Post-esophagectomy anastomotic leaks
The role of the anastomotic location

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OBJECTIVE: *Esophageal anastomotic leaks are associated with significant morbidity and mortality. The purpose of this study was to retrospectively assess the role of the anastomotic positioning (thoracic or cervical) on the incindence of the anastomotic leak and its severity.*
METHODS: *In the period 2002-07, we have performed extended esophagectomy with a curative-intent in 63 patients with esophageal cancer. The clinical outcome of the 46 patients where a cervical anastomosis was performed (Group A) has been compared with that of the 17 with thoracic anastomosis (Group B), in terms of leak incidence, pattern of healing, morbidity, and mortality.*
RESULTS: *Leaks occurred in 11% patients of the in group A and in 8% of the group B. When the dehiscence has occurred in the cervical region 1/4th of patients died before the 30th post-operative day compared to the 3/5th of those where the leak occurred at the level of the thorax.*
CONCLUSIONS: *On the basis of our findings we suggest the adopt the cervical anastomosis due to lower mortality rate related when leaks occur.*

KEY WORDS: Post-esophagectomy anastomotic leaks

Introduction

Despite vast advancements in surgical technique (including the peri-operative management and the oncological care), esophagectomy maintains a relatively high mortality and peri-operative morbidity rates, respectively 8-11% and 40-50% [1]. About 40% of post-operative deaths is related to anastomotic leak [2], regardless of surgical technique or type of organ used for esophageal reconstruction [3]. However, when the anastomosis is performed in the neck rather than in the chest there is variability in terms of incidence of leaks and related mortality.
The incidence of cervical and thoracic leaks are 10-25% (cervical) vs 3-25% (thoracic), with mortality rate ranging from 10% and 60% respectively [4-7]. Nowadays, the management of the esophageal fistula is still an issu of open discussion and, so far, there is no standard or commonly accepted treatment. In the English literature, some Authors recommend an aggressive surgical treatment, while others prefer a conservative approach by using peri-anastomotic drainage, total parenteral nutrition (TPN), nasogastric decompression of the transposed organ (stomach or colon) and prolonged antibiotic therapies [5,7-9]; the

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management of the esophageal fistulas can also take advantage of an endoscopic approach with the use of self-expandable metal prostheses or endo-clips [10].
The aim of our study was to investigate the impact of the anastomotic leak location on the incidence and severity of leaks.

Methods

In the period between 1/02-12/07, we have performed 63 esophagectomies for cancer (out of 263 surgical procedures involving the esophagus): 46 were performed with a cervical semi-mechanical anastomosis (group A) and 17 with intra-thoracic anastomosis by circular stapler (group B). In the group A, 30 cases were treated with transhiatal esophagectomy (THE) and 16 with the triple access technique. In all cases the alimentary tract was reconstructed through the transposition of a gastric tubule with the exception of 5 cases in which the left colon was used in antiperistaltic way. Pre-operatively, all patients underwent staging by total body CT-scan, EGDS and colonoscopy with biopsies (when colic transposition was expected); in addition, as of 1/05 all patients underwent PET/SCAN to complete the staging and, as of 1/07 EUS was routinely performed in each case.
Patients in which the clinical staging procedure highlòighted a locally advanced disease underwent induction therapy. The tumour status has been therefore re-staged after one month (circa) from the completion of the induction treatment (clinical restaging). Before surgery, the nutritional status and pulmonary and cardiological functionality were comprehensively assessed in all patients. According to the organ used for the reconstruction and the number of wrapped anastomoses, a peri-anastomotic drain was placed in the neck, chest or abdomen in all cases. In the reconstruction phase, the tubularized stomach has been preferentially used with its transposition in the mediastinum (in 5 cases the colon was transposed because of previous Billroth II gastrectomy). After surgery all patients were monitored for at least 24 hours in the intensive care unit. In order to detect subclinical anastomotic leak, in the fourth post-operative day the the anastomosis was checked by oral administration of methylene blue. TPN was administered up to the 7th pod when a barium swallow x-ray test has been performed in all cases; in the absence of any leaks antibiotic therapy was stopped. Data on the leakage rate and related mortality were retrospectively analyzed . We have classified the degree of leakage according to the four stages as defined by Lerut (Table I).
In the case of cervical fistula (group A) the management algorithm provided: GRADE-I: broad-spectrum antibiotic therapy associated with antifungal drugs, TPN, correction of the albumin value (> 3 g / dl), maintenance of the peri-anastomotic drainage and naso-gastric tube until the next (negative) radiological control (after 7 days). This strategy was adopted in all cases of dehiscence as the standard of management for all types of treatments (higher grades). GRADE-II: opening of surgical wound. GRADE-III: chest tube placement and radiological control to clinical resolution. In case of failure: endoscopy with placement of glue, clips or endoscopic self-expandable prosthesis according to the diameter of the fistula. In case of necrosis (GRADE-IV) we performed a surgical bipolar exclusion with jejunostomy and revaluation after 30 days for surgical reconstruction of the para-physiological transit. Regarding the patients with thoracic fistula (group B) we have used a different algorithm depending on the size of the dehiscence at the radiological control and we have defined three groups: i) continent fistula (extravasation of contrast agent in a small area); ii) incontinent fistula (important extravasation of contrast agent) and iii) complete bowel dehiscence. In the case of continent fistula we have placed endoscopic surgical clips, and therefore endoprosthesis in the case of failure of the clips positioning. In the incontinent fistula cases: endoprosthesis and therefore bipolar exclusion in the case of failure and re-evaluation after 30 days for surgical reconstruction of the para-physiological transit. Finally, in the tubule dehiscence we have performed a first step bipolar exclusion and subsequent recosntruction.

TABLE I - *Leak classification according to Lerut*

Grading	Definition
I - Radiological	Subclinical leakage
II - Minor clinical	Wound inflammation or leakage of contrast agent, fever, leukocytosis
III - Major clinical	Sepsis
IV - Necrosis	Necrosis of bowel tubule (endoscopically confirmed)

Statistical analysis

Statistical analysis was performed on the sample of 63 patients by analyzing the following variables: gender, age, co-morbidities, albumin value, cholesterol value, histology, p-stage, surgical approach, organ used for transposition, surgical margin neoplastic infiltration, induction therapy, date of onset and gradind of the leak. We have performed a stratification into two groups according to the site of the anastomosis (cervical and thoracic). The homogeneity between the two groups was done comparing variables using T-tests for continuous variables and Chi-square for categorical variables. Considering 30-day mortality related to the anastomotic leak as the outcome, we made a statistical comparison between the two groups

TABLE II - *Population features*

Esophagectomy for cancer	63	
Mean age	68,5(±11,29)	
Male/Female	41/22	
Squamous cell carcinoma	53%	
Mean Hospital stay	16,6 (±9,84)	
Cervical anastomosis	46 (30 TJ -16 TrA)	(Group A)
Thoracic anastomosis	17	(Group B)
	Group A	Group B
Comorbidities	25/46	6/17
Stage I (12,5%)	6	1
Stage IIa (25%)	15	1
Stage IIb (9,4%)	4	2
Stage III (53,1%)		
Colic Transposition	4	1
Induction therapy	5	5
Overall mortality	12%	10%
Leak	11%	7.3%
Mean survival	35(±19.27)	35(±9.95)

and identified the prognostic factors by using a logistic regression analysis. We also analyzed the long-term survival by using the Kaplan-Meier and Cox regression analysis. Follow-up was performed considering interval from surgery to death or to last contact with the patient. All the associations with p-value <0.05 were considered and, in multivariate analysis, variables with p-value <0.1 were included.

Results

The features of the population are summarized in Table II. The dehiscence rate was 11% in group A and 8% in group B (p Log Rank 0.11 - ns). By univariate analysis, no correlation was found between sex, age, co-morbidities, albumin value, cholesterol value, histology, p-stage, occurrence and leak grading. Male/female ratio was 41/22 and mean age was 68.5 ± 11.29 years. Pre-operative co-morbidities (diabetes, previous myocardial infarction, liver disease, kidney disease, lung disease, chronic atrial fibrillation and moderate dyspnea) was equally distributed in group A (25/46) and B (6/17) (Log Rank p 0.408 - ns). The surgical resection margin was infiltrated in two patients only (one patient in group A and one in group B). At pathological examination 12.5% of patients were in stage I (6 group A and 1 group B), 25% in stage 3 group B). 53.3% of patients had squamous cell carcinoma. Observed mean hospital stay was 27.5 ± 15.29 days with a range of 11 to 60 days. Overall 30-day mortality was 14.5% (6.4% Group A1 vs. 23.5% Group A2 vs. 20% Group B). 41.6% of these patients had anastomotic leak. In group A 24.5% of patients with anastomotic leak died before the 30th p.o.d. whilst this

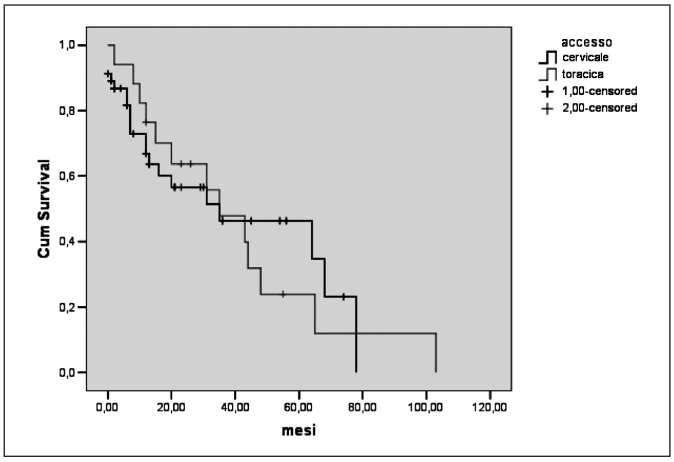

Fig. 1: Survival stratified by anastomotic location.

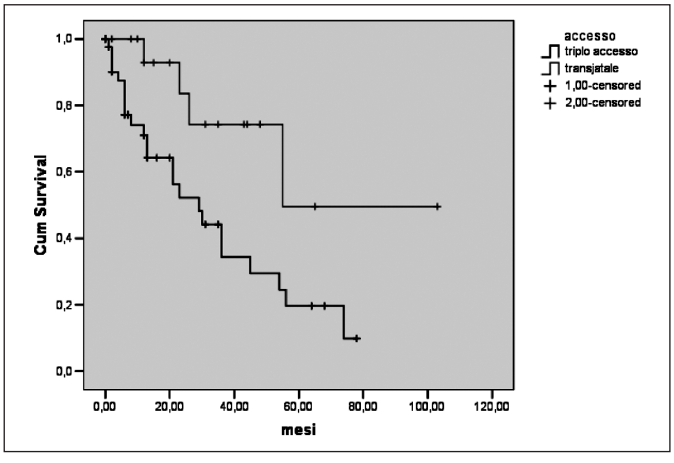

Fig. 2: Survival stratified by surgical approach.

TABLE III - *30 day mortality related to anastomotic leak.*

	N°	Leak	30 day mortality	30 day mortality	(leak)
Cervical anastomosis	46	11%	12%	24%	
Thoracic anastomosis	17	7,3%	10%	60%	
					p<0,001

percentage topped at 60% in group B (Table 3). Only one patient among those who had undergone induction therapy (group A) died at the 30th p.o.d.. The median survival was 35 ± 19.27 months for group A and 35 ± 9.95 months for group B (p Log Rank 0.98 - ns) (Fig. 1). In group A, according to surgical access, patients undergoing transhiatal esophagectomy showed a median survival of 68 ± 54.37 months compared to 20 ± 13.29 months of patients who underwent triple access esophagectomy (Log Rank p 0.01) (Fig. 2): this data is mainly due to selection of patients with mediastinal lymph node involvement.

Discussion

Controversies still exist regarding the best surgical approach in case of esophageal cancer. This is not only determined on the basis of oncological reasons, but to the high rate of post-operative (often fatal) complications too. In the English literature, the incidence rate of the anastomotic leak after esophagectomy is extremely variable and in some centers is as high as 53% [12]. This variability is related to an inverse proportion among volume of surgery of the center and incidence of fatal complications [13,14], the anastomosis site and it does not seem to be related to the type of organ, site adopted for transposition or anastomosis technique. In the case of anastomotic fistula, the surgeon is faced with a complication associated with a mortality rate that can reach as much as 60% [6,7] if no evidence based standardized treatment algorithm is adopted. Good results obtained by multidisciplinary approaches, including early endocscpic procedure, has prompted us and others to put them into the standardised treatment algorithms [10,15,16].
Worth to be noted is the fact that the thoracic leak anastomosis stays as an independent prognostic factor that correlates significantly with the risk of death [12]. Cervical leak appears to have a higher incidence than the chest leak but mortality rate due to cervical fistula is significantly lower than that localized in the chest, as also reported by recent multi-disciplinary protocols [17].

Conclusion

According to the results reported in our experience and that of other Authros, we recommend to perform a transhiatal esophagectomy with a cervical anastomosis since cervical fistula is more easily treated conservatively, with good results of the early endcoscopic approaches. As well, it is subject to a lower mortality rate within the 30th p.od.

Riassunto

La fistola anastomotica dopo esofagectomia è associata ad un alto tasso di morbilità e mortalità. Scopo di questo studio è stato quello di misurare l'effetto della sede dell'anastomosi (toracica o cervicale) sull'incidenza e severità della deiscenza.
Tra il 2002 ed il 2007 abbiamo eseguito 63 esofagectomie per cancro. I dati relativi a 46 esofagectomie con anastomosi cervicale (Gruppo A) e 17 con anastomosi toracica (Gruppo B) sono stati analizzati confrontando il tasso di deiscenza, morbilità e mortalità ad essa correlata.
Il tasso di deiscenza osservato è stato del 11.1% nel gruppo A e 7,93% nel gruppo B. Quando la deiscenza si è verificata al collo il 24.5% dei pazienti è deceduto entro la trentesima giornata post-operatoria, contro il 60% dei pazienti con deiscenza dell'anastomosi toracica. Sulla base dei nostri dati consigliamo l'uso dell'esefogectomia con anastomosi cervicale perchè associata ad un accettabile tasso di mortalità correlato alla deiscenza.

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