Editorial

Intraoperative molecular imaging—a bright navigator for thoracic surgeons in the era of limited resection

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Lobectomy or greater pulmonary resection with complete mediastinal lymph nodes dissection is currently the standard surgical procedure for operable non-small cell lung cancer (NSCLC), regardless of tumor size or location (1). However, limited sublobar resection, either segmentectomy or partial resection, is sometimes considered for high-risk patients with small-sized NSCLC who are not suitable for standard resection because of compromised respiratory and/or cardiac function (2). In contrast to these "passive" limited resections, so-called "active" or intentional limited resections for patients with small-sized NSCLCs have also been proposed (3). The feasibility and outcomes of these limited resections have been evaluated by many retrospective studies (4-6). In addition, a nonrandomized confirmatory phase III study (JCOG0804/WJOG4507L) (7) proved that limited resection (mainly partial resection) offered sufficient local control of lung adenocarcinomas with radiologically-predicted noninvasive tumors, i.e., consolidation/tumor ratio of 0.25 or less and tumor size of 2.0 cm or less (8). For other types of small-sized NSCLCs, prospective trials (the JCOG0802/WJOG4607L and JCOG1211 trials) are currently being conducted to evaluate the feasibility of segmentectomy, and the results will be available in the near future.

Thoracic surgeons face two main challenges when performing limited resections, partially due to the widespread use of video-assisted thoracoscopic surgery (VATS) and robot-assisted thoracic surgery (RATS). One issue is the detection or identification of tumor(s), and the other is establishing an adequate distance from the surgical margin to the tumor, which can be greater than the size of the tumor itself (9). Thoracic surgeons usually try to solve these two issues intraoperatively via visual inspection of the pulmonary surface and manual palpation.

The identification of the tumor(s) is sometimes difficult when the tumor(s) mainly consist of ground-glass opacity (GGO). Such tumors are challenging to detect, because they often lack parenchymal abnormalities and tactile irregularities. In the aforementioned clinical trial (JCOG0804/WJOG4507L) (7), partial resection was planned for such GGO tumors in 330 patients; however, 10 of these patients (3%) received segmentectomy, rather than partial resection, solely because the thoracic surgeons could not find the tumors.

The acquisition of adequate surgical margins can become an issue during any limited resection. The edges of a tumor are usually judged by manual palpation; however, the GGO part of tumors is often not palpable. Furthermore, the judgement of adequate surgical margins is complicated by the potential microscopic spread of cancer cells from the edge of tumors, including the spread through air spaces (STAS) (10). In addition to macroscopically checking the distance between the surgical margin and the edge of the tumor, thoracic surgeons often use intraoperative pathological examinations to confirm the negativity of the surgical margins. However, during the surgery, it is virtually impossible to detect the microscopic spread of tumor cells, and to determine the GGO part of the tumor; therefore, final permanent pathological examinations occasionally conclude a closer surgical margin to the tumor than the

thoracic surgeons have intended.

Intraoperative molecular imaging is one possible solution to these two issues. Several kinds of molecules have been used to detect tumors intraoperatively. Indocyanine green (ICG) is one of the most widely used agents to detect many kinds of malignancies, including NSCLCs, together with near-infrared (NIR) fluorescence imaging (11,12). Although ICG is not a tumor-specific fluorescence dye, it accumulates in certain types of tumors because of the enhanced permeability and retention effect (13). Intraoperative molecular imaging using ICG is reportedly able to detect small tumors in the lung (12,14); however, hyperplastic or inflammatory nodules may cause false-positive results (12) and ICG cannot distinguish between the tumor itself and the inflamed tissue around the tumor (11). Another potentially useful agent is the folate receptor (FR) targeted NIR tracer (OTL0038) that targets the FR-alpha that is expressed in 90% of pulmonary adenocarcinomas and 70% of squamous cell carcinomas (15,16). OTL0038 has successfully been used by Predina and his colleagues for the intraoperative imaging of several thoracic malignancies, including pulmonary adenocarcinomas (15,16), squamous cell carcinomas (16,17), metastatic lung tumors of osteosarcomas (18), and mesotheliomas (19). However, as intraoperative molecular imaging may be especially useful during limited pulmonary resections, the data of intraoperative molecular imaging for small-sized tumors with/without GGO is clinically important.

Predina and his colleagues have very recently published the data of intraoperative molecular imaging using OTL0038 for pulmonary small nodules with GGO in the *Journal of Thoracic Oncology* (20). This study recruited 20 patients with 21 pulmonary tumors, comprising nine pure GGOs and 12 GGOs with a solid component, which were suspicious for lung neoplasms. The median tumor size was only 1.3 cm. The participants received 0.025 mg/kg of OTL0038 intravenously 3 to 6 hours prior to the pulmonary resection. Intraoperatively, surgeons first used thoracoscopic visualization and finger palpation to identify known lesions. Next, molecular imaging was applied to confirm lesion fluorescence or to detect lesions that were unidentifiable using the traditional methods. All lesions were wedge resected and imaged *ex vivo* prior to being submitted for pathological examination to compare the molecular imaging margins and the pathological margins with permanent histopathological analysis. Additional pulmonary parenchyma was resected if the molecular imaging identified close margins.

In this trial, there were no drug-related adverse events observed perioperatively or within 30 days postoperatively (20). Sixteen of 21 tumors with GGO displayed lesion-specific fluorescence during NIR imaging, and the depth from the pleural surface was the sole determinant for the successful detection of lesions by intraoperative molecular imaging. However, 20 of 21 lesions displayed signal upon back-table NIR evaluation; the single exception was an adenocarcinoma lesion that lacked FR-alpha expression by immunohistochemistry, causing the negative result of the molecular imaging on the back-table. The margins assessed by *ex vivo* molecular imaging and those evaluated by final permanent histology were surprisingly similar, with a median difference in margin length of within 1 mm. Based on the margin evaluation by molecular imaging, three patients received immediate re-resection. All tumors were confirmed to be adenocarcinomas, either invasive adenocarcinoma, minimally invasive mucinous adenocarcinoma (one case), or adenocarcinoma in situ (AIS).

Although these results are encouraging, further evaluation using larger cohorts is necessary before we apply this technique in clinical practice. There are also several clinical questions that need to be addressed. The first question is whether this technique can be applied in patients with "dirty" lungs, such as those with severe pulmonary emphysema, anthracosis, or inflammatory adhesions around the lung. Another question is whether this molecular imaging can detect GGO lesions other than lung adenocarcinomas, as many types of diseases may present with GGO on computed tomography (CT) imaging, including infection, collagen vascular disease, drug toxicity, fibrosis, and pulmonary metastasis from malignant melanoma (although this is rare) (21). In addition, further challenging is essential to improve this technique so that it can detect deeper lesions from the parenchyma surface *in vivo*, although intraoperative molecular imaging using ICG has the same issue (12)

The widespread use of CT examination, especially in developed countries, enables the early detection of small-sized lung cancers, including AIS. As not all lesions detected in the lung by CT imaging are malignant, several biomarkers that may be able to distinguish lung cancers from benign diseases have been suggested (22). Furthermore, not all adenocarcinoma or atypical adenomatous hyperplasia progresses clinically, and there might be clinical or molecular biomarker(s) that will predict tumor progression (23). The development of surgical instruments for VATS and RATS means that

pulmonary resections are becoming safer and less invasive. Furthermore, completed and ongoing large prospective trials will provide the rationale to perform limited pulmonary resection for some small-sized NSCLCs in the near future. I believe that the intraoperative molecular imaging highlighted in this editorial will help thoracic surgeons to perform successful limited resections with adequate surgical margins. I expect that all these efforts will change lung cancer from the leading cause of cancer-related mortality in the world into a curable disease.

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Footnote

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