RESEARCH COMMUNICATION

Role of Preoperative Chemotherapy in Squamous Cell Carcinoma of Esophagus in Kashmir, a Cancer Belt - A Pilot Study

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Abstract

Background: Esophageal carcinoma is the fifth leading gastrointestinal malignancy and is one of the leading causes of cancer related death. Despite improvements in surgical technique over the last few decades, the outcome has been dismal, with overall 5 year survival not exceeding 15%-25%. Aims and Objectives: To evaluate the effect of preoperative chemotherapy on resectability, complication rate and overall survival in patients with squamous cell carcinoma esophagus. Materials and Methods: 50 patients with histologically confirmed squamous cell carcinoma (SCC), with localised or loco-regional disease (stage 4 excluded) were divided into 2 groups. Group A patients were subjected to 2-3 cycles of pre-operative chemotherapy (5FU-CDDP), whereas Group B patients were directly operated on. Observations: 3 (12%) patients in group A showed complete pathological response to chemotherapy and 18 (72%) showed a partial response, with four patients (16%) showing resistance to chemotherapy. There was no statistically significant difference in terms of response to chemotherapy with respect to degree of differentiation of tumor. There was no significant difference in the overall resectability rates between the two groups ($p>0.05$), but R0 resection was achieved in 20 (80%) of group A and only 10 (40%) of group B, the difference being statistically significant ($p<0.05$). The rate of overall complications was also much higher in the control group. Initially there was no significant difference in the survival between the two groups, but later (20 months) the study group showed a slight non-significant advantage. Conclusion: Preoperative chemotherapy significantly increases the rate of R0 resection without significantly increasing postoperative morbidity and mortality in patients with squamous cell carcinoma of esophagus. However, to assess the impact on survival the study period needs to be extended.

Keywords: Esophageal cancer - squamous cell carcinoma - pre-operative chemotherapy

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Introduction

Esophageal cancer is one of the ten most common malignancies worldwide (Parkin et al., 1999). The Kashmir region because of its geographical location is a part of the so called "Asian Esophageal Cancer Belt" (Deshpande et al., 2000), which extends from the northern provinces of China in the east to the southern shores of Caspian Sea in the west. It is one of the most common malignancies seen in the Kashmir valley with incidence reported to be in the range of 43.6/1, 00,000 population (Khuroo et al., 1992).

Surgery until recently was the mainstay in the management of esophageal cancer. However the long term survival for these patients is still less than 15% (Wingo et al., 1998) and has changed little over last several decades, despite improvements in anesthesia and refinement of surgical techniques. Even in those patients who have clinically localized disease at presentation, only < 25% survive at 5 years, with majority of these succumbing to metastatic disease (Müller et al., 1990; Daly et al., 1996).

Because of the high rates of distant and loco-regional failure, stress has been laid on the systemic therapy which will take care of the clinically inapparent metastasis (micrometastasis) and will also control the local disease preoperatively. There are reports which suggest improved resectability and survival using preoperative chemotherapy (Kelsen et al., 1983; 1986; Kies et al.,

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1987; Hilgenberg et al., 1988). Randomized controlled trials comparing preoperative chemotherapy with surgery alone (Roth et al., 1988; Nygaard et al., 1992; Schlag et al., 1992; Law et al., 1997) have, shown a significant response in 50% of patients and significant down staging in the chemotherapy group.

No study using chemotherapy in preoperative setting in patients of esophageal cancer has been reported so far from the Kashmir valley. Therefore, we designed a pilot study to evaluate the role of pre-operative chemotherapy in the squamous cell carcinoma of esophagus in our population.

Materials and Methods

This is a single institute, pilot study, in which patients of squamous cell carcinoma (SCC) esophagus were randomized into two different treatment groups. Investigators from the departments of Cardiovascular and Thoracic Surgery and Medical Oncology at Sheri-Kashmir Institute of Medical Sciences (SKIMS), a tertiary care institute in Srinagar, Kashmir, were involved in the design and conduct of this study.

A total number of 50 patients enrolled from September 2004 to October 2006 were randomly divided into two groups (A&B) of 25 each, with group A patients subjected to preoperative chemotherapy followed by surgery and group B to surgery alone. The inclusion criteria were: (i) Biopsy proven SCC of the thoracic esophagus (located below cervico-thoracic inlet and above GE junction), (ii) Clinical tumor stage 1, 2 and 3 (according to AJCC 6th edition), (iii) Age > 18 years and < 70 years, (iv) ECOG performance status < 3, and (v) Adequate hematological, hepatic, renal and pulmonary functions. Patients with tracheo-esophageal fistula, any other malignancy diagnosed during last 5 years or prior history of radiotherapy, chemotherapy or surgery for esophageal cancer were excluded. Informed consent was procured before randomization.

Pre-Treatment Evaluation

It included complete history and physical examination, complete blood count, Glomerular filtration rate (GFR) measurement, biochemical screening (Liver function tests and Kidney function tests), x-ray chest, electrocardiogram, echocardiography, Barium swallow, Upper GI endoscopy (Figure 1), CECT chest and upper abdomen (Figure 2). CECT was the standard investigative tool for assessment of mediastinal invasion, involvement of tracheo-bronchial tree and Aorta and mediastinal nodal assessment. Patients subjected to preoperative chemotherapy were re-evaluated by repeating pre-treatment workup, to assess the response. Video-endoscopic and CT images were used for monitoring the response to chemotherapy.

Chemotherapy

Patients assigned to chemotherapy received two or three cycles of Cisplatin (CDDP), 5-Fluorouracil (5-FU) and calcium leucovorin before surgery. Cisplatin (100mg/m2 of body surface area) was given as a rapid intravenous (IV) infusion in divided doses for 3 days after prehydration and was followed by 5-Fu (350mg/m^2 BSA/day) infused daily over 4 hours for four days by 4route. Calcium leucovorin (5mg) was given by IV route from day 1 to 3. The cycle was repeated on day 22 and 42. Surgery was performed 3 weeks after completion of last cycle. Toxicity was graded according to WHO guidelines.

Response to chemotherapy was assessed endoscopically (Figure 3) and radiologically (Figure 4) using response evaluation criteria in solid tumors (RECIST) (Therasse et al., 2000) as given in Table 1. Absence of evidence

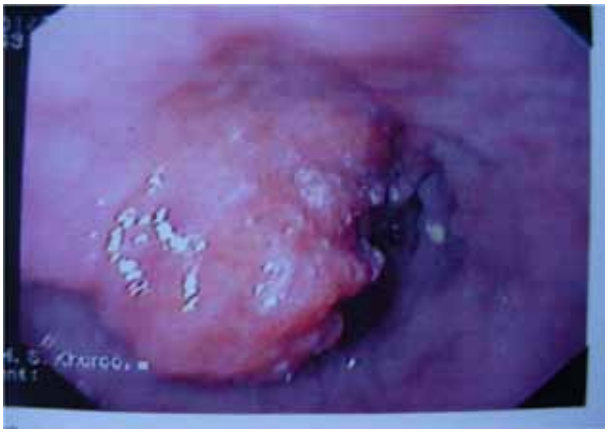

Figure 1. UGIE Picture Showing a Polyoid Growth in the Esophagus

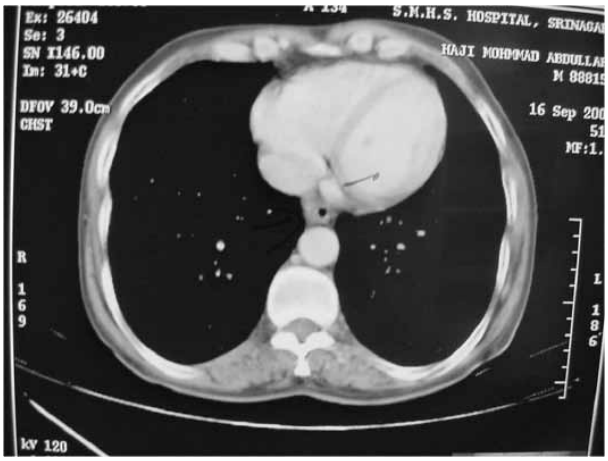

Figure 2. CECT Chest Showing Esophageal wall Thickening and Luminal Narrowing in Subcarinal Esophagus Consistent with Ca Esophagus. The surrounding fat planes are maintained

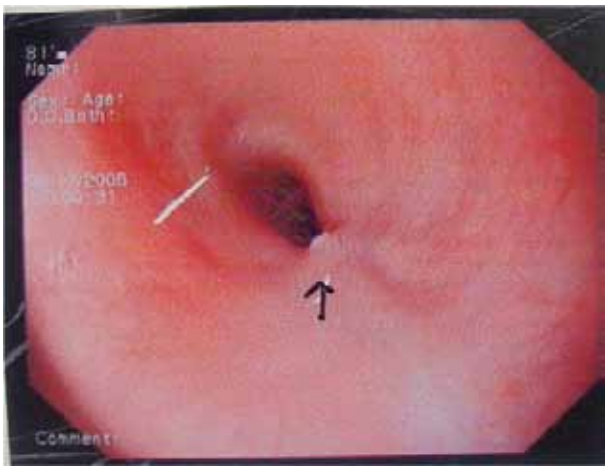

Figure 3. UGIE Photograph Showing what has Remained of the Growth Shown in Figure 1 after being Subjected to Two Cycles of Chemotherapy

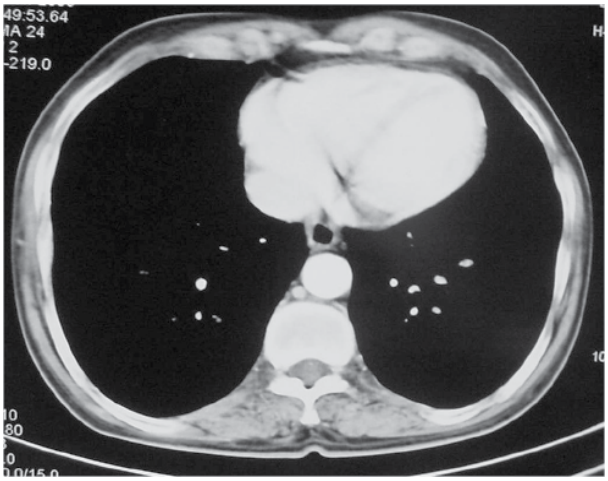

Figure 4. CECT Chest of the Same Patient as in Figure 2 Showing Restoration of Esophageal wall Thickness and Lumen after Two Cycles of Chemotherapy

Table 1. Definition of Best Response According to RECIST Criteria

Response	Criteria
Complete Response (CR)	Disappearance of All Measurable Disease
Partial Response (PR)	30% Decrease in Tumor Dimension
Progressive Disease (PD)	20% Increase in Tumor Dimension
Stable Disease (SD)	Neither PR nor PD Criteria Met

Table 2. Patient Characteristics

S. No.	Characteristics	Group A	Group B	P value
1.	Age (Years)			
	Mean Age	51.90	54.4	> 0.05
	Range	35 – 65	30 – 65	> 0.05
2.	Sex			
	Male / Female Ratio	1.7:1	2.12:1	> 0.05
3.	Residence			> 0.05
	Rural	20 (80%)	24 (96%)	
	Urban	5 (20%)	1 (4%)	
4.	Symptomatology			> 0.05
	Dysphagia	25	25	
	Weight Loss	6 (24%)	12 (48%)	
	Anorexia	6 (24%)	11 (44%)	
	GI Bleed	1 (4%)	3 (12%)	
5.	Location of Lesion			> 0.05
	Lower	13 (52%)	10 (40%)	
	Middle	11 (44%)	14 (56%)	
	Upper	1 (4%)	1 (4%)	
6.	Degree of Differentiation of Tumor			> 0.05
	Well / Moderate Well Diff.	11 (44%)	16 (64%)	
	Poorly diff	14 (56%)	9 (36%)	
7.	Stage at Presentation			> 0.05
	Stage – I	1 (4%)	4 (16%)	
	Stage – II	14 (56%)	12 (48%)	
	Stage – II B	9 (36%)	4 (16%)	
	Stage – III	1 (4%)	5 (20%)	

Table 3. Response to Chemotherapy

Response	Number (%)
CPR	3 (12%)
PR	18 (72%)
Pd	4 (16%)

of any tumor on histopathological examinations of the resected specimen was classified as complete pathological response (CPR).

Surgical Procedure

The patients assigned to group B were subjected to surgery immediately after pre-operative workup. The similar type of operation was performed in group A patients after completion of chemotherapy. The surgical procedures used were (i) Ivor-Lewis esophagogastrectomy for high thoracic lesions and (ii) transhiatal esophagectomy for lower thoracic esophageal lesions. At least 5 cm tumor free margin was taken at each end. Removal of all palpable lymph nodes was strongly emphasized at the time of surgery. Resection was classified as curative when all gross tumor was removed and microscopic examination revealed all margins to be free of tumor (R0). Resection was considered palliative either when microscopic examination revealed positive margins (R1) or when there was residual local (but not distant) gross disease (R2).

Continuity of gut was restored by constructing a gastric tube in all cases and was accompanied by a drainage procedure (pyloroplasty or seromyotomy) to prevent postoperative gastric stasis. Gastric tube was constructed in two layers- inner interrupted 2-0 silk and outer continuous 3-0 prolene. A single layer anastomosis with omental reinforcement was performed. Feeding jujenostomy was created for feeding in early postoperative period and was usually removed three weeks after surgery on follow-up. The pleural cavity was routinely drained. Before starting the patient on orals anastomotic leak was ruled out by performing barium study.

After discharge, the patients were followed regularly initially every 4 weeks for first 3 months, then every 2 months for next 6 months, then every 3 months. Upper GI endoscopy was done after first 3 months to rule out local recurrence and CECT chest was done when extra-luminal recurrence was suspected.

Statistical Analysis

All the statistical analysis was carried out in statistical software SPSS-11 using appropriate tests for different variables. The primary end-point was overall survival. Secondary end points included effect of chemotherapy on the rate of resection and effect of chemotherapy on postoperative morbidity and mortality.

Results

Patient Characteristics: During the period of 2 years from September 2004 to October 2006, 146 patients of carcinoma esophagus were admitted. Out of these 50 eligible patients were randomly chosen for the study and divided into two groups of 25 each. The patient characteristics are tabulated below in Table 2. The two groups di not differ significantly from each other.

Chemotherapy

A full course of chemotherapy was given to all the 25 patients belonging to group A. Most of the patients experienced relief from their symptoms after receiving 1st

Table 4. Response vis-à-vis Degree of Differentiation of Tumor

Type of Response	Number	
	Well/Mod Well Diff.	Poorly Diff.
CPR (n)	1	2
PR (n)	9	9
PD (n)	1	3

Table 5. Toxicity due to Chemotherapy

Toxicity	Grade			
	I	II	III	IV
Nausea	9 (36%)	13 (52%)	3 (12%)	-
Vomiting	4 (16%)	17 (68%)	3 (12%)	1 (4%)
Diarrhea	3 (12%)			
Weight loss	7 (28%)	2 (8%)		
Anemia	6 (24%)	3 (12%)		

Table 6. Surgical Procedures and Outcome

S. No.	Characteristics	Group A	Group B	p value
1.	Type of Procedure			> 0.05
	Ivor Lewis	18 (72%)	10 (40%)	
	Orringer	3 (12%)	6 (24%)	
2.	Type of Resection			
	Unresectable	4 (16%)	9 (36%)	
	R_0	20 (80%)	10 (40%)	< 0.05
	R_1	1 (4%)	6 (24%)	< 0.05
3.	Postoperative Complications			
	Overall complications	11 (44%)	18 (72%)	< 0.05
	Respiratory tract infection	6 (24%)	6 (24%)	> 0.05
	Wound infection	6 (24%)	6 (24%)	> 0.05
	Anastomotic leak	2 (8%)	6 (24%)	> 0.05
	Anastomotic stricture	5 (20%)	1 (4%)	> 0.05

Table 7. Survival on the Basis of Response to Chemotherapy

Outcome	Type of Response			Total
	CPR	PD	PR	
Surviving	3	1	17	21
Expired	0	3	1	4

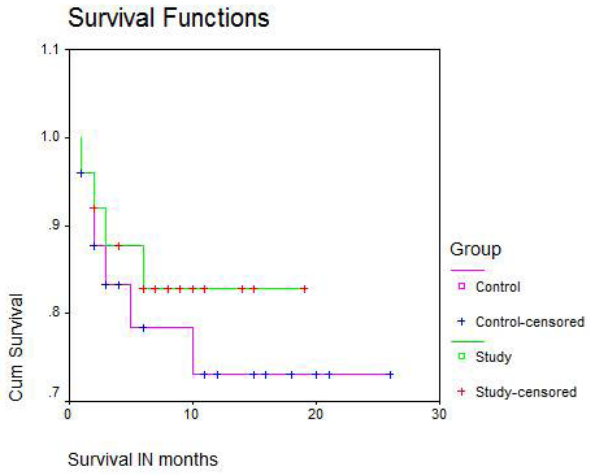

Figure 5. Kaplan Meier Survival Plots Stratified according to Treatment Received

cycle. In our study 3 patients (12%) showed CPR, with no evidence of tumor found in the resected specimen, 18 (72%) showed PR, with 4 (16%) experiencing progression of disease while on chemotherapy (Table 3). No statistically significant difference was found in terms of response to chemotherapy vis a vis degree of differentiation of tumor (Table 4).

The most common adverse effect due to chemotherapy was nausea and vomiting (Table 5). We did not encounter any deaths or infections related to chemotherapy. Anemia was seen in 9 (36%) patients of whom 3 needed transfusion.

Surgical Procedures & Outcome

Four patients (16%) of the group A and 9 (36%) of group B had unresectable growths. R_0 resection was achieved in 20 patients (80%) of group A and 10 patients (40%) of group B and R_1 in 1 (4%) and 6 (24%) patients of group A and B respectively. No gross tumor was left behind in any patient. The type of resectability achieved in the two groups had a statistically significant difference (p=0.012) showing a favourable trend in the study group (Table 6).

The likelihood of overall post-operative complications in the control group was 3.74 times more than the study group (odds ratio = 3.74) and this difference was statistically significant (p = <0.05). The anastomotic leak rate was higher in the control group and the anastomotic stricture (fibrous) was more frequent in the group A patients. There was no postoperative death noted in either group (Table 7). The average postoperative hospital stay of 10 days was similar in both groups.

Survival

The average follow up period for patients in group A was 8.04 months (range 1-19 months) and for those in group B was 11.0 months (range 1-26 months). At the time of analysis (October 2006) 21 (84%) patients of group A and 19 (76%) of group B were still following up regularly. Three patients of the group A had died because of recurrence of disease and one was lost to follow up. Four patients of group B had expired because of recurrence and 2 were lost to follow up. Thus on the basis of current surviving status, the likelihood of survival in group A is 1.66 times more than the controls but the difference is not significant (p > 0.05).

The Kaplan Meier survival plots demonstrated a mean survival of 16 months for patients belonging to group A and 20 months for patients in group B. However, the survival at 20 months was 82% for group A and 72% for group B. Thus showing a slight advantage for patients receiving chemotherapy (Figure 5), however statistically insignificant. The patients who had shown response to chemotherapy (CPR, PR) had a better survival than the non-responders (p=0.002) (Table 7).

Discussion

Cancer of the esophagus is an extremely common disease in India (Desai et al., 1969) and is one of the most common malignancies in Kashmir contributing nearly 22.7% of all cancers. Esophageal squamous cell carcinoma is associated with poor prognosis (Clark et al., 1996) and little has improved in terms of survival, despite remarkable progress in surgery over recent decades (Earlam et al., 1980).

In order to improve the long term survival in patients

of esophageal cancer multi-modality approach has been adopted over the last few decades with a particular interest in neo-adjuvant regimens. Although the results have been mixed (Kies et al., 1987, Hilgenberg et al., 1988, Roth et al., 1988, Schlag et al., 1992, Kelsen et al., 1998), a recent study carried out by Medical Research Council Oesophageal Cancer Working Group (MRCOWG) has shown a significant improvement in over all survival with preoperative chemotherapy (2002). Similarly, a meta-analysis of 11 randomized trials involving 2051 patients has shown a survival advantage in patients subjected to preoperative chemotherapy but only in long term (Malthaner et al., 2003).

The aim of our study was to assess the effect of preoperative chemotherapy on the resectability and survival of patients diagnosed to have SCC of esophagus. Since our study was carried out in a single centre, the variations in surgical technique and postoperative management associated with multi-institution trials were nullified.

The chemotherapeutic agents used (5-FU + CDDP) are the most commonly used agents for carcinoma esophagus (Malthaner et al., 2003). We used a low dose regimen, as has been used in some studies (Aroori et al., 2004) although we used slightly different dose and schedule.

The response to chemotherapy was much higher (84%:-12% CPR and 72% PR) in our study as compared to other studies (Kelsen et al., 1983; Kelsen et al., 1986; Kies et al., 1987; Hilgenberg et al., 1988; Roth et al., 1988; Schlag et al., 1992; Kelsen et al., 1998; Aroori et al., 2004). This may be due to the differences in biological behaviour of this tumour in our population as compared to rest of the world, which in turn might be related to the etiological risk factors which are specific to this region (Khuroo et al., 1992). In our study we did not find any relationship between the degree of differentiation of tumor and response to chemotherapy which is concordant with some studies (Law et al., 1997).

Nausea and vomiting were the most common adverse effects noticed in our patients due to chemotherapy. Grade I and II hematological toxicity in the form of anemia was seen in 9 patients (36%). We did not encounter any major adverse effect due to chemotherapy neither were there any chemotherapy related deaths. This is similar to other studies using low dose chemotherapeutic regimens (Aroori et al., 2004), but most of other studies have reported more severe adverse effects (Kelsen et al., 1983; 1986; Kies et al., 1987; Hilgenberg et al., 1988; Roth et al., 1988; Schlag et al., 1992).

The rate of overall resectability and R0-resection was significantly higher (84% and 64% respectively) in the group A patients as compared to group B patients (64% and 40% respectively) ($p<0.05$). These findings are different from other randomized trials (Roth et al., 1988, Schlag et al., 1992; Kelsen et al., 1998, Malthaner et al., 2003). The possible reason can be the high response rate we have noticed in our study as compared to these trials, which has translated into higher resectability rate and R_0-resection.

The overall postoperative complication rate was significantly lower in group A (44%) as compared to group B (72%). The postoperative mortality was zero in each group. These results are in variance with other studies (Roth et al., 1988, Schlag et al., Law et al., 1997; Kelsen et al., 1998; MRCOWG, 2002; Malthaner et al., 2003). This could be explained by (i) higher response rate and hence symptomatic improvement in the chemotherapy group, which leads to normal food intake and hence improved nutritional status before surgery, which is an important factor in determining surgical outcome and (ii) decreased tumor burden before surgery in higher number of patient which in turn again is an important determinant of surgical outcome.

Although we have compiled and presented data of only first two years of our study and also patients have entered our study at different points of time, the survival derived from the Kaplan Meir survival plots demonstrated a mean survival of 16 months for patients in group A and 20 months for patients in group B. However the 20 month survival was 82% for group A and 72% for group B. We presume on this basis that the survival on further follow up is going to significantly favour the chemotherapy group as has been shown in some latest studies, (MRCOWG 2002; Malthaner et al., 2003) although older studies have failed to show any benefit with this approach (Roth et al., 1988; Schlag et al., Kelsen et al., 1998). Further, we have noted a significantly improved survival for patients responding to chemotherapy ($p=0.002$). A similar trend has been noted by most of the other studies (Roth et al., 1988; Schlag et al., 1992; Law et al., 1997; MRCOWG 2002; Malthaner et al., 2003; Aroori et al., 2004). Whereas those being chemo-resistant fared worst in our and in other studies.

To conclude, we have observed that preoperative chemotherapy resulted in significant tumor down staging, with increased rate of resectability and R0 resection, without increase in postoperative morbidity or mortality, although patients have to bear few non-life threatening complications related to chemotherapy. There was a trend towards improved survival in chemotherapy group although not statistically significant and this reached to a significant level in patients who responded to chemotherapy. Perhaps if more patients are recruited and the follow up period extended a clearer picture might emerge. It needs to be emphasized that a reliable method should be devised that can determine risk factors and predict responsiveness to chemotherapy, so that those not likely to respond, do not have to wait for surgery unnecessarily and are not subjected to unnecessary potentially toxic and expensive treatments.

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