ORIGINAL RESEARCH PAPER

NEOADJUVANT CHEMORADIOThERAPY IN ESOPHAGEAL OR GASTRO-OESOPHAGEAL JUNCTION CANCER

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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 grade 1 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 4.1:1 relative to females. The incidence of esophageal carcinoma varies according to geography. Squamous cell carcinoma and adenocarcinomab 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 pathological 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 chemoradiation 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 trimodality 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.

Table No. 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow - up (year)</th>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Pathologic Complete Response %</th>
<th>Three - Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urb et al. (Michigan)</td>
<td>8.2</td>
<td>5-FU-CDDP-Vinb/45 GySurg</td>
<td>50</td>
<td>28</td>
<td>CMT/Surg:30% Surg alone: 16%</td>
</tr>
<tr>
<td>Bosset et al. (EORTC)</td>
<td>4.6</td>
<td>CDDP/37 GySurg</td>
<td>143</td>
<td>20</td>
<td>CMT/Surg:33% Surg alone: 36%</td>
</tr>
<tr>
<td>Walsh et al. (Ireland)</td>
<td>1.5</td>
<td>5-FU-CDDP/40 GySurg</td>
<td>58</td>
<td>22</td>
<td>CMT/Surg:32% Surg alone: 6%</td>
</tr>
<tr>
<td>Burmeister et al. (Austria)</td>
<td>5.4</td>
<td>5-FU-CDDP/35 GySurg</td>
<td>128</td>
<td>16</td>
<td>CMT/Surg:35% Surg alone: 31%</td>
</tr>
</tbody>
</table>
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% to 40% 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. TDS/5 of heart is about 65Gy 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 T1N0 or T2 N0-M0, both squamous cell carcinoma and adenocarcinoma aged 18 to 70 years are included. Cases with tracheo-oesophageal fistula, serum creatinine >1.5mg/dl, absolute neutropenia, esophagitis, nausea/vomiting, fatigue, anorexia and 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 anteroposterior 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/m2/minute) and paclitaxel 50mg/m2 of 8SA. 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 version 4.0 (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 to 70 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 were 17 (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 chemoradiation, anaemia and neutropenia was seen developing after 3 weeks and increasing up to 6 weeks. Grade 1 anaemia in 4.55% patients at 3 weeks and it increased to 31.82% at 6 weeks. As the treatment continued, grade 1 anemia was seen in almost all patients. Only 2 patients (9.09%) developed grade 2 neutropenia, 15 patients (68.18%) had grade 1 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 grade 3 fatigue at 6 weeks. The occurrence of toxicities are given in the table no.2.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 3</td>
<td>Week 6</td>
<td>Week 3</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4.55%</td>
<td>31.82%</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4.55%</td>
<td>68.18%</td>
<td>9.09%</td>
</tr>
<tr>
<td>Nausea</td>
<td>40.91%</td>
<td>72.73%</td>
<td>4.55%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31.82%</td>
<td>63.64%</td>
<td>18.18%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>68.18%</td>
<td>-</td>
<td>31.82%</td>
</tr>
<tr>
<td>Fatigue &amp; Anorexia</td>
<td>50%</td>
<td>13.64%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>4.55%</td>
<td>31.82%</td>
<td>-</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4.55%</td>
<td>95.45%</td>
<td>-</td>
</tr>
</tbody>
</table>

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 stage 1, and 9 patients(40.5%) 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. Post-surgical 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.

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 adenocarcinoma 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 response 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 neopetuna, 9.09% had grade 2 neopetuna. No grade 3 or grade4 neopetuna reported but another study noted grade3 neopetuna in 15%, and grade 4 neopetuna in 12% of patients (20). Certain other studies also reported grade 3 neopetuna in 2%, leucopenia in 60%(13) and 9% had grade 2 neopetuna in other study(27). In this study 27.7% of pathological response is grade 2 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: