ANTICANCER RESEARCH *41*: 385-389 (2021)
doi:10.21873/anticanres.14787

Clinical Outcomes of Fully Covered Self-expanding Metallic Stent Placement for Palliation of Incurable Esophageal Cancer With or Without Radiotherapy

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Abstract. *Background/Aim: A combination therapy of esophageal stent and chemoradiotherapy (CRT) is currently considered risky for severe complications. The aim of this study was to assess the safety and efficacy of a fully covered self-expandable metallic stent (FCSEMS) placement in palliating incurable esophageal cancer before and/or after CRT. Patients and Methods: We retrospectively reviewed clinical outcomes of 64 incurable advanced esophageal cancer patients with FCSEMS placement. Forty-two of 64 patients had FCSEMS placement with RT. Results: The rate of all of stent-related complications tended to be higher in patients who had RT, although no significant difference was observed. The stent-related deaths occurred in one patient due to hemorrhage after FCSEMS placement in the RT-negative group. Conclusion: Palliation of dysphagia or fistulas with FCSEMS in patients with incurable esophageal cancer before and/or after RT is not associated with an increased risk of life-threatening complications.*

Advanced esophageal cancer patients often have significant symptoms and burden at the time of initial diagnosis or after treatment. They require palliative intervention if they cannot undergo curative treatment or reject active treatment. Dysphagia due to esophageal strictures and esophagorespiratory fistulas are usual symptoms in patients with incurable esophageal cancer. To relieve them, fully covered self-expanding metallic stent (FCSEMS) placement has been widely accepted as an option for palliation with a high success and low complication rates (1, 2). Few studies reported superior results for esophageal stenting followed by radiotherapy (RT) with regard to both improvement of dysphagia and survival in patients with inoperable esophageal cancer (3-5). However, several studies reported a high rate of life-threatening complications in patients who received radiotherapy and/or chemotherapy (CT) before and after stenting (6-10). We, therefore, retrospectively aimed at evaluating the efficacy and complication of FCSEMS for palliating dysphagia and fistula in patients with incurable esophageal cancer with or without RT.

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Key Words: Self-expanding metallic stent, palliation, incurable esophageal cancer.

Patients and Methods

Patients. We enrolled esophageal cancer patients with palliative FCSEMS placement for malignant stricture and fistula from August 2011 to June 2019 in our department and their medical records were retrospectively reviewed. We divided the patients into two groups (one with chemoradiotherapy (CRT) or RT and the other without it) and compared the efficacy and complications of stenting in these groups. Patient performance status (PS) was evaluated according to Eastern Cooperative Oncology Group grading (11). All the information on esophageal cancer described herein was based on the clinical pathology guidelines for esophageal cancer issued by the Japan Esophageal Society (12) and the 8th UICC-TNM classification (13).

Table I. *Patient, tumor and FCSEMS characteristics (number (%)) with or witout RT.*

Total (n=64)	Total (n=64)	RT positive (n=42)	RT negative (n=22)	*p*-Value
Age, y, median (range)	68.5 (44-89)	68.0 (44-88)	76.0 (51-89)	0.109
Gender				
Male/Female	55 (85.9)/9 (14.1)	39 (92.9)/3 (7.1)	16 (72.3)/6 (27.3)	0.032
PS (ECOG)				
0/1/2/3/4	2 (3.1)/18 (28.1)/18 (28.1)/ 22 (34.4)/4 (6.3)	0 (0)/12 (28.6)/12 (28.6)/ 14 (33.3)/4 (9.5)	2 (9.1)/6 (27.3)/6 (27.3)/ 8 (36.4)/0 (0)	0.010
Location of the tumor				
Ce/Ut/Mt/Lt/Ae	1 (1.6)/7 (10.9)/25 (39.1)/ 27 (42.2)/4 (6.3)	1 (2.4)/6 (14.3)/15 (35.7)/ 18 (42.9)/2 (4.8)	0 (0)/1 (4.6)/10 (45.5)/ 9 (40.9)/2 (9.1)	0.548
Histological type				
SCC/ADC/Others	58 (90.6)/4 (6.3)/2 (3.1)	39 (92.9)/2 (4.8)/1 (2.4)	19 (86.4)/2 (9.1)/1 (4.6)	0.326
Stage (UICC 8th)				
II/III/IVa/IVb	1 (1.6)/20 (31.3)/ 33 (51.6)/10 (15.6)	1 (2.4)/19 (45.2)/ 20 (47.6)/2 (4.8)	0 (0)/1 (4.6)/13 (59.1)/ 8 (36.4)	<0.001
Reasons for stenting				
Stricture/Fistula	51 (79.7)/13 (20.3)	32 (76.2)/10 (23.8)	19 (86.4)/3 (13.6)	0.324
Type of FCSEMS				
Standard/Anti-reflux/ Without oral side flare	28 (43.8)/34 (53.1)/ 2 (3.1)	19 (45.2)/22 (52.4)/ 1 (2.4)	9 (40.9)/12 (54.6)/1 (4.6)	0.869
RT				
Before stenting/After stenting/ Both of them		33 (78.6)/5 (11.9)/4 (9.5)		
Definitive CRT/the others		27 (64.3)/15 (35.7)		

FCSEMS, Fully covered self-expandable metallic stent; RT, radiation therapy; PS, performance status; ECOG, the Eastern Cooperative Oncology Group; Ce, cervical esophagus; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Ae, abdominal esophagus; SCC, squamous cell carcinoma; ADC, adenocarcinoma; Stage status, TNM Classification of the International Union Against Cancer (UICC), 8th edition; CRT, chemoradiotherapy.

Stent types and placement. HANAROSTENT® (M.I. Tech Co., Ltd. Seoul, Korea) constructed of nitinol alloy wire and completely covered with a silicon membrane at the inside of the mesh was used for all of patients. Three types of HANAROSTENT® are as follows: i) standard type, ii) stent with anti-reflux valve for lower portion, and iii) stent without oral side flare for upper portion were used, depending on the tumor location. Stents were placed through endoscopic and fluoroscopic guidance, and well procedures under conscious sedation using pentazocine and midazolam.

Assessment of dysphagia and complications. We evaluated dysphagia before stenting and at discharge. Dysphagia score (DS) was graded on a 5-point scale as follows: 0, able to eat normal diet; 1,unable to swallow certain solids; 2, able to swallow semisolids foods; 3, able to swallow liquids only; 4, unable to swallow liquids (14). We explained he relationship of the complications and prior treatment. Finally, he evaluates period until oral intake after stenting and survival time.

Statistical analysis. We expressed continuous variables as median and range. We also expressed categorical variables as number (percentage). The Wilcoxon test for nonparametric continuous data and Chi-squared test for categorical data to compare the proportions between the two groups. We considered p-value <0.05 was to be statistically significant. Finally, we performed all statistical analyses using JMP Pro 15 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. Table I summarizes the clinico-pathological characteristics of the patients with or without RT. There were 55 males and 9 females, with the median age of 68.5 years (range=44-89). We observed PS of 0, 1, 2, 3, and 4 in 2 (3.1%), 18 (28.1%), 18 (28.1%), 22 (34.4%), and 4 (6.3%) patients, respectively. We noted that most of the tumors in the esophagus were located in the middle- or lower third of the esophagus in 52 patients (81.3%), and in the upper third of the esophagus in the other 12 (10.9%). The most common histological type was squamous cell carcinoma (n=58, 90.6%), while four patients (6.3%) had an adenocarcinoma as the least. The reasons for stenting were stricture in 51 patients (79.7%) and fistula formation in the remaining 13 (20.3%). Twenty-eight patients (43.8%) underwent insertion of standard-type stent (Figure 1a), and 34 (53.1%) used stent with an anti-reflux valve for lower esophagus (Figure 1b) to avoid gastroesophageal reflux. Thereafter, two (3.1%) used stent without oral side flare for upper portion (Figure 1c) to reduce throat discomfort. Forty-two of 64 patients had RT, and 22 of 64 patients received chemotherapy (CT) with 5-fluorouracil and cisplatin. Thirty-three of 42 (78.6%) had RT before

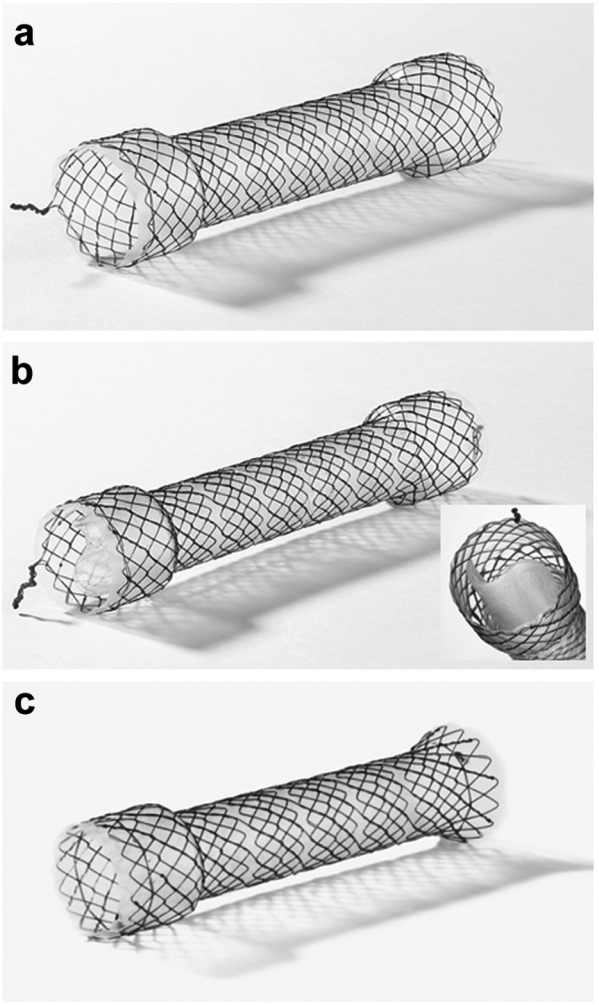

Figure 1. *HANAROSTENT® (M.I. Tech Co., Ltd. Seoul, Korea). a. Standard type. b. Stent with an anti-reflux valve for lower esophagus. C. Stent without oral side flare for upper esophagus. © 2020 Boston Scientific Corporation. All rights reserved.*

stenting, 5 of 42 (11.9%) had RT after stenting, and 4 of 42 (9.5%) had RT before and after stenting. The median RT dose was 50 Gy (range=9-70 Gy), and the fractional doses were 1.8-2.0 Gy. Twenty-seven of 64 had definitive CRT received a total dose of more than 50Gy radiation. Patients of RT positive group had significantly lower stage compared to RT negative group ($p<0.001$).

Improvement of dysphagia. Table II shows how the oral intake status affected DS of patients before and after stenting in both groups. FCSEMS placement was technically successful in all patients and improved the DS from 3.51±0.67 to 1.92±0.91 ($p<0.0001$). DS improved from 3.67±0.57 to 1.95±0.94 ($p<0.0001$) and 3.23±0.75 to 1.76±0.77 ($p<0.0001$), in both RT-positive and -negative groups. Fifty-eight patients (90.6%) showed an improvement of DS, and achieved resumption of oral intake. Six patients could not swallow anything after stenting due to aspiration pneumonia in two, hemorrhage in one, and nausea in one in the RT positive group, pneumonia in one, hemorrhage in one in the RT negative group, respectively. The average number of days until the resumption of oral intake after stenting was 3.4±1.9 (1 to 9) in all patients.

Morbidity and mortality. Table III summarizes the major complications after stenting with or without RT. We observed major complications in 45 patients (70.3%) in all patients. More than half of patients (n=33, 51.6%) experienced transient retrosternal pain requiring analgesics, and 15 (23.4%) had fever. Five patients had hemorrhage and two of these needed blood transfusion. We treated three patients with stent migration with re-stenting. The stent-related deaths occurred in one patient due to hemorrhage after FCSEMS placement in the RT negative group. The rate of all of stent-related complications tended to be higher in patients who had RT, although no significant difference was observed ($p=0.160$).

Survival time after stenting. The median survival time of all patients, the RT-positive group and the RT-negative group after stenting were 89.5 (range=14-489), 92.5 (range=15-489) and 75 (range=14-229) days, respectively. There was no significant difference in survival between patients with or without RT (Table IV).

Discussion

We conducted this retrospective study to assess the clinical outcomes of FCSEMS placement for palliation of incurable esophageal cancer with or without RT. In the present study, FCSEMS placement was technically successful in all patients and improved the DS from 3.51±0.67 to 1.92±0.91 ($p<0.0001$). Three patients could not swallow anything after stenting due to aspiration pneumonia. Hence, careful evaluation of swallowing function and patient selection before stenting is important.

Several studies reported a high rate of life-threatening complications in patients who received radiotherapy and/or chemotherapy (CT) before and after stenting (6-10). Considering the risk of severe complications, a combination therapy of stenting and RT is currently hard to be accepted as standard treatment for incurable esophageal cancer. However, in the present study, there was no significant difference in the stent-related complication rate between the RT-positive and -negative group, although we observed complications in 70.3% of the study population. Stent-related deaths occurred in only one patient in the RT-negative group

Table II. *Comparison of the dysphagia score before and after stenting with or without RT (mean±SD).*

Dysphagia score								
Total (n=64)			RT positive (n=42)			RT negative (n=22)		
Before stenting	After stenting	*p*-Value	Before stenting	After stenting	*p*-Value	Before stenting	After stenting	*p*-Value
3.51±0.67	1.92±0.91	<0.0001	3.67±0.57	1.95±0.94	<0.0001	3.23±0.75	1.76±0.77	<0.0001

RT, Radiotherapy; SD, standard deviation.

Table III. *Stent palacement related complications [number (%)].*

Complications	Total (n=64)	RT positive (n=42)	RT negative (n=22)	*p*-Value
Total	45 (70.3)	32 (76.2)	13 (59.1)	0.1598
Retrosternal pain	33 (51.6)	24 (57.1)	9 (40.9)	0.2163
Fever	15 (23.4)	12 (28.6)	3 (13.6)	0.1662
Peumonia	5 (7.8)	4 (9.5)	1 (4.6)	0.4624
Nausea	5 (7.8)	3 (7.1)	2 (9.1)	0.7849
Hemorrhage Bleeding	5 (7.8)	3 (7.1)	2 (9.1)	0.7849
Migration	3 (4.7)	2 (4.8)	1 (4.6)	0.9689
Sepsis	2 (3.1)	3 (4.8)	0 (0)	0.1899

RT, Radiotherapy.

Table IV. *Survival time after stenting with or without RT.*

	Total (n=64)	RT positive (n=42)	RT negative (n=22)	*p*-Value
Survival time after stenting, days, median (range)	89.5 (14-489)	92.5 (15-489)	75 (14-229)	0.309

RT, Radiotherapy.

due to hemorrhage after stenting, despite including 42 patients who underwent RT. Raijman *et al*. reported that RT before stenting did not increase the risk of life-threatening complications (15), and Song *et al*. also reported that patients who underwent RT before stenting experienced substantially less complications than those who underwent RT after stenting (5). A multicenter randomized controlled trial (RCT) reported that stenting and additional radiotherapy significantly reduced bleeding events compared to stenting alone (16). A RCT reported that 30 Gy RT after stenting effectively prolongs duration of dysphagia relief and improves overall survival in inoperable esophageal cancer without increasing the incidence of complications (3).

The type of FCSEMS may play an important role in the low rate of stent-related complications. *In vitro* analysis, which evaluated the radial and axial force of SEMS, reported that HANAROSTENT®, which we used, had a moderate radial force and relatively low axial force to explain results of stent patency and the occurrence of complications (17). Higher radial force is needed to maintain luminal patency and ensure proper fixation of the stent. A lower axial force is needed to adapt well to the esophagus less invasively as they are considered optimal mechanical properties of SEMS (17, 18), indicating a low frequency of severe adverse event. Uncovered sharp ends and larger diameters at the proximal and distal ends of SEMS may increase the radial force, which can result in an ulcer and chronic inflammatory reaction (19, 20). Characters of HANAROSTENT®, full-covered and diameters at the ends are relatively smaller than the others, also should indicates a low frequency of severe adverse event.

This study has several limitations. The sample size of patients who received FCSEMS was small. In addition, the study population enrolled in this study were not part of a prospective protocol, such as for performance status, location

of the tumor, UICC stage, reasons for stenting, or dose of RT. Larger prospective studies are warranted to determine the efficacy and complication of FCSEMS in patients with incurable esophageal cancer with or without RT.

In conclusion, palliation of dysphagia or fistulas with FCSEMS in patients with incurable esophageal cancer before and/or after RT is not associated with an increased risk of life-threatening complications.

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Received September 15, 2020
Revised December 2, 2020
Accepted December 4, 2020