Does Vein-first Lobectomy Control Postoperative Circulating Tumor Cells in Lung Cancer?: a Retrospective Observational Study

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Research Article

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Abstract

Background: Vein-first dissecting lobectomy in lung cancer surgery is speculated to limit the amount of circulating tumor cells. We aimed to assess the clinical significance and prognostic impact of Vein-first dissecting lobectomy according to changes in circulating tumor cell status throughout the perioperative period.

Methods: Among patients with pulmonary nodule who underwent surgery, we extracted and evaluated patients who underwent lobectomy for lung cancer and had underwent circulating tumor cell testing before and immediately after the completion of lobectomy. The primary evaluation item was the detection rate of postoperative circulating tumor cell according to the sequence of pulmonary vessel processing. The secondary evaluation items were the 2-year recurrence-free survival and overall survival rates according to the status of Vein-first dissecting lobectomy and postoperative circulating tumor cell.

Results: Between June 2014 and June 2018, 302 patients with pulmonary nodule underwent surgery, among them we selected 86 patients who underwent lobectomy for lung cancer and had circulating tumor cell testing done before and immediately after the completion of lobectomy. The circulating tumor cell identification rates in the postoperative period were 54.4% (37/68) and 66.7% (12/18) (p=0.8) in vein-first dissecting lobectomy group and no-vein-first dissecting lobectomy group, respectively. The mean postoperative circulating tumor cell count was not significantly different between the vein-first dissecting lobectomy and no-vein-first dissecting lobectomy groups (3.0 ± 3.6 vs 3.2 ± 5.0, p=0.8). The 2-year recurrence-free survival and overall survival rates were also not significantly different. However, the presence of circulating tumor cell after surgery was a predictor of recurrence.

Conclusions: Although the detection of circulating tumor cell after surgery is a predictor of cancer recurrence, no significant difference was observed in the status of postoperative circulating tumor cell s between vein-first dissecting lobectomy and no- vein-first dissecting lobectomy groups in lung cancer surgery.

Background

Lung cancer is one of the leading causes of cancer death [1], and there is a need to increase and control the accuracy of lung cancer treatment. Lung cancer can recur despite complete resection [2], and some of these recurrences are attributed to residual tumor cells after surgery [3]. Circulating tumor cells (CTCs), which are tumor cells in the peripheral circulating blood, can develop into recurrent tumors [4]. Thus, decreasing the number of shed CTCs will also reduce the risk of metastasis. In lung cancer surgery, the amount of postoperatively shed CTCs might be reduced via vein-first dissecting lobectomy (VFL). VFL has been reported to be associated with good prognosis after pulmonary lobectomy for lung cancer [5–7]. However, several studies also found that VFL has limited therapeutic benefit for reducing recurrence [8–11]. A recent prospective randomized study [12] revealed that among lobectomy patients with lung cancer, the postoperative increase in CTC count was more limited in the VFL group than that in the no-

VFL group. Further, a retrospective propensity score matching analysis revealed superior survival in the VFL group than that in the no-VFL group [12].

Assessing the perioperative CTC status and the prognosis of VFL and no-VFL cases will be helpful to understanding the clinical implication of VFL for lung cancer. Under our hypothesis that VFL could reduce the frequency of CTC detection after surgery and achieve good recurrence-free survival, this study aimed to assess the clinical significance and prognostic impact of VFL according to changes in the CTC status in the perioperative period.

Methods

Study design and patient selection

This study was approved by the institutional review boards of Hoshigaoka Medical Center (HMC) (No.1718) and Nara Medical University Hospital (NMU) (No.1412). Informed consent was obtained from all participants who were included in the study. The study protocol is performed in accordance with the relevant guidelines.
Among patients with pulmonary nodule with a final diagnoses of lung cancer, who were retrospectively evaluated in an observational manner, we enrolled patients who underwent lobectomy and CTC testing before and immediately after the completion of lobectomy. The primary outcome measure was the detection rate of postoperative CTC according to the sequence of pulmonary vessel processing. The secondary outcome measures were the 2-year recurrence-free survival and overall survival rates according to the status of VFL and postoperative CTC.

Surgical methods

All patients underwent routine enhanced thin section computed tomography (CT) (1.0 mm width) to obtain multi-planar reconstruction (axial, coronal, and sagittal shadow), on which we assessed the method of surgery. VFL was defined as pulmonary vein (PV) cut was completed before any pulmonary artery (PA) cut; when the PA was cut before the PV was cut completely, the surgery was not classified as VFL.

Thoracic surgery was performed under general anesthesia and with a double-lumen endotracheal tube. The patient was placed in a position with the ipsilateral upper extremity flexed and fixed onto the hand shelf. The surgeon stood on the left side of the patient. An access port was made in the 7th or 8th intercostal space at the line. A utility incision (4–5 cm) was made at the posterior axillary line in the 4th space, and another one (1–2 cm) was made at the anterior axillary line in the 4th intercostal space. These ports allowed the concomitant use of two instruments. In addition, an assistant port (0.6 cm) was used at the posterior axillary line in the 9th intercostal space if needed.

Detection of circulating tumor cells

Peripheral arterial blood (3 mL) was collected inside the operating room immediately before surgery and placed in an ethylenediaminetetraacetic acid tube. Another blood sample was obtained after completion of pulmonary resection. All samples were processed within 4 h from the end of the operation. The presence of CTCs in the blood samples was evaluated using the ScreenCell® CTC selection kit (ScreenCell MA, USA), which uses a size-based selection method [13]. The extracted cells were then stained with hematoxylin and eosin and observed under a light microscope.

The presence of CTCs was determined based on a cytology atlas for CTCs from solid cancers [14]. Suspicious cells were not considered CTCs in the present study. The CTC detection results were divided into three types based on the morphological findings: no CTCs detected (N), only single CTCs were detected (S), and CTC clusters were detected (C). A “cluster” was defined as ≥ 4 cells to minimize the contribution of collection- or preparation-related artifacts. All CTC evaluations were performed by a surgeon (NS), and the diagnoses were confirmed by pathologists (IT or CO).

Data collection and follow-up

Data were collected from the medical records, and videos of the surgeries were also collected by one investigator (NS). Mortality and recurrence data were collected by the primary physician (NS). All patients were followed at 1-month to 3-month intervals, and follow-up included physical and chest radiography examinations as well as blood testing for tumor markers. The patients also underwent thoracoabdominal CT scans at 6-month intervals. The patients were followed up for a median of 50 months (range, 24–74 months), and the last follow-up examination was performed in January 2020. Recurrence was classified as none, local (i.e., resection margin recurrence), regional (i.e., ipsilateral intrathoracic recurrence), or distant (i.e., metastasis outside the ipsilateral intrathoracic cavity).

Statistical analysis

Inter-group comparisons were performed using the t test and Fisher’s exact test, as appropriate. Multivariable logistic regression analysis of VFL in the end point of detecting CTC postoperatively, was performed with covariates of tumor vessel invasion, types of CT appearance (solid or not), and size of invasion. Survival was evaluated based on Kaplan-Meier curves and compared using the log-rank test. All statistical analyses were performed using freely available ‘EZR’ software [15], which is based on R and R commander. Differences were considered statistically significant at p-values < 0.05.

Results

Patient characteristics and CTC status

The flow chart of patient extraction is shown in Fig. 1. Among 302 patients with pulmonary nodule who underwent surgery at HMC or NMU between June 2014 and June 2018, we enrolled 86 patients who underwent lobectomy for lung cancer and had undergone CTC testing before and immediately after the completion of lobectomy.

The most frequently involved lobe was the right upper lobe (34.9%), followed by the right lower lobe (29.1%), left upper lobe (18.6%), left lower lobe (14.0%), and right middle lobe (3.5%). Most of the lesions were pure solid lesions on CT (82.6%), and most common pathological diagnoses were invasive adenocarcinoma or squamous cell carcinoma (81.5%). Other histological diagnoses were pleomorphic carcinoma (n = 5), large cell neuroendocrine carcinoma (n = 4), not otherwise specified (n = 3), adeno-squamous cell carcinoma (n = 2), and carcinoid (n = 1). The characteristics of the overall cohort and of the VFL groups are shown in Table 1. Overall, 25% of the patients had pathological stage > I disease, and 33% received adjuvant treatment (oral tegafur/uracil or intravenous carboplatin plus paclitaxel). There were significant differences in operation time and time of completion of pulmonary vein dissection between the VFL and no-VFL groups, but other variables were not significantly different.

Table 1
Clinicopathological patient characteristics according to status of vein-first lobectomy

Variables		Overall group	VFL group	No-VFL group	*p*-value
n		86	68	18	
Sex (male/female)		44 (51.2)/42 (48.8)	32 (47.1)/36 (52.9)	12 (66.7)/6 (33.3)	0.2
Age*		68.0 ± 8.8	67.2 ± 9.0	81.0 ± 7.8	0.1
Involved lobe	RUL	30 (34.9)	27 (39.7)	3 (16.7)	0.1
	RML	3 (3.5)	3 (4.4)	0(0)	
	RLL	25 (29.1)	15 (22.1)	10 (3.1)	
	LUL	16 (18.6)	13 (19.1)	3 (16.7)	
	LLL	12 (14.0)	10 (14.7)	2 (11.1)	
Computed tomography findings	Solid/solid + GGO	71 (82.6)/15 (17.4)	56 (82.4)/12 (17.6)	15 (83.3)/3 (16.7)	0.1
	Whole tumor size* (cm)	2.7 ± 1.5	2.9 ± 1.6	2.3 ± 1.3	0.2
	Solid size* (cm)	2.5 ± 1.6	2.6 ± 1.7	2.1 ± 1.4	0.3
Clinical stage	IA1	10 (11.6)	8 (11.8)	2 (11.1)	0.6
	IA2	38 (44.2)	30 (44.1)	8 (44.4)	
	IA3	20 (23.2)	14 (20.6)	6 (33.3)	
	IB	18 (20.9)	16 (23.5)	2 (11.1)	
Operation time (min)	Total	164.2 ± 80.2	179.1 ± 83.2	107.7 ± 23.8	< 0.01
	Completion of vein dissection	42.1 ± 15.9	38.1 ± 10.5	56.9 ± 23.0	< 0.01
Tumor histology	Invasive adenocarcinoma	58 (67.4)	44 (64.7)	14 (77.8)	0.06
	Squamous cell carcinoma	13 (15.1)	9 (13.2)	4 (22.2)	
	Others	15 (17.4)	15 (22.1)	0 (0)	

Data are presented as numbers (percentages) or the mean ± standard deviation.

Abbreviations: GGO, ground-glass opacity; IV, intravenous; LLL, right lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; VFL, vein-first lobectomy

Variables		Overall group	VFL group	No-VFL group	*p*-value
Pathological findings	Tumor size* (cm)	2.8 ± 1.7	2.9 ± 1.8	2.4 ± 1.2	0.2
	Inversion size* (cm)	2.5 ± 1.6	2.7 ± 1.6	2.1 ± 1.2	0.2
	Pleural invasion	32 (37.2)	27 (39.7)	5 (27.8)	0.4
	Vessel invasion	51 (59.3)	44 (64.7)	7 (38.9)	0.06
	Lymphatic duct invasion	58 (67.4)	41 (60.3)	7 (38.9)	0.1
Pathological stage	IA1	18 (20.9)	16 (23.5)	2 (11.1)	0.2
	IA2	22 (25.6)	15 (22.1)	7 (38.9)	
	IA3	6 (7.0)	3 (4.4)	3 (16.7)	
	IB	15 (17.4)	13 (19.1)	2 (11.1)	
	2A	8 (9.3)	8 (11.8)	0 (0)	
	2B	10 (11.6)	7 (10.3)	3 (16.7)	
	3A	7 (8.1)	6 (14.7)	1 (5.6)	
Adjuvant therapy	No	58 (67.4)	42 (61.8)	14 (77.8)	0.6
	Oral	15 (17.4)	13 (19.1)	2 (11.1)	
	IV	13 (15.1)	13 (19.1)	2 (11.1)	
Data are presented as numbers (percentages) or the mean ± standard deviation.					
Abbreviations: GGO, ground-glass opacity; IV, intravenous; LLL, right lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; VFL, vein-first lobectomy					

The CTC status in the overall cohort and in the VFL and no-VFL groups are shown in Table 2. The preoperative CTC detection rate was 39.5%, and the CTC count was 1.6 ± 3.1 (mean ± standard deviation). The CTC detection results were N, S, and C in 65.1%, 12.8%, and 22.1% of the patients, respectively, and there were no significant differences between the VFL and no-VFL groups. Postoperatively, the CTC detection rate was 57.0%, and the CTC count was 3.0 ± 3.8 (mean ± SD). There were 43.0%, 15.1%, and 41.9% of the patients who had N, S, and C CTC results, respectively, and there were also no significant differences between the VFL and no-VFL groups.

Table 2
Circulating tumor cell status according to the status of vein-first lobectomy

Variables			Total	VFL	No-VFL	*p*-value
n			86	68	18	
Preoperative						
	Detection	N/P	52 (60.5)/34 (39.5)	48 (70.6)/20 (29.4)	14 (77.8)/4 (22.2)	0.8
	Count*		1.6 ± 3.1	1.3 ± 2.3	2.9 ± 4.1	0.1
	Morphology	N/S/C	56 (65.1)/11 (12.8)/19 (22.1)	48 (70.6)/7 (10.3)/13 (19.1)	8 (44.4)/4 (22.2)/6 (33.3)	0.1
Postoperative						
	Detection	N/P	37 (43.0)/49 (57.0)	31 (45.6)/37 (54.4)	6 (33.3)/12 (66.7)	0.4
	Count*		3.0 ± 3.8	3.0 ± 3.6	3.2 ± 5.0	0.8
	Morphology	N/S/C	37 (43.0)/13 (15.1)/36 (41.9)	31 (45.6)/7 (10.3)/30 (44.1)	6 (33.3)/6 (33.3)/6 (33.3)	0.1
Data are presented as numbers (percentages) or the mean ± standard deviation.						
*Clustered CTC is counted as one.						
**Only a single CTC was detected before surgery.						
Abbreviations: CTC, circulating tumor cell; C, clustered CTC; N, not detected; P, positive; S, single CTC; VFL, vein-first lobectomy						

In multivariable logistic regression analysis that included VFL, tumor vessel invasion, types of CT appearance (solid or not), and size of invasion as covariates, it was revealed that only tumor vessel invasion was independent, when the end point was set as detecting CTC postoperatively (Table 3).

Table 3
Multivariable logistic regression analysis of vein-first lobectomy in the end point of postoperative circulating tumor cell detection

Variables	OR	95% CI		p-value
No-VFL	3.24	0.90	11.60	0.07
V (+)	5.25	1.79	15.40	< 0.01
Solid in CT	1.83	0.46	7.24	0.39
Invasion size (cm)	1.17	0.82	1.67	0.38

Abbreviations: CT, computed tomography; OR, odds ratio; V (+), tumor vessel invasion positive; VFL, vein-first lobectomy

Follow-up results

There were 8 cases of death, of which 6 cases were cancer related. In addition, 25 cancer recurrences were observed, of which 10 cases were distant (5, 2, 2, and 1 at the bone, liver, lung, and brain, respectively) and 15 cases were regional (8, 6, and 1 at the pleural space, mediastinal lymph nodes, and lung, respectively).

The survival curves according to recurrence and the VFL status are shown in Fig. 2. The 2-y overall survival (OS) rates were 92.4% and 92.4% in the VFL and no-VFL groups, respectively (p = 0.8), and the 2-y recurrence-free survival (RFS) rates was 75.8% and 77.0% in the VFL and no-VFL groups, respectively (p = 0.9). In the analysis of overall and recurrence-free survival according to the presence of postoperative CTC (Fig. 3), there were no significant differences in overall survival between the two groups. However, the presence of postoperative CTC was a predictor of recurrence.

Discussion

The prognostic impact of VFL and its therapeutic benefit for controlling CTCs are yet to be clarified. In this study, there was no significant difference in the postoperative CTC detection rate and the postoperative mean CTC count between the VFL and no-VFL groups. Further, the 2-y OS and RFS rates were also not significantly different. However, the presence of CTC after surgery was a predictor of recurrence.

Cancer metastasis occurs when CTCs develop into tumors in the appropriate microenvironment [16], and the presence of postoperative CTC is a predictor of recurrence [17, 18]. These findings may confirm that surgery causes the release of CTCs, and suppressing the amount of CTCs may help decreasing the risk of postoperative recurrence. In lung cancer surgery, VFL might suppress the release of CTCs, and clinical observation studies have shown that VFL helps reduce recurrence [5–7]. However, contrasting findings have also been reported [8–11]. A recent study by Wei et. al. [12] conducted using propensity score

matching reported better OS and RFS in VFL patients than in no-VFL lobectomy patients, further, VFL suppressed the release of CTCs, as assessed quantitatively using real-time polymerase chain reaction. However, in our current study, there was no significant difference in the CTC status between the VFL and no-VFL groups, although the statistical significance was borderline in the multivariate logistic regression analysis where tumor vessel invasion was an independent predictor of CTC detection postoperatively. This might be because in the study shown by Wei et. al., VFL was performed intentionally, i.e. the pulmonary vein is cut very quickly at the beginning of lobectomy compared to the conventional method which was performed in this setting [12].

Aside from VFL, other modalities can also cause the release of CTCs. Bronchoscopic biopsies cause CTC release [19]. In addition, preoperative bronchoscopy with fluoroscopic imaging has been reported to be associated with a high incidence of recurrence [20]. Further, pulmonary wedge resection for lung cancer has low efficiency for CTC detection after surgery when ring forceps are used without tumor release [21]. There is a report revealing significantly better prognosis in patients with early stage lung cancer who underwent pulmonary wedge resection with ring forceps at the tumor site before lobectomy than in those who did not undergo wedge resection [22].

The efficacy of vein first technique for suppressing metastasis in cancer is under investigating. A multicenter prospective randomized trial was conducted to compare between conventional technique and no-touch isolation technique (NTIT) (reducing amount of CTC shedding in to circulating blood) for primary tumor resection in patients with colorectal cancer (JCOG1006) [23]. The preliminary results showed that NTIT was not superior to the conventional technique [24]. The results may be attributable to the efficacy of adjuvant therapy and because the effectiveness of surgical procedures other than vascular processing may vary among patients. Besides, there is a report revealing the prognostic benefits of lung cancer surgery are influenced by the experience of the surgeon [25],

The present study has several limitations. First, the VFL carried out in this setting was not intentional. Second, the CTCs were identified visually, although the accuracy of visual CTC evaluation has been proven in previous studies [26]. Further, the method used in this study (ScreenCell®) has the highest recovery rate [27], thus yielding more accurate results. Third, the sample size was small, and the patients were only recruited from two centers. Fourth, the observational study design indicates a potential risk of bias. Further prospective research is needed to verify the implication of VFL.

Conclusion

Retrospectively assessed, VFL for lung cancer could not adequately control postoperative CTCs. However, since postoperative CTC detection after surgery were predictors of cancer recurrence, finding other NTIT methods than sequence of pulmonary vessel dissection is anticipated.

Abbreviations

Computed tomography: CT

Circulating tumor cells: CTC

No-touch isolation technique: NTIT

Overall survival: OS

Pulmonary artery: PA

Pulmonary vein: PV

Recurrence-free survival: RFS

Vein-first dissection lobectomy: VFL

Declarations

Declarations:

Not applicable

Ethics approval and consent to participate:

This study was approved by the institutional review boards of Hoshigaoka Medical Center (HMC) (No.1718) and Nara Medical University Hospital (NMU) (No.1412). Informed consent was obtained from all participants who were included in the study.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

NS: Study concept and design, acquisition and analysis of data, and interpretation of data. SN: interpretation of data, and draft revision. DY: Draft and Revision. TW: Draft and Revision. KK: Draft and Revision. All authors read and approved the final manuscript.

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Prior presentation

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Figures

Figure 1

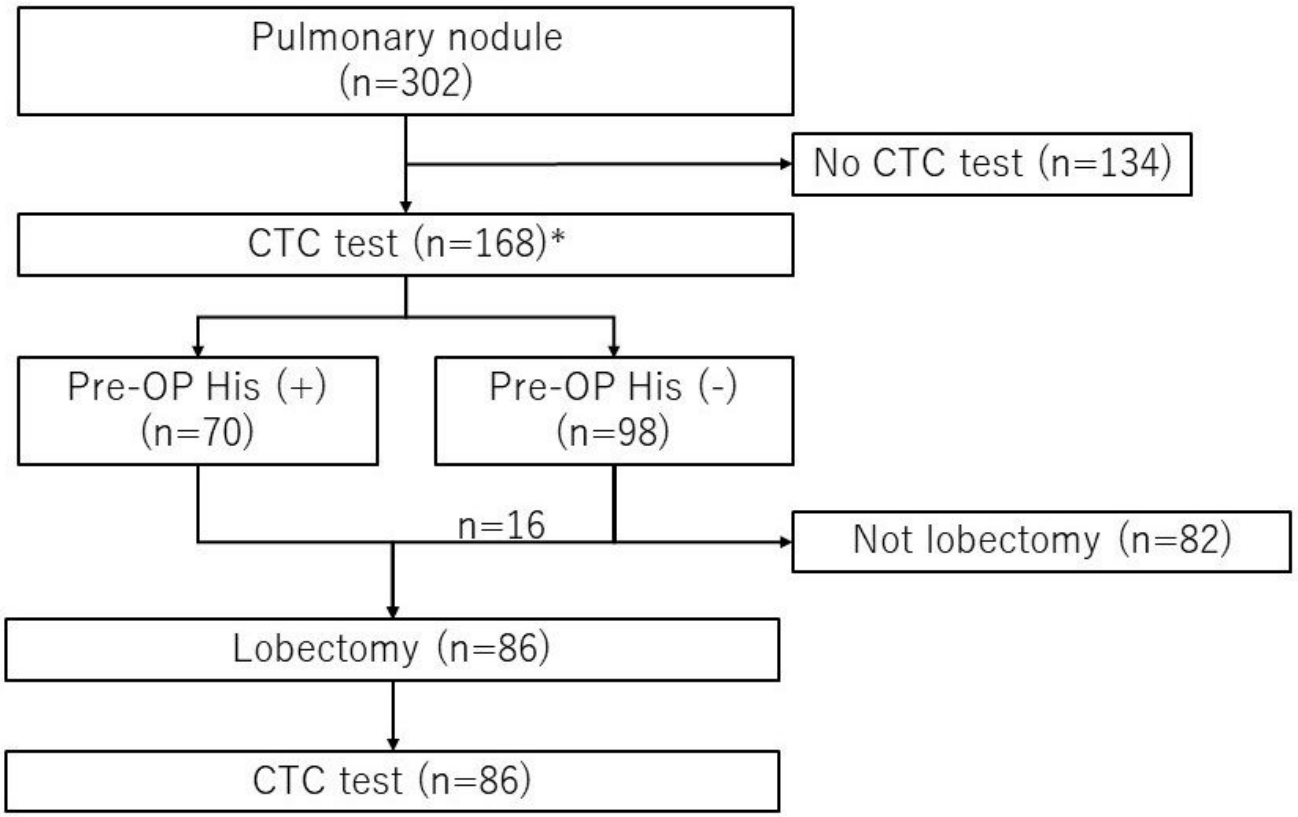

Figure 1

Flow chart of patients' selection Abbreviations: CTC, circulating tumor cell; Pre-OP, preoperative; His, histological diagnosis; *, there is an informed content about CTC test.

Figure 2

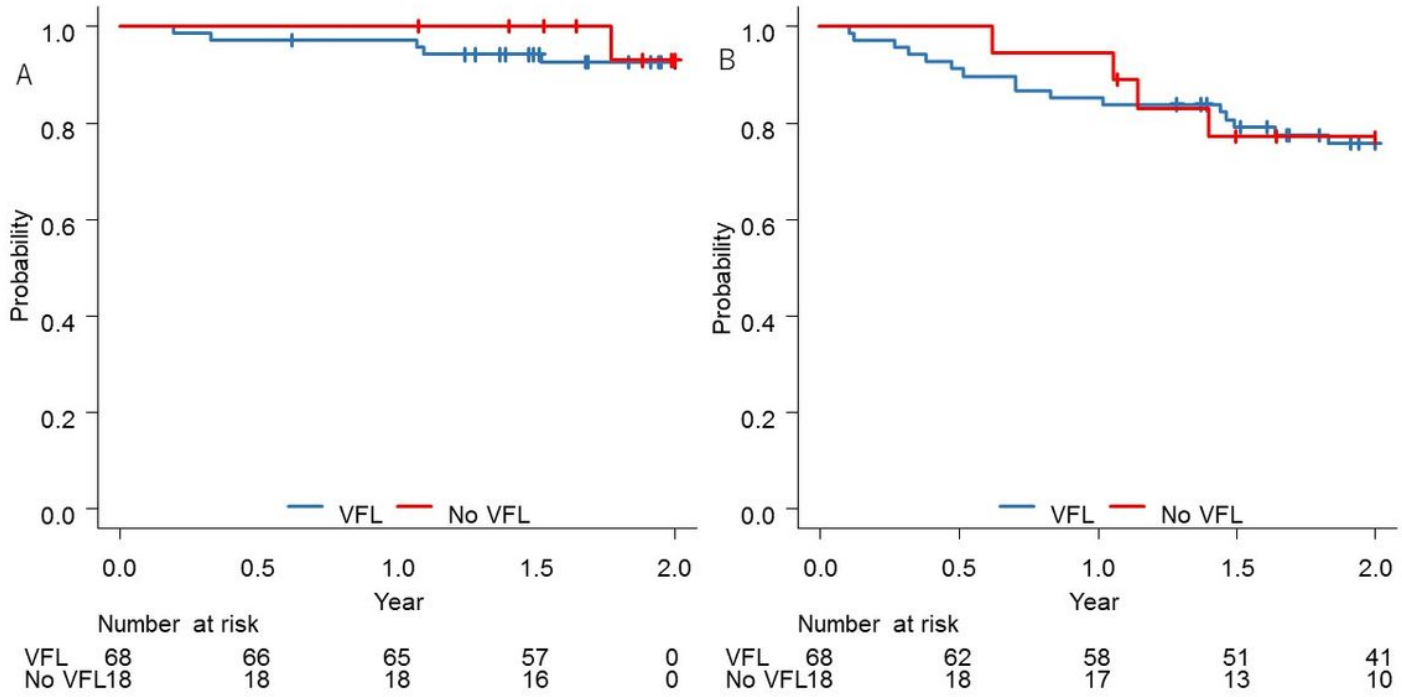

Figure 2

Kaplan-Meier curves of recurrence-free and overall survival according to the type of pulmonary vein dissection. The 2-year overall survival rates were 92.4% and 92.4% in the vein-first lobectomy (VFL) and no-VFL groups, respectively (p=0.8). The 2-year recurrence-free survival rates were 75.8% and 77.0% in the VFL and no-VFL groups, respectively (p=0.9).

Figure 3

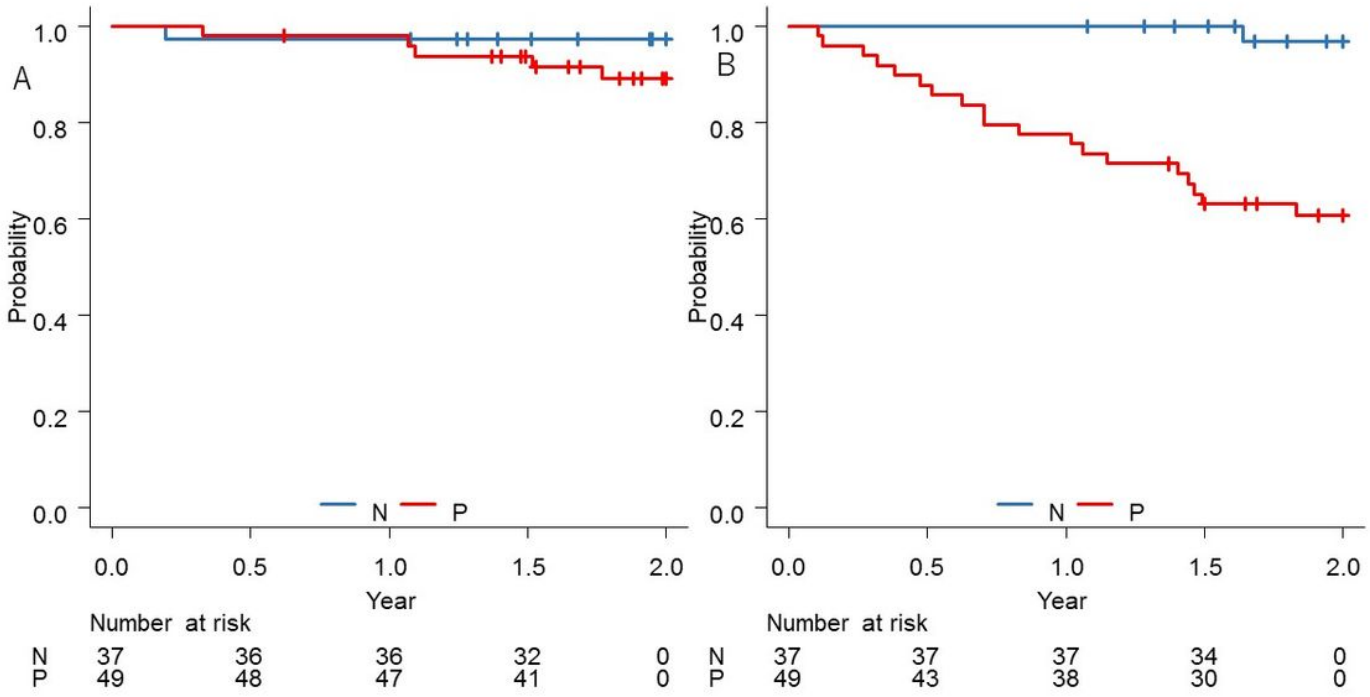

Figure 3

Kaplan-Meier curves of recurrence-free and overall survival according to the status of postoperative circulating tumor cell. The 2-year overall survival rates were 97.3% and 89.0% in the patients in whom circulating tumor cells were not detected (N) and were detected (P) postoperatively, respectively (p=0.8). The 2-year recurrence-free survival rates were 96.9% and 60.9% in the N and P groups, respectively.