

# Self-Expanding Metallic Stents (SEMS) in Inoperable Esophageal Cancer: A Prospective Analysis of Morbidity and Survival Outcomes

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## Abstract

**Background:** Palliative treatment for inoperable esophageal cancers by self-expanding metallic stents (SEMS) overcomes disease-related symptoms, preserves the quality of life, and prolongs survival. The aim of this study was to determine dysphagia relief, complications, and patient survival after SEMS in patients with inoperable esophageal cancer. **Methods:** This is a hospital-based open cohort study conducted over 9 years between January 1, 2009, and December 31, 2017, from the Sub-Himalayan region of the Indian subcontinent. The last patient was recruited on November 16, 2017 and the minimum of follow-up was either death or survival till December 31, 2017. All the patients attending gastroenterology clinic or admitted in medical wards and fulfilling the definition of inoperable esophageal cancer, subsequently treated with SEMS were included. Data were prospectively gathered on demography, dysphagia scores, morbidity, mortality, and survival outcomes. Follow-ups were done during hospital visits or through a telephonic conversation with the patient and/or caregiver. **Results:** Of 239 patients, 147 (61.5%) were male and 92 (38.5%) were female. Most of the patients (60.7%) are in the age group of 51–70 years. Squamous cell carcinoma (SCC) was diagnosed in 205 (85.7%) and adenocarcinoma (ADC) in 34 (14.2%). Lower one-third was the most common site of tumor and observed in 125 (52.3%) patients. ADC was diagnosed equally in males and females and the mean age of presentation with ADC was equal to SCC. All the patients had dysphagia score 4, which improved to score 1 after SEMS insertion. Females had better survival than that of males. The difference was found to be statistically significant. **Conclusion:** SEMS effectively reduced dysphagia in inoperable esophageal cancer. Better survival rates were observed in females than males.

**Keywords:** Cancer, dysphagia, esophagus, palliative therapy

## INTRODUCTION

Esophageal cancer is the ninth-most common cancer and the sixth-most common cause of cancer death globally.<sup>[1]</sup> In India, it is the fourth-most common cancer in males and the fifth-most common in females.<sup>[2]</sup> Patients with esophageal cancer experience few symptoms until advanced disease or severe luminal narrowing has occurred.<sup>[3]</sup> Dysphagia is a predominant problem which compromises nutrition. It is one of the most distressing and debilitating symptoms, thus compromising the quality of life of these patients.<sup>[4]</sup> Undernutrition is possibly one of the most powerful predictors of survival in patients with esophageal cancer.<sup>[5]</sup> More than half of the patients with esophageal cancer are not amenable to surgery and need palliative treatment to overcome progressive dysphagia.<sup>[6]</sup> Various options available

for palliation of malignant dysphagia include chemotherapy and/or radiotherapy, endoluminal stents, esophageal dilatation, laser ablation, photodynamic therapy, brachytherapy, and resection or bypass surgery.<sup>[7]</sup> Esophageal stenting with self-expanding metallic stents usually offers rapid relief of dysphagia, manages oropharyngeal secretions, reduces aspiration risk, prevents starvation, restores nutrition, and hydration thus extending survival. Over the past decade, self-expanding

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metal stents (SEMS) have replaced surgical bypass and rigid plastic stents as the gold standard safe and effective mechanical palliation of this disease.<sup>[7]</sup> The median survival in patients with metastatic esophageal cancer without treatment is <6 months.<sup>[8]</sup> Palliative therapy aims to control disease-related symptoms, preserve as good a health-related quality of life score as possible, and prolong survival.<sup>[8]</sup> The aim of this study was to study the profile of esophageal cancer at our center and to determine dysphagia relief, complications, and patient survival after SEMS in patients with inoperable esophageal cancer.

## METHODS

This was an open cohort prospective analytical study conducted at a tertiary care hospital of Himachal Pradesh, India. Patients were recruited from January 1, 2009 to November 16, 2017. A total of 239 histologically proved esophageal carcinoma attending gastroenterology clinic or admitted in medical wards and treated with SEMS were included in this study. The decision to proceed with palliative treatment with SEMS was taken based on dysphagia score of 4, extensive local spread, the presence of distant metastasis, poor functional status, postradiotherapy stricture, tracheoesophageal fistula, postfeeding gastrostomy, and patient's wish. This represented a group of individuals for whom a minimum of follow-up was either death or survival till December 31, 2017. The median follow-up for males was 107 days (interquartile range [IQR] 127) and for females 144 days (IQR 127). Informed consent was obtained from all patients or their available family members before undergoing stent placement regarding the expected benefit, risk, and possible short and long-term complications. Patients' data were prospectively gathered on demography, clinical features, histopathology type, dysphagia scores, morbidity, mortality, and survival outcomes after SEMS implantation. Fully covered Nitinol stents were used. The length of the stents was selected in such a way that it covered 2 cm above and 2 cm below the growth. To prevent reflux, patients were educated to have their meals 2 h before lying down, keep head end raised and were prescribed prokinetics. Follow-ups were done at regular intervals during hospital visits or through a telephonic conversation with the patient and/or caregiver. For patients who died, date of death was obtained from family members. The outcome was assessed with regard to dysphagia scores, early complications (including chest pain, perforation, bleeding, infection, and death), late complications (including stent migration, overgrowth, obstruction, tracheo-oesophageal fistula, and gastrointestinal hemorrhage), and survival. This study was approved by the Institutional Ethical Committee. Dysphagia scores were noted prospectively, both before and after stent placement, by the use of Ogilvie's scale: 0 = nil; 1 = normal diet avoiding certain foods such as raw apple and steak 2 = semi-solids diet; 3 = fluids only; 4 = complete dysphagia for even liquids.<sup>[9]</sup> The data were entered in MS office and analyzed using SPSS version 21 (IBM corporation, Armonk, New York, USA). A comparison in the survival experience of two groups (males and females) was established using survival curves. To compensate for the

limitation in interpreting survival curves, log-rank test was used to test the null hypothesis that there is no difference between the two groups in the probability of an event (here a death) at any time point.

## RESULTS

A total of 239 patients were recruited from January 1, 2009 to December 31, 2017 over 9 years. Of 239 patients, 147 (61.5%) were male and 92 (38.5%) were female. The male-to-female ratio is 1.6:1. The mean age of the patients was  $64.1 \pm 11.2$  years. For male patients, the mean age was  $63.8 \pm 10.7$  years and for female patients, the mean age was  $64.5 \pm 11.9$  years. The age-wise distribution is shown in Table 1. Most of the patients (60.7%) were in the age group of 51–70 years. The mean age with adenocarcinoma (ADC) was  $65.1 \pm 12.9$  years. For male patients with ADC, the mean age was  $66.8 \pm 9.6$  years and for females, it was  $63.5 \pm 15.8$  years. Mean age with squamous cell carcinoma (SCC) was  $63.9 \pm 10.9$  and for males, it was  $63.4 \pm 10.8$  and for females, it was  $64.8 \pm 10.9$  years. Table 2 shows the frequency distribution of histopathology types of esophageal carcinoma in this study. The distribution of the site of malignancy with the histopathological types is shown in Table 3. The diseases had locally spread in 236 (99.2), and distant metastasis was observed in 21 (8.8) patients. All the patients had dysphagia score 4, which improved to score 1. The acute and long-term complications after SEMS insertion are shown in Table 4. Mean survival in days was  $147 \pm 7.9$  (95% confidence interval 163.4–124). The mean survivals among males and females patients are shown in Table 5. Figure 1 shows the comparison in the survival experience of two groups (males and females). As Figure shows, the survival curves differ, thereby pointing to a difference in the survival of males and females. Females appear to have better survival than males. We could compute survival curves for each group and compare the proportions surviving at any specific time. However, the survival curves do not provide a comparison of the total survival experience of the two groups, but rather gives a comparison at some arbitrary time point (s). As could be seen in figure, the difference in survival is greater at some times than others and eventually becomes zero. Therefore, we used the log-rank test, to take up the whole follow-up period into account. On the application of log-rank test, it is seen that females have better survival than males. The difference was found to significant statistically ( $P < 0.05$ ).

**Table 1: Frequency distribution of patients in different age groups (n=239)**

Age groups (years)	n (%)
<30	1 (0.4)
31-50	30 (12.6)
51-70	145 (60.7)
71-90	61 (25.5)
>90	2 (0.8)

**DISCUSSION**

In esophageal carcinoma, the treatment plans are tailored depending on clinical tumor stage, subsite, histology of the tumor, performance status, and comorbidity status of the patient. Most patients diagnosed with this cancer are not eligible for curative therapy or will develop tumor recurrence despite curatively intended treatment.<sup>[10-12]</sup> Extensive treatment might be associated with a considerable decline in health-related quality of life and yet still a poor prognosis.<sup>[8]</sup> Esophageal stenting as palliative treatment has now become the treatment option of choice for advanced esophageal malignancy. This study is a single-center experience of 239 patients with SEMS placement as a palliative measure in inoperable esophageal cancer.

The mean age in our patients was in the sixth decade regardless of sex and histopathology type. Data from various population and hospital-based studies globally reveal that esophageal cancer incidence increases with age and peaks

in the sixth decade.<sup>[13]</sup> This pattern is uniformly followed in developed and developing countries, including India. Commonly ADC is acquired 10 years earlier than SCC.<sup>[14]</sup> However, in our study, the mean age of patients with ADC was similar to patients with SCC. In a study from south India, the fourth decade was the mean age for patients with ADC.<sup>[15]</sup> The male-to-female ratio in our study was 1.6:1. Indian data reveal a low sex ratio with a national average of 1.2:1 for a male-to-female ratio.<sup>[13]</sup> Our results are consistent with the average national ratio and are in variation with the global data. Male predominance has been observed in all the cancer registries across the world. Esophageal cancer continues to be a male dominant disease, and this difference is more marked in ADC histopathology type.<sup>[16]</sup> In our study, ADC was distributed equally in both males and females which is in contrary to the other studies.<sup>[17,18]</sup> The mean male-to-female ratio is 3:1 for esophageal SCC and 6:1 for esophageal ADC, although this ratio varies considerably across geographical regions.<sup>[8]</sup> Exceptions to this trend include Iran, where the incidence of ADC is similar in males and females.<sup>[18]</sup> Obesity as a risk factor among women is a possible explanation for this observation in our study. This assumption is conjectural as we did not calculate body mass index in our patients. The prevalence of metabolic syndrome has been documented to be overwhelmingly predominant in Himachali women in comparison to men and is probably due to their lifestyle, including sedentary habits and longer staying at home.<sup>[19]</sup> Himachal Pradesh has a high alcohol and tobacco use among men at 39.7% and 40.5%,

**Table 2: Frequency distribution of histopathological type (n=239)**

Histopathology	n (%)	Male	Female
ADC	34 (14.2)	17	17
SCC	205 (85.7)	130	75

SCC: Squamous cell carcinoma, ADC: Adenocarcinoma

**Table 3: Distribution of esophageal cancer according to site of involvement (n=239)**

Site of tumour	n (%)	SCC	ADC
Upper third	2 (0.8)	2 (0.8)	0
Middle third	112 (46.9)	99 (41.4)	13 (5.4)
Lower third	125 (52.3)	104 (43.5)	21 (8.8)

SCC: Squamous cell carcinoma, ADC: Adenocarcinoma

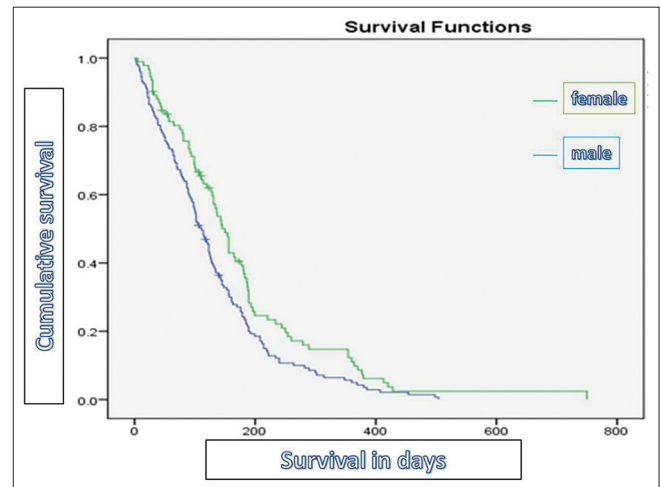
**Table 4: Complications of self-expanding metallic stents**

Complications	Number of patients (%)
Acute	
Pain	120 (50.2)
Hemorrhage	24 (10)
Perforation	2 (0.8)
Long term	
Aspiration	2 (0.8)
Stent migration	5 (2)
Stent overgrowth	36 (15)

**Table 5: Interpreting survival of two groups using log-rank (mantel-cox) equation**

Group	n (percentage age)	Survived (percentage age)	Mean days of survival ± SD (95% CI)	P*
Male	147 (61.5)	3 (2)	130.9±8.6 (113-147)	0.010
Female	92 (38.5)	7 (7.6)	175.9±15.1 (146-205)	
Total	239 (100)	10 (4.2)	147±7.9 (124-163)	

\*Using log-rank (mantel-cox). SD: Standard deviation, CI: Confidence interval



**Figure 1: The comparison in the survival experience of two groups (Green: female; Blue: Male)**

respectively. In comparison, alcohol and tobacco use among women is 0.3% and 0.5%, respectively.<sup>[20]</sup> This study has provided an insight into the pattern of histological subtypes of esophageal cancer from this region. SCC was observed in 85% of patients and 15% of patients had ADC. Globally, SCC is the most common histological subtype of esophageal cancer.<sup>[8]</sup> Our geographical area seems to fall in the “Asian esophageal cancer belt,” the highest risk region, and the results reflect the pattern of histopathological types from this region. SCC was predominant among women patients also and the difference was not statistically significant. Alcohol consumption and tobacco use are the main risk factors for SCC.<sup>[8]</sup> Epidemiological transition is occurring in the prevalence of cancers, and ADC is increasing in countries with higher human development index.<sup>[21]</sup>

The distribution according to the site of tumor in this study revealed that all the patients had disease in the lower 2/3<sup>rd</sup> except for two patients. In the lower two thirds, the slight predominance of lower 1/3<sup>rd</sup> in comparison to middle 1/3<sup>rd</sup> was observed. This pattern was followed irrespective of the histopathological variant. The distal third was the most common location observed in 16 years study from south India.<sup>[15]</sup> Dysphagia score improved from Grade 4 to Grade 1 in all the patients. Improvement in dysphagia score is the main objective of esophageal stenting. The pain was the main acute complication followed by the self-limiting mild hemorrhage. Both the patients with perforation were managed in operation theater with gastrostomy followed by Ryle’s tube insertion and SEMS implantation. Both the patients who aspirated following SEMS implantation died. Female patients displayed better survival rates compared with males in this study. However, while analyzing the sex difference in the prognosis adjustments for age, histology type, staging, and other relevant clinical prognostic factors were not done. Female sex has been reported to have a better prognosis with esophageal carcinoma.<sup>[22-24]</sup> The influence of younger age and hormones such as estrogen and androgen determine a role in better survival among female patients.<sup>[23,24]</sup>

## CONCLUSION

Two observations in this study require future research. First, the mean age of patients with ADC is similar to patients with SCC and second, the equal distribution of ADC among male and female patients. The exposure to common risk factors for the two histopathological types and higher prevalence of obesity among women in this region are possible reasons for these observations. The role of risk factors such as gastroesophageal reflux disease and Barrett’s esophagus in ADC require future research in this region.

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## Conflicts of interest

There are no conflicts of interest.

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