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ORIGINAL ARTICLE

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Preoperative percutaneous needle indigo carmine and lipiodol mixture marking in lung segmentectomy

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Key question

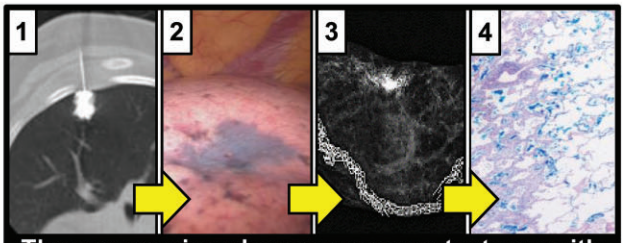
Is preoperative indigo carmine and lipiodol mixture marking effective to secure surgical margins for lung segmentectomy?

Key finding(s)

Tumors were successfully localized in 66 of 69 cases, including 11 with emphysema, and no had positive surgical margins.

Take-home message

Preoperative indigo carmine and lipiodol mixture marking may be useful in lung segmentectomy for small malignancies located deep parenchyma.



Thoracoscopic pulmonary segmentectomy with preoperative marking using the indigo carmine and lipiodol mixture (Marking group, n = 69)

Surgery date after marking	
Same day	42 (61)
One day later	27 (39)
Tumor localization	
Dye pigmentation alone	62 (90)
Intraoperative fluoroscopy	4 (6)
Unsuccessful case	3 (4)
Surgical margin distance, mm	20 (15–21)
Surgical margin assessment, positive	0 (0)
Local recurrence on surgical margin	0 (0)

Abstract

OBJECTIVES: For successful nodule localization and appropriate surgical margin distances in pulmonary segmentectomy for patients with lung malignancies, the effectiveness and feasibility of preoperative marking using an indigo carmine and lipiodol mixture remain unclear.

METHODS: Patients who underwent thoracoscopic pulmonary segmentectomy with (marking group, $n = 69$) and without (non-marking group, $n = 265$) preoperative marking at our institution from January 2013 to March 2020 were retrospectively reviewed and compared in terms of surgical outcomes. All markings were performed using a fine needle to percutaneously inject an indigo carmine and lipiodol mixture under the guidance of computed tomography fluoroscopy.

RESULTS: Successful localization was achieved in 66 (96%) patients, of whom 62 (94%) underwent dye pigmentation and 4 (6%) underwent intraoperative fluoroscopy. On images, the marking group showed a significantly longer distance between the lung surface and tumour [mm, 9 (1–17) vs 0 (0–10); $P < 0.01$] and smaller maximum tumour size [mm, 16 (11–21) vs 17 (13–23); $P = 0.03$] and consolidation tumour

ratio [0.4 (0.3–1) vs 0.8 (0.4–1); $P < 0.01$] than the non-marking group. Both groups had comparable operative outcomes, perioperative complications, pulmonary function changes and surgical margin distances [mm, 20 (15–21) vs 20 (15–20); $P = 0.96$] without any local recurrence on the surgical margin. Propensity score-matching analysis also showed similar findings for both groups.

CONCLUSIONS: Thoracoscopic pulmonary segmentectomy with preoperative marking using an indigo carmine and lipiodol mixture may be an acceptable therapeutic option for small malignancies located in deep lung parenchyma.

Keywords: Pulmonary segmentectomy • Preoperative marking • Nodule localization • Surgical margin • Pulmonary function

ABBREVIATIONS

CT	Computed tomography
CTR	Consolidation tumour ratio
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GGO	Ground-glass opacity
MIL	Mixture of indigo carmine and lipiodol
NSCLC	Non-small-cell lung cancer

INTRODUCTION

Recent advancements in radiological diagnostic and surgical techniques have gradually facilitated the widespread use of pulmonary segmentectomy for lung malignancies [1, 2]. Studies have suggested that the prognosis is comparable between patients with small-sized non-small-cell lung cancer (NSCLC) undergoing segmentectomy and those undergoing lobectomy and that segmentectomy preserves postoperative pulmonary function better than lobectomy [1–3]. Ensuring appropriate margin distances is important for both achieving oncological benefits and preserving pulmonary function following segmentectomy [2–5]. Insufficient surgical margins could increase the risk of local recurrence, whereas excessive resection might cause pulmonary dysfunction. Technical difficulties of ensuring adequate margin distances in segmentectomy can vary according to tumour size and location [6]. Securing sufficient margin distances with minimal lung resection for small ground-glass opacity (GGO)-dominated NSCLCs localized deep lung parenchyma is more difficult because of the lack of visual and tactile recognizability. Therefore, preoperative localization techniques might be helpful in segmentectomy, which are often performed in such tumours to ensure adequate margin distances.

Although several techniques for localizing pulmonary nodules have been described, no consensus has yet been reached on a universally preferred technique, particularly for segmentectomy [7–10]. We previously reported the utility of percutaneous computed tomography (CT)-guided needle marking using a mixture of indigo carmine and lipiodol (MIL) as a nodule localization technique before thoracoscopic surgery, particularly wedge resection [11]. However, the clinical usefulness of this marking approach has yet to be thoroughly investigated for segmentectomy, particularly regarding its impact on surgical outcomes, including margin distances. Furthermore, because few reports have documented the clinical outcomes after this surgical procedure, its appropriate indications have remained unclear. Therefore, this study was designed to evaluate whether preoperative MIL marking in segmentectomy for patients with lung malignancies can localize pulmonary nodules intraoperatively and secure adequate margin distances without adversely impacting surgical outcomes.

PATIENTS AND METHODS

Study design and patients

This retrospective study was approved by the Institutional Review Board of the Aichi Cancer Center on 24 February 2021 (approval number: 2020-1-570). Clinicopathological data were collected from medical records. Among the 2925 patients who underwent lung resection at our institution between January 2013 and March 2020, we reviewed those who underwent segmentectomy (Fig. 1). The exclusion criteria were as follows: (i) patients who underwent thoracotomy, (ii) those who underwent simultaneous resection of different lobes and (iii) those who had pathologically non-malignant disease. The indications for surgery and preoperative marking were established during our multidisciplinary tumour board meetings after informed consent was obtained from the patients preoperatively. Candidates for marking should have the following: pure solid tumours and part solid GGOs that were <20 mm in diameter with >5-mm tumour depth from the nearest pleural surface or pure GGOs that were expected to be difficult to visually or tactilely confirm under a thoracoscope (Fig. 2) [6, 11]. The patients were divided into 2 groups: the marking group (i.e. segmentectomy with preoperative MIL marking; $n = 69$) and the non-marking group (i.e. segmentectomy without preoperative marking; $n = 265$). The primary end points included nodule localization, operative time, blood loss, margin distance, mortality, morbidity, postoperative pulmonary function and local recurrence on the margin.

All patients were evaluated using high-resolution CT, 18-fluorodeoxyglucose positron emission tomography/CT, brain magnetic resonance imaging, biochemistry (including tumour markers), electrocardiography, echocardiography and pulmonary function tests within 6 weeks before surgery. Patients with primary lung cancer were staged according to the eighth edition of the Tumour, Nodes, and Metastasis Classification of Malignant Tumors [12]. The patients were classified into curative and palliative indications based on the decision of the preoperative tumour board. The curative indications included NSCLC with a tumour diameter of ≤2 cm and a consolidation tumour ratio (CTR) of ≤0.25 and patients who can tolerate lobectomy [3].

Marking and surgical procedures

Experienced radiologists performed all marking procedures preoperatively. MIL was created by mixing 2 ml of indigo carmine (Daiichi Sankyo Co. Ltd., Tokyo, Japan), 2 ml of lipiodol (Fuji Pharma Co Ltd, Tokyo, Japan) and 1 ml of lidocaine gel (Aspen Japan K.K.) [11]. A lidocaine gel was used to increase the viscosity of the MIL to prevent diffusion into the lung parenchyma. After confirming that the 23-G needle tip was near the tumour, at least 0.5 ml of MIL was injected into the lung parenchyma while

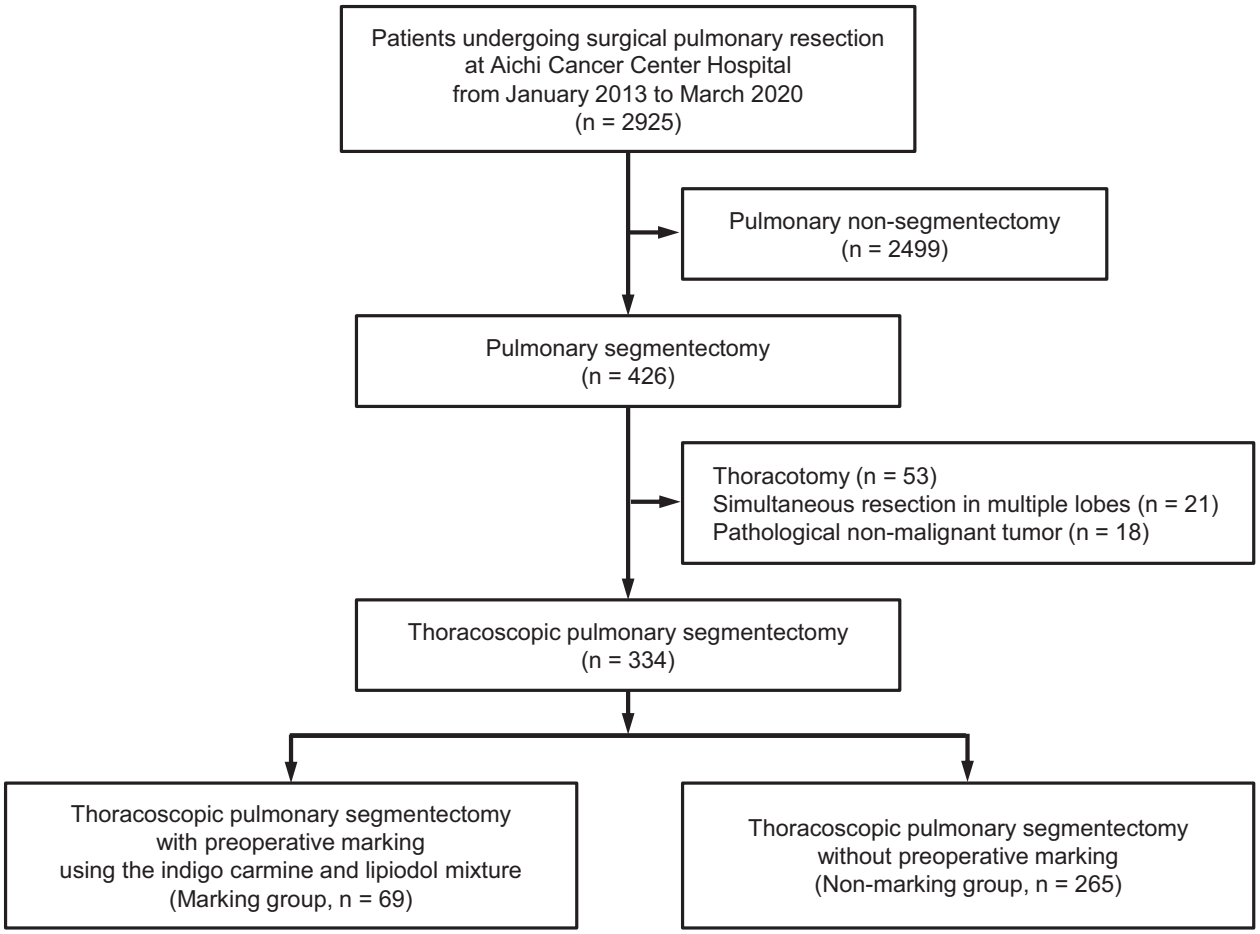


Figure 1: Flow chart for patient selection.

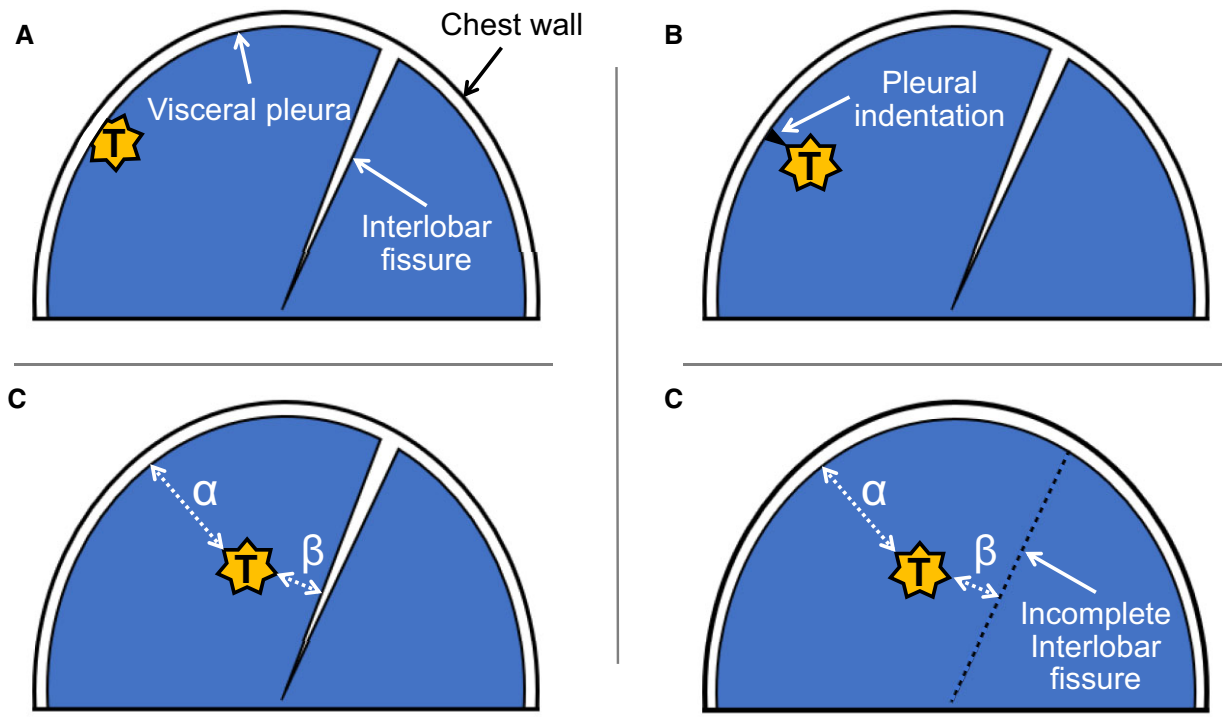


Figure 2: Schema of the distance measurement between the tumour and the nearest pleural surface. The distance is evaluated as 'zero' when the tumour directly contacts the visceral pleura or has pleural indentation (**A** and **B**) and 'α' instead of 'β' in cases with incomplete interlobar fissure (**C** and **D**).

withdrawing the needle until lipiodol accumulation reached the pleural surface under the guidance of real-time CT fluoroscopy.

Four experienced attending general thoracic surgeons exclusively performed the surgeries under thoracoscopic view, mainly using 4 ports. The blue pigment of indigo carmine on the visceral pleura was searched for; if not identified, C-arm fluoroscopy (OEC Brivo Essential; GE Healthcare Japan, Tokyo, Japan) was performed to identify the radiopaque lesion. Successful localization was defined as the tumour detection through dye pigmentation or intraoperative fluoroscopy.

Pathological and follow-up evaluations

The surgical margin closest to the tumour edge on a collapsed lung was macroscopically measured after removing the staples. If necessary, a frozen section of the margin was evaluated under a microscope. The tumour was evaluated as 'positive' when it reached the margin and 'close' when the distance between the tumour and margin was <1000 μm. Additional resection was performed, when possible, to secure the surgical margin in patients with a positive or close surgical margin.

Perioperative complications were classified and graded according to the Common Terminology Criteria for Adverse Events, version 5.0, analysing all grade 2 (moderate) or higher complications [3]. Perioperative mortality was defined as death within 30 days after surgery. Patients with primary or recurrent lung cancer were followed up from the day of surgery and examined, including a physical examination, biochemistry, chest/abdominal CT and brain magnetic resonance imaging, at intervals of 3–6 months for the first 5 years and once yearly after that. Patients with metastatic lung cancer were generally followed up by the relevant departments (e.g. gastrointestinal or breast surgery). Pulmonary function was reassessed 6 and 12 months after surgery. Biopsy was performed for the histological confirmation of local recurrence, if necessary. Otherwise, radiological evidence of local recurrence, including positron emission tomography/CT, was accepted by the institutional multidisciplinary tumour board.

Statistical analysis

Data are presented as numbers or medians with the first and third quartiles of the distribution. Differences between the groups were evaluated using Fisher's exact test and the Mann–Whitney *U*-test for categorical and continuous variables, respectively. Changes in pulmonary function were compared using repeated-measures analysis of variance. Time-dependent changes in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were determined. Recurrence-free survival was estimated using the Kaplan–Meier method, whereas differences between the groups were determined using the log-rank test. Nearest neighbour matching was performed using a calliper width of 0.20. Clinicopathological variables, such as age, sex, body mass index, year of surgery, smoking, comorbidities, pulmonary function, tumour location, emphysema on CT, tumour size on CT, CTR, tumour depth from the pleura, induction or adjuvant therapy, resection volume (total number of subsegments), indication for segmentectomy and pathological diagnosis, were multiplied by a coefficient calculated using logistic regression analysis. The *c*-statistic value for this matching was 0.89. Patients with equivalent propensity scores in the groups were selected through 1-to-1 matching. All statistical analyses were performed using JMP, version 14.0 (SAS Institute, Cary, NC, USA). Two-sided *P*-values of <0.05 were used to indicate statistical significance.

RESULTS

In this study, 426 patients who underwent segmentectomy at our institution were analysed. We excluded patients who underwent thoracotomy ($n = 53$), those who underwent simultaneous resection of different lobes ($n = 21$) and those who had pathologically non-malignant diseases ($n = 18$). The final study cohort comprised 334 patients who underwent thoracoscopic segmentectomy for lung malignancies, with 69 (21%) patients in the marking group and 265 (79%) patients in the non-marking group, with median follow-up periods of 47 and 46 months, respectively.

Table 1 summarizes the patient characteristics in both groups. The marking group had more tumours in the right upper and lower lobes, whereas the non-marking group had more in the left upper. On CT images, the marking group had a significantly longer distance between the tumour and the nearest pleural surface [mm, 9 (1–17) vs 0 (0–10); $P < 0.01$], smaller maximum tumour size [mm, 16 (11–21) vs 17 (13–23); $P = 0.03$] and lower CTR [0.4 (0.3–1) vs 0.8 (0.4–1); $P < 0.01$] than the non-marking group. Pathological diagnoses of both groups were primary ($n = 256$, 77%), metastatic ($n = 73$, 22%) and recurrent lung cancers ($n = 5$, 1%), without a significant difference in their proportions. Pathologically, the marking group had a significantly smaller maximum [mm, 11 (9–17) vs 15 (11–20); $P < 0.01$] and invasive [mm, 7 (3–11) vs 10 (5–17); $P < 0.01$] tumour sizes than the non-marking group.

The marking procedure is summarized in Table 2. All marking procedures were performed after admission: 42 (61%) on the day of surgery and 27 (39%) on the day before surgery. Tumour localization was confirmed by dye pigmentation alone in 62 (90%) cases and intraoperative fluoroscopy in 4 (6%). Finally, successful localization was achieved in 66 (96%) cases, including 11 (16%) with emphysema. Among the 3 failures, 1 failed due to pneumothorax requiring chest tube drainage; the remaining 2 cases of failure, who underwent marking the day before surgery, could not be confirmed using either dye pigmentation or intraoperative fluoroscopy. Although pneumothorax was the most common marking-related complication, only 1 (1%) patient required chest tube drainage.

Figure 3 shows the actual resected lung areas in both groups. In the marking group, the segments of right upper lobe were frequently involved (Fig. 3A). In the non-marking group, the left upper division was most commonly involved ($n = 45$, 17%), followed by the left apicoposterior segment ($n = 31$, 12%) (Fig. 3B).

As shown in Table 3, of all patients, 231 (69%) underwent palliative segmentectomy in both groups. Most palliative cases had multiple palliative factors; the most common was age >75 years ($n = 89$, 39%), followed by metastatic lung cancer ($n = 73$, 32%) and low pulmonary function ($n = 34$, 15%). The marking group had a lower proportion of patients undergoing simple segmentectomy (17% vs 38%; $P < 0.01$) than the non-marking group, including the resection of the right superior, left superior, upper division and lingular segments. No significant differences in operative time [min, 181 (145–216) vs 175 (151–212); $P = 0.78$],

Table 1: Clinicopathological factors

Variables	All patients ($n = 334$)			Propensity score-matched pairs ($n = 90$)			
	Marking group ($n = 69$)	Non-marking group ($n = 265$)	*P*-Value	Marking group ($n = 45$)	Non-marking group ($n = 45$)	*P*-Value	SMD
Age (years)	67 (59–73)	70 (63–77)	<0.01	67 (59–75)	67 (58–74)		0.05
Sex, female	38 (55)	138 (52)	0.69	25 (56)	25 (56)		<0.01
Body mass index	22 (20–24)	22 (20–25)	0.47	22 (19–24)	21 (20–23)		0.06
Smoking, never	37 (54)	131 (49)	0.59	24 (53)	23 (51)		0.04
Tumour location lobe			0.02				0.09
Right upper	19 (28)	53 (20)		11 (25)	13 (29)		
Right middle	1 (1)	0 (0)		0 (0)	0 (0)		
Right lower	18 (26)	45 (17)		10 (22)	12 (27)		
Left upper	18 (26)	112 (42)		14 (31)	10 (22)		
Left lower	13 (19)	55 (21)		10 (22)	10 (22)		
Comorbidities							
COPD/interstitial pneumonitis	5 (7)	26 (10)	0.64	4 (9)	3 (7)		0.08
Diabetes mellitus	8 (12)	42 (16)	0.45	6 (13)	5 (11)		0.07
Cardiovascular dysfunction	25 (36)	123 (46)	0.14	4 (9)	2 (4)		0.18
Renal dysfunction	6 (9)	16 (6)	0.42	4 (9)	3 (7)		0.08
Pulmonary function							
Forced vital capacity (l)	2.8 (2.4–3.3)	2.9 (2.4–3.5)	0.97	2.9 (2.5–3.4)	2.8 (2.5–3.9)		0.05
Forced expiratory volume in 1 s (l)	2.1 (1.8–2.7)	2.2 (1.8–2.7)	0.81	2.1 (1.8–2.6)	2.2 (1.8–3.0)		0.05
Emphysema on CT	13 (19)	70 (26)	0.21	10 (22)	10 (22)		<0.01
Tumour size on CT (mm)	16 (11–21)	17 (13–23)	0.03	16 (11–21)	15 (12–20)		0.07
Consolidation tumour ratio	0.4 (0.3–1)	0.8 (0.4–1)	<0.01	0.5 (0.3–1)	0.5 (0.3–1)		0.04
Tumour depth from the pleura (mm)	9 (1–17)	0 (0–10)	<0.01	7 (0–15)	8 (0–19)		0.05
Pathological diagnosis			0.95				0.05
Primary lung cancer	54 (78)	202 (76)		36 (80)	35 (78)		
Metastatic lung cancer	14 (21)	59 (22)		8 (18)	8 (18)		
Recurrent lung cancer	1 (1)	4 (2)		1 (2)	2 (4)		
Pathological tumour size (mm)	11 (9–17)	15 (11–20)	<0.01	13 (9–18)	14 (11–19)	0.31	
Invasive tumour size (mm)	7 (3–11)	10 (5–17)	<0.01	7 (3–11)	8 (2–15)	0.41	

Values are presented as *n* (%) or median (the first and third quartiles).

COPD: chronic obstructive pulmonary disease; CT: computed tomography; SMD: standardized mean difference.

Table 2: Details of marking

Variables	$n = 69$
Marking position	
Supine	20 (29)
Prone	37 (54)
Right lateral decubitus	10 (14)
Left lateral decubitus	2 (3)
Puncture length from the body surface (mm)	51 (38–60)
Number of punctures per session	
One puncture	66 (96)
Two punctures	3 (4)
Surgery date after marking	
Same day	42 (61)
One day later	27 (39)
Tumour localization	
Dye pigmentation alone	62 (90)
Intraoperative fluoroscopy	4 (6)
Marking in emphysema lung	
Successful localization	11/13 (85)
Complications without intervention	
Pneumothorax	18 (26)
Alveolar haemorrhage	4 (6)
Complications requiring intervention	
Pneumothorax	1 (1)

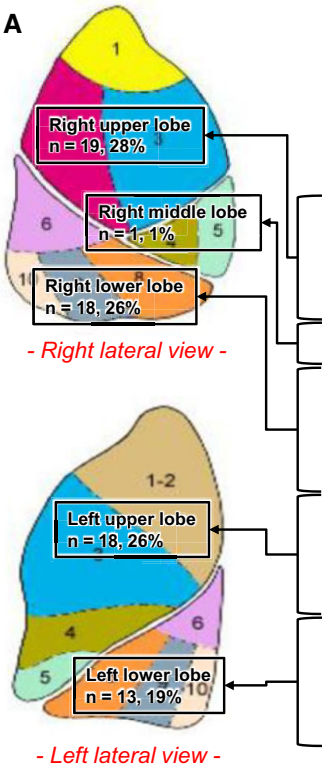
Values are presented as *n* (%) or median (the first and third quartiles).

blood loss [ml, 5 (1–20) vs 5 (1–10); $P = 0.41$] and median margin distance [mm, 20 (15–21) vs 20 (15–20); $P = 0.96$] were observed between both groups. Pathologically, 2 (1%) and 5 (2%) cases in the non-marking group and 0 (0%) and 2 (3%) in the marking group had positive and close surgical margins, respectively ($P = 0.77$). Of the 2 cases with a positive margin, 1 was an 8-mm pure solid tumour located 12 mm from the visceral pleura; the other was a 15-mm part solid GGO in direct contact with the visceral pleura. No significant differences in the length of hospital stay [days, 3 (2–4) vs 3 (2–5); $P = 0.33$] and drainage [days, 0 (0–1) vs 0 (0–1); $P = 0.75$] were observed between the groups. No perioperative mortality or local recurrence on the margin occurred in either group throughout the study period.

Table 4 indicates that no significant differences in intraoperative or postoperative complications were observed between the groups. Propensity score-matched pair analysis showed similar findings.

Preoperative and postoperative pulmonary function test results were available in 231 (69%) patients, excluding cases that required conversion to thoracotomy. During the postoperative course, both groups showed comparable pulmonary function, without significant differences in the ratios of postoperative to preoperative FVC ($P = 0.33$) (Fig. 4A) and FEV1 ($P = 0.97$) (Fig. 4B). Furthermore, propensity score-matching analysis showed similar

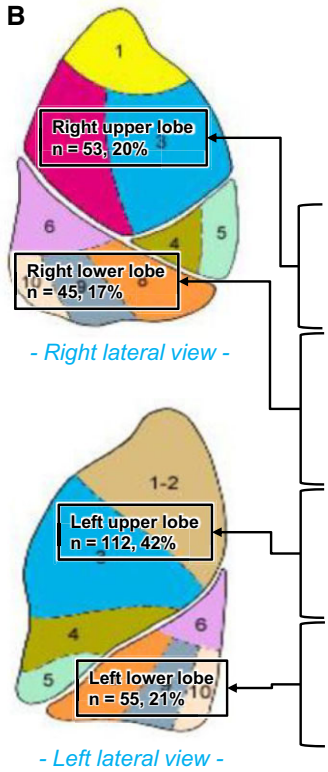
A



Resected anatomical lung segment and subsegment			
Details of tumor location	**n (%)**	**Top 10 areas and others**	**n (%)**
Right apical (RS1)	10 (14)	RS1	7 (10)
Right posterior (RS2)	5 (7)	RS2	4 (6)
Right anterior (RS3)	4 (6)	RS3	3 (4)
		Others	5 (7)
Right medial (RS5)	1 (1)	Others	1 (1)
Right superior (RS6)	10 (14)	RS6	7 (10)
Right anterior basal (RS8)	1 (1)	RS10	3 (4)
Right lateral basal (RS9)	2 (3)	RS6 and RSS10a	2 (3)
Right posterior basal (RS10)	5 (7)	Others	6 (7)
Left apicoposterior (LS1+2)	5 (7)	LS3	3 (4)
Left anterior (LS3)	8 (12)	Others	15 (22)
Left superior lingular (LS4)	4 (6)		
Left inferior lingular (LS5)	1 (1)		
Left superior (LS6)	4 (6)	LS9 and LS10	4 (6)
Left anteromedial basal (LS8)	3 (4)	LS6 and LSS10a	2 (3)
Left lateral basal (LS9)	3 (4)	LS8	2 (3)
Left posterior basal (LS10)	3 (4)	Others	5 (7)

L, left; R, right; S, segment; SS, subsegment.

B



Resected anatomical lung segment			
Details of tumor location	**n (%)**	**Top 10 areas and others**	**n (%)**
Right apical (RS1)	10 (4)	RS3	15 (6)
Right posterior (RS2)	22 (8)	RS2	14 (5)
Right anterior (RS3)	21 (8)	RS1 and RS2	8 (3)
		Others	16 (6)
Right superior (RS6)	26 (10)	RS6	23 (9)
Right medial basal (RS7)	1 (0)	Others	22 (8)
Right anterior basal (RS8)	5 (2)		
Right lateral basal (RS9)	6 (2)		
Right posterior basal (RS10)	7 (3)		
Left apicoposterior (LS1+2)	82 (31)	Upper division	45 (17)
Left anterior (LS3)	17 (6)	LS1+2	31 (12)
Left superior lingular (LS4)	7 (3)	Lingula	12 (5)
Left inferior lingular (LS5)	6 (2)	Others	24 (9)
Left superior (LS6)	27 (10)	LS6	20 (8)
Left anteromedial basal (LS8)	8 (3)	LS9 and LS10	7 (3)
Left lateral basal (LS9)	8 (3)	LS10	6 (2)
Left posterior basal (LS10)	12 (5)	Others	22 (8)

L, left; R, right; S, segment.

Figure 3: The 10 most frequently resected areas and others for thoracoscopic pulmonary segmentectomy with (**A**; the marking group) or without (**B**; the non-marking group) preoperative marking using the indigo carmine and lipiodol mixture.

Table 3: Perioperative outcomes

Variables	All patients ($n = 334$)			Propensity score-matched pairs ($n = 90$)			
	Marking group ($n = 69$)	Non-marking group ($n = 265$)	*P*-Value	Marking group ($n = 45$)	Non-marking group ($n = 45$)	*P*-Value	SMD
Indication of segmentectomy			0.11				<0.01
Palliative	42 (61)	189 (71)		29 (64)	29 (64)		
Curative	27 (39)	76 (29)		16 (36)	16 (36)		
Simple segmentectomy[a]	12 (17)	100 (38)	<0.01	11 (24)	10 (22)	>0.99	
Operative outcomes							
Operative time (min)	181 (145–216)	175 (151–212)	0.78	182 (151–218)	166 (152–208)	0.52	
Blood loss (ml)	5 (1–20)	5 (1–10)	0.41	5 (1–20)	5 (1–10)	0.08	
Conversion to thoracotomy	0 (0)	2 (1)	>0.99	0 (0)	0 (0)	>0.99	
Transfusion	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99	
Number of dissected subsegments	3 (2–4)	3 (3–5)	<0.01	3 (2–4)	3 (2–4)		<0.01
Surgical margin distance (mm)	20 (15–21)	20 (15–20)	0.96	20 (20–20)	20 (15–20)	0.18	
Surgical margin assessment			0.77			0.62	
Negative	67 (97)	258 (97)		44 (98)	42 (93)		
Close	2 (3)	5 (2)		1 (2)	3 (7)		
Positive	0 (0)	2 (1)		0 (0)	0 (0)		
Polyglycolic acid sheet	62 (90)	241 (91)	0.82	40 (89)	41 (91)	>0.99	
Fibrin glue	63 (91)	242 (91)	>0.99	41 (91)	40 (89)	>0.99	
Additional margin resection	1 (1)	12 (5)	0.48	0 (0)	3 (7)	0.24	
Number of dissected lymph nodes	1 (0–1)	2 (1–5)	<0.01	2 (1–4)	1 (1–3)	0.29	
Number of staples[b]	4 (3–5)	3 (3–4)	0.02	4 (3–5)	3 (3–4)	0.07	
Postoperative outcomes							
Hospital stay, days	3 (2–4)	3 (2–5)	0.33	3 (2–5)	3 (2–5)	0.62	
Drainage (days)	0 (0–1)	0 (0–1)	0.75	0 (0–1)	0 (0–1)	0.69	
Drain removal on the operative day	45 (65)	169 (64)	0.89	30 (67)	27 (60)	0.66	
Mortality (30 days)	0 (0)	0 (0)	>0.99	0 (0)	0 (0)	>0.99	
Local recurrence on surgical margin	0 (0)	0 (0)	>0.99	0 (0)	0 (0)	>0.99	

Values are presented as *n* (%) or median (the first and third quartiles).

[a]Resection of the right superior, left superior, upper division and lingular segments.

[b]Number of staples for intersegmental formation.

SMD: standardized mean difference.

Table 4: Perioperative complications

Variables	All patients ($n = 334$)			Propensity score-matched pairs ($n = 90$)		
	Marking group ($n = 69$)	Non-marking group ($n = 265$)	*P*-Value	Marking group ($n = 45$)	Non-marking group ($n = 45$)	*P*-Value
Intraoperative any complication (grade ≥2)	3 (4)	29 (11)	0.11	3 (7)	4 (9)	>0.99
Any organ injury	3 (4)	19 (7)	0.59	3 (7)	3 (7)	>0.99
Aorta	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99
Pulmonary artery	1 (1)	9 (3)	0.69	1 (2)	0 (0)	>0.99
Pulmonary vein	0 (0)	3 (1)	>0.99	0 (0)	1 (2)	>0.99
Bronchus	0 (0)	3 (1)	>0.99	0 (0)	0 (0)	>0.99
Phrenic nerve	1 (1)	0 (0)	0.21	1 (2)	0 (0)	>0.99
Recurrent nerve	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99
Atelectasis	1 (1)	3 (1)	>0.99	1 (2)	1 (2)	>0.99
Anatomical misidentification	0 (0)	3 (1)	>0.99	0 (0)	1 (2)	>0.99
Postoperative any complication (grade ≥2)	4 (6)	27 (10)	0.35	4 (9)	3 (7)	>0.99
Air leak (>5 days)	1 (1)	7 (3)	>0.99	1 (2)	2 (4)	>0.99
Respiratory disorder	0 (0)	9 (3)	0.21	0 (0)	1 (2)	>0.99
Pneumonitis	0 (0)	4 (2)	0.58	0 (0)	0 (0)	>0.99
Effusion	3 (4)	3 (1)	0.11	3 (7)	0 (0)	0.24
Secondary pneumothorax	0 (0)	1 (1)	>0.99	0 (0)	1 (2)	>0.99
Atelectasis	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99
Acute exacerbation of IP	0 (0)	3 (1)	>0.99	0 (0)	0 (0)	>0.99
Intrathoracic bleeding	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99
Wound infection	0 (0)	3 (1)	>0.99	0 (0)	0 (0)	>0.99
Atrial fibrillation	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99
Pseudomembranous colitis	0 (0)	2 (1)	>0.99	0 (0)	0 (0)	>0.99
Hepatic dysfunction	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99
Chronic pain	0 (0)	1 (1)	>0.99	0 (0)	0 (0)	>0.99
Central nervous system disorder	0 (0)	1 (1)	>0.99	0 (0)	1 (2)	>0.99

Values are presented as *n* (%).

IP: interstitial pneumonitis.

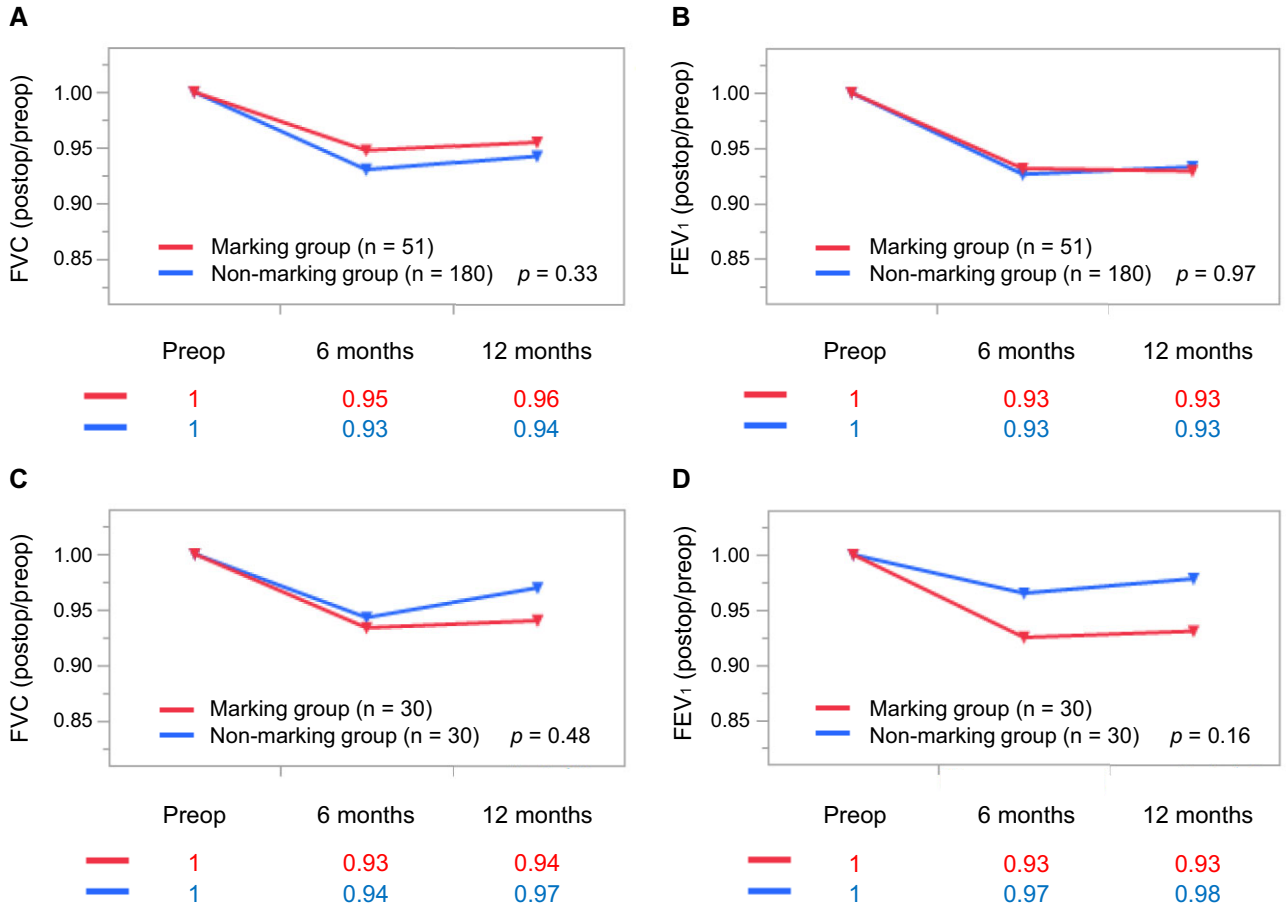


Figure 4: Changes in forced vital capacity and forced expiratory volume in 1 s following thoracoscopic pulmonary segmentectomy with (the marking group) or without (the non-marking group) preoperative marking using the indigo carmine and lipiodol mixture for all patients (**A** and **B**) and propensity score-matched pairs (**C** and **D**) [marking group (upper row); non-marking group (lower row)]. The *y*-axis shows the postoperative to preoperative ratio (postop/preop).

findings for both FVC ($P = 0.48$) (Fig. 4C) and FEV1 ($P = 0.16$) (Fig. 4D).

Of 256 cases with primary lung cancer, the marking group had a higher percentage of pathologically non-invasive and early-stage cancers than the non-marking group (Supplementary Material, Table S1), and the 5-year recurrence-free survival rates were not significantly different between both groups (96% vs 91%; $P = 0.61$) or their propensity score-matched pairs (94% vs 96%; $P = 0.32$).

DISCUSSION

Typical existing markers include hook wires, radionuclides, dyes and lipiodol; each has specific issues [7–11]. Serious complications, such as air embolism, have been reported with the use of hook wires. Radionuclide injection requires special equipment and is prohibited in uncontrolled areas. Dyes have a lower localization rate than other markers because they diffuse easily into the lung parenchyma. Lipiodol requires intraoperative fluoroscopy with the risk of radiation exposure for detection. However, mixing dye and lipiodol can compensate for the drawbacks of both as markers [11]. This study showed that the overall localization rate was 96%, consistent with the previously reported results [7–11]; however, the overall localization rate was only 90% without intraoperative fluoroscopy. Preoperative MIL marking may achieve high localization rates despite being less invasive and requiring fewer additional instruments than conventional methods. In contrast, our findings showed that 2 patients with severe anthracosis who underwent MIL marking the day before surgery could not be localized using either dye or lipiodol, perhaps due to the total amount of the injected MIL. Reports have suggested that marking on the day of surgery made the dye more easily identifiable [11]; surgeries should be performed as soon as possible after MIL marking, preferably within the same day. When impossible, particularly for heavy smokers who are expected to have severe anthracosis with dark spots on the lung surface, the total amount of MIL injection should be increased above normal.

Generally, segmentectomy is often performed for poorly visible and tactile nodules located deep lung parenchyma, where wedge resection cannot provide sufficient deep margin distances. Although tumours that lack visual and tactile recognizability seem to be good indications for preoperative localization, the need for it has been less discussed for segmentectomy than for wedge resection because the resection area in segmentectomy is determined by anatomical structures, such as pulmonary vessels

[10]. However, we believe that preoperative localization of such tumours during segmentectomy will make it easier and safer to achieve sufficient margin distances with minimal lung resection. Our results showed that the marking group had smaller tumours, lower CTR and deeper localization in the lung parenchyma than in the non-marking group. Thus, the marking group had reasonable indications for preoperative marking.

Since our previous report focused on investigating the advantages and disadvantages of MIL as a marker compared with existing markers, only patients who underwent preoperative MIL marking were included [11]. Therefore, the report did not compare the surgical outcomes between the patients with and without MIL marking; its impact on surgical outcomes was not fully investigated. This study showed no significant differences in operative time, blood loss, margin distance, mortality, morbidity, postoperative pulmonary function and local recurrence on the margin between the groups. Although the marking group included several complicated segmentectomies that made securing sufficient margin distances technically difficult, both groups had comparable median margin distances. Furthermore, although complex segmentectomy has been reported to increase the operative time [13], no significant differences in surgical outcomes were observed between the groups. Thus, preoperative MIL marking for complex segmentectomies may help secure adequate margin distances while reducing the operative time.

Limitations

This study has several limitations. First, it was a single-centre retrospective study involving a relatively small number of patients. The surgical outcomes in this study might be related to not only the use of MIL as a marker but also many other variables. Second, postoperative pulmonary function tests, particularly diffusion capacity for carbon monoxide, could not be performed in some cases. Third, the follow-up period was insufficient to perform an accurate survival analysis.

CONCLUSION

Lung segmentectomy with preoperative MIL marking could be an acceptable treatment option for pulmonary malignancies. However, future multicentre prospective studies are needed to validate the outcomes reported in this study.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Takuya Matsui: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Visualization; Writing—original draft. **Yusuke Takahashi:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing—review & editing. **Takeo Nakada:** Investigation; Validation. **Noriaki Sakakura:** Investigation; Validation. **Takaaki Hasegawa:** Investigation; Methodology; Validation. **Yozo Sato:** Supervision; Validation. **Yoshitaka Inaba:** Supervision; Validation. **Hiroshi Haneda:** Supervision; Validation. **Katsuhiro Okuda:** Supervision; Validation. **Ryoichi Nakanishi:** Supervision; Validation. **Hiroaki Kuroda:** Conceptualization; Investigation; Methodology; Supervision; Validation; Writing—review & editing.

Reviewer information

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