ORIGINAL RESEARCH PAPER

Oncology

KEY WORDS: esophageal cancer, chemoradiotherapy, toxicity, quality of life.

NEOADJUVANT CHEMORADIOTHERAPY IN ESOPHAGEAL OR GASTRO-OESOPHAGEAL JUNCTION CANCER

Dr. Prema. K R Associate Professor in Radiotherapy, Government Medical College, Thrissur, Kerala.

Dr. Shinto Rajappan* Junior Resident, Government medical college Thrissur *Corresponding Author

Dr. R. Mahadevan Professor in radiotherapy, Government medical college Thrissur

ABSTRACT

Background: Esophageal cancer is a serious malignancy with regard to mortality and prognosis. The incidence of squamous cell carcinoma is increasing in the developing countries and adenocarcinomas in the developed countries. Although modest improvements in survival have been achieved by combining neoadjuvant chemoradiation and surgery in resectable esophageal cancer, patients treated with chemoradiation alone or surgery alone have high locoregional relapse rate and high mortality rate.
Materials and methods: A single arm prospective study was conducted at Government Medical College, Thrissur, India during the period 2013- 2015, with a total of 22 patients with primary resectable esophageal or esophagogastric junction cancers. The aim of the study was to assess the response of preoperative chemoradiation, and acute toxicities of this treatment.
Results: Preoperative chemoradiation has resulted in downstaging of primary disease in 81.82% of patients with acceptable grade1 and grade 2 toxicities and minimum number of grade 3 toxicity during treatment. Pathological complete response in 22.7%, and moderate pathological response in 50% patients was obtained.
Conclusion: Neoadjuvant concurrent chemoradiotherapy is found to be an effective modality of treatment in stage 2 and stage 3 esophageal cancer in terms of downstaging and further surgery, with acceptable toxicity, and also improving the quality of life after treatment, and improving the survival.

INTRODUCTION

Esophageal carcinoma accounts for approximately 6% of all gastrointestinal malignancies, most cases occur in males, at a rate of 4:1 relative to females. The incidence of esophageal carcinoma varies according to geography. Squamous cell carcinoma and adenocarcinoma are the common pathological types (1). Adenocarcinoma of the distal esophagus predominates in the west, whereas squamous cell carcinoma, which tends to localise in the middle and upper thoracic esophagus predominates in the east. Alcohol and tobacco use are the major risk factors for squamous cell carcinoma, and is associated with low socioeconomic status, accounting for 80% to 90% of cases (2). Risk factors for adenocarcinoma are obesity, longstanding reflux leading to Barrett's esophagus (GERD) (3). Since both histological types present as different diseases in terms of epidemiology, pathogenesis and tumor biology, a "Surveillance, Epidemiology, and End- results"(SEER) study of 4753 patients revealed no difference in prognosis between the two types(4).

Surgery:

The controversy regarding the optimal surgical approach for esophageal cancer remains unresolved. Trans-hiatal esophagectomy and trans-thoracic esophagectomy were associated with high local recurrence rate and poor overall survival - 34% for trans-hiatal and 36% for trans-thoracic resection (5). Many previous reports have shown the superiority of extended lymph node dissection over two-field lymph node dissection, 5-year survival was better with 3-field(64.8%) than 2-field dissection(48.0%)(6,7,8,9). However 3 field lymph node dissection is not always considered a standard procedure in western countries (10), particularly in adenocarcinoma of esophagogastric junction. This is mainly due to high frequencies of systemic and local tumor recurrence. Hence multimodality treatment with chemoradiation followed by surgery has the potential to down-stage the disease, to increase the rate of complete resection with negative circumferential margins and to eradicate occult micrometastatic disease. Thus concurrent chemo radiation followed by surgery appears to have better long-term results also.

Neoadjuvant Chemoradiation: The role of neoadjuvant chemoradiotherapy has been debated for several decades. The rationale for trimodal therapy, chemoradiotherapy followed by surgery, is based on the pattern of both local and distant failure associated with surgery alone and chemoradiotherapy without surgery, which are the two treatment options established as standards of care based on data from randomized controlled trials. Two Intergroup trials showed higher rates of local failure (44% and 53%) among chemoradiotherapy alone group (11,12). Recently, a large-scale randomized trial (CROSS STUDY) from the Netherlands has shown that preoperative chemoradiation with carboplatin, paclitaxel and radiotherapy 41.4Gy improves survival of patients with potentially curable esophageal cancer (13). The median overall survival was 49 months in the preoperative chemoradiation plus surgery group, versus 24 months in the surgery only group. In addition two meta-analyses have demonstrated improvement in pathological response rate, local and regional control and 3 year overall survival, in preoperative chemoradiation + surgery group (14, 15). Multiple randomized trials have directly compared surgery with or without preoperative chemoradiotherapy for patients with potentially resectable esophageal carcinoma

;- results are summarised in the table no 1(13 ,16, 17, 18, 19, 20). Two of the studies demonstrate a significant survival benefit from combined modality therapy, both using a concurrent preoperative chemoradiation, followed by surgery (19, 20).

Table No. 1

Study	Median follow - up (year)	Regimen	Number of Patients	Pathologic Complete Response %	Three - Year Survival
Urba et al.[17] (Michigan)	8.2	5-FU-CDDP-Vinb/45 GySurg	50 50	28 -	CMT/Surg:30% Surg alone: 16%
Bosset et al.[16] (EORTC)	4.6	CDDP/37 GySurg	143 138	20 -	CMT/Surg:33% Surg alone: 36%
Walsh et al.[19] (Ireland)	1.5	5-FU-CDDP/40 GySurg	58 55	22 -	CMT/Surg:32% Surg alone: 6%
Burmeisteret al.[18] (Austria)	5.4	5-FU-CDDP/35 GySurg	128 128	16 -	CMT/Surg:35% Surg alone: 31%

Tepper et al.[20] (USA)	6.0	5-FU-CDDP/50 GySurg	30 26	40 -	CMT/Surg:39% Surg alone: 16% (5 Years)
Van Hagen et al.[13] (Netherland)	3.8	Pac-Carbo/41.4 GySurg	180 188	29 -	CMT/Surg:58% Surg alone: 44%

TOXICITY:

The toxicity of chemoradiotherapy depends on total dose of radiation, what technique is used, and whether the patient has received chemotherapy. Most common acute toxicities are esophagitis, nausea/vomiting, fatigue, and anorexia, commencing 2 to 3 weeks after the start of radiation therapy; Anaemia, neutropenia may also be seen 3 to 4 weeks after starting chemoradiation. Majority are grade 1 and grade 2 toxicities. The incidence of acute grade 3 toxicity was 25%, and grade 4 toxicity was 3% (11,21). Other toxicities are alopecia and peripheral neuropathy due to addition of chemotherapy along with radiation. Fistula may also occur rarely during radiotherapy, due to perforation, which is a life- threatening toxicity. Moderate to severe and even life-threatening toxicities have been reported in 50% to 66% of patients in one of the study(11). The most common late effects following radiotherapy are stenosis and stricture. The incidence of stricture in patients receiving radiation alone or chemoradiation is 20% to40% in modern series and up to 60% in historical series (22). The incidence of stricture is lower(12%) in series in which careful radiation technique is used(23). The incidence of stricture and fistula is also reduced by removing irradiated portion of esophagus in surgery after chemoradiation. Radiation pneumonitis is a relatively common pulmonary complication, which occurs 2 to 6 months after radiotherapy completion. In patients undergoing 3D and IMRT radiation therapy, only 5% and 1% experienced grade 3 and grade 5 radiation pneumonitis, respectively (24). The incidence of long term cardiac toxicities such as pericarditis, pericardial effusion occur with median onset time of approximately 5 months. This depends on total dose of radiation, volume of heart irradiated and dose per fraction. TD5/5 of heart is about 60GY when 25% or less of heart is irradiated and 45Gy if 65% of the heart is irradiated, assuming 2Gy per fraction. So minimization of lung and heart volume irradiation is important in the preoperative radiation planning to reduce toxicity.

AIM OF THE STUDY.

To assess response of preoperative chemoradiotherapy in oesophageal or esophagogastric junction cancer, and also assessing the acute toxicities of the treatment.

MATERIALS AND METHODS:

This single arm prospective study was conducted at Government Medical College, Thrissur, Kerala during the period of 2013 - 2015. 22 newly diagnosed patients with histologically confirmed carcinoma of esophagus or esophagogastric junction, with performance status ECOG 0-2 are included in this study. Diagnostic workup include esophagogastroduodenoscopy and biopsy, CECT chest and abdomen. Patients with tumors of clinical stage T1N1 or T2-3 N0-1M0, both squamous cell carcinoma and adenocarcinoma aged 18 to 70 years are included. Cases with tracheo-esophageal fistula, serum creatinine >1.5mg|dl, absolute dysphagia, tumors extending to within 5 cms below the upper esophageal sphincter, type2 and type 3 gastroesophageal junction tumors are excluded from the study. All patients were treated with external beam radiation on cobalt machine, for a total dose of 41.4Gy in 23 fractions of 1.8Gy each with five fractions per week. The gross tumor volume was defined by the primary tumor and enlarged regional lymph nodes seen in the CECT scan. GTV + 4cm proximal and distal margins are included in the planning target volume. In case of tumor extension into stomach, a distal margin of 3cm is included in the planning target volume. 2 cm radial margins around the GTV is the lateral margin of the PTV. Parallel opposed anteroposteror and posteroanterior fields are used for treatment.

Concurrent chemotherapy was given on days 1, 8, 15, 22 and 29 with carboplatin (targeted at an area under the curve of 2mg/mm/minute) and paclitaxel 50mg/m2 of BSA. All the patients were monitored weekly during the course of chemoradiation for assessing the toxicity. The patients were further evaluated with CT scan after four to six weeks, disease status assessed and operable patients were sent for surgery. Histopathological reports of these patients were collected and pathological response were assessed. These patients were followed up for one year. The SPSS software (version16.0) was used to analyse the data. Toxicity was graded according to National cancer institute common terminology criteria for adverse effect version4.0 (CTCAE).

RESULTS

A total of 22 cases of carcinoma esophagus or esophagogastric junction were studied. Out of this 17(77.3%) are males and 5(22.7%) females. Majority of our patients belong to low socioeconomic status (81.8%).The age group ranged from 35 to 70 years. Only 3 patients (13.64%) belonged to the age group 35 to 50 years, 6 patients (27.27%) belonged to the age group 50 to 60 years, and 13 patients in the age group 60 to70 years. Commonest symptom was dysphagia and weight loss (20 patients-90.9%), and gastroesophageal reflux was present in only 50% patients (n=11). In this study patients with esophageal malignancy were17 (77.3%), and esophagogastric junction tumors were 5(22.7%). 4 patients had adenocarcinoma and 18 patients had squamous cell carcinoma. 50% of our patients belong to stage 2, and 50% belong to stage 3 disease. During concurrent chemoradiotherapy anaemia and neutropenia were seen developing after 3 weeks and increasing up to 6 weeks. Grade1 anaemia in 4.55% patients at 3 weeks and it increased to 31.82% at 6 weeks. As the treatment continued, grade 1 alopecia was seen in almost all patients. Only 2 patients (9.09%) developed grade 2 neutropenia, 15 patients (68.18%) had grade1 neutropenia. There was no grade 3 or grade 4 haematological toxicity seen in our patients. GI toxicities such as esophagitis, nausea, vomiting, anorexia and fatigue started at 3 weeks and maximum at 6 weeks at the end of chemoradiation, and only 6 patients developed grade 3 esophagitis and grade3 fatigue at 6 weeks .The occurrence of toxicities are given in the table no.2.

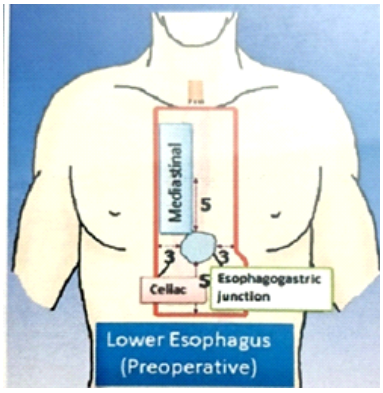


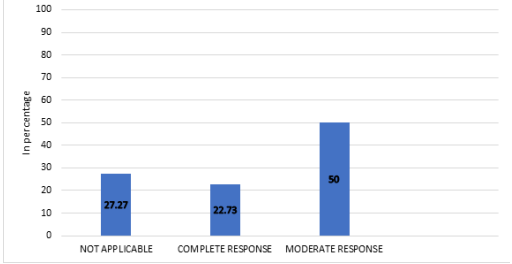
Table No 2

Toxicity	Grade I		Grade II		Ggrade III Week 6
	Week 3	Week 6	Week 3	Week 6	
Anaemia	4.55%	31.82%	-	-	-
Neutropenia	4.55%	68.18%	-	9.09%	-
Nausea	40.91%	72.73%	-	4.55%	-
Vomiting	31.82%	63.64%	-	18.18%	-
Esophagitis	68.18%	-	31.82%	72.73%	27.27%
Fatigue & Anorexia	50%	13.64%	45.5%	63.64%	22.73%
Peripheral Neuropathy	4.55%	31.82%	-	-	-
Alopecia	4.55%	95.45%	-	-	-

Peripheral neuropathy was seen in only 7 patients (31.82%), which is only grade 1 and it appeared after 3 weeks. Contrast Enhanced CT scan was taken 6 weeks after radiation treatment. In this study two patients(9.09%) showed complete remission, where their contrast enhancing CT scan were normal and patients had no dysphagia. 16 patients had partial remission with contrast

enhancing CT scan showing residual disease, but symptomatically no dysphagia. Of this 7 patients (31.82%) with stage2 disease were down-staged to stage1, and 9 patients(40.9%) with stage 3 were down-staged to stage 2 disease after chemoradiotherapy. In this study 2 patients showed primary disease progression and 2 patients had lung metastasis and found inoperable and they were sent for palliative chemotherapy. Post CCRT down-staging was possible in 18patients (81.82%) in our study, and sent for surgery. Out of these, two patients were not willing for surgery and they were also kept under follow up. Postsurgical histopathological examination shows pathological complete response in 5 patients(22.7%), and moderate response in 11 patients(50%), with R0 resection in all operated patients(72.7%). Details are given in figure no 1. They were followed up for one year. One patient with inoperable disease died of progressive disease three months after completion of chemoradiotherapy. 21 patients (95.45%) alive after one year.

FIGURE 1: Graph showing pathological response rate



DISCUSSION:

Preoperative chemoradiotherapy followed by surgery is now considered the standard for stage 2 and stage 3 cancer of esophagus and gastroesophageal junction cancers. This strategy has been shown to achieve radiological and pathological down-staging and increased overall survival as well as to improve the quality of life in such patients. In this study majority are males (77.3%) and 22.7% are females, and majority are smokers (72.7%). In other studies also the percentage of males ranged from 78% (25) to 93% (16, 26). So this may be due to increased incidence of alcoholism and smoking in Indian males (27). 13 patients were between 60 and 70 years of age (59.09%). It is well known that carcinoma of the esophagus is a disease predominantly seen in the elderly (28). In this study 22.7% patients had tumors in the esophagogastric junction as in the CROSS trial(13).The number of squamous cell carcinomas in this study was higher (81.8%) than adenocarcinoma(18.2%)(29).Where as in other two studies adenocarcinomas are more than 70% (13,20).This may be due to increasing incidence of adenocarcinoma in western countries. Radiological downstaging achieved in 81.82% of cases, which is similar to other studies (13,20). Pathological downstaging was possible in 72.7%of cases. In this study, complete pathological respose in 22.73% of patients, which is more than in certain other studies where complete pathological respose is between 16-19%(16,18). In our study 68.8% shows grade1 neutropenia, 9.09% had grade 2 neutropenia. No grade 3 or grade4 neutropenia reported. But another study noted grade3 neutropenia in 15%, and grade 4 neutropenia in 12% of patients (20). Certain other studies also reported grade 3 neutropenia in 2%, leucopenia in 60%(13) and 9% had grade 2 neutropenia in other study(27). In this study 27.7% of patients had grade 3 esophagitis which is similar to another study where 27% had grade 3 esophagitis(20). The toxicities like anorexia, and fatigue are comparatively less in other studies (13,28). This is due to poor nutritional status of Indian population, when compared to western population. Only grade2 nausea is reported in this study, whereas grade3 nausea is reported(11%) in other study(20).

CONCLUSION:

Neoadjuvant chemoradiation in esophageal or esophagogastric junction cancers is associated with radiological and pathological down-staging in majority of our patients, with acceptable levels of toxicity .No grade 4 toxicity reported in this study. Overall survival at one year was 95.45%. But longer duration of follow up is needed to clearly assess the loco regional control of disease, long term toxicities and survival of these patients, for designing appropriate treatment strategies.

REFERENCE

1. Enzinger PC, Mayer RJ. Esophageal cancer. N Eng J Med. 2003; 349: 2241-2252.
2. Ozel,Matsuo K, Wakai K, Nagata C,Mizoue T, Tanaka K, Tsuji I, Sasazuki S, Inoue M, Tsugane S. Alcohol drinking and esophageal cancer risk:an evaluation based on a systematic review of epidemiological evidence among the Japanese population. Jpn J ClinOncol. 2011; 41: 677- 692.
3. Vid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch- Jensen P. Incidence of adenocarcinoma among patients with barrettsesophagus. N Engl J Med. 2011; 365:1375- 1383.
4. Chang DT, Chapman C,Shen J, Su Z, Koong AC. Treatment of esophageal cancer based on histology , a surveillance epidemiology and end results analysis. Am J ClinOncol. 2009; 32: 405- 410.
5. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of mid/ distal esophagus: five year survival of randomized clinical trial. Ann Surg 2007; 246(6): 992.
6. Baba M, Aikou T, Yoshinaka H, et al. Long term results of subtotal esophagectomy with three field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg. 1994;219: 310-316.
7. Tachibana M,KinusagaS,Yoshimura H et al. Clinical outcomes of extended esophagectomy with three field lymph node dissection for esophageal squamous cell carcinoma . Am J Surg 2005; 189:98- 109.
8. Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. Am J Surg 1998; 175: 47-51.
9. Udagawa H, Ueno M, Shinohara H, et al. The importance of grouping of lymph node stations and rationale of three field lymphadenectomy for thoracic esophageal cancer. J SurgOncol 2012; 106: 742-747.
10. Grotenhuis BA,VanHeijl M, ZehetnerJ,et al. Surgical management of submucosalesophageal cancer: extended or regional lymphadenectomy? Ann Surg 2010; 252: 823- 830.
11. Herskovic A, Martz K, Al-sarraf M, et al.Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus.NEng J Med 1992; 326(24):1593.
12. Minsky B, Pajak T, Ginsberg RJ et al.INT 0123(Radiation therapy oncology group 94-05) phase 3 trial of combined modality therapy for esophageal cancer: high dose versus standard dose radiation therapy. J ClinOncol 2002;20(5): 1167
13. Van Hagen P, Hulshof MC,VanLanschot JJ, et al.Preoperativechemoradiotherapy for esophageal or junctional cancer. N Eng J Med 2012; 366: 2074.
14. Urschel JD, Vasan H. A metaanalysis of randomized controlled trials that compared neoadjuvantchemoradiation and surgery to surgery alone for resectableesophageal cancer. Am J Surg 2003;185: 538-543.
15. Fiorica F, Di BonaD, Schepis F, Licata A, Shahied L, Venturi A, F alchi AM, Craxi A,C amma C. Preoperative chemoradiotherapy for esophageal cancer: a systematic review and meta-analysis. Gut. 2004; 53: 925-930.
16. Bosset JF, GignouxM,Triboulet JP, et al.Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. N Eng J Med 1997; 337: 161.
17. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregionalesophageal carcinoma. J ClinOncol 2001; 19: 305.
18. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemotherapy followed by surgery for resectable cancer of the esophagus: a randomized controlled phase 3 trial. Lancet Oncol 2005; 6: 659.
19. Walsh TN, Noonan N, Hollywood D,et al. A comparison of multimodal therapy and surgery for esophagealadenocarcinoma.NEngl J Med 1996; 335: 462.
20. Tepper J, Krasna MJ, Niedzwiecki D, etal.Phase 3 trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J ClinOncol 2008; 26: 1086.
21. Al- sarraf M, Martz K, Hersovic A, etal.Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J ClinOncol 1997; 15: 277.
22. Minsky BD. The Adjuvant treatment of esophagealcancer.SemRadiatOncol .1994; 4: 165 23.Coia LR, Soffen EM, SchulteissTE,et al. Swallowing function in patients with esophageal cancer treated with concurrent radiation and chemotherapy. Cancer 1993; 71: 281.
24. Hart JP, McCurdy MR, Ezhil M, et al. Radiation pneumonitis correlation of toxicity with pulmonary metabolic radiation response. Int J RadiatOncolBiolPhys 2008;71:967-971
25. Apinoop C,Puttisak P, Preecha N. A prospective study of combined therapy in esophageal cancer. Hepatogastroenterology1994; 41: 391-393.
26. Le Prise E, Etienne PL, MeunierB,et al. A randomized study ofchemotherapy , radiation therapy, and surgery versus surgery for localised squamous cell carcinoma of the esophagus. Cancer 1994; 73:1779.
27. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al.Cancerstatistics, 2008. CA Cancer J Clin 2008; 58: 71-96.
28. Annual report 2012 National Cancer Registry Program New Delhi; Indian Council Of Medical research, 2014.
29. Oota K,Shin L. Histological typing of gastric and esophagealtumors.Geneva: World Health Organization, 1977.