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LONG TERM FOLLOW UP AFTER BRONCHOSCOPIC LUNG VOLUME REDUCTION IN PATIENTS WITH EMPHYSEMA

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ABSTRACT

Background: Bronchoscopic lung volume reduction (BLVR) is a novel emphysema therapy. We evaluated long-term outcome in patients with heterogeneous emphysema undergoing BLVR with one-way valves.

Methods: Forty patients undergoing unilateral BLVR entered this study. Preoperative mean forced expiratory volume in 1 second (FEV_1) was 0.88 L/s (23%), total lung capacity (TLC) was 7.45 L (121%), intrathoracic gas volume was 6 L (174%), residual volume (RV) was 5.2 L (232%), the 6-minute-walk-test (6MWT) was 286 meters. All patients required supplemental oxygen; the

Medical Research Council (MRC) dyspnea score was 3.9. High resolution computed tomography (HRCT) were reviewed to assess the presence of interlobar fissures.

Results: 33 patients had a follow-up longer than 12 months (median: 32 months). 37.5% of the patients had visible interlobar fissures. 40% of the patients died during follow-up. Three patients were transplanted and 1 underwent lung volume reduction surgery. Supplemental O_2, FEV_1, RV, 6MWT and MRC score showed a statistically significant improvement (p = < 0.0001, 0.004, 0.03, 0.003, < 0.0001 respectively). Patients with visible fissures had a functional advantage.

Conclusions: BLVR is feasible and safe. Long-term sustained improvements can be achieved. HRCT visible interlobar fissures is a favorable prognostic factor.

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Emphysema is a worldwide leading cause of disability and death affecting approximately 1.8% of the global population (1). The current standard maximal medical treatment includes smoking cessation, administration of bronchodilators, pulmonary rehabilitation and long-term oxygen therapy; it allows to improve exercise capacity and quality of life. However, it shows some limitations in case of advanced disease. For his reason, according to radiological and functional details and the clinical status of the patients, a number of surgical procedures have historically been proposed. They include bullectomy (2), single and double lung transplantation (3) and, more recently, lung volume reduction surgery (LVRS) (4). The latter is based on the hypothesis that dyspnea may be related to severe impairment of respiratory mechanics owing to increased end-expiratory lung volumes with lungs and thorax overinflation. In fact, when target areas of hyperinflated lungs are resected, the residual lung and chest wall mechanics are significantly improved with consequent symptomatic relief. However, LVRS gained popularity too fast and without control; this posed important questions regarding the real value of the procedure and the appropriate selection of patients. Patients with a most advanced functional deterioration had a higher mortality and less encouraging results, suggesting that LVRS should be considered more carefully in these situations (5).

Some authors have speculated that similar results could be achieved by less invasive bronchoscopic approaches, isolating and deflating the most hyperinflated parts of the emphysematous lungs. Several bronchoscopic alternatives have been proposed: endobronchial occluders (6), sealants (7), coils (8) steam (9) and airway by-pass (10, 11). Bronchoscopic lung volume reduction (BLVR) with one way valves has been attempted in the experimental laboratory (12) and in selected clinical settings (13, 14, 15, 16). A randomized clinical study (17) has contributed to validate feasibility, safety, short and medium term effectiveness, allowing the procedure to advance one step beyond in the clinical arena.

We have previously reported a feasibility and safety study with short term results (13). We hereby report long term results in a larger population of patients.

PATIENTS AND METHODS

We conducted a prospective, nonrandomized, single-center longitudinal study to evaluate the long term efficacy of BLVR performed by placing one-way endobronchial valves (Zephir® valves, Pulmonx corporation, Redwood City, CA, USA; previously Emphasys, Redwood City, CA, USA) in the bronchi supplying the most hyperinflated parts of the emphysematous lungs. Forty patients (37 men, 3 women; mean age 60.5 ± 9.8 years) were enrolled. The protocol was approved by the ethical committee of the Policlinico Umberto I – Sapienza University of Rome (Prot. 350/03). Formal informed consent was obtained from each patient. Only patients undergoing unilateral BLVR were included; patients receiving bilateral treatment (included in our previous report) were excluded.

The inclusion and exclusion criteria are listed in Table I. The critical point was the presence of marked hyperinflation with regional variations in the distribution of emphysema providing "target" areas ("surgical" heterogeneous disease). Thus, all patients had heterogeneous emphysema with one or more lobes clearly more compromised than the rest of the lung. Heterogeneity was subjectively assessed by at least two members of the team at High Resolution Computed Tomography (HRCT) and lung perfusion scan; we treated only lobes showing a clear density reduction with no perfusion. The presence of interlobar fissures was retrospectively blindly determined by our radiologist (FF) using 3D reconstructions at CT and multiplanar evaluation. All patients received optimal medical therapy at the time of evaluation and all of them required supplemental oxygen. A formal rehabilitation program was not required for this study, although all patients received long term rehabilitation at the referral center. The preoperative functional variables are reported in Table II.

On-site evaluation included physical examination, body pletismography, diffusing capacity of the lung corrected for alveolar ventilation (DL_{CO}/VA), arterial blood gas analysis (ABG), six minute walk test (6MWT), chest x-ray, HRCT, lung perfusion scan and transthoracic echocardiography; dyspnea was quantified by the Medical Research Council (MRC) grading

system. Time points for postoperative evaluation were after 24-72 hours, 1 and 3 months, 1, 3 and 5 years.

All the procedures were performed in the operatory room under intravenous anesthesia (Propofol infusion) and spontaneous assisted ventilation through an endotracheal tube or a laryngeal mask. Local anesthesia (lydocaine 2%) was administered within the target bronchus before deploying the valves to prevent coughing. The characteristics of the valves and the deployment technique were previously reported by our group (13, 18).

Continuous variables were reported as mean ± standard deviation. The variation of means during follow-up was compared by one-way ANOVA and Post-hoc tests (LSD – least significative difference, Bonferroni and Sidak) for multiple comparisons. The comparison during follow-up between means and presence or absence of interlobar fissures was performed by not paired Student's T test. The correlation between the variables trend and the presence or absence of interlobar fissures was calculated by the Spearman's RHO correlation coefficient. All the statistical tests were two-tailed and a significance level of 0.05 was accepted. Survival curves were calculated from valve placement to death or last follow-up and were constructed according to the Kaplan-Meier method. The Log-Rank test was performed to compare survival between patients with and without visible fissures. Statistical analysis was performed using SPSS 17.0 software for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

One hundred forty two valves were placed with a mean of 3.6 per patient; 39 valves (27.5%) were placed in the left upper lobe, 66 (46.8%) in the right upper lobe, 4 (2.8%) in the middle lobe, 20 (14.1%) in the right lower lobe and 13 (9.3%) in the left lower lobe. The devices were placed in the left upper lobe in 13 patients (32.5%), in the right upper lobe in 17 (42.5%), in the right upper and middle lobe in 2 (5%), in the right lower lobe in 5 (12.5%) and in the left lower lobe in 3 (7.5%). Thus, the middle lobe was always treated together with the upper lobe. The median operative time was 39 minutes (range 15 to 95 minutes). The median follow-up was 32 months. Thirty-three patients were evaluated after one year, 18 after 3 years and 9 after 5 years

No intraoperative complications were observed. The mean hospital stay was 5 days (range 2 to 32) One contralateral pneumothorax occurred 15 days after the procedure while the patient was at home. Two patients had pneumonia in the lobe adjacent to that were the valves were inserted. One patient requiring anticoagulation after coronary artery revascularization presented mild hemoptysis 3 years after valve placement; in this patient no endobronchial abnormalities related to the presence of the valves were endoscopically detected. Two patients had small granulations growing in front of the valve; however, they didn't require any treatment since the device was not obstructed and there were no symptoms. Two patients underwent single lung transplantation (SLT) and one received double lung transplantation (DLT) at a mean of 6.3 months after valve placement; two of them died after the transplant with no valve-related complications and one is still alive and well. The 2 SLT patients were transplanted on the side were valves were previously placed. One patient died of respiratory failure on the waiting list for DLT 13 months after valve placement; in this patient, fiberoptic bronchoscopy was performed through the tracheostomy during the last hospitalization and all the valves previously placed were patent. One patient is currently on the waiting list for transplantation. One patient underwent LVRS one year after valve placement; one patient had the valves removed at another center after 3 months; the latter was not included in the survival analysis. Sixteen patients (40%) died during follow-up (lung cancer: 4 (25%); myocardial infarction with

intractable arrhythmia: 3 (18.7%); end-stage respiratory failure: 7 (43.8%); post transplant: 2 (12.5%)). The functional results at each time point are reported in Table III. No significant modification was observed immediately after the procedure. Only two patients experienced complete lobe atelectasis 1 and 3 weeks after the procedure. At 1 and 3 months there was a significant improvement in terms of FEV_1 and a decrease of the residual volume (RV); also Total lung capacity (TLC) and intrathoracic gas volume (ITGV) mildly decreased without reaching statistical significance and the 6MWT significantly improved. Overall, most of the patients showed an improvement of the MRC score with a significant reduction of symptoms, persisting after 1, 3 and 5 years. Most of the patients required less supplemental oxygen with a stable mean paO_2 and O_2 saturation. Improvement in terms of O_2 requirement, FEV_1, FVC, 6MWT and MRC score remained stable during follow-up. Post hoc tests confirmed that most of the improvement was during the first year. However, 6MWT and MRC improvements are significative at all time points; supplemental O_2 is significative up to the third year, RV is significative at 1 and 5 years and FVC improvement is significative at 1 year but it is not significative for the complete duration of follow up. The median preoperative FEV_1 was 0.77 L/sec; patients were stratified according to this value into two groups (20 patients in each group); the group of patients below the median FEV_1 showed a 28% FEV_1 improvement (from a mean of 0.65 L/sec to 0.83 L/sec); the group above the median had a 12.6% improvement (from 1.11 to 1.25 L/sec). Both improvements were statistically significant (p: < 0.0001 and 0.03 respectively). However, there were no statistically significant differences between the two groups. The same stratification was performed below and above the median RV without observing any statistically significant difference.

The mean and median survival were 36 ± 4.3 and 30 ± 4.6 months respectively. Survival at 1, 3 and 5 years were 81.6%, 47.4% and 22.4% respectively. Actuarial survival is shown in Fig. 1.

The review of HRCT allowed to visualize the interlobar fissures in 15 (37.5%) patients out of 40. The relative percentage of patients with visible fissures increased during follow-up (45.5%, 50% and 72% at 1, 3 and 5 years respectively). Functional results with respect to presence/absence

of interlobar fissures are reported in Table IV, demonstrating some functional advantages for patients with visible fissures. Mortality during follow-up was higher in the group of patients without HRCT visible interlobar fissures, as confirmed by the Log-Rank test (Fig. 2).

DISCUSSION

LVRS is the greatest advancement in COPD surgical management since the development of lung transplantation more than 30 years ago. It certainly provides a reliable palliation of symptoms in a well selected group of patients. The NETT trial reported improvements in survival and functional benefits in those with upper lobe predominant heterogeneous disease and limited exercise capacity (19). However, this procedure still carries a relatively high price tag with poor cost effectiveness related for the number of adverse clinical outcomes, the potentially prolonged hospitalization and long term care (20). Patients with the most advanced disease show a high mortality rate and achieve less favorable results, suggesting caution in case of excessively low FEV_1 and either homogeneous disease or very low DL_{CO} (5).

For these reasons, many investigators have pursued research into innovative and alternative methods to achieve similar results reducing morbidity and costs. Both thoracic surgeons and pulmonologists have considered whether emphysema palliation might be accomplished endoscopically, possibly becoming an outpatient procedure. These new endoscopic procedures should also be seen as an opportunity to benefit a larger group of symptomatic patients who may not be candidates for LVRS or transplantation, or bridge them to these operations, allowing to improve long term control of symptoms and survival. The airway bypass was investigated (10, 11) and assessed in a multicenter clinical study on 35 patients (21) with homogeneous emphysema. This procedure was designed to facilitate lung deflation and improve expiratory flow and respiratory mechanics; it is achieved by puncturing the wall of segmental bronchi and inserting a dedicated stent to create internal bronchopulmonary communications “bypassing” the “high resistance” airway during expiration. This procedure has been proposed for patients with homogeneous emphysema, in which collateral ventilation allows a preferential route of airflow through the artificial airway with a uniform deflation of the lung. In that study, the airway bypass contributed to reduce hyperinflation and to improve pulmonary function and dyspneoa. One patient died due to massive bleeding during the procedure. The duration of benefit appears to correlate with the degree

of pre-treatment hyperinflation and bypass patency. Patients with heterogeneous emphysema are not ideal candidates for this procedure since collateral ventilation within the whole lung is less pronounced and uniform deflation is more difficult to achieve. For this reason they have been approached with other endobronchial techniques. Some of these procedures should be considered still experimental; however, BLVR with one way valves have been extensively tested and validated also in clinical trials (17, 22). These unidirectional valves allow air to be vented from isolated lung segments or lobes during expiration and prevent air from refilling the parenchyma during inspiration. They functionally isolate the airway supplying the most hyperinflated parts of the lung during inspiration, favoring deflation and even atelectasis. This mechanism should mimic LVRS.

Thus, BLVR with the Zephir® (Pulmonx corporation, Redwood City, CA, USA; previously Emphasys, Redwood City, CA, USA) one way valves represents an attractive procedure. Many reports have previously demonstrated feasibility and safety, with encouraging short and medium term results (13, 14, 15, 16). The functional characteristics of the valves have favored their use also in case of bullous disease (23), bridge to transplant (24), closure of persistent parenchymal air leaks (25) and overinflation of the contralateral lung after SLT (26). A multicenter randomized trial on 321 patients with emphysema was recently published (17). This study was designed to compare safety and efficacy of endobronchial valve therapy in patients with heterogeneous emphysema versus standard medical care; it proposed for BLVR what the NETT trial did for LVRS. The conclusions of that study showed that greater radiographic evidence of heterogeneity (as assessed by HRCT) and fissure completeness were associated with an enhanced response to treatment. However, the results of that trial were somehow questionable since overall improvement in lung function, exercise tolerance and symptoms were modest; this mild improvement was achieved at the cost of more frequent COPD exacerbations, pneumonia and hemoptysis. These results resemble the discouraging initial interpretation of the LVRS NETT trial. In that case it was required a more careful analysis (20) to draw definitive conclusions and find a specific subgroup of patients likely to benefit. Also for the BLVR trial a more careful assessment of the results allows more encouraging

conclusions. Only heterogeneity (the difference in emphysema percentage between lobes in the treated lung) remained as an interaction in the multivariate mixed model for both FEV_1 and 6MWT. This was also true in case of fissure integrity for FEV_1, FEV_1/FVC ratio and 6MWT. The enhancing effect of heterogeneity (with a cutoff at a median heterogeneity score of 15%) sustained the finding of grater FEV_1 and 6MWT improvements in the high heterogeneity group (10.7%, $p = 0.004$ and 12.4%, $p = 0.002$ respectively). Patients with complete fissures showed improvements in FEV_1 of 16.2% and 17.8% at 6 months and 12 months respectively ($p < 0.001$ for both) in contrast to insignificant changes of 2% and 2.8% respectively in the group with incomplete fissures; this was indeed the most favorable variable in that study. The development of atelectasis was not specifically investigated in that trial, although previous single center reports were able to individuate it as a favorable prognostic variable (27).

Our previous report (13) was in line with the results obtained in the trial and in other single center studies (14, 15). However, outcome needed to be validated with longer follow up. Only one study reported a long-term extension of a previous pilot study on a small number of patients (16 patients with a follow-up longer than 12 months) (28). In that study both unilateral and bilateral BLVR were included; the authors demonstrated that a selected group of patients (6 out of 16 – 37.5%) may achieve long-term sustained improvements in pulmonary function; better results were observed in those with higher hyperinflation at baseline and higher TLC and RV/TLC ratio. There were no differences in baseline FEV_1, FVC and DL_{CO} between responders and non-responders.

The present study, performed on the largest single center group of patients available so far, extended the period of follow-up and confirmed our previous short-term encouraging results. FEV_1 was significantly improved also at these longer time points; O_2 supplemental requirements, 6MWT and MRC were improved as well. The percentage of improvement looks higher in patients with a FEV_1 below the median, opening a new scenario for patients unsuitable for LVRS. These results were clearly more marked in the group of patients with visible fissures at HRCT. In particular, 50% out of 18 patients assessable at 3 years and 72% out of 9 at 5 years had complete fissures, justifying

the stable improvement at these time points and demonstrating an advantage of this viable during long term follow-up. Complete fissures prevent interlobar collateral ventilation and guarantee better results. This variable will be evaluated more reliably with the new technology nowadays available; in fact, an endobronchial catheter is currently under evaluation to assess endobronchial flows from adjacent lobes and resistance of collateral channels. This system relies on the measurement of spontaneous airflow from a sealed and isolated target compartment during spontaneous ventilation in awake subjects. The identification of the critical value of collateral channels resistance above which atelectasis or volume reduction occurs will certainly help to exclude patients with less favorable results (29). Computed tomography with volume rendering may contribute to improve evaluation of hyperinflation before and after valve placement (30).

Mortality was significant during the study period (40 % overall); however, no deaths were related to the procedure; lung cancer, COPD progression with intractable end stage respiratory failure and complications after lung transplantation were the main causes of death. We recorded an increased mortality during the follow-up period in patients with non visible fissures at HRCT.

Overall, BLVR is confirmed to be feasible and safe. Morbidity is low if the selection of patients is carefully performed. Specific subgroups with marked hyperinflation, clear heterogeneity and the presence of interlobar fissures at HRCT are most likely to benefit from this endoscopic, low invasiveness procedure.

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TABLES

Table I: Inclusion and exclusion criteria. Legend: FEV_1: Forced expiratory volume in one second; RV: Residual volume; DL_{CO}/VA: Diffusing capacity of the lung corrected for alveolar ventilation (ml/min/mmHg/L)

Table II: Preoperative variables. Legend: FEV_1: Forced expiratory volume in one second (L/sec); RV: residual volume (Liters); TLC: Total Lung capacity (Liters); FVC: Forced vital capacity (Liters); DL_{CO}/VA: Diffusing capacity of the lung corrected for alveolar ventilation (ml/min/mmHg/L); MRC: Medical research council; HRCT: High resolution computed tomography.

Table III: Functional variables of the patients at the different time points. Legend: §: Liters/minute; §§: %; *: mmHg; **: mmHg; ***: Forced expiratory volume in 1 second (L/min); ****: Forced vital capacity (Liters); #: residual volume(liters); §§§: Total lung capacity (Liters); ##: Intrathoracic gas volume (liters); ###: Diffusing capacity of the lung corrected for alveolar ventilation (ml/min/mmHg/L); ####: Six minute walking test (meters).

Table IV: Functional variables at one, two and three years compared according to the presence or absence of interlobar fissures visible at HRCT (High Resolution Computed Tomography). Legend: *: L/min; **: %; ***: mmHg; $: mmHg; #: Forced expiratory volume in 1 second (L/sec); ##: Forced vital capacity (liters); ###: Residual volume (Liters); $$: Diffusing capacity of the lung corrected for alveolar ventilation (ml/min/mmHg/L); §: Six minute walking test (meters).

ILLUSTRATIONS

Fig. 1: Survival according to the Kaplan – Meier method.

Fig. 2: Survival comparison between patients with and without visible fissures.

Table I

Inclusion criteria
Heterogeneous emphysema at HRCT and lung perfusion scan
FEV_1 < 35%
RV > 180%
Age between 35 and 75 years

Exclusion criteria
Homogeneous emphysema at HRCT and lung perfusion scan
Currently smoking
Presence of isolated bulla
$PaCO_2$ > 50 mmHg
DL_{CO}/VA < 20%
Productive cough
Small airway disease

TABLE II

Variable		Percentage Predicted	Range
FEV_1	0.88 ± 0.3 L/sec	23 %	15 – 51 %
RV	5.2 ± 0.9 L	232 %	177 – 328 %
TLC	7.45 ± 1.1	122 %	85 – 134 %
FVC	2.0 ± 0.9 L	45 %	33 – 62 %
ITGV	6.0 ± 1.1 L	174 %	134 – 220 %
PaO_2	72.7 ± 11.3 mmHg	_____	57 – 102 mmHg
$PaCO_2$	41.2 ± 4.5 mmHg	_____	28 – 46 mmHg
O_2 sat	94.9 ± 3.1 %	_____	91.2 – 97.1 %
DL_{CO}/VA	2.95 ± 1.9 ml/min/mmHg/L	33 %	27 – 76 %
Supplemental O_2	1.87 ± 1.2 L/min	_____	1 – 3 L/min
6 Minute Walking Test	286 ± 72 meters	_____	124 – 458 meters
MRC scale	3.9 ± 0.8	_____	3 - 5
Visible fissures at HRCT	15 patients	_____	_____

TABLE III

Variables	Baseline	24-72 h	1 month	3 months	6 months	1 year	3 years	5 years	P value
Suppl. O_2[§]	1.87 ± 1.2	0.5 ± 0.2	0.5 ± 0.20	0.5 ± 0.20	0.6 ± 0.2	0.8 ± 0.8	0.8 ± 0.8	1.0 ± 1.0	< 0.0001
O_2 Sat.[§§]	94.9 ± 3.1	95.2 ± 2.9	94.8 ± 2.9	95.1 ± 1.8	94.9 ± 1.9	94.7 ± 1.9	94.4 ± 1.9	95.7 ± 2.4	0.2
PaO_2[*]	72.7 ± 11.3	74.1 ± 8.9	73.4 ± 7.2	74.2 ± 8.1	74.3 ± 6.9	74.6 ± 6.7	71.9 ± 6.3	72.9 ± 10.3	0.7
$PaCO_2$[**]	41.2 ± 4.5	39.4 ± 4.4	39.1 ± 4.7	39.1 ± 3.7	39.4 ± 3.2	39.5 ± 3.4	39.3 ± 2.6	39.7 ± 2.9	0.2
FEV_1[***]	0.88 ± 0.3	0.9 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	1.09 ± 0.4	1.08 ± 0.4	1.2 ± 0.5	0.004
FVC[****]	2.0 ± 0.6	2.1 ± 0.5	2.3 ± 0.6	2.3 ± 0.8	2.3 ± 0.5	2.4 ± 0.6	2.4 ± 0.5	2.5 ± 0.6	0.06
RV[#]	5.2 ± 0.9	4.5 ± 0.8	4.7 ± 1.0	4.7 ± 0.9	4.4 ± 1.1	4.4 ± 1.2	4.4 ± 1.2	3.98 ± 1.3	0.03
TLC[§§§]	7.45 ± 1.1	7.39 ± 1.3	7.49 ± 1.1	7.41 ± 0.9	7.3 ± 1.1	7.28 ± 1.0	7.29 ± 1.1	7.3 ± 1.3	0.7
ITGV[##]	6.0 ± 1.1	5.1 ± 0.9	5.4 ± 1.0	5.4 ± 1.1	5.3 ± 1.0	5.3 ± 1.1	5.2 ± 1.3	5.3 ± 1.2	0.1
DL_{CO}/VA[###]	2.95 ± 1.9	3.03 ± 1.9	2.99 ± 1.8	2.81 ± 1.5	2.84 ± 1.2	2.88 ± 1.5	3.35 ± 1.3	3.86 ± 1.2	0.2
6MWT[####]	286 ± 97	312 ± 72°	371 ± 88	408 ± 91	388 ± 87	349 ± 105	355 ± 90	402 ± 113	0.003
MRC	3.9 ± 0.8	3.4 ± 0.9	2 ± 0.6	2 ± 0.7	2.2 ± 0.7	2.4 ± 0.6	2.6 ± 0.5	2.6 ± 0.7	< 0.0001

TABLE IV

Timing		N° Pts	Suppl O_2 *	Sat O_2 **	PaO_2 ***	$PaCO_2$	FEV_1 #	FVC ##	RV ###	DL_{CO}/VA $$	6MWT §	MRC
Pre Treatment	No Fissure	25	2.16	93.4	69.8	41.6	0.82	1.99	5.07	2.6	251	3.7
	Fissure	15	1.4	94.9	77.6	40.7	0.97	2.29	4.84	3.3	342	3.1
p value			**0.05**	**0.1**	**0.03**	**0.3**	**0.2**	**0.1**	**0.4**	**0.1**	**0.002**	**0.03**
1 Year	No Fissure	18	1.22	94.2	74.3	39.2	1.04	2.27	4.74	2.8	302	2.7
	Fissure	15	0.33	95.4	74.9	39.7	1.16	2.62	4.04	3.3	406	2.13
P value			**0.002**	**0.08**	**0.8**	**0.9**	**0.4**	**0.1**	**0.09**	**0.3**	**0.002**	**0.004**
3 Years	No Fissure	9	1.33	93.8	70.4	40.2	0.92	2.24	5.04	3.3	321	2.77
	Fissure	9	0.44	94.9	73.4	38.3	1.25	2.62	3.79	3.4	388	2.44
P value			**0.02**	**0.2**	**0.3**	**0.07**	**0.1**	**0.09**	**0.02**	**0.9**	**0.1**	**0.3**
5 Years	No Fissure	3	2.0	95.2	70.3	41.3	0.9	2.26	5.12	4.1	350	3.0
	Fissure	6	0.5	95.9	74.2	38.9	1.37	2.59	3.4	3.7	428	2.5
P value			**0.02**	**0.7**	**0.6**	**0.1**	**0.2**	**0.5**	**0.05**	**0.4**	**0.3**	**0.4**

Figure 1

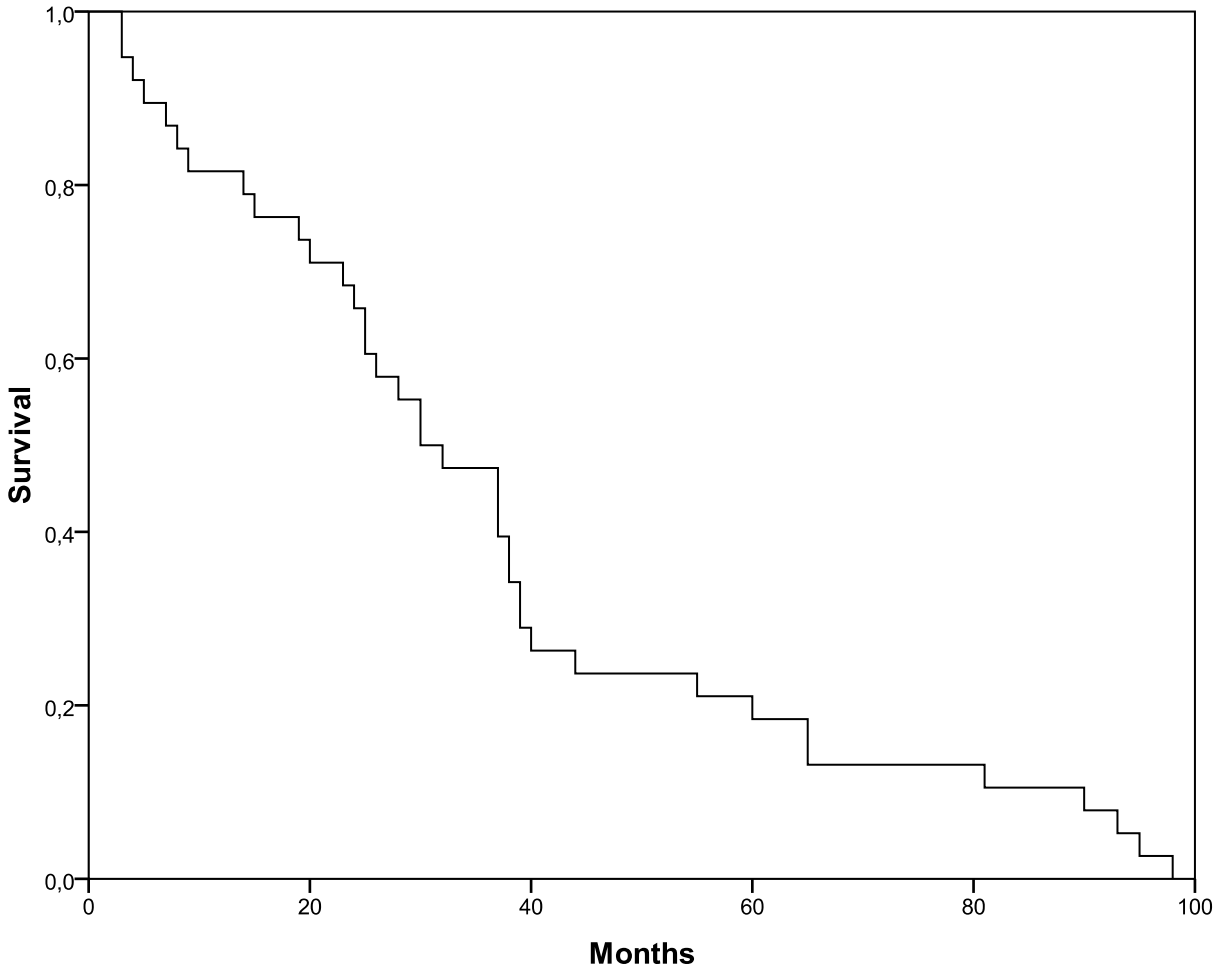
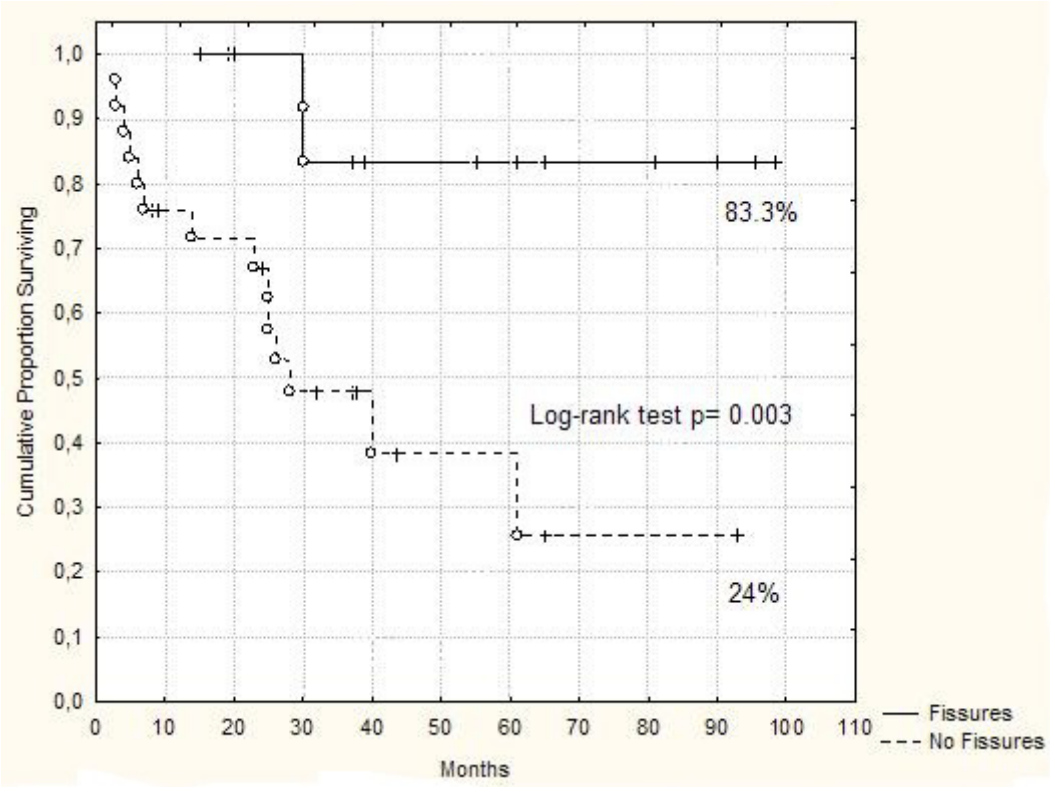


Fig. 2


Cumulative Proportion Surviving
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
10
20
30
40
50
60
70
80
90
100
110
Months
83.3%
Log-rank test p= 0.003
24%
Fissures
No Fissures