

Survival in Advanced Esophageal Cancer – Experience from a Tertiary Cancer Center

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ABSTRACT

Introduction: Esophageal cancer is the eighth most common malignancy worldwide. In the Western world, esophageal adenocarcinoma has surpassed the incidence of squamous cell carcinoma (SCC). However in developing countries, SCC is still the most common type of esophageal cancer with adenocarcinoma being relatively less common. In this study a retrospective analysis of demographic data and survival in locally advanced carcinoma esophagus treated with chemoradiation (CRT) at our institute was done.

Material and Methods: A total of 83 patients with the pathological diagnosis of carcinoma esophagus treated at our institute from January 2008 to December 2013 were retrospectively analyzed from treatment and follow up records. Statistical analysis was done by using SPSS 20 software.

Results: The median age was 56 years, with male:female ratio of 1.6:1. SCC was the most common histology (87%). Lower thoracic was the most common tumor location followed by middle and upper third. Follow up data was available for 47 patients. Among them 35 patients received treatment with curative intent with CRT and the median overall survival was 22 months.

Conclusion: SCC was the predominant histology. Most of the patients sent for CRT were in an advanced stage. Survival was similar to other published data.

Keywords: Esophageal Carcinoma, Radiotherapy, Chemoradiation.

INTRODUCTION

Esophageal cancer is an aggressive neoplasm with poor 5-year survival rates of around 15%.¹ Majority of the cases of esophageal cancer occur in developing countries as per the GLOBOCAN data.² According to GLOBOCAN 2012 estimate, in India, there were 42,000 new cases of esophageal carcinoma with a mortality of 39,000. Cancer of the esophagus has an overall ratio of mortality to incidence of 0.88. Esophagectomy remains the optimal standard for treatment of localized disease. Very early cases are being treated with less radical procedures like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Recent evidences advocate multimodality treatment in higher stages.³ Vast majority of patients with esophageal carcinoma present in advanced stages and are often unresectable. The treatment options available for such patients are neoadjuvant chemoradiation followed by attempt at definitive surgery or a definitive chemoradiation (CRT). Definitive CRT can also be considered for patients who are inoperable due to medical reasons. Study aimed to retrospectively analyze demographic data and survival in locally advanced carcinoma esophagus treated with chemoradiation (CRT) at our institute.

MATERIAL AND METHODS

We performed a retrospective analysis of patients in Department

of Radiation Oncology treated with CRT in our Institute between 2008 and 2013. All patients with a histopathological diagnosis of locally advanced carcinoma esophagus including gastroesophageal (GE) junction treated with radiotherapy (RT) between 2008 and 2013 were included in this analysis. Demographic data, patient characteristics, type of carcinoma, differentiation pattern, organ involved, treatment details and follow up data were obtained from the records available in the department.

STATISTICAL ANALYSIS

Microsoft excel 2010 and SPSS 20 were used for the statistical analysis. Mean and percentages were used to interpret the data. Survival was analyzed using Kaplan Meier estimates.

RESULTS

A total of 83 patients with esophageal malignancies were identified from our treatment records. The median age was 56 years (range 30 to 84) with male: female ratio of 1.6:1. SCC was the most common histology seen in 73 (87.9%) patients whereas nine (10.8%) had adenocarcinoma and one patient had neuroendocrine carcinoma. In SCC, 11% were well differentiated (WD), 58% moderately differentiated (MD) and 14% poorly differentiated (PD). There was no further characterization for remaining 17%. Lower third of the thoracic esophagus was the most common site of tumor location followed by middle and upper third. 42 (50.6%) patients had disease confined to lower third and 29 (34.9%) patients had lesion confined to middle third thoracic esophagus. 11 patients (13%) had disease involving the proximal third. One patient had very extensive disease involving the entire esophagus. Gastro-esophageal (GE) junction was involved in 12 patients [Table-1].

13 patients were metastatic at presentation. Six had liver metastasis, six had lung metastasis and one patient had both lung and liver metastases. Three patients had secondary deposits in bone. Other sites of metastases included omentum, retroperitoneal nodes, mediastinum and spleen.

77 (93%) patients presented with dysphagia of which 43 (55.8%) had grade 2 or worse dysphagia. Epigastric pain and nonspecific epigastric discomfort were reported by a few patients. 70 patients (84%) needed feeding procedures of which

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How to cite this article: Deepa Joseph, Monica Malik Irukulla, Syed Fayaz Ahmed, Deepthi Valiyaveetil. Survival in advanced esophageal cancer – experience from a tertiary cancer center. International Journal of Contemporary Medical Research 2017;4(2):350-353.

62 (75%) patients underwent endoscopy guided nasogastric (NG) tube insertion, five patients (6%) underwent either feeding jejunostomy or gastrostomy and three patients (4%) had esophageal stent insertion. 13 patients (16%) did not undergo any feeding procedure. [Table-2]

A total of 59 patients were treated with curative intent. 44 patients received radical RT with concurrent chemotherapy. Eight patients received neoadjuvant CRT and seven received adjuvant CRT. The RT dose in radical CRT varied from 50 to 63 Gy in 1.8 or 2 Gy per fraction. Neoadjuvant RT dose varied from 40 to 50.4 Gy in 1.8 to 2 Gy per fraction. The adjuvant RT dose was 45 to 50.4 Gy in 1.8 Gy per fraction. The most common concurrent chemotherapy regimen used was weekly cisplatin 40 mg/m². Other less commonly used regimens were cisplatin with 5 Fluoro-uracil (5 FU), weekly carboplatin and 5 FU and 5FU +leucovorin. 21 patients were treated with palliative RT; either to the primary site for palliation of dysphagia or to the metastatic site. Three patients did not take any treatment. [Table-3]

Three patients died during treatment. Follow up data was available for 47 patients. Among them 35 received treatment with curative intent (Definitive: 25, Adjuvant: 6, Neoadjuvant: 4) and 12 with palliative intent. Median overall survival for patients treated with curative intent was 22 months. 5-year overall survival was 22% [Figure-1].

DISCUSSION

Esophageal cancer ranks eighth in incidence and sixth in mortality globally amongst all malignancies. Incidence is lower in Asian as compared to the Western population except along the "Esophageal cancer belt" regions which extends from northeast China to the Middle East.⁴ A very high incidence has been reported in certain parts of India like Assam, West Bengal, Maharashtra, Tamil Nadu⁵ and Kashmir.⁶⁻⁸ Squamous cell carcinoma (SCC) is more common than adenocarcinoma (AC) in India, unlike the western population.^{9,10} The reported data from India shows a predilection towards lower third location⁹ which is very similar to the observation in our patient subgroup. There was a slight male preponderance with male to female ratio of 1.6:1 in our study. Similar male to female ratio has been reported in other studies from India.¹¹ A slightly higher male to female ratio of 2-2.4:1 has been identified by a few other authors.^{12,13} The higher incidence in India has been linked to tobacco and alcohol consumption.⁵ A study by Sehgal S et al¹² established snuff (smokeless tobacco) as the most powerful risk factor of esophageal cancer in Jammu region, followed by the salt tea, smoking and the sun dried food. Retrospective studies suggest a potential two-fold increased risk of esophageal cancer associated with the intake of pickled vegetables.¹⁴ However, there is a lack of clear cut prospective data on this link. Obesity is increasingly being reported as a risk factor for development of carcinoma of esophagus.¹⁵ However, this association is generally not described in the Indian population.

Dysphagia and weight loss are the most common presenting symptom of esophageal cancer. Persistent dysphagia initially experienced for solids but eventually progresses to include liquids. An adult with dysphagia should always be evaluated with an upper gastrointestinal endoscopy to rule out esophageal cancer. Other less common symptoms include nonspecific epigastric pain, neck swelling in case of supraclavicular lymph

Median age (years)	56
Age Range (years)	30-84
Males	51
Females	32
Male: Female Ratio	1.6:1
Adenocarcinoma	9 (10.8)
Squamous-cell carcinoma	73 (87.9)
Other	1 (1.2)
Proximal third	11 (13)
Middle third	29 (34.9)
Distal third	42 (50.6)
GE Junction	12 (14.4)
Upper Middle and Lower	1(1.2)
Table-1: Clinical Characteristics of the Patients	

Clinical Presentation	
With Dysphagia - no. (%)	77 (93)
Grade 2 or more	43 (55.8)
Feeding Procedure – no. (%)	
None	13 (16)
NG Tube	62 (75)
FJ	4 (5)
FG	1 (1)
Stent	3 (4)
Table-2: Clinical Presentation and Feeding Procedure	

Treatment – no. (%)	
Radical	44 (53)
Adjuvant	7 (8.4)
Neoadjuvant	8 (9.6)
Palliative	21 (25.3)
Defaulted for RT	3 (3.6)
Table-3: Treatment received	

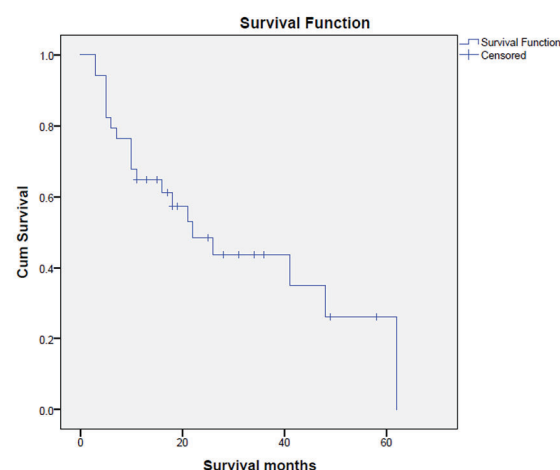


Figure-1: Figure showing survival in months by Kaplan Meier method.

node involvement and melena due to bleeding. Patients with advanced disease may present with features of local compression like hoarseness of voice, persistent cough, features of trachea-esophageal fistula or bone pain in case of bone metastasis. Patients with dysphagia usually require a feeding procedure. In surgical candidates, feeding gastrostomy is generally avoided as the stomach forms the conduit in surgically treated patients.

Most patients require a feeding procedure before starting RT. Blind passage of NG tube will fail in many patients with advanced esophageal cancers. These patients will benefit from endoscopy guided NG tube placement which is a non-invasive procedure. Endoscopy guided placement of nasogastric feeding tube was done in majority of our patients and enabled them to improve and maintain their nutritional status during treatment.

Flexible endoscopy with biopsy is the method of diagnosing carcinoma esophagus.¹⁶ The clinical practice guidelines released by society of thoracic surgeons (STS) assist physicians in acceptable approaches for the diagnosis and staging of esophageal cancers.¹ According to them, computed tomography (CT) or positron emission tomography (PET) of the chest and abdomen are optional investigations in staging of very early disease whereas these tests are recommended for loco-regionally advanced disease. They are more useful in detecting metastatic disease than in demonstrating local invasion. Endoscopic ultrasound (EUS) provides a more accurate evaluation of the depth of invasion¹⁷ and is recommended in patients who are negative for metastatic disease by CT or PET CT. All the three investigations are comparable in detecting mediastinal lymph nodal involvement. An additional investigation that may be considered is bronchoscopy in upper and middle third esophageal lesions as it has more diagnostic accuracy in detecting a bronchus involvement when compared to CT scan or EUS.¹⁸

Patients with very superficial tumors can be treated with endoscopic resection. Moderate- or well-differentiated grade, lack of lymphovascular invasion, lesion size less than 3 cm, and confinement to the mucosa are all features of good prognosis when this approach is used.^{19,20} Eradication therapy like radiofrequency ablation (RFA) is recommended to treat the residual Barrett's esophagus after endoscopic treatment of esophageal adenocarcinoma.²¹ Recurrence rates of malignancy approach around 30% in patients who undergo endoscopic resection without adjuvant eradication therapy.^{22,23} The definitive treatment of locally advanced malignancy is esophagectomy. There is growing evidence to suggest the use of neoadjuvant CRT or neoadjuvant chemotherapy.²⁴ The results of the Dutch Phase III CROSS trial using neoadjuvant CRT in operable esophageal and GE junction showed significant survival improvement (median overall survival of 48.6 month versus 24 months in the surgery alone arm).²⁵ This has become the standard of care in many centers. Majority of our patients presented in very advanced stage and were found inoperable and hence were treated with radical CRT. Very few patients received neoadjuvant treatment and majority of them did not undergo surgery subsequently. The overall survival of 22 months in our patient group was very similar to other published data.²⁶

The role of definitive CRT in esophageal carcinoma was addressed in RTOG 85-01 phase III trial where definitive radiotherapy was compared against CRT.²⁷ Five-year survival rates for chemoradiotherapy vs. radiotherapy were 26% and 0%, respectively. Persistent disease was reported in 37% of RT alone arm when compared to 26% in the combined modality.²⁶ Subsequently, Intergroup trial 0123 trial was designed with the aim of assessing radiation dose escalation as a way to improve local control and survival.²⁸ RT dose of 64.8 Gy was compared against 50.4 Gy, with 5-FU and cisplatin as the concurrent

chemotherapy regimen in both the arms. The higher radiation dose did not increase survival or local/regional control. There was a higher treatment-related mortality rate in the patients assigned to the high-dose radiation arm. Although this higher mortality rate was reported to be unrelated to the RT dose, 50.4 Gy was established as the optimal dose in definitive CRT from this trial.

The major cause of treatment failure in CRT was disease persistence and high local recurrence. Hence a trimodality approach with neoadjuvant CRT followed by surgery was explored. Earlier trials showed conflicting results or were closed due to poor accrual.²⁹

Two trials have examined definitive CRT against CRT followed by surgery.^{30,31} Both these trials did not report any significant difference in overall survival. French FFCD 9102 trial reported higher local control (65% vs. 57%, $P < 0.05$), and fewer stents required (5% vs. 32%, $P < 0.001$) in tri-modality arm compared with CRT. In the German trial, there was a higher rate of 2-year freedom from local progression (64% vs. 41%, $P = 0.003$) when surgery was added.

Role of neoadjuvant chemoradiation before definitive surgery has been evaluated in two phase III randomized trials with conflicting results. The CROSS study using paclitaxel and carboplatin demonstrated significant improvement in R0 resection and median overall survival.²⁵ The French FFCD 9901 showed no improvement in R0 resection and survival. There was a significant increase in postoperative mortality for chemoradiation arm.³² This trial used cisplatin and 5-FU as the concurrent chemotherapy regimen.

CONCLUSION

Despite the recent advances in radiotherapy, surgical techniques and chemotherapy, the prognosis of locally advanced esophageal carcinoma remains poor. Most patients present in an advanced stage and require multimodality treatment. Considering the significant association of tobacco and alcoholism in almost all reported data of Indian population, life style modification and health education is warranted among our population.

REFERENCES

1. Varghese TK, Jr., Hofstetter WL, Rizk NP, et al. The society of thoracic surgeons guidelines on the diagnosis and staging of patients with esophageal cancer. *The Annals of thoracic surgery*. 2013;96:346-56.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of cancer Journal international du cancer*. 2015;136:E359-86.
3. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *New England Journal of Medicine*. 2012;366:2074-84.
4. Li JY. Epidemiology of esophageal cancer in China. *Nat Cancer Inst Monogr*. 1982;62:113-20.
5. Chitra S, Ashok L, Anand L, Srinivasan V, Jayanthi V. Risk factors for esophageal cancer in Coimbatore, southern India: a hospital-based case-control study. *Indian J Gastroenterol*. 2004;23:19-21.
6. Paymaster JC, Sanghvi LD, Gangadharan P. Cancer in the gastrointestinal tract in western India. *Epidemiologic*

- study. *Cancer*. 1968;21:279-88.
7. Desai PB, Borges EJ, Vohra VG, Paymaster JC. Carcinoma of the esophagus in India. *Cancer*. 1969;23:979-89.
 8. Khuroo MS, Zargar SA, Mahajan R, Banday MA. High incidence of oesophageal and gastric cancer in Kashmir in a population with special personal and dietary habits. *Gut*. 1992;33:11-5.
 9. Cherian JV, Sivaraman R, Muthusamy AK, Jayanthi V. Carcinoma of the esophagus in Tamil Nadu (South India): 16-year trends from a tertiary center. *Journal of gastrointestinal and liver diseases: JGLD*. 2007;16:245-9.
 10. Gupta NM, Jindal R, Prakash O, Gupta R, Bhasin DK. Comparison of the clinical profile and outcome for squamous cell carcinoma and adenocarcinoma of the distal esophagus and cardia in India. *Surgery today*. 2001;31:400-4.
 11. Giri PA, Singh KK, Phalke DB. Study of socio-demographic determinants of esophageal cancer at a tertiary care teaching hospital of Western Maharashtra, India. *South Asian Journal of Cancer*. 2014;3:54-6.
 12. Sehgal S, Kaul S, Gupta BB, Dhar MK. Risk factors and survival analysis of the esophageal cancer in the population of Jammu, India. *Indian journal of cancer*. 2012;49:245-50.
 13. Sankaranarayanan R, Duffy SW, Padmakumary G, Nair SM, Day NE, Padmanabhan TK. Risk factors for cancer of the oesophagus in Kerala, India. *International journal of cancer Journal international du cancer*. 1991;49:485-9.
 14. Islami F, Ren JS, Taylor PR, Kamangar F. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. *British journal of cancer*. 2009;101:1641-7.
 15. Thrift AP, Shaheen NJ, Gammon MD, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. *Journal of the National Cancer Institute*. 2014;106.
 16. Glaws WR, Etkorn KP, Wenig BL, Zulfiqar H, Wiley TE, Watkins JL. Comparison of rigid and flexible esophagoscopy in the diagnosis of esophageal disease: diagnostic accuracy, complications, and cost. *The Annals of otology, rhinology, and laryngology*. 1996;105:262-6.
 17. Choi J, Kim SG, Kim JS, Jung HC, Song IS. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. *Surgical Endoscopy*. 2010;24:1380-6.
 18. Berry MF. Esophageal cancer: staging system and guidelines for staging and treatment. *Journal of Thoracic Disease*. 2014;6:S289-S97.
 19. Manner H, Pech O, Heldmann Y, et al. Efficacy, safety, and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. *Clin Gastroenterol Hepatol*. 2013;11:630-5; quiz e45.
 20. Buskens CJ, Westerterp M, Lagarde SM, Bergman JJ, ten Kate FJ, van Lanschot JJ. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. *Gastrointestinal endoscopy*. 2004;60:703-10.
 21. Rubenstein JH, Shaheen NJ. Epidemiology, Diagnosis, and Management of Esophageal Adenocarcinoma. *Gastroenterology*. 2015;149:302-17 e1.
 22. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut*. 2008;57:1200-6.
 23. Haidry RJ, Dunn JM, Butt MA, et al. Radiofrequency ablation and endoscopic mucosal resection for dysplastic Barrett's esophagus and early esophageal adenocarcinoma: outcomes of the UK National Halo RFA Registry. *Gastroenterology*. 2013;145:87-95.
 24. Ronellenfitch U, Schwarzbach M, Hofheinz R, et al. Preoperative chemo(radio) therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data. *Eur J Cancer*. 2013;49:3149-58.
 25. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *The lancet oncology*. 2015;16:1090-8.
 26. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *Jama*. 1999;281:1623-7.
 27. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *The New England journal of medicine*. 1992;326:1593-8.
 28. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2002;20:1167-74.
 29. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2008;26:1086-92.
 30. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCO 9102. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2007;25:1160-8.
 31. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation With and Without Surgery in Patients With Locally Advanced Squamous Cell Carcinoma of the Esophagus. *Journal of Clinical Oncology*. 2005;23:2310-7.
 32. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCO 9901. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2014;32:2416-22.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 12-01-2017; **Published online:** 26-02-2017