ORIGINAL ARTICLE

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Long-Term Survival and CANARY-Based Artificial Intelligence for Multifocal Lung Adenocarcinoma

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Abstract

Objective: To investigate whether an artificial intelligence (AI)–based model can predict tumor invasiveness in patients with multifocal lung adenocarcinoma (MFLA).

Patients and Methods: Patients with MFLA who underwent surgical resection were enrolled to a prospective registry trial (NCT01946100). Each identified nodule underwent retrospective computer-aided nodule assessment and risk yield (CANARY)–based AI to determine a quantitative degree of invasiveness. Data regarding age, sex, medical and surgical management, and survival were collected and analyzed. Pathologic review was performed by a pulmonary pathologist with comprehensive histologic subtyping.

Results: From January 1, 2013, through December 31, 2018, 68 patients with MFLA underwent at least 1 surgical resection. Five-year survival for the cohort was 91%, and 10-year survival was 73.6%. No significant differences in survival were observed when separated by sex, number, or size of the nodules. A 10-year survival trend was seen when comparing patients with unilateral (100% survival) vs bilateral disease (66%). Retrospective CANARY-based AI analysis demonstrated that the majority of the nodules present at the time of diagnosis (229/302; 75.8%) were classified good, with an average score of 0.19, suggesting indolent clinical behavior and noninvasive pathology. However, AI-CANARY scores of the surgically removed nodules were significantly higher compared with those of the nonresected nodules (P=.001).

Conclusion: The long-term survival for patients with N0, M0 MFLA who have undergone surgical resection may approach those of stage I non–small cell lung cancer. CANARY-based AI has the potential to stratify individual nodules to help guide surgical intervention versus observation of nodules.

Trial Registration: clinicaltrials.gov Identifier: NCT01946100

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Patients with suspected multiple primary lung cancers present numerous diagnostic and therapeutic clinical challenges. Multifocal lung cancer almost exclusively represents tumors on the adenocarcinoma spectrum. Therefore, it is frequently extremely difficult to accurately differentiate whether multiple pulmonary nodules are intrapulmonary metastases or multiple primary lung cancers to appropriately stage and manage patients and provide them with prognostic information about their prognosis.[1–3] Besides accurate staging, the treatment of multifocal lung cancer is challenging partly because of the paucity of high-quality data to guide the care of these patients. This stems from numerous factors, such as changing definitions of multiple primary lung cancers over time, variable inclusion criteria for patients in studies, and a high level of discordance for staging multiple tumors among clinicians and pathologists.[4–8]

The true incidence of multifocal lung cancer is not clear, and the reported incidence over time is influenced by advances in pathologic classification and genomic testing, improved availability and quality of radiologic examinations, advances in diagnostic procedures, implementation of lung cancer screening programs, and changes in smoking habits. This gap in knowledge is reflected by the wide-ranging reported incidence of multiple primary lung cancer in the literature from <1% to over 10%.[9,10]

Historical definitions for multiple primary lung cancer, dividing them into synchronous and metachronous lesions,[5] leave unaddressed the dilemma of how to manage multiple concurrent (synchronous) tumors. Accurate independent primary versus metastatic classification would theoretically distinguish prognostic subgroups; however, the data around this is weak at best and leave many questions about how to treat an individual patient in real-world practice. Clinically, patients are usually assumed to have independent primary lesions if there is no evidence of local nodal or distant metastases. Further complicating the situation is the lack of knowledge about specific outcomes for treated patients with independent vs metastatic lesions and whether it matters for guiding therapy. The current gold standard for pathologic classification of multiple independent primaries vs metastatic pulmonary adenocarcinoma is comprehensive histologic subtyping of each lesion, with morphologic comparison.[7] However, this system is far from perfect because it is prone to interobserver disagreements and can only realistically be performed on surgically resected tumors. Various genomic studies can differentiate multifocal lung adenocarcinoma (MFLA) from metastatic disease.[11–15] Reports indicate that the concordance of multiple molecular markers, such as PD-L1 expression, is higher in pulmonary metastases compared with MFLA.[16,17]

Currently, treatment for MFLA is not standardized, and individualized decisions for patients are typically guided by multidisciplinary reviews.[18–21] Previous studies evaluating the efficacy of surgery for such patients have heterogeneous results. Single-center retrospective studies include differences in tumor types (both synchronous vs metachronous and ground-glass opacities (GGOs)/lepidic tumors vs solid tumors), differences in surgical techniques, and frequently do not represent modern advances in molecular testing, imaging, and treatment approaches.[9,15,21–38] For those who are not surgical candidates, stereotactic body radiotherapy (SBRT) may be an effective option.[39–42]

However, many patients with MFLA present with tumors with significant noninvasive (lepidic) growth, such as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and lepidic-predominant adenocarcinoma.[43] These lesions typically have a significant ground-glass component (GGO) on computed tomography (CT) imaging (corresponding to areas of lepidic growth), with favorable tumor biology, leading to slow growth and absent to low metastatic potential.[43–45] In such cases, determining which lesions to resect, observe, and/or treat with alternative modalities is unclear. Computer-aided nodule assessment and risk yield (CANARY) is a novel radiomics/artificial intelligence (AI) tool that has been trained and validated to analyze pulmonary nodules of the lung adenocarcinoma spectrum based on CT imaging data. CANARY can noninvasively predict tumor invasiveness and postsurgical survival outcome for these lesions.[46,47] Consequently, CANARY analysis may facilitate treatment decisions in the setting of MFLA by identifying the most invasive/aggressive lesions, supporting clinical decisions of aggressive local therapy versus continued active surveillance.

This study is a prospective trial describing the survival outcomes for a defined patient cohort with MFLA who have undergone surgical resection. CANARY analysis was used retrospectively to independently predict which nodules appeared more invasive, and findings were correlated with the nodules that were selected for surgical intervention.

PATIENTS AND METHODS

Data Collection

From 2013 to 2018, we prospectively identified patients with multifocal lung cancer. Our definition of MFLA was as follows:

- 2 or more lung lesions of >0.5 cm, which were radiographically concerning for

malignancy, at least one of which contains a subsolid or ground-glass component.
- Clinical N0, mediastinum clinically negative for nodal metastases by CT-positron emission tomography (PET).
- Clinical M0, no evidence of distant disease by CT-PET and brain magnetic resonance imaging.

Patients were required to be older than 18 years, present with no other cancer in the past 5 years, be able to undergo surgical resection of at least 1 lung lesion, and not be pregnant or lactating. Patients reviewed and signed institutional review board–approved informed consent forms. The Mayo Clinic Institutional Review Board approved this study. A total of 68 patients were enrolled from 2013 to 2018. Data were collected regarding sex, age, medical history, surgical and medical management, pathology, and survival. CT scan was reviewed and time zero for our survival analysis was determined based on when the scan met our criteria for multifocal lung cancer.

RADIOLOGY EVALUATION AND CANARY

A dedicated thoracic radiologist (B.J.B.) reviewed CT scans for all patients enrolled in the study and identified all nodules (302 nodules across 68 patients) present at the time of diagnosis of MFLA. Patients with previous CT scan were reviewed, and time zero was determined based on when the patient met multifocal criteria based on the aforementioned definition. For our CANARY analysis, each nodule was segmented, processed with the CANARY tool, a score indicative of lung cancer aggression (SILA) was calculated, and nodules were stratified into good (G), intermediate (I), and poor (P) risk groups based on the CANARY assessment.[46,47] The CANARY modeling has been previously reported, and the methods of the algorithm have been published.[47] In summary, the technology uses 774 regions of interest (ROIs, 9 × 9 voxels) spanning the spectrum of radiologic appearance of adenocarcinomas (form pure ground glass to pure solid). The similarity of the radiologic features between ROIs was compared using a pairwise similarity metric and 9 characteristic ROI clusters (ie, groups of radiologically similar ROIs) and corresponding ROI exemplars were identified using Affinity Propagation, an unsupervised clustering algorithm.[47] Based on the CANARY data, all lesions were retrospectively categorized from most invasive to least invasive based on the CANARY features, SILA, and CANARY risk group assessment.

Pathology

All available surgical pathology hemoxylin-and-eosin–stained slides were centrally reviewed by an experienced pulmonary pathologist with confirmation of diagnosis and determination of maximum invasive size. Tumors were classified per WHO criteria as AIS, MIA, or invasive adenocarcinoma. Comprehensive histologic subtyping was performed for all resected tumors, with assessment of observed growth patterns in 5% increments (lepidic, acinar, papillary, micropapillary, solid, cribriform, and mucinous) and assignment of predominant growth pattern for all adenocarcinomas.

Statistical Analysis

Date of diagnosis of MFLA based on our definition was used as time zero for our survival analysis. Overall survival was calculated using Kaplan-Meier survival analysis.

RESULTS

Patient Characteristics

Sixty-eight patients with presumed MFLA were enrolled. The majority were female (n=42, 61.8%), with a median age of 70.7 years (range, 45-82 years) (Table 1). Review of CT scan at diagnosis demonstrated that all patients had at least 2 lesions, with some patients having 6 or more lesions. The majority of these lung nodules were bilateral (n=46, 67.6%), followed by right only (n=14, 20.6%), and fewer isolated to the left side (n=8, 11.8%) (Table 1).

All patients underwent at least 1 of the following surgical intervention: wedge resection (n=46, 67.6%), segmentectomy (n=10, 14.7%), or lobectomy (n=26, 38.2%) (Table 1). No patients showed a positive resection margin. Thirty-six patients underwent a second surgery, whereas 10 patients underwent 3 surgical interventions and 2 patients 4 surgeries for MFLA. At the time of initial

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TABLE 1. Patient and Tumor Characteristics

	Value
N	68
Age (y)	
Mean (SD)	69.4 (8.0)
Median	70.7
Q1, Q3	65.7, 75.2
Range	45.5-82.2
Sex	
Female	42 (61.8)
Male	26 (38.2)
Laterality	
Unilateral	22 (32.4)
Bilateral	46 (67.6)
Initial No. of nodules at presentation	
2	21
3	11
4	15
5	4
6+	17
Smoking history	
Never	7
Former	53
Current	8
Size (cm)	
<3	57 (83.8)
>3	11 (16.2)
Initial surgery	
Wedge	30 (44.1)
Segment	7 (10.3)
Lobe	20 (29.4)
Multiple wedge	2 (2.9)
Wedge+segment	3 (4.4)
Wedge+lobe	6 (8.8)
Pathologic stage (after first surgery)	
I	58 (85.3)
II	6 (8.8)
III	3 (4.4)
IV	1 (1.5)

Values are n (%) unless specified.

TABLE 2. Summary of Pathologic Diagnosis for All Nodules Resected

Diagnosis	Number
Acinar predominant adenocarcinoma	58
Minimally invasive adenocarcinoma	56
Lepidic-predominant adenocarcinoma	18
Papillary predominant adenocarcinoma	13
Solid predominant adenocarcinoma	11
Adenocarcinoma in situ	11
Cribriform predominant adenocarcinoma	6
Invasive mucinous adenocarcinoma	6
Micropapillary predominant adenocarcinoma	5
Other (nonlung cancer)	5
Large cell neuroendocrine carcinoma	1
Total	194

surgery, 127 nodules were removed, with the majority being less than 3 cm (n=109, 90.8%).

Final pathologic diagnosis for all nodules is summarized in Table 2. Of the total 194 nodules identified on final pathology, 30% were acinar predominant adenocarcinomas (n=58), and 29% were MIAs (n=56). Six nodules were found to not be adenocarcinoma (3%). The pathology is these cases were MALT lymphoma, fibrinous pleuritis, and organizing pneumonia. We correlated 177 CANARY-analyzed nodules that were in fact surgically resected. After all surgeries were performed, the final pathology was re-reviewed by our thoracic pathologist and 194 nodules were classified.

In addition to surgery, 18 patients received adjuvant systemic therapy (26.5%), such as chemotherapy (n=11), immunotherapy (n=6), and targeted therapy (n=1). Twenty-two patients underwent adjuvant local therapy (32.3%), such as SBRT (n=18), ablation (n=2), and conventional radiation (n=2). As part of the initial work up, all patients were clinically N0 based on CT and PET scan. Fifteen patients underwent either mediastinoscopy (n=4) or endobronchial ultrasound/endoscopic ultrasound (n=11) mediastinal staging before surgery. Three patients were found to harbor occult N2 disease (4.4%). At the time of the initial surgery, 1 patient showed a positive 4R lymph node. In this case, the patient underwent right upper lobectomy with 2 lesions, a 3.2-cm acinar predominant adenocarcinoma and 0.7-cm MIA. This patient was subsequently treated with adjuvant platinum-based chemotherapy. At the time of the second surgery, 1 patient recorded a positive station 7 lymph node. In this case,

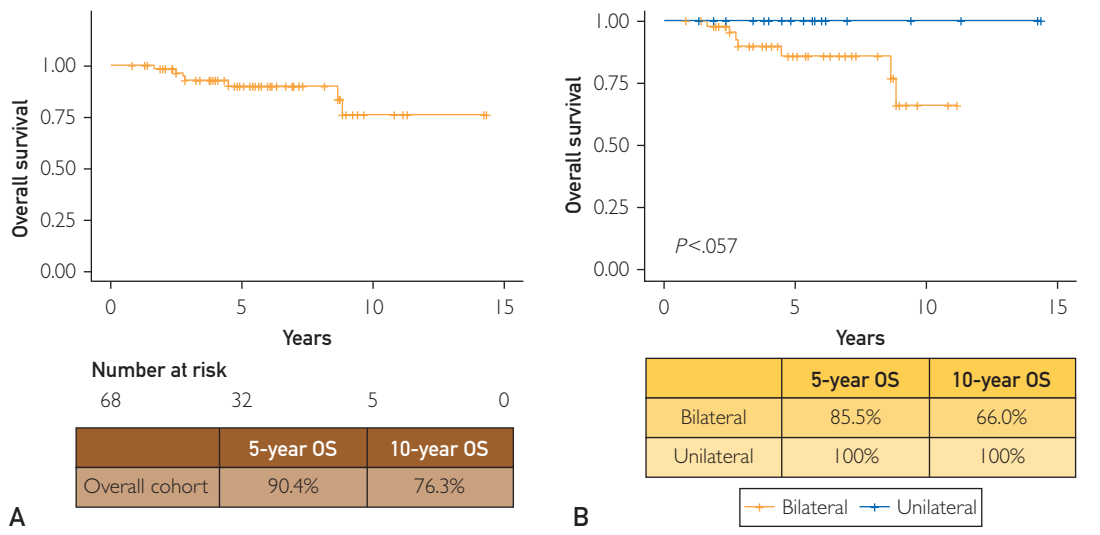

FIGURE 1. (A) Overall survival Kaplan-Meier curve demonstrating long-term survival in our multifocal cohort of patients: 5-year survival was 90% and 10-year survival was 76%. (B) Overall survival in patients with unilateral disease compared with that in those with bilateral disease demonstrates a trend toward increased survival with unilateral disease. In our patient population, 67% of patients presented with bilateral disease.

the patient's original surgery was a video-assisted thoracoscopic surgery right lower lobe segmentectomy with a 2.6-cm acinar predominant adenocarcinoma. A year and a half later, she developed a right hilar mass with a positive station 7 lymph node biopsy proven by endobranchial ultrasound. The patient was found to harbor an *EGFR* mutation and underwent systemic treatment with osimertinib, followed by a completion right lower lobectomy and right middle lobectomy. Finally, one patient recorded a positive station 8 lymph node at the time of her third surgery. This patient underwent a previous right middle lobectomy with a 1.1-cm mucinous adenocarcinoma, followed by a left upper segmentectomy 4 years later for a 0.8-cm MIA. At the time of the third surgery approximately 5 years from initial surgical resection, she presented with a right lower lobe wedge for a 1.3-cm solid predominant adenocarcinoma, where a station 8 LN was positive. This patient subsequently received platinum-based therapy, followed by immunotherapy.

During follow-up, 4 patients developed progression to distant metastatic disease. The first patient had metastatic disease spread to several bones 7.8 years after the diagnoses of papillary, AIS, and acinar predominant adenocarcinoma. A year after identification of metastatic disease, this patient was alive, being treated with a combination of SBRT, pembrolizumab, and chemotherapy. The second patient experienced spread of disease to the femur and ribs 2.4 years after initial diagnosis of acinar predominant adenocarcinoma. Unfortunately, she passed 6 months after this diagnosis despite treatment with SBRT and chemotherapy. The third patient was found with brain metastasis 2 years after initial diagnosis of lepidic-predominant adenocarcinoma, MIA, and solid predominant adenocarcinoma. This patient was alive 8 months later after treatment with γ-knife and pembrolizumab. The fourth patient showed metastatic disease to an adrenal gland a year after their initial diagnosis of acinar predominant adenocarcinoma. The patient was treated with chemotherapy, but unfortunately passed away 6 months later.

Survival Data

Overall survival for this population of patients with multifocal lung cancer was 91% at 5 years and 76.3% at 10 years (Figure 1A). Sex, number of tumors, tumor size, type of resection, and number of surgeries did not

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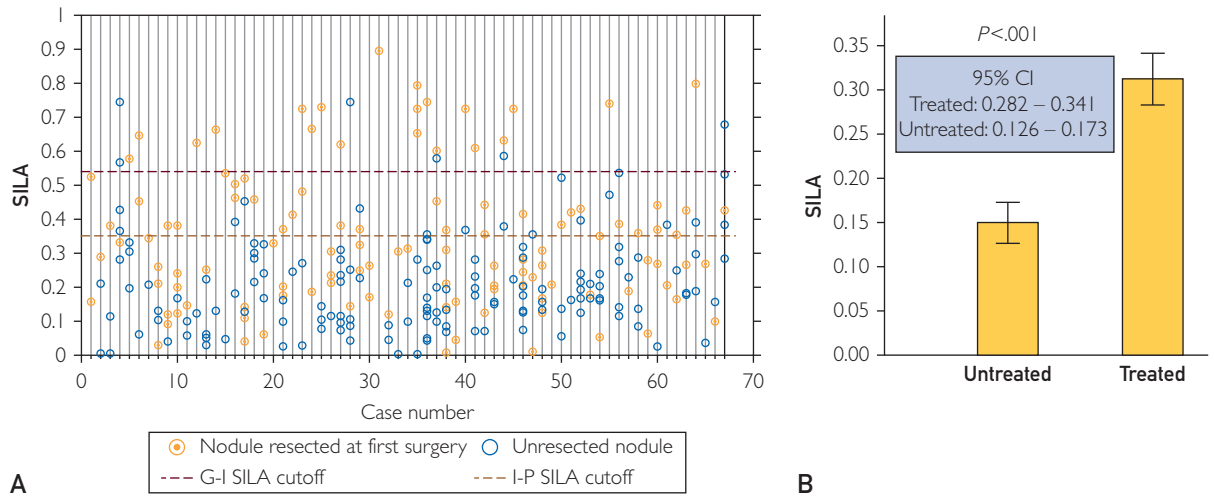

FIGURE 2. (A) Distribution of SILA for all nodules (N=302) across all cases (N=68). The plot shows that majority of the nodules in the intermediate (29/45) and poor (22/28) categories were surgically resected. A substantial number of G nodules (76/229) were also surgically resected. (B) SILA of treated lung nodules had a significantly higher score than that of untreated nodules.

significantly impact patient survival. However, there was a trend for patients with unilateral disease toward a better 5-year survival compared with those with bilateral disease, 100% versus 85.5%, respectively (Figure 1B).

CANARY and SILA

The majority of the nodules present at the time of diagnosis (229/302; 75.8%) were classified good with an average SILA of 0.19, suggesting indolent clinical behavior and noninvasive pathology (Figure 2). As expected, SILA of the surgically removed nodules were significantly higher compared with that of the nonresected nodules (P=.001). (Figure 2) The CANARY-based SILA strongly differentiated the treated and untreated lesions at the time of the first surgery (area under the curve, 0.923; P<.001) and overall (area under the curve, 0.964; P<.001) (Figure 3). In addition, histologic tumor invasive size, as determined by final pathologic examination, correlated well the CANARY results. Nodules classified with as Poor by CANARY with a high SILA had an average tumor invasive size of 2.7cm, whereas intermediate CANARY nodules (intermediate SILA) had an average invasive tumor size of 1.5 cm and a good CANARY nodule (low SILA) had the smallest amount of tumor invasion size at an average of 0.7 cm.

DISCUSSION

Multifocal lung adenocarcinoma remains a poorly defined and not well-characterized clinical entity. Multiple reports suggest that the subset of patients with MFLA have better-than-expected outcomes with infrequent nodal or extrathoracic recurrences, suggestive of a biologic behavior different from that of typical non–small cell lung cancer cases.[5,7,11–14,18,48] However, many authors have highlighted the heterogeneity regarding clinical definitions and management approaches in the existing literature.[5,7,18,48] Furthermore, although there are many reports describing the management of single or multiple GGOs, all are retrospective in nature with heterogeneous clinical definitions and surgical approaches. There is a clinical perception that cases of MFLA are detected at an increasing rate. However, this increased incidence is at least in part due to the increased utilization of diagnostic and screening CT of the chest, improved CT resolution, and heightened awareness of this unique disease entity.

In this prospective study, we identified 68 patients with MFLA based on a practical, real-

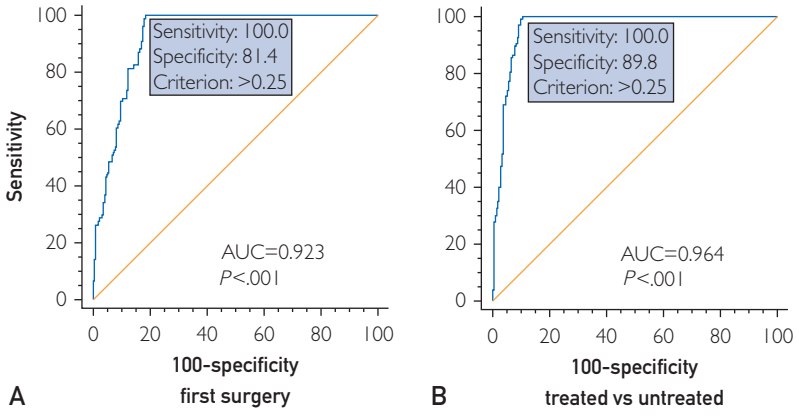

FIGURE 3. Area under the curves for the CANARY-based SILA score to differentiate surgically targeted from nontargeted lesions: (A) Target tumors treated at the first surgery versus nontarget lesions and (B) all targeted versus nontargeted lesions.

world definition. These patients have undergone a combination of treatment modalities; however, all patients underwent at least 1 surgical resection. Our survival curves highlight that those patients with a diagnosis of multifocal lung cancer can have excellent 5-year survival. This emphasizes that despite having bilateral lung cancers, if these patients are carefully staged and receive appropriate treatment, their survival is similar to that of stage I disease. The natural history for patients left untreated remains unknown. Recent proposals for International Association for the Study of Lung Cancer (IASLC) staging suggest that for multifocal ground-glass/lepidic tumors, the T category be determined by the highest T lesion, with either the number of tumors or m in parentheses to denote the multifocal nature and that a single N and M category be used for all lesions collectively—for example, T1a(3)N0M0 or T1b(m)N0M0.[7] Furthermore, the T stage for lepidic-predominant tumors is determined by the maximum invasive size, not the overall size of the entire lesion.[1] Understanding how and when to accurately apply this staging system is critically important in the setting of MFLA to avoid overstaging these patients because there is typically a preponderance of tumors with lepidic growth in this patient cohort. Thus, it is not surprising that there was a pronounced overrepresentation of AIS, MIA, and lepidic-predominant adenocarcinomas in our study, which constituted 44% of all resected nodules.

Currently, there is no standardized treatment algorithm for MFLA. Ideally, given the lack of prospective data, clinical decision making for these patients should be based on multidisciplinary reviews. In patients with multiple concerning nodules, it can be difficult to know which nodules should undergo surgical resection or other local treatment modalities versus continued observation. In this study, we demonstrated the use of AI, specifically CANARY analysis, may facilitate the selection of the most aggressive lesions for local therapeutic interventions. Nodules with CANARY features more suggestive of aggressive/invasive disease (higher SILA or in the intermediate/poor risk category) would potentially benefit from more aggressive management than those with indolent and less-invasive features. Thus, we may need to switch our surgical approach to treating the nodule predicted to be most aggressive by CANARY, even if this means a more extensive surgical resection. In the active monitoring of nodules that have not been resected or treated, the changes in features such as increase in SILA over time, development of CANARY features suggestive of more invasive components or transition from a lower risk category to a higher risk category can trigger reassessment of the management plan. In this study, we found that the majority of nodules resected

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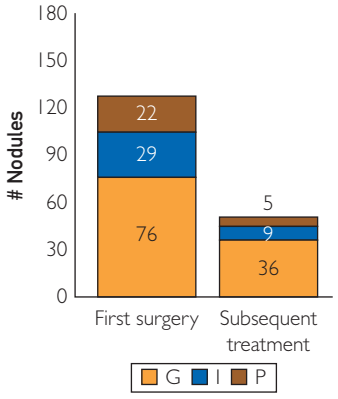

FIGURE 4. SILA risk group distribution between first surgery and subsequent treatment: 40% of nodules were classified as intermediate or high risk at the time of the first surgery and 28% at the time of subsequent treatment.

had a low SILA (Figure 4), suggesting perhaps these nodules could have been followed up instead of surgically treated. Early detection of nodules that demonstrate changes may allow optimization of the timing of therapeutic intervention, and objective confirmation of stability may increase confidence in the watchful waiting approach to management.

CONCLUSION

In summary, we demonstrated excellent survival outcomes can be obtained with surgical resection in patients who have clinical N0, M0 MFLA. We also described the utility of AI-CANARY imaging algorithm to potentially guide intervention vs observation management decisions of patients with MFLA.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Abbreviations and Acronyms: **AI,** artificial intelligence; **AIS,** adenocarcinoma in situ; **CANARY,** computer-aided nodule assessment and risk yield; **GGO,** ground-glass opacity; **MIA,** minimally invasive adenocarcinoma; **MFLA,** multifocal lung adenocarcinoma; **SBRT,** stereotactic body radiotherapy; **SILA,** score indicative of lung cancer aggression

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