Efficacy of intraoperative CT feedback of wedge resected lung for the assessment of surgical margin

Protocol Version #2
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Research Objectives

Aim1: To assess how surgical outcomes are impacted by intraoperative CT feedback.
Aim2: To assess the validity of the additional resections.

Study Background

Lung cancer is the most prevalent cancer and the leading cause of cancer death in Canada. In 2020, lung cancer resulted in the deaths of 21,200 Canadians (1). The high mortality reflects both its high incidence and low survival. Although it is one of the most aggressive malignant tumors, as with many other types of cancer, patients can live cancer-free if the diagnosis is accurate and timely treatment is administered. Low-dose computed tomography (LDCT) scans can help find abnormal areas in the lungs that may be cancerous. Research has shown that scanning patients at higher risk of lung cancer using LDCT saved more lives compared to chest x-rays (2). In Canada, opportunistic screening is occurring in at least six provinces and implementation of organized programs is expected in the coming years (3). The increased prevalence of CT screening and advances in diagnostic technology, particularly the widespread use of thin-slice computed tomography, have enabled increased detection of early-stage small lung cancers (4). Early-stage lung cancer is often featured as a ground-glass opacity (GGO) associated with a pathological lepidic growth pattern that is considered to be related to a more favorable prognosis (5). Therefore, these GGO-dominant lung cancers could be optimal candidates for sublobar resections, which is to remove a section of a lobe of the lung that contains the lung cancer and a margin of healthy tissue around the cancer. This is an alternative to the conventional, more radical, pulmonary lobectomy (6, 7). Sublobar resection, including segmentectomy and wedge resection, is less invasive, sparing more healthy lung tissue and is associated with improved patient recovery. However, an increasing number of hazy lung tumors are also being detected, which are difficult to localize intra-operatively as they are

neither palpable, nor visible to the naked eye. To address the challenge of identifying small pulmonary nodules during surgery we have studied the accuracy of CT-guided insertion of microcoils prior to lung surgery (8). In addition, CT-guided microcoil localization was also associated with excellent recurrence-free survival for small lung tumors (9). The other challenge regarding sublobar resection is the possibility of locoregional cancer recurrence due to positive stump cytology and insufficient surgical margins which is defined as the amount of normal lung tissue excised around the tumor. These factors correlate with postoperative local recurrence but sometimes contradicted the results, in other words, positive stump cytology with negative surgical margin and vice versa (10). Therefore, keeping sufficient safety margins is important to ensure a complete resection. Currently, at least 15 mm distance or tumor size distance from the gross tumor is considered as a safe surgical margin in sublobar resections for prevention of local surgical recurrences in lung cancer (10, 11). Same can be said for metastatic lung tumors where margin length has been reported to be associated with the predicted probability of local recurrence (12, 13).

If the surgical margin is insufficient, additional resection or postoperative radiation therapy may be required which can cause patients additional stress. To date, there is no established method for confirming whether sufficient surgical margin was obtained during surgery, only as a pathological specimen post operation. To address this intraoperative limitation of margin assessment, we evaluated a radiological evaluation for sublobar resection specimen using CT during surgery. This method was demonstrated to be feasible for the assessment of the surgical margin as described below. However, the previous study did not include any feedback of the results intraoperatively, which did not contribute to decision-making and treatment strategy. The ability to accurately evaluate surgical margins intraoperatively could reduce the risk of locoregional recurrence and eliminate the need for additional treatment after surgery. Moreover, optimal intraoperative feedback to surgeon could influence surgical decision making and contribute to the satisfactory outcome.

Pre-clinical study

1) Protocol establishment for lung specimen preparation

Pre-clinical *ex-vivo* pig lung experiments assessed the feasibility of the image

acquisition and surgical margin measurement procedure by CT. A total 30 pig lung resected specimen were evaluated for the assessment. Resected lungs required re-inflation by injecting air to obtain the specimen CT image with sufficient quality for further analysis. After image acquisition, the lung specimen was instilled with 10% formalin neutral buffer solution using a 25-gauge needle and then soaked in the solution for at least 24 h. Microscopic histological specimen analysis was possible after standard tissue processing including fixation, gross assessment, and staining. We concluded that the additional steps can be easily integrated into the existing work flow without compromising specimen integrity since all imaged specimens were adequate for subsequent histopathologic analysis.

2) Evaluation of CT margin measurement

In order to simulate the surgical margin measurement by CT after sublobar lung resection, a pseudo lung nodule was created by injecting agar gel into the pig lung specimen. We confirmed that it was possible to measure the distance between the edge of pseudo tumor and cut surface. This CT based margin assessment measurement was then compared to the measurement carried out by pathology, which is the gold standard for assessing margin length. In all evaluated lungs (n=30), surgical margin measured by CT was 3.50 mm +/- 2.69 mm greater than that measured by pathology. This discrepancy was possibly attributable to tissue shrinkage by formalin fixation during standard pathology process (14). Based on the result of this preclinical study, clinicians should keep in mind that margin length shortening would be expected by tissue processing.

Clinical study

1) Protocol

The Previous clinical study was conducted to assess the feasibility of CT margin measurement (REB #22-5528). From October 2022 to March 2023, patients treated with sublobar resection (Segmentectomy or wedge resection) for clinical lung malignancies were introduced to the study by their treating surgeon. Of those, the patients who provided consent to the study after explanation by research coordinator were enrolled. Patients data including age, gender, CT findings (tumor diameter, location, distance between pleura to tumor), surgical data (surgical procedure, preoperative marking, operative time, blood loss), pathological diagnosis, margin data (CT margin, pathological margin) were collected.

CT margin was calculated as follows: i) resected lung specimen was inflated with 25-gauge needle and an appropriately syringe, while monitoring to prevent alveolar wall destruction using a pressure transducer. ii) The specimen was placed on a CT scanner with adjustment of staple line perpendicular to CT axial line and scanned CT in Spatio-temporal targeting and amplification of radiation response (STTAAR) innovation center. iii) CT margin was defined as the distance between tumor and tumor side of the staple line, and measured. After the assessment, the specimen was delivered to the surgical pathology department, and standard pathological examination was performed.

2) Results

54 patients were enrolled. In this study. In 4 patients (7.4%), poorly inflated specimen caused the tumor to be undetectable, which we subsequently excluded. Consequently, 92.6% of cases, 50 patients (52 specimens) were analyzed. Surgical margin measured by CT was significantly longer than pathological margin (11.74 ± 8.52 VS 10.08 ± 7.22, p = 0.033). 21% surgical margin length reduction was observed from CT to pathological assessment. Medial correlation was found between CT assessed margin and pathological margin (r = 0.7679). Margin assessment for resected lung is feasible and accessible way to identify tumor and surgical margin during surgery. Surgeons should be aware that CT assessed surgical margin will be longer than pathological margin.

Sample size

We aim to evaluate 80 cases over 2 years. We would like to include all 9 thoracic surgeons in our division to evaluate the impact to the surgical outcome “surgical margin” over the course of the study. As this is unlikely as not all surgeons will perform wedge resections, we will enroll consecutive patients regardless of who the attending surgeon is.

Patient Groups

Inclusion criteria:

・Patients scheduled for lung wedge resection for primary lung cancer or metastatic lung tumor (included suspected lesions).

・18 years of age or older.

Exclusion criteria:

・Any patients with inability to give informed consent

・Wedge resection for non-therapeutic purpose, e.g. diagnostic purpose.

Study Plan and Methods

This is a single center clinical trial. We will ask thoracic surgeons in our institution to work together for this research. A total of 80 patients scheduled for wedge resections for lung malignancies (including suspected patients) will be enrolled in this study. The attending surgeon will introduce the study to the patients and a research coordinator will then go through the consenting process, answer any questions and enroll the patient if they wish to participate within one month before surgery.

We will enroll 80 patients in 2 years for this study. Prior to first surgery, every surgeon will be asked to complete a questionnaire 1 to investigate the background of surgeon. At each surgery, we ask for questionnaire 2 orally before and after resection to assess the contribution of feedback to margin results. Once the wedge resection is performed, the resected specimen will be brought to 7th floor in STTARR innovation center in Princess Margaret Cancer Research Tower (PMCRT). Resected lung specimen will be inflated with 25-gauge needle and appropriately sized syringe. The air injection pressure as well as the total inflation pressure will be continuously monitored to prevent alveolar wall destruction using a pressure transducer. For the precise surgical margin measurement, the staple line is adjusted perpendicular to CT axial line. Surgical margin will be measured and its image will be captured. Surgical margin is defined as the distance from tumor to the tumor side of staple line (not including the width of staple line). The data (included CT image and CT surgical margin) will be numbered and exclude individual information (only include study number and date). The data will be transferred from CT scan to our laptop using universal serial bus (USB), then shared with surgeons by tablet in operating room through online storage service

such as OneDrive or directly with laptop or USB. These processes are expected to take about up to 20 minutes. Surgeons will wait and refer to these results, and make a decision if additional resection should be made. The lung specimen will be delivered to the pathological laboratory and routine pathologic work up will be proceeded per standard care, including fixation, gross assessment, and selection of clinically relevant tissue blocks for sectioning, staining, and microscopic assessment. Within several days after surgery, we will send the CT measured margin length and reconstructed 3D image of the resected specimen to the attending surgeon, and ask them to complete the rest of questionnaire 2. This is to evaluate the usefulness of the CT image feedback and the surgeon's satisfaction for each case.

Additionally, once the pathological result for each patient is revealed, surgeons will receive the results of the margin length comparison (CT based margin and pathological margin). After the total course of surgery, we will ask each surgeon individually for questionnaire 3 after feedback of the individual result of this study to assess the satisfaction by intraoperative feedback.

Benefits

Intraoperative feedback of surgical margin measured by CT correlates to pathological margin length, and could help make a decision for additional resection. Patients with a confirmed sufficient margin could have better local cancer control.

Risks

Additional resection could induce complication such as air leakage.

Extra time commitment for patients

The entire intraoperative feedback process takes about up to 20 minutes, further increasing the operation time.

Outcome Measures

The primary outcome of the study will include (1) the contribution of intraoperative feedback to treatment decision, and its validity, and (2) assessing how intraoperative feedback affects surgical margins over the course. The secondary outcome will be the assessment of surgeons' satisfaction with intraoperative

feedback.

Statistics

A linear mixed model will be performed to analyze the difference of the process between expected and actual margin over the course. Pearson's correlation analysis will be performed to analyze the correlation between the parameters measured on CT and on pathological analysis. Limits of agreement analysis will be performed per the Bland-Altman method to evaluate agreement between preoperative expectation for surgical margin and actual margin. ROC curves will be used to assess the CT margin to predict short pathological margin. GraphPad Prism8 (GraphPad Software, La Jolla, CA, USA) and R (for linear mixed model) will be used for statistical analysis. All p-values will be based on a two-sided hypothesis, with p-values < 0.05 indicating statistical significance.

Data Collection and Monitoring

The following data will be collected prospectively using source documents and a database specially constructed for the purpose. Data will be collected prospectively on all patients. Due to the low risk and influence for the patients involved in this study, a DSMB is not required.

(1) Patients' background (age, gender, body weight, body mass index, history, smoking habit, preoperative diagnosis)

(2) Preoperative CT information (tumor location, tumor size, CT appearance, Consolidation tumor ratio, distance between tumor and pleura)

(3) Surgical information (surgery date, attending surgeon's study number, operative procedure, operative duration, preoperative marking, intraoperative CT image acquisition time, tumor size in intraoperative CT, margin length in intraoperative CT, additional resection, procedure change, intraoperative findings)

(4) Pathological results (pathological diagnosis, tumor size, tumor spread through air space, pathological margin length)

(5) Others (postoperative complication, length of stay)

(6) Questionnaire results including surgeons' study number (see questionnaire section)

Access to Source Data/Documents

Access to the study data will be permitted for study investigators, coordinators,

and UHN REB.

Consent

All patients will receive both verbal and written information about the study and will be asked to give informed consent using study-specific consent forms. Nine thoracic surgeons in the division of thoracic surgery in Toronto General Hospital has received the explanation of this study and accepted to participate in this study in the previous conference. We will ask them to provide written consent for this study prior to the study.

Data Handling and Record Keeping

All data will be de-identified. Each subject will be given a study number with data stored securely in a locked cabinet. As described in the consent form, we will maintain a list for each patient, study number for the specimen, corresponding CT scan identification and questionnaire. This list will be kept by the study investigator in a secure place, separate from the study file for up to 10 years. We will follow storage, transport and destruction of confidential information policy.

References

1. Brenner DR, Weir HK, Demers AA, Ellison LF, Louzado C, Shaw A, et al. Projected estimates of cancer in Canada in 2020. Cmaj. 2020;192(9):E199-e205.
2. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.
3. [Internet] CPAC. Lung cancer screening in Canada environmental scan 2019-2020. at: https://s22457pcdnco/wp-content/uploads/2021/01/lung-cancer-screening-environmental-scan-2019-2020-Jan132021-ENpdf.
4. Aberle DR, Berg CD, Black WC, Church TR, Fagerstrom RM, Galen B, et al. The National Lung Screening Trial: overview and study design. Radiology. 2011;258(1):243-53.
5. Park CM, Goo JM, Lee HJ, Lee CH, Chun EJ, Im JG. Nodular ground-glass opacity at thin-section CT: histologic correlation and evaluation of change at follow-up. Radiographics. 2007;27(2):391-408.
6. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group.

Ann Thorac Surg. 1995;60(3):615-22.
7. Whitson BA, Groth SS, Andrade RS, Maddaus MA, Habermann EB, D'Cunha J. Survival after lobectomy versus segmentectomy for stage I non-small cell lung cancer: a population-based analysis. Ann Thorac Surg. 2011;92(6):1943-50.
8. Donahoe LL, Nguyen ET, Chung TB, Kha LC, Cypel M, Darling GE, et al. CT-guided microcoil VATS resection of lung nodules: a single-centre experience and review of the literature. J Thorac Dis. 2016;8(8):1986-94.
9. Rodrigues JCL, Pierre AF, Hanneman K, Cabanero M, Kavanagh J, Waddell TK, et al. CT-guided Microcoil Pulmonary Nodule Localization prior to Video-assisted Thoracoscopic Surgery: Diagnostic Utility and Recurrence-Free Survival. Radiology. 2019;291(1):214-22.
10. Sawabata N, Ohta M, Matsumura A, Nakagawa K, Hirano H, Maeda H, et al. Optimal distance of malignant negative margin in excision of nonsmall cell lung cancer: a multicenter prospective study. Ann Thorac Surg. 2004;77(2):415-20.
11. Mohiuddin K, Haneuse S, Sofer T, Gill R, Jaklitsch MT, Colson YL, et al. Relationship between margin distance and local recurrence among patients undergoing wedge resection for small (≤2 cm) non-small cell lung cancer. J Thorac Cardiovasc Surg. 2014;147(4):1169-75.
12. Nelson DB, Tayob N, Mitchell KG, Correa AM, Hofstetter WL, Sepesi B, et al. Surgical margins and risk of local recurrence after wedge resection of colorectal pulmonary metastases. J Thorac Cardiovasc Surg. 2019;157(4):1648-55.
13. Özdil A, Tekneci AK, Dökümcü Z, Divarcı E, Keçeci B, Sezak M, et al. Pulmonary Metastasectomy of Sarcoma: Is the Ratio of Surgical Margin to Nodule Size a Prognostic Factor? Thoracic Cardiovasc Surg. 2019;67(8):675-82.
14. Park HS, Lee S, Haam S, Lee GD. Effect of formalin fixation and tumour size in small-sized non-small-cell lung cancer: a prospective, single-centre study. Histopathology. 2017;71(3):437-45.