ERJ Express. Published on June 4, 2010 as doi: 10.1183/09031936.00049809

Combined Airway and Esophageal Stenting in Malignant Airway-Esophageal Fistulas: A Prospective Study

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Conflicts of interest statement: None of the authors have any conflicts of interest to report

Word count: Abstract: 248, Text: 2188

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Key Words: Tracheoesophageal fistula, oesophageal cancer, Lung cancer, self expandable metallic stents, palliative therapy.

Abstract:

Background: Malignant airway-esophageal fistulas are a serious complication of advance esophageal or lung cancers.

Aims: To assess the quality of life pre and post stent insertion and to examine the role of treatment and location of AEF as factors influencing survival in patients with AEF managed with airway and/or esophageal stent insertion

Methods: 112 patients with airway–esophageal fistula were prospectively included. 83 patients (74%) had advanced lung cancer and 29 patients (26%) esophageal cancers.

Results: Airway stents were inserted in 65 patients (58%), esophageal in 37 (33%) patients and both airway and esophageal stents in 10 (9%) patients. 7 patients (6 %) developed respiratory failure and required transient ventilator support in the intensive care unit (4 patients with airway stenting, 2 patients with double and 1 in the esophageal stenting group). None of the patients developed stent migration or needed stent repositioning. Overall, mean survival was 236.6 days (airway stent 219.1 days, esophageal stent 262.8 days and combined airway-esophageal stent 252.9 days). Backward stepwise regression revealed the site of stent placement (airway and/or esophagus) ($p < 0.028$), exact location of fistula in airway ($p= 0.011$) and additional treatment with chemotherapy and/or radiation ($p < 0.001$) as independent risk factors predicting increased survival. The mean quality of life score (EQL-30 (QOL) was 81 prior to stent insertion and 72 post stent insertion ($p < 0.001$).

Conclusion: To conclude, airway and/or esophageal stent insertion provides an effective approach to improve the quality of life in patients with malignant AEF.

INTRODUCTION:

Malignant airway esophageal fistulas (AEF) are a complication of primary tumor growth or recurrence in esophageal and lung carcinomas resulting in a persistent communication between the airways and the upper esophageal tract. AEF may also occur secondary to radiation or chemotherapy resulting in tumor dehiscence. This leads to frequent aspiration with contamination of the airways and poor nutrition. Mortality is a common complication and the mean survival time ranges between 1 and 6 weeks with supportive management alone.[1] Patients with underlying thoracic tumors presenting with symptoms of recent onset of coughing after feeding should raise a high index of suspicion for AEF. A diagnosis is often made using radiological tools such as barium/gastrograffin esophagography or CT scan. Bronchoscopy and esophagogastroduoedenoscopy (EGD) will help in localizing the fistula, extent of tumor infiltration and size of the defect.

Treatments of these fistulas are difficult considering that most of these patients have an inoperable tumor at the time of diagnosis. Therefore supportive and palliative treatment forms the basis of improving the quality of life (QOL). Direct surgical fistula closure, bypass or fistula resection do not yield good results and endoscopic stenting or endoprosthesis are palliative options in this situation.[1] Stents can be placed bronchosocpically in the airways, via EGD in the esophagus or both in the airways and esophagus.to seal the defect and thereby restoring the patency of the passages with resumption of oral feeds. [2-5]

Plastic and silicone cuffed stents were initially used in the management of AEF. [6,7] With the use of self expandable metallic stents (SEMS) there is an increase in the quality of

life in patients with inoperable esophageal and lung tumors. [8-10] A recent study has reported improvement of symptoms in 90% of patients with AEF treated with insertion of esophageal SEMS [11]. The success rate for closure of AEF using endoscopic methods varies from 87– 91% [11-13].

Data are sparse regarding the benefits of airway or esophageal stent insertion in the management of malignant AEF. In the endoscopic management of AEF, whether single stent placement in either of the passages is better compared to double stent placement is not clear. This prospective study was performed to assess the role of self expandable nitinol airway and/or esophageal stents in AEF, evaluate the pre and post stent insertion quality of life (QOL) and examine the role of treatment and location of AEF as factors influencing survival in patients with AEF managed with airway and/or esophageal stent insertion.

MATERIALS AND METHODS:

Patients

All patients with malignant AEF secondary to esophageal or lung cancer were prospectively included in the study over a period of three years. All patients had advanced lung or esophageal cancer. Based on the symptom profile or site of primary cancer patients were treated with bronchoscopic stent insertion in the airways or endoscopic stent insertion in the esophagus. The decision regarding stent placement was based on the location of the stenosis. If airway stenosis was present, then airway stents were inserted first and in case of esophagal stenosis, an esophagal stent was inserted first. If the fistula was not closed with the first stent, another stent was implanted directly in the other system. If the fistula was not satisfactorily closed as noted with dye injection with the first stent deployment, immediately then a second stent was inserted in the other system (airway plus esophageal stent insertion). All procedures were performed under general anesthesia using flexible video bronchoscopy, rigid bronchoscopy or EGD (Olympus Europe) Airway and/or esophageal Ultraflex nitinol stents (Boston Scientific; Natick, MA) were used for all patients. The dimensions of the stent were chosen based on the site and size of the AEF and the length of the lesion. Fluoroscopy was routinely used for the placement of esophageal stents while airway stents were placed under direct endoscopic vision. Informed consent was obtained in all patients and the study was approved by the local ethics committee.

Data Acquisition

The baseline study characteristics were recorded including site of tumor, concurrent treatment with chemotherapy, radiation or surgery. Successful stent

deployment, symptomatic relief and complications were also noted. Complete survival follow up was obtained in all patients.

Quality of Life Analysis

The European Organisation for Research and Treatment of Caner quality of life questionnaire (EORTC QLQ-C30) which has been developed to assess the QOL of cancer patients (http://www.eortc.be/home/qol/) was used. The QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and QOL scale. Several single-item symptom measures are also included in this score. The first QOL questionnaire was administered to all patients prior to stenting. A second follow up QOL questionnaire was given to all patients at 6 weeks during follow up. High score on a symptom scale or item indicates a high level of problem.

Statistical Analysis

Baseline statistics were compared between the three groups (airway stent only, esophageal stent only and both airway plus esophageal stents) to the outcomes of complications, survival and QOL scores. All data analyses were computed using the R statistical software [14]. Because all patients died at the time of the analysis, survival times actually correspond to times until death. Survival data are therefore uncensored. Survival times are expressed as mean [95% CI]. Between classes comparisons of means were performed using an ANOVA F-test. Factors influencing survival were identified using multiple linear regression (MLR). A stepwise backward elimination was performed in order to remove factors that were not influencing survival. The relative importance of each modality of the significant factors was assessed by constrained

multiple correspondence analysis. Paired t-test was used to test the significance of the change in questionnaire scores before and after the intervention.

RESULTS

Demographics

One hundred and twelve patients (Males = 98, Females = 14) underwent stent insertion in the airways and/or esophagus secondary to a malignant AEF. Eighty three (74%) patients had advanced lung cancers (non small cell lung cancers [NSCLC] = 73, small cell lung cancers [SCLC] = 10) and 29 (26%) patients had esophageal non-small cell cancer. The median age was 52 years [37; 81]. Sixty five patients (58%) underwent airway stent insertion, 37 (33%) esophageal stent insertion and 10 (9%) underwent both airway plus esophageal stent insertion (Table 1). All patients had initial success of fistula closure with the above procedures.

Complications

Seven patients (6%) developed respiratory failure following stent insertion and required mechanical ventilation in the intensive care unit lasting for less than one day (four patients with airway stents, one patients with double stents and two with esophageal stent). None of the patients developed stent migration or required repositioning of the stent. None of the patients had recurrence of AEF until 6 weeks after initial stenting. During the follow up period, 24 (17 airway, 1 both and 6 esophageal stents) had a recurrence of fistulas accounting for primary failure of stent placement or ineffective closure of AEF, thereby requiring a second stent insertion. There were no complications of perforation or mediastinitis. All patients were followed up and died of due to advanced underlying illness.

Survival Analysis

Survival

All survival times were uncensored. No patients died in the first 30 days after stent insertion. The mean survival (time to death from stent insertion) for the entire group was 236.6 days [221.5; 251.6]. The mean survival was 219.1 days [197.3; 240.9] for the airway group (n=65); 262.8 days [244.4; 281.3] for the esophageal group (n=37); and 252.9 days [192.9; 3312.9] for the double stent group (n=10). Survival was noted to be significantly lower in the group of patients who received only airway stent placement compared to those who received oesophageal and double (airway plus esophageal) stent insertion (F-test, p-value= 0.023). The survival times based on the treatment and localization of fistula are shown in Figure 1.

Multivariate Analysis

Specific independent risk factors were analyzed for success rates in terms of survival times for all patients. The individual factors analyzed in this study were age, gender, and localization of the fistula site in the airway and site of stent placement (airway or esophageal), treatment with radiotherapy and/or and complications. The site of stent placement (p value < 0.011), localization of fistula in the airway (p-value $= 0.023$) and treatment (p-value < 0.001) were identified as independent risk factors predicting increased or better survival times (Figure 2). For the site of stent placement, esophageal and airway plus esophageal sites had a higher survival compared to airway alone. For the localization of fistula, carina, left main bronchus and trachea had a higher survival than right main bronchus.

Quality of Life Index EQL -30 (QOL)

The Quality of Life index (Pre and Post stent insertion) scores are shown in Figure 3. The scores were calculated for individual functional and symptoms scores for the esophageal group, the airway group and for the double stenting group. There was significant improvement in QOL scores pre and post stent insertion at 6 weeks (Figure 3). There was also marked improvement in the overall global health and quality of life (paired t test: p value < 0.001).

DISCUSSION

Malignant AEF poses as a serious complication in patients with advanced neoplasia involving the esophagus or the lung. The American College of Chest Physicians (ACCP) guidelines for palliative care in patients with a malignant AEF or bronchoesophageal fistula recommends stent insertion of both the tracheobronchial tree and the esophagus for symptomatic relief. [15]. However, there is paucity of evidence and the net benefit being moderate in terms of morbidity and mortality in the endoscopic palliative management of malignant AEF. The findings of our study show that endoscopic stenting in the management of airway esophageal fistulas improves the overall quality of life post stent insertion and thereby have a significant role in the management of malignant AEF.

The goal of stent placement in AEF is to provide a seal between the airway and the esophagus thereby permitting enteral feeding and reducing bronchial contamination.[16,17] Potential complication of stent placement in the esophagus include perforation when placed in the cervical regions of the esophagus, respiratory compromise due compression of major airways and stent migration. Covered self expandable metallic stents have nevertheless an advantage over plastic or silicon stents in not only covering large defects, but having lower rates of migration along with adequate maintenance of patency of the passages [3,18,19]. We observed a primary success of fistula closure in all patients who underwent stenting either in the airway, esophagous or both systems. Twenty four patients developed a recurrence of fistula after a period of 6 weeks due to progressive disease. Appropriate deployment of a second stent thereby improved the overall success rate and survival in these patients. No major technical difficulties were experienced, thereby supporting that airway and/or

esophageal stent insertion have an important role in the palliation of malignant AEF. Earlier, studies have proposed combined airway and esophageal stenting for malignant AEF.[20-22] The current study was not designed to examine the benefits of combined esophageal and airway stenting compared to airway or esophageal stenting in patients with malignant AEF.

The overall mean survival time for the patients in the current study was 236 days. The survival times were higher for the patients receiving esophageal or combined esophageal and airways stents than patients who received only airway stents. The reason why the airway group performed worse than the other groups is not clear (Figure 2), but it is possible that the airway group had more advanced disease; moreover patients with stents placed distally (right main bronchus, Figure 1) performed worse as compared to those stents that were placed proximally in the airway (trachea). Among the distally placed airway stents, those stents placed in the right main bronchus had significantly poorer survival than those placed in the left main bronchus. Anatomically, the trachea and left main bronchus have more proximity to the esophagus compared to the right main bronchus. Hence, an AEF at the level of the right main bronchus would reflect more severe disease, thereby plausibly explaining the lower survival in this group. Similarly mortality did not seem to be influenced by stent placement as none of the patients died of stent related complications. Patients who also received chemotherapy and radiotherapy seem to have a prolonged survival as compared to patients who did not receive these therapies.

The overall QOL scores improved significantly after placement of stents (Figure 3). The core QOL was considered appropriate in this study considering the diverse study population consisting of both esophageal and lung cancers. The improvement in QOL

within 10 days post stent insertion was quite evident in most of the patients. There was no significant difference between the groups, thereby stating that airway and/or esophageal stent insertion was appropriate in improving the overall quality of life. Percutaneous endoscopic gastrostomy (PEG) is also an alternative optional procedure which can be considered from nutritional perspective in patients with AEF.[23] To our knowledge there are no clear guidelines for PEG placement in patients with AEF. The role of PEG was not examined in this study.

To conclude, airway and/or esophageal stent insertion provides an effective approach to improve quality of life in patients with malignant AEF.

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Table 1: Demographic data of the patients

(NSLC- Non small cell lung cancer; SCLC – Small cell lung cancer)

	Airway Stents	Esophageal Stents	Double Stents (airway & esophageal stenting)	Total
Number of patients N (%)	65 (58%)	37 (37%)	10 (9%)	112
Mean Age – Years (Min- Max)	52 [37- 73]	56 [42- 71]	57 [39- 81]	54.3 [37- 81]
Gender (M:F)	53: 12	36:1	9:1	98:14
Type of Cancer (N.)				
Esophageal	14	14	1	29
NSCLC - Left Lung	25	11	4	40
- Right Lung	17	12	4	33
SCLC	9	0	1	10
Localization of Fistula in Airway (N)				
Trachea	44	5	22	71
Carina	0	2	6	8
Left main bronchus	17	2	9	28
Right main bronchus	4	1	0	5
Complications (respiratory failure)	4	2	1	7
Median Survival Time (Days (IQR)]	182 [243; 279]	249 [274; 294]	245 [278; 294]	261 [213; 293]

FIGURES

Figure 1: Survival Analysis with independent factors between stent groups. Left Panel: Box plot showing the relationship between survival times and concomitant treatment. Right Panel: Box plot showing the relationship between survival and localisation of the fistula. The 25th, 50th and 75th percentiles and extreme values are shown.

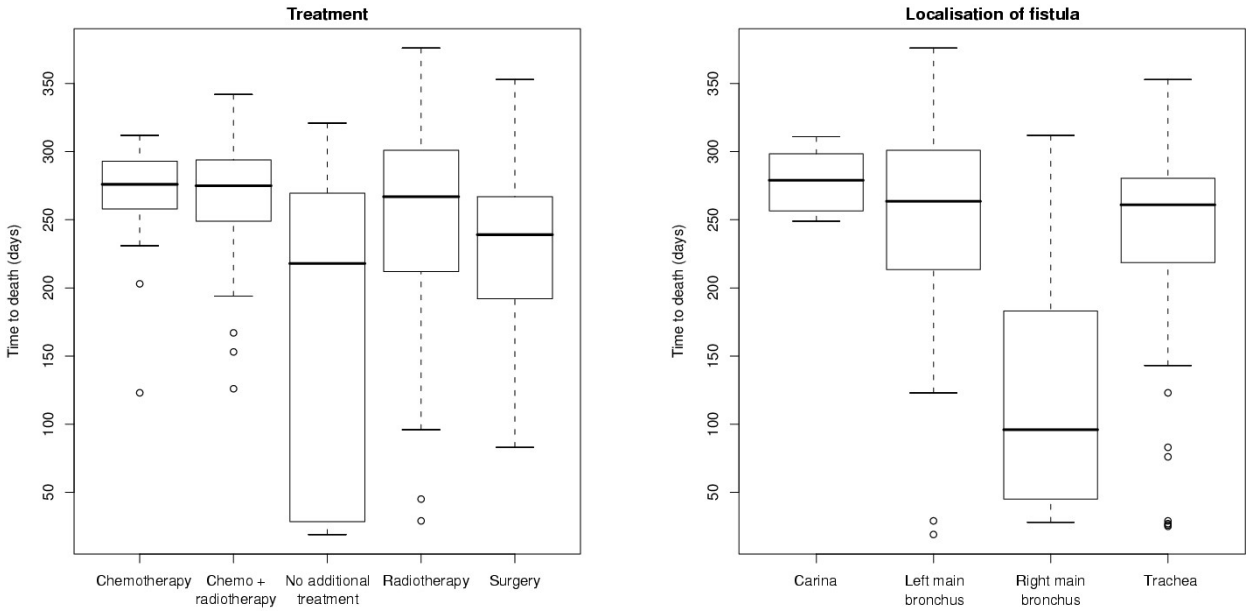


Figure 2: Multiple correspondence analyses of factors influencing survival. X-axis displays the factors modalities ordinated by the individuals and after accounting for survival times. Y-axis shows how factor modalities are ordinated by individuals without constraints. This mixed plot shows a gradient of survival from the lower left corner (low survival) to the upper right corner (high survival). For example, the combination of factors, site of stent placement = esophageal + localization of fistula = Carina + Post treatment = surgery leads to a relatively better prognosis in terms of survival.

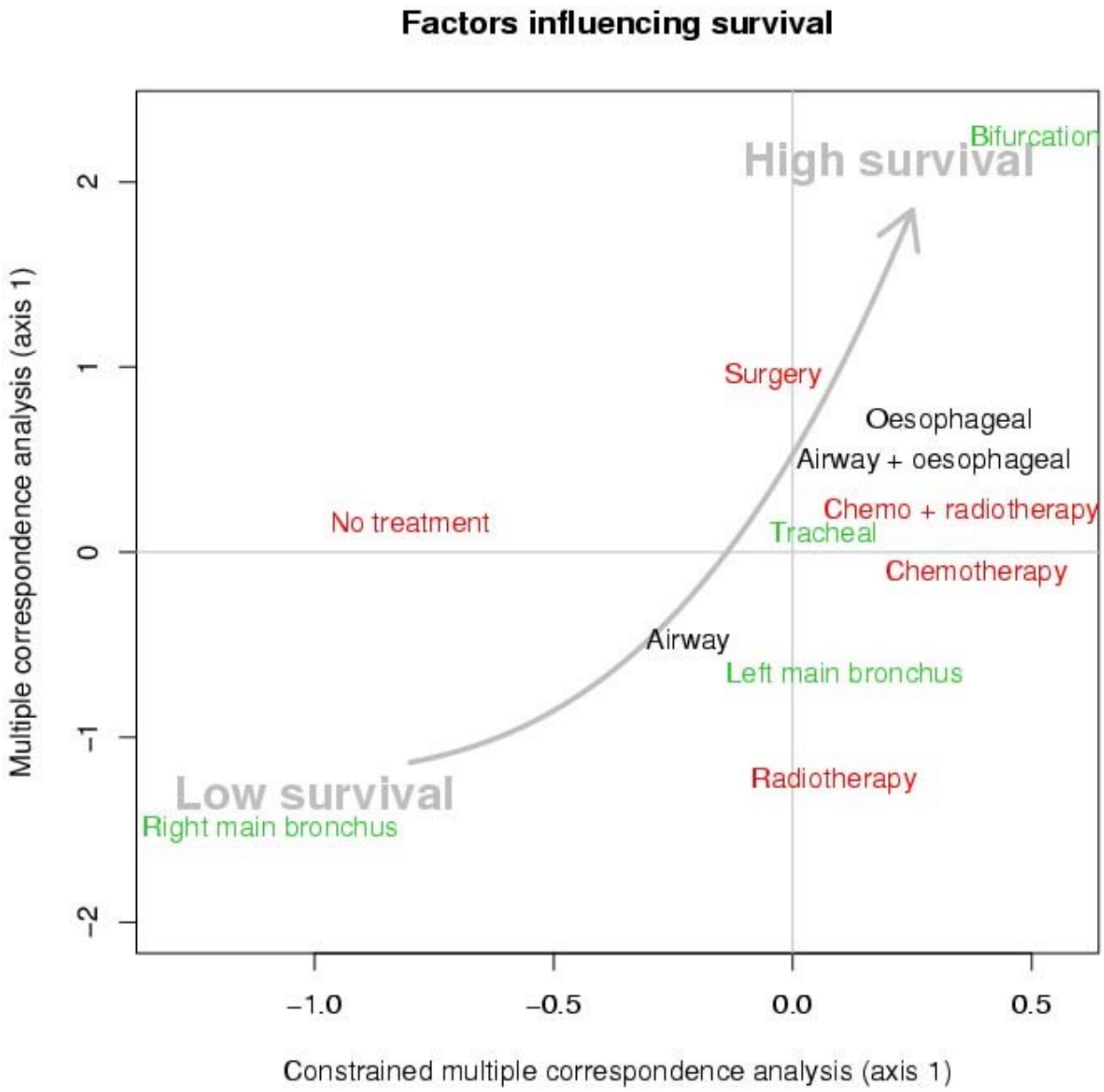
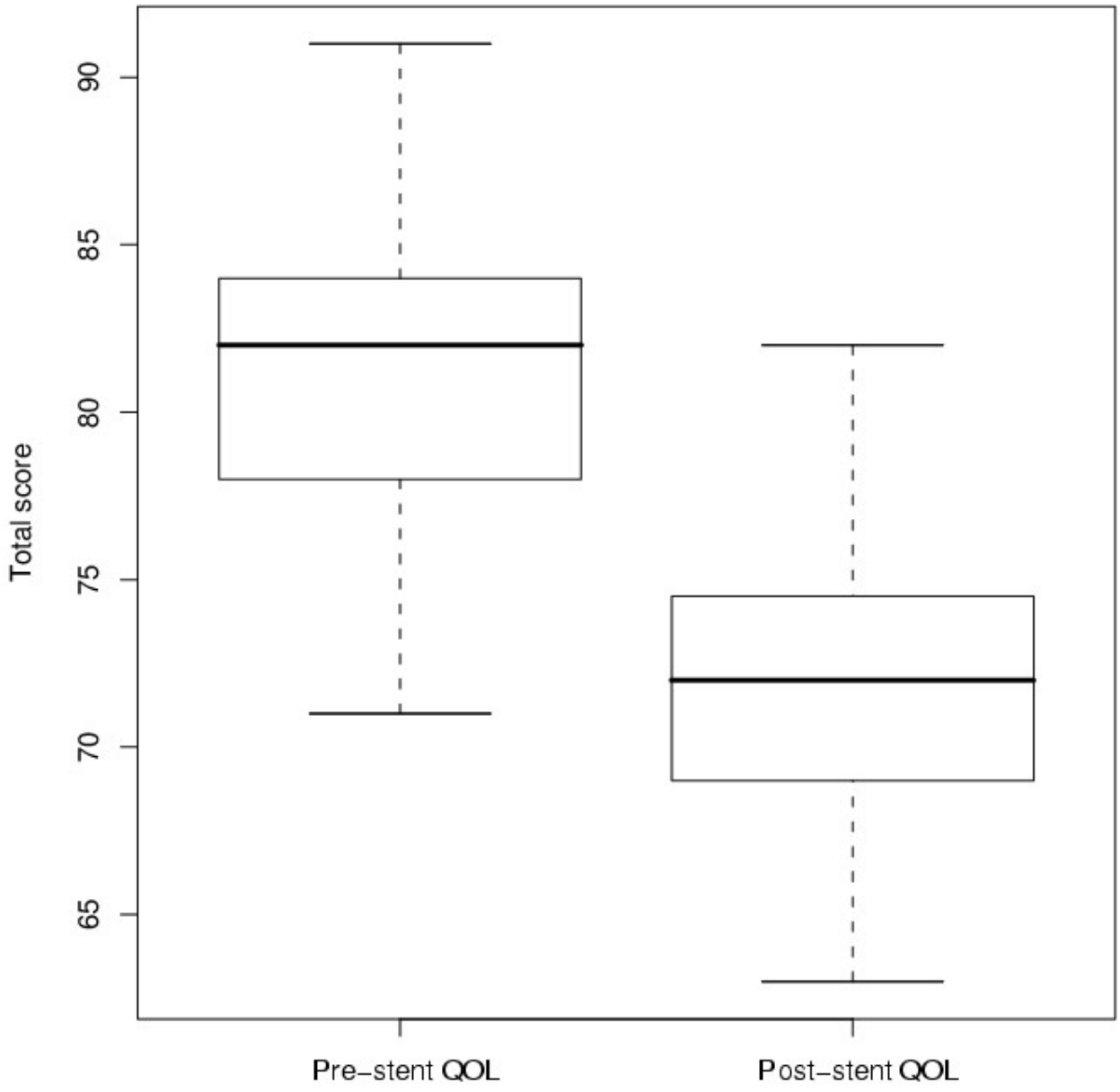


Figure 3: Analysis of Quality of Life (QOL) scores. The box plot shows the mean QOL scores for questions 1-28 pre- and post –stent insertion. The 25th, 50th and 75th percentiles and extreme values are shown.


Total score
90
85
80
75
70
65
Pre−stent QOL
Post−stent QOL