

Gastrointestinal Cancer

Preoperative Chemoradiation in Locally-Advanced Resectable Carcinoma of the Esophagus in a Single Rural Cancer Hospital in Western India

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Abstract



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Keywords

- ▶ esophageal cancer
- ▶ neoadjuvant chemoradiation
- ▶ rural cancer hospital

Background The current standard of care for the treatment of surgically resectable carcinoma of the esophagus is preoperative chemoradiation followed by surgery. There is strong evidence that this trimodality approach improves survival as compared with surgery alone.

Objective The objective of this study is to determine the feasibility of this approach in a rural cancer institute in western India.

Materials and Methods The data of all the 157 consecutively treated patients with locally-advanced carcinoma of the esophagus from March 2013 to March 2017 who were started on preoperative chemoradiation were analyzed retrospectively.

Results Of the 157 patients who were started on preoperative chemoradiation, 68 patients underwent surgery. There are various practical reasons for not undergoing the definitive surgery, with the important being the socioeconomic support to the patients during the course of treatment.

Conclusion This study gave us insight into the strategic selection of patients for the trimodality approach as well as the need for continuous socioeconomic support throughout the treatment course.

Introduction

Esophageal carcinoma has the poor prognosis in spite of the advancement in treatment modalities. The incidence of newly diagnosed cases of carcinoma of the esophagus worldwide per year is 572,034, while the mortality is 508,585. The corresponding figures of India are 52,396 and 46,504, respectively.¹ The treatment has evolved from single modality to multimodality approach over the past few decades.

Conventionally, esophagectomy has been the main choice of treatment for resectable middle and lower-third esophageal cancers. The trimodality approaches involving neoadjuvant chemoradiotherapy (NACRT) followed by surgery for resectable middle and lower-third esophageal cancer have been studied.² The feasibility of this combination treatment needs to be evaluated in developing countries, especially in the rural background. Here, we present an audit of the retrospective

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analysis of prospectively maintained data of such combination treatment practiced in a single rural cancer center in Western India.

Materials and Methods

This is a retrospective study of 157 consecutive patients diagnosed with nonmetastatic carcinoma of the esophagus, and who were treated in a single cancer institute in rural Western India from March 2013 to March 2017. All case records and electronic data were retrieved and analyzed. All patients underwent endoscopic evaluation of the upper gastrointestinal tract (GIT). The disease was documented, and biopsies were collected. Patients underwent staging investigations with contrast-enhanced computed tomography (CT) scan of the neck, thorax and upper abdomen, and hematological counts for determining fitness for chemotherapy. All histology proven, treatment naïve cases of carcinoma of the middle and lower-third esophagus were included in the study. Histology other than squamous carcinoma and adenocarcinoma were excluded from the study. Patients with only localized disease with or without regional nodes were included. Patients with performance status 0, 1, and 2 and who would complete the intended neoadjuvant treatment were included for the treatment. All the patients carried out discussions with the surgical oncologist, radiation oncologist, and medical oncologist before initiating the treatment.

Treatment Details

Radiotherapy

The patient underwent neoadjuvant external radiotherapy to primary and regional nodes, with the help of photons, by conformal techniques such as either three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) at doses of 41.4 Gy to 45 Gy in conventional fractionation over the duration of 5 weeks.

Chemotherapy

Patients received concomitant chemotherapy maximum of five cycles after ensuring adequate hematological and renal functions along with radiotherapy. The drugs received were either paclitaxel (50 mg/m²) with carboplatin (area under the curve = 2), cisplatin (30 mg/m²) with 5 fluorouracil (500 mg/m²), cisplatin (30 mg/m²) alone, or capecitabine (825 mg/m² BD) alone. The choice of chemotherapy was at the discretion of the treating oncologist.

Response Evaluation

Response to NACRT was evaluated with contrast-enhanced CT scan 4 to 5 weeks after NACRT, with response evaluation criteria in solid tumor criteria. Patients having complete response, partial response, or stable disease were evaluated for surgery. Patients with progression of disease underwent salvage treatment at the discretion of treating physician. Salvage treatment consisted of either completion of radiotherapy, chemotherapy, or best supportive care.

Surgery

Patients underwent esophagectomy, either open or thoracoscopic, 4 to 6 weeks after NACRT. All complications of surgery and histopathology were documented.

Follow-up and Evaluation

Patients were followed-up every 3 months for initial 2 years after completion of treatment and later at every 6 months. Disease status at each follow-up was documented.

Statistical Analysis

SPSS software version 21 was used for statistical analysis. Survival was calculated using the Kaplan–Meier method. Overall survival (OS) was calculated from the date of registration to the last date of follow-up or death. Disease-free survival was calculated from the date of surgery to the date of recurrence of the disease.

Results

One hundred and fifty-seven patients were started on NACRT. The demographic details were captured for all patients (→Table 1). The details of radiation therapy, chemotherapy, and surgery were documented (→Table 2). An effort was made to find the causes of default after neoadjuvant therapy through either telephonic contact with the patient or personal home visit by the hospital representative. The treatment-related toxicities and survival were captured (→Tables 3 and 4).

Table 1 Demography

Characteristics	Value	Absolute (%)
Study duration	March 2013–March 2017	
Number of patients	157	
Age (years), median (range)	55 (30–81)	
Gender	Male	82 (52)
	Female	75 (48)
Category	Private	27 (17)
	Scheme	130 (83)
Comorbidities	Nil	107 (68)
	One or more	50 (32)
Addictions	Nil	62 (40)
	One or more	95 (60)
Site	Middle third	69 (44)
	Lower third	88 (56)
Histology	Squamous carcinoma	136 (87)
	Adenocarcinoma	21 (13)
T stage	T2	5 (3)
	T3	152 (97)
N stage	N0	52 (33)
	N1	85 (54)
	N2	20 (13)

Table 2 Treatment details

Treatment details	Absolute number	Percentage
NART dose		
45 Gy/25 [#]	136	87
41.4 Gy/21 [#]	7	5
NART technique		
3DCRT	67	43
IMRT	90	57
NART breaks		
Yes	17	11
No	140	89
Reasons for NART breaks		
Machine breakdown	4	–
Death	2	
Toxicity	1	
Default	10	
Concomitant CT given		
Yes	141	90
No	16	10
Reason concomitant CT not given		
Death	2	–
Unfit	2	
Financial	12	
Concomitant CT drugs		
P + C	100	–
5 FU + cisplatin	16	
Cisplatin	3	
Capecitabine	22	
Number of concomitant CT cycles, median	5	–
Concomitant CT breaks		
Yes	50	–
No	91	
Concomitant CT breaks reasons		
Toxicity	41	–
Fitness	2	
Financial	6	
Communication gap	1	
Response CT scan done		
Yes	124	–
No	33	
Radiological response to NACRT		

(Continued)

Table 2 (Continued)

Treatment details	Absolute numbers	Percentage
Complete response	1	
Partial response	86	
Stable disease	16	
Progressive disease	21	
Surgery done		
Yes	68	43%
No	89	57%
Reasons for no surgery		
PD	20	–
Financial	39	
Social	6	
Asymptomatic (patient's decision)	9	
Unfit	6	
Death	5	
Unwilling for surgery	3	
Second primary	1	
Duration between RT completion and surgery (days), median (range)		
49 (33–316)		–
Surgery type		
Thorascopic esophagectomy with 2-field lymphadenectomy	36	–
Thorascopic esophagectomy with 3-field lymphadenectomy	6	
Transthoracic esophagectomy with 2-field lymphadenectomy	9	
Transthoracic esophagectomy with 3-field lymphadenectomy	8	
Transhiatal esophagectomy	9	

Abbreviations: 3DCRT, three-dimensional conformal radiation therapy; CT, computed tomography; FU, fluorouracil; IMRT, Intensity-modulated radiation therapy; NART, neoadjuvant radiotherapy; NACRT, neoadjuvant chemoradiotherapy; PD, progression of disease RT, radiotherapy.

Discussion

The intention of this retrospective audit was to check the feasibility of NACRT followed by surgery in resectable carcinoma of the esophagus in a rural cancer center in western India.

Table 3 Treatment-related toxicity details

Toxicity	Absolute numbers	Percentage
NART toxicity		
Radiation dermatitis		
Grade I	108	69
Grade II	49	31
Grade III–IV	0	0
Esophagitis		
Grade I	84	54
Grade II	62	39
Grade III	11	7
CT toxicity (grade III)		
Anemia	1	0.7
Neutropenia	7	5
Thrombocytopenia	1	0.7
Renal	15	11
Significant surgical complications		
Pulmonary	10	15
VC palsy	8	12
Death	6	9
Chyle leak	6	9
Wound Infection	2	3

Abbreviations: CT, computed tomography; NART, neoadjuvant radiotherapy; VC, vocal cord.

Table 4 Treatment outcome

Treatment outcome	Value number
Pathological response after surgery (%)	
Complete response	27 (40)
Partial response	41 (60)
OS in all patients (157 patients), months	11 (1–63)
OS in patients who underwent surgery after neoadjuvant therapy (68 patients), months	18.5 (3–63)
OS in patients who defaulted for surgery after neoadjuvant treatment (89 patients), months	8 (1–35)
OS in patients who underwent surgery within 60 days of RT (51 patients), months	20 (3–63)
OS of patients who underwent surgery after 60 days of RT (17 patients), months	17 (4–52)
DFS in all patients in surgery group (68 patients), months	16.5 (3–62)
DFS in complete response group (27 patients), months	12 (3–62)
DFS in partial response group (41 patients), months	15 (3–62)

Abbreviations: DFS, disease-free survival; OS, overall survival; RT, radiotherapy.

We neither aim to prove the efficacy of this approach nor do we question the efficacy of this approach in the rural setting.

We want to highlight the practical problems that we faced in the implementation of this approach and the reasons for noncompliance to the treatment.

NACRT was tolerated well by all the patients with acceptable toxicity profile. The surgical complication rates were acceptable and less than reported in the literature.²

The practice at our institute till 2013 was upfront surgical resection, followed by adjuvant treatment for resectable carcinoma of the esophagus. The landmark randomized trial published in 2012 showed a significant OS benefit of 49.4 months in trimodality treatment versus 24 months in surgery alone arm.² The “Evidence-Based Medicine Conference” conducted annually by the Tata Memorial Center, Mumbai, which discussed the guidelines for esophageal cancers in 2013 gave us the confidence to change our practice. We discussed the new strategy in our Institutional Review Board and started the new protocol from March 2013. Here, we present the retrospective audit of the patients afflicted with resectable carcinoma of the esophagus, and with curative intent, consecutively treated using NACRT. Fifty-six percent of the patients had carcinoma of the lower third of the esophagus; the most common histology was squamous cell carcinoma, in 87% of the patients, indicating squamous cell carcinoma is common histology even in the lower-third esophagus in our population. More than two-third of the patients were treated under one of the applicable government-sanctioned schemes, without any financial burden of the treatment on the patient or the family, but with certain limitations. The dose of radiotherapy for neoadjuvant setting in carcinoma of the esophagus varies in different randomized clinical trials. The range varies from 18.5 Gy to 50.4 Gy with different fractionation schedules.^{3–10} We implemented conventional fractionation schedules at doses of 41.4 Gy to 45 Gy with either 3DCRT or IMRT planning. The concomitant chemotherapy administered along with radiotherapy in neoadjuvant setting varies in different studies. The most commonly used drugs are cisplatin, 5 fluorouracil (5FU), paclitaxel, mitomycin, and etoposide.

Based on the CROSS trial results, we offered paclitaxel plus carboplatin regimen. However, due to financial reasons, this regimen was accepted by 72% of the patients. The rest received cisplatin or cisplatin with 5FU or capecitabine regimen. Sixteen patients received only neoadjuvant radiotherapy without concomitant chemotherapy, as they were unfit for chemotherapy. All the surgical specimens were reviewed by the single oncopathologist. There was no case with close or positive surgical cut margin in our group of patients. The pathological complete response rate was 40%, which is comparable with the published literature.^{3–10}

The OS of patients who underwent the trimodality treatment and those who defaulted for surgery after neoadjuvant treatment was 18.5 months and 8 months, respectively, showing the obvious benefit of the completion surgery (→Fig. 1).

Out of 89 patients who did not complete the intended treatment, 45 patients could have completed their intended treatment, provided necessary intervening measures would have been taken such as financial support and social support.

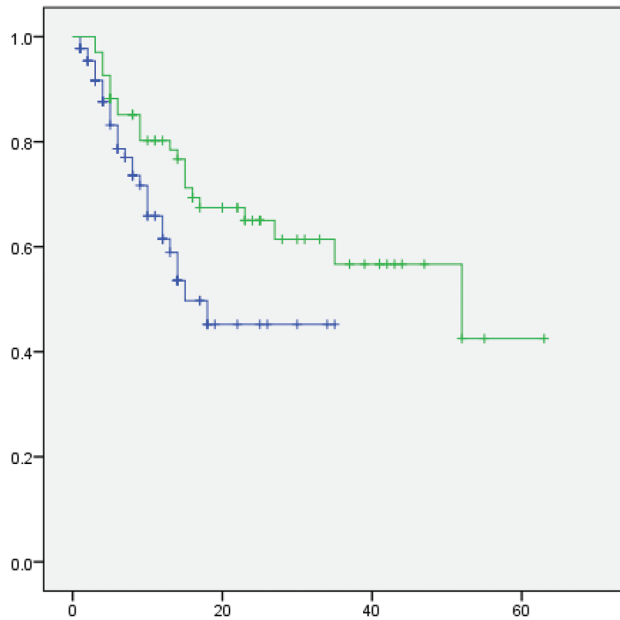


Fig. 1 Kaplan–Meier plot of overall survival. Green = patient receiving trimodality treatment; blue = patients defaulted after neoadjuvant chemoradiotherapy (NACRT). $p = 0.025$ (log-rank test).

The treating oncologist tried to contact all these patients through telephonic conversations or home visit by the representative. In spite of the treatment being partly or fully covered under government scheme, the priority of their daily wages prevented these patients from completing their treatment.

The next common reason for noncompliance was symptomatic relief due to neoadjuvant treatment in nine patients. Although the efforts were taken to stress the importance of surgery in spite of complete clinical benefit after neoadjuvant therapy, these patients never turned up for surgery.

Of the 20 patients who progressed after NACRT, 10 patients progressed at a distant site, while 10 patients progressed locally. These patients were advised palliative treatment or best supportive care.

This study gave us an insight into careful selection and counseling of the patients beforehand, ensuring lasting financial and social support through the course of the treatment in the rural setting in India. Interestingly, we found that the patients who underwent surgery within 60 days of completion of neoadjuvant treatment had a median overall survival of 20 months versus 17 months for those who came for surgery after 60 days. Majority of the delays in surgery was due to finances and logistics for surgery. This highlights the importance of adherence to the treatment schedule, especially after NACRT.

Conclusion

Our results for patients who completed the trimodality treatment are similar to those in the literature. However, the drop-out rate after NACRT was a matter of concern. This study gave us insight into the fact that trimodality treatment is feasible in rural India, provided the strategic selection of the patients and continuous socioeconomic support through the course of the treatment is ensured.

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Nil.

Conflicts of Interest

None declared.

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