RESECTABILITY RATES IN LOCALLY ADVANCED ESOPHAGEAL CARCINOMA FOLLOWING NEO-ADJUVANT CHEMO-RADIOTHERAPY

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Background: Purpose of this study was to assess the resectability rates in un-resectable (Stages III and IV) cancers of the esophagus, to assess the complete pathological response and to compare the efficacy between two chemotherapy regimens. Methods: From January 1999 to June 2002, medical records of the patients with un-resectable esophageal cancers were reviewed, who received radiation-therapy with concomitant chemotherapy using following regimens:- Arm A:- 5FU 500 mg/m^2 intravenous push (IVP) on first 5 and last 5 days of radiation. Arm B:- 5FU 1 Gm/ m^2/Day 96 hour continuous infusion (CIV) and Cisplatin 70 mg/ m^2 on day one and twenty eight of radiation. At completion of neoadjuvant chemo-radiation patients were offered surgery after four to six weeks. Results: 35 patients had un-resectable esophageal cancer. Twenty-six received arm A, and 9 arm B treatment. Of 26 patients in arm A, in 13 the disease was made resectable and two of them showed complete pathological response in surgical specimen, thirteen had progressive disease. On the other hand, of 9 patients receiving arm B treatment, in 7 the disease was made resectable and out of them 5 showed complete pathological response in surgical specimen and two had progressive disease. Conclusion: Resectability in patients receiving arm B treatment was better than the patients treated arm A. The data is not mature enough to assess the effect on disease free survival or overall survival, this will be seen and published later.

Keywords: Un-resectable esophageal cancer, neo-adjuvant chemoradiation

INTRODUCTION

Locally advanced (Stage III) carcinoma of the esophagus caries a poor prognosis. Most of these patients have been treated with palliative intention. In a study Roohulla et al[1] stated that 87 % of the patients presenting were of squamous cell histology and most of them were found in stage III and beyond. These patients were mainly treated with palliative radiation therapy, some of these were also treated with chemotherapy along with radiation, but the overall survival remained poor. A few patients had also palliative surgery prior to radiotherapy. In another study by Malik et,al[2], only 54 % of patients with squamous cell or adenocarcinoma of the esophagus could be offered any surgical procedure, in 31 % patients palliative resection with esophageal bypass was performed and in 13 % only bypass was possible .

Preoperative chemoradiation has been used in several series in an attempt to downstage the disease, including that from Veteran Administration Hospital and Oregon Health Sciences University, Portland VA Medical Center[3], in which preoperative chemo-radiotherapy down-staged 36% of patients with a pathological complete response in 15 %. Survival was prolonged significantly in patients receiving radiotherapy, i,e 20.6 months versus 9.6 months for those (Stage II or III) patients not receiving radio-chemotherapy.

In another series from Johns Hopkins School of medicine, Baltimore, USA.[4] Of 39 patients who proceeded to surgery, 29 had responded to preoperative treatment, 11 achieved pathological complete response and 18 achieved a lower post treatment stage, the two-year survival rate was 62 %. The two-year survival rate for pathological complete responders was 91 % compared with 51 % in patients with complete tumor resection with residual tumor. In a report from Japan[5,6], concurrent chemo-radiation therapy followed by surgery was an effective, safe multimodality therapy for patients with primary inoperable T4 squamous cell carcinoma of the esophagus .

Does pre-operative chemo-radiotherapy downstage the un-resectable (Stage III/IV) esophageal cancers in our patients? To assess the efficacy of neo-adjuvant chemo-radiotherapy followed by surgery, this regimen was followed in Shaukat Khanum Memorial Hospital (SKMCH).

MATERIALS AND METHODS

This observational study was conducted at the department of radiation oncology SKMCH, Lahore. A questionnaire was developed addressing, patient identification, age, radiological stage, histopathol-ogy, performance status, the treatment regimen used and the resectability. The medical records of the patients were reviewed to complete the questionnaire. Patients were staged according to the TNM staging system. Study period extends from January 1999 to June 2002

Primary objective was to compare the efficacy of both regimens in down-staging the tumor. The secondary objectives were to compare the pathological complete response rates in resected specimens in both regimens.

Patients of any age with ECOG performance status of 0-2 and radiologically stage III/IV locally advanced squamous cell carcinoma or adenocarcinoma of lower thoracic esophagus who had completed neo-adjuvant chemoradiation therapy. Patients with ECOG 3-4., uncertain diagnosis and with concurrent malignancy other than skin cancer were excluded.

All patients received external beam radiation-therapy 40 Gy in twenty fractions at the rate of 200 cGy daily, five days a week to antero-posterior and postero-anterior fields on Co-60 teletherapy machine with five centimeter margin to tumor and also covering celiac axis lymph-nodes **(Fig.1).** 10 Gy boost was delivered via oblique fields **(Fig.2,3)** sparing the spinal cord to give total dose up-to 50 Gy. Chemotherapy was given concomitantly with radiation using one of the following regimens -

Arm A - 5FU 500 mg/m^2 intravenous push (IVP) first 5 and last 5 days of radiation half to one hour before radiation.

Arm B - 5FU 1 Gm/ m^2/Day 96 hour continuous infusion (CIV) and Cisplatin70 mg/ m^2 eight hour infusion on day one and twenty eight of radiation.

Four to six weeks after completion of chemoradiation C.T/MRI scan of the chest was repeated and patients were offered surgery (Transhiatal esophagectomy), if the disease had become resectable and surgical specimen was submitted to histopathology to see the response.

RESULTS

Characteristics and histopathology of 35 patients who fulfilled the inclusion criteria are given in table 1 and 2 respectively in each treatment arm. Twenty-six patients received arm A regimen, in 13 the disease was made resectable and surgical specimen in two of them showed pathological complete response. Of thirteen patients who had un-resectable disease, 3 lost to follow-up (These were considered to have progressive disease), eight had progressive disease to celiac lymph nodes and bone metastases, and in two surgery was not carried out because of the development of myocardial infarction.

Table-1: Patient characteristics

Variables	**ARM A (# 26)**	**ARM B (#9)**
Age		
≤ 50 year	12 (46%)	07 (77%)
> 50 year	14 (54%)	02 (22%)
Sex		
Male	17 (65%)	03 (33%)
Female	09 (35%)	06 (67%)

On the other hand out of nine patients who received arm B regimen, in seven the disease was made resectable and surgical specimen in five patients had no viable tumor. In two with unresectable disease, one had progressive disease (Ascites) and one lost to follow-up. These results are summarized in table 3.

Table 2- Histopathology of patients

Histopathology	**Arm A (n=26)**	**Arm B (n=9)**
Poorly differentiated squamous cell carcin-oma	06 (23%)	04 (44%)
Moderately differentiated squamous cell carcin-oma	16 (61%)	04 (44%)
Adenocarcinoma	04 (15%)	01 (11%)

Table 3- Resectability rates.

VARIABLE	**ARM A** (N=26)	**ARM B** (N= 09)
Resectable	13 (50%)	07 (77%)
Un-resectable	13 (50%)	02 (22%)

Figure-1: Simulation film of AP/PA field to 40 Gy. Lower border covers the celiac axis

DISCUSSION

Locally advanced esophageal carcinoma (Stage III/IV) is un-resectable disease and caries a poor prognosis.[1] Curative surgery of thoracic esophageal cancer involves a subtotal or total esophagectomy. Surgery has been the standard treatment for thoracic esophageal carcinoma, but two largest series by Erlam and Cunha-Melo[7], review 122 papers involving more than 83,000 patients treated primarily by surgery. The overall 5-year survival rate for patients with resected tumors was 12 %. Patients treated with palliative intention had a survival range of 2-6 months. Studies by Walsh et al[8] and Urba et al[9] report 6 % and 15 % 3 year survival in the surgery alone arm, respectively.

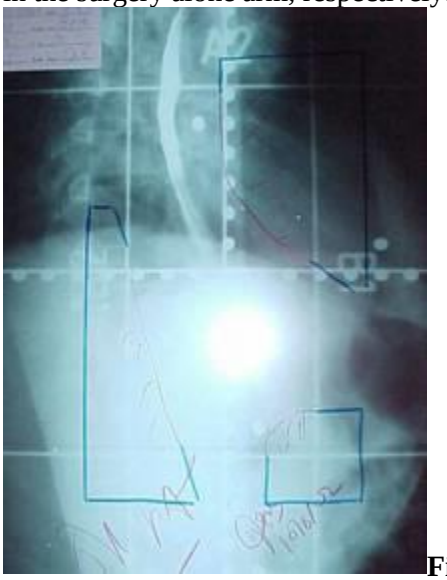

Figure-2: Simulation film of right anterior oblique field sparing the spinal cord

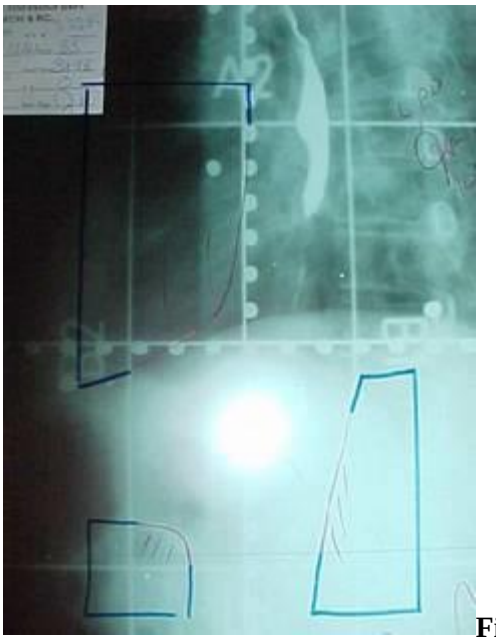

Figure-3: Simulation film of left anterior oblique field sparing the spinal cord

Poor patient outcome with surgery alone has led to the development of alternative primary treatment or adjuvant therapy in conjunction with surgery. When the disease is in-operable because of tumor extent or medical contraindications, radiation alone has been given. In a thorough review Earlam and Cunha-Melo[10] analyzed 49 series involving more than 84,000 patients treated primarily with radiation between 1954 and 1979. They found overall survival rates at 1,2 and 5 years to be 18 %, 8 % and 6 % respectively.

Data from the University of Michigan[11] described the use of preoperative chemoradiation in 43 patients. Transhiatal esophagectomy was performed 21 days after the completion of chemo-radiotherapy and 41/43 patients underwent resection. Thirty-six patients had a pathologically complete response and there was no local failures. The overall loco-regional failure rate was 26 %. For patients who underwent a curative resection, 3-year survival rates were 36 % and 43 % for adenocarcinoma and squamous cell carcinoma, respectively (p=0.589). Patients who had a complete pathological response had a median survival of 70 months and 60 % were alive at 5 years. The data in all of the prospective trials definitely trends toward and support the use of a tri-modality approach for locally advanced stage III carcinoma of the thoracic esophagus.

In our patients at SKMCH, all the un-resectable patients were offered preoperative chemo-radiotherapy using two different chemotherapy regimens. One arm A, as out patient basis. The arm B consisted of continuous infusion. From the results it can be seen that patients receiving continuous infusion of two drugs had better resectability rates and moreover the pathological complete response was superior in the later regimen. At present, four phase II trials have reported on a pre-operative combination of Cisplatin, Paclitaxel, and radiotherapy.[12-14]

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