Differences in the pattern of anastomotic leakage after oesophagectomy in two high-volume centres

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ABSTRACT

INTRODUCTION: Complications to oesophageal and junctional cancer surgery are common and have not diminished much during the past ten years. An unusually high occurrence of anastomotic dehiscence occurred in Denmark in 2009 and 2010 as seen in the national database for oesophagus, cardiac and gastric cancer (ECV).

MATERIAL AND METHODS: In accordance with national guidelines, all patients resected for oesophageal and junctional cancer in Denmark from 2003 were prospectively entered into a national database. Data concerning anaesthesia, peri- and post-operative course, complications, reoperations and time spent in intensive care unit were obtained retrospectively from hospital records. An in-depth analysis of data from two high-volume centres performing ECV cancer surgery according to national guidelines was performed.

RESULTS: A total of 881 patients (Centre 1: 438; Centre 2: 443) were resected for oesophageal and junctional cancer. A total of 79 patients with anastomotic insufficiency (AI) were detected (Centre 1: 36; Centre 2: 43). By using a grading system, it was shown that AI was more severe and occurred earlier in one centre than in the other. Possible factors of influence are discussed, including neoadjuvant oncological therapy, use of thoracoscopically performed anastomosis and perioperative inotrophic drugs.

CONCLUSION: Thanks to the establishment of a nationwide database in pursuance of national guidelines, it was possible to detect variations in quality of surgery over time, evaluate serious complications early and undertake an in-depth analysis of possible aetiological factors. Particularly, comparison was facilitated by the use of a standardised grading system for complications.

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The surgical approach for oesophageal cancer with resection ad modum Ivor Lewis has not changed much over the past 40 years, except for added lymphadectomy and in some cases a minimally invasive approach [1, 2]. The previously preferred technique was open laparotomy with the preparation of a gastric conduit and a thoracotomy with an intrathoracic anastomosis [3]. However, during the past ten years, a tendency towards accelerated post-operative care and minimally invasive surgery has become apparent [2]. Previously, the complication rate was high [4], probably because many departments did not have a sufficient patient volume. After centralization through the establishment of specialized centres with higher volumes, the complication rate has diminished over the years [5, 6]. Nevertheless, it has been difficult to compare the complication rates between centres as the reporting of complications is very heterogeneous, and well-defined standards are missing, for example for anastomotic insufficiency (AI) [7]. A national database with mandatory registration of all upper gastrointestinal resections for malignant diseases was established in 2003 and results from this database have since been published annually in a public report [6]. In 2009/2010, an increase in AI was observed in two centres [6] and an in-depth audit was performed identifying several factors of importance.

It further became evident that patients were treated differently at the two centres. One centre (Centre 2) used an accelerated post-operative regimen and had also modified their operative and post-operative procedures in order to introduce minimally invasive surgery. The other centre used a conservative set-up. The present study aimed to demonstrate the importance of registration in a national database for further in-depth analysis of surgical and post-operative factors which may explain complications.

MATERIAL AND METHODS

The database records of all resected oesophageal and junctional (EJ) cancer patients in the oesophageal, cardiac and gastric cancer (ECV) database from the 2003-2011-period who had been treated at one of the two centres were investigated. Data from the two other centres in Denmark were omitted as complete registration of complications was pending at one centre and the other was not a high-volume centre [6].

Information concerning methods of treatment, type of resection, pathology report, etc. was collected from the database (**Table 1**). Specific data concerning operation technique, length of hospital stay, days to diagnosis of AI, complications during anaesthesia and post-operative care and use of inotrophic drugs were obtained ret-

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TABLE 1

Characteristics of resected patients.

	Centre 1	Centre 2	p-value
Patients resected, n	438	443	NS
Patients with AI, n	36	43	NS
Patients with AI, age, yrs, median (range)	63 (41-83)	67 (47-84)	NS
Preoperative co-morbidity, n			
None	25	29	NS
Cardiac	5	8	NS
Respiratory	6	6	NS
Operative and post-operative difference			
Gastric conduit	Wide	Narrow	–
Phrenotomy	All	None	–
Gastric tube removal	7 days	3-4 days	–
Fluoroscopy	Routine at day 7	Not performed	–

AI = anastomotic insufficiency; NS = non-significant.

TABLE 2

Number of patients in the different grades of anastomotic insufficiency (differences are significant: $p < 0.05$). Data remain significant even when corrected for patients with no clinical evidence of anastomotic insufficiency (grade 1) ($p < 0.05$).

	Grade						
	I	II[a]		III[a]		IV[a]	
Centre 1	9	a: 0	b: 12	a: 2	b: 6	a: 1	b: 6
Centre 2	0	a: 2	b: 5	a: 17	b: 15	a: 3	b: 1

Grade I: Patients with few or no symptoms and anastomic insufficiency found on routine X-ray control of anastomosis at day 7.
Grade II: Patients with symptoms but no need of re-operation nor intensive care unit.
Grade III: Patients with septic anastomotic leakage demanding either thoracal re-operation, but only overnight stay at post-operative care unit, or conservative treatment (no re-operation), with a prolonged stay in intensive care unit
Grade IV: Patients with septic anastomotic leakage demanding thoracal re-operation and subsequently stay in intensive care unit.
a) All grades were divided into a or b in relation to occurrence before or after day 6.

rospectively from hospitals records. AI was defined as an oesophago-gastric anastomotic dehiscence recognised 1) radiologically by water-soluble X-ray contrast medium at day 7 post-operatively or earlier if it was suspected clinically, or 2) by acute computed tomography (CT) performed due to clinical signs of leakage (fever, chest pain) or by upper gastrointestinal (GI) endoscopy in critical ill patients at the intensive care unit.

AI was classified into four grades (**Table 2**), modified according to Urschel and Dindo et al [8, 9]. Grading is performed on a combination of treatment choices and severity based on the clinical state of patients and day of occurrence.

Perioperative hypotension was defined as a systolic blood pressure below 100 with anaesthesia records stating that hypotension had been present and treated.

Differences between the two centres could potentially have been due to specific aspects such as use of pyloroplasty, covering of stapler lines, post-operative fasting, but as data on these factors were not present in the ECV database, it was not possible to perform a multivariate analysis. Neoadjuvant oncological therapy such as chemo-irradiation (squamous-cell cancers) and perioperative chemotherapy (adenocarcinomas) was introduced in 2009-2010 in both centres. Data concerning initiation of neoadjuvant therapy were present in all data records.

Surgical and post-operative care procedures

During the whole period, the standard technique used was the Ivor-Lewis procedure with a two-phase abdominal and right chest approach for en-bloc subtotal oesophagectomy followed by an oesophagogastric anastomosis and a D1 resection extended with dissection of the truncal celiac adjacent nodes [10]. In Centre 1, the gastric tube was fashioned as a wide tube (> 5 cm in diameter) using a double-stapling technique [11], all stapler lines were covered and pyloroplasty was done in all cases. In Centre 2, the same technique was applied until 2008, when laparoscopy was introduced and from 2009 with added thoracoscopically performed intrathoracic anastomosis in a number of cases. At laparoscopy, a narrow gastric tube (3-5 cm) was constructed in the abdomen, no phrenotomy nor pyloroplasty was done and no stapler lines were covered. All anastomoses were performed with a circular stapler in both centres. Postoperatively, Centre 1 used seven days of decompression with a gastric tube and Centre 2 allowed oral intake after day 2-3 as part of an accelerated post-operative regimen introduced in 2002 [12].

Statistics

Categorical data were compared using the χ^2-test or Fischer's exact test. Continuous data are shown as median ± range and were compared using the Mann-Whitney test. In testing for trend, a non-parametric test was performed (JT-test). A two-sided p-value < 0.05 was considered statistically significant. The SPSS statistical package (version 19.0; SPSS inc., Chicago, IL) was used for most analyses. MatLab 2012 was used for data analysis and figures.

Ethics

The Danish Data Protection Agency approved the collection and processing of data in this study (2012-331-0068 and 2007-58-0015).

Trial registration: not relevant.

RESULTS

A total of 881 patients (Centre 1: 438; Centre 2: 443) were resected for EJ cancer. As shown in Table 1, there were no differences in patient characteristics, except for

Patient with conservatively treated anastomotic insufficiency.

the above-mentioned differences in operative procedures and post-operative care.

A total of 82 patients with AI were identified. The temporal distribution showed a median AI frequency of 8% (range 3-13%) and 11% (range 3-21%) in Centre 1 and Centre 2, respectively, but with a marked increase in frequency after 2008 in both centres. Numbers were corrected for three patients for whom the records could not be located. Analysis was then performed on 36 patients from Centre 1 and 43 patients from Centre 2.

A large number of patients were severely septic in Centre 2 (Table 2), even if corrected for cases discovered by routine X-ray in Centre 1 (nine patients). A high proportion of dehiscence (92%) occurred after day 6 in Centre 1 (Table 2, **Figure 1**). After correcting for silent cases, the number of patients with dehiscence was not different between centres (Centre 1 (6%) versus Centre 2 (10%) ($p = 0.06$)).

Three patients with AI in Centre 1 had squamous-cell carcinomas and nine in Centre 2; the rest had adenocarcinomas (not significant).

In Centre 2, 42% (n = 18) of the AI occurred in patients operated with a laparoscopic approach, and in some of these cases (11%) the procedure was supplemented by thoracoscopically performed anastomosis. However, the number of patients with AI in Centre 2 was identical in open and laparoscopically performed operations (25 of 288 procedures (9%) versus 13 of 138 procedures (9%)), but was significantly increased in patients with laparoscopy who also had a thoracoscopical anastomosis (five of 17 procedures (29%)). In 2009, neoadjuvant therapy was introduced and a multivariate analysis showed no influence of this in relation to the occurrence of AI in the two centres (Centre 1 odds ratio (OR) 1.2 (0.5-3.3; Centre 2 OR 1.3 (0.3-5.7)). When adjusting for oncological therapy, a significant influence was found among patients with thorascopically performed anastomoses (OR 1.9 (1.1-3.3)).

We found that 56% of AI in Centre 1 were not diagnosed on the primary fluoroscopy X-ray. Most were diagnosed with CT at a later stage when symptoms presented. There was a significant difference between the centres, as day of diagnosis was earlier at Centre 2 (median day 6 (range 1-20 days)), especially when corrected for clinically silent cases in Centre 1. Specifically, the median time to diagnosis at Centre 1 was eight days (range 5-29 days) ($p < 0.05$), and when corrected for silent cases, 11 days (Figure 1).

We chose to look into other factors which would possibly differentiate the two centres (**Table 3**). In both, two thirds of the patients with AI were hypotensive and a marked difference in median blood loss during surgery was found between the centres. Inotrophic drugs were used for a significantly longer period perioperatively in Centre 2 than in Centre 1 (three hours versus 24 hours, $p < 0.05$).

DISCUSSION

AI is a serious complication following oesophagectomy and there has been speculation concerning its aetiology [8, 13, 14]. The rate of AI has generally been reported to be below 10% [1, 4, 8, 12-15]. In Denmark, variations

FIGURE 1

Time to diagnosis of anastomotic insufficiency ($p < 0.05$) after correction for silent cases at day 7 (day 9 at Centre 1). The distribution between centres differs significantly ($p < 0.05$). Curves are Poisson distributions.

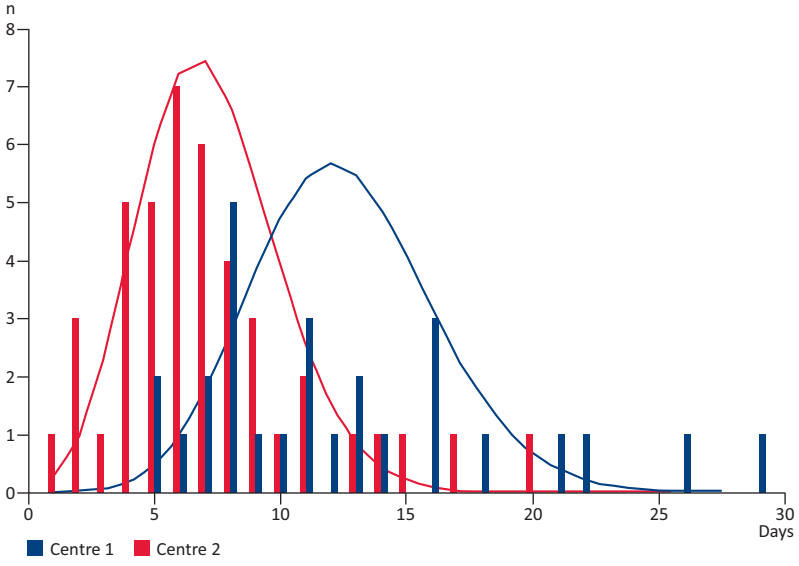

TABLE 3

Differences between centres post-operatively in anastomotic insufficiency patients.

	Centre 1	Centre 2	p-value
Hypotensive patients, n	20	31	NS
Blood volume loss, ml, median (range)	800 (350-2,600)	500 (100-2,100)	< 0.05
Patients with AI, age, yrs, median (range)	63 (41-83)	67 (47-84)	NS
Hospital mortality among AI, n (%)	5 (14)	9 (20)	NS
Length of stay, days, median (range)	38 (10-87)	37 (12-200)	NS
Median time of vasopressor use, h, median (range)	3 (0-24)	24 (0-169)	< 0.05
Stages, n			
T-stage T0-2	25	26	NS
T-stage T3-4	11	15	NS
T-stage not stated	0	2	NS
N-stage 0	21	19	NS
N-stage ≥ 1	15	22	NS
N-stage not stated	0	2	NS

AI = anastomotic insufficiency; NS = non-significant.

over time have been observed after a national database was established [6].

From these data it could be observed that the mean value of AI on the two largest centres has been acceptably low over the past ten years (8% and 10%) with an increase in patients with AI occurring in 2009 and 2010. A morbidity/mortality audit on data from 2010 made it apparent that at Centre 2 – where minimally invasive surgical (MIS) procedures were introduced in late 2008 – the majority of the dehiscences occurred early and were to some extent due to the learning curve in thoracoscopically performed anastomosis. Neoadjuvant therapy was introduced in 2009-2010 and a multivariate analysis showed that it was not of importance for AI. When adjusting for neoadjuvant oncological therapy, the only significant factor for AI was seen in thoracoscopically treated patients, thus confirming a learning curve. However, as only 17 patients had a thorascopical anastomosis and as there was no difference in the AI frequency between laparoscopical and open cases, MIS seems not be the only explanation. Furthermore, it was shown that more than 50% of AI cases occurred before or at day six in Centre 2 compared with 8% in Centre 1, and the median time to diagnosis of AI in Centre 1 was 11 days. The literature is scarce concerning the time to occurrence of AI [8], but it is widely accepted that more than 50% of failures occur before day 8 [13-15]. Our data point at two peaks of AI in oesophagectomies. This has not been reported before since the cases in previous reports are few and mostly from single centres. In our material, the first peak is in the early post-operative period as seen in Centre 2, and is accompanied by severe septic complications, as also stated in Urschell [8]. The second peak, as seen in Centre 1, is observed after 8-10 days in patients with normal oesophageal fluoroscopy and at the time when oral feeding is commenced. This peak is the one most commonly described in the literature, as the mean time to diagnosis is usually eight days [13-15]. The reason for the late occurrence could be that gastric tube decompression delayed the AI which was then overlooked at fluoroscopy due do fibrin sealing.

Various reasons have been suggested for AI [8]. With respect to early failures, it seems that peri-operative and immediate post-operative vascular insufficiency may be of importance, and it has been shown that during liberation of the gastric remnant the oxygen tension in the tissue drops by as much as 29% and is up to four days in returning to normal values [16, 17]. The dissection causes venous stasis and a scarce arterial flow to the anastomotic region. Further stasis and diminished flow can be caused by a too small foramen at the passage of the diaphragm and is probably also due to a narrow gastric conduit as performed in Centre 2 [18]. Hypotension during operation and post-operatively has also been suggested to be of importance [19] and the use of vasopressor agents and the time of their administration are of significant importance for the failure rate as demonstrated in univariate analyses [3]. Thus, early failures could be explained by diminished microcirculation in gastric conduit or oesophageal remnant during and after operation. In our material this may explain why Centre 2 that applied prolonged use of vasopressors had early AI with a high morbidity. Furthermore, Centre 2 reinstated oral feeding early and the resulting gastric distension is possibly involved in both early and late occurring AIs. AI actually occurs after day 7-8, up to day 23 [6, 9, 13, 14, 16] and in our series day 29 in patients presumably healed on fluoroscopy. Tomaszek et al [20] has recently shown that very late reinstatement (four weeks) of oral intake results in a lower rate of AI.

A limitations in this study is the retrospective design of the data supplement from hospital records in patients with AI. This makes multivariance analysis impossible for several of the proposed important aetiological factors.

CONCLUSION

In conclusion, differences in the handling of patients with oesophagogastric resection may cause different patterns of AI as exemplified by our investigation. We assume that in our cases some of the aetiology of AI may be gastric distension at the time of oral feeding, modified by two different surgical and perioperative regimens.

We found it of importance to grade all anastomostic failures using our own grading system since a large variety of anastomotic failure rates have been reported – up to 35% [6]. Many studies include a variety of anastomotic failures ranging from contained sinus dehiscence to patients in septic shock due to massive conduit

tip necrosis. Dindo et al [9] introduced their own complication grade score, but did not take into consideration time until complication; nor did they involve patients found with anastomotic dehiscence on routine fluoroscopy. We found that time of occurrence and treatment of anastomotic failures also should be included when grading AI.

By establishing a nationwide database and relying on national guidelines for treatment, we have been able to show important differences in complications, demonstrating future investigational areas into the aetiology of post-operative complications and their standardization.

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