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# Generalized cardiovascular disease on a preoperative CT scan is predictive for anastomotic leakage after esophagectomy

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ABSTRACT

*Background:* Recent studies demonstrated that calcification of arteries supplying the gastric tube is associated with anastomotic leakage after esophagectomy. However, it remains unclear whether this association only derives from local flow limitations, or generalized vascular disease as well. The purpose of this study was to determine whether calcification throughout the entire cardiovascular system is associated with anastomotic leakage.

*Methods:* Consecutive patients who underwent an esophagectomy with gastric tube reconstruction and cervical anastomosis for esophageal cancer were analyzed. Diagnostic CT images were scored for the presence of arterial calcification on 10 locations based on a visual grading system. The association with anastomotic leakage was studied using logistic regression analysis.

*Results:* A total of 406 patients were included for analysis of whom 104 developed anastomotic leakage (25.6%). Presence of calcification in the coronary arteries (minor calcification: 36.5% leakage; no calcification: 18.1%, $p = .001$), supra-aortic arteries (minor calcification: 30.9% leakage; major calcification: 35.3%; no calcification: 16.1%, $p = .007$ and $p < .001$, respectively) and thoracic aorta (major calcification: 33.3% leakage; no calcification: 19.4%, $p = .011$) was associated with leakage. In multivariable analysis, minor calcification of the coronary arteries (OR 2.29, 95% CI: 1.28–4.12, $p = .005$) and calcification of the supra-aortic arteries (OR 2.48, 95% CI: 1.30–4.74, $p = .006$ for minor calcification and OR 2.72, 95% CI: 1.49–4.99, $p = .001$ for major calcification) remained independently associated with leakage.

*Conclusions:* Calcification of the coronary and supra-aortic arteries on routine CT are predictive of cervical anastomotic leakage after esophagectomy. These results suggest that generalized cardiovascular disease is a strong indicator for the risk of leakage.



## Introduction

Anastomotic leakage after esophagectomy for patients with esophageal carcinoma is a frequently encountered complication (10–30%), resulting in increased postoperative morbidity and mortality [1–9]. Several studies have aimed to identify preoperative risk factors for anastomotic leakage after esophagectomy [2,10,11]. Patient-related factors associated with anastomotic leakage include obesity, heart failure, coronary artery disease, peripheral vascular disease, hypertension, steroids, diabetes, renal insufficiency and tobacco use [2]. The majority of these risk factors underline the current hypothesis that ischemia is one of the most important contributors to anastomotic leakage, since most of these factors negatively influence microvascular perfusion and thus compromise anastomotic healing [2,4].

Preoperative identification of patients with esophageal cancer at high risk of anastomotic leakage may provide opportunities to modify these risk factors or more fully optimize patients to reduce their risk of anastomotic leakage. However, predicting anastomotic leakage based only on standard patient-related risk factors remains challenging, encouraging further research into prediction strategies [11].

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Radiographic findings such as atherosclerotic calcification on a computed tomography (CT) scan can be used to objectively evaluate a patients' vascular status and risk of cardiovascular events [12–14]. Recent studies demonstrated that atherosclerotic calcification of the thoracic aorta and right postceliac arteries is associated with anastomotic leakage after esophagectomy [11,15]. To date, however, it remains unclear whether the association between anastomotic leakage and calcification detected on a CT scan applies to local vascular disease (with accompanied local flow limitations) only, or to generalized vascular disease as well. Therefore, the purpose of this study was to determine whether the presence of atherosclerotic calcification throughout the entire cardiovascular system as determined on routine CT images is associated with anastomotic leakage after esophagectomy for cancer.

## Patients and methods

This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (number 15/624); the requirement for written informed consent was waived.

### *Study population*

All consecutive patients who underwent elective esophagectomy for cancer with gastric tube reconstruction and hand-sewn cervical anastomosis from October 2003 to October 2015 at the University Medical Center Utrecht were considered for inclusion. Exclusion criteria included premature discontinuation of surgery due to the discovery of T4b or M1 disease during surgery, combined laryngeal resection, salvage surgery and insufficient quality of CT scan.

Patient and treatment-related characteristics, and surgical outcome data (e.g. anastomotic leakage), were collected from a prospectively maintained database. Anastomotic leakage was defined by either visible loss of saliva through the cervical wound, extravasation of water-soluble contrast material during a contrast swallow study or CT scan, or visualization of anastomotic dehiscence or fistulae during endoscopy or surgical re-intervention.

### *Image acquisition*

CT images of the neck, thorax and (upper) abdomen were routinely conducted during diagnostic workup with multidetector row CT scanners from various vendors at our own or referring institutions. Images were acquired with a tube potential varying from 100 to 140 kV, a minimum tube current of 8–500 mAs (median 73 mAs), a maximum tube current of 33–500 mAs (median 181 mAs) and typically with a field-of-view of 500 mm. The scans were typically contrast-enhanced (90.1%). All routine preoperative CT protocols with a maximum slice thickness ≤7 mm were considered suitable for inclusion. Median slice thickness was 3.0 mm (range 0.9–7.0 mm, IQR 4.0 mm), with a slice thickness of 5.0 mm or less in 98.8% (401/406) of patients. The interval between CT scanning and primary surgery ranged from 1 to 280 days, with a median of 114 days.

### *Image evaluation*

A detailed visual grading system was developed in order to consistently score CT images on arterial calcification at ten different locations (Table 1). The selected locations included the supra-aortic arteries (i.e. the brachiocephalic trunk, left common carotid artery and left subclavian artery), coronary arteries, aortic valve, thoracic aorta (with special attention to a possible calcified ductus arteriosus that was not scored as a calcification), abdominal aorta, celiac axis, common iliac arteries (left and right) and external iliac arteries (left and right). Scores of 0, 1 or 2 were assigned, corresponding with absence, minor presence or major presence of calcification, respectively. Examples of arterial calcification on CT images are presented in Fig. 1.

Images were typically analyzed in the transverse plane with software from Sectra: PACS IDS7™ version 17.3. All CT images were scored independently by one reader (A.S.B.), trained and supervised by a radiologist with 10 years of experience in thoracic and abdominal CT evaluation (P.A.d.J.). In addition, a random sample of 30 patients without missing data was scored twice by one reader (A.S.B.) after a 12-month interval between readings, as well as scored independently by a second reader (L.G.) to determine intra- and interobserver reproducibility and agreement, respectively. In previous studies, this type of grading calcification has been shown to yield good to excellent intra- and interobserver reproducibility and agreement [12,15,16]. The readers were blinded for patient and treatment-related factors, and outcome in terms of anastomotic leakage.

### *Statistical analyses*

The association between patient and treatment-related characteristics and anastomotic leakage was studied univariably. Depending on the cell count, the $\chi^2$ or Fisher's exact test was used

**Table 1**
Definitions used to visually grade arterial calcification on preoperative CT images.

| Anatomical location | Calcification scores | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| Coronary arteries | absent | multiple foci *or* 1 calcification extending over ≥2 slices | calcified arteries covering a large segment of a coronary branch |
| Supra-aortic arteries | absent | calcification in 1 supra-aortic artery | calcification in >1 supra-aortic artery |
| Aortic valve | absent | 1 small calcification on 1 leaflet | >1 small calcification on 1 leaflet |
| Thoracic aorta *(heart − celiac axis)* | absent | ≤9 foci *or* ≤3 calcifications extending over ≥3 slices | >9 foci *or* >3 calcifications extending over ≥3 slices |
| Celiac axis | absent | single focus with MCSD ≤10 mm *or* extending over <3 slices | MCSD >10 mm *or* extending over ≥3 slices *or* involving proximal (aortoceliac) and distal (hepatosplenic) parts |
| Abdominal aorta *(celiac axis − bifurcation)* | absent | ≤9 foci *or* ≤3 calcifications extending over ≥3 slices | >9 foci *or* >3 calcifications extending over ≥3 slices |
| Common iliac arteries | absent | ≤5 foci *or* 1 calcification extending over ≥3 slices | >5 foci *or* >1 calcification extending over ≥3 slices |
| External iliac arteries | absent | ≤5 foci *or* 1 calcification extending over ≥3 slices | >5 foci *or* >1 calcification extending over ≥3 slices |

*MCSD:* maximum cross-sectional diameter.

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