Editorial

Targeted intraoperative fluorescence imaging for the visualization of ground-glass nodules in the lung

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The ability to detect small pulmonary nodules has improved with the widespread use of computed tomography (CT) lung screening (1). Minimally invasive surgery, such as video-assisted thoracoscopic surgery (VATS) or robot-assisted thoracoscopic surgery (RATS), is considered to be one of the preferred choices in cases involving an unsuccessful diagnosis via percutaneous transthoracic needle biopsy, or when the resection of small pulmonary nodules is needed. VATS, however, can provide limited identification of small pulmonary nodules due to the inability of a surgeon to visualize or palpate the lesions directly with their own eyes or hands during the procedure (1). In robotic surgery, lesion localization is even more challenging due to the lack of haptic feedback from thoracoscopic palpation (2).

Preoperative localizations, performed using hookwires, microcoils, radiotracers, radio contrasts, and dyes, are currently used in clinical practice to overcome the limitations that may be encountered when attempting to visualize small pulmonary nodules during minimally invasive surgeries (1). These techniques, however, only provide an image of the material, not the tumor itself, making it challenging to identify the resection margins accurately.

Singhal and colleagues first reported that intravenously injected indocyanine green (ICG) could successfully visualize lung cancer under the near-infrared (NIR) fluorescence imaging system (3). This is consistent with our previous studies demonstrating similar results in pulmonary neoplasms, as well as thymoma and esophageal cancer (4-6).

Recent reports from the JCOG0802 trial showed that small ground-glass nodule (GGN) lung cancers with diameters ≤2 cm and a consolidation-to-tumor (C/T) ratio >50% have similar postoperative complication rates and prognostic results after being treated with either lobectomy or segmentectomy (7). Additionally, the 5-year disease-free survival rate, post-surgical resection, of lung adenocarcinoma *in situ* and minimally invasive adenocarcinoma is 100% (8). The intraoperative visualization of small GGNs, therefore, is crucial for retaining an increased amount of normal lung parenchyma, improving quality of life, and providing a similar prognosis to that of a lobectomy. Because ICG is not a cancer-specific agent (9) and has fast hepatic uptake with a short blood half-life and a low quantum yield dose (10), it is impossible to visualize such early-stage small lung cancer.

The OTL38 NIR tracer was initially designed to target pulmonary adenocarcinomas due to their overexpression of folate receptor alpha, and it has been found that the tracer highlights a broad range of tumors, including squamous cell carcinomas, small cell lung cancers, and even granulomas with hypothetical aid in the expression of folate receptor beta (11). Furthermore, the possibility of visualizing small GGNs using a fluorescence thoracoscope has been demonstrated (12), showing that this procedure could be utilized in RATS, using a new imaging feature with a 785 nm excitation wavelength instead of a conventional one (805 nm). The continuous efforts of Dr. Singhal's group give us hope that intraoperative molecular imaging techniques may potentially be standardized for minimally

invasive oncological surgeries.

Nevertheless, there is ample room for improvement in the present study. First, OTL38 has shorter excitation and emission wavelengths compared to ICG, which requires modifying the optical path and light source of the current imaging systems in clinical settings. This concern would be resolved as wavelength-tunable scopes are developed. Second, OTL38 is not always accurate when discriminating tumors from benign lesions, especially between GGN and pneumonia. Therefore, further studies are required to understand the specific types of GGOs that OTL38 can accurately identify. Third, this technology has well-documented limitations in its penetration depth; however, this was not observed in the currently reported study cohort, which primarily included pleural surface lesions. Fluorescence from the second NIR spectral window (NIR-II; wavelengths of 1,000–1,700 nm) might be one solution, allowing for deep tissue imaging at a high resolution, owing to reduced light scattering, minimal light absorption, and extremely low levels of autofluorescence (9).

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Footnote

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