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1 **EARLY-STAGE NON-SMALL CELL LUNG CANCER BEYOND LIFE EXPECTANCY: STILL NOT TOO**
2 **OLD FOR SURGERY?**

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27 **Abstract**

28 **Objective:** We investigated on the benefit/risk ratio of surgery in octogenarians with early-
29 stage non-small cell lung cancer (NSCLC)

30 **Material and methods:** From 2005 to 2020, 100 octogenarians were operated on for a
31 clinical stage IA to IIA NSCLC. All patients had undergone whole body PET -scan and brain
32 imaging. Operability was assessed according to current guidelines regarding the
33 cardiopulmonary function. Since 2015, patients followed a dedicated geriatric evaluation
34 pathway. Minimally invasive approaches were used in 66 patients, and a thoracotomy in 34.

35 **Results:** Clavien-Dindo grade ≥ 4 complications occurred in 15 patients within 90 days,
36 including 7 fatalities. At multivariable analysis, the number of co-morbidities was their single
37 independent prognosticator. Following resection, 24 patients met pathological criteria for
38 adjuvant therapy among whom 3 (12.5%) received platinum-based chemotherapy. Five-year
39 survival rates were overall (OS) 47 ± 6.3 %, disease-free (DFS) 77.6 ± 5.1 %, and lung cancer-
40 specific (CSS) 74.7 ± 6.3 %. Diabetes mellitus impaired significantly long-term outcomes in
41 these 3 dimensions. OS was improved since the introduction of a dedicated geriatric
42 assessment pathway (72.3% vs. 6.4%, $P= 0.00002$), and when minimally invasive techniques
43 were used (42.3% vs. 11.3%; $P=0.02$). CSS was improved by the performance of systematic
44 lymphadenectomy (55.3% vs. 26.9%; $P=0.04$). Multivariable and recursive partitioning
45 analyses showed that a decision tree could be built to predict overall survival on the basis of
46 diabetes mellitus, high co-morbidity index and low ppoDLCO values.

47 **Conclusions:** The introduction of a dedicated geriatric assessment pathway to select
48 octogenarians for lung cancer surgery was associated with OS values that are similar to
49 outcomes in younger patients. The use of minimally invasive surgery and the performance of
50 systematic lymphadenectomy were also associated with improved long-term survival.

51 Octogenarians with multiple co-morbid conditions, diabetes mellitus, or low ppo DLCO
52 values may be more appropriately treated with SBRT.

53

54 **Key-words:** Lung cancer surgery, Elderly (>80 years), Thoracoscopy, Robotics, Thoracotomy

55 **1. Introduction**

56 Current demographic and epidemiological trends make lung cancer in the geriatric
57 population being recognized as a public health concern, the magnitude of which is expected
58 to peak in 2030. Age standardized incidence rates increase sharply at the age of 40 and over,
59 reaching a maximum value of 378.5/100 000 in males aged 80 to 84 [1]. Contemporary
60 octogenarians are aged beyond their life expectancy, which was less than 60 years in France
61 at their birth, both for males and females, and still below 80 years currently in males [2].
62 Treatment decision making is extremely difficult, in particular in the oldest, when an early-
63 stage non-small cell lung cancer (NSCLC) is diagnosed or suspected. First, the disease is
64 usually asymptomatic, when the objectives of the treatment at those ages have to prioritize
65 the preservation of both quality of life and autonomy over survival. Second, very elderly
66 patients are intuitively at increased risks of peri-procedural morbidity and mortality, making
67 the selection of candidates a particularly demanding process. Third, many potential
68 neoplastic or non-neoplastic causes of mortality may compete with that of NSCLC. Fourth, in
69 the era of stereotactic body radiation therapy (SBRT), surgery is not the only curative option
70 of early-stage NSCLC anymore. Finally, this population is under-represented in clinical trials,
71 and detailed prospective observational cohorts are seldom reported.

72 We therefore planned a single-institution retrospective study based on a prospectively
73 implemented clinical database focusing on patients with early-stage NSCLC and older than
74 80 years who underwent surgery with a curative intent. The aim of the study was to report
75 on real world early- and long-term outcomes of surgery, with special attention to surgical
76 approaches and types of lung resection, quality of the surgery, overall risks and specific
77 geriatric complications, additional therapies, mode of disease recurrences, and cause-
78 specific mortality in this particular population.

79

80 **2. Material and Methods**

81 This study adhered to the tenets of the declaration of Helsinki. The institutional review
82 board approved the project (RGPD/Ap-Hm PADS20-74) and waived the requirement of
83 informed consent for the use of the patients' medical data for this retrospective
84 observational study.

85 **2.1 Data sources.**

86 All patients who underwent surgery for an early stage NSCLC with curative intent at a single
87 academic tertiary institution were reviewed for the period January 2005 to June 2020. They
88 were identified from a prospectively maintained lung cancer database contributing to
89 EPITHOR®, the French Society of Thoracic and Cardiovascular Surgery general thoracic
90 surgery registry. Patients consent was obtained for entry into the database and they were
91 aware that these data would be used anonymously for research purposes.

92 **2.2 Staging work-up.**

93 According to national guidelines [3], the standard pretreatment workup included routine
94 high- resolution CT scans of the thorax and the abdomen, integrated PET-CT and brain
95 imaging with either magnetic resonance imaging or infused CT, and selective staging of
96 invasive mediastinal lymph nodes (LN).

97 **2.3 Geriatric assessment.**

98 Before 2015, a geriatric consultation was done on demand only, depending on the clinical
99 evaluation performed by surgeons and/or anesthesiologists. Since 2015, with the
100 implementation of the G8 tool as routine screening method to identify older patients
101 requiring more detailed assessment [4], a dedicated pathway was established, leading to a
102 comprehensive geriatric assessment performed at our institutional geriatric day-care

103 hospital. All patients with a G8 screening score of 14 or less (out of 17), and also all patients
104 with a normal G8 score but with suspected frailties undetected by the G8 scale (i.e.
105 depression, postural instability or autonomy loss) which could have interfered with surgery
106 were routinely referred [5]. In case of detection of potentially correctable disorders,
107 targeted interventions were initiated. This geriatric evaluation also included an estimation of
108 individual life expectancy and contributed to the anticipation of discharge destination, either
109 home or dedicated rehabilitation facilities.

110 **2.4 Fitness for surgery.**

111 Both Eastern Cooperative Oncology Group/World Health Organization Performance Status
112 (ECOG/WHO PS) [6], and American Society of Anesthesiologists (ASA) score [7] were
113 systematically defined in each individual. The degree of baseline functional disability due to
114 dyspnea was assessed by the modified Medical Research Council (mMRC) scale [8]. Cardiac
115 and pulmonary functions assessment was conducted consistently with current European
116 guidelines [9]. Predicted postoperative (ppo) lung function was calculated using the
117 anatomical segment technique. A co-morbidity index was used as a metric of co-morbid
118 conditions integrating in a single formula the sum of co-morbidities and their respective
119 severity which was graded depending on whether they were controlled or uncontrolled by
120 their specific treatment, or untreated, and whether or not they influenced patients care. The
121 score attached to each co-morbidity ranged from 0 (a condition under control by its
122 treatment that did not alter patient care) to 5 (untreated condition influencing patient care).
123 Each proposal of surgery was validated within a multidisciplinary team.

124 **2.5 Surgical methods**

125 The surgical approaches were either a posterolateral thoracotomy, a muscle-sparing lateral
126 thoracotomy, a three-trocar full thoracoscopic posterior approach, or a three-arm robot-

127 assisted technique. The standard lung resection was a lobectomy. Sublobar resections were
128 performed only in few selected high-risk patients. Intraoperative nodal evaluation was
129 qualified by the surgeon in the operative report as none, selective (lobe-specific), or
130 systematic lymphadenectomy.

131 **2.6 Pathology & staging**

132 Clinical and pathological staging results were reassessed according to the 8th edition of the
133 TNM classification of lung cancer [10]. Only patients with a clinical stage IA to stage IIA
134 NSCLC were included. An uncertain resection (R_u) was defined when resection margins
135 were proved to be free of disease microscopically, but one of the following applied: the
136 intraoperative lymph node evaluation did not satisfy the IASLC guidelines (at least 3 N1 and
137 3 lobe-specific N2 stations including station 7 in all cases), the highest mediastinal node
138 removed was positive, invaded lymph nodes were removed in fragments, and the bronchial
139 margin showed carcinoma in situ. Cases with extracapsular extension of tumor in nodes
140 removed separately, or those at the margin of the main lung specimen, were classified as R1.

141 **2.7 Outcomes**

142 In-hospital mortality was defined as death occurring during the index hospital stay,
143 regardless of its timing. Morbidity was defined as the occurrence of at least one
144 postoperative complication, including those events having led to unplanned readmission
145 within 90 days since the date of operation. Complications were defined according to
146 standards as provided by the ESA-ESICM joint taskforce on perioperative outcome measures
147 [11]. Acute urinary retention and delirium were looked at as age-specific events. All
148 complications were graded according to the Clavien-Dindo classification [12]. A special
149 attention was paid to major (grade ≥ 3), life-threatening (grade ≥ 4), and lethal (grade=5)
150 complications. In addition, the comprehensive complication index (CCI[®]) [13] that integrated

151 all events with their respective severity was calculated with an online tool provided on
152 <http://cci.assessurgery.com>.

153 All patients were followed at the outpatient clinic according to a standardized protocol
154 including a first visit one month after hospital discharge with a chest X-Ray, and then routine
155 whole-body CT-scan every 6 months during the 2 first postoperative years, and every year
156 the next 3years, with interval visits if clinically necessary. The clinical status and the cause of
157 death, if applicable, was obtained in all patients on the basis of medical charts or contact
158 with the attending physician, family and relatives. The exact date of death was collected
159 from the registrar of deceased persons maintained and updated monthly by the National
160 Institute of Statistics and Economic Studies. The three survival outcomes of interest were
161 overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS). Disease-
162 specific events included local, regional, and metastatic progression of the initial lung tumor,
163 as well as the occurrence of a metachronous lung cancer. Follow-up was completed on 1
164 September 2020 and patients were censored accordingly. Survival rates are presented as
165 Kaplan-Meier plots and five-year survival rates.

166 **2.8 Statistical analysis**

167 Categorical variables were presented as simple proportions and compared using the
168 Pearson's χ^2 test or the Fisher's exact test, according to expected frequency. Continuous
169 variables were expressed as median and/or mean \pm standard deviation (SD), with the Mann-
170 Whitney test used to compare the distributions of unpaired non-parametric continuous
171 values. Survival probabilities were calculated from the date of surgery using the Kaplan-
172 Meier method. The log-rank test was used to compare different curves statistically. A p-
173 value less than 0.05 was considered to indicate statistical significance. All the variables with
174 a P value ≤ 0.1 from this univariable method were analyzed in a multivariable analysis using

175 a Cox proportional hazard regression model to determine the factors predictive of 90-day
176 grade ≥ 4 complications and for survival data. All reported confidence intervals are two-
177 sided. Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). In
178 addition, recursive partitioning analysis was performed with R package rpart v4.1-15 to
179 create a decision tree that strived to identify clusters with heterogeneous overall survival
180 based on several dichotomous independent variables.

181

182 **3. Results**

183 **3.1 Demographics**

184 From January 2005 to June 2019, among 3528 patients who were operated on for a NSCLC
185 with a curative intent, 161 (4.6%) octogenarians were identified. Among them, 100
186 presented with a clinical early stage disease who constituted the population study. The
187 number of octogenarians with a stage IA-IIA disease almost doubled each 5-year interval of
188 the study period. None were institutionalized prior to surgery. None had a fall history in the
189 3 months preceding surgery. Characteristics of the patients are given in table 1, with a focus
190 according to the surgical approach. Two patients only had no co-morbidity. Other patients
191 had 1 to 8 co-morbid conditions. A history of one or more previous or concomitant
192 malignancies was noted in 44 patients and considered under control. Chronic arrhythmia was
193 noted in 24 patients, and a history of stroke in 9. The use of antiplatelet agents or oral
194 anticoagulants was quoted in 40 and 9 patients, respectively. Histology was available
195 preoperatively in 28 patients. Eleven patients underwent invasive lymph node evaluation
196 either by EBUS or mediastinoscopy on the basis of CT and/or PET findings. All patients
197 received surgery as the first line treatment.

198 **3.2 Surgery**

199 The surgical approach was a video- assisted (VATS: n=50) or robot-assisted (RATS: n=16)
200 thoracoscopy, or a thoracotomy (n=34). Six minimally invasive procedures had to be
201 converted to thoracotomy: 5 VATS (10%) and 1 RATS (6.2%). Lobectomy was the most
202 frequently performed type of lung resection (n=87). In addition, there were 13 sublobar
203 resections: 6 wedge resections and 7 segmentectomies. Intraoperative nodal evaluation was
204 not performed at all in 9 patients, and consisted of lobe-oriented dissection in 29, and
205 systematic lymphadenectomy in 69. A mean of 13.3 ± 8 lymph nodes was harvested and
206 examined: 5.8 ± 3.9 intrapulmonary and hilar, and 7.5 ± 6.3 mediastinal lymph nodes.
207 Adherence to IASLC guidelines regarding intraoperative LN evaluation was satisfied in 55
208 patients overall.

209 **3.3 Pathology**

210 The mean tumoral size was 28.7 ± 16.2 mm. Nodal upstaging occurred in 17 patients: cN0
211 to pN1 in 8 patients and cN0 to pN2 in 9. Nodal upstaging was observed in 3 of the 11
212 patients (27.3%) who underwent preoperative invasive lymph node evaluation. An R0
213 resection was achieved in 54 patients, an R1 in 40 due to insufficient nodal assessment in
214 all cases, and an R2 in 6 due to extracapsular extension at the margins of the resected lymph
215 nodes in 5 and bronchial stump invasion in 1.

216 **3.4 Early outcomes**

217 A total of 61 patients experienced a mean of 1.1 ± 1.2 complications within the 90 days
218 after surgery, consisting of 113 events. Thirty-four patients developed more than 1
219 complication. The mean CCI[®] was $20.7 \pm 25.4\%$ at 3 months after surgery. Clavien-Dindo
220 grade ≥ 4 complications occurred in 15 patients within 90 days: pneumonia in 9, renal failure
221 in 2, bronchial fistula, postoperative hemorrhage, myocardial infarction, and sudden death
222 in 1, respectively.

223 Comparing early outcomes with the implementation of the G8 questionnaire according to
224 the periods 2005-2014 vs. 2015-2020, the respective rates of major, life-threatening and
225 lethal complications were: 37.5% vs. 17.3% (P=0.043), 20.8% vs. 9.6% (P=0.162), and 8.3% vs.
226 5.8% (P=0.707). Respective mean CCI[®] values were 26.9 +/- 27% vs. 15 +/- 22.5% (P=0.005).
227 The mean CCI[®] value was significantly higher for patients who were operated on through a
228 thoracotomy as the intent-to-treat approach when compared with patients who underwent
229 a minimally invasive technique (31.5 +/- 28.7% vs. 15.2 +/- 21.7%, p=0.001). It did not differ
230 while comparing patients having undergone adequate lymphadenectomy to those in whom
231 the lymphadenectomy did not comply with the IASLC recommendations (22.3 +/- 23.1% vs.
232 18.8 +/- 28%, p=0.16).

233 Acute urinary retention and delirium occurred in 14 and 9 patients, respectively.
234 Postoperative delirium occurred as a single complication in 2 patients, required admission to
235 the ICU in 3, but with no mortality, and resulted in discharge to inpatient rehabilitation
236 facilities in 4.

237 Median postoperative hospitalization stay was 7 days [range: 3-111; SD: +/-12]. Length of
238 hospital stay was significantly higher after open surgeries when compared with minimally
239 invasive procedures (12.2 +/- 8.6 days vs. 7.7 +/- 13.2 days; p= 0.000003). Minimally invasive
240 approaches when compared with thoracotomy resulted in a less frequent need for
241 postoperative rehabilitation (21.7% vs. 61.8%, p=0.0009).

242 A total of 7 patients died postoperatively within 90 days: 4 died during the index
243 hospitalization, and one at home within 90 days. Seven patients had to be readmitted within
244 90 days after surgery, with 2 additional deaths (readmission mortality rate of 28.6%). None
245 of the 90-day survivors had to be institutionalized in the year following surgery.

246 In-hospital, 30-day and 90-day mortality rates were 4%, 5% and 7%, respectively. At
247 univariable analysis (table 2), significant predictors of 90-day adverse events (grade \geq 4)
248 included: presence of a coronary artery disease, number of co-morbidities, highest co-
249 morbidities index values. At multivariable analysis, the single significant predictor was the
250 number of co-morbidities. Patients who had more than 4 co-morbidities experienced more
251 severe complications than those who had less co-morbid conditions (mean CCI[®] 30.2 +/-
252 27.8% vs. 15.1 +/- 22.2%, P=0.001).

253 **3.5 Postoperative treatments**

254 According to current guidelines applicable to younger patients, twenty-four 90-day survivors
255 (25.8%) should have received adjuvant systemic treatments. Among them, 18 patients (75%)
256 were deemed unfit after a renewed onco-geriatric assessment, 3 (12.5%) declined, and 3
257 (12.5%) received adjuvant Platinum-based chemotherapy. Among the 6 patients with
258 microscopically positive margins, one (16.7%) received adjuvant radiotherapy.

259 **3.6 Long-term outcomes**

260 Median 5-year overall survival was 38 months. 5-year Kaplan-Meier probabilities of survival
261 were: overall 47 ± 6.3 %, disease-free 77.6 ± 5.1 %, and lung cancer-specific 74.7 ± 6.3 %.
262 Significant predictors of overall, disease-free and cancer-specific survival are listed in table 3,
263 4, and 5, respectively. Survival curves according to time intervals of the study period and to
264 surgical modalities are given by figures 2 to 4 (supplemental material).

265 At follow-up, remote deaths were attributable to NSCLC in 15 patients (41.7%), another
266 malignancy in 4 (11.1%), and non-cancer related causes in 17 (47.2%). Among the 18
267 patients whose disease recurred, the pathological stages were IA (n=4), IB (n=5), IIA (n=3),
268 IIB (n=2), and IIIA (n=4), and the resection had been microscopically incomplete in 3. Ten
269 patients had been eligible to an adjuvant treatment, and 2 had received it (chemotherapy in

270 1, radiotherapy in 1). The site of first recurrence was local-regional in 6 after a mean follow-
271 up of 24 months, distant metastases in 7 after a mean follow-up of 28 months, and a
272 metachronous lung cancer in 5 patients after a mean follow-up of 29 months.

273 To consider both linear and non-linear effects of prognostic variables for overall survival and
274 handle complex interactions among them efficiently, recursive partitioning and regression
275 tree was done, and identified 5 clusters with significantly different survival curves (figure 1).
276 The co-morbidity index value was identified as the most important predictor associated with
277 octogenarian's overall survival, followed by diabetes mellitus and low ppoDLCO values.

278

279 **4. Discussion**

280 The most meaningful findings of this study were the value of the geriatric assessment, which
281 had a statistically and clinically meaningful association with improved outcomes, and the use
282 of minimally invasive approaches both to lower the surgical risk and improve overall survival
283 in octogenarians operated on for an early-stage NSCLC. This study also provides a prediction
284 model based on few clinical variables to improve patient's selection for surgery, and to
285 direct high-risk candidates to alternative treatments.

286 Postoperative mortality is a poor early outcome metric as it does not reflect the in-depth
287 reality of the surgical insult [14]. To conduct a comprehensive evaluation of early
288 postoperative outcomes, we evaluated life-threatening complications and mortality out to
289 90-days. Furthermore, we also used the comprehensive complication index (CCI®), which
290 better reflects on the complications burden while integrating in one single formula all
291 recorded complications weighted by severity [13]. We extended the observation period to
292 the 90 days following surgery in order to capture delayed adverse events, including those
293 leading to unplanned readmissions, which are known to double in incidence when compared

294 with 30-day figures [14]. Our results are in line with those reported by Rueth et al. who
295 found 30- and 90-day mortality rates of 4.2% and 6.3%, respectively, through a review of
296 SEER-Medicare data limited to North American patients less than 80 years of age with stage I
297 NSCLC [15]. They also approximate the 6% and 7% operative mortality rates retrieved
298 recently for octogenarians on population-based samples from the Dutch Lung Surgery Audit
299 database [16], and the French Administrative database [17], respectively.

300 As shown in table 1, VATS/RATS techniques were adopted and developed since 2010 at our
301 department. This development was done in the frame of an enhanced recovery after surgery
302 (ERAS) program [18]. Both concurred to reduce the surgical insult in this age demographic,
303 resulting in less complications, shorter in-hospital stay, less frequent need for postoperative
304 rehabilitation when compared with thoracotomy, and improved overall survival significantly
305 and independently.

306 Our closer collaboration with onco-geriatricians since 2015 was associated with a significant
307 decrease of major postoperative complications, and an improved overall survival, thus
308 testifying of a more appropriate selection and preparation of candidates for surgery.
309 Postoperative delirium occurred less frequently than one could have expected in this age
310 group [19], and this finding might have been the consequence of the individualized
311 screening and counselling done at comprehensive geriatric assessment.

312 Our univariable analysis identified a history of coronary artery disease as a strong predictor
313 of 90-day adverse events, a feature already disclosed in younger patients [20]. At
314 multivariable analysis, the crude number of co-morbidities was the only independent
315 predictor of 90-day adverse events. Furthermore, patients with more than 4 co-morbid
316 conditions experienced more severe complications up to 90 days after surgery.

317 Even if surgeons declared having performed a systematic lymphadenectomy in almost 70%
318 of the patients, adherence to IASLC guidelines was effective in roughly half of the whole
319 cohort only, probably with the belief behind to limit the risks of complications. Our findings
320 are in line with those of the ACOSOG Z0030 randomized trial that showed in younger
321 patients that there was no additional morbidity associated with systematic nodal dissection
322 when compared with systematic sampling [21]. They sustain the contention that the
323 legitimate quest for less invasive surgery should not trigger the imperative needs to stick to
324 fundamental principles of lung cancer treatment, even in the older old. Indeed,
325 lymphadenectomy resulted in a 17% nodal upstaging rate in this population, and thus
326 contributed to increase the rate of complete resections, which is the primary goal of NSCLC
327 surgery at any age. As a matter of fact, the performance of a systematic lymphadenectomy
328 was associated with an improved lung cancer specific survival. In contrast, upstaging did not
329 translate in better treatment allocation since the vast majority of the patients were ineligible
330 for or refused adjuvant chemotherapy.

331 In this study, diabetes mellitus has been identified as a predictor of overall, disease-free and
332 cancer specific survival. The association of diabetes mellitus with poorer overall survival
333 amongst lung cancer patients, especially the surgically treated NSCLC patients, is well-known
334 [22]. Hyperinsulinemia, hyperglycemia, and metabolic disorder of cancer cells may be the
335 potential factors contributing to the development of lung cancer. Hyperinsulinemia may
336 have impact on cancer-promoting through the insulin-like growth factor-1 pathway.
337 Hyperglycemia can promote cancer proliferation via the induction of epidermal growth
338 factor (EGF) expression and transactivation of EGF receptor. However, these hypotheses do
339 not necessarily suggest a causal link between diabetes and worse cancer prognosis, as data
340 concerning disease-free or cancer specific survival are scarce, and most results remain

341 insignificant or controversial [22]. Indeed, patient with diabetes have also an enhanced risk
342 of developing several kinds of potentially lethal comorbidities such as cardiovascular
343 diseases including acute myocardial infarction and stroke.

344 Beside diabetes mellitus, our statistical analysis of predictors of overall survival emphasized
345 the impact of co-morbidities through numerous indicators: ASA scoring, number of co-
346 morbidities, co-morbidity index and ppo DLCO values, the last having been disclosed as an
347 independent predictor at multivariable analysis. The diffusing capacity of the lungs for
348 carbon monoxide estimates the severity of interstitial pneumonia and has been reported to
349 be correlated both with the risk of postoperative complication and poor overall survival
350 following NSCLC surgery [23].

351 Oncological outcomes were significantly and independently influenced by 2 surgical
352 features. The number of anatomical segments removed was identified as protective as
353 regards disease-free survival. This finding does not suggest the efficacy of sublobar resection
354 in this context and is consistent with data extracted from the SEER database that showed
355 that, compared to lobectomy, sublobar resection was associated with significantly worse
356 overall survival and worse lung-cancer specific survival in proportional hazards sampling.
357 This finding was unchanged in the subgroup cohort of patients aged beyond 75 years with a
358 tumor size of less than 2 cm. Likewise, this finding was preserved even if the sublobar
359 resection cohort was limited to those patients operated on by video-assisted surgery or
360 having undergone anatomic segmentectomy, and in propensity score matching analysis [24].

361 The performance of systematic lymphadenectomy was identified as protective as regards
362 cancer specific survival. This finding contrasts with that of Okaska et al. who concluded that
363 radical lymphadenectomy did not confer a significant survival benefit in their patients aged
364 70 years and older and suggested that it could be omitted [25]. This issue will remain

365 controversial in the absence of randomized evidence in this particular age segment of the
366 population. However, one may oppose that combining sublobar resection with the absence
367 of lymphadenectomy is exactly what does the radiotherapist with SBRT, while sparing the
368 risks of surgery. To date, the comparison between these two last options has been
369 addressed by 3 randomized studies. The British SABRTOOTH trial aimed at determining the
370 feasibility and acceptability of conducting a phase III randomized controlled trial comparing
371 SBRT with surgery in patients with peripheral stage I NSCLC considered at higher risk of
372 complications from surgical resection. It showed that such a study was not feasible in the
373 National Health Service: patients had pre-existing treatment preferences, which was a
374 barrier to recruitment, and a significant proportion of patients randomized to the surgical
375 group declined and chose SBRT [26]. There are 2 still ongoing trials in similar populations,
376 i.e., the VALOR (NCT02984761) and STABLE-MATES (NCT02468024) studies which are open
377 to recruitment in North America and may answer this important research question.

378 The comparison between surgery and SBRT has been done on the basis of propensity score-
379 matched analyses of large databases. Using the National cancer Database, differences in 90-
380 day post-treatment mortality between surgery and SBRT have been shown to increase as a
381 function of age, with the largest differences in favor of SBRT observed among patients older
382 than 80 years, including when surgery consisted of sublobar resections (HR: 1.37; 95% CI:
383 1.17 - 1.61) [27]. Using the Surveillance, Epidemiology, and End Results– Medicare–linked
384 database, whereas lobectomy provided the best overall and lung cancer-specific survival in
385 comparison with either sublobar resection or SBRT, the last appeared to offer equivalent
386 long- term outcomes in frail patients with very advanced age when compared to those
387 associated with sublobar resection [24].

388 Finally, except diabetes mellitus, our findings fit with those of Hino et al who showed that
389 prognostic factors for non-cancer-specific death were different from those of cancer-specific
390 death [28]. French people aged 75 years and beyond, without cancer, have currently a mean
391 life expectancy of 9.59 years [2]. This estimation falls sharply with the diagnosis of lung
392 cancer with an expected 5-year survival rate of 10% [29]. The 5- year survival rate of
393 octogenarians with lung cancer and treated by surgery has been reported to range from 24%
394 to 66 % [30]. In our cohort, the 5-year Kaplan-Meier probability of overall survival was
395 estimated at 47 ± 6.3 %, at the exact middle of this interval. In each individual, we used the
396 Lee prognostic index to assess the benefit/risk balance before any treatment decision. This
397 index, which provides an estimate of the probability of 4-year mortality, has been developed
398 on the basis of age, sex, self-reported conditions and functional measures [31].

399 This study carries the usual limitations inherent to its retrospective design, mainly the
400 possibility of a selection bias. However, it provides very detailed information on the quality
401 of surgery in terms of completeness of resection and lymph node evaluation, as well as
402 precise early- and long-term outcomes with 100% follow-up. Another limitation is that it
403 does not include patient-reported data of health-related quality of life, which are of
404 paramount importance in the context of shared decision making to find an optimal trade-off
405 between harms and benefits. We were, however, able to highlight that none of the mid-
406 term survivors had to be institutionalized in the year following surgery, thus suggesting the
407 maintenance of their autonomy and the relevance of their selection for the surgical
408 treatment.

409

410 5. Conclusions

411 In conclusion, surgery is a reasonable an option for the treatment of early-stage NSCLC in
412 octogenarians in a multidisciplinary setting including a dedicated geriatric assessment
413 pathway, provided that fundamental principles of lung cancer surgery, i.e., lobectomy with
414 systematic lymphadenectomy, are adhere to, and minimally invasive video- and/or robot
415 assisted techniques in the frame of an ERAS program are performed. However, in this
416 situation associated with the most favorable oncological prognosis, patients with co-morbid
417 conditions resulting in a co-morbidity index value of 9 and higher, and those with diabetes
418 mellitus or a ppoDLCO value of less than 46%, are poor candidates for surgery, and less
419 invasive ablative therapies such as SBRT could be preferred alternatively because of
420 competing risks of non-cancer-specific death in this age-segment of the population.

421 **Author contributions statement**

422 **Pascal Alexandre Thomas:** Conceptualization; Methodology; Formal analysis; Data curation;
423 Writing—original draft; Writing—review & editing; Validation. **Anne-Laure Couderc:** Data
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426 Investigation; Writing—review. **Aude Charvet:** Data curation; Formal analysis; Writing—
427 review. **Geoffrey Brioude:** Investigation; Data curation; Writing—review. **Delphine Trousse:**
428 Investigation; Data curation; Writing—review. **Xavier Benoît D’Journo:** Investigation; Data
429 curation; Writing—review. **Fabrice Barlesi:** Data curation; Methodology; Supervision;
430 Writing—review; Validation. **Anderson Loundou:** Methodology; Statistical analysis;
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432

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436

437 **Figure legend**

438 **Figure 1. Overall survival classification tree for octogenarians.**

439 Legend: Survival classification tree was built (a), which identified five clusters with
440 significantly different survival curves (b). Cox regression model was used to compare the
441 outcomes among clusters (cluster 1 as reference) and represented by hazard ratio (HR), 95%
442 confidence interval (95%CI), and the P value (c).

443

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492 (ESICM); European Society of Anaesthesiology; European Society of Intensive Care

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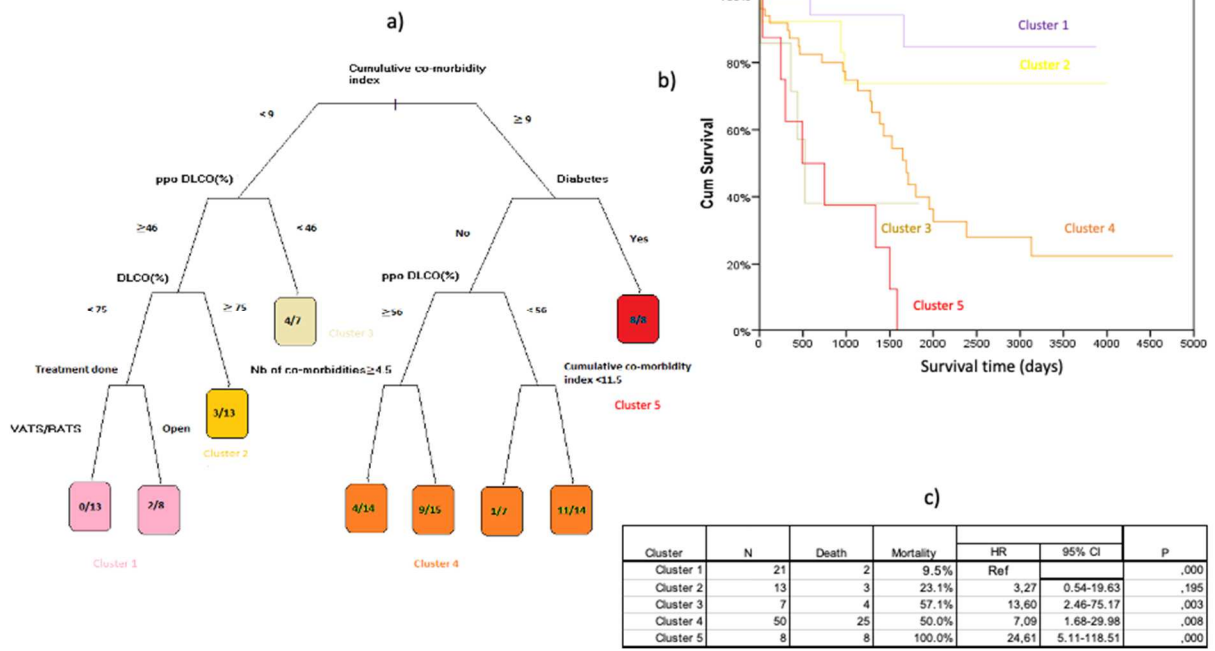
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586 **Figure 1.**

587



588

589

Table 1. Characteristics of the patients

Characteristics	Cohort			P value
	Full sample (N=100)	VATS/RATS (N=66)	Open (N=34)	
Age (years)	81.8 +/- 1.8	82 +/- 1.9	81.6 +/- 1.6	0.35
Gender				
Male	74	48	26	0.69
Female	26	18	8	
BMI				
Normal (BMI 18.5-24.9 kg/m ²)	47	30	17	0.74
Underweight (BMI<18.5 kg/m ²)	2	2	0	
Overweight (BMI 25-29.9 kg/m ²)	39	27	12	
Obesity (BMI ≥30 kg/m ²)	12	7	5	
Performance Status ECOG/WHO				
0	46	33	13	0.52
1	41	25	16	
2-3	13	8	5	
mMRC Dyspnea scale				
0-1	58	40	18	0.52
2-3	42	26	16	
ASA score				
<3	62	41	21	0.97
≥3	38	25	13	
Smoking status				
Never-smoker	22	16	6	0.45
Current/Former Smoker	78	50	28	
Packs-year	36.2 +/- 20.3	38 +/- 22.4	33 +/- 15.9	0.31
FEV1ppo (%)	75.8 +/- 18.2	74.7 +/- 18.8	78 +/- 17.1	0.39
DLCOppo (%)	54.6 +/- 14	54.4 +/- 14.1	55.2 +/- 14.1	0.82
FEV1/FVC	74.7 +/- 11.4	74.3 +/- 10/7	75.5 +/- 12.8	0.60
Nb of co-morbidities	3.8 +/- 1.8	3.8 +/- 1.8	3.9 +/- 1.6	0.74
Co-morbidity index	9.6 +/- 5.8	9.8 +/- 6.3	9.1 +/- 4.7	0.60
COPD	28	19	9	0.81
Coronary artery disease	21	11	10	0.13
Diabetes	11	7	4	0.99
Other malignancies	44	30	14	0.68
Histology				
Squamous cell carcinoma	26	19	7	0.53
Adenocarcinoma	70	45	25	
Other	4	2	2	
Clinical stage				
I-A	63	44	19	0.02
I-B	26	19	7	
II-A	11	3	8	
Type of surgery				
Wedge resection	6	4	2	0.89
Segmentectomy	7	4	3	
Lobectomy	87	58	29	
Side				
Right	65	46	19	0.17
Left	35	20	15	

Type of lymphadenectomy				
None	9	6	3	0.99
Selected	29	19	10	
Systematic	62	41	21	
Number of lymph nodes removed	13.3 +/- 8	13.5 +/- 7.9	12.9 +/- 8.1	0.75
N1	5.8 +/- 4	6 +/- 4.1	5.4 +/- 3.6	0.51
N2	7.5 +/- 6.3	7.2 +/- 6.2	8.2 +/- 6.6	0.44
Lymphadenectomy (IASLC guidelines)				
Yes	55	34	21	0.33
No	45	32	13	
N upstaging	17	9	8	0.21
N1	8	3	5	
N2	9	6	3	
Surgery duration (min)	122.7 +/- 45.6	134.1 +/- 46.1	100.8 +/- 36	0.0004
Tumor size (mm)	28.7 +/- 13.2	27 +/- 13.5	31.9 +/- 12.4	0.09
Pathological stage				
I-A	45	34	11	0.15
I-B	23	15	8	
II-A	7	2	5	
II-B	11	6	5	
III-A	14	9	5	
R completeness				
R0	54	33	21	0.52
Run	40	29	11	
R1	6	4	2	
Year of treatment				
2005-2009	16	1	15	<0.001
2010-2014	32	19	13	
2015-2020	52	46	6	

Legend: BMI body mass index, ECOG/WHO Eastern Cooperative Oncology Group/World Health Organization, mMRC modified Medical Research Council, ASA American Society of Anesthesiologists, FEV1 forced expiratory volume in 1 second, FVC forced vital capacity, DLCO diffusing lung capacity for carbon monoxide, ppo predicted postoperative, COPD chronic obstructive pulmonary disease, VATS video-assisted thoracoscopic surgery, RATS robot-assisted thoracoscopic surgery.

In bold: factors statistically significant at an P value of less than 5%

Table 2. Factors Associated With 90-day Mortality

Associated factors	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Male	5.83 (0.73-47.77)	0.098		
Smoking history	10.98 (0.59-203.52)	0.108		
Coronary artery disease	4.44 (1.38-14.23)	0.012		
Comorbidities (number)	1.73 (1.19-2.54)	0.005	1.65 (1.01-2.68)	0.045
Comorbidities (index)	1.11 (1.01-1.22)	0.028		
ppo FEV1	0.97 (0.94-1)	0.082		
Open approach (intent-to-treat)	2.59 (0.85-7.90)	0.094		
VATS/RATS (treatment done)	0.28 (0.07-0.99)	0.042		

Legends: ppo FEV1 predicted postoperative value of forced expiratory volume in 1 second, VATS video-assisted thoracoscopic surgery, RATS robot-assisted thoracoscopic surgery. OR odd ratio.

In bold: factors statistically significant at un P value of less than 5%

Table 3. Factors associated with overall survival

Associated factors	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Male gender	2.21 (1.02-4.77)	0.044		
ASA score \geq 3	2.16 (1.17-3.96)	0.013	2.56 (1.01-6.47)	0.047
Smoker	2.19 (0.92-5.19)	0.076		
Diabetes	3.98 (1.84-8.59)	0.0004	5.63 (1.76-17.97)	0.004
Nb of co-morbidities	1.28 (1.07-1.54)	0.007		
Co-morbidity index	1.09 (1.03-1.15)	0.001		
DLCO (%)	0.98 (0.95-0.99)	0.038		
ppo DLCO (%)	0.97 (0.94-0.99)	0.022	0.95 (0.92-0.99)	0.014
VATS/RATS (treatment done)	0.21 (0.06-0.76)	0.018	0.06 (0.01-0.29)	0.0004

Legends: ASA American Society of Anesthesiologists, ppo predicted postoperative value, DLCO diffusing lung capacity for carbon monoxide, VATS video-assisted thoracoscopic surgery, RATS robot-assisted thoracoscopic surgery. HR hazard ratio.

In bold: factors statistically significant at un P value of less than 5%

Table 4. Factors associated with disease-free survival

Associated factors	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
BMI (kg/m²)	1.16 (1.02-1.31)	0.020		
ASA score ≥ 3	2.65 (1.03-6.84)	0.044		
mMRC Dyspnea scale 2-3	2.58 (0.97-6.89)	0.059		
Diabetes	5.19 (1.79-15.06)	0.002	6.36 (2.12-19.09)	0.001
Nb of co-morbidities	1.32 (0.99-1.76)	0.054		
Co-morbidity index	1.01 (1-1.18)	0.042		
Nb of removed lung segments	0.76 (0.57-1.01)	0.055	0.71 (0.53-0.96)	0.024
VATS/RATS (intent-to-treat)	0.37 (0.14-1)	0.050		
Adequate lymphadenectomy (IASLC)	0.41 (0.16-1.11)	0.078		
Systematic lymphadenectomy	0.32 (0.11-0.90)	0.031		
Uncertain resection Run	3.31 (0.88-12.43)	0.076		

Legend: BMI body mass index, ECOG/WHO Eastern Cooperative Oncology Group/World Health Organization, mMRC modified Medical Research Council, ASA American Society of Anesthesiologists, VATS video-assisted thoracoscopic surgery, RATS robot-assisted thoracoscopic surgery, HR hazard ratio.

In bold: factors statistically significant at un P value of less than 5%

Table 5. Factors associated with cancer-specific survival

Associated factors	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
BMI (kg/m ²)	1.13 (0.99-1.29)	0.053		
ASA score ≥ 3	3.25 (1.23-8.55)	0.017	5.51 (1.72-17.61)	0.004
Diabetes	8.01 (2.59-24.75)	0.0003	14.26 (3.95-51.46)	0.0001
Nb of co-morbidities	1.32 (0.99-1.76)	0.058		
Co-morbidity index	1.01 (1.10-1.20)	0.033		
Nb of removed lung segments	0.76 (0.57-1.02)	0.066		
Preoperative invasive lymph node evaluation	5 (1.30-19.22)	0.019		
Adequate lymphadenectomy (IASLC)	0.43 (0.16-1.17)	0.098		
Systematic lymphadenectomy	0.32 (0.11-0.90)	0.031	0.15 (0.05-0.51)	0.002
Uncertain resection Run	3.47 (0.90-13.29)	0.070		

Legend: BMI body mass index, ECOG/WHO Eastern Cooperative Oncology Group/World Health Organization, ASA American Society of Anesthesiologists, HR hazard ratio.

In bold: factors statistically significant at un P value of less than 5%