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Assessment of preoperative noninvasive ventilation before lung cancer surgery: The preOVNI randomized controlled study

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3 **Assessment of Pre-operative Noninvasive Ventilation before Lung cancer Surgery:**
4 **the preOVNI Randomized Controlled Study**

5
6 Short title: Preoperative NIV before lung resection surgery

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30 **Video legend:** Presentation of the preOVNI study, Dr Nicolas Paleiron, MD.

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44 **Prior abstract publication/presentation**

45 Data have previously been presented at the annual congress of the European Respiratory
46 Society, 15–19 September 2018, Paris, France.

47 **Abbreviations list**

48 FEV: forced expiratory volume; FVC: forced vital capacity; TPC: total pulmonary capacity;
49 TLco/AV: diffusion coefficient of carbon monoxide per unit alveolar volume; NIV:
50 noninvasive ventilation

51 **Central message:** In this randomized controlled study, preoperative NIV before lung cancer
52 surgery did not reduce post-operative complications.

53 **Perspective statement:** NIV alone failed to reduce post-operative complications but, in the
54 NIV group, a non-significant lower rate of post-operative pneumopathies was observed.
55 Further studies should focus on specific comorbidities (such as COPD or cardiac

57 pulmonary rehabilitation or physiotherapy could be evaluated for fragile patients.

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63 **Objectives.** The preOVNI study was a randomized controlled open-label study that
64 investigated whether pre-operative noninvasive ventilation (NIV) could reduce post-operative
65 complications after lung cancer surgery.

66 **Methods.** Adult patients with planned lung cancer resection and with at least one cardiac or
67 respiratory comorbidity were included and randomly assigned to preoperative NIV (at least 7
68 days and 4 h/day) or no NIV. The primary endpoint was the rate of post-operative protocol-
69 defined complications.

70 **Results.** Three hundred patients were included. In the NIV group, the median NIV duration
71 was 8 days. No difference of post-operative complication rates was evidenced: 42.6% in NIV
72 group and 44.8% in no-NIV group ($p=0.75$). The rate of pneumonia was higher in no-NIV
73 group compared to NIV group, but statistical significance was not achieved (28.0 vs. 37.7%,
74 respectively; $p=0.08$). The type of surgery (open or mini-invasive) did not impact these results
75 after multivariable analysis.

76 **Conclusion.** No benefit was evidenced for preoperative NIV before lung cancer surgery.
77 Further studies should determine the optimal peri-operative management to decrease the rate
78 of post-operative complications.

79

80 **Keywords:** Noninvasive ventilation; Lung cancer surgery; Post-operative complications;
81 Randomized controlled trial.

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87 Surgery is the recommended treatment for localized non-small-cell lung cancer (NSCLC),
88 achieving a 5-year survival >50% for stages I–II.^{1, 2} Complication rate is 24–42% (mainly
89 persistent air leak, pneumonia, acute respiratory insufficiency and atelectasis) and 38% for
90 patients with COPD.^{3, 4} The main risk factors for complications are impaired respiratory
91 function, general health, general anesthesia, surgery-related diaphragmatic trauma and surgery
92 duration > 80 min.^{4, 5} The relative risk of death related to pulmonary complications is 14.9
93 (95% confidence interval [CI], 4.76–26.9), mainly related to the most serious respiratory
94 complications.^{4, 6–8} Therefore, guidelines of the European Respiratory Society and the
95 American Thoracic Society recommend preoperative assessment of the respiratory function
96 before lung cancer surgery.^{9, 10}

97 Preoperative noninvasive ventilation (NIV) seems to improve functional parameters when
98 realized during induction of anesthesia.^{11–14} Pathophysiology remains unclear, but
99 improvement in bronchial drainage and respiratory flow and volume could explain these
100 improved functional parameters. Preoperative NIV could also train patient to this procedure if
101 NIV is necessary after surgery. Regarding cardiac insufficiency, positive expiratory pressure
102 is known to favor alveolar recruitment and to decrease alveolar edema.¹⁵ A preliminary
103 prospective clinical trial studied pre- and postoperative NIV (BPAP) to prevent postoperative
104 pulmonary function impairment.¹⁶ Thirty-two patients with FEV1 < 70% were randomly
105 assigned to NIV from D-7 to D+3 vs. no NIV. NIV patients had significantly improved
106 respiratory parameters (PaO₂, FVC and FEV1) immediately after surgery suggesting an effect
107 of preoperative treatment.

108 The POPVNI trial assessed systematic postoperative prophylactic NIV on acute respiratory
109 events after major lung resection in patients with chronic obstructive pulmonary disease with
110 no reduction of acute respiratory events.¹⁷

112 NIV before lung cancer surgery. We tested the hypothesis that pre-operative NIV with BPAP
113 reduced the rate of post-operative complications in high-risk patients after lung cancer
114 surgery.

115

116 **MATERIALS AND METHODS**

117 **Study design**

118 The preOVNI study was a randomized controlled open-label multicentric trial performed
119 from 2012 to 2017 in 19 French centers. The primary objective was to demonstrate that pre-
120 operative NIV reduced the rates of post-operative complications in high-risk patients after
121 lung cancer surgery. The secondary objectives were to identify subgroups of patients
122 who benefited the most from preoperative NIV and to evaluate the safety of NIV.

123 The protocol was conducted in accordance with Helsinki's statement and was approved by an
124 independent Ethics Committee ("Ouest VI"). Written informed consent was obtained from
125 each patient. This study is registered with the ClinicalTrials.gov identifier NCT01685580.
126 The protocol of this study has been previously published.¹⁸

127 **Patients selection and inclusion criteria**

128 Patients ≥ 18 years were included if scheduled for lung resection (lobectomy or
129 segmentectomy) for NSCLC or suspicion. In addition, they should have at least one of the
130 following criteria: obstructive lung disease (FEV/FVC $< 70\%$ and predicted FEV $< 80\%$);
131 restrictive lung disease (FVC $< 80\%$ or TLC $< 80\%$); ratio TL_{CO}/AV $< 60\%$; history of
132 hypercapnic respiratory failure within previous year; long-term oxygen therapy; heart failure;
133 history of acute cardiogenic pulmonary edema; obesity (> 30 kg/m²). These criteria were
134 chosen to include high-risk patients for post-operative complications. The cardiac

136 cardiac insufficiency is strongly associated with post-operative complications.⁴

137 Main exclusion criteria were: planned pneumonectomy, patients refusing surgery or with
138 unresectable tumors or inoperable; contra-indication to NIV (lack of technical understanding,
139 facial malformation, tight stenosis of the upper airway, uncontrollable vomiting, unable to
140 remove the mask); cognitive impairment or severe psychiatric disorders; patient already on
141 invasive ventilation or NIV; pregnancy.

142 **Study conduct**

143 Visits and procedures of the study are described in **Figure 1**. Patients signed written consent
144 and were randomized at visit V1 (D-30 to D-7 before surgery). During visit V2 (consultation
145 or day hospital D-15 to D-7), clinical examination, spirometry and blood gas analyses were
146 performed and NIV was started under the supervision of a pneumologist. The device was
147 VPAP ST ventilator, ResMed[®]. The following pressures were proposed: from 3 to 6 cm H₂O
148 for positive expiratory pressure and from 10 to 14 cm H₂O for inspiratory pressure, but
149 investigators could modify them. These parameters were proposed but were not mandatory
150 because patients had very different comorbidities, sometimes associated. Indeed, parameters
151 of NIV are very different for obstructive or restrictive lung disorders or in case of cardiac
152 insufficiency. Parameters could be modified in case of poor tolerance. In order to detect sleep
153 apneas, a record was performed in the NIV group under continuous pressure of 4 cm H₂O for
154 the first night only (SHAM CPAP). The SHAM CPAP is not the gold standard for the
155 diagnosis of obstructive sleep apnea. It was used because observational studies showed no
156 decrease of apnea-hypopnea index (AHI) with 4 cm H₂O and airflow limitations are correlated
157 to AHI. Unlike previous study, NIV was stopped after the last night before surgery since the
158 objective was to specifically evaluate the pre-operative effect of NIV.¹⁶

160 home once during the NIV period and provided one phone call. In case of non-adherence or
161 safety event, the investigators were contacted. Compliance was precisely assessed with the
162 memory card of the device. The recommended daily duration of NIV was at least 6 h, either
163 continuously or discontinuously. It was thus proposed to perform NIV for 3 h after lunch and
164 in the evening; if NIV was well-tolerated during sleep, it could be prolonged throughout the
165 night. The provider completed a form on patient's compliance. Preoperative physiotherapy
166 was accepted if prescribed before randomization.

167 Post-operative NIV was allowed only in case of complications. Three visits were scheduled
168 after surgery: at hospital discharge (for clinical examination, record of complications during
169 hospitalization, spirometric tests, blood gas analysis), one month after surgery (for clinical
170 examination and record of complications) and after three months (telephone call for late post-
171 operative complications).

172 Spirometric tests were performed for all patients at visit V2 (NIV initiation for NIV group),
173 just before surgery, and at hospital discharge, using Piko-6 spirometer (nSpire Health, USA).
174 Blood gas were analyzed at visit V2, just before and after surgery, and at hospital discharge.

175 **Statistical analysis**

176 The primary endpoint was the rate of cardio-respiratory complications within one month after
177 surgery defined as: pneumonia or lower respiratory tract infection, prolongation of post-
178 operative intubation > 24 h, hypoxemic and/or hypercapnic acute respiratory insufficiency,
179 atelectasis, *de novo* atrial fibrillation, acute heart failure or death. Each complication was
180 precisely defined in the previously published protocol, stratified on CTACAE scale V3 and
181 blindly adjudicated by the scientific committee.¹⁸ For example, pneumonia was considered in
182 case of rapid onset of radiological findings (>72 h) with fever >38°C or inflammatory

184 analysis was also performed with patients without major protocol deviations.

185 Secondary endpoints were all separate items of the primary endpoint, duration of stay at
186 hospital and in intensive care unit (ICU), NIV safety (mask tolerance, facial cutaneous
187 lesions, air leakage duration) and adherence, respiratory and blood-gas parameters,
188 myocardial infarction, bronchial fistula, acute myocardial ischemia, post-operative
189 confusional state, post-operative venous thromboembolism, pneumothorax,
190 pneumomediastinum, sub-cutaneous emphysema and pleurisy.

191 Considering a rate of expected post-operative respiratory and cardiovascular complications
192 (primary endpoint) of 30% in control group and 15% in NIV group, 150 patients in each
193 group were necessary (bilateral alpha risk, 5%: power 83%; lost to follow-up 5%). Patients
194 were randomized 1:1 with block size of 4 and with stratification on centers.

195 Categorical variables were compared by Chi-square test (or Fisher's exact test) and
196 continuous variables by two-sided Student's t-test (or Wilcoxon test). Tests were two-sided
197 and a p value lower than 0.05 was considered to be statistically significant.

198 The primary endpoint was adjusted on clinically relevant variables, which are recognized as
199 predictive factors for postoperative complications: type of surgery (open or thoracoscopy
200 because there was significantly more thoracoscopies in the no-NIV group), COPD and CO
201 transfer (this was performed using logistic regression).

202 The analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

203

205 **Patients characteristics**

206 From 2012 to 2017, 300 patients were randomized: 153 in NIV group and 147 in no-NIV
207 group; 297 were included in ITT analysis (withdrawn/loss of consent for 3 patients) (**Figure**
208 **2**). The study centers were opened between 2012 and 2015. The objective was 15 active
209 centers and one center was closed because of low accrual. Seven centers included the majority
210 of patients. All centers were chosen because NIV-trained investigators were available.

211 There were 86 major deviations in ITT population (inclusion/exclusion criteria, $n = 7$; lost to
212 follow-up or patient decision, $n = 3$; surgery cancellation, $n = 9$; NIV ≤ 4 h per day or missing
213 data, $n = 67$). Per-protocol population included 211 patients: 135 in no-NIV group and 76 in
214 NIV group. Early study discontinuation occurred for 15 patients in each group. The primary
215 endpoint was assessed in 139 patients of no-NIV group and 145 patients of NIV group of ITT
216 population and in all patients of per-protocol population.

217 Patient characteristics in ITT population were as follows: mean (SD) age 64.3 (8.8) years,
218 male 70.7%, current smokers 32.2% and former smokers 63.7%, mean body mass index 25.6
219 (5.1) kg/m^2 (**Table 1**). Inclusion in the study was mainly due to obstructive lung disease
220 (47.1%), heart failure (27.9%), $\text{TL}_{\text{CO}}/\text{AV} < 60\%$ (22.1%) and obesity (17.3%). Other
221 comorbidities were history of cancer (14.5%), diabetes (11.4%) and hypertension (14.1%).

222 Lung cancers were mainly adenocarcinoma (55.2%) and squamous cell carcinoma (34.5%) at
223 stage I–II (89.1%) (**Table 2**).

224 **Perioperative management**

225 At visit V1, median FEV1 was 2080 mL, median forced vital capacity (FVC) was 3170 mL
226 and median FEV1/FVC was 0.7. Preoperative exams performed were echocardiography
227 ($n = 212$ patients, abnormal 69.3%), electrocardiogram ($n = 241$, abnormal 91.3%), $\text{TL}_{\text{CO}}/\text{AV}$

229 walk test (n = 28).

230 Median PaO₂ was 78.0 mmHg (n = 232 patients) at V2 and 81.0 mmHg (n = 167) before
231 surgery; the corresponding values for PaCO₂ were 38.0 (n = 231) and 39.0 mmHg (n = 167).

232 Patients underwent NIV for a mean (SD) of 9.8 (5.1) days and 6.9 (4.9) h/day (**Table 3**). The
233 mean percentage of days with NIV \geq 4 h was 68.1%. The compliance varied according to the
234 study centers: a median NIV use \geq 4 h per day was reported in 57.1% to 100% of patients in
235 centers that included two or more patients (**Supplement data table 1**). The mean (SD) initial
236 expiratory and inspiratory positive airway pressures were 5.1 (1.4) mmHg and 11.3 (2.3)
237 mmHg, respectively. During the first night, the mean (SD) residual apnea-hypopnea index
238 was 3.7 (6.0) per hour and sleep apnea syndrome was suspected for 22.9% of patients. A total
239 of 11.1% (15/135) of patients of no-NIV group and 19.0% in NIV group (27/142) underwent
240 preoperative respiratory physiotherapy (p = 0.067).

241 Surgery was more frequently thoracoscopy in no-NIV group compared to NIV group (26.4%
242 vs. 14.4%; p = 0.013) (**Table 2**). Locoregional anesthesia was performed in 16.7% of cases
243 and peridural anesthesia in 54.4%. The surgical procedure was most frequently lobectomy
244 (80.0%). Mean (SD) duration of surgery was 132 (65) min with no difference according to
245 treatment groups.

246 **Post-operative complications**

247 The overall rates of post-operative cardio-respiratory complications within one month after
248 surgery (main criteria) were 44.6% (62/139) in no-NIV group and 42.8% (62/145) in NIV
249 group for ITT analysis (p = 0.75) (**Table 4**).

250 The rate of pneumonia was higher in no-NIV group compared to NIV group, but statistical
251 significance was not achieved (37.7% vs. 28.0%, respectively; p = 0.08). The other

253 frequent were hypoxemic and/or hypercapnic acute respiratory insufficiency (15.3 vs. 14.1%,
254 respectively), atelectasis (13.2 vs. 12.3%), *de novo* atrial fibrillation (10.3 vs. 13.1%). No
255 difference was evidenced for the rates of complications with severity grade ≥ 3 .

256 Subgroup analyses did not evidence categories of patients who could benefit from NIV. There
257 was no decrease of complication rate with NIV in the COPD subgroup patients. The
258 complication rate in each group was adjusted on the type of surgery (open vs. mini invasive),
259 COPD and CO transfer < 60%: the adjusted odd ratio (NIV vs no NIV) was 0.86 (95% CI,
260 0.53–1.38; $p = 0.52$). Subgroup analyses did not evidence categories of patients who could
261 benefit from NIV. Concerning the higher rate of thoracoscopies in the no-NIV group, the odds
262 ratio for postoperative complications (NIV vs. no NIV) was 0.94 (95% CI, 0.71–1.24) in the
263 thoracotomy group and 0.75 (95% CI, 0.31–1.82) in the thoracoscopy group. Therefore, there
264 is no treatment effect heterogeneity associated with the type of surgery (**Table 5**). In per-
265 protocol analysis, the overall rates of complications were 45.2% for no-NIV vs. 42.1% for
266 NIV ($p = 0.67$).

267 The rates of the other complications were also comparable in no-NIV and NIV groups; the
268 most frequent were pneumothorax (12.6 vs. 10.9%, respectively), sub-cutaneous emphysema
269 (9.6 vs. 12.4%) and pleurisy (4.4 vs. 5.8%).

270 Mean (SD) duration of stay at hospital was 11.6 (6.4) days for no-NIV group and 11.9 (8.7)
271 days for NIV group ($p = 0.43$); mean durations of stay in ICU were 6.3 (6.6) and 5.9 (7.0)
272 days, respectively ($p = 0.45$). Mean duration of post-operative air leakage was 3.1 (4.0) days
273 in no-NIV group and 2.3 (3.5) days in NIV group ($p = 0.26$).

274 The day after surgery, median PaO₂ and PaCO₂ were 79.0 and 42.0 mmHg ($n = 77$ and
275 $n = 78$) in no-NIV group and 79.0 and 40.0 mmHg ($n = 80$) in NIV group, respectively. At

277 group and 72.5 and 38.5 mmHg (n = 70) in NIV group.

278 A total of 94.8% (127/134) of patients in no-NIV group and 89.7% (130/145) in NIV group
279 underwent postoperative respiratory physiotherapy (p = 0.11). A total of 22.9% (32/140) of
280 patients in no-NIV group and 28.1% (41/146) in NIV group underwent postoperative NIV
281 (p = 0.31) for a mean duration of 4.0 (3.5) and 5.9 (5.4) days, respectively (p = 0.096). Post-
282 operative NIV was realized only in case of complication.

283 **Safety**

284 Adverse events were comparable in both groups: 37.0% (54/146) in no-NIV group vs. 39.0%
285 (59/151) in NIV group including post-operative air leakage: 3.1 (4.0) days vs. 2.3 (3.5) days
286 (p = 0.26). Serious adverse events were 17.8% (26/146) vs. 17.2% (26/151), respectively.
287 Facial cutaneous lesions were reported in 1.6% (2/151) of NIV patients. NIV was
288 discontinued by 13.4% (17/151) of patients (mask intolerance, n = 1; intolerance to pressure
289 levels, n = 3; other, n = 13).

290

291 **DISCUSSION**

292 In this randomized controlled open-label trial, pre-operative NIV did not decrease post-
293 operative complication rate after lung cancer surgery (**Graphical abstract**). However, the
294 generalization of these results to other countries cannot be taken for granted due to differences
295 in patient care practices (for example, length of stay was longer than in other databases and
296 was dependent on centers). A multivariable analysis adjusted on type of surgery, COPD and
297 diffusion alteration did not change this result. Per-protocol analysis confirmed the intent-to-
298 treat analysis. There was only a non-significant decreased rate of pneumonia in the NIV
299 group, one of the items of the composite endpoint (37.7% vs. 28.0%; p = 0.08). There is a

301 preoperative NIV on functional parameters in thoracic surgery,¹⁶ NIV seemed to decrease
302 post-operative complications after aortic surgery. Thus, in an open-label monocentric study,
303 30 COPD patients were randomized to receive NIV 15 days before and after surgery.¹⁹ NIV
304 patients experienced less pulmonary complications (0% vs. 33%; $p = 0.004$) and shorter
305 duration of intensive care unit stay (2.5 vs. 6.5 days, $p < 0.001$). Although these results were
306 promising, sample sizes were small and protocols for NIV administration were heterogenous.

307 The strengths of our trial are the large sample size and the high rate of randomized patients
308 analyzed for the primary endpoint (94.7%). These strengths reinforce the conclusion of an
309 absence of effect of NIV in this population of patients. These results raise some questions:

310 The rate of cardio-respiratory complications in the control group was higher than expected
311 (44.8% vs. 30%). The initial 30% rate was the basis for the calculation of the sample size. The
312 objective of a decrease of 50% of postoperative complications seems too ambitious. Even
313 though a higher sample size could achieve statistical significance, we have no guarantee
314 however for a clinically significant difference. Nevertheless, the result concerning the most
315 frequent post-operative complication (pneumonia) is promising.

316 Another limitation is the open-label nature of the trial. The trial was not blinded for evident
317 reasons. Nevertheless, each cardio-respiratory complication was blindly adjudicated by the
318 scientific committee. Anyway, the limitations of open-label studies are rather questioned
319 when a difference between groups is observed.

320 The choice of the components of a composite endpoint is always difficult and the risk is to
321 mask a specific signal among too many individual components generating high background
322 noise. Therefore, we chose the most frequent and serious post-operative cardio-respiratory
323 complications.

325 thus complicating comparisons with other studies. These parameters were deliberately low
326 because we wanted to enhance compliance (patients had no other reason than surgery to
327 undergo NIV). Even with these parameters and individual adjustments by trained
328 investigators, adherence was low, thus suggesting that this regimen was difficult to follow for
329 these patients. We could not assess whether patients with poor compliance were those with a
330 higher risk of complications.

331 We selected patients on the basis of their high risk not on a single at-risk condition (obesity or
332 COPD, for example), which is another source of heterogeneity. The effects of NIV could have
333 been diluted, but no subgroup of patients seemed to benefit from NIV. About 30% of patients
334 were included because of cardiac insufficiency and NIV seemed to have absolutely no effect
335 regarding post-operative cardiovascular complications. Thus, it is possible that the choice of
336 the inclusion criteria and the main judgment criteria had an impact on the overall results.
337 Moreover, surgery type (open or VATS) may have also diluted the effect of NIV. Patients
338 without NIV underwent more pre-operative physiotherapy ($p=0.067$). Even considering this
339 result as non-significant, it could impact the result of the study.

340 The effects of NIV on functional respiratory parameters, including FEV1 and FVC, and the
341 high level of complications in COPD patients are rationale for an effect in COPD patients.
342 This treatment could be combined with smoking cessation, respiratory physiotherapy and
343 improvement of nutritional status; indeed, malnutrition is associated with increased
344 postoperative ventilation and increased length of hospital stay in COPD patients undergoing
345 lung reduction surgery.²⁰⁻²²

346 In recent years, noninvasive procedures such as stereotaxic radiotherapy or radiofrequency
347 have been developed for the most fragile patients. Moreover, thoracic surgery has been
348 improved: in France, 40% of patients actually benefit from video-assisted thoracoscopy or

350 This point should be considered for future studies, as the rate of thoracoscopies may have
351 biased our results.²³⁻²⁷

352 **CONCLUSION**

353 In this large-scale randomized study, no benefit was evidenced for preoperative NIV before
354 NSCLC surgery (**Figure 3**). Decreasing the rate of post-operative complications remains a
355 public health concern. Further studies should focus on particularly at-risk patients, excluding
356 those with cardiac insufficiency who are not reliable for noninvasive treatment of localized
357 NSCLC; stratification according to the type of surgery and the presence of obstructive sleep
358 apnea must be performed.

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364 **Author contributions**

365 Nicolas PALEIRON: conception and design, analysis and interpretation, writing the article,
366 critical revision of the article, final approval of the article, data collection, provision of
367 materials, patients, or resources, obtaining funding, literature search, administrative, technical,
368 and logistic support; Frédéric GRASSIN: conception and design, final approval of the article,
369 data collection, provision of patients; Christophe LANCELIN, Cécile TROMEUR, Jacques
370 MARGERY and Claudia NATALE: final approval of the article, data collection, provision of
371 patients; Francis COUTURAUD: conception and design, analysis and interpretation, writing
372 the article, critical revision of the article, final approval of the article, data collection,
373 provision of patients and statistical expertise.

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379 **Conflicts of interest**

380 No conflict of interest was reported by the authors for this study.

381

382

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456

457

458

460 groups had similar presentations.

	No-NIV group (n=146)	NIV group (n=151)	P-values
Age (year), mean (SD)	64.3 (8.9)	64.3 (8.8)	0.9780
Male, n (%)	100 (68.5)	110 (72.8)	0.4097
Body mass index (kg/m ²), mean (SD)	25.8 (5.3)	25.5 (4.9)	0.5939
Inclusion criteria, n (%)			
Obstructive lung disease	73 (50.0)	67 (44.4)	0.3313
Restrictive lung disease	13 (9.0)	19 (12.8)	0.2973
TL _{CO} /VA < 60%	34 (23.4)	31 (20.8)	0.5851
History of hypercapnic respiratory failure	1 (0.7)	3 (2.0)	0.6226
Long-term oxygen therapy	1 (0.3)	1 (0.7)	0.4932
Heart failure	38 (26.2)	44 (29.5)	0.5253
History of acute cardiogenic pulmonary edema	3 (2.1)	5 (3.4)	0.7230
Obesity	25 (17.2)	26 (17.4)	0.9624
COPD ^a	82 (56.9)	75 (50.0)	0.2328
Score of dyspnea (MRC), n (%)			
0	69 (50.7)	74 (52.1)	0.1899
1	51 (37.5)	44 (31.0)	
≥ 2	16 (11.8)	24 (16.9)	
Performance status (ECOG), n (%)			
0	83 (59.3)	87 (60.0)	0.6222
1	52 (37.1)	48 (33.1)	
≥ 2	5 (3.5)	10 (6.9)	
Epworth score, n (%)			
≤ 8	119 (90.2)	109 (80.1)	0.0304
9–14	13 (9.8)	26 (19.1)	
≥ 15	0	1 (0.7)	
Smoking, n (%)			
Current smoker	47 (32.2)	38 (25.2)	0.0639
Former smoker	93 (63.7)	97 (64.2)	
Never smoker	6 (4.1)	16 (10.1)	

461 NIV : non invasive ventilation, MD, missing data; SD : standard deviation, TL_{CO}, transfer factor of
 462 the lung for carbon monoxide ; VA, alveolar volume, COPD : chronic obstructive pulmonary disease,
 463 MRC : medical research council, ECOG : Eastern Cooperative Oncology Group.

464 ^a Defined as forced expiratory volume in one second (FEV1) divided by forced vital capacity (FVC)
 465 < 70%.

466

468 noticed in terms of type of cancers, staging, anesthesia. More thoracoscopies were performed
 469 in the no-NIV group.

	No-NIV group (n=146)	NIV group (n=151)
Lung cancer histology, n (%) ^a		
Adenocarcinoma	46 (54.1)	45 (56.3)
Squamous cell carcinoma	26 (30.6)	31 (38.8)
Small cell cancer	3 (3.5)	1 (1.3)
Carcinoid cancer	6 (7.1)	1 (1.3)
Other	4 (4.7)	2 (2.5)
Missing	132	61
Cancer stage (cTNM) at inclusion, n (%)		
I	84 (67.2)	83 (68.0)
II	29 (23.2)	24 (19.7)
III	10 (8.0)	14 (11.5)
IV	2 (1.6)	1 (0.8)
Missing	21	29
Type of surgery, n (%) ^b		
Thoracotomy	103 (73.6)	125 (85.6)
Thoracoscopy	37 (26.4)	21 (14.4)
Surgical procedure, n (%)		
Lobectomy	107 (78.1)	119 (83.8)
Pneumonectomy (unscheduled)	6 (4.4)	4 (2.8)
Segmentectomy	5 (3.6)	6 (4.2)
Wedge resection	19 (13.9)	13 (9.2)
Duration (min) from incision to closure, mean (SD)	128 (60)	136 (68)
Locoregional anesthesia, n (%)	21 (15.8)	25 (17.6)
Peridural anesthesia, n (%)	71 (53.0)	78 (55.7)

470 NIV : non invasive ventilation

471 ^a p = 0.2487 for lung cancer histology

472 ^b p = 0.013 for comparison of rates of thoracotomy vs. thoracoscopy.

473

475 of patients; 22.9% of patients presented with suspected sleep apnea syndrome.

	NIV group (n=151)
Initial parameters of NIV (Visit 2), mean (SD)	
Expiratory positive airway pressure (mmHg)	5.1 (1.4)
Inspiratory positive airway pressure (mmHg)	11.3 (2.3)
Minimal frequency (per min)	10.1 (2.4)
Compliance with pre-operative NIV	
Number of days with NIV, mean (SD)	9.8 (5.1)
Days with NIV \geq 4 h, n (%)	6.9 (4.9)
Percentage of days with NIV \geq 4 h, mean (SD)	68.1 (33.7)
Residual apnea-hypopnea index (per h), mean (SD)	3.7 (6.0)
Suspicion of sleep apnea syndrome during the first night, n (%) ^a	
No	74 (77.1)
Slight	11 (11.5)
Moderate	6 (6.2)
Severe	5 (5.2)

476 NIV : non invasive ventilation, SD : standard deviation.

477 ^a With continuous positive airway pressure 4 cm H₂O.

478

480 after surgery in the preOVNI study. No difference was found for the primary endpoint and the
 481 secondary endpoints.

	No-NIV group (n=146)	NIV group (n=151)	P ^a
Primary endpoint			
Post-operative cardio-respiratory complications, n (%)	62 (44.6)	62 (42.8)	0.75
Missing	8	8	
Components of the composite primary endpoint, n (%)			
Pneumonia or lower respiratory tract infection	52 (37.7)	40 (28.0)	0.08
Atelectasis	18 (13.2)	17 (12.3)	0.82
Hypoxemic and/or hypercapnic acute respiratory insufficiency	21 (15.3)	20 (14.1)	0.77
Prolongation of post-operative intubation > 24 h	2 (1.5)	0 (0)	0.25
Acute heart failure	3 (2.2)	8 (5.7)	0.14
<i>De novo</i> atrial fibrillation	14 (10.3)	18 (13.1)	0.47
Death	4 (2.9)	7 (4.8)	0.39
Other complications			
Myocardial infarction	1 (0.7)	2 (1.4)	1.00
Bronchial fistula	0	1 (0.7)	1.00
Acute myocardial ischemia	3 (2.2)	8 (5.7)	0.14
Post-operative confusional state	9 (6.7)	5 (3.6)	0.25
Post-operative venous thromboembolism	0 (0)	1 (0.7)	1.0
Pneumothorax	17 (12.6)	15 (10.9)	0.66
Pneumomediastinum	1 (0.7)	1 (0.7)	1.00
Sub-cutaneous emphysema	13 (9.6)	17 (12.4)	0.46
Pleurisy	6 (4.4)	8 (5.8)	0.59
Hospital stay (days)	11.5 (6.4)	11.9 (8.7)	0.44
ICU stay (days)	6.3 (6.6)	5.9 (7.0)	0.45
Air leak duration (days)	2.7 (3.8)	2.3 (3.5)	0.26

482 ICU: intensive care unit.

483 ^a Chi-square test.

484 **Table 5.** Subgroup analysis evaluating the effect of NIV vs. no NIV. Logistic regression analysis was performed as planned only for "previous
485 COPD", "TLCO <60%" and "type of surgery".

	Univariate analysis		Logistic regression analysis	
	Odds ratios (95% CI) for postoperative complications (NIV vs. no NIV)	P-value	Odds ratios (95% CI) for postoperative complications (NIV vs. no NIV)	P-value
NIV	0.93 (0.58–1.48)	0.75		
Age > 60 years	1.05 (0.60–1.83)	0.87		
Male sex	0.75 (0.43–1.30)	0.3		
BMI > 30 kg/m ²	2.13 (0.71–6.37)	0.17		
Active smoker	0.86 (0.36–2.09)	0.74		
Previous cardiovascular disease	0.94 (0.38–2.34)	0.9		
Previous COPD	1.26 (0.57–2.80)	0.57	0.91 (0.57–1.48) ^a	0.72
Previous stroke	0.71 (0.14–3.58)	0.68		
Previous cancer or hemopathy	0.75 (0.20–2.85)	0.68		
TLCO < 60%	0.44 (0.16–1.23)	0.54	0.87 (0.47–1.59) ^b	0.65
Thoracoscopy	0.67 (0.20–2.27)	0.52	0.85 (0.53–1.37) ^c	0.5
Loco-regional anesthesia	1.30 (0.40–4.20)	0.66		
Peridural anesthesia	0.66 (0.34–1.26)	0.2		

486 NIV, non-invasive ventilation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; TLCO, carbon monoxide free transfer.

487 ^a COPD vs. no COPD

488 ^b TLCO < 60% vs. ≥ 60%

489 ^c Open vs. thoracoscopy.

491 **Figure 1.** Visits and procedures during the preOVNI study. Patients were randomized at visit
492 V1. During visit V2, clinical examination, spirometry and blood gas analyses were performed
493 and NIV was started under the supervision of a pneumologist. Three visits were scheduled
494 after surgery: at hospital discharge (for clinical examination, record of complications during
495 hospitalization, spirometric tests, blood gas analysis), one month after surgery (for clinical
496 examination and record of complications) and after three months (telephone call for late post-
497 operative complications). NIV, noninvasive ventilation; V, visit; D, day.

498

499 **Figure 2.** CONSORT flow diagram of the preOVNI study. From 2012 to 2017, 300 adult
500 patients scheduled for lung resection (lobectomy or segmentectomy) for NSCLC or suspicion
501 were randomized: 153 in NIV group and 147 in no-NIV group; 297 were included in ITT
502 analysis. ITT, intent-to-treat; NIV, noninvasive ventilation.

503

504 **Figure 3.** Graphical abstract of the preOVNI study. The preOVNI study was a randomized
505 controlled study evaluating preoperative bilevel positive airway pressure (BPAP) before lung
506 cancer surgery; 300 patients were 1:1 randomized. There was no difference in terms of post-
507 operative complications between the two groups. CO, carbon monoxide; COPD, chronic
508 obstructive pulmonary disease; R, randomization.

300 

Lung resection for lung cancer

AND

COPD, restriction, altered CO diffusion,
cardiac insufficiency or obesity

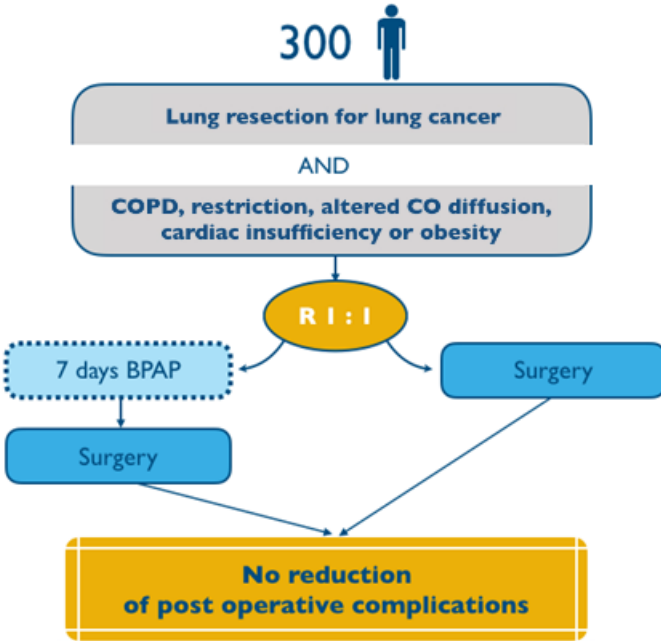
R I : I

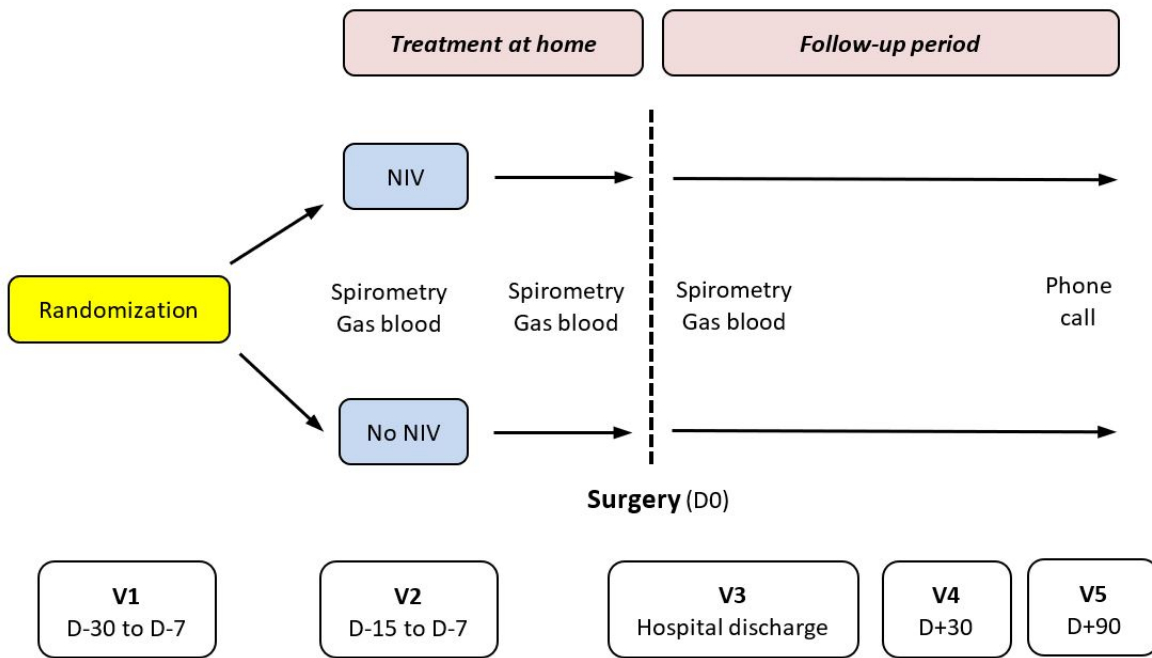
7 days BPAP

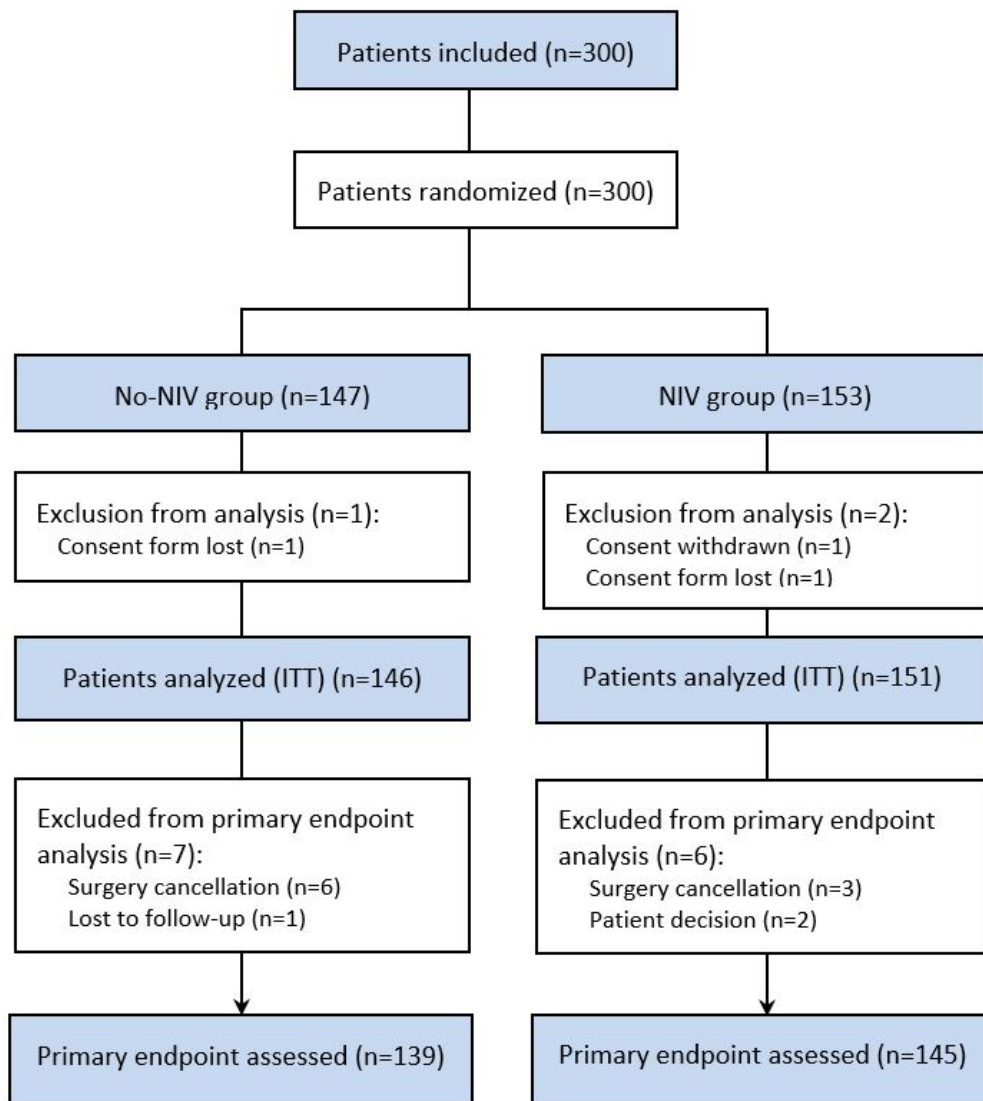
Surgery

Surgery

No reduction
of post operative complications







300 

Lung resection for lung cancer

AND

COPD, restriction, altered CO diffusion,
cardiac insufficiency or obesity

R I : I

7 days BPAP

Surgery

Surgery

No reduction
of post operative complications



Supplement Table. Adherence data for non-invasive ventilation in each center.

		Centers															
		All	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C12	C13	C15	C16	C17
		(N=151)	(N=16)	(N=50)	(N=9)	(N=9)	(N=4)	(N=1)	(N=2)	(N=34)	(N=2)	(N=9)	(N=2)	(N=1)	(N=3)	(N=8)	(N=1)
NIV adherence (median use >4h/day)	NA	36 (23.8%)	2 (12.5%)	4 (8%)	9 (100%)	2 (22.2%)	2 (50%)	0 (0%)	2 (100%)	2 (5.9%)	0 (0%)	7 (77.8%)	1 (50%)	0 (0%)	3 (100%)	1 (12.5%)	1 (100%)
	No	39 (33.9%)	6 (42.9%)	15 (32.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (37.5%)	1 (50%)	2 (100%)	0 (0%)	1 (100%)	0 (0%)	2 (28.6%)	0 (0%)
	Yes	76 (66.1%)	8 (57.1%)	31 (67.4%)	0 (0%)	7 (100%)	2 (100%)	1 (100%)	0 (0%)	20 (62.5%)	1 (50%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	5 (71.4%)	0 (0%)

NA, not available

C1: CHRU de Brest; C2: HIA Clermont-Tonnerre ; C3: HIA Clamart ; C4: HIA Saint-Anne ; C5: CHI Créteil ; C6: Hôpital Pasteur CHU de Nice ; C7: Centre Hospitalier Victor Dupouy ; C8: Clinique du Grand Large ; C9: Hôpital Pontchaillou ; C10: Hôpital de Boisguillaume ; C11 : HIA Laveran ; C12: Hôpital Nord Ouest ; C13: Centre hospitalier du Pays d'Aix ; C14: CHG Roanne ; C15: CHU Angers ; C16: CHU Limoges ; C17: CHU Saint-Etienne.

Primary objective:

The main objective of the preOVNI study is to demonstrate that bi level positive airway pressure at home during the 7 days preceding lung cancer surgery (lobectomy or segmentectomy) reduces postoperative pulmonary and cardiovascular complications in patients with obstructive or restrictive ventilatory disorder, obesity or chronic heart failure. The secondary objective is to determine the subgroups of patients who benefited most from preoperative non-invasive ventilation and the tolerance of this technique.

Type of study:

This is a French open-label multicenter randomized controlled trial comparing preoperative non-invasive ventilation with standard care.

Inclusion criteria:

Patient over 18 years of age, scheduled to undergo a planned lung cancer surgery (lobectomy or segmentectomy) for primary bronchial cancer and:

- Obstructive ventilatory disorder (FEV₁ / FVC <70% and FEV₁ <80% of the theoretical) or restrictive (CVF <80% or CPT <80%) or decreased TLCO / VA <60% or previous history of hypercapnic respiratory decompensation with Pa CO₂ > 45 mmHg in the year before surgery
- Or heart failure (precise definition given in the protocol)
- Or obesity (BMI > 30 kg / m²)

All patients included in the study must have benefited prior to the inclusion of the following exams: Cardiac ultrasound with evaluation of left ventricular ejection fraction, filling pressures, pulmonary arterial pressure on tricuspid insufficiency, aortic, mitral, pulmonary and tricuspid valve function 12-lead electrocardiogram

Respiratory function tests: spirometry (FEV₁, FVC, DEM₂₅, DEM₅₀, DEM₇₅), DLCO and DLCO / VA measurement, plethysmography (VR, CPT, VR / CPT)

Performing a ventilation/perfusion scintigraphy and VO₂max measurement to assess operability is at the discretion of the investigator, as recommended by the European Respiratory Society.

Criteria for non-inclusion:

The criteria for non-inclusion are the impossibility to consent, the contraindications to non-invasive ventilation (poor understanding of the technique, facial malformation, tight stenosis of the upper airways, uncontrollable vomiting, inability to remove the mask, disorders cognitive or psychiatric severe compromising adherence to NIV), uninsured patients social or already undergoing invasive or non-invasive ventilation. The planned pneumonectomy is a criterion of non-inclusion because the complications are rather different and a priori little influenced by the realization of preoperative NIV sessions.

Criteria for judgment:

The primary endpoint is a combined endpoint comprising the following postoperative cardio-respiratory complications: pneumonitis, hypoxemic and/or hypercapnic acute respiratory failure, segmental, lobar or pulmonary atelectasis, cardiac insufficiency, AC/FA.

The secondary criteria are: mortality, length of stay in hospital, tolerance of NIV on the number of hours of use and local complications, changes in functional respiratory parameters and haematosis, duration of postoperative bubbling, bronchial fistulas, pneumothorax, pneumomediastins, extensive subcutaneous emphysema, pleurisy, venous thromboembolic events, postoperative confusion syndromes and all items of the primary endpoint, taken individually. Postoperative respiratory and cardiac complications have been precisely defined in the protocol. Their severity is measured by the

Practical arrangements:

Non-invasive ventilation will be started in the hospital (in consultation or day hospital, at the discretion of the principal investigator of the center), 7 to 15 days before surgery, under the supervision of a pulmonologist. The device used in this study is the S9 VPAP ST (Resmed®). It will be performed at home by an accredited provider with experience of this type of treatment. To ensure good compliance, the provider will commit to come to the patient the day after the start of treatment, then ensure at least 1 telephone contact before surgery. The provider will communicate the compliance of NIV to the investigator by completing a standardized form. Non-invasive ventilation may be continued after surgery at the discretion of the investigator. The interface will be a naso-oral mask or nasal or oral. The following parameters will be used to initiate ventilation, and may be modified by the investigator depending on the patient's tolerance:

- AI: 10 to 14 cm H₂O,
- PE: 3 to 10 cm H₂O,
- Minimum frequency: 7 to 15 / min,
- Slope: 150 ms.

The recommended daily duration will be 6 hours a day, recommending 1 session of 3 hours a day, and a session of 3 hours in the evening. If the patient supports it, non-invasive ventilation may be continued overnight.

Following the surgical procedure, the patient will be able to benefit from non-invasive ventilation sessions (regardless of his randomization arm) in case of complications. The indication, the ventilatory mode, the interface, the daily duration and the number of sessions will be indicated in the CRF. Postoperative "systematic" NIV is not allowed.

Statistical analysis:*Descriptive statistics*

Calculation of frequencies and 95% confidence intervals for categorical variables; calculation of means and standard deviations after verification of a normal distribution for continuous variables. A flow chart will be realized. The sample will be described using the usual statistical parameters.

Analytical statistics

The main analysis will be done in "intent to treat"; a secondary analysis "per protocol" will be realized

Univariate analysis

The analysis of the primary endpoint will be performed by comparing the frequencies of patients with complication (primary endpoint) in both arms, using a Chi² test.

Regarding the secondary criteria, the two arms will be compared:

- using a Student's test for quantitative variables (or a Wilcoxon test in case of non-normality of the distribution of the variable considered)
- using a Chi² test for qualitative variables (or a Fisher test if necessary)
- using a log-rank test for survival data type variables

Multivariate analysis

Multivariate analyzes will complement the previously defined univariate analyzes, in order to obtain an adjustment for possible confounding factors on the one hand, and to look for possible interactions on the other. The models used will be: logistic regression, linear regression, Cox model.

300 

Lung resection for lung cancer

AND

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R I : I

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