Emergency oesophagectomy for oesophageal perforation after chemoradiotherapy for oesophageal cancer

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ABSTRACT

INTRODUCTION Oesophageal perforation following chemoradiotherapy for oesophageal cancer is a devastating condition but there have been no studies investigating the role of emergency oesophagectomy for this life threatening situation.

METHODS This retrospective study comprised all cases of emergency oesophagectomy for oesophageal perforation after chemoradiotherapy for oesophageal carcinoma at a major centre for oesophageal surgery in Germany between 2004 and 2013.

RESULTS A total of 13 patients (mean age: 58.9 years) were identified. During the same time period, 356 elective oesophagectomies were performed. Tumour entities were squamous cell carcinoma ($n=12$) and adenocarcinoma of the oesophagus ($n=1$). Alcoholism (odds ratio [OR]: 25.79, 95% confidence interval [CI]: 6.70–121.70, $p<0.0001$) and chronic pulmonary disease (OR: 3.76, 95% CI: 1.06–14.96, $p=0.027$) were more common among the emergency cases.

Oesophageal rupture was caused by perforation of an oesophageal stent (10 cases) or perforation during implantation of a percutaneous endoscopic gastrostomy tube (3 cases). Emergency oesophagectomy was carried out either as discontinuity resection (10/13) or oesophagectomy with immediate reconstruction (3/13).

Compared with the elective cases, patients undergoing emergency oesophagectomy had significantly higher odds for sustaining perioperative sepsis (OR: 4.42, 95% CI: 1.23–16.45, $p=0.01$), acute renal failure (OR: 6.49, 95% CI: 1.57–24.15, $p=0.005$) and pneumonia (OR: 24.33, 95% CI: 3.52–1,046.65, $p<0.0001$). Furthermore, slow respiratory weaning was more common and there was a significantly higher tracheostomy rate (OR: 4.64, 95% CI: 1.14–16.98, $p=0.02$). Oesophageal discontinuity was eventually reversed in eight patients.

Emergency oesophagectomy patients had odds that were three times higher for fatal outcome (OR: 3.59, 95% CI: 0.77–13.64, $p=0.05$). The overall mortality was 4/13. The remaining nine patients had a mean survival of 25.1 months (range: 5–46 months). The two-year-survival-rate was 38.5% (5/13).

CONCLUSIONS Despite the most unfavourable preconditions, the results of emergency oesophagectomy for oesophageal perforation after chemoradiotherapy are not desperate. The procedure is not only justified but life saving.

KEYWORDS

Emergency oesophagectomy – Oesophageal cancer – Emergency

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Salvage oesophagectomy following full dose chemoradiotherapy for oesophageal carcinoma is a most challenging procedure, which is usually only advocated for a very carefully selected subset of patients suffering from local tumour recurrence or persistent disease.^{1–3} Despite its very selective use in fit patients with resectable carcinoma, salvage oesophagectomy is associated with substantial morbidity and mortality rates up to 25% have been reported.^{4–7} Given the technical difficulty caused by radiation, scar tissue and tumour growth, salvage oesophagectomy is generally considered to be a procedure not to be embarked on lightly.¹

On the other hand, oesophageal perforation is a devastating condition even in modern times. Population-based data from Denmark showed an overall national mortality rate of 21% for patients with oesophageal perforation including spontaneous rupture and iatrogenic perforation.⁸ Contemporary reports from specialist centres of foregut surgery show comparable results. The Northern Oesophago-Gastric Unit (Newcastle upon Tyne, UK), for example, observed a mortality rate of 24% in a series of 101 patients with oesophageal perforation.⁹

Oesophageal perforation after chemoradiotherapy for oesophageal cancer is an even more desperate situation. If

management by non-operative means is not feasible, emergency salvage oesophagectomy remains as a last resort to save the patient's life. As salvage oesophagectomy is not performed here in an elective setting but in a situation of the highest urgency, it is questionable whether the outcome justifies the procedure. There has as yet been no in-depth analysis on the role of emergency oesophagectomy for oesophageal perforation following chemoradiotherapy for oesophageal carcinoma and this study intended to address that void.

Methods

All patients who underwent emergency salvage oesophagectomy for oesophageal perforation after or during chemoradiotherapy for oesophageal cancer were enrolled in a retrospective study. All procedures were performed exclusively by two well trained general thoracic surgeons (MS and HJS) at the Klinikum Nürnberg. Our institution is one of Germany's largest tertiary referral hospitals and a major provider for thoracic surgery in southern Germany. The Department of Surgery is particularly dedicated to oesophageal surgery. The study was approved by a local ethics committee and the need for individual consent was waived owing to the retrospective study design.

Elective oesophagectomy

During the whole study period, elective oesophagectomy was routinely performed as an abdominothoracic *en bloc* oesophagectomy with two-field lymphadenectomy, interposition of a pulled up gastric tube and intrathoracic stapled anastomosis above the level of the tracheal carina.¹⁰ Transhiatal extended total gastrectomy included resection of the distal oesophagus and intrathoracic stapled oesophagojejunostomy below the level of the tracheal carina.¹⁰ Furthermore, limited resection of the distal oesophagus with jejunal interposition and a stapled intrathoracic oesophagojejunostomy (Merendino procedure) was carried out.¹¹

Chemoradiotherapy

Definitive chemoradiotherapy for oesophageal cancer meant two cycles of platinum-based chemotherapy (cisplatin and fluorouracil) given concurrently with 66Gy of external beam radiotherapy followed by two cycles of adjuvant chemotherapy. Neoadjuvant chemoradiotherapy consisted of two cycles of platinum-based chemotherapy (cisplatin/fluorouracil) administered concurrently with 50.4Gy of external beam radiotherapy.

Emergency oesophagectomy

Emergency oesophagectomy was defined as non-elective, emergent oesophagectomy in patients who had already undergone chemoradiotherapy for oesophageal cancer with curative intent. The procedure was carried out as a transthoracic oesophagectomy with oesophageal discontinuity through a right thoracotomy for the best possible exposition of the oesophagus. The oesophagogastric junction was stapled shut at the level of the oesophageal hiatus and the proximal oesophageal remnant was brought out as

a cervical end oesophagostomy. The affected pleural cavity was washed out carefully and large bore chest tubes were placed. A jejunal feeding tube was inserted for enteral nutrition via a mini-laparotomy.

As the patients underwent surgery in a situation of the highest urgency, we usually avoided immediate reconstruction and opted instead for a staged procedure. After sufficient recovery, the patients underwent a laparotomy with creation of a gastric tube, which was brought up to the neck through the retrosternal route. The continuity of the foregut was re-established by a handsewn end-to-side oesophagogastrostomy.

If the remaining stomach was not suitable for reconstruction, colonic interposition was carried out. The left colon was used as conduit and pulled up via the retrosternal route. The cervical anastomosis was performed as a handsewn end-to-side oesophagocolostomy. The blood supply of the pulled up colon was drawn from the left colonic artery.

Statistical analysis

The following data concerning initial presentation, characteristics, operative procedure, postoperative course and overall outcome were collected: demographic characteristics, pre-existing co-morbidity, type of tumour, radiation dose, reason for oesophageal perforation, operative treatment, postoperative morbidity and mortality, way of reconstruction and overall survival. Statistical analysis was performed with R statistical software (R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org/>). The independence of the variable pairs studied was tested using Fisher's exact test.

Results

The study comprised 13 patients (12 male) who underwent emergency oesophagectomy for intrathoracic oesophageal perforation (Table 1). The mean age was 58.9 years. Only adults suffering from oesophageal carcinoma were included while other conditions associated with oesophageal disruption such as Boerhaave's syndrome or peptic stenosis were excluded. Twelve patients had squamous cell carcinoma and only one case of oesophageal adenocarcinoma was encountered. None of the patients had distant metastases or T4 disease and it was mandatory that the initial treatment had been given with curative intent. Reasonable performance and nutritional status were also required. Patients receiving palliative treatment or best supportive care were not eligible for surgery. During the study period, emergency oesophagectomy was offered to all patients fulfilling these conditions.

Definitive chemoradiotherapy had been intended in all patients with squamous cell carcinoma while neoadjuvant chemoradiation had been carried out in the one case of oesophageal adenocarcinoma. At the time of oesophageal perforation, definitive chemoradiotherapy had been fully completed in six cases (66Gy) whereas the remaining six patients were still receiving chemoradiation (Table 1). The mean radiation dose, which had been administered until the perforation occurred, was 50Gy (range: 10.8–66Gy).

Table 1 Characteristics of the study population

Patient number	Age / sex	SCC	EAC	Definitive CRT	Neoadjuvant CRT	Radiation dose
1	71 M		1		1	50.4Gy
2	46 M	1		1		66Gy
3	54 M	1		1		66Gy
4	49 M	1		1		50Gy
5	60 M	1		1		66Gy
6	73 M	1		1		10.8Gy
7	66 M	1		1		66Gy
8	49 M	1		1		60Gy
9	65 M	1		1		66Gy
10	64 M	1		1		66Gy
11	53 M	1		1		60Gy
12	57 M	1		1		10.8Gy
13	59 F	1		1		10.8Gy

SCC = squamous cell carcinoma; EAC = oesophageal adenocarcinoma; CRT = chemoradiotherapy

Oesophageal rupture was either caused by stent perforation (10 cases) or by perforation during implantation of a percutaneous endoscopic gastrostomy (PEG) tube (3 cases). Stent related perforation following endoscopic stent insertion for relief of tumourous stenosis and dysphagia usually occurred a few days after initial successful stent placement. The mean time interval between endoscopic stent insertion and oesophageal rupture was 19.3 days (range: 1–42 days). In contrast, oesophageal perforation during implantation of a PEG tube was always evident immediately.

Pre-existing co-morbidity

A considerable level of pre-existing co-morbidity was found in the study population. Chronic alcoholism was present in nine cases and three drinkers had already developed alcoholic liver cirrhosis. Most of the emergency oesophagectomy patients were heavy smokers. As a consequence, chronic obstructive pulmonary disease (COPD), peripheral arterial occlusive disease and cardiovascular disease were encountered in 8, 3 and 5 cases respectively. Furthermore, congestive heart failure (2 cases), chronic kidney disease (1 case), diabetes mellitus (1 case), stroke (1 case) and a chronic gastric ulcer (1 case) were present. The medical records of three patients revealed a previous malignant disease unrelated to the oesophageal carcinoma.

During the study period, 356 elective oesophagectomies were performed at our institution. There were 299 men and 57 women. The mean age was 64.2 years and 111 patients had undergone neoadjuvant therapy. Adenocarcinoma was more frequently encountered than squamous cell carcinoma (231 vs 115 cases). The mean ASA (American Society of Anesthesiologists) grade was 2.25. Compared with these elective cases, the patients undergoing emergency oesophagectomy had a significantly higher burden of pre-existing co-morbidity. In particular, alcoholism (9/13

vs 28/356, odds ratio [OR]: 25.79, 95% confidence interval [CI]: 6.70–121.70, $p < 0.001$) and COPD (8/13 vs 106/356, OR: 3.76, 95% CI: 1.06–14.96, $p = 0.027$) were significantly more common in the salvage group.

Emergency oesophagectomy

Emergency oesophagectomy was performed as discontinuity resection with delayed reconstruction in ten cases. Oesophageal rupture was caused by perforation of an endoscopic stent in seven of these cases and by oesophageal rupture during endoscopy for implantation of a PEG tube in the remaining three. Transthoracic oesophagectomy was accomplished successfully in nine patients whereas fatal haemorrhage occurred in one case. In the latter case, the oesophageal stent had not only caused oesophageal rupture but also stent related aortic erosion. Massive bleeding started suddenly during the oesophagectomy and only then did stent related fistulisation between the aorta and the oesophagus become apparent.

In general, the postoperative course was rather stormy. (See below.) One patient died from severe sepsis with septic shock and multiorgan failure. He was a heavy drinker with alcoholic liver cirrhosis. The remaining eight patients eventually recovered well and were able to undergo reconstruction. Oesophageal discontinuity was reversed after a mean of three months (range: 1–6 months). Reconstruction of the foregut was achieved by pulling up a gastric tube in seven cases and by colonic interposition in one patient.

A single stage approach with immediate reconstruction and anastomosis was chosen in three cases. These cases comprised two patients who had not yet completed definitive chemoradiotherapy (radiation dose 10.8Gy and 50Gy) and the one patient receiving neoadjuvant therapy (50.4Gy). The latter had only responded poorly to neoadjuvant chemoradiation and oesophagectomy was intended six weeks later. Endoscopic stent insertion was carried out

to ameliorate severe dysphagia and 16 days later, perforation of the stent through the oesophageal wall occurred. As he was suffering from an adenocarcinoma of the distal oesophagus, a single stage emergency salvage oesophagectomy was carried out as an abdominothoracic *en bloc* oesophagectomy with gastric pull-up and intrathoracic stapled anastomosis above the level of the tracheal carina. In contrast, cervical anastomosis was preferred in the two other patients, who were suffering from a squamous cell carcinoma of the middle part of the oesophagus.

Postoperative course and perioperative morbidity

The postoperative course was severely overshadowed by the devastating effects of oesophageal rupture. In particular, the salvage group was affected by a high rate of pulmonary complications. Pneumonia occurred in 12 of the 13 patients. Pneumonia was defined as infectious inflammatory affection of the lung with one or more of the following conditions: putrid sputum, bronchoscopy with putrid bronchial secretion, positive microbiological culture and presence of typical radiographic signs of pneumonia.

Compared with the elective cases, the odds of developing pneumonia were 24 times higher (12/13 vs 117/356, OR: 24.33, 95% CI: 3.52–1,046.65, $p < 0.0001$). Furthermore, pleural empyema was significantly more frequent in the emergency group (6/13 vs 35/356, OR: 7.78, 95% CI: 2.04–28.77, $p = 0.001$). Respiratory failure caused prolonged postoperative mechanical ventilation in eight patients. Eventually, five of them required a tracheostomy to wean off ventilatory support. The tracheostomy rate was also significantly higher for the emergency patients (5/13 vs 42/356, OR: 4.64, 95% CI: 1.14–16.98, $p = 0.016$).

Despite all treatment efforts, perioperative sepsis occurred in seven cases. The odds for developing perioperative sepsis were more than four times higher than for the elective cases (OR: 4.42, 95% CI: 1.23–16.45, $p = 0.01$). In addition, emergency patients also had significantly higher chances of sustaining septic acute renal failure (5/13 vs 31/356, OR: 6.49, 95% CI: 1.57–24.15, $p = 0.005$). Acute renal failure was defined as acute impairment of the kidney function requiring haemofiltration or haemodialysis. A postoperative chyle leak with consecutive chylothorax was observed in one case. It was managed successfully by conservative means.

Reoperation was mandatory in seven cases. Three patients underwent video assisted thoracoscopic surgery (VATS) of the right chest for pleural empyema whereas rethoracotomy was unavoidable in one patient owing to advanced pleural empyema. Cervical re-exploration because of cervical anastomotic leakage was carried out in three cases. It is noteworthy that leakage of the cervical anastomosis occurred in both patients with a single stage emergency salvage oesophagectomy and immediate cervical anastomosis. However, in both cases, the leak was managed successfully by reopening the cervical wound.

Perioperative mortality

Compared with the results of elective oesophagectomy, perioperative mortality was significantly higher in the emergency group. Overall, four cases of fatal outcome

were observed (OR: 3.59, 95% CI: 0.77–13.64, $p = 0.05$). As mentioned above, one patient died from intraoperative fatal haemorrhage caused by stent related aortic erosion. Following the first stage (transthoracic oesophagectomy with oesophageal discontinuity), one patient died from persistent sepsis with septic multiorgan failure despite all treatment efforts.

Furthermore, two patients died after reversing oesophageal discontinuity. One of them sustained postoperative pneumonia and, eventually, pulmonary sepsis with fatal multiorgan failure. No surgical complications were found in this case. Cervical anastomotic leakage following the second step of staged emergency oesophagectomy was responsible for the fourth case of fatal outcome. The neck wound was reopened and drained. However, the patient's condition did not improve and computed tomography revealed that the leakage had spilled into the right pleural cavity via the superior thoracic aperture, causing massive pleural empyema. Despite VATS pleural debridement, he died from persistent septic disease.

Long-term survival

A total of nine patients finally recovered well and were discharged to rehabilitation facilities that specialised in oncological and pulmonary disorders. It is noteworthy that all three patients undergoing a single stage emergency oesophagectomy with immediate reconstruction survived despite the occurrence of cervical anastomotic leakage in two of them. Following rehabilitation, they were able to go back to their normal life.

In contrast, only six of the patients with a staged procedure eventually recuperated. Recovery took much longer in these cases. Between the two stages of the procedure, some patients were admitted to nursing homes because of general weakness and problems with enteral nutrition via the inserted jejunal feeding tube. Others stayed at home but required professional assistance. After reversing oesophageal discontinuity, all six survivors were transferred to rehabilitation facilities where they stayed for at least six weeks. Subsequently, they were able to go back to their normal life and were followed up on a regular basis.

The mean survival of the nine patients who made it through the perioperative period was 25.1 months (range: 5–46 months). The two-year survival rate for the whole study population was 38.5% (5/13). If we only consider the nine initial survivors, the two-year survival rate reached 55% (5/9) and the three-year survival rate was still 22% (2/9). The two longest survival periods observed were 44 and 46 months.

Discussion

Salvage oesophagectomy is generally considered to be a procedure not to be embarked on lightly.¹ It is a rare treatment option for those patients in whom definitive chemoradiotherapy has failed. Only a carefully selected subset of patients with non-metastatic (M0) either persistent or recurrent locoregional oesophageal cancer is eligible to undergo salvage oesophagectomy.^{2,3} The procedure is highly demanding

technically. Excessive scar tissue in the mediastinum caused by external beam radiation in combination with an often locally advanced carcinoma result in an utmost challenging situation. Nevertheless, salvage oesophagectomy is frequently the only available treatment option with curative intent.⁶

During the last decade, several case series have addressed the role of salvage oesophagectomy. These studies have shown that long-term survival with five-year survival rates of approximately 30% is achievable.^{2,5,6,12} It has, however, also been established that the procedure is associated with considerable morbidity and mortality. Postoperative mortality rates between 10% and 25% have been reported even by centres experienced in oesophageal surgery.⁴⁻⁷ Furthermore, pneumonia, respiratory complications in general and sepsis have been identified as negative factors that considerably impair the postoperative course and the overall outcome.¹⁵

There has as yet been no in-depth analysis on emergency salvage oesophagectomy in patients sustaining oesophageal perforation after chemoradiotherapy. Non-operative treatment is often preferred for managing oesophageal rupture. In particular, endoscopic oesophageal stenting using self-expandable covered metal stents has gained widespread acceptance as the primary treatment approach for benign as well as malignant oesophageal perforation.¹⁴ However, this is not longer a valid option if an endoscopic stent itself has perforated through the oesophageal wall. In our series, 10 out of 15 oesophageal disruptions were caused by stent related perforation.

The damage caused by stent related oesophageal rupture is normally not reversible by implantation of a new or larger stent. In our experience, even stent-in-stent placement with two self-expandable metal stents attempting to bridge the extensive defect of the oesophageal wall offers no realistic alternative in this situation.

The same is true for oesophageal perforation occurring during PEG implantation. The devastating rupture of the oesophagus caused by pulling down a PEG tube through a malignant stenosis cannot usually be managed by endoscopic means. Moreover, limited surgical interventions such as oesophageal repair or surgical drainage are not valid alternatives either. These methods play no role in the management of malign perforations as they fail to control the underlying disease. More aggressive treatment has therefore been advocated.^{15,16} Oesophagectomy has the advantage of eliminating the oesophageal rupture, the source of sepsis and the underlying oesophageal carcinoma.¹⁵ It is the only available treatment given with curative intent.

Transthoracic oesophagectomy with oesophageal discontinuity and delayed reconstruction is an established procedure to save patients with massive oesophageal disruption. Centres experienced in oesophageal surgery have achieved good results with this approach.^{15,16} For this reason, we opted for transthoracic oesophagectomy with oesophageal discontinuity as the primary treatment option for patients suffering from oesophageal disruption after chemoradiotherapy. Further benefits of the procedure include the possibility of washing out the pleural cavity and the avoidance of a risky oesophageal anastomosis. We performed a total

of ten emergency oesophagectomies with oesophageal discontinuity and were able to save eight patients this way.

Conversely, the downside of this approach is that a second stage is unavoidable for reversing oesophageal discontinuity. In our experience, all patients surviving the first stage push for reconstruction as early as possible. In addition, thoracotomy might further impair the pulmonary function of patients who are already affected by pneumonia and respiratory insufficiency. However, we feel that the benefits of the procedure offset the disadvantages.

Reversing oesophageal discontinuity is associated with substantial morbidity and mortality.^{17,18} Delayed reconstruction with either gastric or colonic interposition should not be regarded as a simple manoeuvre. It is therefore not exceptional that we observed two more cases of fatal outcome following the second stage. Pneumonia, which was responsible for one of the deaths, is a major factor for adverse outcome following emergency oesophagectomy.⁷ Given that our patients suffered from a malignant primary disease, had a considerable burden of pre-existing co-morbidity, had received chemoradiotherapy and had also sustained life threatening oesophageal disruption, our results are more than acceptable. If we bear in mind that one patient died from stent related aortic erosion, we were able to save six out of nine patients despite a substantial rate of perioperative sepsis and multiorgan failure. Medical complications caused a fatal outcome in two cases and only one patient died from a surgical complication.

Furthermore, our experience suggests that single stage emergency salvage oesophagectomy is also a viable option for selected cases. Our three patients had either not yet completed definitive chemoradiotherapy or had received neoadjuvant therapy. Consequently, the radiation dose did not exceed 50.4Gy. Moreover, these patients had a superior performance status compared with the remaining study population. Although anastomotic leakage occurred, it was managed by cervical wound opening and all three patients recovered well. The amount of radiation administered initially has a crucial influence on the result of salvage oesophagectomy. Previous studies have shown that a radiation dose not exceeding 55Gy is associated with improved short and long-term outcomes.⁷ Emergency oesophagectomy with immediate anastomosis might be a practicable solution for these patients. We therefore feel that individual strategies should be developed on a case-by-case basis and that this should be preferred to a general recommendation for staged procedures.

Despite the most unfavourable preconditions, the median survival was 25.1 months. Two years after oesophageal perforation had occurred, five patients were still alive. The results of patients who overcame septic disease caused by oesophageal rupture were only slightly inferior to the outcome of patients with an elective salvage oesophagectomy. As a result, it seems justified to assume that emergency oesophagectomy offers the possibility of curative therapy.

Study limitations

Our study has some limitations. First, it was a retrospective analysis and the study population was small. However,

neither a prospective study nor a larger series are to be expected any time soon. Salvage oesophagectomy is a very rare event, even at high volume centres for oesophageal surgery, and salvage oesophagectomy under emergency conditions is only performed in isolated cases. There is therefore no realistic chance of a prospective study with larger numbers. Unfortunately, no objective facts or data regarding health related quality of life had been recorded for our study. Furthermore, no reliable information was available on weight loss, dysphagia, swallowing or ability to eat and drink.

Conclusions

Emergency oesophagectomy for oesophageal perforation following chemoradiotherapy for oesophageal cancer is not only justified but also life saving. The results of our study hint that even long-term survival is achievable in selected patients with non-metastatic, locoregional cancer who are able to overcome the severe septic complications associated with oesophageal rupture. Consequently, salvage oesophagectomy under emergency conditions should be considered in reasonable cases and inoperability should not be confirmed until an experienced oesophageal surgeon has assessed the patient.

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