Original Article

Radiomic score is prognostic in clinical stage I lung adenocarcinoma ≤2 cm undergoing surgery

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Background: As sub-lobar resection becomes acceptable for lung cancer ≤2 cm, a preoperative marker of tumor aggressiveness to choose an appropriate extent of resection becomes necessary. We sought to assess the utility of Computer-Aided Nodule Assessment and Risk Yield (CANARY), a validated radiomic tool, in clinical stage I adenocarcinoma ≤2 cm.

Methods: We performed a retrospective review of resected lung cancer patients from 2016–2022. Our eligibility criteria included clinical stage I adenocarcinoma, availability of pre-operative computed tomography (CT) imaging, and a lesion size of ≤2 cm. Preoperative imaging was input into the CANARY program, and this was then used to categorize each lesion into good, intermediate, and poor. Kaplan-Meier curve was used to compare the recurrence-free survival (RFS). Descriptive statistics and log-rank tests were conducted to compare RFS between risk groups.

Results: Study population (n=134) had a median age of 68.6 and follow up of 2.9 years. By CANARY profile, 29 patients (21.6%) were good risk, 52 (38.8%) intermediate, and 53 (39.6%) poor. By procedure, 52 patients (38.8%) received wedge resections. Overall, the 3-year RFS was 96.3%, 92.0%, and 72.7% for patients with good, intermediate, and poor risks, respectively. There was a statistically significant difference in RFS between each risk group (χ^2=12.6, P=0.002). Patients with poor risk were associated with a significantly increased risk of recurrence relative to those with good/intermediate risks [hazard ratio (HR) =5.7, 95% confidence interval (CI): 1.9–17.5].

Conclusions: Poor risk on CANARY analysis is significantly associated with increased risk of recurrence after resection in clinical stage I adenocarcinoma lesions ≤2 cm.

Keywords: Lung cancer; radiomics; sub-lobar resections

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Introduction

The National Lung Screening Trial (NLST) demonstrated that lung cancer screening with low-dose computed tomography (CT) resulted in 20% risk reduction in lung cancer mortality (1). As lung cancer screening with low-dose CT becomes more prevalent, the incidence of early-stage lung cancer is expected to increase. For stage I non-small cell lung cancer (NSCLC), lobectomy has been the standard of care since 1995 (2). Recently, the surgical management of early-stage NSCLC has seen dramatic changes. Landmark trials in Japan (JCOG 0802) and in

North America (CALGB 140503) showed that in stage IA NSCLC patients with tumors ≤2 cm, sublobar resection (wedge or segmentectomy) is not inferior to lobectomy (3,4). Based on these study results, sublobar resection may become the new standard of care for this specific population that may be on the rise with screening. Currently, staging is based on anatomic factors alone (5). As sublobar resection becomes more widely accepted for stage IA patients, it becomes more important to determine the true tumor aggressiveness to decide the best extent of resection for each patient. An important goal in this clinical setting is to determine the tumor aggressiveness preoperatively, especially since some ≤2 cm tumors may have an aggressive behavior.

One potentially useful preoperative tool can come in the form of radiomics since almost everyone undergoing resection will have CT scans. Computed Tomography-Based Score Indicative of Lung Cancer Aggression (SILA) is a validated score to predict recurrence in surgically resected lung adenocarcinoma (LUAD) using Computer-Aided Nodule Assessment and Risk Yield (CANARY), a computer-based analytic measure (6-8). CANARY receives input from CT scans, utilizing an unsupervised clustering algorithm and nine radiographically distinct clusters to generate a corresponding outcome-predictive score (6). Prognostic value of SILA has not been tested in the setting of stage IA ≤2 cm LUAD patients. In the current study, we sought to determine the prognostic value of SILA in this specific population. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-923/rc).

Highlight box

Key findings

- Radiomic score is associated with risk of recurrence in patients undergoing resection for clinical stage I adenocarcinoma lesions ≤2 cm.

What is known and what is new?

- Clinical stage is associated with prognosis in lung cancer.
- Radiomic score provides a potential pre-operative prognostic tool in clinical stage I adenocarcinoma lesions ≤2 cm.

What is the implication, and what should change now?

- Radiomic score provides a pre-operative tool to assess tumor biology, which can potentially be utilized to guide in clinical decision making.

Methods

Institutional data source & study population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by our Institutional Review Board (Inova Health System Institutional Review Board, No. U23-06-5093), and it was deemed that patient consent for this retrospective analysis was not needed. This was a retrospective review of a prospectively maintained database that our institution has been maintaining since August, 2016 as part of our contribution to the Society of Thoracic Surgeons (STS) national database. We initially queried for all lung resections performed for cancer from August, 2016 to April, 2022 (n=572). From this database, we reviewed the data per our inclusion criteria for the current study, which included clinical stage I LUAD, availability of pre-operative CT imaging, and a lesion size of ≤2 cm on pre-operative CT. Of the 572 patients with resected, stage I lung cancer, 294 patients were excluded for non-adenocarcinoma lesions and unavailable imaging. Fifty-two patients did not meet criteria due to clinical upstaging, and 92 patients had lesions over the size criteria cut off. The final number of patients analyzed was 134 (*Figure 1*).

Data collection

A retrospective chart review was conducted for the study population. For each patient, demographic information including age, gender, race, and ethnicity (defined as Hispanic or non-Hispanic origin) was collected. Smoking status was obtained, and lung function was assessed using pre-procedural forced expiratory volume in 1 second (FEV1) and diffusion capacity of the lungs for carbon monoxide (DLCO). Surgical procedure, resected lobe, and laterality were collected as well as any postoperative complications. Tumor-related variables including clinical and pathologic stage, grade, morphology, size (pre-operative and pathologic), visceral pleural invasion (VPI), lymphovascular invasion (LVI), and maximum standardized uptake value (SUV) on positron emission topography (PET) scans were also collected. Morphology was further grouped into low/intermediate grade (lepidic, acinar, papillary) and high grade (solid, micropapillary, and cribriform) (9). SUV was classified as low or high using a cutoff of 2.5 as described in similar literature (10,11). Lastly, recurrence status and date of last follow up and/or death were collected. Staging was

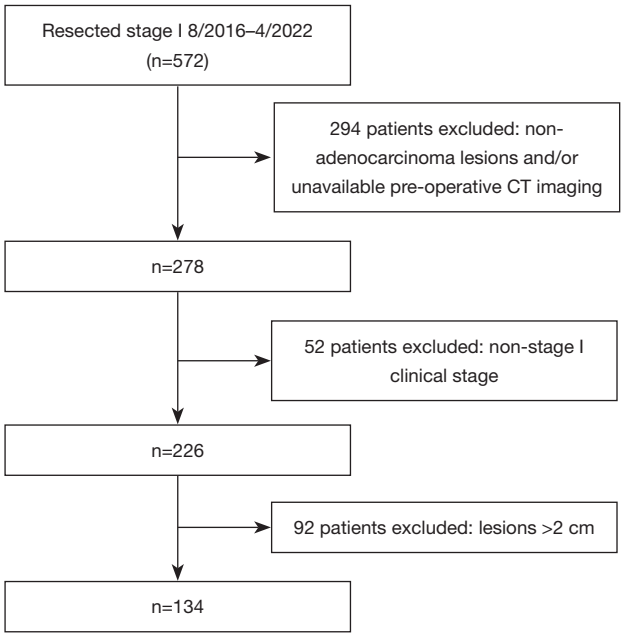

Figure 1 Flowchart diagram of study cohort determination. Of the 572 patients with resected, stage I lung cancer, 294 patients were excluded for non-adenocarcinoma lesions and unavailable imaging. Fifty-two patients did not meet criteria due to clinical upstaging, and 92 patients had lesions over the size criteria cut off. The final number of patients analyzed was 134.

performed per the 8th edition of the TNM classification (5).

Image analysis

Preoperative CT scans in lung window were downloaded in anonymized fashion using custom DICOM query tool for image analysis. For each CT scan, we annotated the lesion in cross-sectional slices and obtained a risk score per CANARY (*Figure 2*). Using their individual SILA, each lesion was categorized into good (SILA: 0–0.338), intermediate (SILA: 0.338–0.675), or poor (SILA: 0.675–1) risk categories (6).

Statistical analysis

Kaplan-Meier curve was used to compare the recurrence-free survival (RFS) among different categories. Descriptive statistics and log-rank tests were conducted to compare RFS between groups. Hazard ratios (HRs) and 95% confidence interval (CI) for poor risk *vs.* good/intermediate risk were obtained from univariate and multivariate Cox regression models adjusted for the patient's gender, race/ethnicity, smoking status, age at surgery, and sub-lobar procedure with P value statistically significant at α=0.05.

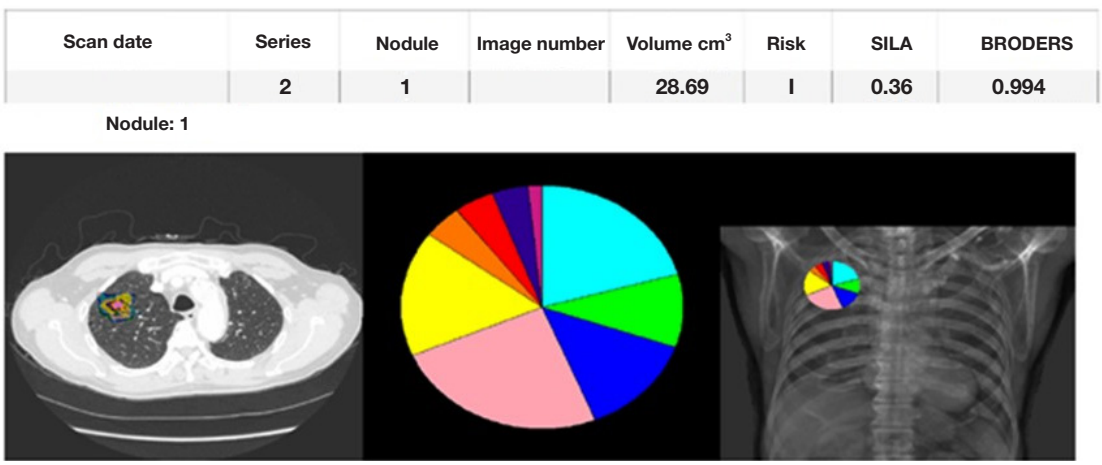

Figure 2 Example of CANARY analysis. Graphic example of nodule demarcation and CANARY analysis output. SILA, Computed Tomography-Based Score Indicative of Lung Cancer Aggression; CANARY, Computer-Aided Nodule Assessment and Risk Yield.

Table 1 Study cohort characteristics

Demographics	Number of patients (%)
Sex	
Female	91 (67.9)
Male	43 (32.1)
Race	
White	101 (75.4)
Black	8 (6.0)
Asian	14 (10.4)
Other	11 (8.2)
Ethnicity	
Non-Hispanic	121 (90.3)
Hispanic	11 (8.2)
Missing	2
Smoking status	
Never smoker	32 (23.9)
Past smoker	78 (58.2)
Current smoker	24 (17.9)
PET-CT performed	
No	22 (16.5)
Yes	111 (83.5)
Missing	1
Mediastinal staging performed	
No	93 (69.4)
Yes	41 (30.6)
Clinical stage	
IA1	18 (13.4)
IA2	116 (86.6)
Pathological stage	
IA1	10 (7.5)
IA2	65 (48.5)
IA3	18 (13.4)
IB	23 (17.2)
IIA	2 (1.5)
IIB	6 (4.5)
IIIA	8 (6.0)
IV	2 (1.5)
Procedure	
Wedge	52 (38.8)
Lobectomy	81 (60.4)
Bilobectomy	1 (0.7)
SILA scores	
Good	29 (21.6)
Intermediate	52 (38.8)
Poor	53 (39.6)
Recurrence	
No	114 (85.1)
Yes	20 (14.9)

PET-CT, positron emission tomography-computed tomography; SILA, Computed Tomography-Based Score Indicative of Lung Cancer Aggression.

Results

Patient and tumor characteristics

A total of 134 patients (mean age at surgery 68.6±9.0 years) were included in the study with a median follow-up of 2.9 years. Cohort characteristics and summary statistics are detailed in *Table 1*. The cohort consisted of 43 males (32.1%) and 91 females (67.9%). There were 24 (17.9%) current smokers, 78 (58.2%) former smokers, and 32 (23.9%) patients who had never smoked. By clinical stage, 18 patients (13.4%) were clinical stage IA1 and 116 patients (86.6%) were clinical stage IA2. By procedure, 81 patients (60.4%) received lobectomy, 1 (0.7%) bilobectomy, and 52 (38.8%) wedge resection. 111 (83.5%) patients received a pre-operative PET-CT scan with a mean SUV of 2.8±2.3.

Clinical outcome and image characteristics

Upon analysis of the CANARY profile, 29 patients (21.6%) had good risk, 52 (38.8%) had intermediate risk, and 53 (39.6%) had poor risk. Of the 52 patients who received a wedge resection, 13 (25.0%), 20 (38.5%), and 19 (36.5%) patients had good, intermediate, and poor SILA scores, respectively. Of the 81 patients who received a lobectomy, 16 (19.8%), 32 (39.5%), and 33 (40.7%) patients had good, intermediate, and poor SILA scores, respectively. The singular patient who received a bilobectomy was

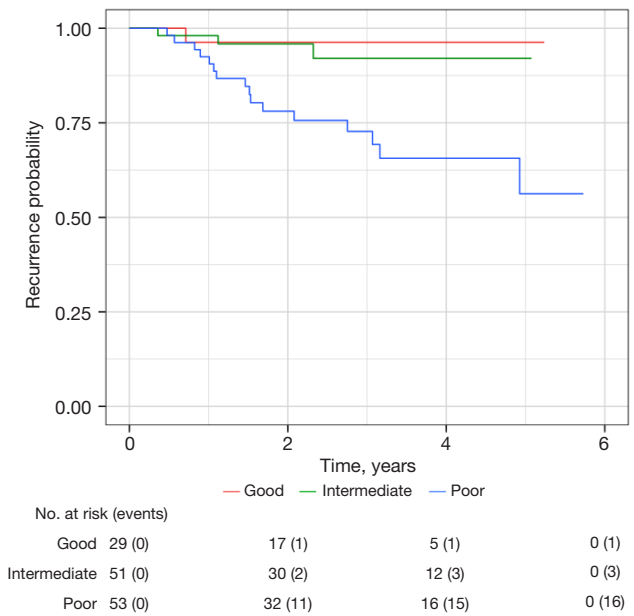

Figure 3 Kaplan-Meier survival curves based on CANARY risk profiles. Recurrence risk in the CANARY risk profile groups in stage I adenocarcinoma lesions <2 cm. Risk profile groups divided by SILA scores into good, intermediate, and poor categories. CANARY, Computer-Aided Nodule Assessment and Risk Yield; SILA, Computed Tomography-Based Score Indicative of Lung Cancer Aggression.

classified as having poor SILA scores. A total of 20 patients (14.9%) had recurrence, of whom 1 (0.7%) had good risk, 3 (2.2%) had intermediate risk, and 16 (11.9%) had poor risk. Overall, the 3-year RFS for the entire group was 84.6% (95% CI: 78.0–91.9%). By SILA, RFS was 96.3% (95% CI: 89.4–100.0%), 92.0% (95% CI: 83.3–100.0%), and 72.7% (95% CI: 60.9–86.9%) for patients with good, intermediate, and poor risks, respectively (χ^2=12.6, P=0.002) (*Figure 3*). Patients with poor risk were associated with a significantly increased risk of recurrence relative to those with good/intermediate risks (HR =5.8, 95% CI: 1.9–17.2). The relationship held true even after adjusting for potential preoperative confounders including age at surgery, gender, race/ethnicity, smoking status, and whether the patient received a sub-lobar resection (HR =5.7, 95% CI: 1.9–17.5).

SILA and other pathologic prognosticators

Upon pathological analysis, 65 patients (48.5%) demonstrated LVI, of which 8 (12.3%), 22 (33.8%), and 35 (53.8%) patients had good, intermediate, and poor SILA scores, respectively (P=0.002) (*Table 2*). Similarly, VPI was seen in 29 patients (22.0%) with 3 (10.3%), 11 (37.9%), and 15 (51.7%) patients having good, intermediate, and poor SILA scores (P=0.16). In terms of morphology, 63 (56.8%) patients fell into the low/intermediate grade (lepidic, acinar, papillary) while 48 (43.2%) patients had high grade (solid, micropapillary, cribriform). 20 (31.7%) of low/intermediate grade patients had good SILA compared to 2 (4.2%) in high grade while 18 (28.6%) of low/intermediate grade patients had poor SILA compared to 24 (50.0%) of high-grade patients (P=0.04). For the final pathologic staging, 10 (7.5%), 65 (48.5%), 18 (13.4%), 23 (17.2%), 2 (1.5%), 6 (4.5%), 8 (6.0%), and 2 (1.5%) patients were pathological stages IA1, IA2, IA3, IB, IIA, IIB, IIIA, and IV, respectively (*Table 1*). Relative to the clinical stages, 66 (49.3%) and 3 (2.2%) patients were up-staged and down-staged, respectively; the remaining 65 (48.5%) patients were not re-staged. We further re-grouped patients in stages I *vs.* II–IV, and there was no significant association between this grouping and SILA risk scores (χ^2=1.36, P=0.51) (*Table 2*). Overall, relative to those with good/intermediate SILA scores, patients with poor SILA scores were significantly associated with a 3-fold increase in risk of having LVI [odds ratio (OR) =3.3, 95% CI: 1.6–6.9] and 2-fold increase in risk of having high grade morphology (OR =2.5, 95% CI: 1.2–5.6).

Discussion

As treatment of NSCLC patients is evolving quickly, it is important that clinicians are personalizing the care for each patient by better understanding each tumor and risk-stratifying every patient. The treatment for surgically resectable NSCLC has undergone dramatic changes recently with landmark studies such as the Checkmate 816 study changing the landscape of lung cancer therapies (12). The same can be said for clinical stage IA patients with lesions ≤2 cm. With the recent results of JCOG 0802 and CALGB 140503 studies, the standard of care surgery may be shifting from lobectomy, which has been the gold standard operation for this population since 1995 (2-4). As we see the surgical landscape shifting, personalizing each tumor and patient becomes essential to appropriately tailor the extent of resection. It is plausible that some ≤2 cm lesions may have aggressive behavior and that sublobar resections may not be an appropriate oncologic resection for all tumors ≤2 cm. To this end, ability to predict tumor behavior preoperatively in

Table 2 Association between SILA scores and pathologic prognostic markers

Pathologic markers	SILA scores, n (%)			χ^2	P value
	Good	Intermediate	Poor		
Lymphovascular invasion				12.4	0.002
No	21 (30.4)	30 (43.5)	18 (27.5)		
Yes	8 (12.3)	22 (33.8)	35 (53.8)		
Visceral pleural invasion				3.73	0.16
No	26 (25.2)	40 (38.8)	37 (35.9)		
Yes	3 (10.3)	11 (37.9)	15 (51.7)		
Morphology				19.12	0.04
Acinar/lepidic/papillary	20 (31.7)	25 (39.7)	18 (28.6)		
Solid/micropapillary/cribriform	2 (4.2)	22 (45.8)	24 (50.0)		
Pathologic stage				1.36	0.51
I	27 (23.3)	44 (37.9)	45 (38.8)		
II–IV	2 (11.1)	8 (44.4)	8 (44.4)		

SILA, Computed Tomography-Based Score Indicative of Lung Cancer Aggression.

this specific population becomes important.

To date, there are no image-based tools routinely utilized to preoperatively risk-stratify stage I lesions and their aggressiveness. CANARY is a radiomic tool that can risk-stratify which LUAD patients may be at high risk of recurrence after curative-intent surgery (7,8). This program assesses imaging characteristics of nodules and classifies radiologically distinct features into color exemplars with an unsupervised clustering algorithm (6). The percentage of exemplars are aggregated into a total risk score with SILA. Since almost all NSCLC patients undergoing resection will have CT scans, CANARY represents a potentially very useful and simple tool that can be used preoperatively to identify tumors with aggressive or indolent behaviors. With the emerging treatment paradigms provided by the JCOG 0802 and CALGB 140503 studies, CANARY and associated SILA can serve as another data point in the decision process of how to appropriately treat patients with ≤2 cm stage I LUAD lesions.

Our results suggest that good SILA may represent the truly indolent groups for whom we would comfortably apply the findings of JCOG 0802 and CALGB 140503 by performing sublobar resections (3,4). In the original study describing the prognostic value of SILA, good, intermediate, and poor groups each had significantly different clinical outcomes. In our study, the good and intermediate groups had similarly good outcomes with 1 and 3 recurrences, respectively. In contrast, those with poor SILA score, despite only making up 39.6% of the study cohort, contributed 16 cases, or 80%, of all recurrences. Moreover, the likelihood of recurrence remains significantly elevated even after adjusting for potential demographic confounders and their resection modality (i.e., whether they received a lobectomy or a sub-lobar resection). Of note, as CANARY is a preoperative tool, we only controlled for preoperative factors. Taken together, our findings could indicate that in the setting of small tumors, prognostic difference between the good and intermediate SILA groups may not be significant and that poor SILA is the main poor prognostic factor. This is likely due to the fact that SILA was designed to predict the histopathologic invasion of lung cancer nodules with indolence noted in nodules with minimal tumor invasion of 6–10 mm on CT imaging (6). Hence, in early-stage cancer with small nodules, there may be a challenge in differentiating depth of tumor invasion leading to overlap in outcomes in the good and intermediate groups. In addition, even though our findings suggest that extent of surgery did not statistically influence the outcome, considering the elevated risk for patients with poor SILA in the setting of ≤2 cm stage I LUAD, a more aggressive surgical approach at the onset might still be more prudent. The extent of the resection should remain the outcome of a joint decision-making process between the patient, their preferences, and the physician's clinical judgments. The

presentation of these cases to a multidisciplinary discussion tumor board will in all likelihood be beneficial for these patients as well.

Our findings also suggest that there is an association between SILA scores and known pathologic prognostic factors. In the original paper by Varghese *et al.*, an association was shown between SILA and histopathologic aggressiveness, in which tumors were categorized as indolent [adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA)] and invasive (6). We did not have any AIS nor MIA tumors in the current study. We did, however, show that SILA is associated with other known histopathologic prognosticators, including LVI, VPI, and morphology, corroborating the findings that SILA shows an association with histopathologic features. This is an important point as SILA provides a potential preoperative tool that can predict aggressive tumors.

In addition to the population in this current study, CANARY may have other utilizations. Ability to predict tumor aggressiveness preoperatively may tailor our preoperative work-up and plan more appropriately. For example, there may be a subgroup of clinical stage I patients who currently would not undergo mediastinal staging but could be at high risk of occult lymph node metastasis. If we are able to identify this subgroup preoperatively, we may consider performing mediastinal staging in this population, the results of which could alter the treatment plan thereafter significantly. Furthermore, for non-surgical candidates electing for radiotherapy such as stereotactic body radiation therapy (SBRT), their SILA scores can potentially provide additional information on risk of recurrence and hence in determining subsequent surveillance.

It is important to note that CANARY is only a component of the increased use of radiomics tool in treatment of LUAD. Multiple research groups have developed their own technology and methodology of analyzing radiographic characteristics to prognosticate pre-operative lesions. In one such efforts, Zhang and colleagues developed a predictive model based on 97 early-stage I LUAD patients based on radiomics features gathered from the Analysis Kit (AK) software (13). Using the same AK platform and roughly similar statistical analysis models, Nie and colleagues also examined radiomics features in a sample of 474 stage I LUAD patients (14). Both studies corroborate our findings that radiographic factors of pre-operative lesions on CT imaging can reliably predict disease-free and overall survival even with the use of a distinct image-analysis program. While this field of study is admittedly still in its early stages, these are positive findings that show the promises of radiomics in the treatment of lung cancer patients.

Limitations of our study include the retrospective nature, single-center design and sample size. Our sample size prevents a more comprehensive analysis, and potential confounding factors such as clinical comorbidities (e.g., pulmonary and cardiac) and extent of resection could not be considered. In addition, not every lesion in the current study fits the exact study inclusion criteria of JCOG 0802 and CALGB 140503 in that they may not be peripheral lesions amenable to wedge or segmentectomy. Furthermore, both studies included all NSCLC lesions, while our analysis is restricted to only LUAD.

Conclusions

Poor risk on CANARY analysis is significantly associated with increased risk of recurrence after resection in clinical stage I LUAD lesions ≤2 cm. Future efforts will focus on assessing CANARY in determining risk of recurrence in sub-lobar resection *vs.* lobectomy in this population.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-923/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-923/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-923/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-923/coif). S.K. has

consulting roles with Medtronic, AstraZeneca, Bristol Myers Squibb, and Roche, none of which are pertinent for the current manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by our Institutional Review Board (Inova Health System Institutional Review Board, No. U23-06-5093), and it was deemed that patient consent for this retrospective study was not needed.

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