ORIGINAL ARTICLE

Neoadjuvant Concurrent Chemoradiation in Locally Advanced Adenocarcinoma of Gastroesophageal Junction & Proximal Stomach (A Single Arm Study): Our Experience From Single Institute From Kashmir Valley

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Abstract

Introduction: The aim of this study was to investigate the efficacy and safety of using a neo-adjuvant concomitant chemoradiation therapy to treat potentially resectable adenocarcinoma of the gastroesophageal junction & proximal stomach. **Methods:** Thirty-nine patients having potentially resectable adenocarcinoma at the gastroesophageal junction & proximal stomach were recruited in this study to investigate the efficacy and safety of using a neoadjuvant concomitant chemoradiotherapy followed by surgery. Radiation Therapy was performed with a total of 41.4 Gy delivered in 23 sessions (05 fractions/week) along with weekly concurrent chemotherapy (Paclitaxel 50mg/m2 & Carboplatin AUC-2). **Results:** Of 39 patients, 38 completed the neoadjuvant concurrent chemoradiation without any severe grade 3-4 toxicities. After completion of the therapy, 89.7% had a significant endoscopic response. Thirty five patients underwent surgery and all patients had an R0-resection. The pathological complete response rate was 14.7%. The maximum & minimum follow ups who completed the treatment protocol (neoadjuvant chemoradiation followed by surgery) reported was 16 & 02 months respectively. 02 patients recurred locally and 01 patient relapsed in bones. Overall one year survival was 91.3%.**Conclusion:** The integration of neoadjuvant concurrent chemoradiation is highly effective over preoperative chemotherapy or surgery alone with acceptable toxicity rates.

Key Words

Gastroesophageal Junction Adenocarcinoma, Neoadjuvant Chemoradiotherapy, Combined Modality Therapy

Introduction

Gastroesophageal cancers (such as oesophageal, gastric & esophagogastric lesions) are usually highly aggressive in nature and hence, account one of the leading cause of cancer related mortality worldwide. There is an increasing trend of oesophageal & esophagogastric adenocarcinoma (EGJ) type of tumours in many Western countries. [1, 2] Surgery is the main therapeutic modality that may cure patients, however, majority of the patients (especially locally advanced stage) develop recurrences soon and expire within two years after surgical resection. The reason for high mortality is due to late presentation with locally advanced tumour stage, where complete surgical resection is not possible (R0 resection) in significant number of patients and lymph node metastases were observed in almost all the patients. [3-5] Neoadjuvant concurrent Chemoradiation has been reported superior to surgery alone in esophagogastric cancer. [6-8] It has been reported that there is improvement in survival by using neoadjuvant chemoradiotherapy in adenocarcinoma of the oesophagus & gastroesophageal junction as compared to preoperative chemotherapy alone, but there are higher risks of increased operative mortality. [9-10] Based on the evidences from above mentioned studies, we proceeded to investigate the efficacy and safety of

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using a neoadjuvant concomitant chemoradiotherapy to treat adenocarcinoma of the gastroesophageal junction & proximal stomach (Sievert II & III) at our centre (SKIMS Srinagar). Hence, the primary objectives of the study were to evaluate the efficacy and safety of neo-adjuvant chemoradiation in resectable gastroesophageal junction adenocarcinomas (sievert I, II & III) in terms of pathological response, resectability at the time of surgery after neoadjuvant concurrent chemoradiotherapy, survival outcome & toxicities of treatment modalities.

Materials & Methods

This prospective study was conducted in the department of radiation oncology, SKIMS Srinagar from September 2013 to May 2015 and was started after clearance from the Institutional Ethics Committee (Sher-i-Kashmir Institute of Medical Sciences, SKIMS Srinagar). Patients having resectable adenocarcinoma at the gastroesophageal junction & proximal stomach (stage II & III) were recruited in this study and were treated with neoadjuvant concomitant chemoradiotherapy followed by surgery.

Eligibility criteria :Patients with histologically confirmed adenocarcinoma esophagogastric junction (stage II & III) were included in this study. A total of thirty nine patients aged 18-80 years having Eastern Cooperative Oncology Group (ECOG) performance status of <2 with adequate hepatorenal, cardiac, haematological & pulmonary functions were studied after taking written informed consent from each study patient. Patients with synchronous second primary or past history of malignancy, poor performance status (ECOG PS >2 and stage I/IV were excluded.

Pre-treatment evaluation

All patients were evaluated with complete history & physical examination, baseline investigations, upper gastrointestinal (GI) endoscopy with biopsy and a contrast CT of the chest, abdomen and neck.

Treatment :Chemotherapy:Paclitaxel 50 mg/m2 & Carboplatin AUC 2 was given by intravenous infusion on days 1, 8, 15, 22, and 29. The total calculated dose of Paclitaxel was diluted in 500 ml of normal saline and infused over one hour. It was followed by the administration of carboplatin infusion over ½ hour which was diluted with 500 ml of Dextrose 5%. The absolute dose of carboplatin was calculated for the target AUC 2 according the following formula: the absolute dose of Carboplatin = [target AUC] x (GFR + 25). All patients were premedicated with Dexamethasone 8mg, Chlorpheniraminemalaete 15 mg, Ranitadine 50 mg & Ondansetron 8mg half an hour before the start of chemotherapy. Dose modifications were made for toxicity, using the National Cancer Institute - Common Toxicity Criteria (NCI-CTC version 4.0).

Radiotherapy: All patients were treated by external beam radiation, using 2-D radiation techniques. Prior to start of the radiation therapy, a planning CT scan was done in all patients in supine positions from the cricoids to second lumber vertebra with a slice thickness of 5 mm. A total dose of 41.4 Gy was given in 23 fractions, 1.8 Gy per fraction, 05 fractions per week, started on first day of the first cycle of chemotherapy & was delivered by anteroposterio/posteroanterior portals with cobalt 60 teletherapy equipment.

Surgery: Surgery was planned within 6-7 weeks after the completion of the chemoradiation. Surgical procedures performed were transabdominal esophagogastrectomy with R0 resection along with D1 or D2 lymph node dissection and patients were closed back in layers giving subhepatic drain. Orals were started 4-5 days after surgical intervention.

Restaging and follow-up: Upper GI endoscopy and CT of the chest and upper abdomen were repeated 5-6 weeks after the completion of the chemoradiation. Follow-up visits were performed every 2 months during the first year and every 4 monthly in second year. During follow up, the main intention was given towards the recurrence & toxic effects.

Statistical analysis

The categorical variables of the study have been shown in frequency and percent, while as, continuous variables in terms of descriptive statistics. Also, the appropriate statistical charts have been made to represent the data graphically.

Results

Patient characteristics: Thirty nine patients were recruited from September 2013 to May 2015 in this study. Written informed consent was obtained from all patients. Characteristics of these 39 patients are summarised in *Table 1.* Of all, 84.6% were male & 46.2% had age above 60 years. All studied patients were adenocarcinomas and had ECOG performance status < 2. The predominant presenting symptom was dysphagia and was reported in 23 (59%) of patients. Besides, 33 (84.5%) patients has tumour epicentre located in the distal oesophagus and esophagogastric junction (sievert I/II) & 06 (15.5%) in the proximal stomach (sievert III). 14 (35.9%) patients presented in stage II & 25 (64.1%) in stage III.

Clinical Response & Toxicity to Neoadjuvant Chemoradiotherapy: Upper GI endoscopy & CT chest/ upper abdomen modalities were used to assess the response after 5-6 weeks of completion of chemoradiation. As per endoscopic findings, regression in growth was seen in 35(89.7%), stable disease 01(2.6%) & Progression of growth 02(5.1%) (*Table 2*). Moreover, 01(2.6%) patient died during chemoradiation due to severe

Table 1. Baseline Patient Characteristics

Characteristic		n(%)
Age(years)	<60/ >60	18(46.2)/ 21(53.8)
Sex	Male/ Female	33(84.6)/ 06(15.4)
Performance Status(ECOG)	0	04(10.3)
	1	32(82.1)
	2	03(7.7)
Predominant Symptom At Presentation	Dysphagia	23(59)
	Upper GI Bleed	06(15.4)
	Pain Epigastrium	08(20.5)
	Generalized Weakness	02(5.1)
Tumour Localization	GE Junction	33(84.5)
	Stomach(proximal)	06(15.5)
Clinical Stage	II-A	04(10.3)
	II-B	10(25.6)
	III-A	16(41)
	III-B	09(23.1)

Table 2. Clinical staging, Endoscopic response and Resectability after neoadjuvant chemo-radiation:

Characteristic		n (%)
Clinical Stage(y_c stage)	0	01(2.6)
	I-A	06(15.3)
	I-B	01(2.6)
	II-A	05(12.8)
	II-B	19(48.7)
	III-A	03(7.7)
	III-B	02(5.1)
	III-C	01(2.6)
	Not Assessed	01(2.6)
EGD Finding	Regression in Growth	35(89.7)
	Stable Disease(No Response)	01(2.6)
	Progressive Disease	02(5.1)
	Not Assessed	01(2.6)
Resectability	Yes	35(89.7)
	No	03(7.7)
	Not Assessed	01(2.6)

Table 3: Chemoradiation induced toxicities

	Event	Grade	n(%)
Gastro-intestinal	Nausea	0/1/2/3	09(23.1)/20(51.3)/10(25.6)/0(0)
	Vomiting	0/1/2/3	18(46.1)/12(30.8)/06(15.4)/03(7.6)
	Diarrhea	0/1/2/3	35(89.7)/04(10.3)/0(0)/0(0)
	Mucosites	0/1/2/3	12(30.8)/18(46.2)/08(20.5)/01(2.6)
Hematological	Leucopenia	0/1/2/3	12(30.8)/15(38.5)/11(28.2)/01(2.6)
	Neutropenia	0/1/2/3	13(33.3)/13(33.3)/12(30.8)/01(2.6)
	Thrombocytopenia	0/1/2/3	17(43.6)/11(28.2)/09(23.1)/02(5.1)
	Anemia	0/1/2/3	20(51.2)/ 09(23)/ 05(12.9)/05(12.9)
Renal	Nephropathy	0/1/2/3	31(79.5)/07(17.9)/01(2.6)/0(0)
Neurological	Neuropathy	0/1/2/3	09(23)/30(77)/0(0)/0(0)

Table 4: Surgery and Pathologic Staging for Patients Undergoing Resection

Finding		n(%age)
Pathological Stage(y_p stage)	0/I-A/I-B/II-A/II-B/III-A/III-B	05(14.7)/14(41.1)/05(14.7)/02(5.8)/06(17.5)/01(2.9)/02(5.8)
Mandard's Score	1/2/3/4/5	05(14.4)/19(52.9)/07(20)/01(2.9)/03(8.6)
R0 Resection	Yes	30(88.3)
	No	05(11.7)
Tumour Differentiation	Well Differentiated	12(34.2)
	Moderately Differentiated	13(37.2)
	Poorly Differentiated	07(20)
	Undifferentiated	03(8.6)

neutropenic sepsis with multiorgan failure. Evaluation with CT showed disease progression in 03(7.7%), partial response in 34 patients and 01 had complete radiological response. Grade III gastro-intestinal & haematological toxicities had been reported in 04(10.2%) & 09(23.2%) patients respectively. 03(7.7%) patients complicated with chemotherapy induced alopecia. However, none of the patient complicated with grade III renal or neurological toxicity (*Table 3*). Surgical & Pathological results: 35 patients had been treated with surgery, 03 patients were deemed unresectable due to locoregional disease progression and 01 patient succumbed during chemoradiation. Postoperative complications were seen in 16 patients (43.6%). These complications were mainly pulmonary (11.4%) or wound dehiscence (8.6% (*Table 5*). Besides, 06(17.1%) complicated with anastomotic leaks. However, there was no mortality due to surgical interventions and all complications were managed conservatively. A radical resection with no evidence of tumour cells at the resection margins (R0-resection) was obtained in 30(88.3%) patients. In 05 patients, no residual tumour noted in the resected surgical specimens & corresponding to a pathological complete response (pCR) rate of 14.7%. The pathological stages of the other resection specimens were: ypIA in 14 patients (41.1%), ypIB in 05 patients (14.7%), ypIIA in 02 patients (5.8%),

Table 5. Surgery related complications

Event	n(%age)
Wound Infection	
Yes/No	03(8.6)/ 32(94.1)
Pulmonary	
Yes/No	04(11.4)/31(88.6)
Cardiac	
Yes/No	02(5.7)/33(94.3)
Mediastinites	
Yes/No	01(2.8)/34(97.2)
Anastamotic Leakage	
Yes/ No	06(17.1)/29(82.9)

Table 6: Treatment Outcome

6a) Pattern of Recurrence.

Survival	n(%age)
Completed one year follow up	19(54.3)
Completed 6 months of follow up	11(31.5)
Completed < 6 month of follow up	05(14.2)
Total	35(100)

ypIIB in 06(17.5%), ypIIIA in 01(2.9%) & ypIIIB in 02 patients(5.8%). Regression grade III, II & I was seen in 19 (52.9%), 07 (20%) and in 05 (14.4%) patients respectively (*Table 4*).

Survival :35 of total 39 recruited patients completed the treatment protocol (neoadjuvant concurrent chemoradiotherapy followed by surgery) & were available (alive) at the time of analysis. 01 patient died while receiving concurrent chemoradiation and 03 patients expired after completion of chemoradiation probably due to progression of disease. Recurrences were seen in 03(8.7%) patients. One patient progressed with skeletal metastasis and 02 recurred locally (*Table 6a*). Mean & median survivals couldn't be analysed because of shorter follow-up time & small sample size. Our maximum & minimum follow up was 16 & 02 months respectively. 19(54.3) & 11(31.5%) patients had completed twelve and six months follow up (*Table 6b)*.

6b) Survival Analysis

			n (%)
Recurrence	Yes	Local	02(5.8)
		Distant	01(2.9)
	No		32(91.3)

Discussion

Neoadjuvant chemoradiotherapy is nowadays widely used in the treatment of patients with potentially resectable oesophageal and gastroesophageal cancers.[11] The reason of using neoadjuvant therapy is to improve resectability which may lead to a better tumour control and improvement in survival. We conducted this study to verify the role of preoperative concurrent chemoradiation in potentially resectable gastroesophageal cancers in terms of resectability, response with neoadjuvant chemoradiation, survival and treatment induced toxicities. In our study, 21(53.3%) patients were less than 60 years of age. Male Female ratio reported was 5:1. Patients having good performance status (ECOG PS 0-2) were included in this study. Majority of the patients were having ECOG 1 performance status which is comparable to other studies. [12, 13] Of 39 patients, 06 were having proximal stomach lesions (sievert III) & 64.1% had clinical stage III. The predominant symptom was dysphagia which was reported in 59% patients followed by pain epigastrium (20.5%), upper gastrointestinal bleeding (15.4%) & generalized weakness (5.1%) which is almost comparable to other studies.[11, 12] All studied patients had adenocarcinoma histology which is comparable with the study done by Burmeister BH *et al*; that took only adenocarcinoma gastroesophageal lesions for multimodality treatment. [13] Chemoradiation toxicities were assessed with RTOG Common Toxicity Criteria. None of the patient developed grade IV toxicity. Generally, majority of the patients complicated with nephropathy (77%) & nausea (76.9%). However 27 patients developed Leucopoenia and was the most common haematological complication reported. In general, 10(25.6%) patients complicated with Grade III toxicities and chemotherapy was interrupted & thus, on average two cycles of chemotherapy were omitted in 14 patients due to toxicities. Complications related to surgical interventions were mainly pulmonary (11.4%) or wound dehiscence (8.6%). Besides, 06(17.1%) patients complicated with anastomotic leaks. However, there was no mortality due to surgical interventions and all events were managed conservatively. Postoperative events in this study were less as compared to CROSS Trial .[11]

Of 38 patients that completed preoperative chemoradiation, only 01 patient had complete clinical response. However, pathological complete response was seen in 05(14.7%) patients. 14.7% patients showed complete pathological response which is in contrast to the study done by Van Meertan E *et al*; and may be due

to small sample size in our study. [7] The significant down staging as a result of chemoradiotherapy had resulted in the substantially higher percentage of R0 resections (30 patients, 88.3%).However, this combination might not be highly effective for reducing the risk of distant metastases.[14] However, Zhao et al. showed in a Phase II study of 76 patients that neoadjuvant chemoradiation with Oxaliplatin+ Capecitabine + 45 Gy was associated with an increased rate of R0 resection versus surgery alone (100% vs. 80%, $p < 0.05$).[15] However, there was no survival benefit demonstrated.Using the same regimen, Tian et al. (n = 132) evaluated neoadjuvant chemoradiation(Oxaliplatin + Capecitabine + 45 Gy) vs. surgery and found an improvement in 3-year OS(63.4% vs. 52.2%, $p = 0.019$).[16] The survival in this study was not comparable with other studies because of less follow up time & small sample size. The maximum & minimum follow ups who completed the treatment protocol (neoadjuvant chemoradiation followed by surgery) were 16 & 02 months respectively. Florica F *et al.* had showed that neoadjuvant radiation improves overall survival (OR 0.62, 95% CI0.46-0.84, $p = 0.002$).[17] Another study showed that Perioperative chemotherapy appears to offer a benefit in survivaland may reduce the risk of distant disease after surgical resection (HR 0.48, 95% CI 0.35-0.67,$p < 0.001$).[18] 02 patients recurred locally and 01 patient relapsed in bones. 32(91.3%), 19(54.3%) & 11(31.5%) completed twelve, six & less than six months of follow-up. In conclusion, this study shows that preoperative treatment with weekly Paclitaxel and carboplatin with concurrent radiotherapy is well tolerated, with nephropathy and leucopoenia being the most common side effects. After chemoradiotherapy, a high rate of adequate resections (R0 resection) was possible with no severe surgery related complications.

Conclusion

In conclusion, the integration of neoadjuvant concurrent chemoradiation is highly effective over preoperative chemotherapy or surgery alone with acceptable toxicity rates.

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Conflicts of Interest

There are no conflicts of interest.

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