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RESEARCH ARTICLE

ESOPHAGEAL CARCINOMA CLINICAL PROFILE AND TREATMENT OUTCOME; INSTITUTIONAL EXPERIENCE

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ABSTRACT

Introduction: Esophageal carcinoma is an uncommon malignancy acNumbering for approximately 1% of all malignancies, 6% of all GI malignancies (http://globocan.iarc.fr/factsheets/cancers/ oesophagus.asp). Its distribution across the world is variable. Esophageal cancer is the 8th most common cancer worldwide & 6th leading cause of death world-wide

Aim of the study: To determine the outcomes of the definitive management of thoracic esophageal cancer using chemoradiotherapy or radiotherapy, at our institute during the period between 20011 and 2014.

Material and Methods: This is a Retrospective study done at our institute from January 2011 and May 2012 patients who received radiotherapy (RT) alone or chemoradiotherapy (CT+RT) for the treatment of carcinoma esophagus.

Conclusion: Our study shows that chemoradiotherapy yields significant survival benefit over the radiotherapy alone in the definitive management of patients with T1-3 N0-1 esophageal tumor, who did not undergo surgery. While the overall survival of the entire cohort (N=185) was 13.9 months, chemoradiotherapy offered a survival advantage of 11.6 months over radiotherapy alone (median survival in the CT+RT versus RT alone groups was 19.1 and 7.5 months, respectively). The overall survival rate (OS) at 1 year following treatment was significantly better in the combined chemoradiotherapy group when compared with RT alone group (56% versus 24%).

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INTRODUCTION

Esophageal carcinoma is an uncommon malignancy acNumbering for approximately 1% of all malignancies, 6% of all GI malignancies (http://globocan.iarc.fr/factsheets/cancers/ oesophagus.asp). Its distribution across the world is variable. Esophageal cancer is the 8th most common cancer worldwide & 6th leading cause of death world-wide (http://globocan.iarc. fr/factsheets/cancers/oesophagus.asp; Blackstock,2007). Cancer of the esophagus poses a significant therapeutic challenge (Suntharalingam, 2007). Almost half of the patients of esophageal cancer present with unresectable or metastatic disease, and less than 15% of the diagnosed patients are cured (Jemal *et al*., 2006). According to data from the US Surveillance, Epidemiology and End Results (SEER) Program, the five-year survival for all patients with esophageal cancer improved only modestly over the last 30 years (http://seer. cancer.gov/csr/1975_2009_pops09). In spite of various developments in therapeutic modalities of carcinoma esophagus in the recent decades, the average 5-year survival rates changed only from 5% in the years 1975 to 1977, to 19% during the period 2001 to 2007 (Berger and Belka, 2009; Siegel *et al*., 2012). The management of local-regionally advanced esophageal cancer has undergone a major evolution over the past 15 years. The low cure rates after locoregional therapy alone prompted the inclusion of systemic chemotherapy in multimodality treatment regimens, to control distant micrometastatic disease and enhance local radiation effects. RTOG 85-01 was the landmark trial in the management of carcinoma esophagus, demonstrating a survival benefit for the addition of cisplatin-based chemotherapy to radiation therapy (RT) in non-surgically treated patients (Cooper *et al*., 1999; Herskovic *et al*., 1992). The trial showed that while all the patients in the RT alone arm (who were treated with 64 Gray (Gy) in 32 fractions (#) of external beam radiotherapy only) died by the end of 3 years due to cancer, the patients who were randomly assigned to receive concurrent chemoradiotherapy (CT+RT) showed a significant improvement in both median survival (14 versus 9months) and 5-yr overall survival (27% versus 0%). The incidence of local failure was also lower in the combined modality arm (47% versus 65%) (Cooper *et al*., 1999; Yeole, 2008). Distant failure constituted three-fourths of all recurrences (Kelsen *et al*., 1998). Thus, concurrent chemo-

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radiotherapy has become the standard of care for patients with esophageal cancers that are not being considered for curative resection. However, as noted above, the incidence and treatment outcomes of esophageal cancers vary significantly around the world. Few studies have been published documenting the role of chemo-radiotherapy & the patient outcomes after treatment of esophageal cancer in and around Manipal. The current study aims at documenting our experience in the management of carcinomas of thoracic esophagus with chemoradiation, and comparing the outcomes with reports from other centers.

Aim of the study

To determine the outcomes of the definitive management of thoracic esophageal cancer using chemoradiotherapy or radiotherapy, at our institute during the period between 2011 and 2014.

MATERIALS AND METHODS

Type of study: Retrospective study.

Study Period: January 2011 and May 2012

Patient population and sampling method

After clearance from ethical committee, data for our study was obtained from medical records of the patients who received radiotherapy (RT) alone or chemoradiotherapy (CT+RT) for the treatment of carcinoma esophagus. All the study subjects belonged to the period between January 2011 and May 2012. Data was collected for one hundred and eighty five patients who met the inclusion and exclusion criteria as mentioned below.

Inclusion criteria

- Age <70yrs
- Karnofsky scale of Performance Status (KPS) score of 60 or more
- Histopathologically proven cases of esophagus - squamous cell carcinoma (SCC) or adenocarcinoma (AC).
- Normal blood Numbers, renal and liver function before commencement of treatment
- No previous history of malignancies

Exclusion criteria

- Growth involving cervical esophagus.
- Growth involving GE junction and/or stomach
- Esophageal tumor with invasion of any neighboring structure (T4 lesion as per TNM staging, 6th edition of the American Joint Committee on Cancer, AJCC (www.cancerstaging.org))
- Evidence of metastatic disease at presentation
- Evidence of TOF at presentation
- Synchronous or metachronous malignancy.
- Pregnancy
- History of cardiac disease
- Patients who have received any prior treatment for carcinoma esophagus outside
- Patients who did not complete prescribed radiotherapy dose or did not have any follow-up examinations

Details of treatment

External beam radiotherapy (EBRT)

Radiotherapy was administered to all patients as per the protocol followed by the department. 3D conformal RT was planned for all patients after appropriate immobilization using a thermoplastic mask. All patients were irradiated with megavoltage beams on a 'multiple energy ELEKTA Linear Accelerator', with conventional fractionation. The gross tumor volume (GTV) included the primary tumor and involved regional lymph nodes as identified by the imaging studies done prior to planning. The clinical target volume (CTV) included GTV with 5 cm of cephalad and caudal margin and a radial margin of 1.5 - 2 cm to include the areas at risk for microscopic disease. The planning target volume (PTV) was generated to include the CTV with 1 cm margin to acNumber for set up errors. Every effort was made to reduce unnecessary radiation dose to the vital organs at risk such as spinal cord, heart, lungs, liver, and kidneys.

Radiotherapy using 6 or 15-MV photons was delivered at a dose of 1.8 or 2 Gy per day, 5 days per week. Four different regimes were utilized to treat ca esophagus patients at our institution during the study period. EBRT dose of:

1. 60 Gy given in 30 fractions @ 2 Gy per fraction.
2. 59.4 Gy given in 33 fractions @ 1.8 Gy per fraction.
3. 50 Gy given in 25 fractions @ 2 Gy per fraction.
4. 50.4 Gy given in 28 fractions @ 1.8 Gy per fraction.

The dose was prescribed to the isocenter at the middle of the planned target volume. The initial 17 fractions radiotherapy was delivered through anterior–posterior opposed portals, and then plan was changed to three-field technique using oblique portals to decrease the spinal cord dose. The total dose to the spinal cord was restricted to 45 Gy or less. Two different methods were followed to administer sensitizing chemotherapy during radiotherapy in our patients. Cisplatinum (cis-daimminedichloroplatinum) was given at either weekly or three weekly intervals during radiotherapy. Cisplatinum was givenas a rapid intravenous infusion over 1 hour after appropriate hydration. Doses of 40 mg per m2 body surface area at weekly intervals or 100 mg per m2 body surface area at three-weekly intervals were used as sensitizing chemotherapy. Few patients in our study received weekly carboplatinum at a dose equivalent to area under the concentration-time curve (AUC) 2 or less.

Brachytherapy/ Intraluminal radiotherapy (ILRT)

After the completion of EBRT some patients were considered for brachytherapy (Figures 7.2 – 7.7).

Eligibility to ILRT

Patients who received ILRT at our institution were selected based on consensus guidelines for brachytherapy of esophageal cancer by American Brachytherapy (ABS) (Czito *et al*., 2007; Gaspar *et al*., 1997). ILRT was prescribed for patients with:

- Tumor confined to thoracic esophagus
- Primary tumor 10 cm or less in length

- Tumor not infiltrating surrounding structures
- No evidence of lymph nodal involvement
- Tumor not involving GE junction
- Tumor responded well at the end of 50 Gy of external RT as documented clinically and by means of barium swallow

Patients who were planned for ILRT received 50 Gy of EBRT and tumor response was documented at the end of EBRT by clinical evaluation and barium swallow. ILRT was delivered to the eligible patients with HDR Microselectron, with Ir192 source. With standard applicators, intraluminal radiation was given, to the tumor site locally. After the introduction of the applicators, dummy sources were introduced. Check x rays were taken and the patients were shifted to the treatment room. Length of the treatment depended on the initial tumor length (as the pre-treatment evaluation) plus 1 cm margin above and below the tumor. The length treated was not more than 10cm in any plan. The dose prescribed was 5 Gy per fraction, at 1 cm from the surface of the applicator. ILRT was delivered in 2 fractions: first was given 2 weeksafter completion of the EBRT and the second was given 1 week after the first fraction. All patients who were prescribed brachytherapy completed the treatment.

Response assessment

Patients were assessed clinically at the end of 1 month and at 3-6 monthly intervals until 2 years after the completion of the treatment. Follow-up data available in the medical records until May 2012 was collected for the study purpose. The median duration of follow up for survivors was 16.9 months (range = 4.5 – 51.2 months). The patients were assessed for tumor recurrence, relief of dysphagia and toxicity during the follow-up period. Barium swallow was done at the end of 1 month and at 6 monthly intervals until 2 years after the completion of the treatment. GI scopy was done when they complained of new-onset dysphagia or pain after completion of treatment or when recurrence was suspected by the physician. CT scan was also obtained for the evaluation of tumor recurrence locoregionally and in the distant organs, when a recurrence was suspected. Recurrence was confirmed by biopsy and histopathological examination. Data on selected acute and late toxicities were recorded for the study purpose from the medical charts. A time period of 3 months after the completion of treatment was taken as cut-off mark for acute toxicity. Data pertaining to neutropenia, esophagitis, pneumonitis, and coronary ischemia was utilized to record acute toxicity. Data pertaining to stenosis or stricture and fistula that developed at least 3 months after the completion of treatment was taken obtained for documenting late toxicity. Grading of the toxicity was done according to "Common Terminology Criteria for Adverse Events (CTCAE)" Version 3.0, Publish Date August 9, 2006 by the National Cancer Institute (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf), as indicated below.

RESULTS

A total 387 patients received definitive or palliative chemoradiotherapy for esophageal cancer at our institution between January 2011 and May 2012, after being diagnosed with inoperable esophageal tumor or refusing surgery due to personal reasons. Data of 185 out of 387 patients, who met the recruitment criteria, was used for the analysis of the results and the rest were excluded. One hundred and fourteen out of those who were excluded from the study received radiotherapy for T4 esophageal tumor (based on the pretreatment evaluation) or had poor general condition at presentation (KPS < 60). Twenty six patients who had metastatic disease or TOF at presentation, and 14 patients diagnosed with cervical esophageal tumor were excluded from the study. At least forty eight patients who did not complete prescribed treatment or have adequate follow-up examinations were also excluded from the study. One hundred and eighty five patients, who had T1-3N0-1 (based on TNM staging, 6th edition of AJCC (www.cancerstaging.org)) esophageal tumor were included in our study. Median follow up period for the surviving patients was 16.9 months (range = 4.5months – 51.2months). Sixty eight patients are still alive and are on follow-up by the end of the study period.

Patient characteristics (Table 1)

		N	%	p value
Gender	Male	133	72%	<0.001
	Female	52	28%	
Age	<50 years	141	78%	0.003
	>50 years	44	22%	
Occupation	Housewife	35	19%	0.034
	Hard Labourer	78	42%	
	Desk Job	21	11%	
	Fishermen	18	10%	
	Retired	11	6%	
	Unknown	22	12%	
Address	Udupi	54	29%	0.002
	Davangere	28	15%	
	Uttara Kannada	33	18%	
	Dakshin Kannada	6	3%	
	Chitradurga	7	4%	
	Chikmangalur	15	8%	
	Haveri	11	6%	
	Balthangadi	5	3%	
	Goa	5	3%	
	North Kerala	8	5%	
	Other	13	6%	
Smoking/ tobacco	Yes	35	19%	<0.001
	No	150	81%	
Alcohol	Yes	122	66%	0.016
	No	63	34%	
Comorbidities	None	111	60%	<0.031
	DM – II only	26	14%	
	HTN only	11	6%	
	Other single	15	8%	
	Multiple	22	12%	
Location in thoracic esophagus	Upper 3rd	41	22%	<0.001
	Middle 3rd	96	52%	
	Lower 3rd	48	26%	
HPE	WDSCC	33	18%	<0.001
	MDSCC	96	52%	
	PDSCC	45	24%	
	AC	11	6%	
LN status	N0	78	42%	0.023
	N1	107	58%	

The patient characteristics of the 185 patients included in our study are as described below.

Survival Analysis

The overall survival rate(OS) estimated for all the study patients at 6 months & 1 year period of follow up was 164 (89%) &87 (47%), respectively. The corresponding median survival for the entire group was calculated to be 433 days or 13.9 months (with a standard error (SE) of 45 days; 95% Confidence Interval (CI) 344-521 days). The OS rate

calculated at 6 months and 1 year in the RT alone, CT+RT groups was 67% versus 95%; 14% versus 56%respectively. The corresponding median survival was found to be 231 days or 7.5 months (SE of 33 days; 95% CI, 166-295 days) in the RT alone group, while it was 606 days (SE of 88 days; 95% CI, 433-778 days) in the CT+RT group. The Disease Free Survival (DFS) calculated for all the study patients at 6 months & 1 year period of follow up was 146 (79%), 67 (36%) respectively. Median DFS for the entire group was calculated to be 354 days or 11.4 months (with a SE of 44 days; 95% CI, 266-441 days). The DFS calculated at 6 months was 55% and 86% and at 1 year was 17% and 46% in the RT alone and CT+RT groups respectively. Median DFS was found to be 181 days or 5.8 months (SE of 40 days; 95% CI, 101-260 days) in the radiotherapy alone group, 470 days or 15 months (SE of 56 days; 95% CI, 359-580 days) in the CT+RT, respectively. The dysphagia free survival (DFI) estimated for all the study patients at 6 months & 1 year period of follow up was 126 (68%), 48 (26%) respectively. Median dysphagia free interval (DFI) for the entire group was 302 days or 9.7 months (with a SE of 26 days; 95% CI 250-353 days). The percentage of patients free of dysphagia at 6 months was 43% and 76% in the RT alone and CT+RT groups, while at 1 year it was 12% and 34%. Median DFI was found to be 161 days or 5.2 months (SE of 14 days; 95% CI, 132-189 days) in the RT alone group versus 354 days (SE of 33 days; 95% CI, 289-418 days) in the CT+RT group.

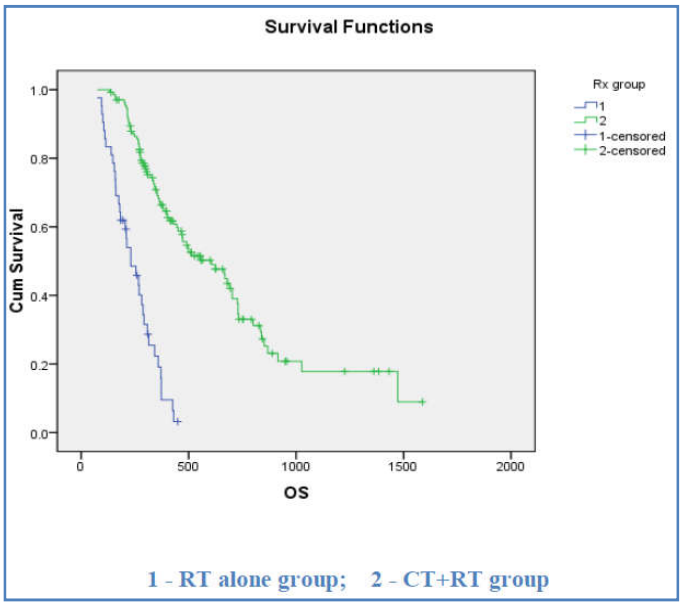
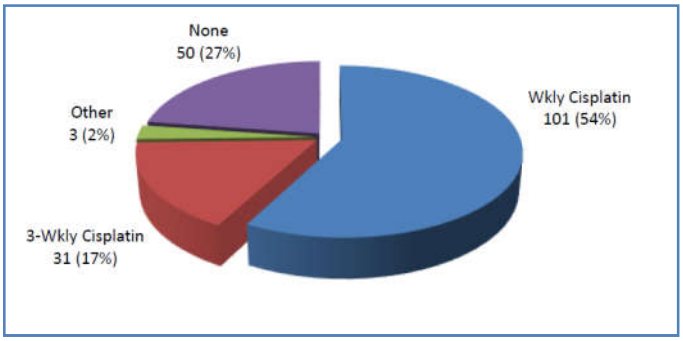


Figure 1. Overall survival in the treatment groups



Chemotherapy used at our institution during the study period: The at least 3 different chemotherapy types were used in the treatment of esophageal cancer at our institution. The weekly cisplatin chemotherapy was most commonly used in 107 (58%) and the 3-weekly cisplatin chemotherapy was used in 31 (17%) of the patients. The median duration of overall survival was 632 days (SE 81 days; 95% CI, 471-792 days), 624 days (SE 211 days; 95% CI, 208-1039 days), 516 days (SE 82 days; 95% CI, 354-677 days) and 231 days (SE 33 days; 95% CI, 166-792 days), respectively, when weekly cisplatin, 3-weekly cisplatin, other and no chemotherapy was used.

Recurrence pattern

Overall the estimated disease free survival at 1 year from completion of treatment was 36% in the entire cohort (N = 185), with an estimated median duration of 354 days or 11.4 months for development of any recurrence. Similarly, the estimated disease free survival at 1 year in the three treatment groups was 17% and 46%, respectively, in the RT alone, CT+RT groups). Median time for development of any type of recurrence in the RT alone, CT+RT groups was found to be 181 days or 5.8 months (SE of 40 days; 95% CI, 101-260 days) versus 470 days or 15 months (SE of 56 days; 95% CI, 359-580 days), respectively. Locoregional failure was observed in 55% (27 out of 50) of patients in the RT alone group, while it was found to be only 41% (55 out of 135 patients) in the CT+RT group. Similarly, distant metastases in the RT alone group were found to be higher than those in the CT+RT group i.e., 24% (12 out of 50 patients) versus 13% (17 out of 135 patients). Simultaneous locoregional and distant recurrences were detected in 5% (2 out of 42 patients) versus 1% (1 out of 135 patients) in the RT alone and CT+RT groups, respectively.

DISCUSSION

Traditionally, definitive radiotherapy alone had been offered to patients with esophageal cancer who had unresectable disease (stage IIA and higher) or in case of co-morbidity precluding a surgical approach. Compared to surgery, radiotherapy at least offers two theoretical and practical advantages: firstly, its applicability to a broader patient population even if reduced health condition is present; secondly, the more effective coverage of diffusely involved tissue and lymphatics. In contrast, main inherent drawbacks of a radiotherapeutic approach are: local tumor control is hampered by the tolerance doses of surrounding normal tissue (i.e., spinal cord, lung, and heart), and symptoms do not resolve as promptly as by surgery. Treatment-related local toxicity may require prolonged supportive care (e.g., for dysphagia) and additional palliative measures once late or consequential late effects have become manifest (for example esophageal stricture, tracheoesophageal fistula). But usage of radiotherapy alone did not yield superior results. Several studies have reported poor outcomes following primary radiation therapy alone in the treatment of clinically localized esophageal cancer with a 3-yr overall survival of 0% and a 5-yr survival rate of approximately 5-20% depending on the tumor extent (Berger and Belka, 2009; Siegel *et al*., 2012; Cooper *et al*., 1999; Herskovic *et al*., 1992; Hussey *et al*., 1980; Newaishy *et al*., 1982; Sun, 1989; Kelsen, 1993, Walsh *et al*., 1996). In our center, all the 185 eligible patients who received treatment for esophageal cancer could be grossly divided into 2 groups: 27% (50 patients) of the patients who received RT alone, 73% (134 patients) of them who received chemotherapy plus radiotherapy (CT+RT). The primary reason why chemotherapy was not offered to these 27% of the patients was due to multiple associated co-morbidities or patient

preference. In our center, the overall survival (OS) estimated for all the patients treated for carcinoma of esophagus, at 6 months & 1 year period of follow up periods, was 164 (89%) & 87 (47%), respectively (Table 1). But in the RT alone group, the OS rate was found to be lower than the entire group, i.e. 67% and 14% at 6 months and 1 year follow up, respectively. The median duration of survival for the RT alone group was also lower than the median survival for the entire group, 7.5 months versus 13.9 months, respectively. These findings are in agreement with literature reviewed. Our study results also indicate that DFI slightly improved in the patients when brachytherapy (intraluminal radiotherapy, ILRT) was administered i.e. 11.4 versus 9.6 months in the ILRT versus no ILRT patients, respectively, although the results did not reach statistical significance ($p>0.05$). Benefit from brachytherapy for symptomatic relief of dysphagia was evident from our results, since 15% more patients were found to be dysphagia-free at 1 year follow up when ILRT was administered ($p=0.05$). Literature on the outcomes of brachytherapy following definitive chemoradiotherapy or RT alone is controversial. In RTOG 9207 trial, Gasper *et al* investigated the results of intraluminal boost following definitive chemoradiotherapy for esophageal cancer (Gaspar *et al*., 2000). They concluded that additional benefit of adding intraluminal brachytherapy to radiation or combined modality therapy, although reasonable, remains unclear.

Drawbacks of our study are as follows:

- Not a prospective randomized study
- Study conducted in selected group of patients
- The poor outcomes in RT alone group may be attributed to multiple comorbidities or patient characteristics in that group
- Follow-up period was limited

Summary and Conclusion

About 80 to 100 patients of esophageal cancer, who have either refused surgery or have an unresectable tumor, are seen in the department of radiotherapy annually at our institution. Our study included 185 patients, who had T1-3 N0-1 esophageal tumor (based on TNM staging, 6th edition of AJCC) treated during the period between January 2011 and May 2012. Median follow up period for the surviving patients was 16.9 months (range 4.5–51.2 months). Sixty eight study patients were still alive and on follow-up by the end of the study period. Our study shows that chemoradiotherapy yields significant survival benefit over the radiotherapy alone in the definitive management of patients with T1-3 N0-1 esophageal tumor, who did not undergo surgery. While the overall survival of the entire cohort (N=185) was 13.9 months, chemoradiotherapy offered a survival advantage of 11.6 months over radiotherapy alone (median survival in the CT+RT versus RT alone groups was 19.1 and 7.5 months, respectively). The overall survival rate (OS) at 1 year following treatment was significantly better in the combined chemoradiotherapy group when compared with RT alone group (56% versus 24%). The local control rate was significantly better with chemoradiotherapy when compared with the radiotherapy alone (59% versus 45%). Median time to any recurrence in the combined chemoradiotherapy group was 15 months and was about 9 months more when compared with RT alone group. Study results also indicated that distant metastases were reduced by approximately 11% in the chemoradiotherapy when compared with RT alone group (24% versus 13%, respectively). Although, the acute toxicity (grade 1-4) was observed more frequently with chemoradiotherapy when compared with the radiotherapy alone, no significant difference was seen between the two groups in the incidence of late toxicities (stricture, stenosis and TOF). Median time for the development of stricture or stenosis (DFI) for the entire group was 9.7 months and it was prolonged by approximately 6 months in the chemoradiotherapy group when compared with the RT alone group. Tracheoesophageal fistula was noted in 7 (4%) out of 185 patients treated in either of the groups, the corresponding median interval for the development of TOF being 5 months from the beginning of the treatment. Brachytherapy was administered in 31 (16%) out of 185 patients, that were included in our study. Results indicate significantly improved local control rate (by approximately 11%) when ILRT was administered, but at the cost of higher rates of acute and delayed toxicity. For example, grade 3 or 4 acute toxicity and TOF were noted in 12% and 7% more patients, respectively, when ILRT was administered. Our study is limited in being non-randomized in nature, with a limited study period conducted in select group of patients. Though the outcomes of our patients are seen to have improved by the addition of chemotherapy to radiotherapy in the treatment of esophageal cancer, our results indicate that there is a scope for further improvement by using additional means: for example, by the including surgery in the treatment plan, or by using more targeted drugs as sensitizers of radiotherapy. Future studies in this direction in our patients might be useful in the definitive management of esophageal cancer.

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