Redistribution of Gastric Blood Flow by Embolization of Gastric Arteries Before Esophagectomy

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Background. Anastomotic leak remains a common and potentially deleterious complication after esophagectomy. Preoperative embolization of the left gastric artery and splenic artery (PAE) has been suggested to lower anastomotic leak rates. We present the results of our 5-year experience with this technique.

Methods. All patients undergoing PAE before esophagectomy since introduction of this technique in 2004 were compared in a 1:2 matched-pair analysis with patients without PAE. Matching criteria were type of anastomosis, neoadjuvant treatment, comorbidity, and age. Data were derived from a retrospective chart review from 2000 to 2006 that was perpetuated as a prospective database up to date. Outcome measures were anastomotic leak, overall complications, and hospital stay.

Results. Between 2000 and 2009, 102 patients underwent esophagectomy for cancer in our institution with an

overall leak rate of 19% and a mortality of 8%. All 19 patients having PAE since 2004 were successfully matched 1:2 to 38 control patients without PAE; both groups were similar regarding demographics and operation characteristics. Two PAE (11%) and 8 control patients (21%) had an anastomotic leak, but the difference was statistically not significant ($p = 0.469$). Overall and major complication rates for PAE and control group were 89% versus 79% ($p = 0.469$) and 37% versus 34% ($p = 1.000$), respectively. Median intensive care unit and hospital stay were 3 versus 3 days ($p = 1.000$) and 22 versus 17 days ($p = 0.321$), respectively.

Conclusions. In our experience, PAE has no significant impact on complications and anastomotic leak in particular after esophagectomy.

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Modern management of esophageal cancer is still based on surgery as key part of the oncologic treatment [1–3]. Reconstruction of the alimentary tract is predominantly performed by using a gastric tube for esophageal replacement. Anastomotic leakage of the esophagogastrostomy and its related sequelae, eg, mediastinitis, pyothorax, sepsis, and stricture formation, remain a major source of concern during the postoperative course [1, 3–5]. The reported anastomotic leak rates range from 3% to 25%, whereby cervical anastomoses are at particular risk of failure (odds ratio, 2 to 3) [6–9].

Impaired blood flow of the gastric tube acts as a major cause of anastomotic leakage after esophageal resection [10–13]. Impaired blood flow may be caused by insufficient arterial blood supply as well as by venous congestion, which may severely disturb gastric microcirculation. Other known risk factors are technical errors, malnutrition, and incomplete tumor resection [9]. To obtain a well-perfused gastric tube, different techniques have been developed during recent decades. The use of a slender gastric tube and the supercharge technique with its additional vascular anastomosis of small vessels of the

proximal part of the gastric tube, as well as the use of mechanical stapling devices to better maintain circulation at the anastomosis, have been proposed [12, 14–17]. To overcome venous congestion, microvascular proximal anastomosis and simple transient venous bloodletting have been reported [15, 18–20]. Further attempts have been made by using intravenous prostaglandin application intraoperatively and postoperatively [21, 22]. Although all these techniques are restricted to intraoperative use, embolization of gastric and splenic arteries can easily be performed preoperatively to redistribute gastric vascularization [10]. Despite the fact that this concept of preoperative arterial distribution was proposed in 1996, clinical experience with this innovative technique remains limited [10, 11].

The aim of this study was to assess our initial experience of preoperative arterial embolization (PAE) in patients undergoing oncologic esophagectomy with a particular focus on anastomotic leakage.

Patients and Methods

The present study is a matched-pair analysis evaluating the impact of preoperative arterial embolization in patients undergoing oncologic esophagectomy in the Department of Visceral Surgery at the University Hospital Lausanne.

Data were extracted from a standardized computer-based database including demographics, tumor and op-

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eration characteristics, (neo)adjuvant treatment, and postsurgical and oncologic outcome. The database was created in 2006 from an exhaustive chart review including all surgical patients with esophageal cancer from January 2000. Since then, data collection was performed prospectively. Preoperative embolization of the left gastric and splenic artery was introduced in 2004 as a new therapeutic option; patients were selected at the surgeons' discretion. Exclusion criteria were the lack of patient consent and the presence of celiac atheromatosis.

The study was approved by the internal Institutional Review Board and the Chair of the Department. All patients signed informed consent before treatment.

Study Population and Matching

Until December 2009, 102 patients were entered in the database. A total of 19 patients underwent PAE from 2004 to 2009. These patients were compared with 38 patients without PAE, using a propensity-balanced 1:2 match. There were five descriptors to match patients, which were, in descending order of priority, (1) type of anastomosis (thoracic versus cervical), (2) neoadjuvant treatment (yes/no), (3) comorbidities assessed by the Charlson comorbidity index [23] (± 2 points), (4) the American Society of Anesthesiologists (ASA) class (± 1), and (5) patient's age (± 5 years).

Outcome Measures

Primary outcome measures were overall postoperative complications (30-day morbidity or in-hospital if length of stay was greater than 30 days) with special emphasis on anastomotic leak. Anastomotic leak was defined radiologically as an evident contrast outpouring on upper gastrointestinal tract enema that was routinely performed on postoperative day 5; clinically symptomatic leaks (ie, fever, mediastinitis, cardiac arrhythmia, pulmonary infection, sepsis) before or after day 5 were confirmed by contrast-enhanced computed tomography. Postoperative complications were graded according to their severity, and a validated therapy-orientated complication score on a 5-point scale was used [24]. Secondary outcome measures included operation time, blood transfusion, pathologic resection status (R status), and lymph node retrieval (N status), as well as intensive care unit and hospital stay.

Preoperative Arterial Embolization

Preoperative arterial embolization was performed as an in-hospital procedure with a 2-day hospital stay. Under sterile conditions and local anesthesia, the femoral artery was punctured and a 5F introducer sheath (Terumo, Radifocus II, Terumo Europe, Leuven, Belgium) was inserted using the Seldinger technique. A 5F hydrophilic catheter with a Cobra or Simmons no. 2 curvature (Terumo Radifocus Glidecath, Terumo Europe) was then passed over a hydrophilic guidewire (Terumo Radifocus Guide Wire, Terumo Europe) up to the origin of the celiac trunk and the superior mesenteric artery to perform digitally subtracted angiographic series, allowing us to appreciate the vascular anatomy. Embolizations of the

left gastric artery and splenic artery upstream and along the origin of the short gastric arteries were then performed, either by releasing 0.035-inch coils of various sizes (Tornado Embolization Coils, Cook, Bloomington, IN) directly through the angiography catheter or by use of 0.018-inch microcoils of various sizes (Tornado Embolization Microcoils, Cook) delivered through a 2.7F microcatheter (Terumo, Pro Great, Terumo Europe) according to the vessel diameter. Position of coils and the efficacy of embolization were verified by angiography at the end of the procedure. The result of the embolization was judged satisfying when the left gastric artery and the splenic artery were totally occluded and the right gastroepiploic artery was identified as the main blood supply to the stomach with retrograde opacification of the left gastric artery. Patients were allowed to resume food immediately after the procedure. All complications were assessed.

Surgical Technique

The operation technique was tailored to the individual patient and varied slightly as a function of time. Most patients with tumors in the middle or lower part of the esophagus were operated on by combined thoracoabdominal approach as described by Ivor Lewis and others [25, 26]. Intrathoracic anastomosis was performed using a 25-mm circular stapler (PCEE A Stapler, Autosuture, Covidien Healthcare, Wollerau, Switzerland). The remaining operations were either transhiatal resections [27] or by means of a triple incision [28]. Cervical anastomoses were handsewn using slowly resorbable 4-0 polydioxanone (PDS II, Ethicon, Norderstedt, Germany) interrupted sutures. The type of gastric tube formation, ie, slender tube or "normal" diameter, was at the discretion of the individual surgeon. Since 2006, the abdominal part of the operations was performed laparoscopically by default.

Statistical Analysis

Statistical analysis was performed by use of Prism 5.2 (GraphPad Software Inc, La Jolla, CA). Descriptive statistics are expressed as mean $\pm$ standard deviation or median and range, as appropriate. The Mann-Whitney *U* test was used to compare continuous variables, and χ^2 and Fisher's exact tests were used for comparison of discrete variables. A probability value of less than 0.05 was considered statistically significant.

Results

In the period from 2000 to 2009, 102 patients underwent oncologic esophagectomy. Most important demographic and outcome data of the whole population are summarized in Table 1.

Eighty-one male and 21 female patients had a median age of 64 years (range, 43 to 84 years); indication for operation was adenocarcinoma in 49 and squamous cell carcinoma in 53 patients. Eighty-two patients were operated on by combined thoracoabdominal approach (Ivor Lewis technique) with an intrathoracic anastomosis,

Table 1. 10-Year Single-Center Experience of Esophagectomies for Cancer: Demographics, Tumor Characteristics, and Outcome

Characteristic	Patients Undergoing Esophagectomy (n = 102) ^a
Demographics	
Age (y)	64 (43–84)
Sex (M/F)	81/21
BMI (kg/m ²)	25 (14–36)
ASA ≥ 3 (%)	36
Preoperative WL > 10%	18
Charlson score [23]	3 (1–9)
GERD	40
Dysphagia	64
Alcohol abuse	67
Smoking	80
Type: adeno/SC	49/53
Preoperative treatment, operation	
Preoperative embolization	19
Neoadjuvant: RCT/CT	31/3
Type of operations	
Ivor Lewis	82
Triple	11
Transhiatal	9
OR time (min)	395 (195–760)
Laparoscopic gastrotomy	22

^a Values are number of patients (%) and median (range) as indicated.

Adeno = adenocarcinoma; ASA score = American Society of Anesthesiologists; BMI = body mass index; GERD = gastroesophageal reflux disease; OR = operating room; (R)CT = (radio)chemotherapy; SC = squamous cell carcinoma; WL = weight loss.

whereas 11 and 9 patients had a cervical anastomosis by either triple incision or transhiatal approach, respectively. Complications occurred in 79% of the patients, being mainly pulmonary complications (67%). Nineteen patients had an anastomotic leak, and 8 patients died in the postoperative course.

Matching and Demographics of the Comparative Groups

Since 2004, 19 patients underwent PAE before esophagectomy. They were matched 1:2 to 38 of 44 eligible patients operated on in the same period without prior PAE who served as the control group for the present analysis. The matching process was successful for type of anastomosis and ASA class in all 38 selected patients. Additionally, 37 of 38 patients concurred with regard to neoadjuvant treatment and the Charlson index. Overall, 25 patients suited for 5 of 5 matching criteria, and 12 patients for 4 of 5. Preoperative arterial embolization and control groups were also comparable for other important demographic and surgical factors as outlined in Table 2.

Preoperative Arterial Embolization

Preoperative arterial embolization was performed at a mean interval of 17 ± 5 days from surgery. Primary success rate of PAE was 89%; the remaining 2 patients

with insufficient primary angiographic control were successfully embolized in a second intervention. A satisfying angiographic result was thus obtained in all 19 patients. The mean procedure time was 56 ± 33 minutes, and a mean number of 16 ± 8 coils were needed to achieve occlusion of the targeted vessels. The splenic and left gastric arteries were embolized in all cases; additionally, short gastric vessels were embolized in 5 patients and the right gastric artery in 1 patient. Five patients reported mild abdominal pain after the procedure, and 1 patient exhibited partial splenic necrosis without need of any treatment.

Impact of Preoperative Arterial Embolization on Outcome After Esophagectomy

Two PAE (11%) and 8 control patients (21%) had an anastomotic leak, but the difference was statistically not significant ($p = 0.469$). Leaks were diagnosed a median of 6 days (range, 3 to 17 days) after surgery. Eight of 10 leaks were suspected on the basis of clinical findings and confirmed by computed tomography; of note, 3 patients had normal upper gastrointestinal series before. The remaining two anastomotic insufficiencies were diagnosed by routine postoperative upper gastrointestinal series. Five patients needed emergency surgery, and 1 patient was stented. Two patients died shortly after occurrence of anastomotic leak; healing without sequelae was achieved in 4 patients (Table 3). Overall, PAE and control groups had equally high complication rates (89%)

Table 2. Matched-Pair Analysis of Patients Undergoing Esophagectomy With and Without Prior Embolization: Demographics, Tumor, and Operation Characteristics^a

Characteristic	PAE (n = 19)	Matched Control (n = 38)	p Value
Demographics			
Age (y)	63 (76–50)	64 (46–82)	0.498
Sex (M/F)	14/5	32/6	0.478
BMI (kg/m ²)	24 (17–34)	25 (18–33)	0.243
ASA ≥ 3 (%)	7 (37%)	10 (26%)	0.541
Charlson score [23]	3 (2–8)	3 (1–9)	0.631
Smoking (%)	15 (79%)	31 (82%)	1.000
Tumor			
Type: Adeno/SC	13/6	26/12	1.000
Aboral distance (cm) ^b	29 (22–37)	34 (19–40)	0.018
Neoadjuvant: RCT/CT	4/1 (26%)	9/2 (29%)	1.000
Operation			
OR time (min)	465 (280–760)	440 (325–600)	0.899
Transfusion (patients)	2 (11%)	3 (8%)	1.000
Anastomosis			
Thoracic/cervical	17/2	34/4	1.000
Mechanical/suture	15/4	33/5	0.463

^a Values are number of patients (%) and median (range) as indicated.

^b Statistical significance ($p < 0.050$).

Adeno = adenocarcinoma; ASA score = American Society of Anesthesiologists; BMI = body mass index; OR = operating room; PAE = preoperative arterial embolization; (R)CT = (radio)chemotherapy; SC = squamous cell carcinoma.

Table 3. Diagnosis, Treatment, and Outcome of Anastomotic Leaks

Variable	PAE (n = 19)	Matched Control (n = 38)
Anastomotic leak (n)	2	8
Time to diagnosis (days: median; range)	10.5 (4–17)	6 (4–11)
Treatment		
Palliative	1	1
Conservative	0	2
Stenting and biologic glue	1	0
Surgery	0	5
Dentatus flap		2
Pectoralis flap		1
Esophagostomy and delayed ileocoloplasty		1
Drainage and thoracic duct ligation		1
Outcome		
Complete healing	1	3
Anastomotic stenosis	0	2
Esophageal ulcer	0	1
Death	1	2

PAE = preoperative arterial embolization.

versus 79%; $p = 0.469$). Major complications occurred in 37% and 34% ($p = 1.000$), respectively, and mortality was at 5% in both groups. Median intensive care unit stay was 3 days for both comparative groups; overall hospital stay was 22 days (range, 5 to 81 days) for PAE patients compared with 17 days (range, 4 to 156 days) in the control group ($p = 0.321$). Clinically relevant anastomotic strictures occurred in 1 PAE and 4 control patients ($p = 0.656$); 3 of them needed repetitive dilatations. All relevant outcome measures are summarized in Table 4.

Comment

Anastomotic leakage after esophageal resection is thought to be mainly related to a disturbed blood supply of the gastric tube, ie, its most proximal part that is connected to the residual esophagus. Preoperative arterial embolization aims to improve gastric vascularization by arterial redistribution and transient ischemic preconditioning. In the present series, we assessed our preliminary experience with this technique. To this end, we performed a matched-pair analysis of 57 patients who underwent oncologic esophageal resection with or without PAE. The overall complication rates and anastomotic leakage rates were similar (89% and 11% versus 79% and 21%), but there was a statistical trend toward an increased risk for anastomotic stricture formation after PAE (32% versus 3%). The mortality rates were 5% in both groups.

To overcome the adverse effects on circulation during gastric tube formation, different strategies have been developed (Table 5). From a purely technical point of

view, the so-called supercharged technique with its vascular anastomoses between the short gastric arteries and veins with the cervical transverse artery and external jugular vein, respectively, is probably the best approach as these additional anastomoses markedly increase blood flow at the anastomotic site [17]. However, they are technically demanding and significantly prolong the operative time [17]. To omit microvascular anastomoses, Kono and associates [29] proposed transient venous bloodletting to improve gastric microcirculation. They could demonstrate an increased tissue blood flow by simple venous bloodletting for 30 minutes, whereby the anastomotic leak rate was 1.5%.

It has been shown that gastric tubulization with ligation of the left gastric artery, the short gastric arteries, and their corresponding veins decreases gastric blood flow up to 70% [10, 12, 13]. A gastric blood flow less than 10 mL/min per 100 g of tissue was found to be associated with an increased leak rate [30]. In an animal model, gastric blood flow was completely restored after 3 weeks [13]. Hence, transient ischemia seems to promote gastric microcirculation and represents the pathophysiologic basic considerations for PAE. Hölscher and colleagues [26] and Schröder and coworkers [31] proposed a two-stage procedure with gastric tube formation during a first operation that is followed by a second intervention after 4 days for gastric pull-up with esophagogastric anastomosis. The time interval should enable restoration of the microcirculation. Indeed, they showed a low rate of anastomotic leakage of 6% that could be treated by temporary stent insertion [26, 31]. Other groups proposed a prolonged time interval between interruption of gastric vascular supply and gastric tube formation [10, 32,

Table 4. Matched-Pair Analysis of Patients Undergoing Esophagectomy With and Without Prior Embolization: Postoperative Outcome^a

Variable	PAE (n = 19)	Matched Control (n = 38)	p Value
Pathology			
Resection R0	17 (89%)	33 (87%)	1.000
Resected lymph nodes	12 (2–79)	14 (1–50)	0.365
Complications ^b			
Total	17 (89%)	30 (79%)	0.469
Major (≥3 according to [24])	7 (37%)	13 (34%)	1.000
Pulmonary	14 (74%)	24 (63%)	0.555
Anastomotic leak	2 (11%)	8 (21%)	0.469
Anastomotic stricture	1 (5%)	4 (10%)	0.656
Mortality (30-day)	1 (5%)	2 (5%)	1.000
ICU stay (days)	3 (1–13)	3 (1–32)	1.000
Hospital stay (days)	22 (5–81)	17 (4–156)	0.321

^a Values are number of patients (%) and median (range) as indicated.^b Complications were assessed until 30 days after surgery or until discharge if length of stay exceeded 30 days.

ICU = intensive care unit; PAE = preoperative arterial embolization.

Table 5. Strategies To Improve Tissue Blood Flow of the Gastric Transplant

Author	Treatment	No. of Patients (Treatment/Control)	Anastomotic Leak (Treatment/Control)	p Value
Akiyama [10, 11]	Preoperative embolization of LGA, RGA, SA	54/25	1/54	NS
Nguyen [33]	Preoperative laparoscopic LGA ligation	9	0	...
Veeramooto [34]	Preoperative laparoscopic LGA ligation	35 ^a /55 7 ^b /55	2 ^a /35 7 ^b /17	0.07
Hölscher [26, 31]	Two-step procedure ^c	83	5/83	...
Miyazaki [35]	IV prostaglandin E ₁	18/26	2/18	NS
Matsuzaki [21]	IV prostaglandin E ₁	6/6	0/6	NS
Murakami [15]	Vascular anastomosis: SG vessels–cervical vessels	15/26	0/15	<0.05
Yoshimi [17]	Vascular anastomosis: SA and SV–ECA and IJV	21/23	0/21	<0.012
Matsuda [14]	Proximal ligation of inferior polar branches of splenic vessels	10	0	...

^{a, b} Preoperative laparoscopic LGA ligation was performed either 2 weeks^a or 5 days^b before esophagectomy [34]. ^c Two-step procedure: LGA and SGA ligation and gastric tubulization as first step before esophagectomy as second step.

ECA = external carotid artery; IJV = internal jugular vein; IV = intravenous; LGA = left gastric artery; NS = not statistically significant; RGA = right gastric artery; SA = splenic artery; SG = short gastric; SV = splenic vein.

[33]. This approach was first performed by Akiyama and colleagues [10], when they coiled the left and right gastric artery as well as the splenic artery 12 days before esophagectomy and reconstruction with a gastric tube. They could demonstrate that gastric blood flow was less decreased after embolization versus no embolization (23% versus 65%) at the time of operation, but there was no impact on anastomotic leakage rate [10]. Similar results have been published by Nguyen and coworkers [32] and Berrisford and associates [33], with no statistical difference of anastomotic leak rates. The precise pathophysiologic changes that are induced by embolization or gastric tube formation are largely unknown. Whether there is real neoangiogenesis with formation of collaterals or simple recruiting of preexisting small arterial and venous vessels has never been shown. Timing between embolization and esophagectomy is therefore controversial [26, 31, 34]. In our series, PAE was performed 17 days before esophagectomy, and leak rates were 11% and 21% with PAE and without PAE, respectively. Because the difference is not statistically significant, our results confirm the reported findings in the literature. Six patients in our series had mild abdominal pain after PAE. One exhibited a partial splenic necrosis, a previously described possible complication of short gastric artery embolization [11, 33]. All were managed conservatively.

All published series have small patient numbers and methodological shortcomings, eg, assessment of complications (Table 4). Despite our series also having a limited number of patients, the well-matched case-control design warrants reliable results. But, nevertheless, it remains difficult to clearly show a clinical benefit of PAE, and it seems that improved gastric microcirculation does not correspond necessarily to decreased leakage rates. This is confirmed by Matsuzaki and colleagues [21] and Tobari and associates [22], who used intravenous prostaglandin E₁ to improve gastric microcirculation. Although this medical treatment was able to improve gastric blood flow, its results on anastomotic leakage are inconsistent.

In conclusion, PAE has no detrimental effect on the overall postoperative morbidity, whereas its final role to decrease anastomotic leakage remains to be elucidated. Studies including more patients and combining PAE with other innovative treatment modalities are needed to further develop the concepts of ischemic preconditioning and neovascularization in the setting of esophageal replacement with a gastric tube.

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