ANTICANCER RESEARCH *38*: 5581-5587 (2018)
doi:10.21873/anticanres.12892

Review

Surgical Endoscopic Vacuum-assisted Closure Therapy (EVAC) in Treating Anastomotic Leakages After Major Resective Surgery of Esophageal and Gastric Cancer

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Abstract. *Background/Aim: Endoscopic vacuum-assisted closure therapy (EVAC) is a promising new technique for repairing upper gastrointestinal defects of different etiologies. As of 2018, however, no standardized recommendation exists. This article reviewed EVAC in treating anastomotic leakage following major resective surgery of esophageal (EC) and gastric cancer (GC). Materials and Methods: Only English-language literature was investigated. Only studies or data on EC and GC were included. Seven popular search engines (PubMed, Web of Science, ScienceDirect, Scopus, Google Scholar, ResearchGate, PubFacts) were utilized. Results: A total of 29 studies (17 retrospective, six prospective and six case reports) with a total of 209 patients. Range of anastomotic leakage closure was 66.7-100%. Anastomotic stricture was the most frequent long-term related complication (18 cases). Conclusion: EVAC appears to be an extremely useful treatment for postsurgical anastomotic leakage in patients with EC/GC. Almost all kinds of anastomotic leakage (silent to symptomatic, small to large) seem to be amenable to this technique.*

Anastomotic leakage (AL) following esophagectomy for malignancy occurs in 5% to 30% of cases and accounts for approximately 40% (range=3.3-67%) of all postoperative fatalities (1). Management of this complication remains controversial since no standardized therapy has been yet established (1). In general, treatment strategy appears clear for minor as well as catastrophic AL (1, 2). Silent minor breakdown requires little specific treatment. On the other hand, surgery remains the mainstay of curative treatment for symptomatic patients (especially those with sepsis and hemodynamic instability) with severely compromised anastomosis or ischemic necrosis of the anastomosed conduit; however, mortality after a second operation is high (>40%) (1, 2). In intermediate conditions, that is, major clinical fistulas complicated with perianastomotic abscess or cavity, the therapeutic choice is more varied: nowadays, the armamentarium of nonoperative techniques includes percutaneous drainage and endoscopic procedures such as fibrin glue infiltration, clipping and stenting (3).

More recently, another endoscopic measure has drawn the attention of the medical community for treatment of major clinical and, in some cases, massive clinical ALs: so-called endoscopic vacuum-assisted closure therapy (EVAC), also known as endoscopic negative pressure therapy. This represents the clinicoendoscopic evolution of the classical vacuum-assisted closure therapy (VAC), a well-established treatment for chronic open wounds (4). Like VAC, in EVAC a polyurethane sponge is placed into the defect to treat with application of a sub-atmospheric pressure, site healing is then achieved by continuous drainage of fluids and edema, reducing bacterial colonization, increasing vascularity and enhancing the formation of granulation tissue (4). Differently from VAC, however, in this case the evacuation tube connected to the system is represented by a nasogastric tube (NGT): its proximal end is tied to a continuous source of negative pressure, while the distal end is sutured to the sponge and then endoscopically positioned within or outside the esophageal lumen (intraluminal or intracavitary EVAC,

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Key Words: Endoscopic vacuum therapy, endoscopic vacuum-assisted closure system, EVAC, endoscopic negative pressure therapy, ENPT, intraluminal, intracavitary, negative pressure wound therapy, NPWT, anastomotic leakage, nasogastric tube, mediastinitis, intrathoracic abscess, review.

respectively) (Figure 1). An additional difference is that while VAC needs fixation such as tapes to keep the sponge in place, EVAC does not require sealing to obtain airtightness, fixation, in fact, occurs by means of the sponge itself through negative pressure and air tightness is maintained by the collapsing esophagus of the patient (1).

EVAC was first successfully employed in 2008 by Weidenhagen and colleagues for closing 26 ALs after anterior resection of rectal and rectosigmoidal cancer (5). The same year, Wedemeyer and colleagues pioneered EVAC for securing AL in two patients who underwent resection of esophageal (EC) and gastric cancer (GC) (6). Since then, resorting to EVAC for treating AL following surgery for upper gastrointestinal cancer has progressively increased.

Our aim was to review the current literature on EVAC performed for esophago-gastric cancer in order to better assess indications, clinical success rate and complications of this promising and interesting minimally invasive measure.

Materials and Methods

Only the English-language literature was investigated. Only studies or data on EC and GC were included. Seven popular search engines (PubMed, Web of Science, ScienceDirect, Scopus, Google Scholar, ResearchGate, PubFacts) were utilized. Endoscopic vacuum therapy, endoscopic vacuum-assisted closure system, E-VAC, EVAC, EVT, endoscopic negative pressure therapy, ENPT, endovac therapy, intraluminal ENPT and intracavitary ENPT were the key words adopted for searching. When a center published more than one article on the same patient population, only the newest data were considered.

Results

We found 29 studies dealing with EVAC in treating AL after resection of EEC or GC (1, 6-33). Main study features are summarized in Table I. Most works were retrospective (17); there were six prospective studies and six case reports. The overall number of patients with cancer treated with EVAC was 209. The average duration of treatment was 18 days; the mean number of sponge changes was 5.4 per patient.

Concerning EVAC placement, connection of the sponge with an NGT was most frequently realized outside the body and then inserted transorally (17 studies); in one case, NGT was positioned on a guide wire running from a chest drain (33). In nine studies, connection was intracorporeal with NGT first inserted transnasally, brought out through the mouth, sutured to a trimmed sponge in its distal end and endoscopically placed (23); in another patient EVAC was accomplished through re-laparotomy (30), whereas for two instances, the information was not given. Depending on the width of the AL (small *versus* large) and the absence *versus* presence of a perianastomotic cavity to drain, the sponge was intra- or extra-esophageal respectively (Figure 1).

Studies enrolling only patients with cancer were a minority, basically case reports (1, 15, 16, 20, 23, 26, 28-33), since most also included non-oncological cases. There were only three retrospective studies based on oncological patients alone comparing EVAC with other regimens (15, 23, 26). In the first, intrathoracic esophageal AL was managed with EVAC (17 cases), repeat surgery (18 cases), self-expandable metal (SEMS) or plastic stents (SEPS) (12 cases), or conservatively (15 cases). In the patients matched for APACHE II score, survival in the EVAC-treated group (88%) was significantly superior to that of the surgically treated patients (50%; $p=0.011$) and in the stented patients (32%; $p=0.00014$) (15). In the second, seven and 11 ALs were respectively treated with EVAC and SEMS (23). The clinical success rate was higher in the EVAC group (100%) than that in the SEMS one (7/11, 63.6%) but there was no statistical significance ($p=0.351$); moreover, the complication rate was lower in the EVAC group (0%) than that in the SEMS one (6/11, 54.5%) with significant difference $p=0.042$). In the third study, the EVAC group was too small compared to the stent and repeat-surgery groups (four, 23 and 10 patients, respectively) to arrive at any safe conclusions (26). Another two studies compared EVAC with SEMS in oncological and non-oncological patients (8,21). Both articles reported a significantly higher closure rate for the EVAC (84.4% and 93.3%) over the SEMS group (53.8% and 63.3%) ($p<0.05$ and 0.038, respectively); moreover, the use of EVAC, the time from diagnosis to endoscopic (stent or EVAC) therapy and the presence of underlying malignancy were independent predictors of poor prognosis at multivariate analysis (8).

Anastomotic stricture was the most frequent long-term related complication (18 cases) requiring endoscopic dilatation. Eleven hemorrhagic episodes were reported: bleeding was fatal in three cases (19-21, 25), whereas a further major aortic bleeding was expeditiously controlled with a covered aortic stent (24).

Discussion

As VAC has already demonstrated suitability for chronic open wounds, similarly EVAC is revolutionizing the management of gastrointestinal defects: our review corroborates this trend. Healing, which is obtained when the site of lea occluded and the wound cavity collapses, is permitted through rapid and continuous removal of necrotic debris, infected tissue, pus, gastric conduit exudation (which is frequently associated with delayed gastric emptying after Ivor-Lewis esophagectomy), interstitial edema, promotion of blood flow and tissue granulation and facilitation of a clean wound base (1, 6-34). Other aspects, however, do not appear to be so well assessed and deserve more discussion.

Indications for EVAC represent a major issue indeed. In the management of upper gastrointestinal defects (including

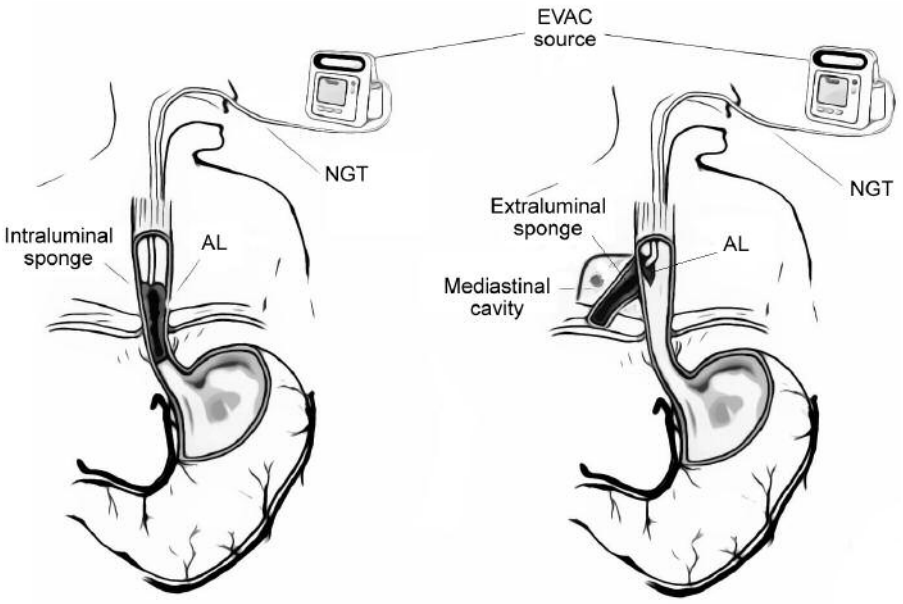

Figure 1. *Representation of intraluminal (left) and intracavitary (right) endoscopic vacuum-assisted therapy. AL: Anastomotic leak; NGT: nasogastric tube.*

both AL and perforations), in fact, as of 2018, no standardized recommendation has been established; as a consequence, no guideline on the use of EVAC exists either. While there is a general consensus on the conservative treatment for asymptomatic, small and well-contained ALs, controversies surround treatment of larger and symptomatic fistulas, especially if complicated by mediastinal cavity, sepsis or hemodynamic instability. Endoscopic fibrin glue infiltration, and clipping and stenting (SEMS and SEPS) represent feasible therapeutic measures for clinical leaks but are subject to important complications. Fibrin glue injection or clip administration is recommended by some authors for small (<30%) leaks (35). Injection of fibrin glue should be repeated into the lumen of the fistula, as well as into the tissue many times and, being a medical blood product from human donors, bears a risk of infection (hepatitis or HIV) (3). Moreover, currently, no comparative data exist to support the use of one sealant (fibrin glue) over the another (for example, cyanoacrylates) (33). Regarding clips, only case reports and small case series were reported for postsurgical ALs (33). Given the small diameter of the esophagus and the larger size of the applying device, clips can be misplaced and occlude the lumen, leaving the fistula opening intact; furthermore, removal of clips can cause bleeding (33). Divergence of AL between 30-70% can be treated with stenting but not without potential complications (35). Mostly for SEPS, in fact, dislocation rates of up to 40% and non-sealing rates of 22% have been documented (1). On the other hand, a complication of SEMS is a failure of stent extraction due to ingrowth of granulation tissue or secondary strictures; for these reasons, resorting to SEMS for AL after esophago- gastric cancer surgery is not recommended (35). Both SEMS and SEPS, eventually, hinder inspection of the wall of the AL as well as the wound cavity, making it difficult to define the optimal time for their removal (7).

All these minimally invasive therapeutic endoscopic options are insufficient and even more detrimental in the case of uncontained leaks. In fact, the mortality rate of patients with insufficiently drained AL may be as high as 80% (1). This is due to the respiration-dependent suction of fluids (including those from AL) into the mediastinum, representing a perfect environment for bacterial growth which inevitably leads to mediastinitis (18). For these kinds of ALs, percutaneous drainage (chest, mediastinal or abdominal tube) or repeat surgery comprise the traditional therapeutic choices (36). EVAC represents a new alternative minimally invasive cogent option for the management of these types of postsurgical AL (1, 6-33).

Initially, EVAC was not performed in the presence of intrathoracic cavity, anastomotic ischemia, ischemia of the gastric anastomosed conduit, mediastinal or systemic sepsis (18, 37); more recently, several articles have reported overcoming such limitations and extended the indications for EVAC (16, 20, 25). To date, contraindications to EVAC seem to remain circular ALs (complete dehiscence), necrosis of the gastric conduit, close vicinity of major vessels and the presence of large, chronic fibrosed multiloculated mediastinal cavities (18, 22, 27).

Table I. *Main features of the world literature dealing with endoscopic vacuum-assisted closure therapy (EVAC) for anastomotic leakage (AL) after major surgery of esophago-gastric cancer.*

Reference	Study type	Number of patients: cancer type	Median age, years/neo-adjuvant treatment[1]	Surgical procedure	NGT insertion	Solo/mixed EVAC[2]	Anesthesia type	Sponge placement/ pressure	EVAC duration/ changes[3]	Feeding during EVAC	Success rate[4]	EVAC related complications/ mortality
1	Retrospective	6: 3 Es SCCs, 2 Es ADC, 1 GC	65.5/none	5 I-Lewis, 1 TE	Transoral	4/2 (FG)	GA at ICU	IC/ND	20/10	JFT	100%	None
6-8	Retrospective	28: ND	63/18	14 I-Lewis; 14 EC	Transnasal	26/2 (1 FG, 1 Re-surgery)	GA at ICU; CS	IC, IL/-125 mmHg	23/7	NJT, TPN	84.4%	3 Strictures; 1 MT; 1 bleeding; 1 Es-bronchial fistula/15.6%
9-11	Retrospective	17: ND (12 EC, 5 GC)	range: 46-84; ND	7 I-Lewis; 5 TE, 5 G	Transoral	10/7 (Ct)	ND	8 IL, 9 IC/-125 mmHg	12/2	NJT, PEG, OLN	94%	1 Es stenosis; 1 gastric conduit ischemia
12	Retrospective	3: ND	>18 years/ none	2 I-Lewis; 1 G	Transnasal	solo (OFD)	ND	IC, IL/-125mmHg	12/ND	NJT	100%	None
13,14	Retrospective	51: ND (36 EC, 15 GC)	ND/>70%	36 I-Lewis; 15 G	Transoral	35/16 (15 Stents, 1 re-surg)	CS>GA	47 IL, 4 IC/-100/125 mmHg	13.3/4	28 NJT, 1 PEG	77.9%	2 Es stenoses
15,16	Prospective (questionnaire)	23: 20 Es ADC, 3 Es SCC	65±9/13	16 I-Lewis; 5 MK;2TE	Transoral	19/4 (2Stents, 2 re-surg)	ND	IC/-70/80 mmHg	25/twice a week	NJT	91%	6 Strictures (26% p=0.005)
17,18	Prospective	10: ND	72/ND	esopha-gectomy and G	Transoral	ND (solo and mixed (re-surg)	GA at ICU or CS	IL, IC/-125 mmHg	12/4	KJT, JFT	82%	1 AS
19-21	Prospective	34: Es ADC and Es SCC; GC	56/23	esopha-gectomy and G	Transoral	3/1 (Stent+Ct)	GA or CS	IL, IC/-100/ 125 mmHg	22/6	21 TPN, 10 NJT, 2 PEG, JFT	94.2% p=0.038	2 Fatal bleedings, 5 minor bleedings, 5 sponge dislocations, 4 strictures/6%
22	retrospective	10: EC	57/ND	7 I-Lewis, 3 robotic I-Lewis	Transnasal	7/3 (1 FG, 1 clipping, 1 re-surg)	CS (midazolam)	7 IL, 3 IC/-80/ 125 mmHg	27/2.7	TPN	66.7% (91.7%)*	2 Patients (1 AS, 1 anastomotic bleeding)
23	Retrospective	6: 5 EC, 1 GC	71/ND	5 I-Lewis, 1 G	Transnasal	Solo	ND	IC/-125 mmHg	19.5/4	TPN, OLN, EN	100%	1 Recurrent AL (treated with EVAC)
24	Prospective	4: EC	ND/ND	I-Lewis	Transnasal	3/1 (Aortic stent and re-surg)	GA	IL, IC/-125 mmHg	n.d./7	JFT	95%	1 Aortic bleeding
25	Prospective	4: EC	58/ND	I-Lewis	Transoral	Solo	GA at ICU, CS	n.d./-70/80 mmHg	28/9	NJT	100%	2 Patients with as (1 giving fatal bleeding)/25%
26	Retrospective	4: EC	63/ND	I-Lewis	ND	4 Mixed (4 Ct, 1 stent, 1 re-surg)	ND	IC/n.d.	ND	ND	ND	ND
27	Prospective	2: EC	56±12/ND	2 Esophagec-tomies	Transnasal	1/1 (1 Ct and re-surg)	GA	IC/-100/ 125 mmHg	15/5.6	TPN	100%	None

Table I. *Continued*

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Reference	Study type	Number of patients: cancer type	Median age, years/neo-adjuvant treatment[1]	Surgical procedure	NGT insertion	Solo/mixed EVAC[2]	Anesthesia type	Sponge placement/ pressure	EVAC duration/ changes[3]	Feeding during EVAC	Success rate[4]	EVAC related complications/ mortality
28	Case reports	2: Es ADC	61.5/1	1 I-Lewis, 1 TE	Transoral	2 Mixed (2 stents, 2 Ct, 1 clip)	ND	1 IC, 1 IL/-75/ 100 mmHg	26/n.d.	1 JFT, 1 ND	100%	1 Stenosis
29	Case report	1: Es SCC	50/0	I-Lewis	ND	Solo	ND	IL/-100 mmHg	9/1	TPN	100%	None
30	Case report	1: Cardial ADC	66/0	I-Lewis	Open	Mixed (stent,re-surg)	GA	IC/n.d.	40/10	ND	100%	None
31	Case report	1: ND (probable GC)	67/0	Gastrectomy	Transoral	Solo	ND	IL/n.d.	18/6	ND	100%	None
32	Case report	1: Es ADC	58/1	I-Lewis	Transnasal	Mixed (clip)	ND	IL/-125 mmHg	31/7	NJT	100%	None
33	Case report	1: Cardial ADC	48/0	VL I-Lewis	Transoral (on Ct guide-wire)	Mixed (Ct, FG)	CS	IL/-125 mmHg	8/2	OLN, EN	100%	Temporary dysphagia (no AS)

NGT: Nasogastric tube; IL: intraluminal (intraesophageal); IC intracavitary (extraluminal); Es: esophageal; SCC: squamous cell carcinoma; ADC: adenocarcinoma; GC: gastric cancer (adenocarcinoma); I-Lewis: Ivor-Lewis esophagectomy; TE: transhiatal esophagectomy; FG: fibrin glue infiltration; GA: general anesthesia; ND: not declared; ICU: intensive care unit; JFT: jejunostomy feeding tube; EC: esophageal cancer; CS: conscious sedation with propofol alone or with midazolam; NJT: nasojejunal feeding tube; TPN: total parenteral nutrition; MT: mucosal tear; Ct: chest tube; PEG: feeding by gastropexy percutaneous endoscopic gastrostomy; OLN: oral liquid nutrition; OFD: open-pore film drainage is a variant of classic EVAC; re-surg: repeat surgery; MK: McKeown three-field esophagectomy; EN: normal enteral nutrition; AS: anastomotic stricture (stenosis); VL: videolaparoscopic. [1]Preoperative treatment with chemotherapy with/without radiation; [2]EVAC performed alone or in combination with other devices or procedures (endoscopic or other type); [3]average number of days/endoscopic sponge changes per patient; [4]clinical success means AL closure; *decrease in AL size.

Regarding EVAC-related complications, apart from anastomotic stenosis which can easily be corrected by endoscopic dilatations (18 cases in our review), NGT-related discomfort (especially when an additional nasojejunal tube was passed through the second nostril for enteral nutrition) and distress of repeating the procedure for sponge changes (37), the main and most dreadful event associated with EVAC is massive bleeding: fatal EVAC-related bleeding occurred in three cases (19-21, 25), whereas a further major episode was promptly controlled with a covered aortic stent (24). While minor bleeding can occasionally occur during the removal of the sponge due to ingrowth of granulation tissue into the EVAC sponge, major bleeding can derive from development of a fistula between the cavity and the aorta (or aortic branches), as well as after formation and rupture of pseudoaneurysm involving such vessels or heart chambers (21, 24). Weakening, erosion, fistulation and pseudoaneurysm of such major vascular structures were due to the ongoing inflammatory process due t. EVAC itself (21); more frequent changes of the device could reduce the risk of this catastrophic event (24).

Despite the reported deaths, as elucidated by our review, overall mortality of EVAC (0-26%) is inferior to that associated with repeat surgery (>40%) (Table I). The cost of EVAC represents another relevant topic: for an average treatment time of 25 days with eight sponge changes, the total cost per patient is approximately 10,188 US dollars (27).

Along with diagnostic, staging and prognostic roles recently documented by our study group, EVAC comprises the newest and most noteworthy application of NGT in medical and surgical oncology of EC and GC (38-51). Randomized clinical trials comparing EVAC with other minimally invasive techniques as well as major surgery are needed in order to better define indications for EVAC and algorithms for treating postsurgical ALs in patients with EC and GC.

Conclusion

EVAC is a new alternative method for treating ALs following surgery for EC and GC. Differently from former articles, recent studies have documented success even in uncontained ALs complicated by mediastinal and systemic sepsis. Randomized clinical trials comparing EVAC with repeat surgery and other minimally-invasive techniques are required to better identify both indications for EVAC and management of postsurgical ALs.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

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Received August 29, 2018
Revised September 18, 2018
Accepted September 19, 2018