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2 Impact of VATS approach on postoperative mortality after lobectomy in octogenarians

3

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26

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37 **Glossary of abbreviations**

38 CI: Confidence interval

39 CCI: Charlson comorbidity index

40 LC: Lung cancer

41 OR: Odd ratio

42 OT: Open thoracotomy

43 PS: Propensity score

44 VATS: Video-assisted Thoracic Surgery

45

46 **Central Picture**

47 Increase in the rate of lobectomies performed by VATS in French octogenarians.

48

49 **Central message**

50 More and more octogenarians are fit for surgical management of localized lung cancer. VATS

51 techniques significantly reduce postoperative mortality after lobectomy in this population.

52

53 **Perspective statement**

54 The life expectancy of octogenarians in western countries is close to 10 years. A minimally

55 invasive approach such as VATS lobectomy is a surgical management option with acceptable

56 postoperative mortality which should be offered to octogenarians with localized lung cancer.

57

58

59 **Abstract**

60 **Objective:** The number of octogenarians who present with localized lung cancer eligible for
61 surgical resection is increasing. Video-assisted thoracic surgery (VATS) lobectomy has been
62 widely accepted, but the potential benefit in octogenarians is not well established, especially
63 for postoperative mortality. This study aimed to assess the impact of a VATS approach on
64 postoperative mortality after lobectomy for lung cancer in octogenarians.

65 **Methods:** From January 2005 to December 2016, all patients over 80 years old who had
66 lobectomy treatment for lung cancer were retrieved from the French Administrative Database.
67 The end point was 30-day postoperative death. A propensity score was generated with 16
68 pretreatment variables and used to create balanced groups with matching (578 matches 1:1).
69 Results are reported as odds ratios and 95% confidence intervals.

70 **Results:** Out of the 75,892 patients operated for lobectomy during this period, 3,560 were
71 octogenarians. VATS was done in 16.7% (n=597) of cases and thoracotomy in 83.23%
72 (n=2,963). From 2005 to 2016, the number of patients over 80 years who were operated for
73 LC increased from 160 to 456 patients a year, and the proportion of lobectomy performed by
74 VATS grew as well (from 3.13% to 37.28%). Unmatched postoperative mortality was 3.85%
75 (n=23) for VATS vs 7.9% (n=234) for thoracotomy (p<0.0001). Matched postoperative
76 mortality was significantly lower in the VATS approach with an odds ratio of 0.51 (95%CI
77 [0.27-0.96]); p=0.038).

78 **Conclusion:** VATS was significantly associated with reduced postoperative mortality as
79 compared to open thoracotomy after lobectomy for lung cancer in octogenarians.

80 **Key-words:** Octogenarians, thoracoscopy, video-assisted thoracic surgery, postoperative
81 mortality, matching

82 **Manuscript**

83

84 **Introduction**

85 Lung cancer (LC) is the fourth most common type of cancer, with estimations of over
86 234,030 new cases in 2018. It is the leading cause of cancer death with around 154,050 cases
87 a year, which represents 25% of all cancer deaths in the US [1]. Lung cancer is diagnosed at a
88 median age of 70 years in the Western world, and the probability of developing LC after 70
89 years of age is around 6.1% for men and 4.8% for women [1,2]. According to the statistical
90 analysis issued by the US Department of Health and Human Services in 2015, the life
91 expectancy of octogenarians is increasing and the total population of octogenarians will
92 increase by 50 to 70% in Europe and US over the next 20 years [3]. As a result, thoracic
93 surgeons are increasingly faced with elderly patients, particularly octogenarians, with
94 localized LC for which surgical management is a subject of debate. At present, lobectomy
95 remains the best treatment for localized LC [4]. When Video-assisted Thoracic Surgery
96 (VATS) is used, there is a significant benefits in terms of postoperative pain, respiratory
97 complications and length of hospital stay after lobectomy [5–8].

98 Since the 1990's, many publications have highlighted the feasibility of LC surgery in
99 octogenarians and the importance of establishing a precise preoperative evaluation of
100 cardiopulmonary function in these patients [9]. In 2011, Rivera et al. described the
101 specificities for surgical management of octogenarians using data from Epithor (French
102 clinical database) [10].

103 However, the available data regarding the results of LC surgery in octogenarians are based on
104 small sample sizes, especially as regards the benefit of VATS on postoperative mortality
105 [9,11–17], making it difficult to draw conclusions about the benefit of VATS in this particular
106 population. The aim of this study was to assess the impact of a VATS approach as compared

107 to open thoracotomy (OT) for lobectomy in octogenarians using the French national
108 administrative database. This database collects data from all hospitals in France performing
109 lobectomy for LC and is much more representative than data collected from specialized
110 centers alone. A propensity score (PS) matching analysis was used to yield a more powerful
111 and comprehensive comparison of postoperative mortality.

112

113 **Materials and Methods**

114 *Data source and study population*

115 All data for patients who underwent pulmonary resection for LC in France from January 2005
116 to December 2016 were collected from the national administrative database. This database,
117 called PMSI (Programme de Médicalisation des Systèmes d'Information), was inspired by the
118 US Medicare system. The reliability and validity of PMSI data have already been assessed
119 [18]. Routinely collected medical information includes the principal diagnosis, secondary
120 diagnoses and procedures performed. Diagnoses identified during the hospital stay are coded
121 according to the International Classification of Diseases, tenth revision (ICD-10) [19]. We
122 selected patients in whom a diagnosis of primary LC was coded as the principal discharge
123 diagnosis (all codes C34). Procedures are coded according to the CCAM (Classification
124 Commune des Actes Médicaux). For all patients, LC was proven by pathology analyses
125 according to the 2004 World Health Organization classification of LC [20]. Surgery-related
126 variables included the surgical technique (thoracotomy or video assisted thoracic surgery).

127

128 *Patients' characteristics*

129 Baseline demographics included age and gender. We included the following comorbidities
130 which were available from the national administrative database: pulmonary disease (chronic
131 bronchitis, emphysema), heart disease (coronary artery disease, cardiac arrhythmia,
132 congestive heart failure, valvular heart disease, pulmonary artery hypertension, pulmonary

133 embolism), peripheral vascular disease, alcoholism, liver disease, cerebrovascular events,
134 neurological disorders (hemiplegia or paraplegia), dementia, diabetes mellitus without
135 complications, diabetes mellitus with complications, kidney disease, coagulopathy, leukemia,
136 lymphoma, ulcer disease, history of malignant disease, obesity, and other therapies
137 (preoperative chemotherapy, steroids). We also calculated a modified Charlson Comorbidity
138 Index (CCI) as a marker of comorbidity [21].

139

140 ***Outcome measurements***

141 Postoperative mortality was defined as any patient who died in hospital (including transferred
142 patients) within the first 30 days after the operation and those who died later during the same
143 hospitalization.

144

145 ***Variables used for PS analysis***

146 Variables used to estimate the PS were age, sex, comorbidities (pulmonary disease, heart
147 disease, peripheral vascular disease, neurological diseases, liver disease, kidney disease,
148 coagulopathy, hematologic disease, infectious disease, and metabolic disease), other
149 treatment, modified CCI score, type of medical center, hospital volume and year of surgery.

150

151 ***Statistical analysis***

152 To determine the independent factors of in-hospital death, we first performed univariate
153 analysis with the chi-squared test for binary and categorical variables and a t-test for
154 continuous variables. The PS is the conditional probability of assignment to a particular
155 treatment given a vector of observed covariates [22]. PS matching was used to balance the
156 distributions of measured potentially confounding covariates for patients treated by VATS or
157 OT. A mirrored histogram was used to measure the discriminatory ability of the PS matching.

158 Matching used a search algorithm to find a set of weights for each covariate so that optimal
159 balance is achieved after matching [23]. We used 1:1 matching without replacement in
160 descending order with a caliper of 0.01. We evaluated PS matching by its ability to balance
161 the measured covariates between VATS and OT by reducing the standardized difference [24],
162 which is the difference between sample means in the VATS and OT groups divided by the
163 standard deviation in the treatment group overall [23]. For postoperative mortality, a logistic
164 regression model was used to generate OR (odds ratios), p-values and confidence intervals.
165 STATA 14 statistical software (StataCorp, College Station, Tex) and R statistical software,
166 for which we used Harrell's Design library (<http://www.r-project.org>), were used for the
167 analyses.

168

169 **Results**

170 *Study cohort*

171 Of the 75,892 patients who underwent lobectomy from January 2005 to December 2016,
172 3,560 were octogenarians. Lobectomy was performed by VATS in 597 patients (16.77%) and
173 OT in 2,963 patients (83.23%). There was a continuous increase in the number of patients
174 over 80 years who were operated for LC over the study period, going from 160 patients in
175 2005 to 456 patients in 2016 (Figure 1). Moreover, there was a progressive increase in the
176 proportion of VATS lobectomies, from 3.13% in 2005 to 37.28% in 2016 (Figure 2).

177 Unmatched patient demographics and hospital characteristics are presented in Table 1. In the
178 OT group, there was a significantly greater proportion of men and of younger patients. They
179 also tended to have a past-history of pulmonary, heart and vascular disease, with a CCI score
180 ≥ 3 and other treatment, but a lower likelihood of liver disease (Table 1). VATS was
181 performed in all health center types, but significantly more often in centers which saw more
182 than 21 lobectomies a year (Table 1).

183 The characteristics of the matched groups are outlined in Table 2. In the matched samples,
184 578 patients were balanced in each group, and none of the patient characteristics are
185 significantly different for the two groups (Table 2).

186

187 *PS estimation*

188 The mirrored histogram shows the well-balanced distribution of the covariates after PS
189 matching (Figure 3). The median distribution of standardized biases was 0.022 for the
190 matching approach (Table 2). The standardized difference never reached the value of 10%
191 (Table 2), which shows that the covariates of two groups were well balanced by matching
192 [25].

193

194 *Postoperative Mortality*

195 Unmatched crude postoperative mortality was 3.85% (n=23) for VATS vs 7.9% (n=234) for
196 OT ($p<0.0001$). After matching, postoperative mortality was 3.46% (n=20) for VATS vs
197 6.57% (n=238) for OT. Over the time period, matched-adjusted postoperative mortality
198 significantly decreased ($p=0.04$) (Figure 4). Matched postoperative mortality was
199 significantly lower in the VATS sample with an OR of 0.51 (95% CI [0.27-0.96]); $p=0.038$).

200

201 **Discussion**

202 In 2015, LC was the second leading cause of death after heart disease in the American
203 population of octogenarians and the leading cause of death by cancer, with around 40,000
204 attributed deaths in 2015 [1]. However, it has been noted that age had a stronger impact than
205 comorbidities on the probability of being offered surgical treatment. Indeed, elderly patients
206 without significant comorbidities were less likely to be recommended surgery as compared
207 with younger patients with significant comorbidities [26].

208 In 2015, an 80-year-old French man was expected to live for an additional 8.6 years and a
209 French woman for 10.8 more years. As a result, radical management for localized LC should
210 be considered a treatment option [3].

211 Since the end of the 1990's, surgeons have revolutionized the surgical management of the
212 elderly. In parallel, research has highlighted the predictable changes in pulmonary physiology
213 occurring with surgery and anesthesia and developed existing knowledge of the factors
214 associated with postsurgical complications. Lobectomy reduces lung capacity, increases
215 diaphragm dysfunction, and impairs gas exchange, cough and mucociliary clearance, leading
216 to the development of postoperative complications particularly in patients with chronic
217 obstructive pulmonary disorder and the elderly [9].

218 In the last decade, significant advances in anesthesia and surgery techniques have led to an
219 increase in the number of elderly patients who are offered surgery, which can be seen in our
220 study. Indeed, the appeal of VATS for lobectomy has been widely acknowledged by thoracic
221 surgeons. In 2016, our data reveals that VATS was used on close to 40% of octogenarians
222 undergoing lobectomy. The sweeping use of VATS for lobectomy in France slightly exceeds
223 the proportion of VATS lobectomy reported by Abdesattar et al. from the US National Cancer
224 database (30.5%), but is lower than the 63% reported in the Society of Thoracic Surgeons
225 database [27,28]. This upwards trend could be explained by the reports of decreased
226 postoperative complications and the benefits for patients with a past history of pulmonary
227 disease, like those seen in our study [29].

228

229 *Postoperative mortality*

230 The impact of VATS lobectomy on postoperative mortality is not yet well established. There
231 have been reported decreases in postoperative mortality in standard populations of LC
232 patients who are operated with the VATS technique. The studies in question took patient

233 records from 3 large databases (one clinical database, [the European Society of Thoracic
234 Surgery], and two administrative databases, [the SEER database and the Nationwide Inpatient
235 Sample database]) and used PS matching analyses [30–32]. However, several other studies
236 (meta-analysis or from The French National Epithor database), did not report a difference
237 between VATS and OT techniques in a general population with localized LC [5–8,33]. A
238 recent paper from the American College of Surgeons National Surgical Quality Improvement
239 Program (ACS-NSQIP) reported less postoperative mortality after VATS in patients less than
240 75 years old, but not for patients between 75 and 80 years old [34]. Moreover, recent results
241 from large RCT comparing VATS to OT for lobectomy found no difference in postoperative
242 mortality [35]. The mean age in these studies ranges from 58 to 75 years old.

243 The patients in our population were all over 80 years old, with a crude postoperative mortality
244 of 3.85% after VATS and 7.9% after OT. Few articles have been published regarding
245 postoperative mortality after lobectomy in octogenarians. Studies which have included a
246 series of more than 100 patients report post-lobectomy mortality rates ranging from 2% to 6%
247 [15–17]. The higher rate of postoperative mortality in our study could be due to several
248 factors. Firstly, around 40% of patients had a CCI score ≥ 3 even after matching, including at
249 least a past-history of pulmonary with cardiac disease and a metabolic dysfunction, which has
250 been correlated to a relative risk of death after 80 years old of 12.76 by Charlson et al. [21]. A
251 recent paper from Eguchi et al. dealing with the cause of death after lobectomy for stage I LC,
252 showed that 30- and 90-day mortality were caused by cardiopulmonary complications, and
253 that low predictive postoperative diffusing capacity of the lung for carbon monoxide was an
254 independent predictor of 1-year mortality and noncancer-specific mortality [36]. Therefore,
255 they also highlighted that noncancer-specific mortality was higher than cancer-specific
256 mortality in patients over 75 years old until 2.5 years after surgery [36].

257 So, the mechanism which permit to obtain a lower postoperative mortality with VATS
258 approach seems to be linked to better postoperative pulmonary function, especially in
259 octogenarians. Detillon et al. recently highlighted percentage of predicted forced expiratory
260 volume in 1 second to be an independent factor of postoperative mortality in individuals over
261 80 years [17]. The postoperative recovery of forced expiratory volume in 1 second has been
262 shown to be faster in patients who undergo minimally invasive anatomic lung resection as
263 compared to OT [37]. The benefit of the VATS approach seems to disappear after 3 months,
264 and, at that point, loss of pulmonary function is equivalent for VATS and OT [38].

265 Secondly, our study was conducted using the French administrative database, which includes
266 all centers performing LC surgery in France whatever the type and the volume of activity.
267 This could explain the higher postoperative mortality compared to other publications whose
268 data was restricted to teaching hospitals or a group of centers with a significant volume of
269 thoracic surgery [11–16].

270 PS matching was used to balance covariates, and consequently the two groups were
271 comparable in terms of preoperative comorbidities and hospitals characteristics. We were
272 therefore able to assess the impact of the chosen technique on postoperative mortality.
273 Potential explanations for the lower postoperative mortality in the VATS group could be
274 attributed to lower postoperative pain and to a de facto lower incidence of respiratory
275 complications, as previously described [5–8]. However, octogenarians are a singular
276 population, in which the weight of preoperative comorbidities, especially past histories of
277 cardiac and pulmonary disease, is a major source of postoperative complications and
278 postoperative mortality.

279 Only one set of recommendations for the management of elderly patients with LC has been
280 published in the last years. However, these guidelines focus on surgery in the elderly, who are
281 generally between 70 and 80 years, and are based on small retrospective studies. No

282 randomized control trials have been conducted on an elderly population whatever the
283 treatment, and, as previously reported, the elderly are frequently underrepresented in clinical
284 trials evaluating new cancer treatments or surgical techniques [39].

285

286 *Strengths and limitations*

287 We recognize that there are limitations to our study. Given our reliance on ICD-10 codes for
288 the selection of patients and the ascertainment of outcomes, there was a potential for
289 misclassification or underdetection-related biases, especially for comorbidities. Coding
290 practices vary significantly among institutions. Nevertheless, coding quality is checked by
291 medical information professionals in each hospital to correct diagnoses and increase the
292 number of recorded comorbidities. No details were available for certain center characteristics
293 (number of beds in surgery departments and intensive care units, number of days spent in
294 intensive care, number of nurses and medical practitioners), the organization of the surgery
295 (multidisciplinary team meeting, use of guidelines, surgeon qualifications, surgery performed
296 by residents) or details about preoperative management (chemotherapy) and postoperative
297 outcomes and complications

298

299 The French Administrative database does not record LC information (type of cancer, stage
300 (TNM classification), type of lobe involved), preoperative pulmonary function (preoperative
301 forced expiratory volume, percentage predicted diffusing capacity of lung for carbon
302 monoxide), American Society of Anesthesiologists score, and data for postoperative
303 complications (prolonged airleaks, pneumonia, atelectasis, empyema, hemothorax, arrhythmia,
304 myocardial infarction) and length of hospital stay. No Information was available regarding the
305 different types of open thoracotomy (postero or antero-lateral OT, muscle sparing OT) or the
306 experience of each centre in VATS lobectomy prior to this study.

307 Analyses using propensity score methods attempt to emulate randomized comparisons
308 because they allow contrasts between patient groups that are on average similar on all
309 observed confounders; however, unlike the randomized assignment of treatments, the
310 propensity score typically does not balance covariates that were not observed. Matching
311 reduces the sample size since matches may not be found for some patients. Though we used a
312 PS to create comparable cohorts, we cannot be certain that the PS perfectly neutralized all of
313 the confounding variables. Moreover, it is advisable to underline that PS cannot replace a
314 randomized control trial. In randomized control trials, random allocation of patients to either an
315 experimental or a control arm guarantees that treatment allocation is unrelated to measured and
316 unmeasured patient characteristics. It enables researchers to draw unbiased conclusions about a
317 treatment, provided that the number of randomized patients is large enough to minimize random
318 variation. However, in this study the large number of patients in both groups allowed for powerful
319 comparisons. Our analyses were based on data from the French administrative database which
320 describes clinical practices over several years, and includes both teaching and non-teaching hospitals.

321

322 **Conclusion**

323 Despite these limits, our study highlights the growing interest of surgical management of LC
324 in octogenarians. Use of the VATS technique led to a significant decrease in postoperative
325 mortality after lobectomy for LC in octogenarians.

326

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444 **Table 1**

445 Patients over 80 years of age: unmatched baseline characteristics

	VATS (n=597)	OT (n=2963)	P-Value
<u>Demographics</u>			
Gender Male	380 (63.65%)	2,083 (77.05%)	0.001
Female	217 (36.35%)	880 (22.95%)	
Age (Years)	82.25 ± 2.12	82.07 ± 2.08	0.05
Past History			
Pulmonary disease	170 (14.7%)	983 (33.2%)	0.025
Heart disease	139 (13.5%)	892 (30.1%)	0.001
Peripheral vascular disease	46 (7.7%)	369 (12.4%)	0.001
Liver disease	6 (1%)	9 (0.3%)	0.016
Neurological disease	25 (4.1%)	177 (6%)	0.085
Kidney disease	28 (4.7%)	149 (5%)	0.728
Anemia	66 (11%)	296 (10%)	0.432
Hematologic disease	18 (3%)	128 (4.3%)	0.142
Infectious disease	6 (1%)	33 (1.1%)	0.816
Metabolic disease	225 (37.7%)	1,180 (39.8%)	0.330
Other treatment	57 (9.5%)	417 (14%)	0.003
Modified CCI score			0.003
0	247 (41.4%)	1,011 (34.1%)	
1	76 (12.7%)	359 (12.1%)	
2	55 (9.2%)	357 (12%)	
≥ 3	219 (36.7%)	1,236 (41.7%)	
<u>Hospital characteristics</u>			
Type Non-teaching	57 (9.5%)	300 (10.1%)	0.895
Private	307 (51.5%)	1,526 (51.5%)	
Teaching	233 (39%)	1,137 (38.4%)	
Volume (procedures/year)			0.0001
< 4	1 (0.1%)	24 (0.8%)	
4 to 21	23 (3.9%)	270 (9.1%)	
>21	573 (96%)	2,669 (90.1%)	

Table 2

Patients' baseline characteristics in matched data with standardized difference. A standardized difference greater than 0.1 (10%) signified a meaningful imbalance in a given variable between treatment groups.

	VATS (n=578)	OT (n=578)	P-Value	Standardized difference
<u>Demographics</u>				
Gender Male	366 (63.32%)	375 (64.88%)	0.713	-0.022
Female	212 (36.68%)	203 (35.12%)		
Age (Years)	82.25	82.26	0.924	-0.06
Past History				
Pulmonary disease	166 (28.72%)	161 (27.85%)	0.794	-0.015
Heart disease	136 (23.53%)	147 (25.43%)	0.495	0.039
Peripheral vascular disease	45 (7.79%)	48 (8.30%)	0.746	0.017
Liver disease	3 (0.52%)	3 (0.52%)	1	0
Neurological disease	25 (4.33%)	20 (3.46%)	0.448	-0.039
Kidney disease	28 (4.84%)	26 (4.50%)	0.781	-0.016
Anemia	64 (11.07%)	56 (9.69%)	0.441	-0.045
Hematological disease	18 (3.11%)	12 (2.08%)	0.267	-0.055
Infectious disease	6 (1.04%)	2 (0.35%)	0.256	-0.051
Metabolic disease	222 (38.41%)	237 (41%)	0.435	0.046
Other treatment	56 (9.69%)	53 (9.17%)	0.689	-0.021
Modified CCI score				
0				
1	70 (12.11%)	72 (12.46%)	1	0
2	55 (9.52%)	49 (8.48%)	0.538	-0.034
≥ 3	216 (37.37%)	233 (40.31%)	0.305	0.06
<u>Hospital characteristics</u>				
Type Non-teaching	55 (9.5%)	56 (9.6%)		
Private	302 (52.25%)	299 (51.8%)	0.860	-0.01
Teaching	221 (38.25%)	223 (38.6%)	0.904	0.04
Volume (procedures/year)	142.22 ± 5.96	134.55 ± 7.21	0.412	-0.047
Overall propensity score				
Mean				0.027
Median				0.022

Figure legends

Figure 1: Number of patients over 80 years old treated by lobectomy each year from 2005 to 2016. The adhesion of the thoracic surgeons to the VATS program is highlighted by the increasing number of patients who were operated with the VATS approach for lobectomy.

VATS: Video-assisted thoracic surgery.

Figure 2: Proportion of octogenarians undergoing lobectomy with the VATS technique each year from 2005 to 2016, highlighting the growth of the VATS program for lobectomy in France.

VATS: Video-assisted thoracic surgery

Figure 3: Propensity score matching in each group of patients who underwent thoracotomy or VATS lobectomy. Each line represents the number of patients with the same propensity score in both groups. After matching, the lines are stackable, therefore covariates are well balanced and the groups comparable.

VATS: Video-assisted thoracic surgery

Figure 4: Thirty-day postoperative mortality rate for patients over 80 years who underwent lobectomy from 2005 to 2016. As the use of VATS expanded, 30-day postoperative mortality dropped to a rate of approximately 0.5%.

Video legend: A video of a VATS left lower lobectomy for pulmonary adenocarcinoma.











