ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-463

Predictors for Treatment Failure of Self-Expandable Metal Stents for Anastomotic Leak after Gastro-Esophageal Resection

Wolfram Bohle[1], Ioannis Louris[1], Andre Schaudt[2], Joerg Koeninger[2], Wolfram G. Zoller[1]

1) Department of Gastroenterology, Katharinenhospital, Klinikum Stuttgart, Stuttgart
2) Department of Surgery, Katharinenhospital, Klinikum Stuttgart, Stuttgart, Germany

Address for correspondence:
Wolfram Bohle
Department of Gastroenterology
Katharinenhospital,
Klinikum Stuttgart
Kriegsbergstr. 60
D-70174 Stuttgart, Germany
w.bohle@klinikum-stuttgart.de

Received: 01.10.2019
Accepted: 17.04.2020

ABSTRACT

Background & Aims: Self-expandable metal stents are used for the treatment of anastomotic leaks after gastro-esophageal surgery. Predictors for treatment failure and complications are unknown. In this observational retrospective study, we summarize our experience with self-expandable metal stents for the treatment of anastomotic leaks, in order to determine the predictors of treatment failure.

Methods: Between 2009 and 2015, 34 patients with anastomotic leak after curative resection of gastro-esophageal cancer were treated with self-expandable metal stents. Gender, histology, comorbidity, body mass index, neoadjuvant therapy, previous surgery, leak size, and stent diameter were analyzed for their predictive value according to treatment success and complication rate.

Results: Leak closure rate was 76%. Risk factors for treatment failure were neoadjuvant chemo-radiotherapy, squamous cell histology, and esophageal tumor location. Gender, comorbidity, body mass index, neoadjuvant chemotherapy, and previous surgery were not correlated with outcome. Mortality rate was 20%, most often due to uncontrolled leak. Severe stent-related complications occurred in 15% of patients, most of them following insertion of a large-sized stent.

Conclusion: Squamous cell histology, neoadjuvant chemo-radiotherapy, and esophageal tumor location are predictors for treatment failure. Severe stent-related complications seem to be preferentially associated with the use of large-sized stents.

Key words: gastro-esophageal cancer – anastomotic leak – self-expandable metal stent – endoscopic therapy – neoadjuvant therapy.

INTRODUCTION

Anastomotic leaks are a serious complication after resection of esophago-gastric cancer, occurring between 2.9 and up to 30% of patients [1-3]. Most often, leaks occur 3-5 days after surgery, and are associated with prolonged stay in intensive care unit and increased mortality [4]. In general, postoperative complications are predictors of worse overall and disease-specific survival [5, 6]. Surgical repair is associated with an increased complication rate [7]. Therefore, endoscopic intervention is the therapy of choice. Depending on the size of leak, different endoscopic techniques, such as clips, fibrin glue, self-expandable metal stents, or, recently introduced, endoscopic vacuum therapy are used [4]. The choice of endoscopic technique often depends on local expertise and personal predilection only. In this observational retrospective study, we summarized our experience with self-expandable metal stents for the treatment of anastomotic leaks, in order to determine the predictors of treatment failure.

METHODS

All patients who underwent resection due to esophageal or gastric cancer between 2009 and 2015 in the department of surgery were retrospectively analyzed for anastomotic leak treated with self-expandable metal stents.

The following demographic variables were analyzed: age, gender, body mass index (BMI), comorbidity (cardio-vascular, renal, pulmonary, diabetes mellitus), tumor location (esophagus, esophago-gastric junction, gastric), histology. Data about treatment were also recorded: neoadjuvant therapy and type of surgery (trans-thoracic esophagectomy, trans-hiatal resection, complete gastrectomy). The time interval between surgery and

diagnosis of anastomotic leak was also noted. For the endoscopic treatment the following data were registered: size of leak, stent diameter, and number of consecutive stents placed, overall duration of stent treatment. The stent-associated complications such as migration, bleeding with a drop of hemoglobin >2 g/dl, stent-induced perforation, stent-induced erosion of adjacent blood vessels were also noted. Recorded data included: outcome according to stent treatment, and overall mortality.

For statistical analysis, chi-squared test and Fisher´s exact test were used (SPSS software). A p-value of <0.05 was considered statistically significant. The study was approved by the local Ethics Committee.

RESULTS

Between 2009 and 2015, 218 patients underwent surgery due to esophageal or gastric cancer at the Department of Surgery, Katharinenhospital, Klinikum Stuttgart.

Forty patients (18.34%) with anastomotic leak were treated with metal stent insertion. Six of them were excluded from the analysis because of incomplete data.

Therefore, 34 patients with a median age of 66.5 years (range 45-79 years) were included in the analysis. Demographic data are summarized in Table I. Most patients (79%) presented with adenocarcinoma. Comorbidities, most often cardiovascular diseases, were present in 85% of patients. BMI was increased in 12 patients (35%).

Trans-thoracic esophagectomy (Ivor-Lewis procedure) was performed in 26 patients (76%), radical gastrectomy in 7 (21%), and trans-hiatal resection in 1 patient (3%). Median interval between surgery and diagnosis of anastomotic leak was 7.5 days (range 3-29 days). All leaks were endoscopically confirmed. In 28 patients (82%) leak size was smaller than 1/3 of anastomotic circumference. Six patients (18%) presented with a leak size between 1/3 and 2/3 of esophageal circumference. The metal stent insertion was performed immediately after the date of diagnosis in 33 patients (97%). In one patient, the stent was placed 22 days later.

Sixty-nine consecutive stents were placed in 34 patients (Table II). Most often, fully covered stents with a body diameter of 20 mm or 28 mm were used. In only one patient, a partial covered stent was placed. Healing was monitored endoscopically. The first surveillance endoscopy was done in median 27 days after the initial stent placement (range 1-111 days). In one patient, the second endoscopy was performed one day after stent insertion due to suspected – and confirmed – stent migration.

The timing of the surveillance endoscopy was dependent on the patient´s clinical course, and at the discretion of the examiner. At the second endoscopy, the stent was removed, and the healing of the leak was assessed endoscopically. In the case of incomplete leak closure, a new stent was placed. In median, two consecutive stents/patient were placed (range 1-7). Sixteen patients (47%) were treated with one stent, 12 patients (35%) with two consecutive stents, and 6 patients (18%) with three or more consecutive stents. Median interval between the stent exchange was 22 days (range 1-141 days), and median duration of complete overall stent treatment was 42 days (range 5-234 days). Details are summarized in Table II.

Table I. Patients characteristics

Age, years (range)	66.5 (45-79)
Gender (Male/Female)	26 (76.5%) / 8 (23.5%)
Comorbidities	
Cardio-vascular diseases	28 (82%)
Kidney diseases	2 (6%)
Pulmonary diseases	7 (26%)
Diabetes mellitus	8 (24%)
Number of comorbidities	
0	5 (15%)
1	14 (41%)
2	14 (41%)
3	1 (3%)
BMI	
<18.5	2 (6%)
18.5 - 24.9	20 (59%)
>25	12 (35%)
Tumor location	
Esophagus	18 (53%)
Esophago-gastric junction	9 (26%)
Stomach	7 (21%)
Histology	
Adenocarcinoma	27 (79%)
Squamous cell carcinoma	7 (21%)
Surgery	
Trans-thoracic Esophagectomy	26 (76%)
Gastrectomy	7 (21%)
Trans-hiatal resection	1 (3%)
Neoadjuvant therapy	
Chemotherapy	16 (47%)
Chemo-radiotherapy	6 (18%)

BMI: body mass index

In 26 patients (76%), anastomotic leak was successfully treated by stent insertion. Healing was monitored by endoscopy in all patients. Of the remaining patients with unsuccessful stent treatment, six died. In all of them, death was due to an uncontrolled leak. One patient with unsuccessful stenting was re-operated 5 days after anastomotic leak and stent insertion; a second patient was treated with fibrin glue and endosponge after 149 days of insufficient stent treatment. Both patients survived. Esophageal tumor site, squamous cell histology, and neoadjuvant chemo-radiotherapy were risk factors for treatment failure in univariate analysis (p<0.05, Table III). Patients with and without successful stent treatment did not differ according to gender, BMI, comorbidity, neoadjuvant chemotherapy, size of leak, length or diameter of stents used, or previous surgery. Details are summarized in Table III.

Migration was the most common complication after stent insertion (24% of stents). Migration risk was not associated with stent diameter (Table IV). In two patients, hemorrhage due to wall erosion by the distal stent flare occurred. Both were successfully treated with interventional endoscopy.

Table II. Endoscopic treatment: self-expendable metal stents (n=69)

Stent body diameter	
20 mm	44 (64%)
22 mm	2 (3%)
24 mm	5 (7%)
28 mm	18 (26%)
Number of consecutive stents/patient	
1	16 (47%)
2	12 (35%)
3	2 (6%)
4	1 (3%)
5	1 (3%)
6	0
7	2 (6%)
Median number of stents/patient	2
Stent dwell time (days) median (range)	22 (1 - 141)
Total duration of stent treatment (days) median (range)	42 (5 - 234)

Severe stent-related complications occurred in 5 patients: perforation due to wall compression by the distal stent flare (2), and erosion of the thoracic aorta (2), or the hepatic artery (1). Perforations were successfully treated with overstenting (1), or external drainage (1). Arterial erosion was treated with intraluminal stenting of the aorta or hepatic artery. However, one of two patients with initially successful aortic stenting died 5 months later due to fatal re-bleeding. The patient with erosion of the hepatic artery died two weeks later due to mediastinitis.

Four of these five patients with severe complications received preoperative neoadjuvant therapy (Table V). Four of them were treated with stents of 28 mm body size. However, stent diameter as well as neoadjuvant therapy failed to be a significant risk factor for stent-related complications in statistical analysis. Furthermore, severe stent complication rate was independent from BMI, comorbidity, or previous surgery. Details are summarized in Table V.

Seven of 34 patients died, leading to a mortality rate of 20%. In 5 of them, death was due to uncontrolled anastomotic leak (Table VI). One patient died due to a cardiac arrest after a successful leak closure. One further patient died due to late stent-induced complication (aortic erosion). Six of these seven patients with fatal outcome had received neoadjuvant treatment. Details are summarized in Table VI.

Table III. Predictors for self-expandable metal stent treatment failure

	Outcome of Metal Stent treatment for Anastomotic Leak		
	Successful	Failed	p
Gender			
Male	20	6	0.62
Female	6	2	
BMI			
<18.5	1	1	0.68
18.5-24.9	16	4	
>25	9	3	
Comorbidities			
Present	22	7	0.66
Absent	4	1	
Tumor site			
Esophageal	11	7	0.043
Gastric	15	1	
Histology			
Squamous cell carcinoma	3	4	0.037
Adenocarcinoma	23	4	
Neoadjuvant chemoradiotherapy			
Yes	2	4	0.018
No	24	4	
Neoadjuvant chemotherapy			
Yes	14	2	0.23
No	12	6	
Type of surgery			
Trans-thoracic esophagectomy	19	7	0.64
Total gastrectomy	6	1	
Trans-hiatal resection	1	0	
Leak size (circumference)			
<1/3	21	7	0.66
>1/3	5	1	
Stent body diameter (mm)			
20	17	3	0.30
24	1	1	
28	8	4	
Stent length (mm)			
80	12	3	0.91
100	8	4	
120	4	1	
140	2	0	

BMI: body mass index

DISCUSSION

According to the literature, anastomotic leak rate ranges between 2.9 and 9% [1, 2]. However, in the multicenter neoadjuvant chemo-radiotherapy CROSS trial, a leak rate of 30% (surgery-only group) has been reported [3]. In our study, anastomotic leak occurred in 18%. The optimal treatment of anastomotic leak is still a matter of debate. The evidence available is based on non-randomized, and often small-sized unicentric cohort studies. In general, conservative treatment is preferred to a surgical approach due to the high mortality up to 64% in cases of re-operation [2, 7]. However, choose of endoscopic technique often depends on local expertise and personal predilection only.

In our cohort, stent treatment was successful in 76% of patients. Mortality was 20%, and most deaths were due to uncontrolled anastomotic leak. Several small case compilations and cohort studies reported successful leak closure with stent insertion in 65-95% [7-11]. These results have been confirmed in a larger retrospective study from Feith et al. [12] with 115 patients: complete leak closure was observed in 70% of

Table IV. Stent migration rate according to body diameter (absolute numbers)

Stent body diameter (mm)	
20	14 / 44
22	0 / 2
24	0 / 5
28	3 / 18

Table V. Severe stent-induced complications

	Wall perforation			Vessel erosion		
	Yes	No	p	Yes	No	p
BMI						
<18.5	0	2	0.55	1	1	0.55
18.5-24.9	1	19		1	19	
>25	1	11		1	11	
Comorbidities						
Present	2	27	1.0	3	26	1.0
Absent	0	5		0	5	
Neoadjuvant chemoradiotherapy						
Yes	1	5	0.07	1	5	0.45
No	1	27		2	26	
Neoadjuvant chemotherapy						
Yes	1	15	1.0	1	15	1.0
No	1	17		2	16	
Previous surgery						
Trans-thoracic esophagectomy	1	25	0.51	2	24	0.51
Other	1	7		1	7	
Stent body diameter (mm)						
20	0	44	0.06	1	43	0.61
22	0	2		0	2	
24	0	5		0	5	
28	2	16		2	16	

BMI: body mass index

patients. In our study, the clinical success rate was 76%. Several variables, such as age, comorbidity, previous surgery, BMI, or size of leak did not influence the outcome. In the study of Hoeppner et al. [10], no difference of clinical success rates was found comparing leaks ≤10 versus >10 mm, whereas Kim et al. [13] reported a better outcome after endoscopic therapy with clipping, fibrin glue injection, or stent insertion in leaks of less than 2 cm size.

Neoadjuvant therapy is well-known for not increasing the rate of anastomotic leakage [3]. Data regarding its impact on the sealing rate of anastomotic leaks by endoscopic treatment are missing in the literature. In our study, neoadjuvant chemo-radiotherapy, squamous cell histology, and esophageal tumor site were associated with failure of stent treatment. Hoeppner et al. [10] observed a similar, but statistically not significant, impact of tumor site. We are aware of the limitations of our study due to the retrospective and unicentric design, and the relatively small size of the studied group.

Stent migration was the most often observed complication in our study (24%). This correlates with other studies, reporting migration rates between 19 and 53% [9, 10, 12, 14]. Stent migration is due to esophago-gastric lumen-to-stent size discrepancies and occurs preferentially in cases of a fully covered stent. However, these stents are preferred against a partially covered stent, because of impaired removal of partially covered stents due to tissue ingrowth. Furthermore, tissue in- and overgrowth can result in certain complications during follow-up, such as stenosis and bolus impaction. In the study of van Boeckel et al. [9], tissue ingrowth caused complications in 15% of patients. Stent-related complications occurred in 46% of their patients [9]. In a small pilot study, Fischer et al. [14] used a specially designed, large diameter (body 36 mm), partially covered stent to prevent stent migration. However, even with this stent design, stent dislocation occurred in 4/11 patients. In our study, stent migration rate was not associated with the stent diameter, and occurred to a comparable rate in stents with a body diameter of 20, 24, or 28 mm.

Severe stent-related complications such as esophageal rupture, hemorrhage, stent migration with consecutive intestinal obstruction, or stent-related death has been reported in up to 10% of patients [9, 12]. In our study, 15% of patients suffered from severe stent-related complications, with a fatal outcome in one patient. Whenever not statistically significant, it is of interest to note, that in 4 of our 5 patients with serious complications, like stent-induced perforation, or erosion of adjacent arterial vessels, a stent with a larger body diameter of 28 mm was used. Most often, the injury was due to wall compression by the distal flare. This is in contrast to the study of Fischer et al. [14] with large diameter stents (body 36 mm),

Table VI. Patients with fatal outcome

Patient	Gender	Age (years)	Neoadjuvant therapy	Surgery	Number of stents	Stent treatment (days)	Outcome
1	M	67	Chemotherapy	Esophagectomy	1	35	Leak-associated death
2	M	62	Chemotherapy	Esophagectomy	5	128	Leak-associated death, early tumor relapse
3	F	63	None	Gastrectomy	1	30	Leak-associated death
4	M	75	Chemotherapy	Esophagectomy	1	29	Cardiac arrest
5.	M	74	Chemo-radiotherapy	Esophagectomy	2	46	Leak-associated death
6	M	52	Chemo-radiotherapy	Esophagectomy	3	116	Leak-associated death
7	F	57	Chemo-radiotherapy	Esophagectomy	2	251	Stent-related death (hemorrhage)

reporting no severe stent-related complications. Probably, this difference is due to the small number of patients treated in their study (11 patients). A different location of the anastomosis in the abdominal-thoracic cavity can be another possible explanation of this discrepancy: in certain circumstances, the stent flare will be positioned in close proximity to large vessels, such as the aortic arch, increasing the risk of arterial erosion. In conclusion, we strongly argue against the use of large diameter stents for anastomotic leak treatment.

Even with endoscopic treatment, anastomotic leak is still a life-threatening event. Mortality ranges from 9 to 21% [2, 11, 12]. In a large multicenter trial, anastomotic leak was the cause of death in 30% of patients with fatal outcome within 30 day after surgery [15]. In our study, 20% of patients died, most often due to an uncontrolled leak. More recently, endoscopic vacuum therapy has been introduced for the treatment of anastomotic leak, with healing rates between 60 and 95% [16-18], and fatal complications due to therapy-associated hemorrhage in up to 4% of patients [19]. A combination of stent insertion with endoscopic vacuum therapy seems to be feasible [20]. However, comparative studies with different endoscopic techniques are lacking. There is an urgent need of a randomized multicenter trial to answer the still-open question for the optimal endoscopic approach to anastomotic leak.

CONCLUSIONS

Squamous cell histology, neoadjuvant chemo-radiotherapy, and esophageal tumor location are predictors for treatment failure of self-expandable metal stents for anastomotic leak after gastro-esophageal resection. Severe stent-related complications seem to be preferentially associated with the use of large-sized stents.

Conflicts of interest: None to declare.

Authors' contribution: W.B., J.K. planed and conducted the study, collected and interpreted data. I.L., A.S.: substantial contribution to study design, collection and interpretation of data. W.G.Z. supervised the study and critically revised the manuscript. All authors approved its final version and agree to be accountable for all aspects of the study.

REFERENCES

1. Carboni J, Valle M, Federici O, et al. Esophagojejunal anastomosis leakage after total gastrectomy for esophagogastric junction adenocarcinoma: options of treatment. J Gastrointest Oncol 2016;7:515-522. doi:10.21037/jgo.2016.06.02
2. Lang H, Piso P, Stukenborg C, Raab R, Jähne J. Management and results of proximal anastomotic leaks in a series of 1114 total gastrectomies for gastric carcinoma. Eur J Surg Oncol 2000;26:168-171. doi:10.1053/ejso.1999.0764
3. Van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084. doi:10.1056/NEJMoa1112088
4. Kähler G. Anastomotic leakage after upper gastrointestinal surgery: Endoscopic treatment. Visc Med 2017;33:202-206. doi:10.1159/000475783
5. Kubota T, Hiki N, Sano T, et al. Prognostic significance of complications after curative surgery for gastric cancer. Ann Surg Oncol 2014;21:891-898. doi:10.1245/s10434-013-3384-9
6. Li QG, Li P, Tang D, Chen J, Wang DR. Impact of postoperative complications on long-term survival after radical resection for gastric cancer. World J Gastroenterol 2013;19:4060-4065. doi:10.3748/wjg.v19.i25.4060
7. Lee S, Ahn JY, Jung HY, et al. Clinical outcomes of endoscopic and surgical management for postoperative upper gastrointestinal leakage. Surg Endosc 2013;27:4232-4240. doi:10.1007/s00464-013-3028-y
8. Shim CN, Kim HI, Hyung WJ, et al. Self-expanding metal stents or nonstent endoscopic therapy: which is better for anastomotic leaks after total gastrectomy? Surg Endosc 2014;28:833-840. doi:10.1007/s00464-013-3228-5
9. van Boeckel PG, Dua KS, Weusten BL, et al. Fully covered self-expandable metal stents (SEMS), partially covered SEMS and self-expandable plastic stents for the treatment of benign esophageal ruptures and anastomotic leaks. BMC Gastroenterol 2012;12:19. doi:10.1186/1471-230X-12-19
10. Hoeppner J, Kulemann B, Seifert G, et al. Covered self-expanding stent treatment for anastomotic leakage: outcomes in esophagogastric and esophagojejunal anastomoses. Surg Endosc 2014;28:1703-1711. doi:10.1007/s00464-013-3379-4
11. Kucukay F, Okten RS, Partak E, et al. Self-expanding covered metallic stent treatment of esophagojejunostomy fistulas. Abdom Imaging 2013;38:244-248. doi:10.1007/s00261-012-9895-1
12. Feith M, Gillen S, Schuster T, Theisen J, Friess H, Gertler R. Healing occurs in most patients that receive endoscopic stents for anastomotic leakage; dislocation remains a problem. Clin Gastroenterol Hepatol 2011;9:202-210. doi:10.1016/j.cgh.2010.12.010
13. Kim YJ, Shin SK, Lee HJ, et al. Endoscopic management of anastomotic leakage after gastrectomy for gastric cancer: how efficacious is it? Scand J Gastroenterol 2013;48:111-118. doi:10.3109/00365521.2012.737362
14. Fischer A, Bausch D, Richter-Schrag HJ. Use of a specially designed partially covered self-expandable metal stent (PSEMS) with a 40-mm diameter for the treatment of upper gastrointestinal suture or staple line leaks in 11 cases. Surg Endosc 2013;27:642-647. doi:10.1007/s00464-012-2507-x
15. Robb WB, Messager M, Goere D, et al. Predictive factors of postoperative mortality after junctional and gastric adenocarcinoma resection. JAMA Surg 2013;148:624-631. doi:10.1001/jamasurg.2013.63
16. Ooi G, Burton P, Packivanathan A, et al. Indications and efficacy of endoscopic vacuum-assisted closure therapy for upper gastrointestinal perforations. ANZ J Surg 2018;88:E257-E263. doi:10.1111/ans.13837
17. Leeds SG, Mencio M, Ontiveros E, Ward MA. Endoluminal Vacuum Therapy: How I Do It. J Gastrointest Surg 2019;23:1037-1043. doi:10.1007/s11605-018-04082-z
18. Schorsch T, Mueller C, Loske G. Endoscopic vacuum therapy of anastomotic leakage and iatrogenic perforation in the esophagus. Surg Endosc 2013;27:2040-2045. doi:10.1007/s00464-012-2707-4
19. Laukoetter MG, Menningen R, Neumann PA, et al. Successful closure of defects in the upper gastrointestinal tract by endoscopic vacuum therapy (EVT): a prospective cohort study. Surg Endosc 2017;31:2687-2696. doi:10.1007/s00464-016-5265-3
20. Valli PV, Mertens JC, Kroeger A, et al. Stent-over-sponge (SOS): a novel technique complementing endosponge therapy for foregut leaks and perforations. Endoscopy 2018;50:148-153. doi:10.1055/s-0043-120442