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Intraoperative pulmonary neoplasm identification using near-infrared fluorescence imaging

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Abstract

OBJECTIVES: Near-infrared (NIR) fluorescence imaging provides surgeons with real-time visual information during surgery. The purpose of this pilot trial was to evaluate the safety and feasibility of the intraoperative detection of pulmonary neoplasms with NIR fluorescence imaging after low-dose indocyanine green (ICG) injection.

METHODS: Eleven consecutive patients who were scheduled to undergo resection of pulmonary neoplasms were enrolled in this study. ICG (1 mg/kg) was administered intravenously 1 day before surgery, and the retrieved surgical specimens were examined for fluorescence signalling by using NIR fluorescence imaging system on a back table in the operating room. We analysed the fluorescence intensity, pathology, size, depth from the pleural surface and metabolic activity of the pulmonary neoplasms.

RESULTS: Fluorescence signalling was detected in all specimens except in one from a patient with primary lung cancer. Two false-positive cases that presented no residual tumour with obstructive pneumonitis, after concurrent chemoradiation therapy for primary lung cancer before the operation, were identified, and their fluorescence intensity was 8.6 ± 0.4. The mean fluorescence intensity of the eight pulmonary tumours was 3.4 ± 1.9, and these tumours did not differ in pathology, size, depth from the pleural surface or metabolic activity.

CONCLUSIONS: NIR fluorescence imaging could safely identify pulmonary neoplasms after the systemic injection of ICG. In addition, low-dose ICG is sufficient for NIR fluorescence imaging of pulmonary neoplasms. However, because the passive accumulation of ICG could not be used to discriminate tumours with inflammation, tumour-targeted fluorescence should be developed to solve this problem in the future.

Keywords: Pulmonary neoplasm • Fluorescence • Surgery

INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide, accounting for 1.4–1.6 million deaths yearly. Surgical resection of early-stage non-small-cell lung cancer (NSCLC) may provide a long-term survival benefit compared with non-surgical therapies. The standard surgical treatment for early-stage NSCLC involves lobectomy or greater resection with complete mediastinal lymph node dissection regardless of the tumour location or size. This extensive resection may be associated with high complication, morbidity and mortality rates, especially in elderly patients who usually have severe comorbidities. The recent increase in the ageing population, advances in radiological screening programmes, patient selection strategies and greater understanding of histological prognostic factors have led to a resurgence of interest in limited resections such as segmentectomy or wedge resection for lung cancer. Limited resection is considered the treatment of choice in high-risk surgical patients who cannot tolerate lobectomy because of a compromised cardiorespiratory reserve. In non-compromised patients, segmentectomy shows equivalent survival rates in cases of small peripheral NSCLC, and in those with favourable pathological and imaging-based prognostic factors. Patients with ground glass opacity-dominant clinical stage IA adenocarcinomas can be successfully treated with wedge resection of a T1a tumour.

Although limited resection has the theoretical advantage of preserving pulmonary function in high-risk patients, the increased local recurrence rate of this approach is of concern [1]. One reason for local recurrence after limited resection is the potential spread of cancer cells from the surgical margin [2]. Therefore, in an effort to improve the surgical margin for local control, an adequate surgical technique that allows a distance from the surgical margin to the tumour that is greater than the size of the tumour itself is frequently used [3].

However, in clinical practice, it is not always easy to define the tumour margin intraoperatively. In particular, during video-assisted thoracoscopic surgery (VATS), it is more difficult to define the tumour outer margin owing to the limitations of digital palpation. A preoperative technique for localizing the tumour lesion by using microcoils, dye, hookwire and lipiodol was developed to identify surgical margins [4]; however, this technique shows the tumour's general location and not its outer margins. Moreover, it requires additional intervention before the operation, and is associated with complications such as pneumothorax and haemothorax.

Near-infrared (NIR) fluorescence imaging was recently introduced to enable real-time intraoperative visualization of the lymph nodes draining a tumour, cancer or premalignant lesion, as well as the vital structures, vascularization and perfusion [5]. Ishizawa *et al*. were the first to demonstrate intraoperative visualization of both colorectal hepatic metastases and hepatocellular carcinoma (HCC) using NIR fluorescence imaging several hours to days after the intravenous injection of indocyanine green (ICG) [6]. This technique has also been used in neurosurgery for the intraoperative identification of high-grade gliomas, meningiomas, haemangioblastomas and pituitary tumours [7]. Okusanya *et al*. recently demonstrated that pulmonary nodules could be identified with intraoperative NIR fluorescence imaging 24 h after the intravenous injection of ICG (5 mg/kg) [8].

In a previous study, we demonstrated that lung perfusion can be visualized by using NIR fluorescence imaging after the injection of ICG (0.6 mg/kg) in a porcine model [9]. An ICG dose of 0.5 mg/kg was usually applied for the intraoperative detection of colorectal liver metastases with NIR fluorescence imaging [10] instead of 5 mg/kg, which is the maximum intravenous dose for humans [11]. Therefore, we assumed that a low dose of ICG could also visualize pulmonary neoplasms.

The purpose of this pilot trial was to evaluate the safety and feasibility of the intraoperative detection of pulmonary neoplasms with NIR fluorescence imaging after a low-dose ICG injection.

MATERIALS AND METHODS

Patients

Eleven consecutive patients who were scheduled to undergo resection of pulmonary neoplasms between December 2014 and January 2015 at Korea University Guro Hospital were enrolled in this study. The pulmonary lesions in all patients were confirmed by reviewing the chest computed tomography (CT) scans obtained by radiologists. Percutaneous needle biopsy or bronchoscopic biopsy was performed in all except 2 patients who were strongly suspected of having metastatic or recurrent lung cancer, and for whom the multidisciplinary team decided not to confirm their pathology preoperatively. Two patients who were found to have primary lung cancer through preoperative biopsy underwent concurrent chemoradiation therapy (CCRT) before the operation but did not undergo a repeat preoperative biopsy. Positron emission tomography/CT (PET/CT) was performed in all patients just before the operation. This study was approved by the ethics committee of Korea University Guro Hospital, and written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Perioperative study protocol

ICG (1 mg/kg) (Diagnogreen, Daiichi-Sankyo Company, Tokyo, Japan) was administered intravenously 24 h before the surgery. The surgical procedure with a curative intent was chosen among wedge resection, segmentectomy, lobectomy and pneumonectomy for each patient. All these operations were performed using VATS, the standard method in our hospital [12–14].

Immediately after resection, all the retrieved surgical specimens were examined for fluorescence signalling by using the SPY imaging system (Novadaq Technologies, Mississauga, ON, Canada), on a back table in the operating room. The SPY imaging system can provide two kinds of fluorescence intensity data: values of pixels compared with some anatomical reference point in the picture, and absolute values that directly evaluated the baseline-compensated intensity of the underlying pixel values. The absolute values of SPY are similar to the signal-to-background ratio. In this study, we used the absolute values of pixels to compare the fluorescence intensity of the pulmonary neoplasms.

All surgical specimens were ultimately evaluated by experienced pathologists in the form of formalin-fixed and paraffin-embedded sections stained with haematoxylin and eosin.

Statistical analysis

The descriptive data are presented as mean and standard deviation. Spearman's rank correlation was used to evaluate the correlation between the fluorescence intensity and the size, depth from the pleural surface or maximum standardized uptake value (SUV_{max}) of the pulmonary neoplasm. Significance was set at $P < 0.05$. Statistical analysis was performed by using SPSS for Windows version 22.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Characteristics of pulmonary neoplasms

On permanent pathological examination, pulmonary neoplasms were confirmed as primary lung cancer in 6 patients (squamous cell carcinoma in 3, adenocarcinoma in 3), recurrent pulmonary adenocarcinoma in 1, pulmonary atypical carcinoid tumour in 1 and metastatic malignant pheochromocytoma in 1 (Table 1). The patient with recurrent lung cancer and the patient with metastatic lung cancer had undergone a pulmonary lobectomy with mediastinal lymph node dissection and subtotal adrenalectomy as previous treatments, respectively. Two patients with Stage IIIa or IIIb primary squamous lung cancer who had undergone CCRT (cisplatin and etoposide with 6000 cGy radiation therapy) before the operation had no residual tumour on permanent surgical pathological examination. A lobectomy was performed with a curative intent in 6 patients, segmentectomy in 2, wedge resection in 2 and pneumonectomy in 1 for each pulmonary neoplasm. There were no adverse effects related to the systemic injection of ICG, and no cases of major morbidity or mortality after surgery were noted.

The mean pulmonary nodule size was 2.3 ± 1.50 cm (range, 0.3–5 cm), whereas the mean depth of the pulmonary nodule from the pleural surface was 3.5 ± 5.13 mm (range, 0–14 mm). The SUV_{max} of the pulmonary neoplasm was 3.6 ± 2.66 (range, 0.8–9.6).

Fluorescence intensity of pulmonary neoplasms

Fluorescence signal was detected in all specimens except in 1 case of primary squamous cell carcinoma that was 2.9 cm in size and located 12 mm beneath the pleural surface (90.9%) (Fig. 1). The

Table 1: Characteristics and fluorescence intensity of pulmonary neoplasms

Patient no.	Sex	Age (years)	Previous treatment	Tumour size (cm)	Tumour depth (mm)	SUV_{max}	Fluorescence intensity	Pathology	Surgery
1	F	77	No	2	5	4.7	2	Atypical carcinoid tumour	Wedge resection
[a]2	M	66	CCRT	No tumour	0	2.5	9	No residual tumour	Lobectomy
3	M	70	No	2.9	12	6.2	No detection	Squamous cell carcinoma	Lobectomy
4	M	31	Subtotal adrenalectomy	0.3	0	2.4	4.5	Metastatic malignant pheochromocytoma	Wedge resection
5	M	66	No	4.1	0	9.6	7	Squamous cell carcinoma	Lobectomy
6	M	58	No	2.2	14	0.8	5	Adenocarcinoma	Lobectomy
7	F	65	Lobectomy	0.9	2	1	1.3	Recurrent adenocarcinoma	Segmentectomy
8	M	52	No	1.5	0	5.5	3.3	Adenocarcinoma *in situ*	Lobectomy
9	M	55	No	5	0	2.1	2	Squamous cell carcinoma	Pneumonectomy
10	F	55	No	1.7	5	2.1	1	Adenocarcinoma	Segmentectomy
[a]11	M	58	CCRT	No tumour	0	2.4	8.2	No residual tumour	Lobectomy

SUV_{max}: maximum standardized uptake value; CCRT: concurrent chemoradiation therapy.
[a]This patient underwent neoadjuvant CCRT for squamous cell carcinoma.

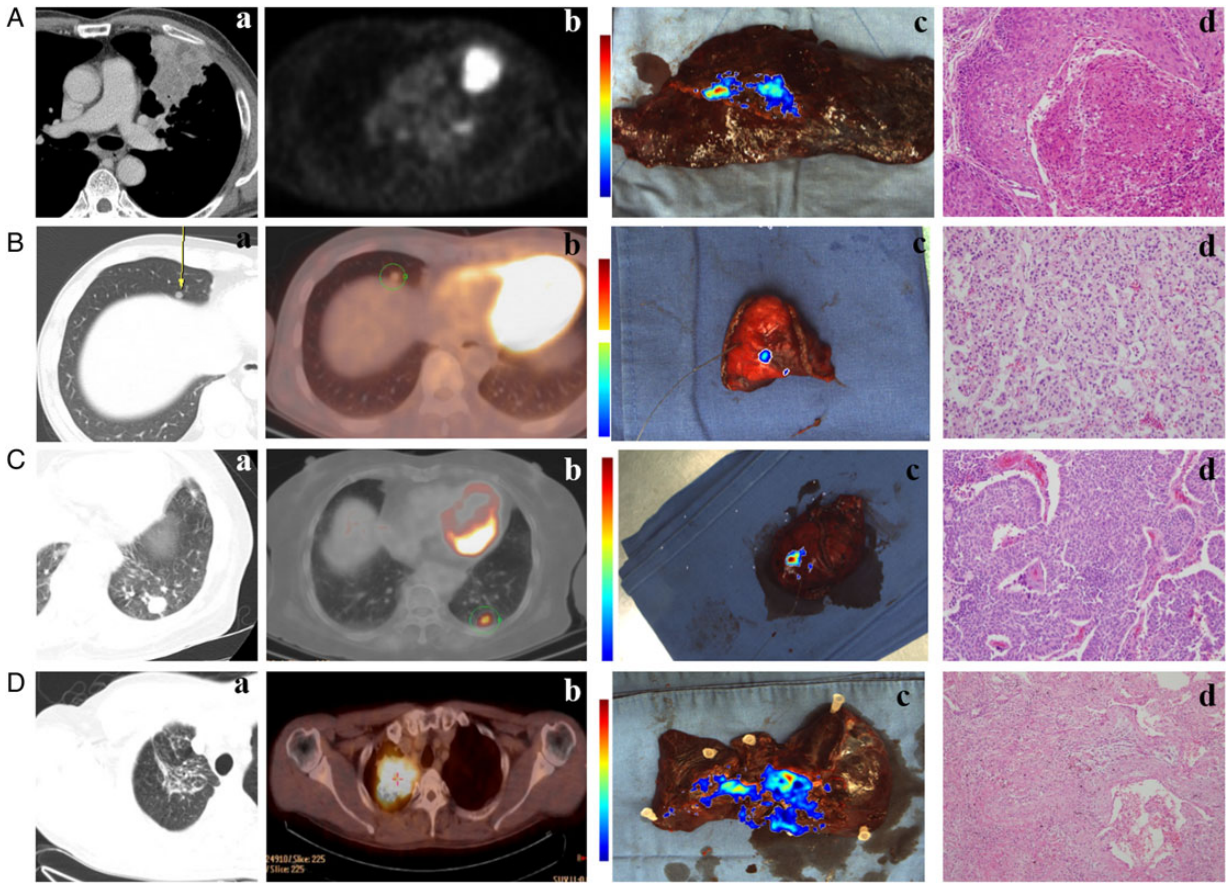

Figure 1: (**A**) Squamous cell carcinoma in the left upper lobe of the lung; (**B**) metastatic pheochromocytoma in the lung; (**C**) atypical carcinoid tumour of the lung; and (**D**) no residual tumour after concurrent chemoradiation therapy [a: computed tomography, b: positron emission tomography; c: fused images of near-infrared fluorescence and visible light; d: microscopic finding by haematoxylin and eosin staining (×200)].

mean fluorescence intensity of the 10 pulmonary masses was 5.1 ± 3.28 (range, 1–10). The mean fluorescence intensity of the pulmonary tumours, including primary lung cancer, recurrent and metastatic lung cancer and atypical carcinoid tumour, was 3.4 ± 1.9. The fluorescence intensity did not differ according to the pathology of the pulmonary tumour. The mean fluorescence intensity of the cases of primary lung cancer, including recurrent lung cancer, was 3.0 ± 2.98 (squamous cell carcinoma, 3.2 ± 2.9; adenocarcinoma, 2.7 ± 1.6); the intensity of metastatic pheochromocytoma was 4.5; and the intensity of atypical carcinoid tumour was 2.0 (Fig. 2). However, the two specimens presenting no residual tumour with obstructive pneumonia on surgical pathology

showed a higher fluorescence intensity (8.6 ± 0.4) than that of other pulmonary tumours.

Correlations among fluorescence intensity, size, depth from the pleural surface and maximum standardized uptake value of pulmonary neoplasms

Fluorescence intensity is likely to be independent of the size of pulmonary neoplasms. In this study, fluorescence signal could be detected even in 0.3-cm pulmonary nodules at a fluorescence intensity of 4.5; otherwise, the fluorescence intensity of the 2-cm pulmonary nodules was 2. The correlation between fluorescence intensity and pulmonary nodule size was not significant ($r = 0.286$, $P = 0.49$) (Fig. 3).

Also, fluorescence intensity is likely to be independent of the depth of pulmonary neoplasms from the pleural surface. In this study, fluorescence signal could be detected even in pulmonary neoplasms located 14 mm beneath the pleural surface at a fluorescence intensity of 5; otherwise, the fluorescence intensity of pulmonary neoplasms located on the pleural surface was 2.1. The correlation between fluorescence intensity and pulmonary nodule depth from the pleural surface was not significant ($r = -0.260$, $P = 0.47$).

Fluorescence intensity is also likely to be independent of the SUV_{max} of pulmonary neoplasms. In this study, the fluorescence intensity of pulmonary neoplasms with an SUV_{max} of 0.8 was 5, whereas that of pulmonary neoplasms with an SUV_{max} of 4.7 was 2. The correlation between the fluorescence intensity and the SUV_{max} of pulmonary neoplasms was not significant ($r = 0.451$, $P = 0.19$).

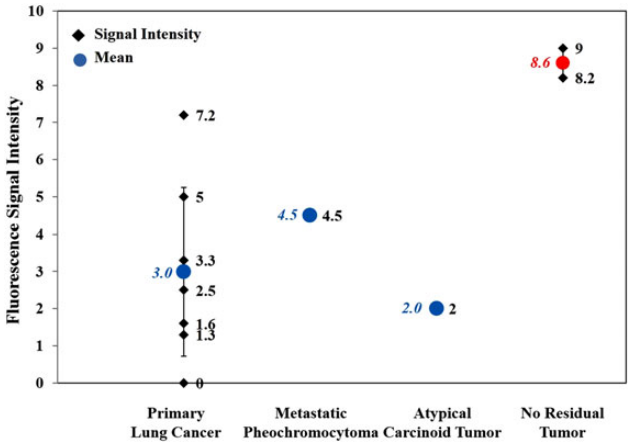

Figure 2: Fluorescence intensity of the pulmonary neoplasms.

DISCUSSION

Intraoperative assessment of the tumour margin by using NIR fluorescence imaging with ICG was introduced in 2009 for both colorectal hepatic metastases and HCC [6]. After its intravenous

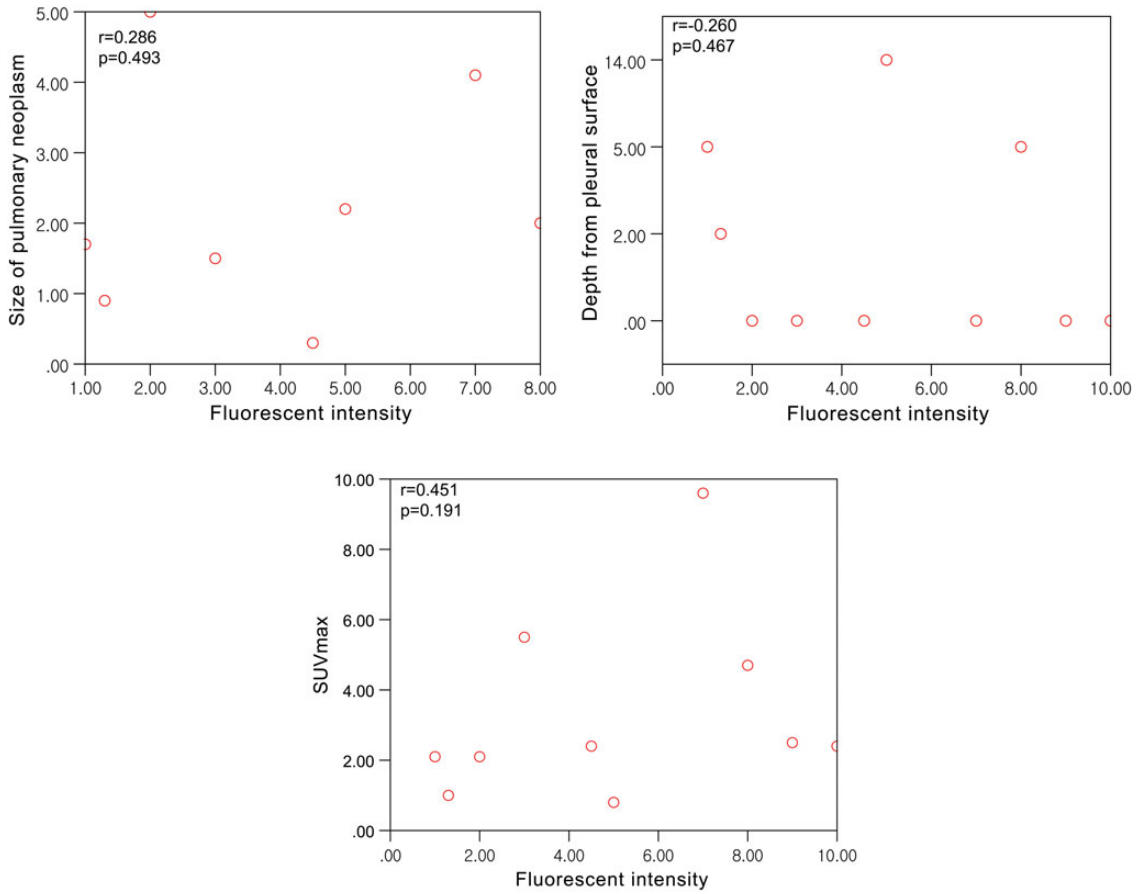

Figure 3: Correlations among fluorescence intensity, positron emission tomography of pulmonary neoplasms, depth from the pleural surface and pulmonary neoplasm size.

administration 12–48 h before surgery, ICG is rapidly taken up by tumoural and non-tumoural hepatocytes. ICG is excreted in the bile and disappears from the healthy liver parenchyma within a few hours, whereas it remains fixed in tumoural hepatocytes and in pathological areas of the liver, particularly around non-hepatocellular tumours [10]. The ICG-emitted fluorescence signal on the liver surface is detected by using an NIR camera with an NIR laser source, and a fluorescent tumour is visualized on the monitor. The application of this novel NIR fluorescence imaging technology is rapidly expanding to neurosurgery for high-grade gliomas, meningiomas, haemangioblastomas and pituitary tumours [7], as well as to partial nephrectomy for renal cell carcinoma [15]. This technology has also shown possible application in surgery for breast tumours [16] and gastric cancer [17]. This phenomenon could be explained by the enhanced permeability and retention effect (EPR), which is associated with promoted vascular permeability and poorly aligned endothelial cells with large gaps and poor lymphatic drainage around the tumour [18]. Although ICG is not a tumour-specific targeting NIR fluorescence agent, like antibodies or peptides specific for cell surface receptors, it is clinically available and can be used to visualize tumours through its passive accumulation.

In 2014, NIR fluorescence imaging technology was first applied in surgical resection for patients with pulmonary nodules in which ICG had passively accumulated [8]. The authors reported that 16 of the 18 pulmonary nodules and 5 additional sub-centimetre nodules could be detected by using a custom-made NIR fluorescence imaging system and with the injection of ICG (5 mg/kg) 24 h before surgery. Although the ICG dose was selected on the basis of their preclinical studies [19], 5 mg/kg ICG is the known maximum intravenous dose for humans [20]. ICG toxicity is very rarely reported but is primarily associated with contrast allergic reactions at doses of >0.5 mg/kg because of its iodine content [21]. The ICG dose for NIR fluorescence image-guided liver surgery was 0.5 mg/kg in an initial clinical trial [6], and a recent study showed that the use of a relatively low dose of ICG (0.13–0.26 mg/kg) allowed reaching an acceptable tumour-to-liver ratio [22]. In a previous study, we reported that ICG (0.6 mg/kg) injection enabled clear visualization of the pulmonary perfusion image on the NIR fluorescence imaging system in a porcine model [9].

The ICG dose and the injection-to-operation interval are considered key determinants for a successful NIR fluorescence image-guided cancer surgery [22]. The optimal dose and injection interval of ICG in pulmonary neoplasms may be different from that in HCC because ICG is primarily excreted through the biliary system. Therefore, in this pilot study, we attempted to use a lower dose of ICG (1 mg/kg) to detect pulmonary neoplasms with the SPY imaging system, the sole device of its kind that is currently approved by the Korean Food and Drug Administration (KFDA).

In this study, the fluorescence signal of the removed pulmonary neoplasms was measured on a back table in the operating room. The SPY imaging system was designed for open thoracotomy surgery; however, for this study, we used VATS, which is our routine surgical approach for lung cancer [12]. The results of this study were used as the preliminary data for the VATS NIR fluorescence image-guided surgery of pulmonary neoplasms by using the Pinpoint endoscopic fluorescence imaging system (Novadaq Technologies, Mississauga, ON, Canada), which is not yet approved by the KFDA. The disease spectrum of the pulmonary neoplasms in this study was variable and included primary and metastatic lung cancer, borderline tumour and inflammation after CCRT for lung cancer, because we wanted to observe if fluorescence images could be obtained irrespective of the pathology of the pulmonary neoplasms.

In 10 of the 11 patients, fluorescence signal could be detected in tumours as small as 0.3 cm. However, no additional nodules were detected. In 1 patient with a 2.9-cm squamous cell carcinoma located 12 mm beneath the pleural surface, no fluorescence signal was detected even after tumour cleavage. Okusanya *et al*. also reported on 2 cases of undetected pulmonary nodules; the reason for the failure in detection was not elucidated [8]. Future studies should further examine this issue.

On the other hand, 2 cases with a high fluorescence signal had no residual tumour and only showed postobstructive pneumonitis after neoadjuvant CCRT for lung cancer before surgery. The inflammatory state features vascular changes that are similar to those of tumours, which leads to an increased proliferation of endothelial cells, perivascular mast cells and microvascular density; thus, ICG is equally likely to accumulate in tumours and inflamed tissue [23, 24]. Therefore, in situations in which there is significant inflammation, the use of NIR fluorescence imaging with ICG is not helpful [25]. In this study, the 2 cases with no residual tumour and pneumonitis that showed higher fluorescence signals than the other tumours may be due to postobstructive pneumonitis causing severe inflammation that increased the EPR effect compared with that of the tumour.

Fluorescence intensity was not correlated with tumour pathology (from borderline tumour to primary or metastatic malignancy), tumour size or metabolic activity on PET/CT, which was also reported by Okusanya *et al*. In 2 cases, the tumours were located 12 and 14 mm, respectively, beneath the pleural surface, which could be visualized on the NIR fluorescence imaging system. Although the tissue penetration of the NIR fluorescence image is limited to 5–10 mm and significant light scattering results in a diffuse image at depths >5 mm, pulmonary nodules have been detected as deep as 13 mm from the pleural surface by using NIR fluorescence imaging [8]. In the collapsed lung, the tumour depth is much lesser than that measured on preoperative chest CT images; therefore, tumours located 12 and 14 mm beneath the pleural surface measured on preoperative chest CT images should have been detectable in this study.

The current techniques for tumour localization, such as hookwire, lipiodol, microcoil and dye, need preoperative intervention under CT or bronchoscopic guidance when inserting those materials around the tumour. These techniques could not provide information on the outer margins, and have the risks of causing pneumothorax as well as bleeding and seeding of tumours along the needle tracts. Moreover, they require additional cost and time, thereby causing burden to patients [4]. On the other hand, NIR fluorescence imaging needs only peripheral intravenous injection before the operation. Therefore, there is no need for preoperative intervention that may cause complications, cost and time issues and patient anxiety.

In conclusion, we confirmed that NIR fluorescence imaging could be used to identify pulmonary neoplasms after the systemic injection of ICG. In addition, a low dose of ICG (1 mg/kg) was sufficient to reveal NIR fluorescence imaging of pulmonary neoplasms. However, because the passive accumulation of ICG could not be used to discriminate tumours with inflammation, tumour-targeted fluorescence should be developed to solve this problem in the future.

Limitations

Although this study is a preliminary pilot clinical trial, the number of patients was small and the disease spectrum of pulmonary neoplasms was heterogeneous. Fluorescence microscopy was not available to enable the microscopic evaluation of the fluorescent tumour cells.

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Conflict of interest: none declared.

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