Computed tomography-guided indocyanine green localization of multiple ipsilateral lung nodules

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Abstract

Introduction: Approximately 20% of lung nodule (LN) patients have more than one moderate-to-high malignant risk LNs. When performing one-stage video-assisted thoracoscopic surgery (VATS) in patients with multiple LNs, the ability to simultaneously localize all of these nodules is critical to operative success.
Aim: To explore the efficacy and safety of computed tomography (CT)-guided indocyanine green (IG) localization for multiple ipsilateral LNs.
Material and methods: This was a retrospective study of 278 LN patients who underwent CT-guided IG localization prior to VATS resection. Of these patients, 68 underwent localization of multiple ipsilateral LNs, whereas 210 underwent localization of a single LN.
Results: In total, 160 LNs were localized in 68 patients in the multiple localization group, while one LN was localized for each of the 210 patients in the single localization group. A 100% technical success rate was achieved in both of these groups, and the mean respective localization durations in the multiple and single LN groups were 11.3 ±4.7 min and 6.3 ±2.7 min (p = 0.001). Of the patients in the multiple and single LN groups, 22 and 15, respectively, experienced pneumothorax (p = 0.001), while 14 and 20 experienced lung hemorrhage (p = 0.016). Wedge/segmental LN technical success rates in both of these groups were 100%.
Conclusions: The CT-guided IG-mediated localization of multiple ipsilateral LNs is a safe and effective strategy, although it requires a longer operative duration and is associated with higher rates of adverse events as compared to single nodule localization.

Key words: indocyanine green, localization, multiple, lung nodules.

Introduction

The increasingly frequent use of computed tomography (CT)-based imaging in clinical practice has led to the detection of increasingly high numbers of lung nodules (LNs) [1]. Accordingly, rates of video-assisted thoracoscopic surgery (VATS) as a means of removing these LNs for analysis have also risen in recent years [2–4]. To improve the technical success rates of VATS sublobar resection procedures and to decrease rates of conversion from VATS to thoracotomy, preoperative LN localization has become an increasingly common strategy [5]. Widely utilized localization materials include hookwire, micro-coil, and liquid-based materials [6, 7], all of which can achieve high (> 90%) success when used for LN localization [8, 9]. Compared to hookwire-based localization, the use of liquid localization materials can yield better safety outcomes [9], while also reducing the duration of the localization

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procedure relative to that required for micro-coil localization [8].

Approximately 20% of LN patients have more than one moderate-to-high malignant risk LNs [10, 11]. Simultaneously resecting multiple LNs has the potential to lower the risk of tumor progression during the period between staging procedures while also shortening patient treatment time [12]. As such, the ability to successfully and simultaneously localize all target LNs is critical to the successful execution of one-stage VATS procedures in patients with multiple LNs [10, 11].

Many researchers have assessed the clinical effectiveness and safety of hook-wire and coil localization for patients with multiple LNs [4, 12]. Compared to single LN localization, simultaneous hook-wire or microcoil localizations for multiple LNs were prone to pneumothorax and hemorrhage [4, 12]. However, studies regarding liquid material localization for patients with multiple LNs are still lacking.

Aim

The present study was designed to evaluate the efficacy and safety of CT-guided indocyanine green (IG) localization in patients with multiple ipsilateral LNs, comparing the success of such localization to that in patients undergoing localization of a single LN.

Material and methods

This was a retrospective single-center study approved by the ethics committee of our hospital. Written informed consent was not required owing to the retrospective design of these analyses.

Study design

In total, 278 LN patients who underwent CT-guided IG localization and subsequent VATS resection between June and September 2022 were included in the present study, of whom 68 (24.5%) and 210 (75.5%) respectively underwent localization of multiple ipsilateral LNs and a single LN.

Indications for IG-based localization included: (a) solid LNs ≤ 10 mm in diameter; (b) solid LNs with a lesion-nearest pleura distance ≥ 10 mm; and (c) ground glass nodule (GGN) with no restrictions on diameter or lesion-pleura distance. Patients were excluded if (a) they underwent localization of multiple bilateral LNs or (b) they exhibited any severe comorbidities.

The indications of resection of LNs were: (a) recent increase in LN size; (b) recent occurrence or enlargement of solid components in the GGNs; and (c) suspicious lung cancers based on the Lung-RADS guideline [1].

CT-guided localization

IG localization was performed under local anesthesia using a 16-row CT (Siemens, Berlin, Germany) instrument. Procedures were performed by two interventional radiologists, each with over 5 years of experience. Patients were appropriately positioned based on the locations of the target LNs, after which a 21G needle (Argon Medical Devices, Inc, TX, USA) was used to puncture the lung parenchyma based on the direction of the target LN. CT scanning was performed repeatedly to ensure appropriate needle tip localization, and the tip was adjusted until it was within 1 cm of the target nodule. IG (2.5 mg/ml, 0.3 ml) was then gradually injected as the needle was slowly removed such that IG was visibly present on the visceral pleura. All LNs were localized with a one-stage CT-guided protocol.

VATS procedures

All VATS procedures were performed within 3 h following IG localization. Initially, IG fluorescence was used to guide sublobar VATS resection. When VATS visualization was sufficient to ensure adequate margins for the target LN, wedge resection was performed, whereas segmental resection was otherwise conducted. After being resected, tissue samples were sent to the Department of Pathology, where they underwent rapid pathological assessment. Pathological results were used to guide subsequent procedures, with no further resection being performed when the nodule was classified as cancer in situ or below, while systematic lymph node dissection (SLND) but not lobectomy was conducted in cases where an LN was classified as a mini-invasive cancer, and both lobectomy and SLND were performed when an LN was identified as an invasive cancer. In cases where multiple invasive lung cancers were identified, lobectomy was performed for the LN exhibiting the highest tumor staging.

Definitions

IG localization was deemed a technical success when IG fluorescence was visible on the surface of

the lung without diffusion away from the site of injection [9]. Wedge/segmental resection procedures were considered a technical success when the target LN was fully present in the resected segment of tissue [9]. The duration of localization was the interval between the time at which patients initially lay down on the CT table to the time that IG injection was complete [13], while VATS time was the interval between the initial incision and wound closure [13]. Lung hemorrhage was defined based on the observation of new consolidative or ground glass opacity near the CT needle tract [14].

Statistical analysis

Quantitative data are given as means ± standard deviation and compared via independent *t*-tests, while categorical data are given as *n* (%) and compared via χ² tests. Logistic regression analyses were used to detect risk factors associated with complications after localization, with variables that were significant ($p < 0.1$) in univariate analyses being included in a multivariate analysis. $P < 0.05$ was the significance threshold, and SPSS 16.0 (SPSS Inc., IL, USA) was used to conduct all analyses.

Results

Patients

In total, 160 LNs were localized in the 68 patients in the multiple localization group whereas a single

Table I. Comparison of patients' baseline data between 2 groups

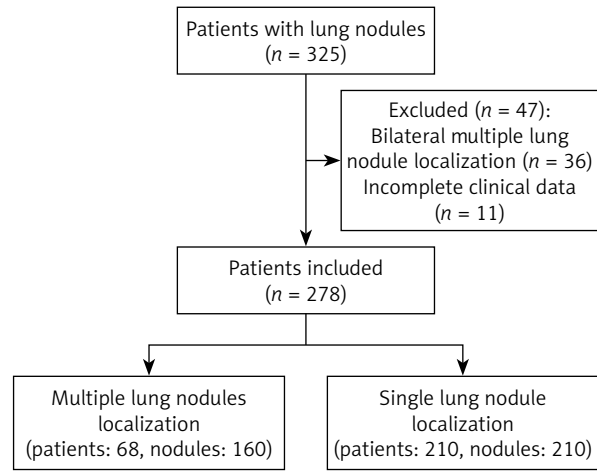| Parameter	Multiple group	Single group	*P*-value
Patients number	68	210	-
Age [years]	53.4 ±11.2	49.3 ±19.7	0.013
Gender:			0.034
Male	14	72	
Female	54	138	
Previous tumor history	8	14	0.176
Smoking history	5	2	0.013
Hypertension	15	37	0.414
Diabetes	3	15	0.609
Coronary heart disease	1	6	0.850
Emphysema	0	4	0.575
Body mass index [kg/m²]	23.2 ±3.0	22.7 ±3.1	0.260

Figure 1. Flow chart of this study

LN was localized in each of the 210 patients in the single localization group. For details regarding the study flow (Figure 1). For details regarding the baseline characteristics of patients in these study groups (Tables I and II).

IG localization

IG localization procedures were a technical success in 100% of cases in both patient groups

Table II. Comparison of lung nodules' baseline data between 2 groups

Parameter	Multiple group	Single group	*P*-value
Pulmonary nodules number	160	210	-
Patients with 2 nodules	47	–	
Patients with 3 nodules	18	–	
Patients with 4 nodules	3	–	
Nature of the nodules:			0.424
Solid	28	36	
Mixed GGN	23	41	
Pure GGN	109	133	
Nodule diameter [mm]	6.1 ±2.9	7.8 ±3.2	0.001
Nodule-pleura distance [mm]	13.9 ±11.7	13.8 ±10.9	0.910
Lung sides:			0.120
Left	61	97	
Right	99	113	
Lung lobes:			0.856
Upper	80	103	
Non-upper	80	107	

GGN – ground glass nodule.

Table III. Localization and VATS related results

Parameter	Multiple group	Single group	P-value
Localization time [min]	11.3 ±4.7	6.3 ±2.7	0.001
Position change (n)	20	Not applicable	-
Complications:			
Pneumothorax	32.3% (22/68)	7.1% (15/210)	0.001
Lung hemorrhage	20.6% (14/68)	9.5% (20/210)	0.016
VATS time [min]	92.0 ±40.9	69.8 ±31.6	0.001
Blood loss [ml]	17.3 ±11.0	14.1 ±7.3	0.027
Type of sublobar resection:			0.048
Wedge	71	72	
Segmental	89	138	
Additional lobectomy	11	38	0.718
Pathological diagnoses:			0.001
Invasive adenocarcinoma	11	36	
Mini-invasive adenocarcinoma	64	98	
Adenocarcinoma *in situ*	31	45	
Squamous cancer	0	2	
Metastasis	2	0	
Benign	52	29	

VATS – video-assisted thoracoscopic surgery.

(Table III). In total, 20 (29.4%) patients in the multiple localization group had to undergo positional adjustments during these procedures. The mean localization durations in the multiple and single localization groups were 11.3 ±4.7 min and 6.3 ±2.7 min, respectively ($p = 0.001$).

Pneumothorax affected 22 (32.3%) and 15 (7.1%) patients in multiple and single localization groups, respectively ($p = 0.001$, Table II), but none of these patients experienced symptoms, nor did they need to undergo chest tube insertion. In the multiple localization group, pneumothorax occurred after the first, second, and third LN localization procedures in 5, 16, and 1 patient, respectively. The risk factors found to be associated with multiple LN localization-related pneumothorax incidence included longer localization time ($p = 0.014$) and position change ($p = 0.004$) (Table IV).

Lung hemorrhage affected 14 (20.6%) and 20 (9.5%) patients in multiple and single localization groups, respectively ($p = 0.016$, Table II), but none

of these patients experienced hemorrhage-related symptoms. Longer localization time ($p = 0.023$) was identified as a risk factor associated with lung hemorrhage in patients undergoing localization of multiple LNs (Table V).

VATS resection outcomes

VATS resection procedures were successfully conducted within 3 h following localization in all cases, and these procedures were a technical success in 100% of patients in both groups (Table III). Conversion to thoracotomy was not required in any cases, and one-stage resection was successfully performed for all target LNs in the multiple LN group. Additional lobectomy was required for 11 and 38 patients due to the identification of invasive lung cancers, and the mean VATS durations in the multiple and single localization groups were 11.3 ±4.7 min and 6.3 ±2.7 min, respectively ($p = 0.001$). The mean respective blood loss in the multiple and single localization groups was 17.3 ±11.0 ml and 14.1 ±7.3 ml ($p = 0.027$). Final pathological diagnosis results for all LNs in this study are summarized in Table III, and rapid pathological results matched final pathological diagnoses in all cases.

Discussion

The present study was performed to explore the relative safety and efficacy of CT-guided IG localization of multiple ipsilateral LNs as compared to localization of a single LN. Technical success rates for this localization strategy and subsequent VATS sublobar resection procedures were 100% in all patients included in the present study. This demonstrates the feasibility of CT-guided simultaneous one-stage IG injection procedures for localization of multiple LNs and the ability to use such localization to guide one-stage VATS sublobar resection of these multiple LNs.

Approximately 1–8% of lung cancer patients have multiple lung cancers [15], and one-stage VATS resection can be beneficial for patients with multiple lung cancers [12]. In this study, 68 of 278 (24.5%) patients required multiple LNs localization, and this rate was comparable to those (22.2–24.1%) in previous studies regarding multiple LN localization [16, 17]. In theory, simultaneous resection procedures should be superior to two-stage procedures as they should be able to better lower the odds of disease progression [12].

Table IV. Predictors of pneumothorax for localization of multiple lung nodules

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age	0.995	0.950–1.041	0.817			
Gender:						
Male	1					
Female	3.529	0.716–17.404	0.121			
Smoking history:						
No	1					
Yes	1.433	0.222–9.264	0.705			
Tumor history:						
No	1					
Yes	1.295	0.280–5.987	0.741			
Hypertension:						
No	1					
Yes	1.542	0.470–5.057	0.475			
Diabetes:						
No	1					
Yes	1.048	0.090–12.214	0.970			
Coronary heart disease:						
No	1					
Yes	0.000	0.000	1.000			
Body mass index	0.975	0.819–1.160	0.772			
Lung side:						
Right	1					
Left	1.722	0.608–4.879	0.306			
Same lobe:						
No	1			1		
Yes	0.321	0.101–1.016	0.053	1.833	0.371–9.052	0.457
Number of nodules:						
2	1					
3	1.179	0.369–3.769	0.782			
4	4.714	0.395–56.324	0.221			
Minimum nodule diameter	1.133	0.829–1.550	0.433			
Maximum nodule-pleura distance	1.001	0.960–1.043	0.974			
Localization time	1.227	1.078–1.396	0.002	1.199	1.037–1.386	0.014
Position change:						
No	1			1		
Yes	9.630	2.878–32.220	< 0.001	9.342	2.033–42.927	0.004

Table V. Predictors of lung hemorrhage for localization of multiple lung nodules

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age	1.051	0.990–1.116	0.104			
Gender:						
Male	1					
Female	1.714	0.336–8.738	0.517			
Smoking history:						
No	1					
Yes	0.000	0.000	0.999			
Tumor history:						
No	1					
Yes	2.673	0.554–12.894	0.221			
Hypertension:						
No	1					
Yes	2.444	0.672–8.889	0.175			
Diabetes:						
No	1			1		
Yes	8.833	0.739–105.575	0.085	14.533	0.934–226.066	0.056
Coronary heart disease						
No	1					
Yes	0.000	0.000	1.000			
Body mass index	0.975	0.796–1.193	0.804			
Lung side:						
Right	1					
Left	1.382	0.417–4.572	0.597			
Same lobe:						
No	1			1		
Yes	0.193	0.039–0.948	0.043	0.438	0.072–2.651	0.369
Number of nodules:						
2	1			1		
3	1.393	0.362–5.355	0.630	0.538	0.100–2.880	0.469
4	9.750	0.786–120.950	0.076	5.593	0.382–81.965	0.209
Minimum nodule diameter	0.912	0.621–1.339	0.637			
Maximum nodule-pleura distance	1.013	0.966–1.062	0.593			
Localization time	1.188	1.038–1.360	0.013	1.229	1.028–1.468	0.023
Position change:						
No	1					
Yes	1.587	0.454–5.547	0.469			

Pneumothorax and lung hemorrhage were the most common complications after multiple LN localization with the incidences of 27.5–56.8% and 18.9–60% [16–18]. In this study, pneumothorax and lung hemorrhage rates in the multiple LN group were 32.3% and 20.6%, respectively, which were consistent with the previous studies. Furthermore, pneumothorax and lung hemorrhage rates were significantly higher in patients who underwent localization of multiple LNs relative to those who underwent localization of a single LN, in line with prior reports pertaining to CT-guided multiple LN localization [16, 17]. However, none of these complications were symptomatic and these complications did not require special treatment, such as chest tube insertion. Therefore, IG localization for multiple ipsilateral LNs is clinically safe.

Localizing multiple nodules necessitates additional needle pathways, patient positional changes, and prolonged localization procedures. Here, longer localization time was identified as a risk factor significantly associated with the odds of pneumothorax and lung hemorrhage, whereas positional change was specifically associated with the risk of pneumothorax. Position change has also been confirmed as a risk factor of pneumothorax in some previous studies [4, 16]. Therefore, we should choose the most reasonable puncture route, and avoid position change as far as possible. Longer localization time was confirmed in a previous study regarding methylene blue localization for multiple LNs [19]. Longer localization time may be caused by repeat puncture procedures, and the air could flow into the pleural cavity more easily. In the 22 patients who experienced pneumothorax in the multiple group, 17 (77.3%) patients had the pneumothorax after the second or third LN localization. This finding may also confirm that longer localization time was a risk factor of localization-related complications.

Just 11 (16.2%) of 68 multiple LN patients in this study were diagnosed with invasive adenocarcinoma and needed to undergo subsequent lobectomy, while multiple sublobar resection was required in the remaining 57 (83.8%) patients. Thus, preoperative IG localization can help patients with multiple LNs retain maximal lung function.

There are some limitations to this study. For one, this was a retrospective study and patients were grouped based on numbers of LNs such that randomization could not be performed. Accordingly,

baseline data such as gender, age, LN diameter, and smoking history varied between these groups. Even so, these factors were not identified as risk factors associated with complication rates in multivariate analyses. Additionally, outcomes associated with IG localization were not compared to those associated with other localization materials in patients with multiple LNs. Hence, additional prospective clinical research will be essential to better compare different localization materials in order to define the optimal approach to simultaneously localizing multiple LNs.

Conclusions

CT-guided IG localization can be effectively and safely used to localize multiple ipsilateral LNs, although it requires a longer operative duration than localization of a single LN and is associated with a higher risk of pneumothorax and lung hemorrhage. Avoiding position change and reducing the localization time as much as possible may help to reduce the incidence of localization-related complications.

Conflict of interest

The authors declare no conflict of interest.

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