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Research Article

Cancer oesophagus: is sequential chemo radiation better in elderly patients or patients with severe dysphagia?

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ABSTRACT

Background: This study was conducted to analyse the local control, regional control and toxicities of sequential versus concurrent chemo radiation in the patients of oesophageal cancer especially in elderly.
Methods: A total of newly diagnosed 50 patients were randomized in concurrent and sequential arm. Two courses of 3 weekly chemotherapy (Cisplatin and 5-FU based) were given concurrently and three courses of same chemotherapy were given neoadjuvantly with EBRT (44 Gys) respectively in randomised arms. HDR-ICBT (2 fractions of 5 Gy) delivered after two weeks of completion of EBRT in both arm.
Results: Concurrent arm had higher incidence of grade III+IV overall all toxicity especially in elderly patients or patients that presented with grade IV or higher dysphagia. Other haematological and non-haematological toxicities were equal in both arms. Complete response at both primary and mediastina was higher in concurrent arm but there was no statistically significant difference.
Conclusions: Our data suggest that if a patient can tolerate the combination of chemotherapy and radiation, this approach offers superior results but at the cost of higher incidence of severe toxicities especially in patients with grade IV or higher dysphagia or elderly patients. So this group could be treated with sequential chemo radiation.

Keywords: Oesophageal cancer, Sequential chemo radiation, Neoadjuvant chemotherapy followed by radiation, Concurrent chemo radiation, Elderly, Severe dysphagia, Radiotherapy

INTRODUCTION

Cancer esophagus is a highly lethal malignancy.[1] The five year survival of all patients with cancer esophagus has only marginally increased from 5% in 1970 to 16% in 2002 based on Surveillance, Epidemiology, and End Results population-based tumour registry reporting. In last 15 years, the management of loco-regional esophageal cancer has improved without significantly increasing the median survival of patients, which remains approximately 9 to 12 months.[2] Treatment failure, despite adequate and satisfactory loco-regional treatment prompted the idea to include chemotherapy as combined modality.[3-9] Chemotherapy has multiple role e.g. tumour debulking or down staging if used as neoadjuvant radiation sensitization or synchronized effect in tumour control when used as concurrent and to tackle the residual tumour when used after the primary therapy e.g. radiation or surgery.[3,4-9] It is obvious that when chemotherapy used as concurrent, the toxicities are equally severe.[5-8] This kind of therapy is not suitable for patient with poor performance status or elderly.

Present study is aimed to compare the results and adverse events of concurrent chemoradiation with neoadjuvant chemotherapy followed by radiotherapy in respect of age,

performance status and grade of dysphagia at presentation.

METHODS

A total of 50 diagnosed newly patients with upper or middle third thoracic esophageal cancer (American joint committee 7th edition on cancer clinical stage T1-3N0-1M0 and 18-32 cm from upper incisors in endoscopy) were included in this study.

All patients were histopathologically proved Squamous cell carcinoma (SCC) and randomly distributed among concurrent arm (25 patients) and sequential arm (25 patients). CBC, RFT and LFT were advised before each course of chemotherapy and on each follow up. Total four follows ups in 12 months at interval of three months were planned. CXR-PA, USG-whole abdomen and Ba-swallow were advised before treatment and on each follow up.

Upper GIT Endoscopy and biopsy and CECT of neck, thorax and upper abdomen were advised as baseline, then after 3 month of completion of treatment for response assessment. Baseline bronchoscopy was also done in all patients. Ryle's tube feeding, blood transfusion; IV-fluids, antibiotics and other symptomatic/supportive treatment were advised as per requirement.

Sequential arm received three courses of neoadjuvant chemotherapy (Inj. Cisplatin 80 mg/m2 divided in D1 and D2 with 5-FU 800 mg/m2/24 hour on D1 and D2) at the interval of 21 days. External beam radiotherapy (EBRT) was delivered after rest of 14 days from last course of the chemotherapy.

Concurrent arm received two courses of same chemotherapy concurrently with EBRT on D1D2, and on D22D23. Both arms received conventional EBRT through anterior-posterior portals; 2 Gy per fraction, 5 fractions per week, total 44 Gy/22 fractions in 4.2 weeks by Co60 Theratron 780E or 780C. High dose rate intracavitary brachytherapy (HDR-ICBT) delivered after 10-14 days of completion of EBRT in both arms. Two fractions, each of 5 Gy, each 4 days apart, were prescribed at 1 cm from mid dwell position by Ir192 Gammamed-12i after loading brachytherapy machine.

Subjective and objective response evaluation was done weekly during treatment and after completion of treatment till end of 12 months. Response assessment was done at 3 month after completion of treatment. For the primary esophageal tumor: Complete Response (CR) was defined as no evidence of residual or recurrent tumor on endoscopy, as verified histologically; all other responses were defined as Non Complete Response (non-CR). For lymph nodes, CR was defined as a reduction in lymph-node size from >1 to <1 cm; all other responses were defined as non-CR.10 Assessment of acute hematological toxicities and radiation induced acute lung and esophageal toxicities was done according to RTOG criteria, while assessment of acute liver and renal toxicities was done according to CTC version 4.012. Statistical analysis was done by SPSS statistical software version 10.[11]

If patient had WBC <2500/mm3, platelets <75000/mm3, serum creatinine >1.5 mg/dl, total billirubin >1.5 mg/dl, AST/ALT >2.5 times the upper limit of normal, body temperature >38.5°C due to infection or Grade III/IV esophagitis, then both chemotherapy and radiotherapy were withheld until such toxicities were resolved.

RESULTS

Table 1 is showing characteristics of the patients. Maximum number of patients in Concurrent arm were from 61-70 years age group i.e.32% while in Sequential arm it was from 41-50 years age group i.e.40% (p>0.05). Male to female ratio was 0.92:1 in concurrent arm and in sequential arm it was 1.27:1 (p>0.05). Maximum numbers of patients were from rural area (37 out of 50) and low socioeconomic status (34 out of 50) in present study.

Rural to urban ratio was 2.57:1 and 3.16:1 in concurrent and sequential arm respectively (p>0.05). Majority of patients had dysphasia grade 3 i.e. 40% (10 out of 25) and 48% (12 out of 25) in concurrent and sequential arm respectively while least number of patients had grade 1 i.e. 0% in both concurrent and sequential arm (p>0.05 non-significant).

The clinical stage I/IIA and IIB/III were equally randomized in between concurrent and sequential arm (p>0.05). Middle third thoracic esophagus was appeared as a common site of primary tumour (64%, 32 out of 50).

Incidence of overall maximum toxicities (table 3) among the concurrent and sequential arm were as follows; grade I 8% vs. 56%, grade II 44% vs. 40%, grade III 36% vs. 20%, and grade IV 12% vs 4% toxicity respectively (p = 0.004) i.e. concurrent arm had higher incidence of grade III+IV overall toxicity, while grade I overall toxicity was dominant in sequential arm.

Grade II toxicity was equal in both arms. Incidence of toxicities of Absolute neutrophil count (ANC) among the concurrent and sequential arm were as follows; grade I 32% vs. 32%, grade II 40% vs 12% and grade II 8% vs 4% toxicity respectively (p = 0.05) i.e. grade II toxicity of ANC was more in concurrent arm, while grade I toxicity of ANC was equal in both arms. High grade toxicities were observed more in concurrent arm as per our expectations because chemotherapy enhances radiation induced toxicities.

Table 1: Characteristics of patients.

Age	Age group (in years)	Concurrent arm	Sequential arm	χ^2	P
		n=25	n=25	3.158	0.368
	25 – 40	6	2		
	41 – 50	6	10		
	51 – 60	4	6		
	61 – 70	8	7		
Sex	Male	12	14	0.321	0.571
	Female	13	11		
Residential	Urban	7	6	0.104	0.747
	Rural	18	19		
Socioeconomic status	Low	15	19	14.471	0.002
	Medium	9	5		
	High	1	1		
Personal habits	Smoking	4	3	16.160	0.043
	Alcoholic	2	3		
	Tobacco chewing	1	3		
	Both smoking & alcoholic	4	4		
	None	14	12		
Grade of Dysphasia at presentation	Grade 1	0	0	0.350	0.950
	Grade 2	7	6		
	Grade 3	10	12		
	Grade 4	6	5		
	Grade 5	2	2		
AJCC Stage	I/IIA (T1-3 N0 M0)	9	10	0.085	0.771
	IIB/III (T1-3 N1 M0)	16	15		
Location of tumour	Upper thoracic esophagus	6	5	0.234	0.890
	Middle thoracic esophagus	16	16		
	Both Upper & Middle Thoracic Esophagus	3	4		
Histo-pathology	Well differentiated SSC	9	5	2.307	0.316
	Moderate differentiated SSC	9	14		
	Poorly/ Un differentiated SSC	7	6		

Table 2: Acute haematological toxicities.

Level of toxicity	Arm (n=25)	0	1	2	3	4	χ^2	P
Hb	Concurrent	10	6	3	3	3	3.091	0.543
	Sequential	15	5	3	1	1		
TLC	Concurrent	13	7	2	3	0	1.387	0.309
	Sequential	16	6	2	1	0		
ANC	Concurrent	5	8	10	2	0	7.658	0.05
	Sequential	13	8	3	1	0		
Platelets	Concurrent	17	6	2	0	0	2.974	0.226
	Sequential	22	2	1	0	0		

This study also observed higher incidence of radiation induced toxicities (table 4) in concurrent arm as compare to sequential arm. Grade I pneumonitis was in 28% and 16% respectively (p =0.306), while grade I esophagitis was 32% and 20%, grade II esophagitis 20% and 8% respectively (p = 0.204). None of patient presented with grade II or higher pneumonitis and grade III or higher esophagitis. Renal and liver toxicities were mainly of grade 0 or I and well tolerated in patients of both arms. Comparison of overall toxicities was also done with age group, sex and grade of dysphagia at presentation (table 8, 9 and 10 respectively). We observed that overall grade III+IV toxicities were less in elderly patients of

sequential arm as compared to concurrent arm i.e. 42.8%(3 out of 7) vs. 62.5% (5 out of 8) respectively (p=0.225). Toxicities were equal in both type of sex groups and well tolerated. Patients that presented with grade IV or higher dysphagia had more grade III+IV toxicities in concurrent arm as compared to sequential arm (100% (8/8) vs 71.4% (5/7), p≤0.001).

These toxicities may be due to nil or poor oral intake of liquid and calories that further enhanced by concurrent chemoradiation in such patients. Complete response (CR) was superior in concurrent arm (Table 6 and 7) but there was no statistically significant difference between both arms.

At primary site, CR observed in 76% (19/25) patients of concurrent arm while it was in 68% (17/25) patients of sequential arm (p=0.529).

At mediastinal lymph node site, CR was observed in 73.66% (11/15) patients of concurrent arm while it was in 64.29% (9/14) patients of sequential arm (p=0.841).

Table 3: Acute non haematological toxicities.

Level of toxicity	Arm (n= 25)	0	1	2	3	4	χ^2	P
SGOT	Concurrent	22	1	2	0	0	2.356	0.308
	Sequential	23	2	0	0	0		
SGPT	Concurrent	19	5	1	0	0	1.505	0.471
	Sequential	22	2	1	0	0		
Alkaline phosphatase	Concurrent	24	1	0	0	0	0.355	0.552
	Sequential	23	2	0	0	0		
Bilirubin	Concurrent	22	3	0	0	0	0.222	0.637
	Sequential	23	2	0	0	0		
Creatinine	Concurrent	18	3	4	0	0	0.772	0.680
	Sequential	20	3	2	0	0		

Table 4: Acute radiation morbidity for lung and esophagus.

Level of toxicity	0	1	2	3	4	χ^2	p
Pneumonitis	Concurrent	18	7	0	0	1.049	0.306
	Sequential	21	4	0	0		
Esophagitis	Concurrent	12	8	5	0	3.178	0.204

Table 5: Overall maximum toxicity per Patient.

Overall toxicity grade	Concurrent Arm	Sequential Arm	χ^2	P
	No.	No.	13.393	
1	2	14		
2	11	20		0.004 (highly significant)
3	9	5		
4	3	1		
Total	25	25		

Table 6: Response at different sites.

Site	Response	Concurrent arm		Sequential arm		χ^2	P
		n=25	%	n=25	%		
Primary Esophageal Tumour*	CR	19	76	17	68	0.397	0.529†
	Non CR	6	24	8	32		
Mediastinal Lymph Nodes*	CR	11	73.33	9	64.29	0.346	0.841†
	Non CR	4	26.67	5	35.71		

* As per response criteria of JCOG.† Non significant.

Table 7: Overall response.

Response	Concurrent Arm		Sequential Arm	
	n=25	%	n=25	%
Primary=CR+ Lymph node=CR	8	32	7	28
Primary=CR+ Lymph node=Non-CR	2	8	1	4
Primary=Non-CR+ Lymph node=CR	4	16	3	12
Primary=Non-CR+Lymph node=Non-CR	2	8	4	16

Table 8: Comparison of overall toxicity in relation to age group in both arms.

Arm (n=25)	Age group (years)	Overall toxicity								χ^2	P
		1		2		3		4			
		No.	%	No.	%	No.	%	No.	%		
Concurrent	≤40	0	-	3	12	2	8	1	4	11.792	0.225
	41-50	0	-	3	12	3	12	0	-		
	51-60	2	8	2	8	0	-	1	4		
	>60	0	-	3	12	4	16	1	4		
Sequential	≤40	2	8	0	-	0	-	0	-		
	41-50	6	24	2	8	2	8	0	-		
	51-60	4	16	1	4	0	-	1	4		
	>60	2	8	2	8	3	12	0	-		

Table 9: Comparison of overall toxicity in relation to sex group in both arms.

Arm (n=25)	Sex	Overall toxicity								χ^2	P
		1		2		3		4			
		No.	%	No.	%	No.	%	No.	%		
Concurrent	Male	1	4	6	24	4	16	1	4	1.923	0.589 (Non Significant)
	Female	1	4	5	20	5	20	2	8		
Sequential	Male	9	36	2	8	3	12	0	-		
	Female	5	20	3	12	2	8	1	4		

Table 10: Comparison of overall toxicity in relation to grade of dysphasia in both arms.

Arm (n=25)	Grade of Dysphagia	Overall toxicity								χ2	P
		1		2		3		4			
		No.	%	No.	%	No.	%	No.	%		
Concurrent	2	2	8	5	20	0	-	0	-	48.119	<0.001 (Highly significant)
	3	0	-	6	24	4	16	0	-		
	4	0	-	0	-	5	20	1	4		
	5	0	-	0	-	0	-	2	8		
Sequential	2	6	24	0	-	0	-	0	-		
	3	8	32	3	12	1	4	0	-		
	4	0	-	2	8	3	12	0	-		
	5	0	-	0	-	1	4	1	4		

DISCUSSION

RTOG 85-06 trial was corner stone control that established the concept of concurrent chemoradiation.[5-7] Concurrent administration of chemotherapy acts as a promoter of the loco-regional effect of radiation as well as direct cytotoxic effects on its own. This regime has been tested in numerous trials, in pre-operative, post-operative and definitive settings.

Some investigators have postulated that induction (neoadjuvant) chemotherapy may be more effective than concurrent chemotherapy and radiation therapy, on the premise that areas of radio necrosis may become sanctuary sites for tumour resistant cells (i.e.,

theoretically may harbour treatment-resistant tumour cells) and that combined toxic effects may limit the dose of chemotherapy that can be given.[7] Patients with poor oral intake and poor performance status may not tolerate toxicities of concomitant chemoradiation.

In such patients neoadjuvant chemotherapy not only improves swallowing capacity but also deals with micrometastases. However, the duration of treatment is longer (disadvantage), but this approach is commonly used in our department for especially for patients with poor tolerance.

In RTOG 85-06 trial,5-7 Patients of concurrent arm received four cycles of 5-FU (1,000 mg/m2/24 hours for 4 days) and Cisplatin (75mg/m2 on day 1) with radiation(50 Gys as 2 Gy/fraction/day, 5 fractions/week), while radiation alone arm received radiation therapy (64 Gys as 2 Gy/fraction/day, 5 fractions/week).

Present study observed less grade III and grade IV acute toxicities in concurrent arm as compared to concurrent arm of RTOG 85-06 trial. Incidence of acute grade III toxicity in concurrent arm of present study was 36% vs 44% and grade IV toxicity was 12% vs 20% as compared to concurrent arm of RTOG 85-06 trial. These lesser acute toxicities in our study arm may be due to following differences.

Patients received 2 courses of chemotherapy instead of 4 courses as in RTOG 85-06. Dose of cisplatin (80 mg/m2) was divided in to 2 days, while 70 mg/m2 cisplatin administered on D1 in RTOG 85-06. Dose of 5 FU was 800 mg/m2/day for 2 days, while it was 1000 mg/m2 for 4 days in RTOG 85-06. Dose of EBRT was 44 Gys as compared to 50 Gys respectively.

Incidence of toxicities in sequential arm of present study was similar to radiation alone arm of RTOG trial (grade III toxicity 20% vs 25% and grade IV toxicity 4% vs 3% respectively).

In RTOG 92-07 trial8, 75 patients of thoracic esophageal carcinoma received combined regimen (cisplatin, 5-FU, and 50 Gy of radiation) followed by a boost with brachytherapy. HDR-ICBT was delivered in 3 fractions, each of 5 Gy and 1 week apart. Present study observed less acute toxicities in concurrent arm as compared to RTOG 92-07 trial.[8] Grade III toxicity was 36% vs 58%, grade IV toxicity was 12% vs 26% and grade V toxicity was 0% vs 8% respectively. These lesser toxicities may be due to similar differences on treatment regime that mentioned earlier and also due to lesser HDR fractions.

Ilson et al conducted a trial on neoadjuvant chemotherapy followed by radiation.[4] All patients received two course of chemotherapy (Cisplatin and 5 FU). Treatment was well tolerated all patient and none of the patient present with grade III toxicity. They summarized that neoadjuvant chemotherapy followed by radiation is a better treatment regime for elderly people and such patients whose general condition can't tolerate higher grade toxicities due to higher grade of dysphagia and poor nutrition.

CONCLUSION

Only a decade ago, it was debatable whether radiation alone is sufficient as definitive treatment of esophageal cancer, or whether chemoradiation is superior. Today, we know that if a patient can tolerate the combination of chemotherapy and radiation, this approach offers superior results.

Chemotherapy not only acts as radiosensitizer but also reduces or eliminates micro metastases. In this study, local control and regional control were superior in concurrent arm as compared to sequential arm. There are some patients in whom it is clear that surgery is not possible, and therefore concurrent chemoradiation should be used.

Some examples 12 include: the patient who has a medical contraindication to surgery, the patient whose tumour would be technically unresectable because of involvement of local structures, the patient who would require a laryngo-esophagectomy for cervical esophageal disease, because of the high incidence of lifelong aspiration after such a procedure and the patient who refuses surgery.

No doubt, incidence of grade III+IV toxicities is higher in concurrent chemoradiation as compared to sequential chemoradiation. Present study observed overall grade III+IV toxicity were 32% vs 20% respectively (p=0.841). This is very important in such patients who are elderly or having severe dysphagia. In this study, elderly patient had grade III+IV toxicity 62.5% vs. 42.8% (p=0.225). Similarly, patients with grade IV or higher dysphagia had higher incidence of severe toxicities in concurrent arm as compared to sequential arm i.e. 100% vs. 71.4% respectively ($p < 0.001$ highly significant). Such patients have deficiency of nutrition and energy and show very poor tolerance for concurrent chemoradiation. So this group could be treated with sequential chemo radiation.

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