

Chapter 2

Cervical or thoracic anastomosis after
esophagectomy for cancer:
a systematic review and meta-analysis

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ABSTRACT

Background

Cervical anastomosis and thoracic anastomosis are used for gastric tube reconstruction after esophagectomy for cancer. This systematic review was conducted in order to identify randomized trials that compare cervical with thoracic anastomosis.

Methods

A literature search for randomized trials was performed in the databases: Medline, Embase, and Cochrane Library.

Results

A total of 4 trials were included. All studies had a small sample size and were of moderate quality. One trial was excluded from the meta-analysis. The following outcomes were significantly associated with a cervical anastomosis: recurrent laryngeal nerve trauma (Odds Ratio (OR) 7.14 (95% confidence interval (c.i.) 1.75-29.14); $p=0.006$) and anastomotic leakage (OR 3.43 (95% c.i. 1.09-10.78); $p=0.03$). None of the following outcomes were associated with the location of the anastomosis: pulmonary complications (OR 0.86 (95% c.i. 0.13-5.59); $p=0.87$), peri-operative mortality (OR 1.24 (95% c.i. 0.35-4.41); $p=0.74$), benign stricture formation (OR 0.79 (95% c.i. 0.17-3.87); $p=0.79$) and tumor recurrence (OR 2.01 (95% c.i. 0.68-5.91); $p=0.21$).

Conclusion

Cervical anastomosis could be associated with a higher leak rate and recurrent nerve trauma. However, the currently available randomized evidence is limited. Further randomized trials are needed to provide sufficient evidence for the preferred location of the anastomosis after esophagectomy.

INTRODUCTION

In the 1940s a 72% peri-operative mortality was associated for esophagectomy for esophageal cancer¹. In order to reduce this mortality 1946 Ivor Lewis introduced a standardized approach to esophageal resection for carcinoma of the middle third of the esophagus². This approach involved a two-stage procedure that included a laparotomy and 1 to 2 weeks later a thoracotomy with thoracic anastomosis. Risks of anastomotic leakage in the thorax with fatal consequences resulted in a three-stage approach with a cervical anastomosis³. In case of a leakage a cervical fistula is a manageable complication⁴. However, an increased incidence of leakage and stricture formation could be associated with a cervical anastomosis.

Nowadays both thoracic anastomosis and cervical anastomosis are used worldwide for gastric tube reconstruction after esophagectomy. Advocates of the cervical anastomosis favor this location despite the possible increased incidence of leakage, benign stricture formation and damage to recurrent laryngeal nerve because of better tumor eradication and reduced mortality and morbidity associated with anastomotic breakdown. Several randomized controlled trials (RCTs) have been published in which cervical anastomosis are compared with thoracic anastomosis. To date no systematic review and meta-analysis of literature has been performed in order to identify the randomized trials performed in the past and to designate the appropriate anastomotic approach after esophagectomy. This systematic review was conducted in order to identify randomized trials that compare cervical with thoracic anastomosis after esophagectomy for carcinoma. A critically appraisal was performed and short- and long-term outcome were assessed.

METHODS

Literature search

The following electronic databases were used for a literature search: Medline (1950 to March 2010), Embase (1947 to March 2010), and the Cochrane Library (2010 issue 1). A comprehensive search was performed using the following search terms: esophageal cancer, cervical, thoracic, anastomosis. Logical combinations of these and related terms (e.g. esophagus, carcinoma, intrathoracic) were used to maximize sensitivity. Furthermore, a truncation symbol was used in each database in order to allow retrieval of all suffix variations of a root word (e.g. anastomos*).

A manual cross-reference search of the bibliographies of relevant articles was conducted to identify studies not found through the computerized search. The “related articles” feature of Pubmed was also used. Two reviewers executed the search independently (SSAYB and KWM).

Study selection criteria

After identifying relevant titles, the abstracts of these studies were read to decide if the study was eligible. The full article was retrieved when the information in the title and/ or abstract appeared to meet the objective of this review. All published randomized trials comparing cervical with thoracic anastomosis after esophagectomy for cancer were included. There were no restrictions with regard to the language of the published study.

Quality assessment of retrieved articles

The two reviewers appraised each included article independently, assessing the methodological quality of the selected studies. A modified critical review checklist of the Dutch Cochrane Centre was used to appraise RCTs [www.cochrane.nl. Last accessed November 2009]. The following items of the checklist are negative for all surgical studies and were therefore not included for further appraisal (items: 1. Patient blinded? 2. Care provider blinded?).

Data extraction and analysis

Data was extracted on preformatted sheets. Two reviewers also performed this independently. The studies were tabulated and methodologically evaluated to assess homogeneity. In the case of heterogeneity between the studies, it would not be justified to pool the assessed outcomes.

The following outcome parameters were assessed: pulmonary complications, anastomotic leakage, mortality, recurrent nerve trauma, positive resection margin (R1), length of hospital stay, stricture of anastomosis, tumor recurrence, pre-defined quality of life assessment.

Statistical analysis

Meta-analyses were performed for outcome parameters when possible. Quantitative data for the primary outcome parameters were entered into the software Cochrane Review Manager (RevMan) version 4.3 and analyzed using RevMan Analyses 1.0.5 (Cochrane Collaboration, Oxford, UK).

Summary estimates, including 95% confidence intervals, were calculated. For continuous outcome data (e.g. length of hospital stay) means and standard deviations were used to calculate a weighted mean difference in the meta-analysis. For dichotomous outcomes (e.g. mortality) the odds ratio (OR) was calculated with corresponding confidence interval (c.i.).

Statistical heterogeneity was tested using X^2 and I^2 tests. Data were pooled using the random effect model, because moderate heterogeneity was suspected (e.g. stapler devices).

RESULTS

The initial search yielded 224 potential literature citations (figure 1). Of these, 218 were excluded after scanning the title. Of the six studies considered potentially relevant, 2 were excluded. One study was excluded which compared manual anastomosis with mechanical anastomosis⁵. Another study was identified as a duplicate report in a non-English language journal⁶. A total of 4 randomized trials were included for the systematic review (table 1)⁷⁻¹⁰. These studies involved 267 patients, of which 132 patients randomized for a cervical anastomosis and 135 patients had a thoracic anastomosis (Table 1).

Figure 1. Identification of eligible randomized controlled trials.

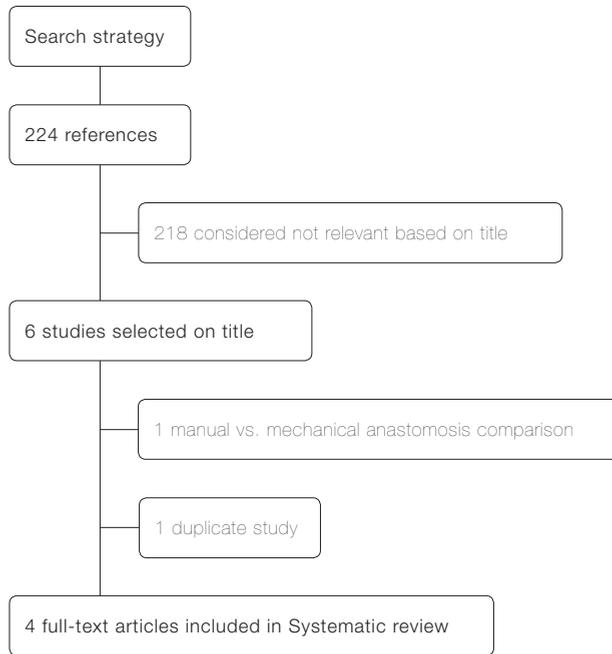


Table 1. Characteristics of the included randomized trials. * Seven patients in the cervical group had a hand-sewn anastomosis.

Reference	Year	Journal	Single center or multi-center trial	Surgical approach	Type of anastomosis		Number of patients included	
					Cervical group	Thoracic group	Cervical group	Thoracic group
Chasseray et al. ¹⁰	1989	Surgery, Gynaecology and Obstetrics	Single center	Transthoracic	Stapled*	Stapled	43	49
Ribet et al. ⁸	1992	Journal of Thoracic and Cardiovascular Surgery	Single center	Transthoracic	Hand-Sewn	Stapled	30	30
Walther et al. ⁷	2003	Annals of Surgery	Single center	Transthoracic	Hand-Sewn	Stapled	41	42
Okuyama et al. ⁹	2007	Surgery Today	Single center	Transthoracic	Hand-Sewn	Stapled	18	14

Quality assessment

The quality assessment of the included studies is shown in table 2. Chasseray et al. excluded 31 patients because a transhiatal approach was subsequently chosen for some patients, there was a nonresectable tumor or because the surgeon did not want to place the gastric tube in the posterior mediastinum¹⁰. Furthermore, concealment of allocation was not reported in this study. In the cervical group 8 patients had a retrosternal positioning of the gastric tube, in 35 patients the gastric tube was placed in the posterior mediastinum. Importantly only 7 of 43 patients in the cervical anastomosis group had a hand-sewn anastomosis.

Ribet et al. excluded 2 patients in the thoracic anastomosis group because a thoracic anastomosis could not be made⁸. These patients were excluded from the analysis; therefore no intention to treat analysis was performed.

Table 2. Methodological quality of the included randomized trials.

Reference	Excluded patients	Treatment allocation concealed?	Eligibility criteria specified?	Groups similar at baseline?	Follow-up?	Intention to treat?	Similar non-trial treatment?
Chasseray et al. ¹⁰	31	Not stated	Yes	Yes	Yes	Yes	Yes
Ribet et al. ⁸	2	Yes	Yes	Yes	Yes	No	Yes
Walther et al. ⁷	47	Yes	Yes	Yes	Yes	Yes	Yes
Okuyama et al. ⁹	Not stated	Yes	Yes	Yes	Yes	Yes	Yes

Walther et al. excluded 47 patients, 17 patients had a nonresectable tumor, of which 3 underwent a bypass procedure⁷. Another 8 patients had tumor located high in the esophagus, 8 patients had a jejunal or colon interposition, 6 patients refused participation, 4 had an palliative resection, 2 patients had a redo esophagectomy and 1 patients was operated in another hospital. The results of the last 29 excluded patients were reported separately in this study. Patients with benign disease were also randomized and analysed (2 patients in the cervical group and 7 patients in the thoracic group). Okuyama et al. did report the exclusion of patients. Eligibility was however described in this study⁹.

Overall, the quality of the included studies is moderate. Chasseray et al. only performed a hand-sewn cervical anastomosis in 7 of the 43 patients; this study was therefore excluded from the meta-analysis. The outcome parameters are depicted in table 3. The meta-analyses are shown in table 4.

Table 3. Outcome parameters.

Reference	Pulmonary complications		Anastomosis Leakage		Mortality		Positive resection margin	
	Cervical group	Thoracic group	Cervical group	Thoracic group	Cervical group	Thoracic group	Cervical group	Thoracic group
Chasseray et al.10	7 (16%)	15 (29%)	11 (26%)	2 (4%)	4 (9%)	7 (14%)	1 (2%)	1 (2%)
Ribet et al.8	21 (70%)	11 (37%)	9 (30%)	3 (10%)	5 (17%)	4 (13%)	3 (10%)	10 (33%)
Walther et al.7	2 (5%)	4 (10%)	1 (2%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)
Okuyama et al.9	2 (11%)	5 (36%)	3 (17%)	1 (7%)	0 (0%)	0 (0%)	Not stated	Not stated

Table 3. Continued.

Reference	Recurrent nerve trauma		Hospital stay (days)		Stricture of anastomosis		Tumor recurrence		Quality of Life assessment	
	Cervical group	Thoracic group	Cervical group	Thoracic group	Cervical group	Thoracic group	Cervical group	Thoracic group	Cervical group	Thoracic group
Chasseray et al.10	Not stated	Not stated	19.5 (3-71)*	18 (2-122)*	10 (23%)	7 (14%)	0 (0%)	0 (0%)	Not assessed	Not assessed
Ribet et al.8	6 (20%)	1 (3%)	24.2 [¶]	16.6 [¶]	4 (13%)	1 (3%)	9 (60%) [†]	5 (36%) [†]	Not assessed	Not assessed
Walther et al.7	1 (2%)	0 (0%)	14 (6-68)*	14 (0-83)*	8 (20%)	12 (29%)	1 (2%)	1 (2%)	Not assessed	Not assessed
Okuyama et al.9	8 (39%)	1 (7%)	Not stated	Not stated	0 (0%)	2 (14%)	4 (22%)	2 (14%)	No significant difference	No significant difference

* reported in median; ¶ reported in mean, no standard of mean was reported; † follow-up data only known for 29 patients

Table 4. Meta-analysis of outcome parameters.

	Pulmonary complications		Anastomotic leakage		Mortality		Recurrent nerve trauma	
	Odds Ratio (95% confidence interval)	P						
Meta-analysis	0.86 (0.13-5.59)	0.87	3.43 (1.09-10.78)	0.03	1.24 (0.35-4.41)	0.74	7.14 (1.75-29.14)	0.006

Table 4. Continued. Meta-analysis of outcome parameters

	Stricture of anastomosis		Tumor recurrence	
	Odds Ratio (95% confidence interval)	P	Odds Ratio (95% confidence interval)	P
Meta-analysis	0.79 (0.17-3.87)	0.79	2.01 (0.68-5.91)	0.21

Outcome parameters

Pulmonary complications

The location of the anastomosis did not influence the incidence of pulmonary complications defined as pulmonary infection (OR 0.86 (95% c.i. 0.13-5.59); $p=0.87$). Chasseray et al. reported a 16% ($n=7$) incidence of respiratory complications in the cervical group. In the thoracic anastomosis group the incidence was 29% ($n=15$). This difference in incidence did not reach a statistical significance.

Anastomosis leakage

A significant difference in incidence of anastomotic leakage is seen when comparing cervical anastomosis with thoracic anastomosis (OR 3.43 (95% c.i. 1.09-10.78); $p=0.03$). Chasseray et al. reported significant more anastomotic leaks in the cervical group (26% vs. 4%; $p<0.02$).

Mortality

Situation of a cervical anastomosis was not associated with a lower mortality (OR 1.24 (95% c.i. 0.35-4.41); $p=0.74$). Okuyama et al. did not observe any peri-operative mortality. Chasseray et al. reported no significant difference in mortality between cervical and thoracic anastomosis groups (9% ($n=4$) vs. 14% ($n=7$)).

Positive resection margin

Only 2 of 3 RCTs eligible for the meta-analysis investigated the resection margins. One study did not observe any positive resection margin and the other study observed more positive margins in the thoracic group (10% (n=3) vs. 33% (n=10)). Okuyama et al. did not report the status of the resection margin. Chasseray et al. reported 1 positive resection margin in each anastomotic group.

Recurrent nerve trauma

A cervical anastomosis was associated with significant more recurrent nerve trauma (OR 7.14 (95% c.i. 1.75-29.14); p=0.006). Chasseray et al. did not report on recurrent nerve trauma in their RCT.

Hospital stay

Two of the 3 RCTs eligible for the meta-analysis reported length of hospital stay. Ribet et al. calculated a mean hospital stay of 24.2 days for the cervical anastomosis and 16.6 days for thoracic anastomosis. Walther et al. calculated median hospital stay which was not significant different between the two groups (14 vs. 14 days).

Benign stricture of anastomosis requiring dilatation

A cervical anastomosis was not associated with a significant higher incidence of stricture of the anastomosis requiring dilatation (OR 0.79 (95% c.i. 0.17-3.87); p=0.79). Chasseray et al. observed no significant difference between the cervical group compared with the thoracic group (23% (n=10) vs. 14% (n=7)).

Tumor recurrence

The location of the anastomosis did not significantly influence the incidence of tumor recurrence (OR 2.01 (95% c.i. 0.68-5.91); p=0.21).

Quality of life

Only Okuyama et al. investigated the quality of life at 6 months after surgery. They assessed heartburn, regurgitation, stenotic sense, abdominal fullness, cough and wound pain. There was no significant difference between the cervical and thoracic anastomosis groups.

DISCUSSION

This systematic review aimed to compare cervical anastomosis with thoracic anastomosis after esophageal resection for cancer. Four randomized trials were identified of which 3 were eligible for the meta-analysis. The small sample sizes and moderate quality of the included studies brings limitations for the meta-analysis. A cervical anastomosis was associated with significant more recurrent nerve trauma, anastomosis leakage. No significant difference was observed in pulmonary complications, peri-operative mortality, benign strictures of the anastomosis requiring dilatation and tumor recurrence. There is insufficient data in this meta-analysis to report about the involvement of the resection margin, hospital stay and the quality of life after a cervical or thoracic anastomosis.

The traditional perception is that a thoracic anastomosis is associated with less frequent leaks, but if occurring have fatal consequences for the patient¹¹. Although the confidence interval of this meta-analysis almost reaches 1, a significant higher incidence of anastomotic leaks is seen when comparing cervical with thoracic anastomosis after esophagectomy. The location of the anastomosis could be a risk factor for leakage. However, cervical anastomoses could suffer more from ischemia of the gastric conduit than thoracic anastomoses¹³. Other possible factors that could contribute to leakage could be of technical nature, related to gastric drainage or low institution and surgeon volume^{14,15}. Walther and coworkers performed a well designed single center randomized trial analysing both included patients and excluded patients⁷. No significant difference in leak rate was identified between the groups. Furthermore, the higher leak rate for cervical anastomoses are generally more accepted because of the lower risk for the patient.

The significant higher leak rate for cervical anastomosis did not result in a significant higher mortality in the meta-analysis. An improved peri-operative care could account for the absence of the direct relationship between anastomosis leakage and mortality in this analysis^{16,17}. Okuyuma and coworkers did not even observe any mortality in their trial⁹. Most surgical groups in the world use a handsewn technique for cervical anastomosis and a mechanical technique for thoracic anastomosis. There seems to be no direct relationship with regard to the influence of the applied technique to outcome¹⁸. However, in order to minimize potential bias only studies comparing handsewn cervical which compared with mechanical anastomosis were included in this systematic review.

A higher incidence of recurrent laryngeal nerve trauma is associated with cervical anastomosis in this meta-analysis. A narrow anatomical relationship exists between the recurrent nerve and the esophagus at cervical level. Careful dissection and active identification of the recurrent nerve could minimize trauma to the nerve^{19,20}. Furthermore, an under-appreciation of recurrent nerve trauma exists in literature, because not all patients with this trauma have symptoms of hoarseness and inter-observer variation exists in diagnosis¹⁹. None of the included trials indicated if a standard laryngoscopy or laryngoscopy on indication was performed postoperatively for recurrent nerve trauma. In literature, recurrent nerve trauma is associated with pulmonary complications. This is thought to be caused mainly by aspiration^{19,21}. In this meta-analysis no significant difference in pulmonary complications is seen when comparing cervical anastomosis with thoracic anastomosis. Other factors could be of more influence in the incidence of pulmonary complications, e.g. adequate post-operative analgesics and physiotherapy.

Only 2 studies eligible for the meta-analysis reported on the involvement of the resection margin^{7,8}. Walther and coworkers did not observe any involvement of the resection margins in both cervical and thoracic anastomosis groups⁷. Ribet and coworkers observed more positive resection margins in the thoracic group. Adequate pre-operative and per-operative assessment probably improves the low incidence of involved resection margins^{22,23}. These assessments also influence the tumor recurrence. No significant difference in tumor recurrence was seen in the meta-analysis. It is therefore probable that the involvement of the resection is comparable between the cervical and the thoracic anastomosis groups.

There are some reports that associate stricture formation with the use of stapler devices^{24,25}. There is also evidence that anastomotic stricture is associated with anastomotic leakage^{25,26}. Although there is a significant higher incidence of anastomosis leakage with cervical anastomosis, benign stricture formation requiring dilatation is not associated with the location of the anastomosis in this meta-analysis. Other factors such as reflux could have more impact on stricture formation. The possible role of proton pump inhibitors (PPIs) in reducing reflux and therefore benign stricture formation has recently been investigated in a RCT²⁷. A lower prevalence of benign stricture formation was observed in the group using PPIs.

The present systematic review has several limitations. There were only 4 RCTs selected for inclusion. These included studies were performed with a relative small sample size. Only three trials were included for the meta-analysis as Chasseray et al. used a stapled anastomosis in the cervical group. Two of these 3 trials were performed in the last 2 decades^{7,9}. The other trial was conducted from 1983 to 1986.⁸ Changes in techniques and peri-operative care can influence outcome. A bias due to change patterns of care, surgical techniques and improved suture devices could be present in this meta-analysis. RCTs from different time periods and continents could include some degree of heterogeneity in clinical approach. To address this issue a random-effect model was used to meta-analyse the data. Furthermore, one should be aware that wide confidence intervals for some comparisons do not completely rule out the possibility of big increases in risk, or big decreases in risk. With regard to exclusion of patients, Chasseray et al. excluded 31 patients for debatable reasons. Okuyama et al. did not even report the exclusion of patients. A selection bias could be possible in these studies. Also, surgical and/ or hospital is well known to influence outcome. None of the included trials reported their yearly volume. Several of the aforementioned limitations of the trials have been recently addressed in literature²⁸.

This systematic review shows that there are only 4 single center randomized trials available in literature with small sample sizes and moderate quality. In the meta-analysis of 3 trials no difference in pulmonary complications, peri-operative mortality, benign stricture formation and tumor recurrence after esophagectomy with a cervical or thoracic anastomosis for esophageal cancer is seen. A cervical anastomosis could however be associated with a higher incidence of recurrent laryngeal nerve trauma and anastomotic leakage. Further randomized trials in current clinical settings are needed to provide sufficient evidence for the preferred location of the anastomosis after esophagectomy for esophageal cancer. New anastomosis techniques could also be of interest for future randomized trials²⁹.

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