J MEDICINE 2007; 8 : 60-63

A COMPARATIVE TREATMENT RESULTS OF OESOPHAGEAL SQUAMOUS CELL CARCINOMA BY NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY VERSUS RADIOTHERAPY ALONE

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Abstract:

Background: *Studies suggest that neoadjuvant chemotherapy prior to radiotherapy results in improved response and survival in large primary lesion. This study aimed to evaluate the role of neoadjuvant chemotherapy prior to radiotherapy in patients with localized oesophageal cancer.*

Method: *In this randomized controlled study 60 selected cases of oesophageal squamous cell carcinoma were randomized to Arm-A & Arm-B. Patients assigned to combination therapies(Arm-A) received two cycles (4 weekly) of injectable 5- fluorouracil(400mg/ m^2/day for five days) and mitomicin C (7mg/ m^2 on D_1) as neoadjuvant chemotherapy prior to radiotherapy(44GY in 22 fractions). Patients of Arm-B received radiotherapy alone as in arm-A. Treatment responses were compared following completion of treatment at six and 12 weeks. Complete response was defined as no difficulty in swallowing and no visible growth in follow-up barium swallow X-Ray. Partial response was defined as difficulty in swallowing semisolids but not liquids and persistence of residual growth in barium swallow X-Ray.*

Results: *The study initially enrolled 68 patients but eight patients dropped out. Complete response occurred in 66.6% (20) patients who received combination therapies (n=30), where as in 40% (12) patients who received radiotherapy alone (P= <0.05). Partial response occurred in 33.33% patients assigned to have pre-irradiation chemotherapy and in 60% patients having radiotherapy alone. Toxicities like dysphagia, anorexia, vomiting was more in combination therapy group, but it was acceptable.*

Conclusion: *Neoadjuvant chemotherapy followed by radiation therapy demonstrated better response than radiation alone at the expense of toxicity in patients with localized oesophageal cancer.*

Introduction:

Oesophageal cancer is a substantial cause of mortality throughout world. Oesophageal cancer is the fourth most common tumour in developing countries like India.[1] The true prevalence and incidence of Oesophageal cancer in Bangladesh is not known. Oesophageal cancer is the most dismal of visceral tumours with a 5 year survival rates of less than 5 percent owing to their generally advanced stages at the time of diagnosis.[2] It is a disease of elderly, usually over the age of 60 years. Ninety percent are squamous cell carcinomas and 10% are adenocarcinomas.[3]

Surgery and radiation therapy is the mainstay of treatment for limited disease, but the role of chemotherapy is still evolving. On the other hand, chemotherapy has become standard treatment for metastatic or locally recurrent disease. The goal of treatment can only be achieved through a multidisciplinary approach, but every patient does not require combination of surgery, irradiation and chemotherapy.[2-5] Large primary lesions may require a planned combined approach. The use of chemotherapy as neoadjuvant to radiation therapy offer improved response and survival.[5-7] Pre-irradiation chemotherapy for advanced lesion specially two cycles neoadjuvant chemotherapy is currently, under intense investigation.

As far our knowledge no work has been carried out in this field in Bangladesh. This comparative study was designed to evaluate the role of neoadjuvant chemotherapy followed by radiotherapy in patients with localized oesophageal cancer who are unfit for

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surgery. This study also aimed to observe the side effects of chemo and radio-therapy.

Materials and Methods:

This study was carried out in the Department of Radiotherapy, Dhaka Medical College, Dhaka from January 2002 to December 2003. This randomized controlled study included 60 diagnosed cases of oesophageal carcinoma (squamous cell) patients. Irrespective of sex, patients(< 70years) with endoscopically and histopathologically proven localized oesophageal carcinoma having Union International Contor Cancer(UICC) performance status score up to grade -2 and with acceptable biochemical and laboratory parameters were selected for trial. Patients with metastasis and who are unfit for surgery were excluded.

Patients were randomly allocated in Arm A and Arm B. Written consents were taken from all the selected patients. Arm A study group received two cycles (4 weekly cycle) of a combination of injectable 5-fluorouracil(400mg/m^2) and mitomicin C (7mg/ m^2) as neoadjuvant chemotherapy prior to RT. Each cycle included one (1) hour infusion of 5-FU for five (5) days with mytomicin C in day one (D_1). Four weeks after chemotherapy, forty-four Gy radiation therapies were delivered in 22 fractions by using a telecobalt unit (200cGy/day) five days in a week. Thirty patients of arm B (control group) treated by radiotherapy alone as in arm A. For Arm-A patient's treatment duration was 12 weeks; whereas for Arm-B patient's duration was 4.5 weeks.

The target tumour volume was defined by barium study and endoscopic findings and included 5 cm margin above and below the tumour and 2-3 cm on each side. The patients were treated on supine position by anterior and posterior parallel fields.

Every patient was monitored routinely for complete and partial responses following treatment. Complete response was defined as no difficulty in swallowing [4] and no visible growth in follow-up barium swallow X-Ray at six and 12 weeks after completion of treatment. Partial responses were defined as mild soreness on swallowing, can swallow liquid without difficulty, but semisolid with difficulty (Hayter CR et al.)[4] and follow up barium swallow at six and 12 weeks after completion of treatment shows persistence of residual growth.

Observations and Results:

Initially 68 patients were enrolled in the study but eight (08) patients dropped out (six discontinued treatment and two failed to come for follow up). Among the 60 patients included in the study 53 were male and 7were female. Majority of the patients belonged to 50-69 years group (90%) with age range of 40-68 years (table-I). Majority of the patients (56.67%) were poor and illiterate (43.33%) (table-I). Out of 60 patients 46 patients were smoker (76.67%) and among these, 18 patients were betel leaf (14 in Arm A and 6in Arm-B) and tobacco chewer. Four (6.66%) patients were alcoholics in addition with smoking and betel leaf chewing. Ninety percent patients were used to take spicy hot food mostly chili. Twenty-seven patients were in UICC Grade I performance status and 33 patients were in Grade II performance status.

Age distribution, clinical presentation, topographic and morphologic distribution of oesophageal carcinoma is described in table-I. Middle third of the oesophagus was the most common site of involvement (51.67%). Macroscopically 35(58.33%) were ulcerative, 16(26.67%) were proliferative. Histopathololologically 51.67% tumours were moderately differentiated, 33.33% were well differentiated and 15% were poorly differentiated.

Complete response (CR) occurred in 20(66.6%) patients of combination group (Arm-A) where as 12(40%) patients of radiotherapy group (Arm B)($P = 0.038$). (Tabel - II) Partial response (PR) occurred in 10(33.33%) patients of Arm-A and 18(60%) patients of Arm B (Table - II). The results are statistically significant. Patients treated with radiotherapy demonstrated symptomatic relief of dysphagia within 15 days on an average. On the other hand patients receiving neoadjuvant chemotherapy prior to radiotherapy showed symptomatic improvement of dysphagia within a mean period of 12 days after starting radiotherapy.

Eighteen patients (63.33%) of Arm A developed chemotherapy toxicities – anorexia, nausea, vomiting and mucositis. Total 34 patients of two groups suffered from radiation reactions like anorexia, nausea, weakness, dysphagia, erythema and pigmentation of skin. These reactions resolved spontaneously 4-6 weeks after completion of therapy and required limited medical support.

Table-I

Socio-demographic characters, clinical presentation, topographic and morphologic distribution of oesophageal carcinoma..

Variable	Number of patients		Total patients (%)
	Arm-A	Arm-B	
Age(years)			
40-49	3	3	6(10%)
50-59	13	15	28(46.67%)
60-69	14	12	26(43.33%)
Education			
Illiterate	11	15	26(44.33%)
Primary	12	8	20(33.34%)
S.S.C	3	3	6(10%)
H.S.C and above	4	4	8(13.33%)
Socio-economic status			
Poor	16	18	34(56.67%)
Middle class	11	11	22(36.67%)
Upper class	3	1	4(6.66%)
Habit			
Smoker	22	24	46(76.67%)
Betel leaf chewer	20	12	32(53.33%)
Clinical presentation			
Dysphagia	30	30	60(100%)
Weight loss	14	17	31(51.67%)
Regurgitation and vomiting	17	15	32(53.33%)
Retrosternal chest pain	2	1	3(5%)
Topographical distribution of carcinoma oesophagus			
Upper third	1	0	1(1.66%)
Upper and middle third	8	13	21(35%)
Middle and lower third	18	13	31(51.67%)
Lower third	0	0	0%
Endoscopic finding			
Ulcerative	18	17	35(58.33%)
Proliferative	7	9	16(26.67%)
Fungating	4	3	7(11.67%)
Others	1	1	2(3.33%)

Table-II

Response pattern of oesophageal carcinoma patients to treatment.

Treatment group	Complete response (CR)	Partial response (PR)	χ^2 Value	P value
	No (%)	No (%)		
Arm-A	20(66.67 %)	10(33.33 %)	4.28	P<0.05
Arm-B	12(40.0 %)	18(60.0 %)		

Discussion:

Oesophageal cancer is the most dismal of visceral tumours with a 5 year survival rates of less than 5 percent owing to their generally advanced stages at the time of diagnosis.[2] Surgery and radiation therapy is the mainstay of treatment for limited disease, but the role of chemotherapy is still evolving. On the other hand, chemotherapy has become standard treatment for metastatic or locally recurrent disease. The goal of treatment can only be achieved through a multidisciplinary approach, but every patient does not require combination of surgery, irradiation and chemotherapy. Large primary lesions may require a planned combined approach. The use of chemotherapy as neoadjuvant to radiation therapy results in improved response and survival.[4,7] Pre-irradiation chemotherapy for advanced lesion specially two cycles neoadjuvant chemotherapy is currently, under intense investigation. The present study was designed to compare the effect of neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone on localized squamous cell carcinoma of oesophagus in patients who are unfit for surgery and also to see the immediate side effects of chemo and radiotherapy.

Most of the patients (90%) were between 50 to 60 years; majority (56.67%) of the patients was poor and illiterate (43.33%).These findings are similar to other studies.[3, 5] Ninety percent patients were used to take spicy hot food; 76.67% patients gave history of smoking and tobacco and betel-nut chewing. .These findings indicate aetiologic relations with oesophageal carcinoma in the study population and are similar to other studies[5]. Middle third of the oesophagus was the most common site of involvement (51.67%) and progressive dysphagia (100%) was the most common presentation in this series. These findings are similar to other studies.[4-6]

Symptomatic relief of dysphagia was earlier and complete response was more (66.66%) in patients who received pre-irradiation neoadjuvant chemotherapy. The results of the present study are comparable to other studies.[3, 7, 8] Previous studies showed better survivals among complete responders.[7,8] Lower radiation dose and younger age were the only significant prognostic factors for shorter overall survival and lower relapse rate in their studies. From the present study we can not make any conclusion on overall short-term survival or rate of relapse due to lack of long-term follow-up.

In conclusion, neoadjuvant chemotherapy followed by radiation therapy demonstrated better response than radiation alone. Though toxicities were more in patients assigned to have combination therapy, it was tolerable. Neoadjuvant chemotherapy prior to radiotherapy in localized nonresectable oesophageal cancer may be a better option. Long term studies with a large number of population and long-term follow-up are required for further comment.

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