aim conducted this study to evaluate the efficacy and acute toxicity of definitive CCRT and RT alone as initial treatment in patients aged 75 years and older with locally advanced ESCC who are not eligible for surgery. Between February 2009 and February 2015, 122 patients older than 75 years with locally advanced ESCC were retrospectively reviewed, in whom 52 patients allocated to the CCRT group were treated with at least 2 cycles of platinum and 5-fluorouracil, 70 patients allocated to the RT group were treated with RT alone, all patients were received a total radiation dose of 54–66 Gy, with 1.8 or 2-Gy/fraction. In the CCRT group, the median PFS and OS were 15.3 and 24.6 months, while 10.6 and 19.4 months in the RT group (P=.008 and P=.018). The 1-year survival rates of the 2 groups were 78.8% versus 64.3% (P=.081), and the 2-year survival rates were 48.1% and 30.0% (P=.042), respectively. The objective RR was 55.8% in the CRT group with 18 complete response (CR) and 18.6% in the RT group with 13 CR. Acute toxicity in the CRT group was higher than in the RT group, especially the grade 3 to 4 acute toxicities.

Servagi-Vernatet al[24] conducted this phase II single-arm study to evaluate the acute toxicities and efficacy of CCRT comprising a single platinum-based agent combined with radiotherapy in elderly patients with EC. Between March 2000 and October 2011, patients aged 75 years and older were prospectively treated with external beam RT combined with cisplatinor oxaliplatin. The RT dose was 50 Gy administered over 5 weeks to the primary tumor and involved lymph nodes. Cisplatin was planned at a dose of 75 mg/m(2) on days 1 and 21 and oxaliplatin at 85 mg/m(2) on days 1, 15, and 29. Treatment was delivered an outpatient setting. Thirty patients with a mean age of 85.2 (range 79.4-92.0) years were included; 28 completed the treatment. Dysphagia was the only grade 4 toxicity to occur during the study; no grade 5 toxicities were observed. Six weeks after the completion of treatment, 16 patients (53.3%) were in complete response. Two patients in complete response died from pneumonitis 5 and 7 months after CCRT. With a 36-month median follow-up, 18 patients died from

cancer (nine from local failure, nine from metastasis). Seven patients died from other causes and two patients were alive 40.3 and 56 months after the end of their treatment. Three-year overall survival was 22.2%.

Zhao L et al[25] conducted this study to identify the efficacy andfactors for optimal treatment approaches for elderly esophageal squamous cell carcinoma (ESCC) treated with RT alone or CCRT.This study included 184 I-III elderly ESCC patients aged ≥70 years treated by oral single agentCCRT (sCCRT) or double agents CCRT (dCCRT) or RT alone at a single institution in China. RT wasdelivered with Intensity Modulated Irradiation Therapy (IMRT) or Volumetric-Modulated Arc Therapy (VMAT). Sequential or simultaneous integrated boost (SIB) approach was applied for GTV dose escalation.Toxicitieswere evaluated by criteria of Radiation Therapy Oncology Group. Statistical analyses wereperformed on survival and failure patterns.At a median follow-up time of 15.5 months, the 2- and 3-year estimated overall survival (OS) were43.5% and 35.2%, respectively. 44% patients experienced treatment failure, among whom 65.4% developed local failure.81.3% local failure occurred in GTV and 70.6% regional failures occurred out of radiation field. dCCRTwasthe only independent prediction factor for grade ≥ 2 neutropenia and gastrointestinal reactions comparedwithsCCRT and RT alone. No significant difference of toxicities was observed between sCCRT and RT alone.

Xu HY et al[26] conducted this study to perform a retrospective analysis to investigate the outcome and toxicity of RT and CCRT in elderly, inoperable patients >70 years old. Between 2003 and 2012, 1,024 patients with squamous cell carcinoma (SCC) of the esophagus were treated at the Department of Thoracic Cancer, West China Hospital (Chengdu, China). Of these patients, 37 were >70 years old and had not undergone surgery, and were selected for analysis. Of these 37 patients, CRT had been administered to20 (54%). Actuarial survival rates were determined by the Kaplan-Meier method. The one-year survival rate in the CRT group (n=20) was 85%, while 35% of patients in the RT group (n=17) survived for more than one year. The overall and progression-free survival in the CRT group versus the RT group were 17 months [95% confidence interval (CI), 11.861–22.139] versus eight months (95% CI, 6.674–9.326) (P=0.013) and 14 months (95% CI, 9.617–18.383) versus five months (95% CI, 2.311–7.689) (P=0.01), respectively. Patients irradiated with a dose of >50 Gy exhibited an improved survival rate compared with patients who received a dose of ≤50 Gy (18 vs. 14 months; P=0.049). The current retrospective study indicated that patients of >70 years old with inoperable esophageal SCC and a good ECOG score exhibit comparably better safety levels with CRT and improved survival rates compared with RT alone.

Lu X et al[27] conducted this retrospective study to analyze the safety and efficacy of CRT in patients aged ≥75 years in order to assess the short- and long-term outcomes of CRT for elderly patients with EC. In this study, based on further refinement of patient age groups and analysis of the Charlson comorbidity score, they performed a statistical analysis of factors such as short-term response, long-term survival and toxicity reactions. The medical records of a total of 312 EC patients aged ≥75 years who had undergone non-surgical treatment at the Affiliated Tumor Hospital of Zhengzhou University (Jinshui, China) between January, 2002 and March, 2008 were retrospectively evaluated. The results of the analysis indicated that the treatment of patients with EC aged ≥75 years with RT and chemotherapy was effective. However, they recommend that customized treatment is based on the stratification of patients into different age groups and the Charlson score, as for patients aged ≥80 years a lower-dose therapy may be more beneficial and for patients aged ≥85 years definitive CCRT should be administered with greater caution.

Bedenne L et al[28] carried out a prospective randomized trial (French FFCD 9102 trial) with 444 eligible patients (operable T3N0-1M0 thoracic oesophageal cancer),259 were randomly assigned ; 230 patients (88.8%) had epidermoid cancer, and 29 (11.2%) had glandular carcinoma. Patients received two cycles of fluorouracil (FU) and cisplatin (days 1 to 5 and 22 to 26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy,days 1 to 5 and 22 to 26) and concomitant radiotherapy. Patients with response and no contraindication to either treatment were randomly assigned to surgery (arm A) or continuation of chemoradiation(arm B; three cycles of FU/cisplatin and either conventional [20 Gy] or split-course [15 Gy] radiotherapy). Two-year survival rate was 34% in arm A versus 40% in arm B (hazard ratio for arm B *v* arm A =0.90; adjust P= 0.44). median survival time was 17.7 months in arm A compared with 19.3 months in arm B. Two-year local control rate was 66.4% in arm A compared with 57.0% in arm B, and stents were less required in the surgery arm (5% in arm A *v* 32% in arm B; P<0.001). the 3 month mortality rate was 9.3% in arm A compared with 0.8% in arm B(P=0.002) and 2 years perioperative mortality approximately 10%. Cumulative hospital stay was 68 days in arm A compared with 52 days in arm B (P=0.02).

Minsky BD et al[29] conducted a prospective single study on 45 patients with clinical stage T1-4, N o-1, M o ESCC of which 38 were eligible. Patients received 3 monthly cycles of 5-FU (1000mg/m²/day 1-5) and cisplatin (75mg/m² day 1) plus concurrent 6480cGy (combine modality therapy). The median follow up in surviving patients was 59 months. For 38 eligible patients, the primary tumour response rate was 47% complete 8% partial, and 3% stable disease. The first site clinical failure was 395 local/regional and 24% distant. For the total patients group, there were 6 deaths during the treatment, of which 9% (4/45) were treatment related. The median survival at 3 years was 30% and at 5 years 20%. This intensive neoadjuvant approach does not appear to

offer a benefit compared with conventional does and technique of combined modality therapy. However, high dose radiation (6480cGy) appears to be tolerable, and is being tested further in intergroup trial INT 0123.
Nishimura Y et al[30] conducted analysis on long term survival and late toxicities of a randomized Phase II study of CCRT for EC were analyzed. Between 2001 and 2006, 91 patients were enrol; 46 were randomized to arm A and 45 to arm B. Eligible patients were, <75 years old and performance status 0-2, and had stages II-IVA oesophageal cancer. For arm A (short term infusion), cisplatin 70 mg/m² Days 1 and 29 and 5-fluorouracil 700 mg/m² days 1-5 and 29-33 were given concurrently with radiotherapy of 60 Gy/30 fr/7 weeks (1 week split). For arm B (protracted infusion), cisplatin 7 mg/m² days 1-5, 8-12, 29-33, and 36-40, and 5-fluorouracil 250 mg/m² Days 1-14 and29-42 were given with the same radiotherapy. Two cycles of consolidation cisplatin/5-fluorouracil chemotherapy were given to both arms. The 2 and 5 years overall survival rates for arm A were 46 and 35% (95% confidence interval: 22-48%), while those for arm B were 44 and 22% (11-35%), respectively. Excluding four patients with early death, seven (17%) patients in arm A, and eight (18%) in arm B showed late toxicities of Grade 3 or more. Most of the toxicitieswere cardiac or pleural toxicities. Patients with severe late toxicities often had coexistent hypothyroidism. There were three patients with a secondary malignancy possible related to treatment. Conclusion: Low-dose protracted infusion chemotherapy with radiotherapy for oesophageal cancer. Late toxicities, including cardiac and pleural toxicities, hypothyroidism and secondary malignancy, should be carefully monitored.

Shim HJ et al[32] conducted a phase II trial. Between December 2007 to December 2009 a total 36 patients of advanced and unresectable squamous cell carcinoma of oesophagus were enrolled. A phase II trial was conducted to assess the efficacy and safety of CCRT with weekly docetaxel and cisplatin. Patients received 20 mg/m² docetaxel and 25 mg/m² cisplatin in weeks 1,2,3,4,5,6 and 7 with concurrent 54Gy radiotherapy at 200cGy/day. Thirty five patients completed planned RT, and 33 completed chemotherapy. Grade 3 or 4 toxicity during CCRT included leucopenia (5.7%). After CRT, 8 patients (22.9%) had a complete response, 22(62.9%) had a partial response, 4(11.4%) had stable disease, and 1 (2.9%) had progressive disease. Improvement of dysphasia was observed in 85.3%. at a median follow up of 26.7 months, the median time to progression was 13.5 months and median overall survival was 26.9 months. The 3 years progression free survival rate was 16.7% and survival rate was 27.8%.

Cho SH et al[33] conducted a pilot study to evaluate the efficacy and safty of concurrent CCRT with S-1 and cisplatin at doses of 70 mg/m²/day for 14 days and 70mg/m² on day 1, respectively, every 3 weeks. Concurrently, RT was started at a dose of 200cGy/day, up to atotal of 5400 cGy. After CCRT, additive chemotherapy was repeated up to six cycles. Thirty patients were enrolled in this study ; of the 27 in whom efficacy could be evaluated, an object response rate was seen in 20 (74.1%), including five (18.5%) complete pathologic responses in primary lesions. Improvement of dysphasia was seen in 21 (76%) patients. In patients with stage II or III oesophageal cancer, the median progression free survival and overall survival were 10.6 +/- 0.6 months (95% CI: 9.4-11.8) and 23.0 +/- 5.1 months (95% CI: 13.0-32.9), respectively. In patients with stage IV oesophageal cancer, the median progression free survival and overall survival were 5.4 +/- 1.6 months (95% CI:2.2-8.6) and 11.6 +/- 1.6 months (95% CI: 8.4-14.8), respectively. The main haematological toxicity was neutropenia, but no neutropenic fever was observed. The major non-haematological toxicities were asthenia and vomiting, mostly of grades 1 and 2. Thus, CCRT with S-1 and cisplatin may be a promising nonsurgical treatment in advanced EC.

Anderson SE et al[34] between 1996 and 2001, twenty five patients with a median age of 77 years (range 66-88) with a diagnosis of stage II-III squamous cell or adenocarcinoma of the oesophagus were treated at Memorial Sloan Kettering with two cycles of concurrent 5-FU<mitomycin-C therapy consisted of 5-FU at a dose of 750-1000mgm^{-2} per day for 4 days given by continuous infusion week 1 and 5. Mitomycin was given at a dose of 7-10 mg m^{-2} on days 1 and 29 of CCRT and 50.4 Gy 5 days per week at 1.8 Gy per day with megavoltage equipment (15 MV) using a multiple field technique. Owing to age and comorbidity, these patients were not considered surgical candidates. The Charlson comorbidity score was used to evaluate patient comorbidity. Nine patients (36%) experienced grade 3-4 haematologic toxicity. Of the 23 patients evaluable for response, 17 patients 68%) had a negative post treatment endoscopy and CT scan without evidence of progressive disease. Eleven patients (44%) were alive and 10 (40%) remained without evidence of recurrent or progressive oesophageal cancer at a median follow-up of 35 months. The median overall survival was 35 months and 2 year survival 64%. There was no significant difference in overall survival between Charlson score ≤2 and those with a score ≥2(P=0.10). Similar survival was observed for patients with adenocarecinoma or squamous carcinoma. Primary chemoradiation with two cycles of 5FU, mitomycin-C and 50.4 Gy in early patients was suggested an active regimen with moderate toxicity, despite the advanced age and heavy comorbidity burden of that cohort. Patients with local/regional oesophageal cancer with adequate fuctional status should not be excluded from potentially curative treatment based on age alone.

Mariette C et al[35] in a review of treatment approach for EC found that surgery was considered the best treatment for EC in terms of loco regional control and long term survival. However, 5 years survival after

surgery alone was about 25% and therefore a multidisciplinary approach that include surgery, RT and chemotherapy, alone or in combination could prove necessary. The role of each that treatment in the management of oesophageal cancer was under intensive research to define optimum therapeutic strategies. Result of the latest randomized trials allow the promising of the following guidelines; surgery was the standard treatment, to be used alone for stage II b disease. For locally advance cancer (stage III) neoadjuvamt chemotherapy or CCRT followed by surgery is appropriate for adenocarcinomas. CCRT should only be considered in patients with squamous cell carcinomas who show a morphological response to CCRT, and produces a similar overall survival to CCRT followed by surgery, but with less post-treatment morbidity. Although the additional of surgery to chemotherapy or CCRT could result in improved local control and survival, surgery should be done in experienced hospitals where operative morbidity and morbidity were low. Moreover, surgery should be kept in mind as salvage treatment in patients with no morphological response or persistent tumour after definitive CCRT.

Liao Z et al[36] between, January 1990 to December 1998 conducted a retrospective review of 132 oesophageal cancer patients with clinical stage II or III treated with CCRT (5FU/cisplatin/etoposide). The median radiation dose was 50 Gy in definitive CTRT group (A) and Gy in the CTRT plus oesophagectomy group (B). The median follow-up of surviving patients was 38 months. Patients in group B had significantly better 5 year overall survivable (52.6%), disease free survival (41.7%) and loco regional control (67.2%) than patientstreated in group A. An improvement in survival occurred in group B in the study, although the observation may have reflected selection bias. The result of the study suggested the need of a randomized trials to compared CTRT with or without oesophagectomy in the treatment of oesophageal cancer.

Urba SG et al[37]experiencing from a pilot study of 43 patients with intensive regimen of preoperative CCRT with cisplatin, fluorouracil and vinblastine before surgery; a median survival of 29 months in comparison with the 12 months median survival in surgery alone arm, one hundred patients with EC were randomized to receive either surgery alone (arm I) or preoperative CCRT (arm II) with cisplatin 20 $mg/m^2/d$ on days 1 through 5 and 17 through 21, fluorouracil 300 $mg/m^2/d$ on days through , and vinblastine 1 $mg/m^2/d$ on days 1 through 4 and 17 through 20. RT consisted of 1.5 Gy fractions twice daily, Monday through Friday over 21 days, to a total dose of 45 Gy. Transhiataloesophagectomy with a cervical esophagogastric anastomosis was performed on approximately day 42. At median follow up of 8.2 years, there was no significantdifference in survival between the treatments arm. Median survival was 17.6 months in arm I and 16.9 months in arm II. Survival at 3 years was 16% in arm II (P=0.15). The study was statically powered to detect a relatively large increase in median survival from 1 year to 2.2 years, with at least 80% power. The randomized trial of preoperative CCRT versus surgery alone for patients with potentially respectable oesophageal carcinoma did not demonstrate a ststistically significant survival difference.

Gebski V et al[38] in an attempt, to clarify the benefits of neoaduvant CCRT or chemotherapy versus surgery alone a meta analysis on randomised trial data undertaken. Ten randomised comparison of neoadjuvant CCRT versus surgery alone (n=1209) and eight of neoadjuvant chemotherapy versus surgery alone (n=1724) in patients with local operative oesophageal carcinoma were identified. The analysis used MEDLINE, Cancerlit, and EMBASE database to identify additional studies with an analysis by an intention-to-treat principle were included, and searches were restricted to those database citing articles in English. The analysis also used published hazard ratios if available or estimates from other survival data or survival curves. Treatment effects by type of tumour and treatment sequencing were also investigated. The hazard ratio for all-cause mortality with neoadjuvant CCRT versus surgery alone was 0.81 (95% CI 0.70-0.93; p=0.002), corresponding to a 13% absolute difference in survival at 2 years, with similar results for different histological tumour types: 0.84 (0.71-0.99 p=0.04) for squamous-cell carcinoma (SCC), and 0.75 (0.59-0.95; p=0.05), which indicate a 2 year absolute survival benefit of 7%. There was no significant effect on all-cause mortality of chemotherapy for patients with SCC (hazard ratio 0.88 [0.75-1.03]; p=0.12), although there was a significant survival benefit was evident for preoperative CCRT and to a lesser extent, for chemotherapy in patients with adenocarcarcinoma of the oesophagus. The findings provide an evidence-based framework for the use of neoadjuvant treatment in management decisions.

Ajani JA et al[39] in a multi-institutional cooperative group setting, patients with LEC who had unresectable cancer, were unwilling to undergo surgery, or were medically unfit for sugary were randomly assigned to received either induction with fluorouracil cisplatin, and paclitaxel and then fluorouracil plus paclitaxel with 50.4 Gy of radiation (arm A) or induction with paclitaxel plus cisplatin and then the same chemotherapy with 50.4 Gy of radiation (arm B). Safety and survival rates were assessed. A total of 84 patients were randomly assigned (arm A, n=41; arm B, n=43) and 72 were assessable (arm A, n=37; arm B, n=35). The median survival time was 28.7 months for patients in arm A and 14.9 months for patients in arm A and 14.9 months for patients in arm B (18.8 months for patients in RTOG 9405). The 1 year survival rate of 75.7% in arm A was close to, but did not meet or surpass, the 77.5% goal. The 2 year survival rate was 56% for arm A and 37% for arm B. Grade 3 (arm A=54%, arm B=43%) and grade 4 toxicities (arm A=27%, arm B=40%) were

frequent. Treatment-related death occurred in 3% of patients in arm A and 6% of patients in arm B. The results of RTOG 0113 demonstrate that although such intense therapies are feasible in a multi-institutional setting, they are associated with considerable morbidity (>80% rate of grade 3 or4 toxicity). Also, neither of the two arms achieved the desired 1 year survival mark.

Teper J et al[40] to assess whether a short preoperative CCRT regimen improves outcomes for patients with resectable EC in a randomized controlled phase III trial; 128 patients were randomly assigned to surgery alone and 128 patients to surgery after 80 mg/m^2 cisplatin on day 1,800 mg/^{2} fluororacil on days 1-4, with concurrent RT of 35 Gy given in fractions. The primary endpoint was progression-free survival. Secondary endpoints were overall survival, tumour response, toxic effect, patterns of failure, and quality of life. Analysis was done by intention to treat. Result shows neither progression-free survival nor overall survival differed between groups (hazard ratio [HR] 0.82 [95% CI 0.61-1.10] and 0.89 [0.67-1.19], respectively). The CCRT and surgery group had more complete resections with clear margins than did the surgery alone group (103 of 128 [80&] vs 76 of 128 [59%], p=0.002), and had fewer positive lymph nodes (44 of 103 [43%] vs 69 of 103 [67%], p=.003). Subgroup analysis showed that the patients with squamous-cell tumours had better progression-free survival with CCRT than did those with non squamoustumours (HR 0.47 [0.25-0.86] vs 1.02 [0.72-1.44]). However, the trial was underpowered to determine the real magnitude of benefit in that subgroup. Preoperative CCRT with cisplatin and fluorouracil does not significantly improve PFS or OS for patients with resectable EC compared with surgery alone. Further assessment was warranted of the role of CCRT in patients with squamous-cell tumours.

Koike R et al[41] conducted a review on clinical results of CCRT in the treatment of patients with advanced EC with fistulae that developed before or during CCRT. A total 16 patients had fistulous oesophageal cancer treated by means of CCRT between 1999 and 2006. Nine patients had fistulae beforCCRT, whereas 7 developed fistulae during CCRT. The group included 12 men and four women with a median age of 55 years (range, 37-77 years). There were 9 patients with Stage III disease and 7 with stage IV disease. All tumours were squamous cell carcinomas. Two course of concurrent chemotherapy were combined with radiation therapy; 60 Gy/30 fraction/7 weeks (1-week split). For 15 patients, low-dose protracted chemotherapy with 5-fluoroutacil (250-300 mg/m^2 x 14 days) and cisplatin (7 mg/m^2 x 10 days) was administered, whereas full-dose cisplatin and 5-luorouracil were administered to the remaining patient. The planned dose of 60 Gy was delivered to 11 patients (69%), whereas RT was terminated early in 5 patients (40-58 Gy) because of acute toxicities, including two treatment-related death. Disappearance of fistulae was noted during or after CCRT in 7 patients (44%). All three esophago-mediastinal fistulae were closed, but only four of 13 esophago-respiration fistulae were closed by CRT. For patients with Stage III, 1- and 2-year survival rate were 33% and 22% respectively. Median survival time was 8.5 months. The study concluded despite significant toxicity, concurrent CCRT appears effective at closing esophageal malignant fistulae.

YchouM et al[42] in an multicenter Phase III trial, overall, 224 patients with resectable adenocarcinoma of the lower oesophageal junction (GEJ) or stomach were randomly assigned to either perioperative chemotherapy and surgery (CS group; n =113) or surgery alone (S group; n=111). Chemotherapy consisted of two or three preoperative cycles of intravenous cisplatin (100 mg/m^2) on day 1 and a continuous intravenous infusion of fluorouracil (800mg/m^2/d) for 5 consecutive days (day 1 to 5) every 28 days and three or four postoperative cycles of the same regimen. The primary end point was OS. Results compared with the S group, the CS group had a better OS (5- years rate 38% v 24%; hazard ratio [HR] for death ; 0.69,95% CI, 0.50 to 0.95; p 0.02); and a better disease-free survival (5 years rate; 34% v 19%; HR 0.65; 95% CI 0.48 to 0.89;l P.003). in the multivariable analysis, the favourable prognostic factors for survival were perioperative chemotherapy (P.01) and stomach tumour localization (P.01). Perioperative chemotherapy significantly improved the curative resection rate (84% v 73%; P .04). grade 3 to 4 toxicity occurred in 38% of CS patients (mainly neutropenia) but postoperative morbidity was similar in the two groups. In patients with resectable adenocarcinoma of the lower oesophagus, GEJ, perioperative chemotherapy using fluorouracil plus cisplatin significantly increase the curative resection rate, disease-free survival and OS.

Kato K et al[43] conducted a phase II study of CCRT for Stage II-III resectableesophageal cancer. Fifty-one patients were enrolled in the study from June 2006 to May 2008. The characteristic of the patients enrolled were median age 64 years; male/female, 45/6; performance status 0/1, 32/19 patients; Stage IIA/IIB/III, 9/20/22 patients, respectively. Patients were delivered RT to a total dose of 54.4 Gy with elective nodal irradiation of 41.4 Gy. Concurrent chemotherapy comprised two courses of 5-flurouracil (1000 mg/m^2/day) on days 1-4 and 2-h infusion of cisplatin (75 mg/m^2) on Day 1; this was repeated every 4 weeks. Two courses of 5-fluorouracil with cisplatin were added. A complete response was achieved in 36 patients (70.6%). The 1- and 3-year overall survival rate 88.2 and 63.8% respectively. The median 1- and 3-year progression-free survival rate was 66.7% (80% CI:57-74%) and 56.6% (80% Ci; 47.1-64.9%), respectively. Eight patients (15.6%) underwent salvage surgery due to residual or recurrent disease. The study concluded that CCRT at a dose of 50.4 Gy with elective nodal irradiation is promising with a manageable tolerability profile in esophageal cancer patients.

Swisher SG et al[44] in a phase II study evaluated definitive CCRT with selective surgical salvage in locoregionally advanced oesophageal cancer in Radiation Therapy Oncology Group (RTOG) affiliated sires. The study was designed to detect an improvement in 1 year survival from 60% to 77.5% (α=0.05; power = 80%). Definitive CCRT involved induction chemotherapy with 5-fluorouracil (5-FU) (650mg/mg^2/day) with cisplatin (15 mg/mg^2/day) over the first 5 days. Salvage surgical resection was considered for patients with residual or recurrent esophageal cancer who did not have systemic disease. Forty-three patients with non-metastatic resectableesophageal cancer were entered from Sept 2003 to march 2006. Forty-one patients were eligible for analysis. Clinical stage was ≥T3 in 31 patients (76%) and N1 in 29 patients (71%) with adenocarcinoma histology in 30 patients (73%). Thirty-seven patients (90%) completed induction chemotherapy followed by CCRT. Twenty-one patients underwent surgery following definitive CCRT because of residual (17 patients) or recurrent (3 patients) oesophageal cancer and 1 patients because of choice. Median follow-up of live patients was 22 months, with an estimated 1 year survival of 71%. The 1 year survival rate was 71%, did not meet the study goal of 77.5%. Surgery was withheld in favour of definitive CCRT in the case of SCC of the cervical oesophagus because adequate surgical resection was often associated significant morbidity and loss of the entire larynx, and the proximal oesophagus.

Fiore FD et al[45] conducted a trial to evaluate the predictive factors of survival in patients with locally advanced squamous cell oesophageal carcinoma (LASCOC) treated with definitive CCRT regimen based on the 5FU/CDDP combination. A total of 116 patients between 1994 and 2000 were retrospectively included in the study. All patients with LASCOC treated with a definitive CCRT using the 5FU/CDDP combination. CCRT regimen was based on the 5FU/CDDP CT combination associated with an external RT. The RT was delivered either by a dose of 50 Gy (50Gy/25 fractions per 5 wk) with concomitant CT courses delivered on wk 1 and 5, or either a dose of 60 Gy (20 Gy/10 fractions x 3 courses separated by a 2 wk break) with concomitant CT courses delivered on wk 1,5 and 9. The CT courses combined 5-FU (750 to 1000 mg/m^2 per day delivered by continuous infusion on 4 d) and CDDP (75 to 100 mg/m^2 delivered on 1 d). The irradiation technique was applied in anterior and posterior oppose fields. At 40 Gy, the radiation portals were reduced to shield the spinal cord. Clinical complete response (CCR) to CCRT was assessed by oesophageal endoscopy and CT scan 2 month after CCRT completion. Prognostic factors of survival were assessed using univariate and multivariate analysis by the Cox regression model. A CCR to CCRT was observed in 86/116 (74.1%). The median survival was 20 months (range 2-114) and the 5 years survival was 9.4%. Median survival of responder patients to CRT was 25 month (range 3-114 as compared to 9 month (range 2-81) in non-responder patients (P<0.001). in univariate analysis, survival was associated with CCCR (P<0.001), WHO performed status <2 (P=0.01), tumour length <6 cm (P=0.045) and weight loss <10% was in limit of significance (P=0.053). In multivariate analysis, survival was dependent to CCR (P<0.0001), weight loss <10% (P=0.034) and WHO performed <2 (P=0.046). The results suggest that survival in patients with LASCOC treated with definitive CCRT was correlated to CCR, weight loss and WHO performance status.

Anbai A et[al46] conducted a retrospective treatment review to examine the treatment outcomes of CCRT for advanced EC and analyze their prognostic factors, from April 2003 through December 2010. Total 439 patients were treated with RT during 2003 to 2010. Among them, the records of patients treated with definitive CRT were reviewed because of advanced stage disease. Patients received Cisplatin (CDDP) (40 mg/m^2) and were administered on days 1 and 8 by intravenous infusion over a period of ≥2 h, and 5-FU (40 mg/m^2) was administered on days 1-5 and again on days 8-12 by continuous infusion. This schedule was started concomitantly with RT and repeated ever fifth week for 2 cycles. When Grade 3 hematologic toxicity developed, the second course of chemotherapy was delayed until recovery. Adjuvant chemotherapy after completion of RT was performed for patients who were deemed able to receive anticancer drugs. Anterior-posterior opposing portal irradiation was initiated at approximately 40 Gy, and oblique portal irradiation was then performed to spare the spinal cord from the radiation field. Patients received conventional fractionated radiation of 1.8 Gy per fraction, to a total dose of 59.4-61.2 Gy, 5 times a week over 7 to 9 weeks. Between 2003 and 2005, i.e. in the early cases, the radiation dose was approximately 30 Gy and the split period was 10 to 14 days. After 2004, the radiation period was not limited and irradiation was continued, unless cytopenia of grade 3 or higher. The dose reference point was located at the iso-center. One hundred and fourteen patients were treated with CCRT. Among them, 84 patients (77.2%) received the complete course of CCRT. Eighteen patients (15.8%) had a complete response, 90 patients (78.9%) had a partial response and 6 patients (5.3%) exhibited progressive disease. The mean follow-up period was 14.6 months (range, 2-90 months). The median overall survival time was 13.0 months. The 2 years and 3 years overall survival rate were 38.1% and 19.2% respectively. Performance status and body weight loss were identified as significant prognostic factors.

Teoh AY et al[47] between, July 2000 and December 2004, 81 patients with resectable squamous cell carcinoma of the mid or lower thoracic oesophagus, randomized to receive esophagectomy or definitive CRT. The primary outcome was the overall survival and secondary outcomes included disease-free survival, morbidities and mortalities. Patient received Cisplatin 60 mg/m^2 with hydration therapy was given on days 1 and

22, whereas 5-FU was administrated as a continuous infusion at 200 mg/m^2/day from day 1 to 42. RT was delivered a total of 50-60 Gy given in 25-30 fractions over 5-6 weeks. Forty-five patients received esophagectomy and 36 patients were treated by definitive CCRT. The overall 5 years survival favoursCCRT but the difference did not reach statistical significance (surgery 29.4% and CCRT 50%, P=0.147). A trend to improved 5 years survival was observed for patients suffering from node-positive disease (P=0.061). The 5 years disease-free survival also showed a tread to significance favouring CRT (P=0.068), p[particularly for suffering from node-positive disease (P=0.017). Both the stage of the disease and albumin level was significant predictors to mortality and disease-free survival.

Michel P et al[48] a phase III randomized to compare the outcomes of postoperative adjuvant CCRT using two different schedules of cisplatin for patients with high-risk ESCC. From Feb 2008 to Aug 2010, 55 patients with high-risk ESCC were included in this study. Patients were randomized into treatment groups that either received 100 mg/m^{2}cisplatin once every 3 weeks (arm A) or 40 mg/m^{2}cisplatin once per week (arm B). All patients were irradiated with 66 Gy in 33 fractions. Of the 50 eligible patients, 26 were assigned to arm A and 24 were assigned to arm B. Both groups of patients received the same mean doses of radiotherapy and cisplatin. However, 88.5% of patients in arm A and 62.5% of those in arm B (P=0.047) received ≥200 mg/m^2 of cisplatin in total. The overall toxicities occurred in patients in arm B Three-weekly high dose cisplatin treatment showed higher compliance, and lower acute toxicity compared to weekly low dose cisplatin treatment.

Xing L[55] conducted this retrospective study to evaluate the feasibility and efficacy of concurrent CCRT or sequential chemoradiotherapy (SCRT) with capecitabine and cisplatin for elderly patients with locally advanced ESCC. A total of 75 patients elder than 65 years with histologically proven stage II-III ESCC were enrolled, in whom 40 patients were treated with CCRT consisted of two cycles of intravenous cisplatin and oral capecitabine during and after RT and 35patients were treated with SCRT as two cycles of capecitabine plus cisplatin before and after RT. Response rate, overall survival, progression-free survival and toxicity were compared. The overall response rate (CR + PR) in the CCRT group (91.6 %) was significantly higher than that in the SCRT group (67.7 %), P = 0.023. The median PFS and median OS were significantly higher in CCRT group (19.7 and 33.6 months) than those in SCRT group (11.6 and 15.7 months), P < 0.05. The acute toxic effect was more severe in the CCRT group than in the SCRT group, but the grade 3-4 acute toxicities were similar in two groups. It suggested that both CCRT and SCRT with capecitabine and cisplatin are tolerable and effective for elderly patients with locally advanced ESCC. Concurrent CRT might be superior to SCRT.

Gupta S et al[56] aimed to assess the efficacy and safety of concurrent capecitabine and cisplatin over concurrent cisplatin and 5-flurouracil (5-FU) in locally advanced squamous cell carcinoma of the head and neck. One hundred and fifty-three patients (all of whom had stage III or IV unresectable disease with no distant metastases and who had received two cycles of taxol and cisplatin chemotherapy) were randomly assigned to receive either concurrent cisplatin (75 mg/m(2) in day 1 and 2) and 5-FU (750 mg/m(2) in day 1, 2, and 3) from the first day of RT at an interval of 3 weeks (Arm I) or cisplatin (75 mg/m(2) in day 1 and 2) and capecitabine (750 mg/m(2) in two divided doses from day 1-14) from the first day of RT at a 3-week interval (Arm II). Results showed that patients in Arm II had a significantly better rate of complete response, fewer nodes, and better overall response compared to those in Arm I.

Chen F et al[57]conducted this retrospective study to evaluate the feasibility and efficacy of definitive concurrent CCRTwith capecitabine and cisplatin for elderly patients with locally advanced ESCC. A total of 90 patients were included from two different centers. Forty-nine patients were treated with CCRT consisting of capecitabine (850 mg/m^2, oral, twice a day for 1–14 days) and cisplatin (20 mg/m^2) weekly during RT. The remaining 41 patients were treated with RT alone. The overall response, overall survival, progression-free survival, and toxicity rates were recorded. Both CCRT with capecitabine and cisplatin and RT alone are feasible to treat elderly patients and yield a good performance status with locally advanced ESCC. CCRT improved the tumor response without increasing the side effects compared to RT alone. CCRT is recommended for patients over 65 with good performance status.

III. OBJECTIVES

1. To compare tumour response between concurrent chemoradiation using oral capecitabine with radiotherapy alone in elderly patients with inoperable esophageal cancer
2. To compare treatment related toxicities between the two arms.

IV. MATERIALS AND METHODS

Study design: Interventional prospective randomized double arm study.

Place of study/ Set Up: Department of Radiation Oncology,RegionalInstitute of Medical Sciences, Imphal, Manipur.Approval from Research Ethics Board, RIMS, Imphal and written informed consent of the patient was taken before starting the study.

Duration of Study:2 years study period,starting from August 1st, 2018 to July31st, 2020. Initial 18 months will be for patient accrual and study and result analysis was done after allowing minimum of 6 months follow-up for the patients.

Study population: Patients who are histopathologically confirmed esophageal cancer, reported to the Department of Radiation Oncology, Regional Institute of Medical Sciences(RIMS), Imphal during the study period.

Inclusion criteria:

1.Histopathologically confirmed EC patients.
2. Aged 60 years or older at the time of diagnosis.
3.Unable or refusing to undergo surgical resection.
4.KPS>60%.
5.Haemoglobin> 10gm%.
6. TLC>4000/mm^2.
7. Platelet count>100,000.
8. Normal Liver function test(LFT), Kidney function test(KFT), blood sugar.
9. NormalElectrocardiogram(ECG).
10. Normal Pulmonary function test(PFT)

Exclusion criteria:

1. Complete dysphagia.
2. Previously treated with radiation therapy/chemotherapy and /or surgery.
3. Patient is suffering from any other second malignancy.
4. Associated medical co-morbidities (eg.Severe diabetes mellitus/chronic obstructive pulmonary disease/Cardiac disease)
5. Presence of distant metastasis.
6. Presence of psychosis.
7. Karnofskyperformancestatus(KPS)<60%.

Sample size:

Sample size is calculated using the formula

$$\mathrm{N} = \frac{(u+v)^2\,[\{p_1\,(100-p_1)\}+\{p_2\,(100-p_2)\}]}{(p_1-p_2)^2}$$

$$= \frac{(o.84+1.645)^2\,[\{74(100-74)\}+\{51(100-51)\}]}{(74-51)^2}$$

$$= 50.166$$

Where N is the size per group

u = 0.84 at 80% power, v = 1.645 at 90% level of significance

p_1 = proportion in one group =74 (reference no-57)

p_2 = proportion in another group = 51 (reference no-57)

The calculated sample size was 50.16 in each group (arm A and arm B). Therefore the total sample size is 100.32 ~ 100.

Taking into consideration that, the dropout rate is 10% in this study, the total sample size was fixed at 110.

Method of Recruitment:

After getting informed consent, patients were allocated into arm A and arm B using block randomisation method. Since there are two treatment options involved, block size of 4 used. Possible treatment allocation within each block are (1)AABB(2)ABAB(3)BABA(4)BBAA(5)ABBA(6)BAAB. Using random number table, a list of block used. For each selected block, there was a sequence of treatment options. The sequence of treatment options were put in a sealed envelope and envelopes were labelled 1, 2, 3, 4,…according to appearance on the list. The sealed envelope with label 1 was opened only when we had first eligible patient and the treatment was allocated. This was continued till the required samples are allocated.

Methods:

All the histopathologically confirmed esophageal cancer patients were subjected for complete history, thorough general physical examination, complete blood count, blood chemistry, ECG, PFT, urine routine examination, blood sugar, chest X-ray (PA and lateral view), Barium swallow x-ray, Upper GI endoscopy, Ultra-sonography (USG) of whole abdomen, CT scan of Thorax and other investigations as required. Informed consent were taken from all the patients.

Patients were randomly allotted to the two arms using sealed envelope technique.

Analysis of study:

1. Early tumour response:4 weeks after completion of treatment.
2.Earlytreatment toxicities:Weekly from Day 1 of the treatment till 1st week

aftercompletion of the treatment.
3. Late treatment toxicity: 6 months after completion of treatment.
4. Survival: At the end of the study period.

Treatment Plan:

Arm-A (Study arm)

Patients were treated with two-dimensional external beam radiotherapy using Source axis distance(SAD) technique. The patients were given a total dose of 50 Gy in 25 fractions by conventional fractionation (5 days in a week) using TheratronTelecobalt machine. In phase I plan, the initial planning target volume(PTV) constituted of primary disease with a margin of 5 cm proximally and a lateral margin of 2cm from most lateral aspect of primary/ regional disease. Patients were treated upto a dose of 36 Gy in 18 fractions by AP/PA portalsin the supine position.For phase IIplan,the remaining dose was boosted by diminished target volume with a margin of 2 cm proximally and 1cm lateral margin from primary diseasebytwo anterior oblique wedge portals in upper 1/3rd tumor in supine position and two posterior oblique portals in middle and lower 1/3rd tumorin prone position respectively till the end of treatment.

CCRT using oral capecitabine was given in a dose of 825 mg/ m^2, twice daily after meal within 30 minutes for 7 days/week from Day 1 till the end of the treatment.

Arm-B (Control arm): RT of same radiation technique, dose and fractionation was given alone as given in Arm –A.

Patient care during treatment:

Patients were checked up once in a week to evaluate the early treatment related toxicities. Patients were subjected to weekly complete blood count and biochemical parameters (LFT, KFT) every 2 week. Treatment was deferred if Hb%<10gm%, TLC<4000/cu-mm and platlet<1lakh/cu-mm. As per derangement in blood parameters, either blood product transfusion or G-Colony stimulating factor(CSF)/ GM-CSF was given.

Follow up:

Follow up was done 4 weeks after completion of the treatment to assess early tumour response (primary and nodal disease) clinically or if needed, radiologically, thereafter every 2 monthly follow up was done by physical examination, Barium swallow x-ray, Upper GI endoscopy, CT scan of thorax, USG of whole abdomen, ECG, Echocardiogram(ECHO) and PFT. Patients was evaluated for late treatment toxicity after 6 months from completion of treatment and survival analysis at the end of study period.

Assessment:

Treatment related toxicity was assessed by Radiation Therapy Oncology Group (RTOG) criteria. Tumour response (primary and late response) were assessed by WHO response criteria either clinically or if needed, radiologically. The results of the study regarding completion of intended treatment, any interruptions in treatment, toxicity and disease status at last follow-up in both the arms documented.

Study variables:

- Age
- Sex
- Stage
- Primary tumour site.
- T stage
- N stage

Outcome Variable:

- Early tumour response.
- Acute treatment related toxicity.
- Late treatment related toxicity.
- Progression free survival(PFS).

Study equipment:

TheratronTelecobalt machine, 780-C. Model number: A112109-101 (M/s AECL Medical, Canada).

Working definitions:

- RTOG criteria: Acute &late radiation morbidity scoring criteriafor grading toxicities in different organs/tissues.
- WHO response criteria: Evaluation of tumourresponse(primary and nodal disease)

Statistical analysis:

- Descriptive data like age and median survival time were presented in terms of mean and standard deviation.

- Data like sex, stage and toxicity profile were presented in terms of percentages and proportions
- Treatment response and toxicity profile across the groups were analyzed using chi square test.
- For late treatment response assessment, Kaplan-Meier survival curve were used.
- Percentages, proportions and statistical significance were analyzed using IBM SPSS statistics 22 for windows (IBM Corp, 1995, 2012).

P value of < 0.05 was considered as significant.

Ethical Approval: Permission of the Institutional Ethics Committee, RIMS, Imphal, Manipur was obtained to conduct the study. Before the enrolment of a study participant, informed written consent was obtained. The benefits and harms involved with the study were clearly explained and refusal to participate was respected. Personal information obtained from the participants was kept confidential and were not shared with anyone without their permission.

V. RESULTS AND OBSERVATION

In this double arm randomized prospective study, total 60 patients with oesophageal carcinoma were recruited in the period spanning 1st August 2018 to 31st July 2020, 30 patients were recruited in the study arm and another 30 patients were in the control arm. The median follow-up for the evaluable 27 patients in the study arm and 28 patients in the control arm were 15 months, 13 month respectively; the shortest being 6 month and longest for 23 months.

TABLE I. AGE DISTRIBUTION

Age Distribution	Study arm (A) (n=30)	Control arm (B) (n=30)	P-value
Age(Y): Range 30-70 Median 30-39 40-49 50-59 60-69	 30-70 50 05(16.6%) 06(20%) 04(13.3%) 15(50%)	 30-70 50 05(16.6%) 08(26.6%) 05(16.6%) 12(40%)	 P=0.73

Table I, represents the characteristic of patients with respect to the age. Maximum patients belong to the age group of 60-69 years; in study arm it was 50% and in control arm was 40%. The accruals in both the arms were comparable and the differences were not significant.

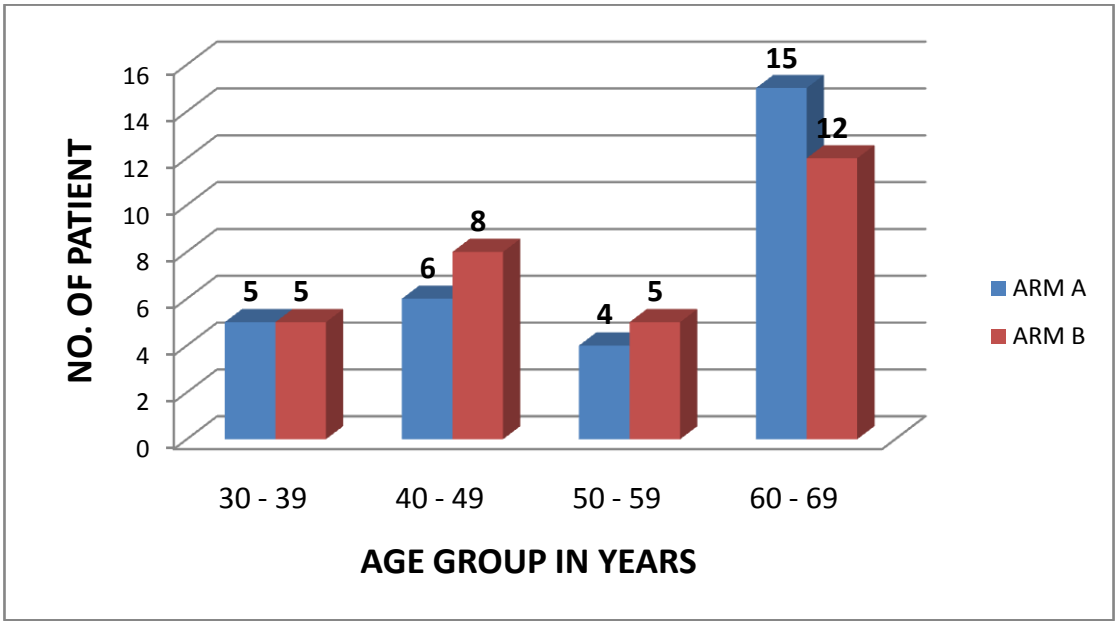

Figure I. Age wise distribution of patients.

Table II. SEX DISTRIBUTION

Sex	Study arm (A) (n=30)	Control arm (B) (n=30)	P-value
Male Female	23(76%) 07(24%)	22(72%) 08(28%)	P=0.747

Table II, shows the sex distribution of patients. Out of 30 patients in each arm, males were 76% in study arm and 72% in control arm and femaleswere 24% in study arm and 28% control arm. Accruals in both arms were comparable without any statistical significant differences.

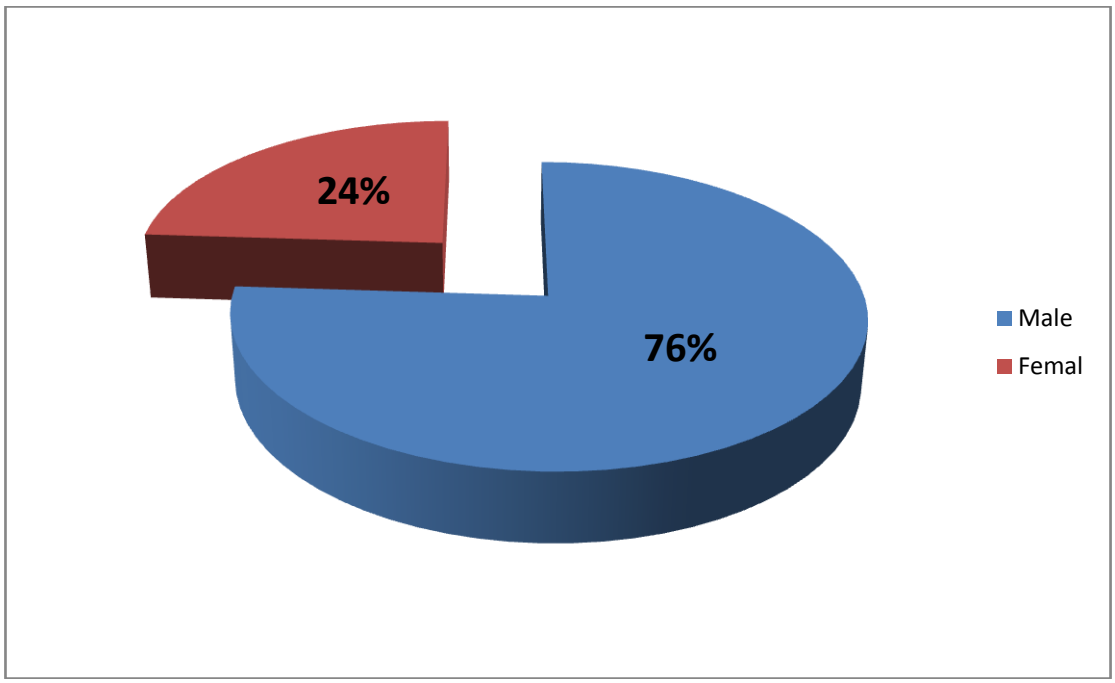

Figure IIA. Sex distribution (study arm)

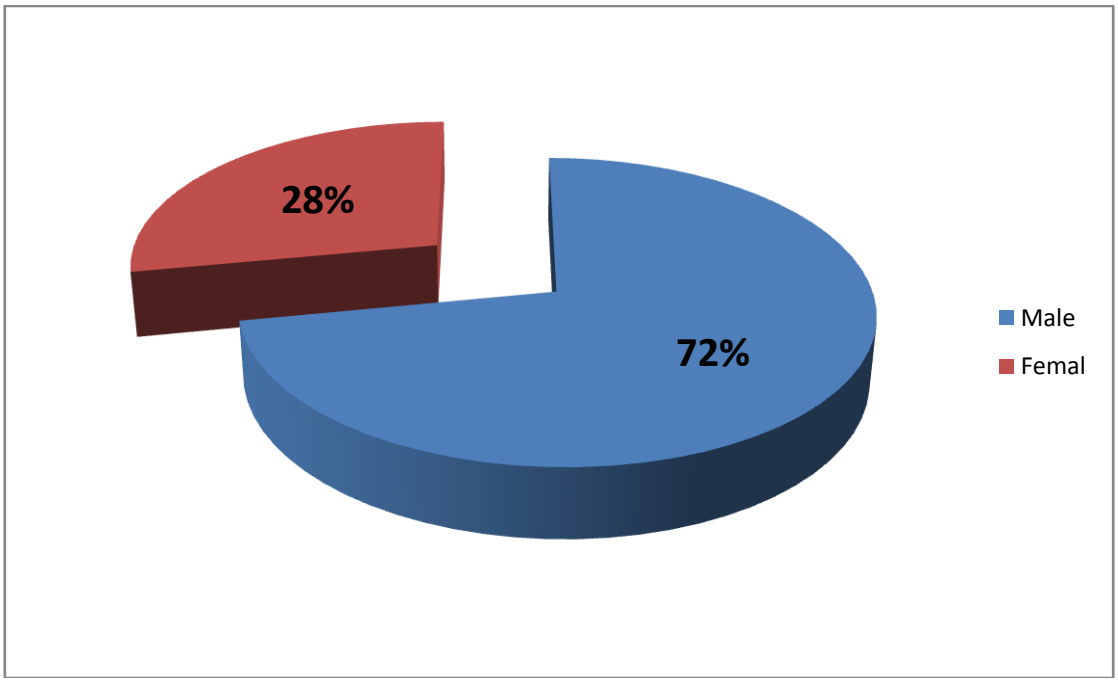

Figure IIB. Sex distribution (Control arm)

TABLE III. PERFORMANCE SCORE OF PATIENTS

Karnofsky score:	Study arm (A) (n=30)	Control arm (B) (n=30)	P-value
90-100% 80-90% 70-80% 60-70%	00 11(36%) 14(48%) 05(16%)	00 10(32%) 14(48%) 06(20%)	P =0.919

Table III, depicts the figures of Karnofsky score (KPS) of patients. Majority of the patients were presented with KPS of 70-80%; in both study and control arm was 48% (range within 70-80%). Accruals of patients in both arms were comparable. There were no statistical significant differences in the accrual of patients.

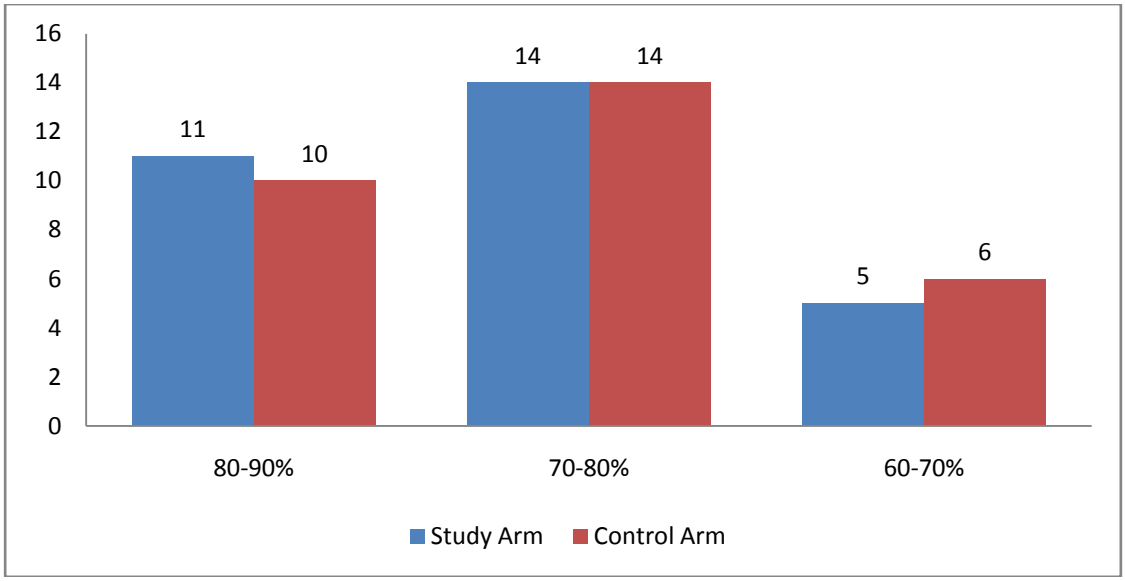

Figure III. Karnofsky performance score of patient

TABLE IV. TUMOUR CHARACTERISTICS

Characteristics	Study arm (n=30)	Control arm (n=30)	P-value
Histopathology			
Squamous	24(80%)	25(84%)	P =0.574
Adenocareinoma	06(20%)	05(16%)	
Other			
Location of primary lesion			
Upper 1/3rd	10(32%)	11(36%)	P =0.765
Mid 1/3rd	20(68%)	19(64%)	
Length of primary lesion			
≤5 cms	11(36%)	12(40%)	P =0.771
>5 cms	19(64%)	18(60%)	
Primary tumour status			
T1	0	0	
T2	10(32%)	09(28%)	P =0.952
T3	18(60%)	19(64%)	
T4	02(8%)	02(8%)	
N-Stage			
Nx	0	0	
N0	11(36%)	10(32%)	P =0.765
N1	19(64%)	20(68%)	
Stage			
Stage I	0	0	
Stage IIA	11(36%)	10(32%)	P =0.904
Stage IIB	04(12%)	05(16%)	
Stage III	15(52%)	15(52%)	

Table IV, shows the tumour characteristic of our patients. Squamous cell carcinoma was predominant in the both arms and was 80% in study arm and 84% in control arm. Most of the primary tumours were located in the

mid-1/3rd of oesophagus, in the study arm was 68% and in the control arm 64%. The size of the tumour with >5 cms in study arm was 64% and in control arm it was 60%. Patients mostly presented with stage III disease, accounts 52% in both arms. The tumour characteristics were comparable of both arms and the differences were not statistically significant.

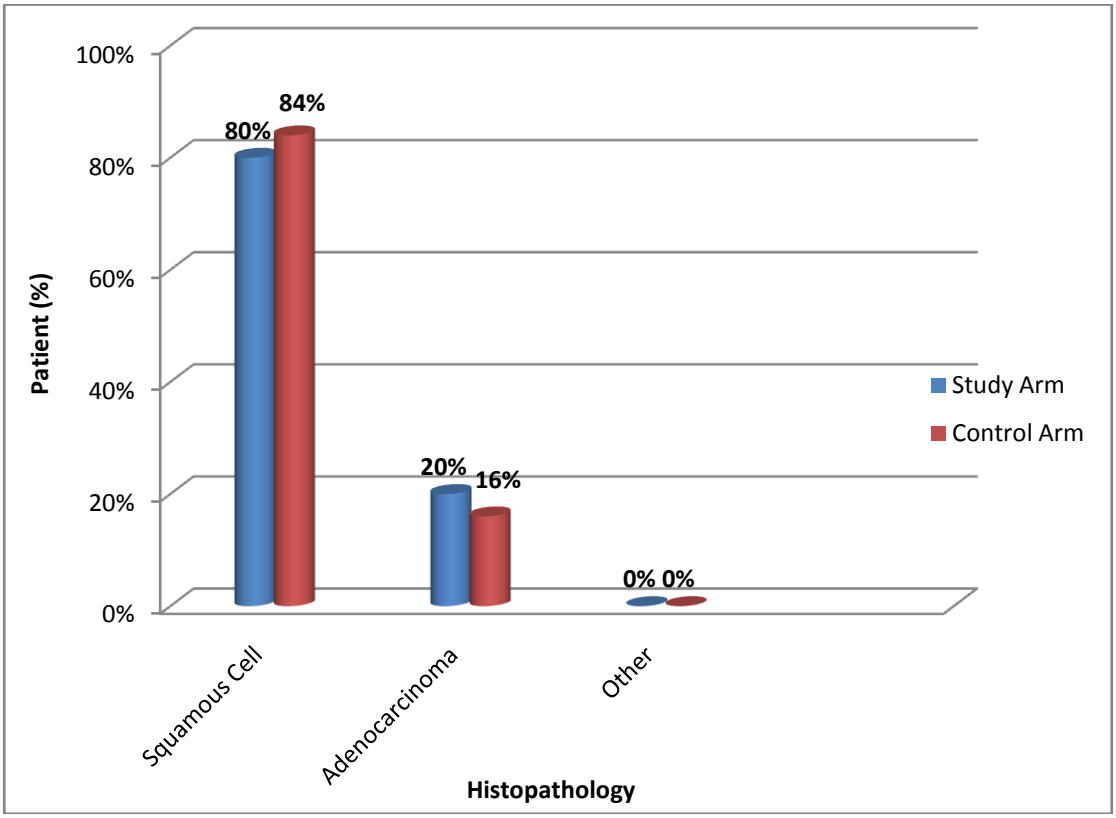

Figure IVA. Histopathology of primary tumour

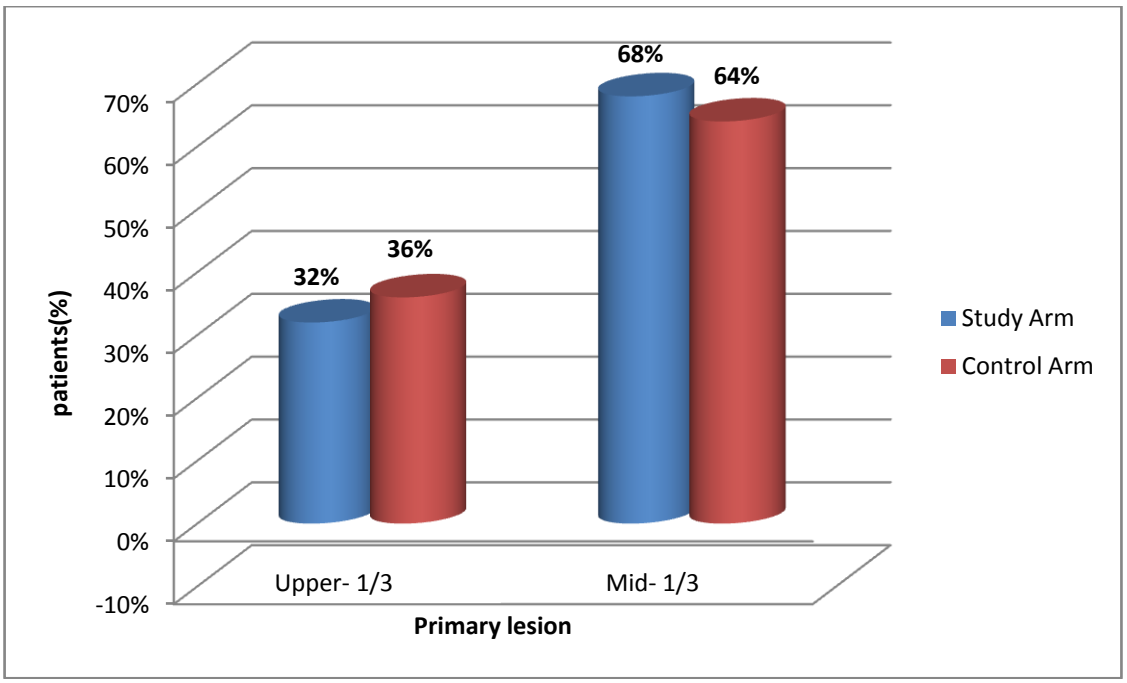

Figure IVB. Primary site of tumour location

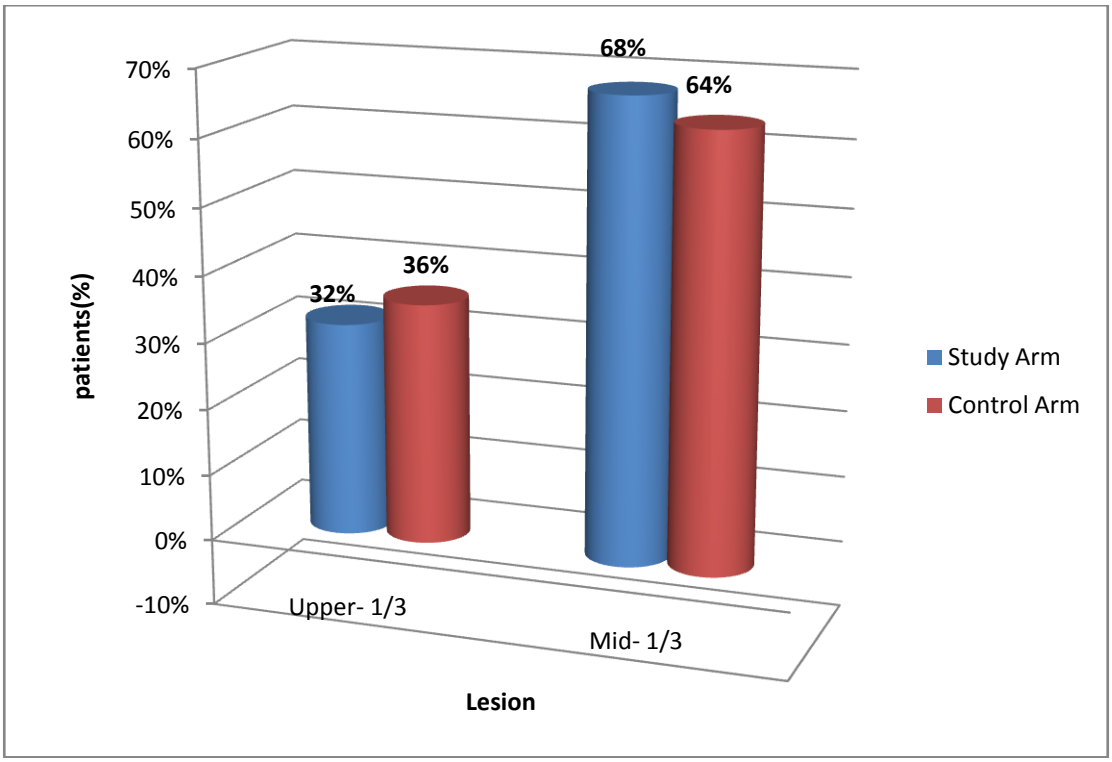

Figure IVC. Length of primary lesion.

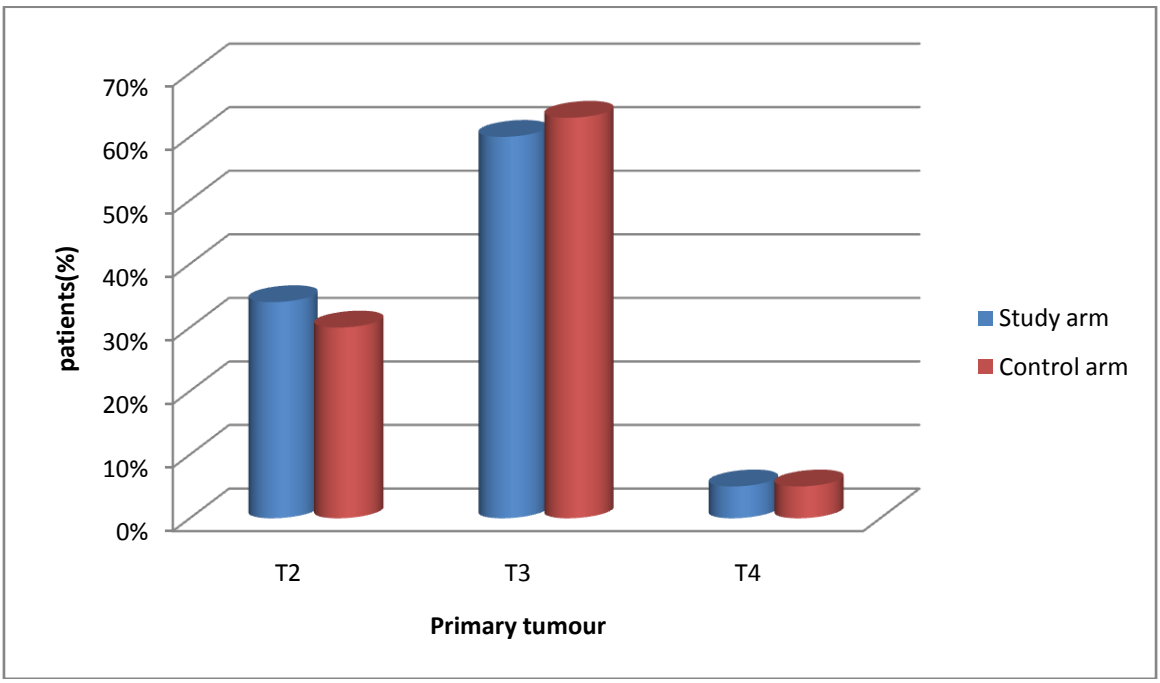

Figure IVD. Primary tumour status.

TABLE V. PRESENTING SYMPTOMS

Symptoms	Study arm (n=30) No. (%)	Control arm (n=30) No. (%)	P -value
Dysphasia No dysphasia(can take Solid) Mild(can take semisolid) Moderate(can take only liquid) Complete(unable to take any)	 01(4%) 06(20%) 20(68%) 03(8%)	 01(4%) 06(20%) 19(64%) 04(12%)	 P = 0.232
	–	–	

Weight loss<10%	18(60%)	19(64%)	
Substernal pain	08(28%)	07(24%)	
Regurgitation	13(44%)	11(36%)	

Table V, represents the symptoms of patients. Maximum of the patients presented with moderate dysphasia, 68% in study arm and 64% in control arm. Weight loss <10% was found 60% of patients in study arm and 64% in control arm. 28% of patients in study arm had substernal pain and 24% in control arm presented with substernal pain. 44% in study arm and 36% in control arm presented with regurgitation. The symptoms of both arms were comparable and differences were statistically not significant.

TABLE VI. EVALUABILITY STATUS

	Study arm (A) **No**	**Control arm (B)** **No**
Lost to follow up	**1**	**02**
Incomplete treatment	**02**	**0**
Evaluable	**27**	**28**

Table VI, shows 2 patient drop out of treatment in study arm and 1 patient was lost to follow-up in study arm and 2 patients in conrol arm. Thereby, only 27 cases in study arm and 28 cases in control arm were available for result analysis.

TABLE VII. EARLY TREATMENT RESPONSE (PRIMARY SITE)
(After one month of treatment completion)

Types of response	**Study arm** **(n = 27)**	**Control arm** **(n = 28)**	**P-value**
	No. (%)	No. (%)	
CR	12(45%)	09(35%)	P = 0.031
PR	10(40%)	9(32%)	
SD	02(7%)	12(42%)	
PD	3(11%)	8(28%)	

CR – Complete response
PR – Partial response
SD – Stable disease
PD – Progression of disease

Table VII, shows the early treatment response, which were analyzed as per WHO Miller's criteria, assessed 1 month from the end of treatment completion. 45% of patients in study arm as compared to 35% in control arm had complete response. Partial responses were seen in 40% in study arm, 32% in control arm. The differences seen in between the arm were ststistically significant (p=0.031). Stable disease was seen in 7%of study arm and 42% of control arm patients. 11% patients from study group and 28% patients from control arm showed progressive disease.

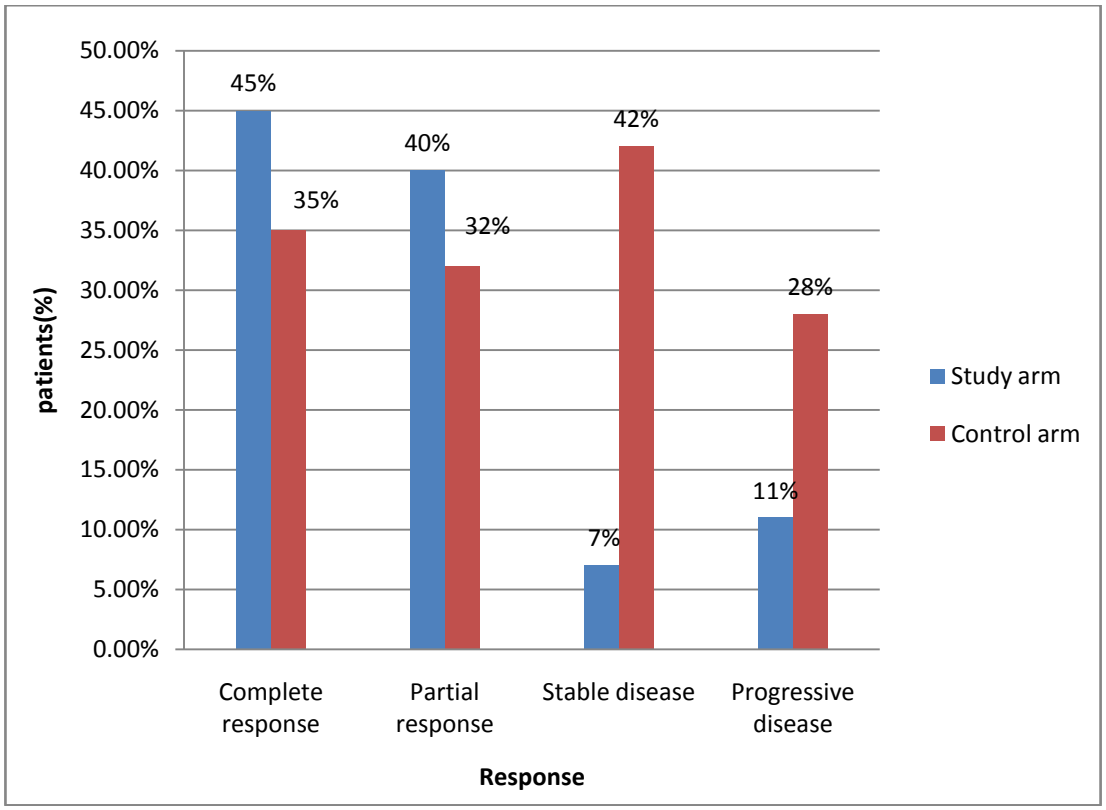

Figure V. Early treatment response

TABLE VIII. ACUTE SIDE EFECTS DURING TREATMENT
(Weekly assessment)

Haematological Toxicity	Study arm (n = 27)	Control arm (n = 28)	P-value
Leucopenia			
Grade 1	03(12.5%)	06(21.4%)	
Grade 2	10(37.5%)	10(35%)	P = 0.015
Grade 3	14(52%)	12(43.4%)	
Grade 4	0	0	
Thrombocytopenia			
Grade 1	04(16.6%)	04(13.0%)	
Grade 2	20(75%)	20(73%)	P = 0.839
Grade 3	03(8.3%)	04(13%)	
Grade 4	0	0	
Haemoglobin			
Grade 1	14(51.8%)	20(71.4%)	
Grade 2	09(33.3%)	07(25%)	P = 0.026
Grade 3	4(14.8%)	1(3.5%)	
Grade 4	0	0`	
			-

Table VIII, shows the acute toxicities during treatment. Among the haematological toxicities, Grade-3 leucopenia was seen more in study arm than control arm (52% vs 43.4%), Grade-3 thrombocytopenia was observed in 8.3% of patients in study arm and 13% in control arm, Grade-3 haemoglobin toxicity was seen in 14.8% in study arm and 3.5% in control arm. Statistically significant difference in haematological toxicities excluding thrombocytopenia between the two arms was observed.

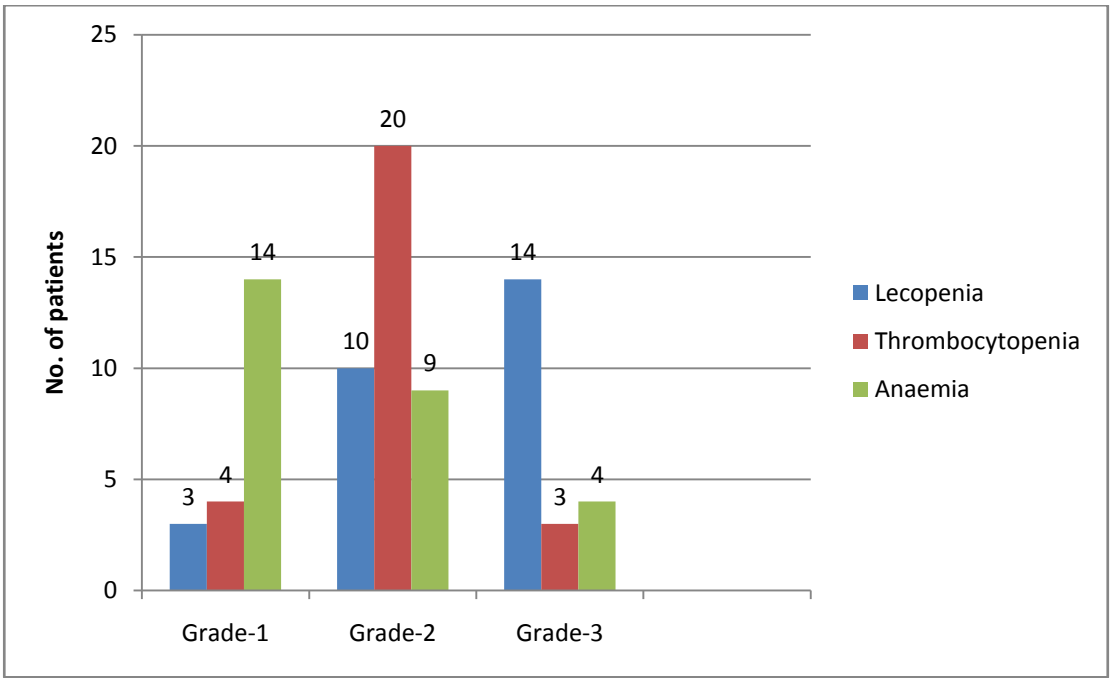

Figure VI-A : Acute haematological toxicity in Study-arm

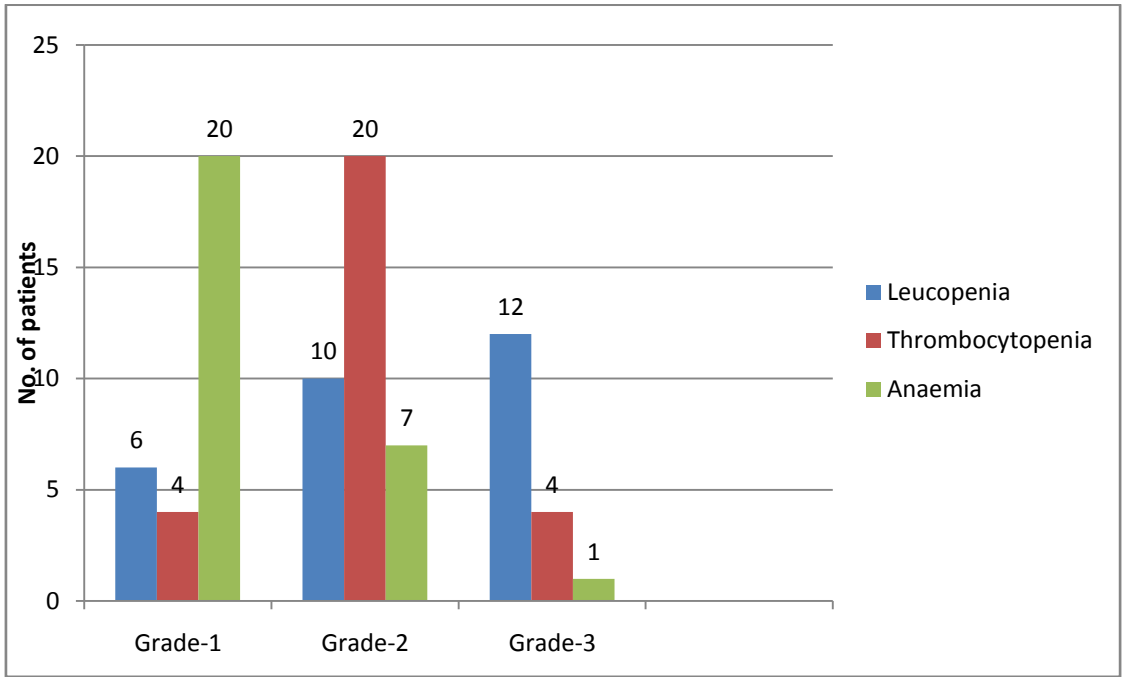

Figure VI-B : Acute haematological toxicity in Control-arm

TABLE IX. ACUTE SIDE EFFECTS DURING TREATMENT
(Non-haematological)
(Weekly Assessment)

Non-haematological Toxicity	Study arm (n=27)	Control arm (n=28)	P-value
Odynophagia			
Grade 1	04(14.8%)	14(50%)	
Grade 2	20(74%)	13(46.4%)	P = 0.01
Grade 3	03(11.1%)	01(3.6%)	
Grade 4	0	0	
Nausea/Vomiting			
Grade 1	03(8.3%)	04(13.0%)	
Grade 2	20(75%)	20(73%)	P = 0.839
Grade 3	04(16.6%)	04(13%)	

Grade 4	0	0	
Esophagitis Grade 1 Grade 2 Grade 3 Grade 4	 10(37%) 12(44.4%) 05(20%) 0	 25(89.2%) 2(7.1%) 01(3.5%) 0	 P = 0.000
Fatigue Grade 1 Grade 2 Grade 3 Grade 4	 02(7.4%) 17(63%) 05(18.5%) 03(11.1%)	 14(50%) 10(35.7%) 03(10.7%) 01(3.5%)	 P = 0.03

Table IX, shows Grade-2 odynophagia more in study arm than in control arm (74% vs 46.4%). Grade2 nausea/vomiting were more common in study arm than control arm (75% vs 73%). Grade-2 fatigue in study arm was 63% and 35.7% in control arm. Grade-2 esophagitis was more in study arm than control arm (44.4% vs 7.1%). Statistically significant difference in non haematological toxicities excluding nausea and vomiting was observed.

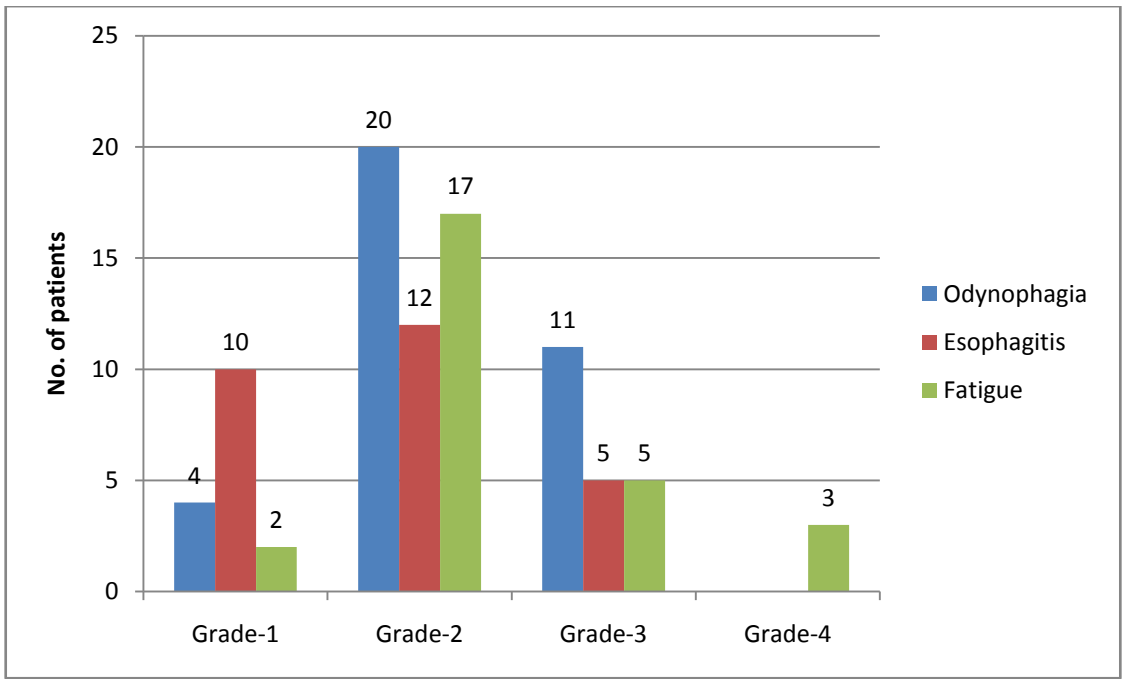

Figure VII A : Acute non haematological toxicity Study- arm

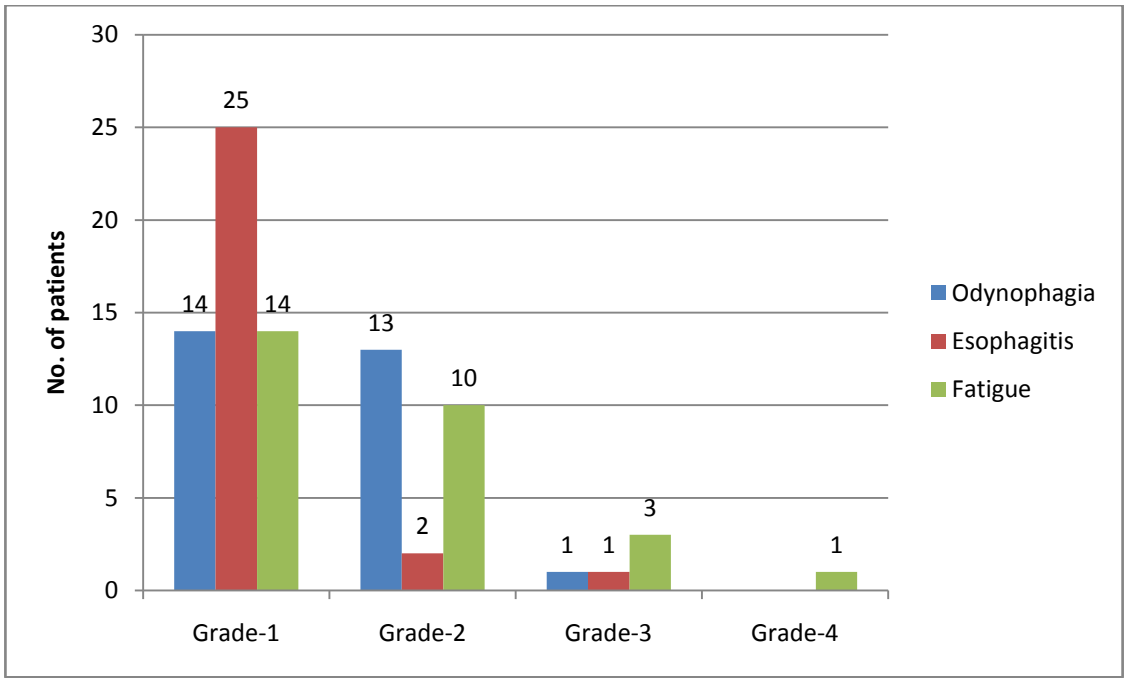

Figure VII B: Acute non haematological toxicity Control- arm

TABLE X. LATE TREATMENT RESPONSES
Median follow up: 15 months for study arm and 13 months for control arm

	Arm A	**Arm B**	**p - Value**
Number of patients	27	28	
Median follow up	15 months	13 months	
Median progression free survival (PFS)	16.6 ± 0.430 months	13.2 ± 0.402months	0.032

*Log rank test

In Table X, in both arms, median follow up duration are comparable. Difference in PFS in between the two arms is found to be significant statistically (p- value = 0.032).

Table XI: Survival status of the patients

Types of response	**Study arm (n=27)**	**Control arm (n=28)**
PFS	2(7.4%)	1(3.5%)
SWD	23(84.2%)	24(85.7%)
Death	02(7.4%)	03(10.7%)

Table XI, shows survival status of the patients at the end of the study period. In study arm, 2 patients (7.4%) were progression free survivors, 23 patients (84.2%) were survivors with disease and 2 patients (7.4%) died whereas in control arm, one patient (3.5%) was progression free survivor, 24 patients (85.7%) were survivor with disease and 3 patients (10.7%) died.

Kaplan Meire Survival Curve

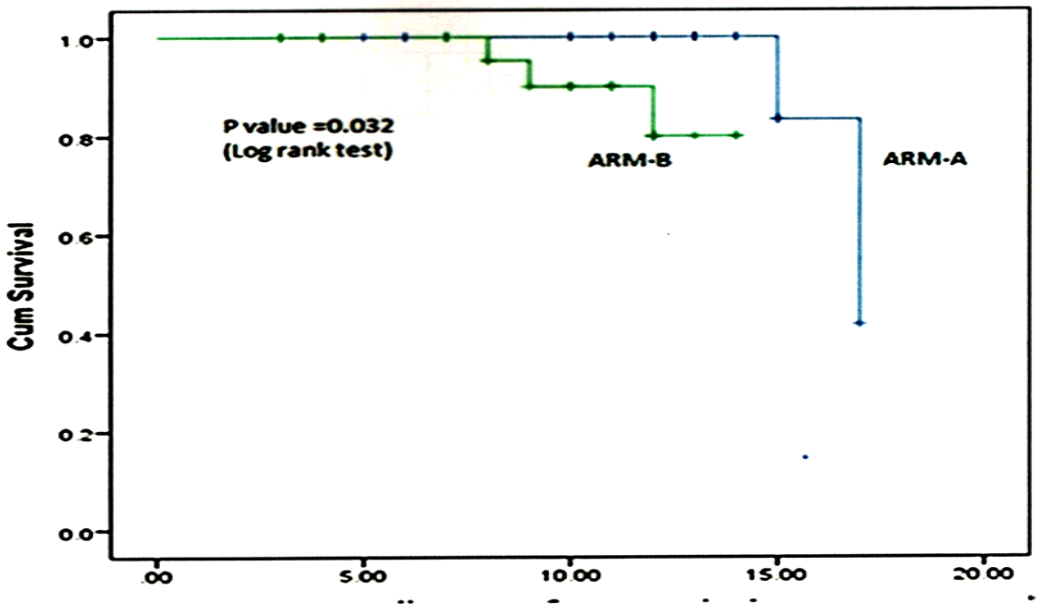

Figure VIII :Duration of progression free survival of the patients when comparing with two arms.

TABLE XII LATE SIDE EFFECTS (RT or CT related 3 monthly entries)
(Assessed after 6 months of treatment)

Side effect	Study arm (n=27)			Control arm (n=28)		
	M9	M12	M15	M9	M12	M15
Radiation induced Stenosis	1(4.3%)	1(4.1%)	-	4(10.03%)	1(4.3%)	-
Perforation	-	-	-	-	-	-
Myelitis	1(4.16%)	-	-	2(8.6%)	-	-
Lung fibrosis	-	-	-	1(4.3%)	1(4.3%)	1(4.3%)
Cardiac Complication	-	-	-	-	-	-

This table XII, shows the late side effects. Patients were followed-up every 3 month to assess the late side effect. There were 4.3% , 4.1% of patients developed radiation induced stenosis, in study arm at 9^{th} and 12^{th} month and 10.03%, 4.3% of patients developed radiation induced stenosis during the same period in the control arm. 4.1% of patient in study arm and 8.6% of patients in control arm showed myelitis at 9^{th} month in both arms. 4.3% of patients developed lung fibrosis at 12^{th} month in the control arm.

VI. Discussion

The primary modality treatment of esophageal cancer is surgery, radiotherapy, and chemo-radiotherapy. There exists controversy in the treatment choice of esophageal carcinoma. Various approaches are being extensively studied but the ideal therapeutic application of these approaches remains elusive due to lack of randomized trial data and suboptimal results with current therapies. As of now surgery is the mainstay of treatment and definitive chemoradiotherapy is a viable option available for the treatment of esophageal cancer.[18,19]

For patients with locally advanced tumors (T3 or higher or node positive), definitive CCRT was preferred, with consideration of upfront surgery for a selected subset of patients who are surgical candidates based on function, co-morbidities, and life expectancy. Higher rates of clinical and pathological complete response were achieved with CRT.[20,21,22,23]

In light of survival advantage of concurrent CCRT over RT alone,[22,23,24,25,26] combining chemoradiotherapy with surgery was attempted, with conflicting results in prospective randomized trials.[35,36,37]

In the recent trial, concurrent chemotherapy followed by surgery versus surgery alone in patients with TINI or T2-3NO-1 oesophageal cancer, pre-operative chemoradiotherapy among potentially curable oesophagealtumour showed excellent outcomes with median overall survival (OS) of 49.4 months. Two randomized clinical trials and meta-analysis, which compared chemoradiation alone with chemoradiation followed by surgery failed to demonstrate benefit of surgery on OS, while addition of surgery to chemoradiation improved local control.[42,47]

The most commonly used chemotherapeutic regimens foresophageal cancer combines cisplatin and 5FU. Neverthless, Cisplatin plus 5FU based concurrent chemoradiotherapy have limited efficacy with substantial toicity.[42,51,52,53] This has prompted investigations of newer chemotherapeutic agents, using Capecitabine in several phase II trial.

In a recent trial, the efficacy and safety of concurrent capecitabine and cisplatin (Arm I) over concurrent cisplatin and 5-flurouracil (Arm II) in locally advanced squamous cell carcinoma of the head and neck were studied and results showed that patients in Arm I had a significantly better rate of complete response, fewer nodes, and better overall response compared to those in Arm II.[55,56,57]

During recent years great concern has been expressed regarding the realistic quality review of treatment practices, patients acceptance, compliances and outcome as well as inherent difference in the therapeautic response in developing countries.

Patients characteristics

Of 60 patients accrued for the study, 45 were male and 15 female, with male : female ratio of 3.1:1 in the study arm and 3:1 in control arm respectively. In both the arms male predominance was seen. Posner MC et al[3] observed almost equivalent numbers between men and women (3:1), even though other studies reported ratios (2.5 : 1, 3.3 : 1 respectively).[6,7]

In this study, median age at presentation in majority of patients were 50 years in both arms. Whereas, Koike R et al[41] showed in his study that median age at diagnosis of advanced esophageal cancer was 55 years. In regard to age distribution among the two arms, it was found that maximum number of patients (50%) were in the age group 60-69 years in comparison to control arm (40%) which was found to be similar with the study conducted by Chen F et al.[57]

In our study Karnofsky score was above 70% in most of the patients which was compareable with study conducted by Cooper S t al[20] where the median KPS were above 60%.

The common symptoms at presentation were moderate dysphasia, 68% in the study arm and 64%weight loss in the control arm.Wweight loss <10% , 60% amng patients in the study arm and 64% in the control arm. Our study was comparable to those study findings conducted byMinsky BD et al[29], in his study moderate dysphasia was in 60% of study arm and 64% of control arm and weight loss <10% 58% in study arm and 60% in control arm were observed.

Tumour characteristics

Squamous cell carcinoma was the commonest histopathology in our study in both study and control group. The rate of squamous cell carcinoma was 80% in study group and 84% in control group. Next common histology was the adenocarcinoma comprising 20% in study group and 16% in control group. Those observation were comparable with that observed by Chen F et al[57] where majority of patients had squamous cell carcinoma (87%) and followed by adenocarcinoma (13%) in. Suh Y et al[31] also reported similar predominance of squamous cell carcinoma in concurrent chemoradiation versus radiation alone group.

In the present study most common primary site of the tumour was in the middle 3rd of oesophagus, contributing 68% and 64% of patients in study and control arm respectively. Suh Y et ^{al31}reported most of the primary site of esophageal cancer was in the mid 3rd of esophagus which were comparable to our study.

In the form of TNM staging (AJCC, 8thed) in our study 52% of the patients had stage III, 12-16% had stage IIb, 32-36% in stage IIAin study arm and in control arm it was52% in stage III, 16% in stage IIb, 32% in stage IIa and no patients presenting with stage I disease in both the arms.The data shows that majority of the patients in this regions are diagnosed usually at late stage similar to the study findings observed by ShinodaM et al[67] where 50-57% of patients were in stage III at presentation.

Esophageal lesion with more than 5cms was observed in 64% of the patients in our study arm and 60 % in control arm, similar to the findings of few studies conducted by Gaspar LE et al[64],Adelstein DJ et al[68] and Nomura M et al[52].

Early treatment response

In the present study, 27 patients out of 30 in study arm and 28 patients out of 30 in control arm were evaluable. In the study arm 12 patients (45%) showed complete response compared to 9 patients (35%) in control arm showing significant benefit in achieving complete response among patients in study group (p= .031). Partial response was found in 10 patients(40%) in study arm and 9 patients(32%) in control arm; stable disease was noted in 7% of patients in study arm and 42% of patients in control arm, as assessed one month after completion of treatment. We observed 3 patients in study arm and 8 patients in control arm with progressive disease during treatment time.

Our study subjects are comparable to the finding by Chen F et al[57] who achieved complete, partial and over all response in CCRT group 48.7%, 38.8% and 87.5%, respectively, while these rate were 44.6%, 36.6% and 81.2% in RT alone group.

Zhao Q et al[23] achieved complete response 44.6% in CCRT group whereas 40.6% in RT alone. Likewise, Bidoli P et al[65], showed complete response in 44% of patients treated with CCRT. Ishida K et al[62] noted an overall response rate of 78.3% with CCRT.

Late treatment response

In the present study, the median follow-up of study-arm was 15 months and 13 months in control-arm. The median progression free survival (PFS) was 16 months for the patients in study arm and 13 months for the patients in control arm.The number of patients surviving without disease was 2 out of 27 patients (7.4%) in study arm and 1 out of 28 patients (3.5%) in control-armrespectively.Number of patients surviving with disease was 23 out of 27 patients (84.2%) in study arm Vs 24 out of 28 patients (85.7%) in the control-arm. Number of overall survivor was 25 out of 27 patients (91.6%) in the study-arm and 25 out of 28 patients (89.2%) in the control arm. Survival curve analysis shows statistically significant difference of PFS in between the arms supporting CCRT.

Findings in our study is comparable to the findings of a study done by Chen F et al[57] who showed thatthe median progression free survival (PFS) was longer in the CCRT group (18.7 months)comparing to the RT group (14.6 months) ($P = 0.026$). Torrente S et al[59] showed CCRT increases PFS, complete response (CR), partial response (PR) but at the expense of increase toxicity. In their study they found survivor with disease was 69% with CCRT which was comparable to our study results.In a study findings by Zhao Q et al[23], in the CCRT group, the median PFS was 15.3 months, while 10.6 months in the RT group (P=.008).Cooper JS et al[20] confirmed thatCCRT significantly increased progression free survival compared with RT alone.

Early side effects

In our study frequently observed haematological toxicities were leucopenia, thrombocytopenia, and haemoglobin toxicity. Fourteen patients of the 27 evaluable patients in study arm and 12 patients out of 28 in control arm showed Grade 3 leucopenia.The incidence of Grade 3 leucopenia was 52% and 43.4% in study and control arm respectively, this difference was statically significant. Compareable thrombocytopenia were observed in the both arms; study-arm (75%) and control-arm (73%). In one similar study of CCRT by Wong RK et al[63], Grade-3 leucopenia were observed in 50% in study group and 40% in control group respectively. Increased but manageable toxicities in our study are supported by few studies of Zang Zet al[69]and ShinodaM et al[67].

Among the non haematological toxicities, Grade-2 esophagitis was observed in 44.4% in study-arm and 7.1% in control-arm, Grade-3 esophagitis in 20% of study arm and 3.5% in control arm. Grade-2 nausea/vomiting was seen in 75% of patients in study arm 73% in control arm and Grade-2 odynophagia noted 74% of patients in study arm and 46.4% of patients in control arm. Grade 2 fatigue occurred 63% in study arm and 35.7% in control arm. The differences of non-haematological toxicities were statistically significant ($p<0.05$) excluding nausea and vomiting.

Grade-2 esophagitis (44.4% and 7.1%) in study and control arm supported by ZangZ et al[69] and Nishimura Y et al[30]. Results of Grade-2 odynophagia in our study are supported by ShinodaM et al[67], in their study they found 73% in study arm and 39% in control arm. Chen F et al[57] reported in his study that acute toxic effects were more with CCRT group.

Late side effects

In our study, in the post treatment follow-up, 4.3% and 4.1% radiation induced stenosis were observed in study-arm at 9th and 12th months while there were 10% and 4.3% noted at 9th and 12th months in control-arm. In addition there was 1 case of lung fibrosis observed in control-arm at 12 months and remain till last 15th months of follow-up. Myelitis was noted in the study-arm in 4.1% of patients and in control-arm 8.6% of patients.

Ohtsuet al[70] reported 4 cases of oesophageal perforation in their study in contrast to our study, where we noted none. Similar to our study Adelstein DJ et al[68] reported 3 cases of radiation induced stenosis at 9 month in study-arm with CCRT and 4 cases of stenosis at 9 monh in control-arm with RT alone.In the meta-analysis by Wong RK et al[63], there was no difference in late toxic effects in CTRT and RT alone arm and no deaths were noted.

VII. CONCLUSION

In our study, 27 patients out of 30 in study arm and 28 patients out of 30 in control arm were evaluable. In the study arm 12 patients (45%) showed complete response compared to 9 patients (35%) in control arm

showing significant benefit in achieving complete response among patients in study group (p= .031). Partial response was found in 10 patients(40%) in study arm and 9 patients(32%) in control arm.

Difference of early treatment response in both arms were statistically significant. More acute haematological toxicity was leucopenia followed by anaemia, leucopenia was more in study group. Grade 2 esophagitis and odynophagia were significant in both study and control arm. The difference of early and late treatment side effects in between both the arms were statistically significant. The progression free survival was longer among people treated with CCRT compared to RT alone, which was statistically significant. Thus, in our study, patients treated with CCRT regime using oral capecitabine were associated with increased treatment response with increased manageable toxicities.

Small sample size and the short follow up were the limitation of our study. Therefore, longer follow up with bigger sample size may be needed for drawing further conclusion.

VIII. SUMMARY

This study was a randomized, prospective study, undertake during the period of 1st August 2018 to 31st July 2020 in the department of Radiation Oncology, Regional Institute of Medical Sciences, Imphal, to compare treatment responses and treatment related toxicities between CCRT using oral capecitabine versus radiotherapy alone in the management of inoperable esophageal carcinoma in elderly patients.

Only patients, who were previously untreated, with Karnofsky performance score of 60% and above, and adequate haematological function, normal kidney function and liver function tests, were taken up. Patients with presence of 2nd malignancy, distant metastasis, medical co-morbidity, psychosis and age > 75 years of age were excluded. Informed concent were taken from all patients before giving treatment.

After thorough out evaluation, patients were randomly allotted to two arms viz.study arm and control arm by block randomization technique. Single blinding was used in the study for patients allocation. Altogether 60 patients were enrolled, 30 each for the study and control arms. The characteristics of patients accrued in both the arms were comparable.

In our study, results, with a median follow-up 15 month of study group and 13 month of control group were available. Our study results shows CCRT using oral capecitabine versus RT alone was comparable. The dose of Capecitabine was chosen 825mg/m^2, twice daily after meal within 30 minutes for 7 days/week from Day 1 till the end of treatment. Radiation dose of 50Gy over 25# to assess the response and side effects there-of and progression free survival using CCRT as the sole treatment modality.

RECIST criteria was used in the analysis of early treatment response and Kaplan Meier survival curves were used for analysis of late treatment responses. Early side effects and late treatment side effects were measured as per RTOG criteria. In the present study, it was found that there was statistically significant improvements in the early and late treatment response in the study arm compared with control arm. There were significant increase in the early treatment haematological side effects (leucopenia, anaemia) in study-arm and non haematological early side effects (esophagitis, odynophagia, fatigue) were also more common in study-arm. Late side effects(radiation induced stenosis, myelitis) were more common in control arm than study arm.

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Dr. Purnima Rani Ghosh, et. al. "A comparative study of concurrent chemoradiation using oral capecitabine versus radiotherapy alone in the management of inoperable esophageal carcinoma in elderly patients." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(10), 2022, pp. 03-31.