Peer Review File

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Reviewer A

It is very innovative in your way to do lung cancer surgery. However, I am not certain for the clinical use. First, it is still very large for intrathoracic usage.

Reply: Thank you for your insightful comment. Yes, our prototype device has a relatively large diameter (46 mm) for elliptical-shaped VATS incision in narrow intercostal space. For intercostal approach, the port incision for trocar usually has a 10-15 mm diameter for camera and instruments, and 30-60 mm length for utility incision. There are limitations for current VATS technique performed through narrow intercostal space with our device. To address this issue, X-ray source using a 7 mm diameter carbon nanotube is under development for our research to reduce the diameter to less than 20 mm in the final product (Page 15 Line 7-9). For intrathoracic usage, the maximal diameter for intercostal approach might be extended to 28 to 33 mm as per studies on thoracoscopic esophagogastric intrathoracic anastomosis. We added the above comment in the Discussion section. (Page 15 Line 11-13).

Second, it can not detect small GGO lesion without additional dye or coil. Small GGO is the product of low dose CT screening and it is the majority of early lung cancer patients.

Reply: We agree with your comment. Our device showed limitation in detecting non-solid lesions without the use of a radiologic marker. As per your comment, the detection of GGO is challenging even in open surgery with finger palpation. However, our device is developed for minimally invasive surgery and we could acquire magnified radiologic images by directly making the device reach target area. However, we hope that our next-generation X-ray device with advanced CNT X-ray source (i.e., small but with high X-ray output) and high-resolution digital image sensor, which is under development, would potentially be beneficial in detecting the GGO lesions without using radiologic markers with the help of an artificial intelligence-based image analysis technology.

Third, if I have a C-arm, why use your device just because the radiation exposure is slightly less? Overall, the article quality is still good.

Reply: During surgery, surgeons face several issues when utilizing C-arm-based real-time localization. First, with respect to the resources, the C-arm device itself incurs high maintenance and operation costs; moreover, it further increases the overall economic burden on the patients. Second, regarding issues with radiation, although C-arm fluoroscopy is a powerful tool, repetitive use of the C-arm causes unnecessary radiation exposure to the medical staff and makes their movement uncomfortable, as they need to wear a lead vest to shield themselves from the X-rays. Finally, considering space constraints, the C-arm is too bulky and its accessories also take up significant space, hampering the movement of medical staff and other surgical instruments. Therefore, we propose a novel intraoperative X-ray imaging device that yields an exceptionally low radiation exposure.

Reviewer B

Authors demonstrated the new device of intraoperative X-ray imager.
I would like to make some comments on this manuscript.
Reply: Thank you for your review of our manuscript.

1. This device did detect peudo-tumor models or solid tumors in human specimen, but not non-solid tumors. However, accurate detection of non-solid tumors is what is currently needed in clinical practice, because solid tumors can be detected manually without the support of such device. In this respect, this method does not solve the clinical problem. Authors also mentioned that tumor margins can be detected by injecting a contrast agent, however, radiation exposure is required at the moment of preoperative injection of the agent, and the benefits of ultra-low-dose cannot be achieved.
Reply: We agree. Clinically, the most urgent factor is localization technology for non-solid tumors, and if this is possible without radiation, it would be the best method. Currently, localization technology using fluorescence techniques without radiation is used. However, even in this case, the fluorescent material is injected while CT is being performed, except in the case of injecting fluorescent material through a navigation bronchoscope. The localization technique using a fluorescent material also has disadvantages in that it is difficult to confirm the exact location owing to the spread of the fluorescent material, or it is difficult to identify a deep lesion. The CT localization technique cannot be skipped with this equipment. It is a device to reduce the radiation exposure of the C-arm during minimally invasive surgery, which is used to find localized lesions in the operating room, which may cause more radiation exposure than CT. With the development of sensors and AI image analysis, it is expected that a technology will be developed that can confirm non-solid tumors during minimally invasive surgery without radiation exposure, such as CT or C-arm, even with such a small device.

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2. They have used a number of devices, but did not provide detailed information about them. The following four points should be accurately stated for all products: the name of the product, the name of the company producing the product, and the name of the city and country where the company is located.
Reply: We have added detailed information on the devices as follows: (Page 11 Line 17-18, Page 12 Line 5-7)
