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RESEARCH ARTICLE

Dose Escalation by Intraluminal Brachytherapy in Cancer Esophagus – A Retrospective Audit

Richa Gupta[1#], Piyush Kumar[2], Ankita Mehta[3$], Ayush Garg[4], Shubhi Agarwal[5@]

ABSTRACT

Introduction- Chemoradiation (CRT) in esophageal cancer as a definitive modality of treatment has shown an increasing trend of utilization over surgical modalities. Local failures after chemoradiotherapy have led to the concept of radiation dose escalation, but simultaneously it leads to the concerns of radiation related toxicities of strictures and fistulas. Considering this fact dose escalation with intraluminal brachytherapy seems and optimal option. The present study retrospectively analyzed the safety and efficacy of using ILBT as a boost after external beam radiotherapy.

Materials and Methods- Records of patients with Esophageal Carcinoma (EC) registered in the radiotherapy department between December 2008 to June 2016 were retrospectively anwalyzed. Data was collected on patient, tumor and treatment characteristics and patient outcomes. The toxicities-hematological or radiation-induced were documented. The response assessment after treatment and survival parameters were analyzed. Univariate and multivariate analyses were done for survival parameters. Statistical significance was considered if *p-value* was less than 0.05.

Results- A total of 69 patients were eligible for the present analysis. Male to female ratio 1.09:1, with median age of 60 years. The common primary side was the middle 1/3rd esophagus. The mean tumor length was 6.4cm and all patients had squamous cell carcinoma. EBRT dose of 59.4 Gy was received 94.2% of patients, 13 (18.8%) received ILRT radiotherapy with 6Gy in a single setting. The median concurrent chemotherapy administered were 5. Grade 3 and 4 acute hematological toxicities were seen in terms of anemia (7.2%), leucopenia (18.8%) and thrombocytopenia (1.4%). Stenosis was seen in 40.6% of patients among which only 13 patients required dilatation. Nine of the patients receiving intraluminal brachytherapy (ILBT) developed fistula. The compete response was better in ILBT group (84.61 vs 57.49%, p=0.07). The median overall survival for all patients was 15 months. Overall survival was increased in patients of ILBT group (41 months versus 12 months, p=0.005).

Conclusion- ILBT has the advantage of high precision and avoidance of dose to critical structures which could be optimally used for dose escalation in patients of cancer esophagus.

Keywords: Cancer esophagus, Diose escalation, Intraluminal brachytherapy.

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INTRODUCTION

Chemoradiation (CRT) in esophageal cancer as definitive modality of treatment has shown an increasing trend of utilization over surgical modalities. Nearly 50% of the patients relapse locally after CRT, with majority being within the Gross Tumor Volume (GTV).[1] This incites the concept of radiation dose escalation and the ideal radiation dose schedule remains a long-standing controversy. Recent meta-analysis[2,3] have proven survival advantage with external beam radiation (EBRT) dose of more than 60 Gy. Because the majority of failures occur within GTV, the dose escalation with the intraluminal brachytherapy (ILBT) technique seems to be an additional boost option after EBRT.

The concept of ILBT for dose escalation was tested nearly two decades back in the multi-centric randomized trial RTOG 9207.[4] The results were discouraging as life-threatening toxicity was observed in nearly 24% of the patients. However, this trial had been criticized because of a relatively higher dose of brachytherapy utilized along with concurrent chemotherapy. Another multi-institutional randomized trial comparing the outcomes with and without ILBT was conducted by the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group.[5] Their findings were contrary to that of RTOG 9207 trial with the ILBT group showing a significant improvement in survival with comparable

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Consultant[1], Professor[2], Senior Resident[3], Assistant Professor[4], Clinical Observer[5]

[1,2,4]Department of Radiation Oncology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India

[3$]Department of Radiation Oncology, Tata Memorial Hospital, Visakhapatnam, Andhra Pradesh, India

[5@]Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota, U.S.A

Corresponding Author: Piyush Kumar, Professor, Department of Radiation Oncology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India
Email- piykumagr@gmail.com

incidence of early and late toxicities. There have been several studies evaluating the efficacy of high dose schedules in carcinoma esophagus with the utilization of contemporary conformal techniques, but only few studies comprising of retrospective series have evaluated the role of ILBT as boost in the past two decades. There is a reluctance to practice ILBT due to the concerns of radiation related toxicities of strictures and fistula. The present study retrospectively analyzed the safety and efficacy of using ILBT as a boost after EBRT.

MATERIALS AND METHODS

Study population

Records of patients with esophageal carcinoma (EC) registered in the radiotherapy department between December 2008 to June 2016 were retrospectively analyzed. Information was gathered on 127 patients. Patients without treatment or with incomplete details were excluded from the evaluation. Further, patients treated with only adjuvant irradiation, chemotherapy without irradiation or radiotherapy of metastasis were also excluded. Finally, patients treated with only definitive concurrent CRT were selected for analysis.

Patients were staged according to AJCC 2017 (8^{th} edition) staging system. Data was collected on patient, tumor and treatment characteristics and patient outcomes. Information was retrieved on outcomes from patient records, telephonic calls, or home visits. Analysis was done on an "intention to treat basis" where the patients who defaulted treatment during treatment were also included. The analysis for surviving patients was done in 2020, presented in 2021 ASCO Annual meeting6, and published as abstract form. In this study, the findings of final analysis were done in 2021 and is being reported.

Treatment planning

All patients were treated with Computed Tomography (CT) based 3D-conformal radiotherapy. CT simulation scan of the thorax with slice thickness 5 mm using oral and intravenous contrast was done in supine position. Gross tumor volume (GTV) was contoured with the help of CT scan and findings of esophagogastroduodenoscopy. In the first phase, the radiation field was designed to include GTV with a clinical target volume (CTV) margin of 4 cm craniocaudal and 2 cm radially. A planning target volume (PTV) margin of 1 cm was added and patients were planned for 36 Gy in 20 fractions by anterior-posterior and posterior-anterior fields. In the second phase, a shrinking field with a CTV margin of 2 cm cranio-caudally and 1.5 cm radially with a 1 cm PTV margin was designed. A dose of 23.4 Gy in 13 fractions was planned with anterior and two lateral fields. The spinal cord was shielded in lateral fields. The plans were optimized individually using field-in-field technique, varying beam weightage and enhanced dynamic/physical wedges. All patients have planned a total EBRT dose of 59.4 Gy in 33 fractions with weekly concurrent chemotherapy. Chemotherapy was withheld temporarily if patients had grade three hematological toxicity, ≥ grade 3 esophageal toxicities and decline in the general condition.

Intraluminal Brachytherapy

Intraluminal radiotherapy (ILRT) was routinely given to patients till December 2012. A minimum of 1-week gap was given for ILBT after the completion of EBRT. The diameter of the applicator used was 6 mm. X-ray-based treatment planning was done. The target volume was taken as the pre-radiotherapy GTV with 1 cm craniocaudal expansion. The dose was prescribed at 5 mm depth from the mucosal surface. A HDR dose of 6 Gy was delivered in a single fraction.

The overall radiotherapy dose was calculated by converting it into equivalent dose in 2 Gy fractions (EQD_2) (considering $\alpha/ß=3$).

Toxicities

Acute hematological toxicity was graded according to CTCAE version 4.03 & late esophageal toxicities by RTOG scoring criteria.

Response assessment and follow-up

Response to treatment was analyzed one month after treatment by esophagogastroduodenoscopy and follow-up details were seen for residual, recurrence, or metastasis by appropriate imaging modalities.

Survival

All survival parameters were calculated starting from date of registration in the radiotherapy department. Overall survival (OS) was defined as the time to death. Survival analysis was calculated on "worst-case scenario" basis. It means that the 21.7% lost to the follow-up cohort were considered as an event (in SPSS evaluation) along with the patients who died. Failure was considered if any suspicious lesion is radiologically documented or pathologically proven. Disease-free survival (DFS) was defined as the time to any failure. Loco-regional DFS (LR-DFS) was defined as any failure within the radiation treatment volume or in the regional lymphatics like a mediastinal or supraclavicular group.

Statistics

Statistical analysis was performed using SPSS software (release 23.0.0). Survival curves were generated using

the Kaplan- Meier method. The influence of categorical variables on survival was investigated with the Log-Rank test for univariate analyses. Multivariate analysis was done using Cox proportional hazards model by the backward stepwise method. The chi-square, Fisher's exact, and t-test were used to detect any correlations between categorical and continuous prognostic variables. Statistical significance was considered with a *p-value* of < 0.05.

RESULTS

A total of 69 patients were eligible for the present analysis out of the 127 patients with esophageal cancer (Figure 1).

Patients' characteristics

The study population had a male to female ratio of 1.09:1 with median age of 60 years. All patients had a Karnofsky performance scale of more than 70. Most of the patients had grade 2 dysphagia. Nearly half of the study population were smokers and one-third were alcoholics. (Table 1)

Tumor Characteristics

The commonest primary tumor site was middle one-third of the thoracic esophagus, while the cervical esophagus location was rare in less than 3% of patients. The clinical stage was T3 in the vast majority of the patients, with most having node negative disease. The mean tumor length was 6.4cm. All patients had squamous cell carcinoma with the most moderately differentiated grade observed in nearly 63.8% of patients. (Table 2)

Treatment Characteristics

Patients were planned for a total radiation dose of 59.4 Gy in 1.8 Gy per fraction. All patients were treated with three-dimensional conformal external radiotherapy to a median dose of 59.4 Gy (range 8-63 Gy). An EBRT dose of 59.4 Gy was received by 94.2% of the patients. Thirteen patients (18.8%) received intraluminal radiotherapy (ILRT), with 6 Gy in single sitting. The median overall treatment time was 45 days. The median concurrent chemotherapy cycles administered were 5 (range 2 to 7) (Table 3).

Toxicities

Grade III and IV acute hematological toxicity was seen in terms of anemia (7.2%), leucopenia (18.8%) and thrombocytopenia (1.4%). Grade III and renal toxicity was seen in 2.9% of patients with no severe liver toxicity. In the present study stenosis was seen in 40.6% of patient (n=28). Among these, dilatations were required only in 13 patients with more than Grade III stenosis. Stenting was done in 4 patients who failed to dilatation. One patient developed a trachea-esophageal fistula (TOF) which was due to disease recurrence. (Table 4)

Table 1: Patient characteristics

Characteristics	*No. (%)*
Sex	
Male	36 (52.2)
Female	33 (47.8)
Age (yr), Median	60 (Range 40-80)
Mean	60.4 ± 10.3
KPS Median	80
Range	70-90
Dysphagia at presentation	
Grade 1	21 (30.2)
Grade 2	31 (44.9)
Grade 3	17 (24.6)
Grade 4	0 (0)
Smoking	
Yes	36 (52.2)
No	33 (47.8)
Alcohol	
Yes	23 (33.3)
No	46 (66.7)
Hb at start of treatment	Mean = 11.7 ± 2.2

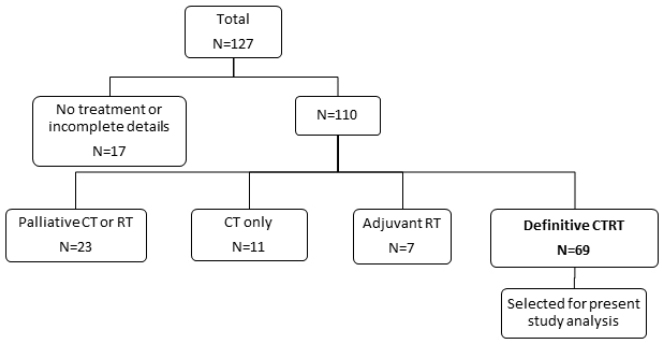

Figure 1: Patient selection

Feeding jejunostomy (FJ) was done in 3 patients, 2 of whom required it due to the development of absolute dysphagia during radiation treatment and succumbed to its complication. The third patient had residual disease after treatment and required FJ due to disease progression. Patients receiving ILBT developed higher incidence of strictures (61,54 vs 35.71%), but a significant difference (p=0.2) could not be demonstrated. The severity of stenosis in terms of grading of dysphagia was also comparable amongst both groups. There were no serious complications in 13 patients who received a higher RT dose by ILBT. One patient had grade 1 stricture. Another 4 patients had grade 2 dysphagia out of which one required a single course of dilatation, while in the other 3 patients who developed grade 3 stenosis, one required dilatation and two needed stenting. None of the patients receiving ILBT developed a fistula but it was

Table 2: Tumor characteristics

Characteristics	*No. (%)*
Primary tumor location	
Cervical	2 (2.9)
Upper	19 (27.5)
Middle	40 (58)
Lower	8 (11.6)
Tumor length (cm), mean	6.4± 2.4
≤6cm	35 (50.7)
>6cm	34 (49.3)
Tumor location	
Above carina	35 (50.7)
At or below carina	34 (49.3)
Tumor stage	
T1	0 (0)
T2	3 (4.3)
T3	63 (91.3)
T4	3 (4.3)
Nodal Stage (clinical)	
N0	42 (60.9)
N1	12 (17.4)
N2	8 (11.6)
N3	7 (10.1)
LN laterality	
N0	42 (60.9)
Unilateral	16 (23.2)
Bilateral	11 (15.9)
HPE grade (SCC)	
WD	7 (10.1)
MD	44 (63.8)
PD	2 (2.9)
NA	16 (23.2)

observed in one patient receiving EBRT alone as a result of recurrent disease.

Response assessment at 1 month after radiotherapy

The complete response was seen in 60.9% (n=42) of the patients analyzed (Table 5). On comparison of complete response of patients treated with additional ILBT, the complete response was better in this group (84.61 vs 57.49%) which showed a statistical trend towards significance (p=0.07).

Patterns of failures

Local recurrence was the major pattern of recurrence found in our study (23.2%). Distant recurrences were found in 8 patients. We found metastasis to brain in 2, liver in 1, lung in 1, vertebra in 1, para-aortic nodes in 1 and, perihepatic mass and peritoneal deposits in 1 patient.

Table 3: Treatment characteristics

	No. (%)
EBRT dose (Gy)	
Median	59.4
Range	9-63
EQD2 (Gy)	
Median	57.02
Range	8.64-69.5
ILRT	13 (18.8)
Chemotherapy	
NACT + CCT	4 (5.8)
CCT only	65 (94.2)
Concurrent CT	
Weekly Cis+5FU	65 (94.2)
Others*	4 (5.8)
No. of Concurrent CT cycles**	
≥5	51 (73.9)
<5	17 (24.6)
Median OTT (days)	45

*Carbo + 5FU=2, Cisplatin alone = 1, Gefitinib = 1
**n = 68, patient on gefitinib excluded.

Table 4: Toxicity

	No. (%)
Acute toxicity (gr 3-4)	
Anemia	5 (7.2)
Leucopenia	13 (18.8)
Thrombocytopenia	1 (1.4)
Renal toxicity	2 (2.9)
Liver dysfunction	0 (0)
Late toxicity	
Stricture	28 (40.6)
Dilatation required (Stenosis grade ≥3)	13 (18.8)
Stenting done (failure of dilatation)	4 (5.8)
TOF	1 (1.4)

One patient had multiple metastasis sites, including lung, liver, abdominal wall, gluteal and scapular region.

Survivals

Patients were followed for a median period of 15 months (range 1-85 months). At the time of last follow-up 11 (15.9%) patients were alive, 43 (62.3%) were dead and 15 (21.7%) were lost to follow-up. Twenty-seven patients were clinically disease-free at the time of last follow-up. Median OS for the entire cohort was 15 months (Figure 2).

On univariate analysis, age, gender, tumor length, number of concurrent chemotherapy cycles, ILRT and response at the end of treatment were found to be statistically significant for OS. On multivariate analysis,

Table 5: ILRT patient characteristics

S. No.	*Age/ Sex*	*Tumor length (cm)*	*T stage*	*Response to treatment*	*Toxicity (Supportive management)*	*Recurrence/ metastasis*	*Status at last follow-up*	*OS (months)*
1	65/F	4.5	T2	CR	-	Local recurrence	Dead	65
2	65/F	12	T3	Non-CR	Grade 3 stenosis (Stenting)	Residual	Dead	12
3	40/F	6	T3	CR	Grade 3 stenosis (Stenting)	NED	LFU without disease	50
4	74/M	2.4	T3	CR	-	Local recurrence	Dead	20
5	55/F	4	T3	CR	Grade 3 stenosis (Dilatation)	NED	LFU without disease	11
6	65/M	3	T2	CR	Grade2 stenosis (Dilatation)	Local recurrence	LFU	18
7	71/M	8	T3	Non-CR	-	Local & distant recurrence	Dead	7
8	45/F	5	T3	CR	-	Local recurrence	Dead	41
9	55/F	8	T3	CR	Grade 2 stenosis (Dilatation)	NED	Dead	67
10	58/F	2.5	T3	CR	Grade 2 stenosis (None)	NED	Alive	85
11	55/F	6	T3	CR	Grade 1 stenosis (None)	NED	Alive	83
12	64/M	4.5	T3	CR	Grade 2 stenosis (None)	NED	Alive	82
13	46/M	7	T3	CR	-	NED	Expired due to myocardial Infarction	3

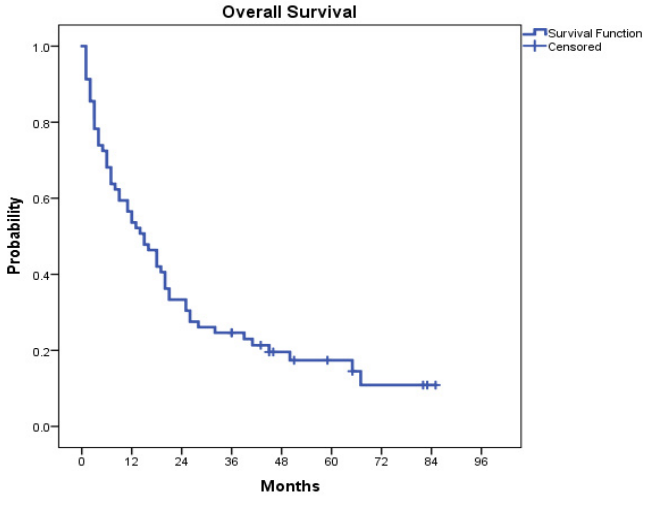

Figure 2: Overall survival (Kaplan Meir method)

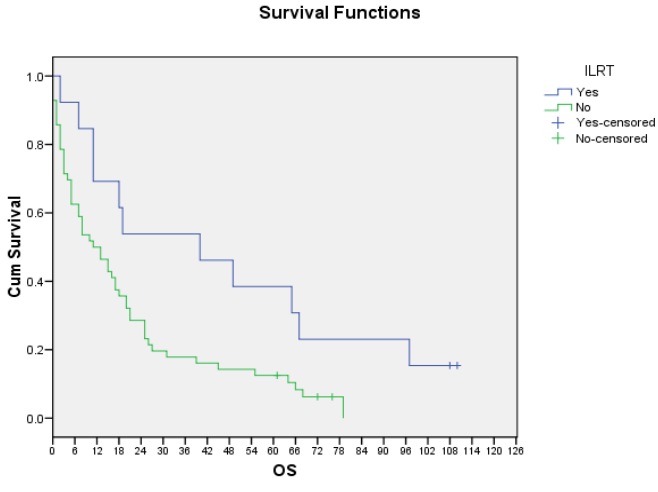

Figure 3: Overall survival of patients treated with EBRT and EBRT + ILBT

response at the end of treatment (HR = 3.406 [1.743-6.656], p <0.001) and gender (HR = 2.999 [1.656-5.429], p < 0.001 remained statistically significant factors. (Table 5)

In separate multivariate analysis for OS by including EQD2 dose and overall treatment time (OTT) along with other variables EQD2 dose (HR = 0.957 [0.933-0.981], p = 0.001) also was found to be statistically significant besides treatment response and gender. (Table 6)

For LR-DFS, on univariate analysis, T-stage, NACT and number of concurrent chemotherapy cycles were statistically significant. On multivariate analysis, EQD2 dose was statistically significant. (Table 5,6) Details of patient treated with ILBT is seen in Table 7. On comparison of survivals between the patients treated with ILBT and those not, significant overall survival was seen (41 vs 12 months, p=0.005). (Figure 3)

DISCUSSION

The dose escalation concept remains a long-standing debate amongst radiation oncologists. In the landmark

Table 6: Univariate analysis

		OS			*LR-DFS*		
Variable	*Total N*	*No. of events*	*Median OS*	*P-value*	*No. of events*	*Median LR-DFS*	*P-value*
Age							
<=65	49	39	18	0.012	24	21	0.098
>65	20	19	7		13	6	
<=60	35	27	19	0.034	17	32	0.158
>60	34	31	7		20	10	
Gender							
Male	36	33	7	0.005	19	18	0.503
Female	33	25	21		18	16	
Site							
Cervical	2	2	7	0.807	2	0	0.450
Upper	19	15	15		10	13	
Middle	40	34	13		20	22	
Lower	8	7	18		5	6	
Relation with Carina							
Above	35	29	14	0.932	19	13	0.972
At or below	34	29	15		18	18	
Tumor Length							
<=6 cm	35	27	20	0.011	19	22	0.382
>6cm	34	31	7		18	10	
<=5 cm	26	19	20	0.008	13	32	0.156
>5cm	43	39	7		24	10	
T stage							
T2	3	3	25	0.131	3	18	0.012
T3	63	52	15		31	21	
T4	3	3	6		3	0	
N stage							
N0	42	35	18	0.743	23	18	0.945
N1	12	10	6		5	5	
N2	8	7	7		4	13	
N3	7	6	19		5	19	
Laterality of nodes							
Unilateral	16	14	6	0.441	6	5	0.674
Bilateral	11	9	15		8	13	
N0	42	35	18		19	18	
HPE grade							
WD	7	4	25	0.385	3	-	0.543
MD	44	38	12		26	10	
PD	2	2	1		1	0	
NA	16	14	18		9	19	
Dysphagia							
Grade 1	21	15	18	0.110	9	-	0.388
Grade 2	31	27	18		18	12	
Grade 3	17	16	12		10	10	
Smoking							
Yes	36	31	7	0.116	17	18	0.828
No	33	27	20		20	16	

Alcohol							
Yes	23	20	9	0.249	12	6	0.764
No	46	38	16		25	18	
Chemotherapy							
CCT	65	54	14	0.493	33	21	0.044
NACT + CCT	4	4	15		4	0	
Chemo regime							
Cis + 5-FU	65	54	15	0.794	34	18	0.660
Others	4	4	9		3	6	
No. of CCT Cycles							
>=5	51	41	18	0.013	24	22	0.023
<5	17	16	8		12	0	
ILRT							
Yes	13	10	41	0.028	6	32	0.291
No	56	48	12		31	13	
Initial Hb							
<=10	10	10	7	0.189	6	0	0.495
>10	58	47	15		31	18	
Response at end of treatment							
CR	42	33	21	< 0.001			
Non CR	25	23	6				

Table 7: Multivariate analysis

Variable	*HR*	*95% CI*	*p-value*
OS			
Gender (Male vs Female)	2.873	1. 590 - 5.192	<0.001
EQD2	0.958	0.935 - 0.982	0.001
Response at the end of treatment (non CR vs CR)	3.172	1.616 – 6.225	0.001
LR-DFS			
NACT	2.671	0.927 – 7.698	0.069
EQD2	0.962	0.939 – 0.986	0.002

RTOG 94-05 phase III trial by Minsky *et al.*[7], the high radiation dose of 64.8 G versus lower dose of 50.4 Gy with concurrent chemotherapy did not increase the OS or loco-regional control. Rather, a higher mortality in the high-dose arm led to interim closure of this study. Henceforth, a standard practice of delivering 50.4 Gy of RT with concurrent cisplatin and 5-fluorouracil was established as standard treatment for EC. But this trial has been criticized because of the utilization of conventional techniques. Also, the majority of the deaths in high-dose arm occurred before a dose of 50.4 Gy was delivered. This questions the validity of standardization of definite EBRT dose to 50.4 Gy.

At our institute, ILBT was in practice till year 2012 but it was stopped because of conflicts and dilemmas regarding its use. We planned to conduct a retrospective analysis in 2017, which showed a significant survival advantage with the addition of ILBT. The analysis was repeated for the surviving patients in the year 2020 and was published in 2021 ASCO Annual meeting.[6] The overall survival was significantly higher (45.3 vs 19.2 months, p=0.005) with comparable incidence and severity of strictures.

Dose escalation is not a recent concept. In the end of last century, a randomized study was conducted by Okawa *et al.*[8] (1999) where patients after completion of EBRT to a dose of 60 Gy were randomized to a 10 Gy boost to the primary tumor by EBRT or ILBT. The ILBT applicator diameter was 1 cm. After the completion of entire radiation course, patients were kept on maintenance with oral etoposide. Their study also showed no significant difference in response rates with either of the approaches. A significant improvement in the overall survival in favor of boost by ILBT over EBRT (64 versus 31.5%; p = 0.025) was seen. Also, the early and toxicities were comparable amongst both groups. This study highlights that boost by ILBT can be more efficacious in improving the outcomes compared to EBRT in a selected group of patients. This supports the findings of our study, proving ILBT to be safe, efficacious, and well-tolerated option.

Results of our study reveal that higher dose of EBRT (in terms of EQD2) was related with better OS as well as LR-DFS. RT dose also had a statistically significant relationship with tumor response. Our results are also supported by several prospective as well as retrospective studies which report higher EBRT dose to be more

Table 8: Studies showing positive correlation between high radiation dose and good oncologic outcome

Author, Year	*Type*	*Protocol Stage/ Histo/Location RT Technique CCT*	*RT Dose Or Arms*	*N*	*Results*		
					OS	*LDFS or LRC*	*Complication rate*
Zhen Zhang[9] 2005	Retro	II-III/any/any 2D-RT Cis/5FU	<51 Gy ≥51 Gy	43 26	3yr 3% 13% (P=0.054)	3yr LCR 19% 36% (P=0.011)	no significant differences
Sara Torrente[10] 2012	Retro	IIa-IVa/ any/any 3DRT Cis- or Carbo-platin/ 5FU	<60 Gy ≥60 Gy	26 14	P=0.53	LRC P=0.02	Gd3 acute toxicity-7.5% Gd4 renal failure in 1 () Gd3 late toxicity 5%
Liru He[11] 2014	Retro	Any/SCC/any 3D-RT/ IMRT/ Proton Weekly platin- or taxane based CCT	≤50.4 Gy >50.4 Gy	137 56	5yr 33% 41.7% (P=0.617)	Local failure rate 34.3 17.9 (P=0.024)	Higher gd 3 skin reaction (12.5% vs 2.2%, $p < 0.001$) ≥gd 3 esophageal stricture (32.1% vs18.2%, p =0.037).
Yang-Gun Suh[12] 2014	Retro	II-III/ALL/ANY 2DRT 5FU based	<60 Gy ≥ 60 Gy	49 77	MedOS 18 mth 28 mth (P=0.26)	2yr LRC 32% 69% (P<0.01)	no significant differences
Wen Yu[13] 2015	Phase I	Any/scc/any IMRT Cis/5FU q3weekly x 2	Escalating radiation dose of 4 levels, with a SIB to the pre-treatment 50% SUVmax area of the primary tumor	25	1 yr OS 69.2%	1 yr LC: 77.4%	Acute toxicities well tolerated
Chih-Yi Chen[14] 2016	Retro	I-III/SCC/any 3D-RT CCRT	50-50.4 Gy ≥60 Gy	324 324	5yr 14% 22% (P<0.05)	-	-
Jianzhou Chen[15] 2016	Phase II	II-IV/any/any SIB-IMRT Cis/ 5FU based	GTV 66 Gy /30f CTV 54 Gy/30f	60	2 yr 72.7%	2 yr LCR 78.6%	≥gd 3 acute toxicity: neutropenia (16.7%), esophagitis (6.7%), thrombopenia (5.0%) ≥gd 3 late toxicity (18.3%); death due to esophageal hemorrhage (3.3%)
James W. Welsh[16] 2017	Phase I/II	Unresectable/all/ any IMRT Docetaxel/5FU or Capecitabine	GTV 58.8–63 Gy PTV 50.4 Gy	44	Med OS 30.8 mth 1 yr OS: 71.3%	At 1 yr: 69.9%	No CTCAE grade 4 or 5 toxicity
Chia-Lun Chang[17] 2017	Retro	I-III/SCC/TH IMRT Cis based	< 60 Gy ≥ 60 Gy	1134 927	2yr OS 26.74% 35.47% (P<.0001)	-	-
Hyun Ju Kim[18] 2017	Retro	II-III/ALL/ANY 3DRT or IMRT 5FU/Cis	<60 Gy ≥ 60 Gy	120 116	Med OS 22.3 mth 35.1 mth (P=.043)	2yr LRC 50.3% 69.1% (P=.002)	no significant differences

Chao-Yueh Fan[19] 2018	Retro	I-IVA/any/any 3DRT/ IMRT/ VMAT Cis/ 5FU or Cis, 5 FU monotherapy	<66 Gy ≥ 66 Gy	44 71	3 yr OS 32.1% 17.9%% (P=0.026)	3yr LPFS 46.1 72.1% (p=0.005)	Acute dermatitis (7% vs 28%, p=0.009)
Hongmin Chen[20] 2018	Retro	I-IVA/ SCC/any 2DRT/ 3DRT/ IMRT CCRT	Low dose <60 Gy Higher dose 60–65 Gy Excessive dose >65 Gy	17 51 56	Higher OS with high dose vs low dose (P=0.026) Higher OS with high dose vs excessive dose (P=0.033)	-	In excessive dose group almost all Gd 4 acute toxicities & ≥ Gd 2 radiation esophagitis
Xuejiao Ren[21] 2018	Retro	I-IVA/SCC/any 3DRT/ IMRT Cisplatin based	50.4-54 Gy 60 Gy	380	10yr OS 13.3% 24% P=0.001	10yr LC 29.8% 52% P=0.028	Ac. Esophagitis (gd 2-3) :27.9% vs 37.4% (not sig.) No sig. difference in >gd 3 toxicities
Navin Nayan[22] 2018	Prosp	I–III/SCC/thoracic 2DRT Cis/5FU q3weekly x 2	50.4 Gy 64.8 Gy	14 14	78.6% in both group (median follow-up 21 mth)	CR- 71% vs 64% (p=0.38)	No toxicity > gd2
Wei Zhang[23] 2018	Retro	II-III/ SCC/ any (who achieved cCR after definitive CRT) 3D-RT or IMRT Platin- based CCT	50.4 - 56 Gy ≥59.4 Gy	43 37	5yr 21% 42.8% P=0.028	LRF 64.5% 37.5% P=0.04	no significant differences

effective (Table 8).[9-23] There is even evidence of a dose-response relationship in systematic reviews.[24-26] In the landmark multi-institutional prospective RTOG 9207 study[4], ILBT was delivered with HDR schedule of 15 Gy in 3 fractions or LDR dose of 20 Gy after a gap of 2 weeks after completion of 50 Gy EBRT. Concurrent chemotherapy was delivered during EBRT and ILBT as well. The toxicity rate was quite high with treatment radiation fistulas observed in nearly 12% of the patients, 24% life-threatening toxicities and 10% treatment-related deaths. Given the high incidence of toxicity, the protocol was amended and dose of HDR brachytherapy was reduced to 10 Gy in 2 fractions. With reduced ILBT dose, none of the patients developed a fistula. Further, a higher number of chemotherapy cycles, concurrent use with ILBT and smaller outer diameter of applicator of 4 to 6 mm only have also been implicated behind the high incidence of toxicities. As the study did not demonstrate any clear benefits of ILBT in terms of tumor response, local control, survival rates, further investigation in phase III setting was not conducted. The dismal outcomes of this trial led to refraining from the practice of ILBT. Comparing this study design to the study by Okawa *et al.*[8], there are key differences in methodologies that possibly explain the difference in survival outcomes with ILBT. In Okawa *et al.*8 study, comparatively ILBT dose was lesser, concurrent chemotherapy was omitted and the applicator diameter was higher. We may infer from both studies that optimizing treatment planning and dose schedules may help in dose escalation with better survivals and lesser toxicities.

With experience and knowledge of radical radiation dose in head and neck malignancies being 66-70 Gy, we find the low dose of 50.4 Gy in EC quite surprising. Anatomically, esophageal mucosa is a continuation of the hypopharynx which is being followed upwards into the oropharynx. By this hypothesis, we were initially treating patients of EC with EBRT dose of 59.4 Gy in 33 fractions with concurrent chemotherapy, followed by single fraction of 6 Gy of esophageal brachytherapy (total Biologically Effective dose (BED)=113 Gy, EQD2=67.2 Gy).

In the present retrospective analysis, the treatment protocol in initial years was EBRT to a total dose of 59.4 Gy in 33 fractions followed by an additional ILBT of 6 Gy in a single fraction. Tis protocol had higher response rates (84.61 vs 57.49%, P=0.07) and overall survival (41 vs 19 months, P=0.005) with comparable incidence and severity of strictures. Further, none of the patients developed a

fistula after ILBT. This protocol seems to optimize the schedule between Okawa *et al*.[8] and RTOG 9207 trial.[4]

In a recent prospective single-arm study by Tanvirpasha *et al*.[27], 20 patients were treated by external beam radiotherapy to a dose of 45 Gy with concurrent chemotherapy (cisplatin and capecitabine) followed by intraluminal brachytherapy 4Gy x 3 fractions, the total BED of 60 Gy. The study showed favorable results with 2-year disease-free survival rate of 60%- and a 5-year survival rate of 47% validating the findings of our study. In terms of toxicity, nine patients developed stricture 3 months after completion of treatment but all of them were successfully managed by dilatation. The tracheoesophageal fistula was reported only in a single patient. This was far lesser compared to the incidence in RTOG 9207 study.[4]

In a dose escalation study by Zhang *et al*.[23], patients showing complete response after a dose of 50.4 Gy, further dose escalation upto 59.4 Gy significantly improved the local control, recurrence-free survival, and overall survival compared to the standard arm.

The findings of National Cancer database (NCDB)[28] analysis reported nearly 6 years back comparing various dose schedules binned as 50 to 50.4 Gy, 51 to 54 Gy, 55 to 60 Gy, and > 60 Gy. This study failed to show any advantage beyond the standard dose schedule of 50 to 50.4 Gy even in subset analysis by histological subtype or IMRT technique. But the findings of recent meta-analysis published in the last 3 years strongly support dose escalation at least upto 60 Gy. A meta-analysis[2] with total radiation dose ranging from 45 to 75.6Gy with most of the patients treated by 3D-conformal radiotherapy or IMRT, a significant benefit in favor of radiotherapy dose > 60Gy was observed in terms of local recurrence free survival, progression-free survival, and overall survival ($P < 0.001$). Another recent meta-analysis[3] compared low dose (38-60Gy) and high dose radiotherapy (50.4–72Gy) in the patients treated by advanced radiation techniques excluding the patients treated by brachytherapy. Like NCDB analysis, there was no significant OS benefit (P 0.43) in subgroups comparing dose of ≤ 50.4 to >50.4Gy. But a dose of ≥ 60 led to substantial survival benefits compared to a dose of< 60Gy (P< 0.0001). Also, there were no significant differences were observed in toxicities in terms of grade 3–5 radiation pneumonitis, esophagitis, treatment-related death, or distant metastasis. The results of these two meta-analyses highlights significant increase in overall survivals beyond 60 Gy. Considering cardiopulmonary toxicities dose escalation can be planned by ILBT. There is need for randomized studies like Okawa *et al.* with optimization in treatment strategy.

The concern with higher dose of RT is the risk of increased toxicities. We found acceptable toxicities in our study that were easily managed conservatively. The initial practice of esophageal brachytherapy was abandoned after the alarm raised by RTOG 9207[4] trial showed increased fistula incidence, especially in conjunction with concurrent chemotherapy. In our study, even patients treated with higher dose of RT by inclusion of ILRT did not experience any grade3/4 toxicities.

In our audit of those patients who were treated with higher RT dose with inclusion of esophageal brachytherapy, we are surprised to see statistically significant increase (P=0.005) in OS (41 months) with no single incidence of fistulas in any case. On the contrary, abandoning the esophageal brachytherapy led to a very low median OS (12 months) in a median follow-up period of 15 months (1–85 months). In comparison to our evaluation done in 2020 and presented in ASCO (2021)[6] though the median survival has decreased (45.3 vs 19.2 months, p=0.005) but the difference of survival has increased (29 months versus 26 months).

In the present study, we included all the planned patients who started with definitive concurrent chemoradiation. Median OS and LR-DFS of entire cohort were 15 and 13 months, respectively. Included in the analysis were 2 patients who expired during treatment due to complications of FJ, 1 who expired due to electrolyte imbalance and 9 who did not complete treatment. Further, 2 patients did not come for first follow-up and 1 patient expired due to MI 1 month after treatment. If we adjust for these 15 patients, the median OS and LR-DFS of remaining cohort rises up to 19 and 32 months, respectively. This is in accordance to the literature for patients treated with definitive CRT.

The incorporation of new radiotherapy techniques such as IMRT and image-guided radiotherapy can improvise the initial protocol of additional ILBT in this retrospective study. The dose to heart and lungs can be reduced to borderline dose constraints by utilizing IMRT plannings to a total dose of 56 -60 Gy in 28 to 30 fractions followed by single fraction of ILBT. Recently, we conducted a dosimetric analysis in patients of cancer esophagus where there was better homogeneity and conformity compared to 3D CRT along with better cardiac sparing.[29] IMRT has become our institute's preferred modality for esophagus cancers. Our study has several limitations. Firstly, small sample size and disproportionate distribution amongst both the groups because of which a post hoc analysis could not be done. Another major limitation of the present study is its retrospective nature. Henceforth, clinical adoption demands further research in large-scale prospective randomized trials. The findings of our study if validated in further large-scale randomized studies can be a major

breakthrough in improving the poor local control rates and survival rates of esophageal malignancies.

CONCLUSION

The ILBT has the advantages of high precision, minimal target motion and avoidance of dose to adjacent critical structures, though increased risks of strictures, stenosis and fistula cannot be ignored. Its clinical adoption demands research in randomized settings. It may emerge as a potential treatment modality to combat the high incidence of loco-regional failures.

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