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ORIGINAL ARTICLE

Effect of implementing the European guidelines for functional evaluation before lung resection on cardiorespiratory morbidity and 30-day mortality in lung cancer patients: a case–control study on a matched series of patients†

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Abstract

OBJECTIVES: We hypothesized that postoperative cardiorespiratory morbidity and/or 30-day death rates decreased after implementing the new European ERS/ESTS guidelines for functional evaluation before lung resection and tested the hypothesis by means of a case–control study.

METHODS: The analysis included a series of 916 consecutive patients who underwent an anatomical pulmonary resection for non-small-cell lung cancer in our centre. Patients were divided into cases (September 2009–August 2012) and controls (December 2002–August 2009). We reviewed the records from a prospective computerized database; the final dataset included no missing data. The primary studied outcomes were the occurrence of cardiorespiratory morbidity or 30-day death after surgery. The patients were 1:1 propensity score matched according to the following variables age, ppoFEV1% and the need of pneumonectomy.

RESULTS: After the matching process, 670 cases (335 cases and 335 controls) entered into the study. The rates of pneumonectomy in cases and controls were 5.7 and 13.2%, respectively, ($P < 0.0001$) in the whole series and 5.7 and 6.9% after matching ($P = 0.52$). Cardiorespiratory morbidity was 8.1% (27 of 308) in cases and 9.8% (33 of 335) in controls [odds ratio (OR): 0.8; 95% confidence interval (CI): 0.4–1.4]. Thirty-day mortality was 0.90% (3/335) in cases and 1, 2% (4 of 335) in controls (OR: 0.7; 95% CI: 0.1–4.4).

CONCLUSIONS: Although we have observed a trend towards lower cardiorespiratory morbidity and 30-day mortality after implementing ERS/ESTS guidelines, the benefit of the guidelines remains unclear. Multicentric analysis including a very large number of cases is needed to demonstrate statistically the effectiveness of the guidelines to reduce operative mortality and cardiorespiratory morbidity. Maybe the effect could be easier demonstrated in series with higher operative mortality or morbidity.

Keywords: Clinical guideline • Surgical risk evaluation • Postoperative mortality • Postoperative cardiorespiratory morbidity

INTRODUCTION

Postoperative morbidity and, especially, 30-day mortality are probably the most important outcomes after lung resection. Any decrease in the rate of these indicators is considered a measure of quality improvement in patient health care.

Clinical Practice Guidelines (CPG) have been developed as powerful tools to improve patient health care [1]. The primary aim of any CPG is to improve the quality of the patient management based on standardizing the procedures [1]. This is based on the application of different and precise diagnostic and/or therapeutic procedures in a specific sequential way for every decision node during the management of the patient. The quality of the evidence used in the development of the guideline will determine the quality of the clinical guide. Sometimes it is not possible to find high-quality evidence for every clinical problem, so reviewing guidelines for continuous improvement is highly recommended [2]. Along the reviewing process, checking its influence on primary outcomes is paramount.

The aim of this study is to evaluate whether the implementation of the 2009 ERS/ESTS guidelines [3] for functional evaluation before lung resection decreased cardiorespiratory morbidity and 30-day death rates in our settings.

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METHODS

We have designed a propensity-matched case historical control study of a population of non-small-cell lung cancer (NSCLS)-operated patients. All data were obtained from a prospective computerized database, the final dataset included no missing data. Quality control of the data was assured by two successive audits made by the quality control manager of the unit (Gonzalo Varela), the first at the moment of patient hospital discharge and the second before sending the final records to the hospital central archive.

Study population

A series of 916 consecutive NSCLC patients that underwent any anatomical lung resection (lobectomy or pneumonectomy) in our institution has been reviewed. Patients were divided into cases: patients operated on between September 2009 and August 2012 and controls: patients operated on between December 2002 and August 2009. Starting date was selected in such a way that perioperative management was comparable all along the study period according to previously published criteria [4].

Patient preoperative assessment

For oncological study, all patients were evaluated through an extensive clinical staging work-up including physical examination, haematological and biochemical tests, ECG, chest Rx, endoscopy, CT scan and PET routinely. Invasive mediastinal staging by Endobronchial ultrasound bronchoscopy and esophageal ultrasound endoscopy or mediastinoscopy was indicated in selected cases with positive mediastinal PET scan or lymph nodes over 15 mm.

Evaluation of the patient's surgical risk was different in case and control series. The selection criteria for operation in the control group consisted of: Karnofski index over 50%, ppoFEV1% over 30, absence of hypercarbia and no concomitant systemic disease encompassing worse prognosis than NSCLC. Calculation of ppoFEV1% was based on the number of non-obstructed pulmonary segments to be resected [5].

In the case series, selection criteria followed the ESTS/ERS clinical guidelines [3] for preoperative evaluation of surgical risk.

Perioperative management

Cases and controls received comparable perioperative management as described in detail in previous papers [4]. In summary, patients' physical status was evaluated and both cases and controls were instructed on the use of incentive spirometer and the first outpatient visit. Also, all patients were encouraged to quit smoking—if needed—and to maintain physical activity according to their age and physical fitness. With the exception of those needing specific physical training, patients were admitted on the ward the day before surgery and intensive chest physiotherapy was started under the supervision of a dedicated physiotherapy team. All patients were operated on by the same surgical team through posterior muscle-sparing or video-assisted axillary mini-thoracotomy with the use of a rib retractor. Pulmonary fisureless technique was used whenever possible. Anaesthesia procedures were indicated and performed by senior cardiothoracic anaesthetists, with epidural catheter placement as a routine procedure for intraoperative and postoperative analgesia. As a rule, patients were extubated immediately after surgery in the operating room. Postoperative analgesia was achieved by epidural bupivacaine and fentanyl for 3 days and paracetamol and non-steroid anti-inflammatory drugs thereafter. Respiratory and general physiotherapy was restarted at the time of the patient's admission in the recovery room and continued at the ward until discharge.

Analysed variables and outcomes

The primary outcomes in the investigation are the occurrence of cardiorespiratory morbidity or 30-day mortality (defined as the patient's death due to any cause during the admission for surgery or within 30 days of hospital discharge). Any of the following postoperative events was considered cardiorespiratory morbidity: pulmonary atelectasis or pneumonia, respiratory or ventilator insufficiency at discharge (pO_2 under 60 mmHg or pCO_2 over 45 mmHg), need of mechanical ventilation at any time after extubation, pulmonary thromboembolism, arrhythmia, myocardial ischaemia or infarct and clinical cardiac insufficiency.

Statistics: propensity score-matched analysis, odds ratio calculation

Descriptive statistics of the whole series have been performed; patient characteristics (age, ppoFEV1%) and pneumonectomy rate between cases and controls before and after the matching process were compared using Student's *t*-test or by the Wilcoxon rank-sum test as appropriated.

Odds ratio (OR) with its 95% confidence intervals (95% CI) was estimated for postoperative morbidity and 30-day mortality on 2-by-2 tables before the matching process. Then, a logistic regression model was generated including the patient's age, ppoFEV1% and type of surgery as the independent variables and the type of risk estimation (before or after implementing ERS/ESTS CPG) as the dependent one. Propensity scores were calculated and cases and controls matched by the nearest neighbour method without replacement. All calculations were performed using the propensity score routine by Leuven and Sianesi for Stata 12.0.

After matching cases and controls, odds ratios with 95% CI were calculated again on 2-by-2 tables for both primary outcomes.

RESULTS

Nine hundred and sixteen anatomical resections for NSCLC were recorded within the study period. Five hundred and eighty-one patients were operated on between September 2002 and August 2009, before implementing CPG (controls) and 335 operated on between September 2009 and August 2012 following the ERS/ESTS CPG implementation (cases).

The analysed variables in cases and controls before and after the matching process are presented in Table 1. Before matching, cases and controls were different in age, ppoFEV1% and rate of pneumonectomy. These differences disappear after matching.

In the whole series (916 cases), 90 cases had some kind of cardiorespiratory complication (9.8%) and 13 (1.4%) died within 30

Table 1: Descriptive data of cases and non-matched and matched-control patients according to the propensity score variables

	Controls (*n* = 581)	Cases (*n* = 335)	*P*	Matched controls (*n* = 335)	*P**
Pneumonectomy	77 (13.2%)	19 (5.7%)	>0.001	23 (6.9%)	0.63
Age	66.4 (20.5–85.2)	66.1 (21.5–81.3)	0.011	67.5 (20.5–84.6)	0.84
ppoFEV1%	57.2 (27.6–108.4)	62 (27.9–107.7)	>0.001	62.1 (27.6–102.5)	0.09

**P*-value of the comparison between cases and matched controls.

Table 2: 2-by-2 table showing the data of cardiorespiratory morbidity and 30-day mortality before the matching process (*n* = 916)

	No	Yes	Total
Cardiorespiratory morbidity			
Control	518	63 (10.8%)	581
Cases	308	27 (8.1%)	335
OR: 0.72; 95% CI (0.43–1.18)			
30-day mortality			
Control	571	10 (1.7%)	581
Cases	332	3 (0.9%)	335
OR: 0.51; 95% CI (0.09–2.02)			

days of surgery. In the control group, cardiorespiratory morbidity was 10.8% (63 of 581) and in the cases group, the rate was 8.1% (27 of 335; OR: 0.72; 95% CI 0.4–1.2). The overall 30-day mortality was 1.4% (13 of 916), 0.9% (3 of 335) in cases and 1.7% (10 of 581) in control group (OR: 0.51; 95% CI: 0.1–2.1, Table 2). Pneumonia and atrial fibrillation (AF) were the most common cardiorespiratory complications in the whole series and within the group of matched patients. Sepsis and adult respiratory distress syndrome (ARDS) were the main causes of mortality (Table 3).

After the matching process, 335 cases and 335 controls entered into the study. Cardiorespiratory morbidity was 8.1% (27 of 335) in cases and 9.8% (33 of 335) in controls (OR: 0.8; 95% CI: 0.4–1.4). The operative mortality was 1.2% (4 of 335) before and 0.9% (3 of 335) after implementing CPG (OR: 0.7; 95% CI: 0.1–4.4) (Table 4).

DISCUSSION

The influence of CPG on medical practice has been discussed for years in the literature. Although its influence on improving the process of care seems to be high [6], especially when introduced in the context of rigorous evaluation [7], the size of the improvements for patients' outcomes are variable. To our knowledge, the effects of the 2009 European ERS/ESTS guidelines [3] for functional evaluation before lung resection on patients' outcomes have not been previously investigated.

ERS/ESTS guidelines [3] were developed by a panel of experts using the best possible available evidences on the studied topic. The level of evidence of the reviewed evidences varied from some level 1 studies to level 2+ and 2++, the last being the most frequent. The quality of the evidence allowed the authors to conclude only type B or C recommendations; however, this was the best possible CPG on fitness for radical treatment on NSCLC when it was developed. Although the main objective of CPG was to improve the quality of the process of selecting NSCLC patient for radical therapy, it could be hypothesized that, at least, the operative mortality of the series should be decreased.

As for the quality of the process of care, implementing the ERS/ESTS guidelines [3] in our settings has contributed to better standardization. First, DLCO, a fundamental parameter for risk estimation [8, 9] was measured in all cases. Second, the indication for high-technology exercise tests was accepted in a multidisciplinary discussion with the Pulmonology Department and, although in some cases we detected lack of compliance to the guidelines [10], considerable improvements in the case selection process were gained.

Regarding the influence of the guidelines on the outcomes, we could not find statistical differences between the rates of cardiorespiratory morbidity and 30-day mortality before and after implementing CPG. Since we have noted a clinically relevant trend towards lower operative mortality and cardiorespiratory morbidity (25 and 17% decrease, respectively) after CPG was implemented, the lack of statistical significance could have been caused by the size of the studied populations and also by the low rates of the primary outcomes.

Licker *et al*. [11], in 2006, published a trend towards decreasing perioperative mortality and respiratory morbidity after lung resection in the last decades and related this finding to less extensive pulmonary resections and the regular use of thoracic epidural catheter. More recently, Brunelli *et al*. [12] also found a decrease tendency for postoperative 30-day mortality and morbidity. Our reported decrease in operative mortality could also be a simple effect of time and non-controlled improvements in patient case. Nevertheless, the inclusion period is not long enough for these differences and also the matching process helps to control unadverted differences in both groups of cases. Our study can be considered a quasi-experimental one because a propensity matching score has been developed to perform the analysis. This

Table 3: Causes of morbity–mortality of the patients

	Control (n = 581)	Matched controls (n = 335)	Cases (n = 335)
Cardiorespiratory morbidity			
Atrial fibrillation	32	16	11
Pneumonia	15	7	11
Cardiac insufficiency	6	3	3
Atelectasis	6	5	1
Adult respiratory distress syndrome	2	1	0
Ictus	1	1	0
Myocardial infarction	1	0	0
Mortality			
Sepsis	3	1	2
Adult respiratory distress syndrome	5	3	1
Cardiac insufficiency	1	0	0
Myocardial infarction	1	0	0

Table 4: 2-by-2 table showing the data of cardiorespiratory morbidity and 30-day mortality after the matching process (n = 670)

	No	Yes	Total
Cardiorespiratory morbidity			
Control	302	33 (9.8%)	335
Cases	308	27 (8.1%)	335
OR: 0.8; 95% CI (0.4–1.4)			
30-day mortality			
Control	331	4 (1.2%)	335
Cases	332	3 (0.9%)	335
OR: 0.7; 95% CI (0.1–4.4)			

methodology has been proposed as a valid method for causal studies in the absence of randomized trials [13]. In this study, we have matched every case with a single control. This gives us the smallest propensity score distance between cases and controls and decreases the risk of biasing the population [13]. Another important point to discuss is the selection of variables to be included in the propensity score model. In our study, we have decided to include only the variables potentially related to the primary outcomes that, once properly matched, have the capability of homogenizing the risk between the control group and the cases group. Age, ppoFEV1 and pneumonectomy are well-known risk factors. After matching these three covariates, all differences should be due to the improvement added by the decision algorithm of the guidelines. To our surprise, we have obtained non-significant differences. This point has a limitation since DLCO was not routinely measured before implementing the ERS/ESTS guidelines and could not be included in the matching process.

In this series, we have analysed the 30-day mortality rate, but it is controversial whether we should have analysed another type of mortality rate. The use of standardized, valid and reliable definitions is fundamental to the accurate measurement of surgical adverse events. Defining row mortality is easy; the problem comes when trying to define different mortality rates attending to the time or where they have occurred and identifying which one is the most appropriated to detect quality of care problems [14]. It is clear that 30-day mortality and all procedure-related mortality are not equal clinical situations and have quality implications over the profile and rankings of the studied departments [14]. In a broad methodological review about surgical adverse events that contribute significantly to postoperative morbidity and mortality [15], the authors realize that the definition of surgical mortality is relatively consistent between monitoring systems but the duration of follow-up of death post-discharge varies considerably: most of the systems only report in-hospital mortality. Following a pragmatic approach, Williams's opinion [16] is that considerable resources are needed to identify those deaths that occur after discharge and before 30 days and the number of cases added to the in-hospital mortality is not relevant, so in-hospital mortality rate is the indicator to be measured. In contrast, Edwards *et al*. [17] consider that patients can make more informed decisions if they have long-term mortality or survival rates. This idea made them estimate the 1-year survival after valve replacement surgery. Recently, a report from the STS national database workforce [18] clarifies and recommends the use of their proposed definition of operative mortality as the standard parameter for comparison and quality control. They propose the term of operative mortality that encompasses all deaths occurring during hospitalization in which operation was performed, even if after 30 days (including patients transferred to other acute care facilities); and all deaths occurring after discharge from hospital but before the end of the 30th postoperative day. Our 30-day mortality rate fits that definition and most of the studies [19–21] supporting the development of the decision algorithm of the guidelines were based on 30-day mortality rates. So probably, 30-day mortality was the correct variety of mortality for analysis.

To conclude, although we have observed a trend towards lower cardiorespiratory morbidity and 30-day mortality after implementing ERS/ESTS guidelines, the benefit of the guidelines remains unclear. Multicentric series analysis including very large number of cases is needed to demonstrate statistically the effectiveness of the guidelines to reduce operative mortality and cardiorespiratory morbidity.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr A.Toker *(Istanbul, Turkey)*: Did you perform any comparison regarding economical analysis?

Dr Novoa: Not really.

Dr Toker: Do you have any idea?

Dr Novoa: We were not looking at that because, surprisingly, even though we didn't find statistical differences between the two ways of selecting patients, we think that we will recommend use of the algorithm, for two reasons. The first because we had a very low rate of cardiorespiratory morbidity and mortality at the beginning, so it was difficult to implement any method to decrease those rates, but also because the exercise testing gives us the opportunity to see in those marginal patients what areas we can improve in order to try to offer them the benefit of surgery. We haven't had any idea or interest in doing any comparison from an economical point of view. Our idea is to continue using this algorithm.

Dr S. Cassivi *(Rochester, MN, USA)*: I had the honour to visit you and see that you do very good work in Salamanca. My question to you on this is (and you may have the data or you may just even have a sense): did your rate of refusal for surgery change with the implementation of the guidelines? Did you have a higher rate of patients not being brought to the operating room? Did it change that rate?

Dr Novoa: That is a very good question. Even though we have a sense that we were rejecting more patients, it was not real. We haven't presented it here, but it is almost the same. But it is true, as you can see from the result tables, that the quality of the patients that we are operating on now is better than it was before, even though we have been rejecting patients with very, very low oxygen consumption.