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Time-trend analysis of the pulmonary function after surgical treatment for esophageal cancer

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Abstract. – OBJECTIVE: To evaluate, in function of time, the modification of pulmonary function after radical esophagectomy with the aim of identifying clinical and/or surgical predictors of functional worsening.

PATIENTS AND METHODS: Data of 57 patients operated from 01/06 to 06/11 were retrospectively reviewed. Thirty-eight patients (67%) underwent transhiatal cervico-laparotomic (CL-Group) and 19 (33%) a Mc-Keown cervico-thoraco-laparotomic esophagectomy (CTL-Group). The pulmonary function has been evaluated before and one month after surgery. The outcome has been benchmarked with demographic/clinical characteristics, the type of operation and the presence of post-operative pulmonary complications (POPCs).

RESULTS: Mean age and male/female distribution were 66.6±10.6 yrs and 39/18, respectively. A total of 14 (24% of total sample) POPCs occurred with a significantly higher occurrence in the CTL-Group (71% vs 28%, $p < 0.001$) and in those patients with a pre-operative concurrent pathological condition (64% in COPD patients vs 36% in patients without COPD, $p = 0.021$). A global worsening of the spirometric parameters (expressed as the baseline percentage change, Δ) emerged, but this decrease was significantly higher in the CTL-Group in terms of Δ-FVC ($p = 0.005$) and Δ-FEV_1 ($p = 0.005$). Similarly, those patients who have experienced a POPC, showed a higher reduction of the pulmonary function regardless of the surgical approach when compared with those who did not (Δ-FVC: $p = 0.053$ and Δ-FEV_1%: $p = 0.015$).

CONCLUSIONS: In the context of a global reduction of pulmonary function, patients who underwent trans-thoracic esophagectomy or experienced a POPC showed a significantly worse pattern. These patients could be the “best target” for therapeutic rehabilitative strategies in the pre-operative and/or post-operative setting. This assumption is to be proven through prospective clinical trials.

Key Words:
Pulmonary function, Esophagectomy, Chest physical therapy, Surgery.

Abbreviations

NAD = Neoadjuvant Therapy; PY = Pack/years Index; BMI = Body Mass Index; FVC = Forced Vital Capacity; FVC% = Forced Vital Capacity (% of the predicted value); FEV_1 = Forced Espiratory Volume in 1 second; FEV_1% = Forced Espiratory Volume in 1 sec (% of the predicted value); RV = Residual Volume; RV% = Residual Volume (% of the predicted value); TLC = Total Lung Capacity; TLC% = Total Lung Capacity (% of the predicted value); PEF = Peak expiratory flow; PEF% = Peak expiratory flow (% of the predicted value); FEV75 = forced expiratory flow at 75% of FVC; FEV75% = forced expiratory flow at 75% of FVC (% of the predicted value); FEV25-75 = forced expiratory flow at 25-75% of FVC; FEV25-75% = forced expiratory flow at 25-75% of FVC (% of the predicted value).

Introduction

Esophagectomy, regardless the surgical techniques adopted (even the less invasive ones) is a major surgical procedure with high rates of morbidity and mortality[1].

Post-operative complications are caused mostly by respiratory problems during the early post-operative recovery period[2,3], this influencing the overall early mortality and the post-operative course.

During the past two decades, several management strategies have been proposed to reduce mortality and morbidity; consequently, post-op-

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erative pulmonary complications (POPCs) have dropped from 50% to below 20%[4,5]. Nevertheless, the rate of POPC is still relatively high after esophageal surgery, higher than in any other type of major surgery, including pulmonary resection.

Although some respiratory risk factors (smoking, COPD, decrease in FEV_1, etc.) may be easily identified in the pre-operative assessment and considered as objective criteria for patient selection, the surgical stress per se (associated to the different invasiveness of the surgical approaches) seems to significantly influence the post-operative course and the functional pulmonary recovery; this was correctly hypothesized by Kehlet et al[6]. In this scenario, some surgical teams have adopted a rehabilitative strategy[7-9] in those patients scheduled for esophagectomy. Nevertheless, to our best knowledge, no specific work reporting a time-trend analysis of the pulmonary function after esophagectomy has been reported so far. The study we report herein is aimed at investigating the risk factors with respect to a post-operative decrease in pulmonary function.

Patients and Methods

From 01/06 to 06/11, 61 patients with esophageal carcinoma (EC) were surgically treated at our institution. Exclusion criteria were both surgical (2 patients with unresectable tumor) and clinical (2 unable to complete the post-operative respiratory functionality assessment due to poor clinical conditions). The study scheme is summarised in a Consort diagram (Figure 1).

Pre-operative Evaluation and Patient Preparation

Before surgery, all patients underwent a complete clinical staging work-up including upper digestive tract endoscopy and a computed tomography of the chest, abdomen, and pelvis. The 18F-FluoroDeoxyGlucose Positron Emission Tomography (FDG-PET) was introduced from 2009 but not routinely performed (data available in 11 cases only). Neoadjuvant chemotherapy (cisplatin 60 mg/m^2 with infusional fluorouracil 200 mg/m^2 per day for 21 days) was administered in 8 patients

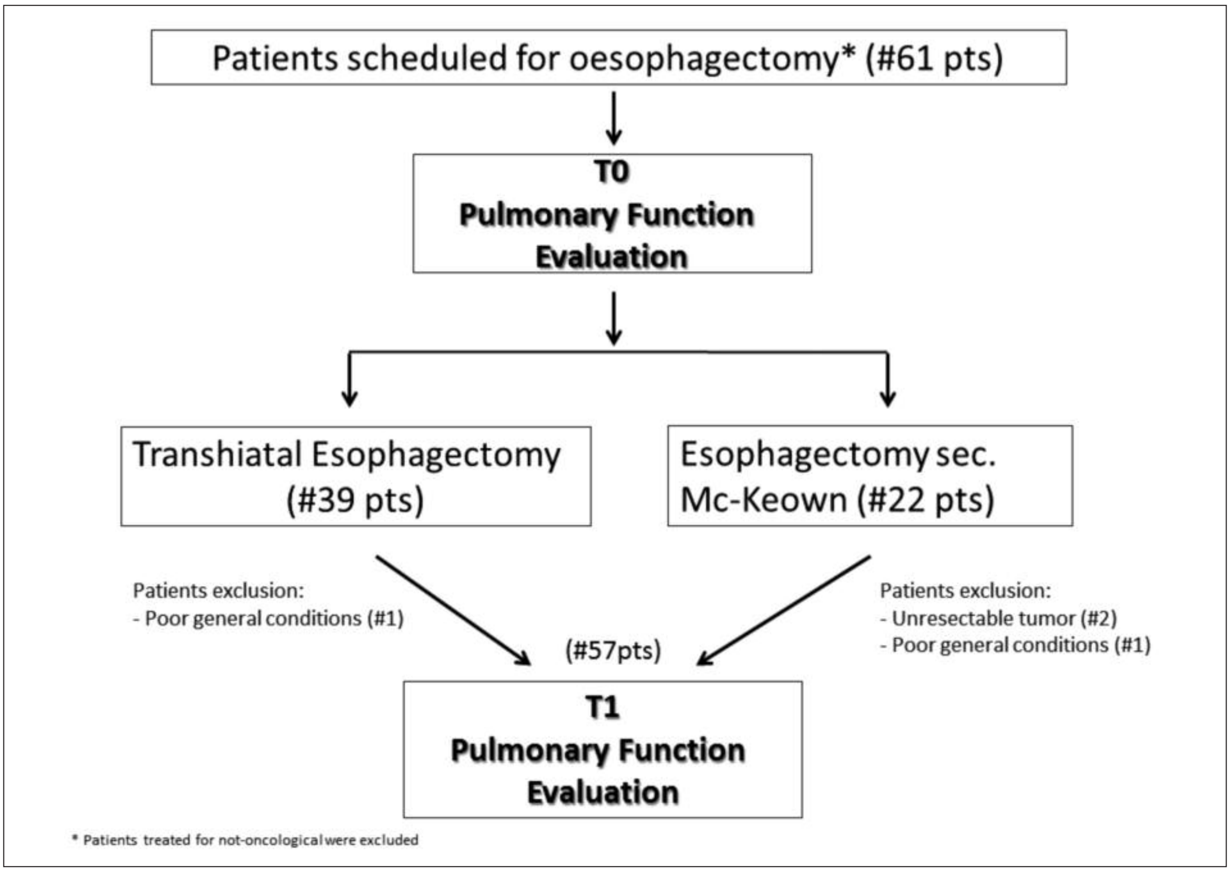

Figure 1. Consort diagram of the study population.

with radiological involvement of mediastinal lymph nodes. Before surgery (T0, see Figure 1) all patients underwent a baseline spirometry as part of the pre-operative evaluation. The assessment of the dynamic and static lung volumes has been performed as already extensively reported[9].

Intra-operative Anaesthesiological Management

Epidural analgesia was not routinely used in the entire population; and its use has been reserved to selected patients, in particular those who underwent the Mc-Keown "triple" approach. In such patients, during the thoracic step, one-lung ventilation is used to create adequate and optimal surgical exposure of the oesophagus.

Surgical Approaches

Our criteria for choosing the surgical approach, although not completely standardized, were substantially based on the clinical staging. A Mc-Keown cervico-thoraco-laparotomic esophagectomy (CTL-Group) has been choose in those patients with locally-advanced disease, while in the remaining cases we adopted a transhiatal cervico-laparotomic approach (CL-Group).

The Mc-Keown esophagectomy technique[10] consists in a three-step procedure (cervical-thoraco-laparotomic approach) where the thoracic preparation and dissection of the oesophagus is performed via right postero-lateral thoracotomy. The transhiatal esophagectomy technique[11] consists in a two-step procedure (cervical-laparotomic approach) where the thoracic preparation and dissection of the oesophagus is replaced with transhiatal dissection via laparotomy and cervicotomy.

Post-operative Evaluation

Epidural analgesia was not routinely used. In those cases in which epidural anaesthesia was used, the catheter was maintained for 48 h post-operatively. POPCs were recorded during the first 30 post-operative days and defined as: (1) the presence of pneumonia confirmed by a positive culture result (endotracheal aspiration or blood sample) or chest X-ray; (2) acute lung injury ($PaO_2/FiO_2 < 300$); or (3) adult distress respiratory syndrome (ARDS) according to the American-European Consensus Conference[12]. Bronchial secretion retention and atelectasis were also included in the definition of POPC because, as suggested by D'journo et al[13], "they can be viewed as the earliest stage of a lung disease that requires measures aim at preventing progression to pneumonia…".

About one-month after surgery, all patients underwent spirometry as part of the post-operative evaluation (T1, see Figure 1). The evaluation of the exercise endurance (6MWD-test) was not routinely performed at T1 and, accordingly, this parameter was not taken into consideration for the statistical data analysis. Similarly, data concerning the quality of life were substantially unavailable and, therefore, not included in the present investigation.

Statistical Analysis

Clinical and demographic data are expressed in terms of frequency and percentage for categorical variables and mean ± standard deviation for quantitative variables.

Fisher exact test was used to assess the relationship between the occurrence of POPCs and, one by one: sex (F/M), age (dichotomized at 65), smoking habit (as smoker, ex-smoker, never smoker), comorbidities (COPD/no COPD), NAD-Therapy (Y/N), type of surgery (CTL/CL), FEV_1% at T0 (dichotomized at 80).

Spirometric parameters are described in terms of mean ± standard deviation at T0 and T1, with the exception of FEV_1%, also depicted in terms of frequency and percentage for the variable dichotomized at 80%.

T0-T1 differences for spirometric parameters are defined in terms of mean ± standard deviation, then compared: – CTL vs CL group; – "POPC" vs "without POPC" group, in both cases using *t*-test. Median values are reported too in tables as data seems a little skewed for some parameters.

Finally, multivariate general linear models were used to assess sex, age, COPD. FEV_1% (dicothomized at 80) at t0, NAD-therapy, type of surgery, POPC occurrence, smoking habit as potential predictor for T0-T1 difference for spirometric parameters expressed in percentage (one by one considered): F-statistics are reported besides the related *p*-values to allow the ranking for relative importance of the independent variables. $p < 0.05$ was considered as statistically significant.

Results

From 01/06 to 06/11, a total of 57 patients underwent a pre-operative (To) and a post-operative (T1) pulmonary assessment after radical esophagectomy (Figure 1). Data regarding demographic, clinical, and surgical characteristics are summarized in Table I. In particular, about one third (35%) of the sample presented with COPD at admission and more than half (58%) with an active or previous smoking habit. Surgical resection consisted in a transhiatal approach in 38 cases (67%) while a cervico-thoraco-laparotomic access was performed in the remaining 19 cases (33%). After surgery we observed a total of 24 complications (42%), being POPCs the most common event (14 cases, 24% of the entire population). In particular we found 10 cases of pneumonia, 2 pulmonary atelectasis and 2 cases of ARDS.

Two patients died during the post-operative course (30-day mortality rate of 3.5%), respectively due to a respiratory failure related to massive pulmonary embolism in the 4th post-op day and for septic shock in the 12th post-op day.

Table I. Clinical and demographic parameters of the study population (n=57).

Variables	n (%)
Sex	
Male	39 (68%)
Female	18 (32%)
Smoke	
Smoker	15 (26%)
Ex-smoker	18 (32%)
Never Smoker	24 (42%)
Comorbidities*	
COPD (only)	20 (35%)
Others (only)	23 (40.5%)
No	24 (42%)
Neoadjuvant therapy	
Yes	8 (14%)
No	49 (86%)
Surgical procedures	
Mc-Keown Esophagectomy (CTL-Group)	19 (33%)
Transhiatal Esophagectomy (CL-Group)	38 (67%)
Complications	
Pulmonary Complications (POPC)	14 (24%)
Total complications	24 (42%)
Mortality	2 (3.5%)
Adjuvant Therapy**	
Chemotherapy (only)	2 (4%)
Radiotherapy (only)	12 (21%)
Chemotherapy and Radiotherapy	14 (25%)
None	28 (50%)
	Mean ± SD
Age	66.6 ± 10.6
PY	16.0 ± 17.7
BMI	23.6 ± 2.4

*More than one comorbidity in 10 patients; **One missing observation.

Baseline Characteristic of Patients with POPCs

We have investigated the distribution of demographic, clinical and surgical characteristics in patients who experienced a POPC and patients who did not. It emerged that the reduced pre-operative pulmonary function (FEV_1 < 80%), the presence of COPD and the CTL-surgical approach were significantly more common in patients who experienced a POPC if compared with patients who did not (Table II). In particular, among the 14 patients who experienced a POPC, 10 (71%) underwent esophagectomy via CTL-approach while only 4 (29%) were previously surgically treated via CL-approach ($p = 0.001$). On the contrary, all the other parameters considered in the analysis were substantially similarly distributed in the two groups of patients.

Time-trend Analysis of Pulmonary Function

A time-trend analysis of spirometric parameters (expressed as the baseline percentage change, ΔT0-T1) in the entire population shows a global worsening of the pulmonary function 1 month after the discharge (Table III), especially in terms of both pulmonary capacity (measured by FVC% and TLC% values) and efficiency of lung emptying (measured by PEF%, FEV_1% and FEF25-75% values). A multivariate analysis was performed with the aim of identifying those clinical and/or surgical factors actually and significantly responsible for the post-operative pulmonary function decrease (see Table IV). The type of surgery (CTL approach, $p = 0.009$) and the occurrence of POPC ($p = 0.043$) were proved to be the only independent factors who negatively influenced the post-op recovery of the pulmonary function (estimated by baseline percentage change-ΔT0-T1-of spirometric parameters). Nevertheless, we should take into account that some variables included in this statistical model, as reported in Table II, are clearly related to other ones (e.g. COPD and FEV_1 < 80% are predictive of the occurrence of POPC). For this reason, we have focused our attention on the time-trend modification of the pulmonary function in these two groups of patients. As reported in Table V and graphically reproduced in Figure 2, the decrease of spirometric parameters was significantly higher in the CTL-Group if compared with the CL-Group in terms of Δ-FVC ($p = 0.005$), Δ-FVC% ($p = 0.001$), Δ-FEV_1 ($p = 0.005$), Δ-FEV_1% ($p < 0.001$), TLC% ($p =$

Table II. Post-Operative Pulmonary Complications (POPC) – Demographic and clinical parameters

Variables	With POPC (n=14) n (%)	Without POPC (n=43) n (%)	*p* value
Sex			
Female	6 (43%)	12 (28%)	0.333F
Male	8 (57%)	31 (72%)	
Age			
> 65 yrs	9 (64%)	27 (63%)	0.491F
< 65 yrs	5 (36%)	16 (37%)	
Smoke			
Smoker	7 (50%)	8 (19%)	0.065F
Ex-smoker	4 (29%)	14 (33%)	
Never smoked	3 (21%)	21 (49%)	
Comorbidities			
Total COPD (n=20)	9 (64%)	11 (26%)	0.021F
No COPD (n=37)	5 (36%)	32 (74%)	
Neoadjuvant therapy			
Yes	0 (0%)	8 (19%)	0.179F
No	14 (100%)	35 (81%)	
Surgical Procedures			
CTL-Group (n=19)	10 (71%)	9 (21%)	0.001F
CL-Group (n=38)	4 (29%)	34 (79%)	
FEV_1 T0 pred %			
≤ 80	7 (50%)	35 (81%)	0.028F
> 80	7 (50%)	8 (19%)	

F: Fisher Exact Test.

0.003) and Δ-PEF% (p = 0.021). Similarly, patients who experienced a POPC, regardless of the surgical approach, showed a higher reduction of pulmonary function (Table V and Figure 3) in comparison with patients who did not.

Discussion

Esophageal cancer carries a poor prognosis and radical surgery, when possible, can offer a 30% chance of cure only[14]. Moreover, the surgi-

Table III. Time-trend analysis of spirometric parameters of the study population (n=57), evaluated before surgery (T0) and one month after the discharge (T1).

Variables	T0 mean ± SD	T1 mean ± SD	Δ T0-T1mean	*p* value
FVC	3.2 ± 1	2.8 ± 1.0	-0.4 ± 0.3	0.016
FEV_1	2.3 ± 0.8	2 ± 0.8	-0.3 ± 0.2	0.007
TLC	5.6 ± 1.3	5.3 ± 1.2	-0.3 ± 0.2	0.069
RV	2.3 ± 0.7	2.1 ± 0.6	-0.2 ± 0.1	0.058
PEF	5.7 ± 1.7	4.8 ± 1.6	-1.0 ± 0.8	0.059
FEF75	0.8 ± 0.7	0.7 ± 0.6	-0.1 ± 0.1	0.128
FEF 25-75	1.9 ± 1.0	1.6 ± 0.9	-0.3 ± 0.2	0.054
FVC-pred%	99.8 ± 19.4	86.3 ± 19.6	-13.1 ± 10.8	< 0.001
FEV_1-pred%	91.4 ± 22.7	79.1 ± 21.8	-12.5 ± 10.4	0.002
TLC-pred%	96.5 ± 16.7	89.6 ± 14.3	-6.6 ± 6.4	0.010
RV-pred%	103.8 ± 26.8	96.9 ± 26.1	-5.9 ± 6.7	< 0.001
PEF-pred%	82.1 ± 20.8	68.9 ± 19.5	-15.4 ± 10.8	< 0.001
FEF 75-pred%	53.1 ± 26.6	48.3 ± 26.2	-9.3 ± 8.8	0.227
FEF 25-75-pred%	63.5 ± 28.5	56.1 ± 25.2	-10.6 ± 10.7	0.075
FEV_1-pred%	n (%)	n (%)		
≤ 80	15 (26%)	26 (46%)		
> 80	42 (74%)	31 (54%)		

Table IV. Multivariate analysis of predictors of pulmonary decrease after esophagectomy.

Variables	ΔFVC% F-value (*p* value)	$\Delta FEV_1\%$	ΔTLC%	ΔRV%	ΔPEF%	ΔFEF75%	ΔFEF25-75%
Sex	0.401 (0.530)	0.646 (0.425)	0.045 (0.832)	0.078 (0.781)	0.001 (0.992)	1.084 (0.301)	3.756 (0.059)
Age	0.34 (0.56)	0.025 (0.872)	0.066 (0.797)	0.025 (0.875)	0.063 (0.801)	1.095 (0.307)	0.467 (0.497)
Smoker	0.42 (0.527)	2.17 (0.159)	0.09 (0.765)	0.66 (0.428)	0.38 (0.546)	3.03 (0.223)	0.31 (0.586)
COPD	0.423 (0.518)	1.772 (0.189)	0.349 (0.557)	0.015 (0.902)	0.002 (0.964)	0.059 (0.810)	0.179 (0.673)
$FEV_1\% < 80\%$	2.820 (0.100)	3.246 (0.846)	0.846 (0.362)	0.499 (0.483)	1.782 (0.188)	0.002 (0.959)	0.581 (0.449)
NAD-Therapy	0.320 (0.574)	0.135 (0.714)	2.512 (0.095)	3.347 (0.072)	1.034 (0.313)	0.027 (0.870)	0.072 (0.788)
Type of surgery (CTL-group vs CL-group)	7.333 (0.009)	15.990 (< 0.001)	2.201 (0.145)	1.344 (0.252)	3.415 (0.071)	1.594 (0.220)	3.297 (0.076)
POPC	4.340 (0.043)	0.171 (0.681)	0.765 (0.386)	0.027 (0.870)	0.888 (0.351)	0.003 (0.955)	1.515 (0.225)

F: Fisher Exact Test.

cal procedures are normally accompanied by a severe risk of complications and a detrimental impact on health-related quality of life (QoL)[15,16]. In addition to this, there is some evidence[17] that "…patients who do not recover physical function, pain, and fatigue scores within 6 months after potentially curative treatment for oesophageal cancer are at significant increased risk of shorter survival…", implying that the management of post-operative complications and the recovery of physical fitness (in particular pulmonary function) after surgery are relevant positive elements with respect to the long-term outcomes. It has been assumed and partly proved that the impact of a post-operative rehabilitation strategy in patients undergoing esophagectomy is beneficial both in terms of long-term outcome[18] and quality of life (QoL)[17].

In this scenario, it is valuable to keep in mind all those factors that might be associated with physical fitness (and more generally with QoL) after surgery, as a significant part of the decision making process (clinical decision) before the final choice of treatment for EC. In this context, considering (1) the strong impact of surgery on the respiratory system and (2) the association between the post-operative pulmonary function and the post-operative physical fitness and QoL (as suggested by several authors[19,20]) we have hypothesized that the optimised and quick recovery of a normal lung capacity after surgery represents a factor of great importance in the overall strategy of care after radical esophagectomy.

The central aim of this study was to perform a comprehensive time-trend analysis of the pulmonary function after radical esophagectomy with the intent of identifying the risk factors with respect to a post-operative decrease in pulmonary function.

Firstly, we have noted a global worsening in pulmonary function in the entire population (Table III) when measured as modification in the spirometric parameters before surgery (T0) and 1 month after discharge (T1). In detail, such worsening consisted of a moderate – up to strong – post-operative change in the lung function (predominantly restrictive ventilator pattern) with decreases both in the vital capacity (FVC, TLC) and in the efficiency of lung emptying (PEF, FEV_1 and FEF25-75). The multivariate analysis suggests that this reduction in the spirometric tests was significantly more marked in patients who underwent CTL-surgery and in those who have experienced a POPC (see Table IV). These

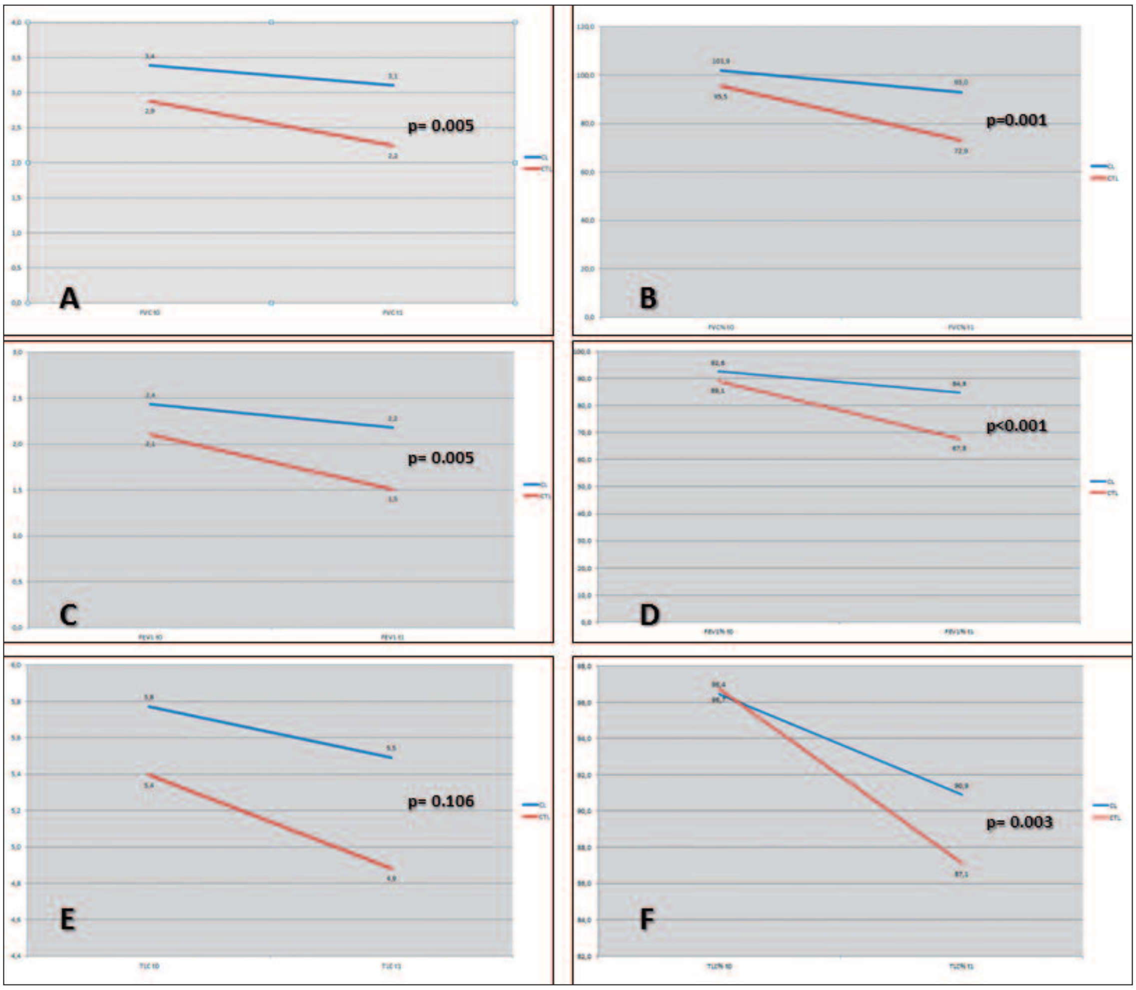

Figure 2. Pulmonary function modifications (T0-T1) according with surgical procedures: FVC ***(A)*** and FVC% ***(B)***; FEV_1 ***(C)*** and FEV_1% ***(D)***; TLC ***(E)*** and TLC% ***(F)***.

factors were proven to be independently related with a higher risk of pulmonary functional reduction after surgery while the baseline respiratory condition did not achieve the statistical significance. Actually, several studies[1,3,13], have already shown as the pre-operative respiratory status (smoking habit, presence of COPD and FVC/FEV_1 values) represents per se a predictive factor for POPC development, as confirmed by us (see Table II). Moreover, we have analysed the different patterns of time-trend pulmonary functional modification according to the surgical access adopted (Table V, Figure 2). As reported elsewhere[9], several patho-physiological mechanisms could be considered as the main cause of major respiratory dysfunction after transthoracic esophagectomy when compared with transhiatal esophagectomy. Firstly, there is an inadequate post-thoracotomy pain control; indeed, the thoracic incisions, in addition to the indirect effect caused by pain itself, strongly affect the integrity of the respiratory muscles and this results in pulmonary functionality reduction and, consequently, in a change in the quality of breathing even for some weeks after surgery[19].

There is, as well, an increasing evidence that patients who have undergone a trans-thoracotomic esophagectomy displayed significantly increased cytokine levels (IL6 and IL8) as a part of the systemic inflammatory response[21]. This, in fact, very probably alters the integrity of pulmonary alveolar-capillary membrane. Therefore, we may reasonably infer that the pattern of pulmonary functional reduction is affected by the interaction of all these causes. According with this evidence, from a theoretical point of view, patients underwent trans-thoracic esophagectomy may particularly benefit from an intensive reha-

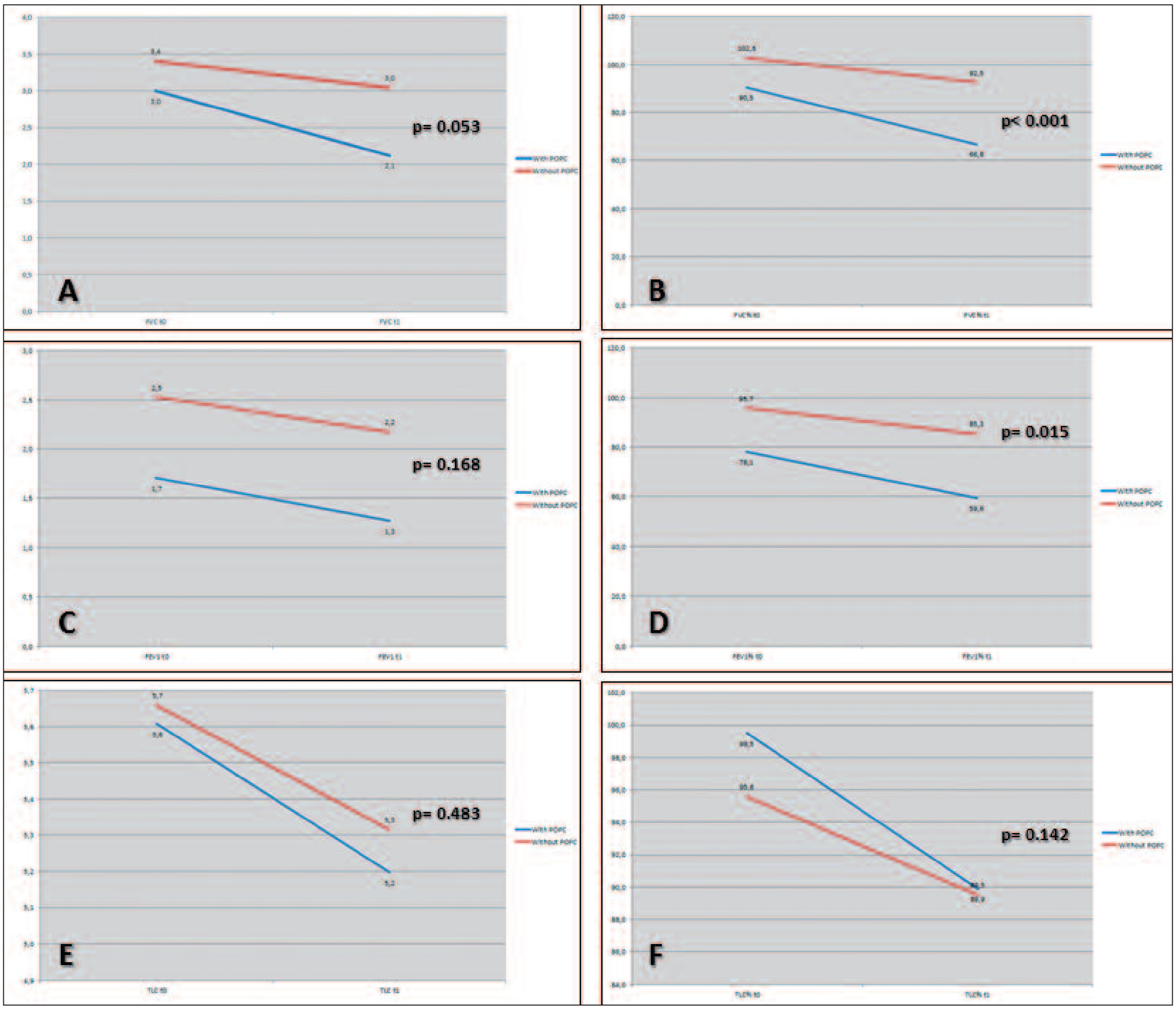

Figure 3. Pulmonary function modifications (T0-T1) according with the occurrence of POPCs: FVC *(A)* and FVC% (B); FEV_1 *(C)* and FEV_1% *(D)*; TLC (E) and TLC% *(F)*.

bilitation program, especially in terms of minor incidence of POPCs and better long-term pulmonary function.

The reduction of the POPC rate after esophagectomy, in particular, is a topic of increasing interest. Good results may be obtained by simply adopting targeted pre-operative interventions[22] but also performing an intensive chest physical therapy after surgery (Nakatsuchi et al[23]). Following this line of reasoning, this study clearly shows that the occurrence of a POPC is independently associated with a worse post-operative pulmonary recovery (see Table IV) and, accordingly, any targeted rehabilitation strategy with the aim of reducing POPC could also have the potentiality and likelihood of improving the long-term pulmonary functionality and physical fitness in such patients.

Despite the criticisms reported below, we may assume that (1) subjects with a respiratory poor baseline condition; (2) subjects scheduled for a CTL-approach and (3) those who experience a POPC after surgery, showed patterns of pulmonary function significantly worse when compared with other subsets of patients, being these subsets probably the best targets when planning multidisciplinary rehabilitation strategies.

This paper provokes usual criticisms associated with retrospective mono-centric studies: the long duration of patient recruitment and the overall limited number of patients. Moreover, a direct evaluation of the QoL before and after surgery was not

Table V. Comparative long term results of pulmonary function between CTL-Group and CL-Group and between patients with and without POPCs (*t*-test).

Variables	CTL-Group Mean ± SD	CTL-Group Median	CL-Group Mean ± SD	CL-Group Median	*p* value
Delta FVC	-0.5 ± 0.4	-0.4	-0.3 ± 0.3	-0.2	0.005
Delta FEV_1	-0.5 ± 0.4	-0.4	-0.2 ± 0.2	-0.2	0.005
Delta TLC	-0.4 ± 0.4	-0.3	-0.3 ± 0.3	-0.2	0.106
Delta RV	-0.2 ± 0.2	-0.2	-0.2 ± 0.2	-0.1	0.082
Delta PEF	-1.0 ± 0.6	-0.9	-0.6 ± 0.4	-0.5	0.215
Delta FEF 75	-0.1 ± 0.2	-0.1	-0.2 ± 0.3	-0.1	0.127
Delta FEF 25-75	-0.1 ± 0.1	-0.1	-0.2 ± 0.3	-0.1	0.404
Delta FVC-pred%	-22.2 ± 15.8	-22.5	-8.6 ± 6.2	-7.0	0.001
Delta FEV_1-pred%	-20.5 ± 13.4	-16.5	-7.4 ± 5.1	-7.0	< 0.001
Delta TLC-pred%	-9.5 ± 9.9	-7.5	-5.4 ± 5.8	-4.0	0.003
Delta RV-pred%	-8.2 ± 7.8	-4.5	-5.6 ± 8.5	-2.5	0.134
Delta PEF-pred%	-17.6 ± 13.9	-15.5	-10.1 ± 7.5	-8.0	0.021
Delta FEF 75-pred%	-6.5 ± 9.0	-3.0	-3.8 ± 3.3	-3.0	0.457
Delta FEF 25-75-pred%	-8.3 ± 10.0	-4.0	-5.9 ± 6.4	-4.0	0.188
Variables	**With POPC Mean ± SD**	**With POPC Median**	**Without POPC Mean ± SD**	**Without POPC Median**	***p* value**
Delta FVC	0.5 ± 0.3	0.4	0.3 ± 0.2	0.3	0.053
Delta FEV_1	0.4 ± 0.3	0.4	0.3 ± 0.3	0.2	0.168
Delta TLC	0.3 ± 0.3	0.3	0.3 ± 0.3	0.2	0.483
Delta RV	0.2 ± 0.2	0.2	0.2 ± 0.2	0.1	0.373
Delta PEF	0.8 ± 0.4	0.8	0.7 ± 0.6	0.6	0.423
Delta FEF75	0.1 ± 0.1	0.1	0.2 ± 0.3	0.1	0.130
Delta FEF 25-75	0.2 ± 0.1	0.1	0.3 ± 0.3	0.1	0.120
Delta FVC-pred%	22.5 ± 17.9	22.0	10.2 ± 7.9	8.0	< 0.001
Delta FEV_1-pred%	17.3 ± 13.0	14.0	10.0 ± 9.3	7.0	0.015
Delta TLC-pred%	8.8 ± 11.1	4.0	6.2 ± 6.2	5.5	0.142
Delta RV-pred%	7.1 ± 7.8	4.0	6.3 ± 8.5	3.0	0.384
Delta PEF-pred%	16.1 ± 14.4	15.0	12.5 ± 9.0	12.0	0.089
Delta FEF 75-pred%	4.2 ± 4.1	3.0	5.0 ± 6.7	3.0	0.350
Delta FEF 25-75-pred%	4.6 ± 5.0	3.5	5.9 ± 8.3	4.0	0.148

performed (EORTC QLQ-C30 was introduced only since 2010). Nevertheless, the primary endpoint of our study was to focus the analysis mainly on the time-trend pulmonary functional values (such as FEV_1) that may be assumed as surrogated indicators of physical fitness and QoL. However, this study has the merit to analyse, as never done before (to the best of our knowledge), the modification of pulmonary function (measured before and after radical esophagectomy) identifying the subsets of patients with a worse respiratory decrease, these representing, theoretically, the best candidates to include in prospective clinical trials with the aim of confirming the efficacy of rehabilitative strategies.

We believe that it is, as well, interesting to investigate the potential impact of (pulmonary) rehabilitative interventions not only in terms of long-term pulmonary function or physical fitness recovery, but also in terms of long-term overall and disease-free survival. In this sense, further investigations on this topic are warmly advocated.

Conclusions

In the context of a global reduction of pulmonary function, patients who underwent transthoracic esophagectomy or experienced a POPC showed a significantly worse pattern. These patients could be the "best target" for therapeutic rehabilitative strategies in the pre-operative and/or post-operative setting.

The validation of this hypothesis and its translation into everyday clinical practice require further investigations indeed performed on adequately powered prospective trials.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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