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Title	Impact of pulmonary vein-first ligation during lobectomy on the postoperative survival and recurrence rates in patients with non-small cell lung cancer : a multicenter propensity score-matched study
Author(s)	Shiia, Haruhiko; Ujiie, Hideki; Chiba, Ryohei et al.
Citation	Surgery today, 54(11), 1369-1378 https://doi.org/10.1007/s00595-024-02852-8
Issue Date	2024-05-30
Doc URL	https://hdl.handle.net/2115/95599
Rights	This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature' s AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: https://doi.org/10.1007/s00595-024-02852-8
Type	journal article
File Information	PAPV._ver.2.2_Surg_Today_R2(submit).pdf



1 **Impact of pulmonary vein-first ligation during lobectomy on**
2 **the postoperative survival and recurrence rates in patients**
3 **with non-small cell lung cancer: A multicenter propensity**
4 **score-matched study**

5

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21 **Article type:** Original Article (Clinical Original)

22

23 **Key Words:** circulating tumor cells; lobectomy; lung cancer; pulmonary
24 vein; surgical procedure

25

26 **Abstract**

27 **Purpose:** Surgical manipulation of the lungs increases the number of
 28 circulating tumor cells and the subsequent metastasis risk in lung cancer
 29 patients. This study investigated whether ligating the tumor-draining
 30 pulmonary vein first during lobectomy could improve the prognosis of these
 31 patients.

32 **Methods:** We retrospectively evaluated patients who underwent curative
 33 lobectomy for solitary non-small cell lung carcinoma between January 2012
 34 and December 2016. We divided patients into the vein-first group, in which
 35 all associated pulmonary veins were dissected and severed before cutting the
 36 pulmonary artery, bronchus, or pulmonary fissure, and other procedures
 37 groups.

38 **Results:** Overall, we included 177 and 413 patients in the vein-first and other
 39 procedures groups, respectively. Propensity score matching yielded 67 patient
 40 pairs. The 5-year overall (85.6% [95% confidence interval, 77.3%–94.8%] vs.
 41 69.4% [58.7%–81.9%], $P = 0.03$) and recurrence-free survival (73.4%
 42 [63.3%–85.1%]) vs. 53.5% [42.5%–67.3%]; $P = 0.02$) were significantly
 43 better in the vein-first group. The cumulative recurrence rate at 5 years post-
 44 surgery was significantly lower in the vein-first group (21.7% vs. 38.3%, $P =$
 45 0.04).

46 **Conclusion:** Our study suggested that first ligating the pulmonary vein during
 47 lobectomy for lung cancer can improve overall survival, recurrence-free
 48 survival, and cumulative recurrence rate.

49

50

51 **Introduction**

52 Surgical manipulation of the lungs during lung cancer surgery has
 53 been reported to promote the dissemination of circulating tumor cells (CTCs)
 54 from tumors into the bloodstream [1–4]. CTCs have been reported to be
 55 associated with subsequent metastasis and a poor prognosis [4–10]. Recently,
 56 several reports have suggested that the sequence of vessel ligation during
 57 pulmonary lobectomy for primary lung cancer affects postoperative overall
 58 survival (OS) and recurrence-free survival (RFS) [11,12]. It has been
 59 suggested that ligating the tumor-draining pulmonary vein (PV) early during
 60 lobectomy contributes to a decrease in the number of CTCs shed into the
 61 systemic bloodstream and reduces the risk of subsequent metastasis [13].
 62 Early ligation of the PV prevents CTCs from spreading through the draining
 63 vein [3,13]. However, the effect of the vein-first procedure on the
 64 postoperative prognosis remains controversial because it has been supported
 65 by only a few clinical studies involving various histological types and
 66 pathological stages. Furthermore, some studies showed that ligating the PV
 67 did not affect prognosis [9,14–16]. Thus, vein first lobectomy is not yet
 68 established as the gold standard for surgical primary lung cancer treatment.

69 In addition, even if the PV is ligated first, surgical procedures, such
 70 as the degree of dissection of the membrane before ligating the vessels, vary
 71 greatly among institutions. For example, some surgeons dissect the PV at the
 72 start of lobectomy and ligate it immediately, then dissect other hilar structures,
 73 while other surgeons ligate the PV first but dissect other bronchovascular
 74 membranes partially or entirely beforehand [13]. Such manipulation of the
 75 lungs before PV ligation may result in the spread of CTCs.

76 Thus, to address this issue, we investigated whether performing
 77 ligation of the PV before dissecting other bronchovascular membranes affects
 78 the OS, RFS, and cumulative incidence of recurrence after curative lobectomy
 79 for primary lung cancer.

80

81 **Material and Methods**

82 **Study design**

83 This study was approved by the Institutional Review Board of
 84 Hokkaido University Hospital (approval number: 022-0289) and Sapporo
 85 Minami-Sanjo Hospital (approval number: R5-6) and was performed in
 86 accordance with the Declaration of Helsinki (as revised in 2013). The
 87 requirement for obtaining individuals' informed consent was waived because
 88 of the retrospective nature of the study; however, information about this study
 89 was made readily available to the patients on the institutional website, and the
 90 opportunity to opt-out was guaranteed.

91 Data on patients who underwent curative lobectomy for solitary
 92 primary lung cancer between January 2012 and December 2016 at Hokkaido
 93 University Hospital and Sapporo Minami-Sanjo Hospital were
 94 retrospectively reviewed. Only patients with pathological stage I–III
 95 adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma
 96 were included to simplify the assessment of the prognostic impact of the
 97 surgical procedure. Patients who underwent resection of more than one lobe,
 98 those with a history of lung resection, those who received neoadjuvant therapy,
 99 those who underwent incomplete resection, and those with insufficient
 100 matching data were excluded. Patients who were lost to follow-up or who
 101 experienced recurrence within 90 days of surgery were excluded because they
 102 were considered to have disease progression rather than disease recurrence.
 103 Patients who underwent rapid intraoperative diagnosis with wedge resection
 104 were also excluded because this may have resulted in tumor isolation before
 105 lobectomy [17]. Among the 652 eligible patients, those with a
 106 consolidation/tumor ratio (C/T ratio) of >0.5 were included in the analysis.
 107 Finally, 590 patients were enrolled (Figure 1).

108

109 **Patient grouping**

110 We defined two groups in this study: the vein-first and the other

111 procedures groups. In the vein-first group, all associated PVs were dissected
 112 and severed before cutting the pulmonary artery (PA), bronchus, or
 113 pulmonary fissures. In the second group, the PA, bronchus, or pulmonary
 114 fissure was dissected and cut before severing the entire associated PV. The
 115 procedure was selected according to the surgeon's preference. Two- to five-
 116 port video-assisted thoracic surgery (VATS) is usually preferred over open
 117 surgery, but the choice and number of ports depended on the surgeon's
 118 preference.

119

120 **Data collection and definitions**

121 Data were collected from the medical records and surgical videos
 122 of Hokkaido University Hospital and an affiliated hospital. Clinical restaging
 123 was performed according to the 8th edition of The Union for International
 124 Cancer Control (UICC) [18], based on computed tomography (CT), brain
 125 magnetic resonance imaging, and positron-emission tomography. The size
 126 and C/T ratio of the solid tumor were evaluated using chest CT using 1–2.5-
 127 mm slices on imaging obtained within 2 months prior to surgery. The C/T
 128 ratio was defined as the ratio of the maximal solid part diameter to the
 129 maximal ground glass opacity (GGO) part diameter, as previously described
 130 [19]. Pathological staging was based on the 7th edition of the UICC
 131 classification [20]. Preoperative comorbidities included hypertension,
 132 ischemic heart disease, arrhythmia requiring treatment, cerebrovascular
 133 disease, dialysis, diabetes mellitus, and connective tissue disease. The
 134 primary outcomes of this study were the 5-year OS, RFS, and cumulative
 135 incidence of recurrence. OS was defined as the number of days from surgery
 136 to death due to any cause. RFS was defined as the number of days from
 137 surgery to recurrence or death due to any cause. Locoregional recurrence was
 138 defined as recurrence in the ipsilateral thoracic cavity, including the resection
 139 stump, ipsilateral pulmonary hilar nodes, contralateral pulmonary hilar nodes,
 140 ipsilateral mediastinal lymph nodes, contralateral mediastinal lymph nodes,

141 metastasis to the ipsilateral lung field, ipsilateral pleura, and ipsilateral pleural
 142 effusions. Distant recurrence was defined as recurrence in the contralateral
 143 thoracic cavity or outside the thoracic cavity, including the contralateral lung
 144 field, contralateral pleural effusions, contralateral pleura, brain, bones,
 145 adrenal glands, liver, supraclavicular nodes, pericardium, pericardial fluid,
 146 and other regions [21]. The observation period was 5 years after surgery. The
 147 follow-up interval was 3–6 months, and the patients underwent CT scans at
 148 least twice a year.

149

150 **Statistical analysis**

151 Statistical analyses were performed using R version 4.1.3 (R
 152 Foundation for Statistical Computing, Vienna, Austria). Categorical data are
 153 presented as numbers and proportions, and continuous data are presented as
 154 medians and interquartile ranges. The Mann–Whitney U test was used to
 155 compare the two groups. For categorical variables, frequencies were
 156 compared using Fisher’s exact test. Kaplan–Meier survival estimates were
 157 used to assess the duration of survival, and the log-rank test was used to
 158 compare differences in OS and RFS. Cumulative incidence curves were used
 159 to assess the duration of illness before recurrence, lung cancer mortality, other
 160 mortality, distant recurrence, and locoregional recurrence, and Gray’s test was
 161 used to compare the differences. When cumulative recurrence and lung cancer
 162 mortality rates were assessed, non-lung cancer death was treated as a
 163 competing risk. When cumulative other mortality rates were assessed, lung
 164 cancer mortality was treated as a competing risk. When cumulative distant
 165 metastasis rates were assessed, locoregional recurrence and mortality were
 166 treated as competing risks. When cumulative locoregional recurrence rates
 167 were assessed, distant metastasis and mortality were treated as competing
 168 risks. In the univariable and multivariable analyses, the Cox proportional
 169 hazard model was used to identify prognostic factors for OS and RFS, and the
 170 Fine–Gray hazard model was used to identify prognostic factors for

171 cumulative incidence. Variables were selected based on their potential effect
 172 on outcomes as well as multicollinearity (variance inflation factor <5). Age
 173 (years), maximum tumor diameter (mm), vein-first ligation (yes/no),
 174 interstitial pneumonia (absent/present), N category ($0/\geq 1$), lymphatic
 175 invasion (absent/present), and vascular invasion (absent/present) were
 176 included as variables, and simultaneous entry was used in the multivariable
 177 analysis before matching. In the multivariable analyses after propensity score
 178 matching, vein-first and lymphatic invasion were included considering the
 179 number of events. All analyses were two-tailed, and statistical significance
 180 was set at $P < 0.05$.

181 Propensity scores were calculated using a logistic regression model,
 182 including age, sex, histological type, presence of comorbidity, history of other
 183 malignancy, presence of obvious interstitial pneumonia (IP) on CT, tumor
 184 localization, solid size ($>20/\leq 20$), C/T ratio ($\geq 0.75/<0.75$), clinical T stage
 185 (1–4), clinical N status (0–2), forced expiratory volume in one second (FEV₁)
 186 to forced vital capacity (FVC) ratio (FEV₁/FVC) ($\geq 70/<70$), operation year,
 187 and operation hospital. Patients were matched in a 1:1 ratio without
 188 replacement using the nearest-neighbor method with a caliper restriction of
 189 0.2.

190

191 **Results**

192 **Patients' characteristics**

193 Overall, 177 patients and 413 patients were included in the vein-
 194 first procedure and in the other procedures groups, respectively. After
 195 propensity score matching, 67 pairs of patients were obtained. The baseline
 196 characteristics of the patients before and after matching are summarized in
 197 Table 1. After matching, both groups comprised approximately 75% of
 198 patients with adenocarcinoma and approximately 20% with squamous cell
 199 carcinoma. Most patients in both groups had tumors with a C/T ratio of ≥ 0.75 ,
 200 and most patients were clinically N0. The presence of IP, previous malignancy,

comorbidity, and smoking history did not differ between the groups (Table 1). The proportion of FEV₁/FVC ≥ 70 , solid tumor size ≥ 20 mm, pure solid tumors, clinical T stage, tumor localization, and operation year were also similar between the two groups (Table 1).

The surgical approach and perioperative outcomes are summarized in Table 2. After matching, approximately 90% of both groups comprised patients who had undergone video-assisted thoracic surgery procedures. The frequencies and breakdown of adjuvant chemotherapy were similar between the two groups (Table 2). There were no significant differences in surgical approach, mediastinal lymph node dissection, operative time, blood loss, duration of chest tube placement, length of postoperative hospital stay, or postoperative complications within 30 days (Table 2).

213

214 **Survival outcomes**

Before propensity score matching, the 5-year OS was similar between the vein-first and other procedures groups (vein-first group, 79.8% [95% confidence interval {CI}, 74.0%–86.1%] vs. other procedures groups, 84.2% [95% CI, 80.6%–88.1%], $P = 0.24$; Supplemental Figure 1). Additionally, the 5-year RFS (vein-first group, 66.1% [95% CI, 59.4%–73.6%] vs. other procedures group, 63.8% [95% CI, 59.1%–68.7%], $P = 0.40$; Supplemental Figure 2) tended to be better, and the 5-year cumulative recurrence rate (vein-first group, 28.0% vs. other procedures group, 32.7%, $P = 0.16$; Figure 2a) tended to be lower in the vein-first group.

Survival curves after propensity score matching are shown in Figure 3. The 5-year OS rate was significantly better in the vein-first group (vein-first group, 85.6% [95%CI, 77.3%–94.8%] vs. other procedures group, 69.4% [95%CI, 58.7%–81.9%]; $P = 0.03$; Figure 3a). The 5-year RFS rate was also significantly better in the vein-first group (vein-first group, 73.4% [95% CI, 63.3%–85.1%] vs. other procedures group, 53.5% [95% CI, 42.5%–67.3%], $P = 0.02$; Figure 3b).

231 The cumulative incidence function curves after matching are
 232 shown in Figure 2b–f. The cumulative recurrence rates at 5 years after surgery
 233 were 21.7% and 38.3% in the vein-first group and the other procedures groups,
 234 respectively. The cumulative recurrence rate was significantly lower in the
 235 vein-first approach group ($P = 0.04$; Figure 2b). The cumulative lung cancer
 236 mortality rate at 5 years after surgery was significantly lower in the vein-first
 237 group (7.8% and 22.3%, $P = 0.03$; Figure 2c). The cumulative other mortality
 238 rates at 5 years after surgery were similar in the two groups (6.6% and 8.4%,
 239 $P = 0.74$; Figure 2d). The cumulative distant recurrence rates at 5 years after
 240 surgery was significantly lower in the vein-first group (9.2% and 26.2%, $P =$
 241 0.01; Figure 2e). The cumulative locoregional recurrence rates at 5 years after
 242 surgery were similar in the two groups (15.6% and 27.5%, $P = 0.09$; Figure
 243 2f).

244 The pathological data and postoperative outcomes are summarized
 245 in Table 3. After matching, the pathological tumor diameter, T status, N status,
 246 pathological stage, and vascular invasion were not significantly different
 247 between the two groups, although lymphatic invasion was more frequent in
 248 the other procedures group (vein-first group, 11 [16.7%] vs. other procedures
 249 group, 23 [34.3%]; $P = 0.03$). Distant metastasis as the first recurrent site
 250 tended to be lower in the vein-first group (vein-first group, 6 [42.9%] vs. other
 251 procedures group, 17 [68.0%]; $P = 0.18$).

252 In the multivariable analysis before matching, the vein-first
 253 approach was not significantly associated with OS, RFS, and cumulative
 254 incidence of recurrence (Supplemental Tables 1–3). However, in the
 255 univariable analysis after matching, the vein-first approach was significantly
 256 associated with OS, RFS, and cumulative incidence of recurrence
 257 (Supplemental Tables 4–6). In the multivariable analysis after matching,
 258 including the vein-first approach and the presence of lymphatic invasion,
 259 lymphatic invasion was significantly associated with OS, RFS, and
 260 cumulative incidence of recurrence (Supplemental Tables 7–9).

Subgroup analysis of patients with clinical N0 was performed. Detailed methods for propensity score matching are described in Supplemental Appendix 1. The baseline characteristics of the patients before and after matching are summarized in Supplemental Table 7. The baseline characteristics were well matched between the two groups. The perioperative outcomes are summarized in Supplemental Table 8. After matching, there were no significant differences between the two groups. Postoperative outcomes are summarized in Supplemental Table 9. After matching, patients in the other procedures group showed more advanced pathological N status and pathological stage than in the vein-first group. Pleural invasion was more frequent in the other procedures group than in the vein-first group. The 5-year OS rate after matching was significantly better in the vein-first group (vein-first group, 92.6% [95% CI, 86.0%–99.9%] vs. other procedures group, 73.6% [95% CI, 63.0%–86.0%]; $P < 0.01$; Supplemental Figure 3). The 5-year RFS rate was also significantly better in the vein-first group (vein-first group, 78.9% [95% CI, 68.9%–90.3%]) vs. other procedures group, 54.2% [95% CI, 42.9%–68.6%], $P < 0.01$; Supplemental Figure 4). The cumulative recurrence rate at 5 years after surgery was significantly lower in the vein-first group (19.3% and 38.8%, $P = 0.02$; Supplemental Figure 5).

280

281 Discussion

In the current multicenter, propensity score-matched study, we found that ligating the PV prior to ligating or cutting the PA, bronchus, or pulmonary fissure was associated with a better OS and RFS and a lower cumulative incidence of recurrence.

The effects of vein-first procedures on prognosis in previous studies have been controversial [9,11,12,14–16]. This may have been partly due to the potential heterogeneity of the study patients and the biases of those studies. Most studies were retrospective studies of non-matched cohorts. Although Kozak et al. reported a prospective randomized trial, the procedures

291 were performed using open thoracotomy [15]. In addition, early studies
 292 published before the 8th edition of the UICC definition [18] did not distinguish
 293 solid nodules from GGOs. He et al. reported that vein-first ligation is
 294 advantageous only in patients with squamous cell carcinoma [16]. In our
 295 study, tumors with a C/T ratio of ≤ 0.5 , which are considered to be less
 296 invasive [19] and therefore less likely to disseminate CTCs, were excluded.
 297 Wei et al. and Sumitomo et al. showed a significant benefit of the vein-first
 298 procedure, particularly in early-stage non-small cell lung cancer (NSCLC)
 299 [11,12]. In this study, we performed propensity score matching for tumor
 300 TNM stage, histology, and GGO ratio (C/T ratio) to minimize bias and
 301 heterogeneity in the patient groups. A recent, relatively large, propensity
 302 score-matched study by Wei et al. showed a significant advantage of the vein-
 303 first approach in terms of OS, disease-free survival, and lung cancer-specific
 304 survival [12], which was consistent with our study and supports the reliability
 305 of our results.

306 In addition to the sequence of vessel ligation, the timing of PV
 307 ligation is an important factor in preventing CTC dissemination [13]. Recently,
 308 Duan et al. reported that early PV ligation, which involves ligating the PV
 309 immediately after dissecting it with subsequent dissection of other hilar
 310 structures, can prevent CTCs from spreading into the circulation [13]. This
 311 result supports the theory that surgical manipulation of the lung before
 312 ligation of the drainage PV may disseminate CTCs. In our study, we defined
 313 the vein-first group as patients who had undergone ligation of the PV before
 314 ligation or cutting of the bronchus or pulmonary fissure, in addition to the PA,
 315 to clarify the effect of early ligation of the PV. Additionally, Duan et al.
 316 provided evidence that early PV ligation can prevent CTCs from spreading
 317 into the circulation via the PV; however, their study did not include clinical
 318 outcomes, such as survival rates [13]. Therefore, the results of our study
 319 provide important evidence that early PV ligation can minimize the
 320 consequences of lung manipulation in terms of CTC dissemination and thus

321 contribute to better OS, RFS, and cumulative recurrence incidence after
322 curative lobectomy.

323 In the multivariable analysis, the vein-first procedure was not an
324 independent prognostic factor after adjusting for other prognostic factors. The
325 influence of the vein-first procedure on prognosis may be relatively weak
326 compared with other established prognostic factors such as tumor diameter,
327 nodal status, lymphatic invasion, and vascular invasion. This may be one of
328 the reasons why previous studies did not show the significant effect of vein-
329 first procedures on survival. In this study, the proportion of patients with
330 lymphatic invasion was significantly higher, and the number of patients with
331 pathological N2 was also higher in the other procedures group even after
332 matching. This imbalance may have occurred due to the limitations of
333 propensity score matching. Before propensity score matching, the proportions
334 of lymphatic invasion and pathological lymph node status were similar
335 between the two groups, with the vein-first group showing a tendency for
336 better RFS and cumulative incidence of recurrence. Therefore, we believe the
337 better outcomes in the vein-first group after matching were due to not only
338 differences in the nodal status and presence of lymphatic invasion but also the
339 vein-first procedure. However, further studies are warranted to confirm our
340 results and determine the characteristics of lung cancer that necessitate the
341 vein-first approach.

342 Over the last few decades, uniportal VATS has been performed to
343 treat lung cancer. Some reports have recommended dissecting and dividing
344 the PA [22,23] or bronchus [24] before ligating the PV to improve the
345 feasibility of uniportal procedures. Similarly, robot-assisted thoracic surgery
346 (RATS) has become the new standard for major lung resection [25], and
347 uniportal RATS has been performed [26]. Our results indicate that a feasible
348 technique for safe vein-first uniportal VATS and RATS should be established.

349 For peripheral small-sized NSCLC, one study has shown that
350 segmentectomy is superior to lobectomy in terms of OS [21], while another

351 study has shown that sublobar resection, including segmentectomy and wedge
 352 resection, is non-inferior to lobectomy in terms of disease-free survival [27].
 353 Considering our results, the effect of vein-first segmentectomy on prognosis
 354 should be investigated in future studies, and the prognoses of vein-first
 355 lobectomy and segmentectomy should be compared.

356 This study had a few limitations. First, it was a retrospective study.
 357 Prospective randomized studies are required to confirm our results. Second,
 358 because of the retrospective nature of this study, the 7th edition of pathological
 359 staging was used; however, only patients with a C/T ratio >0.5 were included
 360 in the analysis to minimize the effect of pathological staging on the outcomes.
 361 Third, the proportion of patients with lymphatic invasion was significantly
 362 higher, and the number of patients with pathological N2 was also higher in
 363 the other procedures group even after matching; therefore, further studies are
 364 warranted to confirm our results. Finally, although this was a multicenter
 365 study, a relatively small number of patients were included after propensity
 366 score matching. Further large-scale prospective studies are needed to confirm
 367 these results.

368

369 **Conclusions**

370 Our study suggests that ligating the PV first during lobectomy for
 371 lung cancer to minimize lung manipulation, which may spread tumor cells
 372 into the circulation, contributes to better OS, RFS, and cumulative incidence
 373 of recurrence. Further studies should focus not only on the sequence of vessel
 374 ligation but also on the manipulation of the lung before ligating the PV. In
 375 addition, further studies are warranted to determine the characteristics of lung
 376 cancers that favor the vein-first approach.

377

378

379 **Acknowledgements:** We would like to thank Editage
380 (www.editage.com) for the English language editing.

381

382 **Conflict of interest disclosure:** The authors declare that they have no
383 competing interests.

384

385 **Funding statement:** This research did not receive any specific grants
386 from funding agencies in the public, commercial, or not-for-profit sectors.

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Tables

Table 1. Baseline characteristics of the patients before and after matching

Data are presented as a number (%) or median (interquartile range).

^aContinuous variables were compared using the Mann–Whitney U-test.

^bFrequencies were compared using Fisher’s exact test for categorical variables.

^cStandardized mean difference for tumor localization was calculated as binary variables (right side vs. left side).

^dStandardized mean difference for clinical T stage was calculated as binary variables (stage 1a, 1b, or 1c vs. 2a, 2b, 3, or 4).

^eStandardized mean difference for clinical N stage was calculated as binary variables (0 vs. 1 or 2).

^fStandardized mean difference for histology was calculated as binary variables (adenocarcinoma vs. SqCC or adenosquamous).

^gStandardized mean difference for operation year was calculated as binary variables (2012, 2013, or 2014 vs. 2015 or 2016).

Abbreviations: CT, computed tomography; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IP, interstitial pneumonia; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SqCC, squamous cell carcinoma; VATS, video-assisted thoracic surgery.

Table 2. Perioperative outcomes before and after matching

Data are presented as a number (%) or median (interquartile range).

^aContinuous variables were compared using the Mann–Whitney U-test.

^bFrequencies were compared using Fisher’s exact test for categorical variables.

Abbreviations: VATS, video-assisted thoracic surgery; LND, lymph node dissection.

Table 3. Postoperative outcomes before and after matching

Data are presented as a number (%) or median (interquartile range).

^aContinuous variables were compared using the Mann–Whitney U-test.

^bFrequencies were compared using Fisher’s exact test for categorical variables.

Figure Legends

Fig. 1 Flow chart of the patients

We included 177 patients in the vein-first procedures group and 413 in the other procedures group. Finally, 590 patients were enrolled in this study. After propensity score matching, 67 pairs of patients were matched.

Abbreviations: CT, computed tomography.

Fig. 2 Cumulative incidence function curves according to the procedure

(a) The cumulative recurrence rate before propensity score-matching tended to be lower in the vein-first group than in the other procedures group ($P = 0.16$ by Gray's test). (b) The cumulative recurrence rate after propensity score-matching was significantly lower in the vein-first group than in the other procedures group ($P = 0.04$ by Gray's test). (c) The cumulative lung cancer mortality rate after matching was significantly lower in the vein-first group (7.8% and 22.3%, $P = 0.03$ by Gray's test). (d) The cumulative other mortality rates after matching were similar in the two groups (6.6% and 8.4%, $P = 0.74$ by Gray's test). (e) The cumulative distant recurrence rate after matching was significantly lower in the vein-first group (9.2% and 26.2%, $P = 0.01$ by Gray's test). (f) The cumulative locoregional recurrence rates after matching were similar in the two groups (15.6% and 27.5%, $P = 0.09$ by Gray's test).

Fig. 3 Overall and recurrence-free survival according to the procedure after propensity score matching

(a) Kaplan–Meier survival curves for the overall survival of patients grouped by procedure. $P = 0.03$ by the log-rank test. (b) Kaplan–Meier survival curves for the recurrence-free survival of patients grouped by procedure. $P = 0.02$ by the log-rank test.

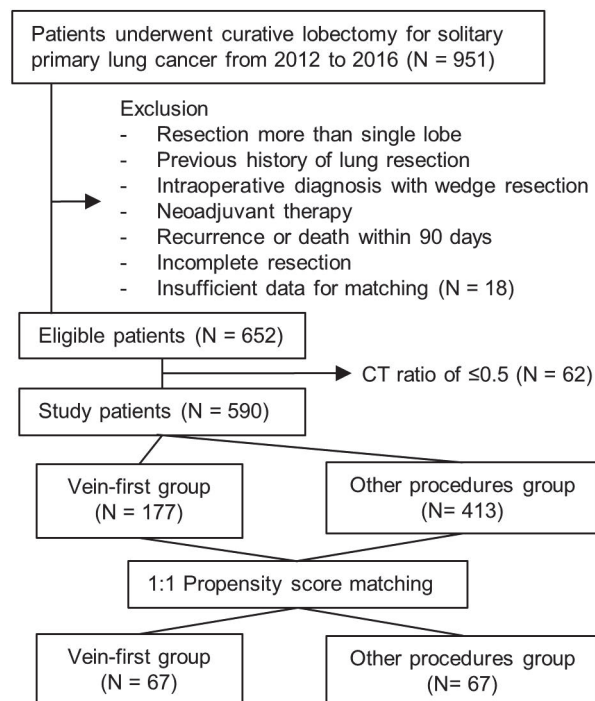
Variables	Before matching				After matching			
	Vein-first	Other procedures	<i>P</i> -value	SMD	Vein-first	Other procedures	<i>P</i> -value	SMD
	(N = 177)	(N = 413)			(N = 67)	(N = 67)		
Age (years)	70.0 (63.0, 75.0)	68.0 (62.0, 73.0)	0.02 ^a	0.162	68.0 (60.0, 74.5)	68.0 (62.5, 73.0)	>0.99 ^a	0.067
Sex, female	84 (47.5)	166 (40.2)	0.10 ^b	0.147	26 (38.8)	29 (43.3)	0.73 ^b	0.091
IP, yes	17 (9.6)	36 (8.7)	0.75 ^b	0.031	9 (13.4)	8 (11.9)	>0.99 ^b	0.045
Previous malignancy, yes	30 (16.9)	57 (13.8)	0.38 ^b	0.087	14 (20.9)	12 (17.9)	0.83 ^b	0.076
FEV ₁ /FVC, ≥70	94 (53.1)	251 (60.8)	0.08 ^b	0.155	35 (52.2)	35 (52.2)	>0.99 ^b	<0.001
Comorbidity, yes	121 (68.4)	228 (55.2)	<0.01 ^b	0.273	45 (67.2)	43 (64.2)	0.86 ^b	0.063
Smoking history, yes	118 (67.8)	281 (70.4)	0.55 ^b	0.057	47 (72.3)	49 (76.6)	0.69 ^b	0.098
Tumor localization			<0.01 ^b	0.280 ^c			0.67 ^b	0.076 ^c
RUL	75 (42.4)	147 (35.6)			33 (49.3)	31 (46.3)		
RML	27 (15.3)	12 (2.9)			6 (9.0)	11 (16.4)		
RLL	29 (16.4)	93 (22.5)			14 (20.9)	13 (19.4)		
LUL	29 (16.4)	98 (23.7)			7 (10.4)	4 (6.0)		
LLL	17 (9.6)	63 (15.3)			7 (10.4)	8 (11.9)		
Clinical T stage			0.66 ^b	0.012 ^d			0.98 ^b	0.061 ^d
1a	2 (1.1)	13 (3.1)			1 (1.5)	2 (3.0)		
1b	58 (32.8)	137 (33.2)			17 (25.4)	19 (28.4)		
1c	58 (32.8)	124 (30.0)			22 (32.8)	21 (31.3)		
2a	37 (20.9)	75 (18.2)			18 (26.9)	15 (22.4)		
2b	8 (4.5)	28 (6.8)			2 (3.0)	2 (3.0)		
3	12 (6.8)	27 (6.5)			7 (10.4)	8 (11.9)		
4	2 (1.1)	9 (2.2)			0 (0.0)	0 (0.0)		
Pure solid, yes	152 (85.9)	320 (77.5)	0.02 ^b	0.218	57 (85.1)	52 (77.6)	0.38 ^b	0.192

C/T ratio, ≥ 75	163 (92.1)	366 (88.6)	0.24 ^b	0.118	60 (89.6)	59 (88.1)	>0.99 ^b	0.047
Solid size, ≥ 20 mm	118 (66.7)	264 (63.9)	0.57 ^b	0.058	50 (74.6)	46 (68.7)	0.57 ^b	0.133
Clinical N stage			0.38 ^b	0.043 ^c			>0.99 ^b	0.047 ^c
0	160 (90.4)	368 (89.1)			59 (88.1)	60 (89.6)		
1	9 (5.1)	32 (7.7)			5 (7.5)	5 (7.5)		
2	8 (4.5)	13 (3.1)			3 (4.5)	2 (3.0)		
Histology			0.97 ^b	0.025 ^f			0.75 ^b	0.07 ^f
Adenocarcinoma	139 (78.5)	320 (77.5)			52 (77.6)	50 (74.6)		
SqCC	36 (20.3)	87 (21.1)			13 (19.4)	16 (23.9)		
Adenosquamous	2 (1.1)	6 (1.5)			2 (3.0)	1 (1.5)		
City hospital, yes	48 (27.1)	381 (92.3)	<0.01 ^b	1.776	36 (53.7)	38 (56.7)	0.86 ^b	0.06
Operation year			0.03 ^b	0.261 ^g			0.20 ^b	0.159 ^g
2012	41 (23.2)	77 (18.6)			25 (37.3)	14 (20.9)		
2013	44 (24.9)	67 (16.2)			14 (20.9)	16 (23.9)		
2014	33 (18.6)	79 (19.1)			8 (11.9)	12 (17.9)		
2015	30 (16.9)	97 (23.5)			10 (14.9)	8 (11.9)		
2016	29 (16.4)	93 (22.5)			10 (14.9)	17 (25.4)		

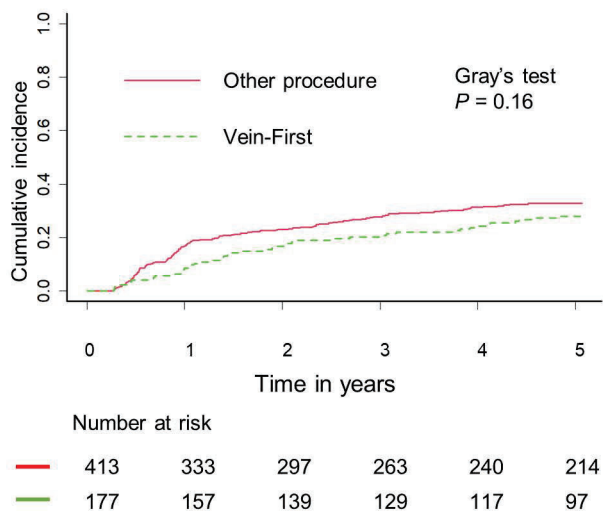
Variables	Before matching			After matching		
	Vein-first	Other procedures	<i>P</i> -value	Vein-first	Other procedures	<i>P</i> -value
	(N = 177)	(N = 413)		(N = 67)	(N = 67)	
Surgical approach			0.05 ^b			0.59 ^b
VATS	164 (92.7)	359 (86.9)		61 (91.0)	58 (86.6)	
Thoracotomy	13 (7.3)	54 (13.1)		6 (9.0)	9 (13.4)	
Mediastinal LND, yes	163 (92.1)	353 (85.5)	0.03 ^b	58 (86.6)	59 (88.1)	>0.99 ^b
Operative time, min	216.0 (175.0, 271.0)	185.0 (153.0, 222.0)	<0.01 ^a	220.0 (175.0, 266.5)	203.0 (166.5, 257.0)	0.46 ^a
Blood loss, mL	50.0 (0.0, 100.0)	50.0 (0.0, 100.0)	0.74 ^a	50.0 (30.0, 128.75)	50.0 (0.0, 100.0)	0.29 ^a
Chest tube placement, days	2.0 (1.0, 4.0)	4.0 (4.0, 4.0)	<0.01 ^a	4.0 (2.0, 4.0)	4.0 (2.0, 4.0)	0.37 ^a
Postoperative hospital stays, days	9.5 (7.0, 12.0)	11.0 (10.0, 13.0)	<0.01 ^a	11.00 (8.0, 13.0)	10.00 (8.0, 12.5)	0.68 ^a
Postoperative complications within 30 days, yes	43 (24.4)	58 (14.0)	<0.01 ^a	16 (23.9)	13 (19.4)	0.68 ^a
Adjuvant chemotherapy						
Platinum-based	23 (13.1)	74 (18.0)	0.18 ^b	12 (18.2)	13 (19.7)	>0.99 ^b
Tegafur uracil	33 (18.6)	115 (27.9)	0.02 ^b	16 (24.2)	13 (19.7)	0.68 ^b

Variables	Before matching			After matching		
	Vein-first (N = 177)	Other procedures (N = 413)	<i>P</i> -value	Vein-first (N = 67)	Other procedures (N = 67)	<i>P</i> -value
pTumor diameter, mm	28.0 (20.0, 39.0)	28.0 (21.0, 38.0)	0.43 ^a	30.0 (23.0, 40.0)	30.0 (22.0, 38.0)	0.90 ^a
pT status			0.13 ^b			0.48 ^b
1a	40 (22.6)	89 (21.5)		8 (11.9)	10 (14.9)	
1b	39 (22.0)	90 (21.8)		18 (26.9)	13 (19.4)	
2a	84 (47.5)	188 (45.5)		34 (50.7)	35 (52.2)	
2b	3 (1.7)	27 (6.5)		2 (3.0)	6 (9.0)	
3	11 (6.2)	19 (4.6)		5 (7.5)	3 (4.5)	
pN status			0.82 ^b			0.10 ^b
0	145 (81.9)	328 (79.4)		59 (88.1)	50 (74.6)	
1	14 (7.9)	39 (9.4)		4 (6.0)	6 (9.0)	
2	18 (10.2)	46 (11.1)		4 (6.0)	11 (16.4)	
pStage			0.69 ^b			0.22 ^b
IA	70 (39.5)	162 (39.2)		26 (38.8)	21 (31.3)	
IB	65 (36.7)	135 (32.7)		28 (41.8)	24 (35.8)	
IIA	16 (9.0)	52 (12.6)		5 (7.5)	9 (13.4)	
IIB	7 (4.0)	14 (3.4)		3 (4.5)	1 (1.5)	
IIIA	19 (10.7)	50 (12.1)		5 (7.5)	12 (17.9)	
Pleural invasion			0.43 ^b			0.47 ^b
Absent	127 (72.6)	285 (69.0)		46 (69.7)	42 (62.7)	
Present	48 (27.4)	128 (31.0)		20 (30.3)	25 (37.3)	
Lymphatic invasion			>0.99 ^b			0.03 ^b
Absent	130 (74.3)	305 (73.8)		55 (83.3)	44 (65.7)	
Present	45 (25.7)	108 (26.2)		11 (16.7)	23 (34.3)	

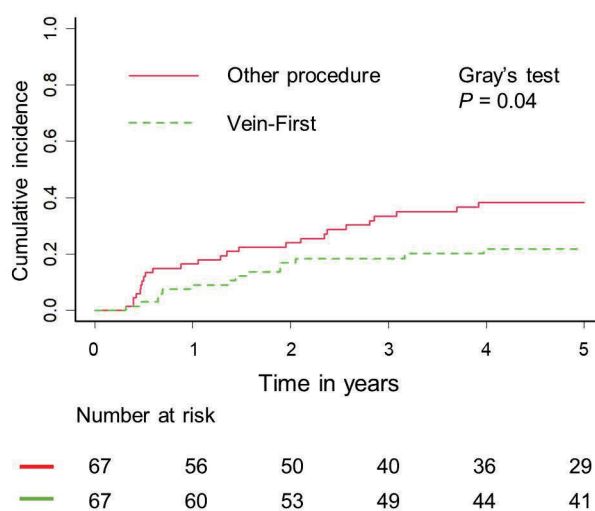
Vascular invasion			<0.01 ^b			0.49 ^b
Absent	95 (53.7)	165 (40.0)		32 (47.8)	27 (40.3)	
Present	82 (46.3)	248 (60.0)		35 (52.2)	40 (59.7)	
Total mortality	34 (19.2)	58 (14.0)	0.14 ^b	9 (13.4)	19 (28.4)	0.06 ^b
Lung cancer mortality	22 (12.4)	40 (9.7)	0.24 ^b	5 (7.5)	14 (20.9)	0.07 ^b
Other mortality	12 (6.8)	18 (4.4)		4 (6.0)	5 (7.5)	
Total relapse	48 (27.1)	129 (31.2)	0.33 ^b	14 (20.9)	25 (37.3)	0.06 ^b
First recurrent site						
Locoregional	29 (60.4)	80 (62.0)	0.86 ^b	10 (71.4)	18 (72.0)	>0.99 ^b
Distant	25 (52.1)	74 (57.4)	0.61 ^b	6 (42.9)	17 (68.0)	0.18 ^b
Both	6 (12.5)	25 (19.4)	0.38 ^b	2 (14.3)	10 (40.0)	0.15 ^b



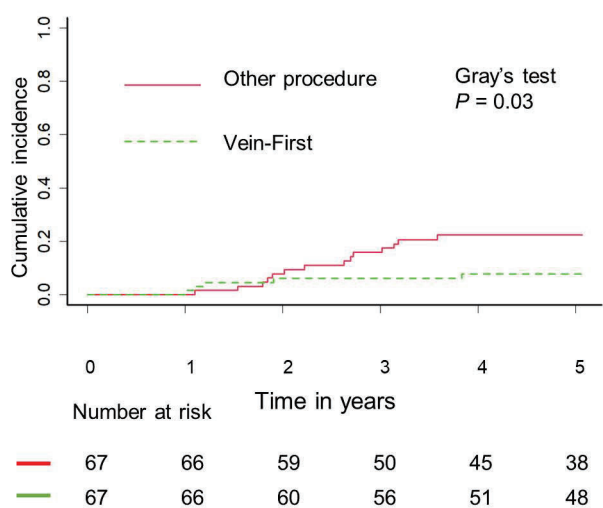
a Cumulative incidence of recurrence



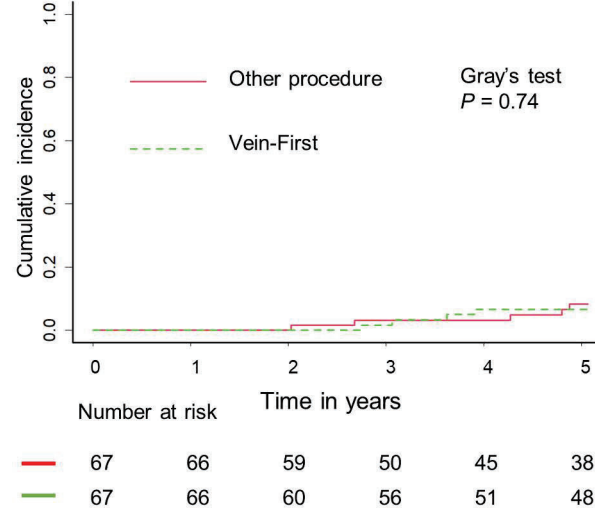
b Cumulative incidence of recurrence



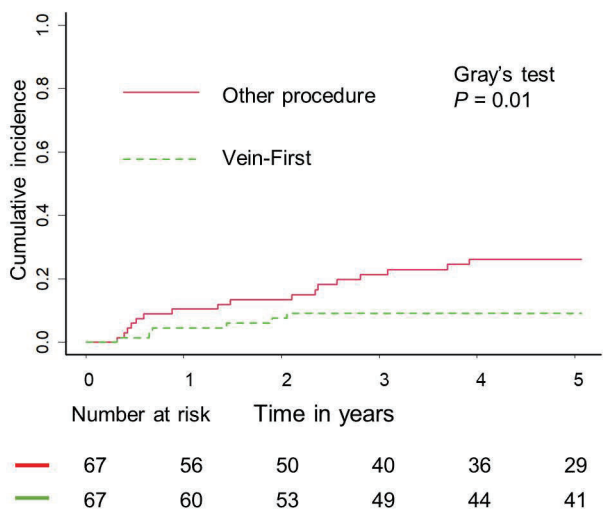
c Cumulative incidence of lung cancer mortality



d Cumulative incidence of other mortality



e Cumulative incidence of distant recurrence



f Cumulative incidence of locoregional recurrence

