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Scrape cytology and radiological solid size correlation can be used in the intraoperative management of subsolid lung nodules

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Abstract

Background: The term radiologic subsolid lung nodule (SLN) represents a heterogeneous group of non-neoplastic and neoplastic lesions. Intraoperative evaluation (IO) is often required to differentiate and diagnose. The current study aims to investigate the feasibility and reliability of scrape cytology (SC) and radiologic solid size correlation for the IO diagnosis of SLNs.

Methods: Sixty-eight patients with SLN signs were eligible to take part in the study due to intraoperatively prepared SC slides. We managed to complete the blind radiologic solid size measurement and cytologic evaluation retrospectively. Cases were grouped into three categories based on their cytological features: Group-0 (Benign), Group-1 (mild atypical features), and Group-2 (severe atypical features/unequivocally carcinoma). IO diagnoses were given by combining the radiologic solid size and cytological findings.

Results: Cytological features of Group-1 were observed in 100%, 93%, 32.5%, and 17% of the AIS, MIA, IA, and benign lesions, respectively. Cytological features of Group-2 were observed in 67.5%, and 7% of the IA and MIA, respectively. By combining cytology with radiologic solid size, 100%, 85%, 71%, and 83% of the AIS, IA, MIA, and benign lesions respectively were diagnosed correctly. Fifteen (15%) percent of the IA cases were underdiagnosed as MIA since their radiological solid sizes were less than 0.5 cm with cytological features of Group-1. Conversely, 29% of the MIA cases were overdiagnosed as IA since their radiological solid sizes were greater than 0.5 cm.

Conclusion: SLNs should be handled with caution in terms of IO management. SC and radiologic solid size correlation both provide a practical and tissue-protecting approach for the IO evaluation of SLNs, ensuring a high consistency between IO and definitive diagnosis.

KEYWORDS

early-stage lung adenocarcinoma, ground glass nodule, intraoperative management of lung cancer, scrape cytology, subsolid lung nodule

1 | INTRODUCTION

Over the several past decades, a widespread use of low-dose chest computed tomography (LDCT) screening has led to a surge in the detection of incidental pulmonary nodules, many of which present as a ground-glass opacity (GGO).[1] The term GGO radiologically describes a hazy opacity that does not obscure the underlying bronchial walls or pulmonary vessels. GGO lesions can be seen as a diffuse or nodular configuration.[2] Nodular GGOs (GGNs) are radiologically divided into two categories as "pure-ground-glass nodule" (P-GGN), and "part-solid ground-glass nodule" (PS-GGN). PS-GGN refers to a GGN lesion with a solid component that obscures underlying lung vessels.[3] P-GGN and PS-GGN are collectively referred to as subsolid lung nodules (SLNs). SLN may be a manifestation of a wide variety of lesions ranging from pre-invasive lesions, including atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS), to invasive lesions such as minimally invasive adenocarcinoma (MIA), or invasive adenocarcinoma (IA); there are also benign and inflammatory conditions such as focal interstitial fibrosis, eosinophilic pneumonia, aspergillosis, bronchiolitis obliterans, organizing pneumonia, and Wegener granulomatosis.[4,5] The radiological interpretation of these nodules depends on several image assessment criteria as well as observation of their stability or progression at the follow-up CT studies. Although distinguishing these entities is not possible without histological sampling, the majority of persistent PS-GGNs have proven to be adenocarcinomas, with several studies showing that the size of the solid component measured on CT images has a strong correlation with the size of the invasive component in the histopathological examination.[5–7] In contrast to solid pulmonary lesions, a preoperative biopsy is generally not recommended for diagnosing SLNs, particularly those with P-GGN, since it may not be feasible or helpful in most cases. Therefore, these lesions are frequently evaluated intraoperatively. In this aspect, pathologists are confronted with the following questions during the intraoperative (IO) examination of SLNs: (I) whether the targeted lesion is correctly identified and resected completely with negative margins (especially for small nodules), (II) whether the targeted lesion is neoplastic, and if so (III) whether and to what size the targeted lesion has an invasive component (for extending the surgical resection as well as including lymphadenectomy).[8]

Frozen section (FS) analysis is the most commonly used method for the IO diagnosis of all kinds of pulmonary lesions.[9,10] However, the FS procedure carries several risks, some of which may be significant for SLNs such as.[11]: (I) underestimation of the invasive component's size due to sampling error; (II) difficulty in histologic evaluation caused by freezing artifacts on both frozen and permanent sections; and (III) diagnostic downstaging due to over-trimming of the invasive focus during FS. On the other hand, scrape cytology (SC) is a practical and cost-effective IO assessment technique that yields cellular smears and secures excellent preservation of cellular details by overcoming freezing-related issues in the evaluation of pulmonary lesions.[12,13] Most lung adenocarcinomas can be easily diagnosed cytologically. However, cytology alone is usually not sufficient to differentiate some of IAs from pre-invasive or minimally invasive lesions. The presence of invasion and its size defines the difference between AIS, MIA, and lepidic-predominant IA. They all refer to lesions with mild atypical features, their cellular characteristics might be identical, whereas a cytological examination, by definition, may be an inadequate tool to distinguish lesions by their type.[14]

In this retrospective study, we intend to evaluate the effectiveness of a practical and tissue-protecting IO approach to SLNs and examined the clinical possibility to predict the invasiveness of these lesions by combining the cytological features with the radiological solid size measured on CT.

2 | MATERIALS AND METHODS

2.1 | Case selection

Upon obtaining the institutional review board's approval (2022.008. IRB1.008) from Koc University, Istanbul, a retrospective search in the local thoracic pathology database for intraoperatively examined lung resections has been performed, looking through the cases between January 2016 and July 2022. A total of 880 lung resection cases were performed during this period. Preoperative radiological features of all cases were reviewed, and those with GGN intraoperatively examined by SC for diagnostic purposes had been included in the study. Among the cases identified, 68 (7.73%) had subsolid consistency on CT as well as intraoperative SC. Thirty-five of these 68 cases also had frozen sections. However, frozen sections of the cases are not included in the intraoperative diagnostic accuracy evaluation in this retrospective study. Clinical parameters of the cases, including age, gender, tumor size, and surgical procedure were collected from the hospital's electronic medical records database.

2.2 | Scrape cytology and frozen section technique

SC samples of the selected cases had been prepared and archived during the IO examination according to the following standardized multistep process. First, the surface of the SLN was gently scraped with the scalpel blade's sharp edge for preparing SC smears. Obtained tissue was smeared on a clean glass slide by a light gliding movement and the slide was immediately fixed in a container filled with 95% alcohol to preserve the cytomorphological details. The alcohol-fixed slides were stained with hematoxylin and eosin (H&E) and further evaluated under the microscope. To obtain more reliable output, at least two slides were prepared per case. Additionally, FS has performed in 35 (51%) cases. For FS analysis, a small piece of the lesion's whole sectional face (depending on the lesion's size and nature) was retrieved, and then embedded in Cryometrix and frozen at −20°C. Finally, samples were cut into 5-μm-thick sections using Leica CM1860-UV cryostat, treated with 95% alcohol, and subsequently stained with H&E.

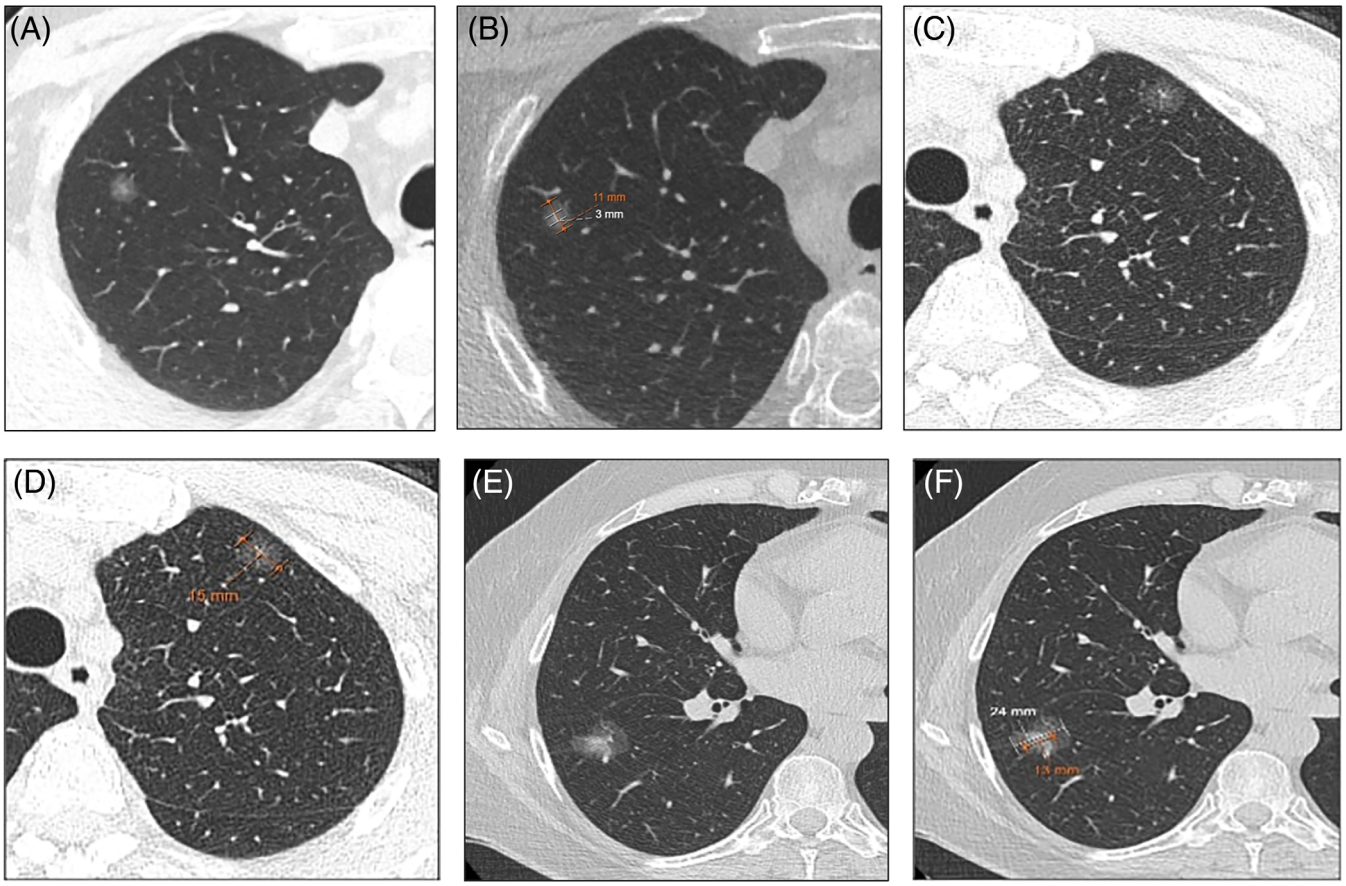

FIGURE 1 Radiologic features of various pure and semi-solid GGNs, and their solid and total size measurements through radiologic images. Radiologic solid size related intraoperative approach (IOA) categories. (A) CT image of PS-GGN in the right upper lobe diagnosed as MIA. (B) The total size is 11 mm, and the solid part is 3 mm. As the scrape cytology (SC) had Group-1 cytologic features "favor MIA" diagnosis is given for this case. (C) CT image of P-GGN in the left upper lobe diagnosed as AIS. (D) The tumor consists of pure ground-glass opacity and the total size is 15 mm. As the SC had Group-1 cytologic features "favor AIS" diagnosis is given for this case. (E) CT image of another PS-GGN in the right lower lobe diagnosed as IA. (F) The total size is 24 mm, and the solid part is 13 mm. As the SC had Group-2 cytologic features "favor IA" diagnosis is given for this case [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | CT examination of subsolid lung nodules

All cases were examined by CT in the Koc University Hospital's radiology department using the multidetector spiral scanners (specifically Somatom Definition Flash or Somatom AS Plus, Siemens Healthcare, Erlangen, Germany). Non-modified unenhanced chest CT examinations were performed under deep inspiratory breath-hold from the apex to the base of the diaphragms. As a result, contiguous non-overlapping axial images were reconstructed with 1 mm section thickness and sharp reconstruction filters. A lung window setting (width 1500 HU; level: -600 HU) was used for image analysis. One thoracic radiologist (Ç.A.) has been involved to review all case-related images and make the measurements of the resected nodules in millimeters by electronic calipers. The largest diameter of the whole nodule and the largest diameter of the solid component was the main focus (Figure 1). Measurements were made in the plane that would reveal the lesion's largest size, involving the axial, sagittal, and coronal planes.

2.4 | Cytologic assessment and radiologic correlation

SC slides (intraoperatively prepared, archived, alcohol-fixed, and H&E-stained) were blindly reviewed by an experienced and competent pulmonary pathologist (P.B.). Hypocellular smears with few epithelial cells and without any nuclear atypia were marked as Group-0 [non-neoplastic (NN)]. Smears incorporating moderate or high amounts of epithelial cells were divided into two criteria-centered groups based on their architectural and cellular features: Group-1 (mild atypical features), and Group-2 (severe atypical features/unequivocally carcinoma). Group-1 (Figure 2) incorporated the smears composed of monotonous epithelial cells with small nuclei, fine chromatin, conspicuous but small nucleoli, ones showing mild nuclear membrane irregularity (sometimes grooves), and ones either forming flat layers (2D cell clusters) or separately distributed. Group-2 (Figure 3) (Table 1) incorporated the smears comprised of epithelial cells with large nuclei, coarse chromatin, convoluted nuclear membrane, and macronucleoli,

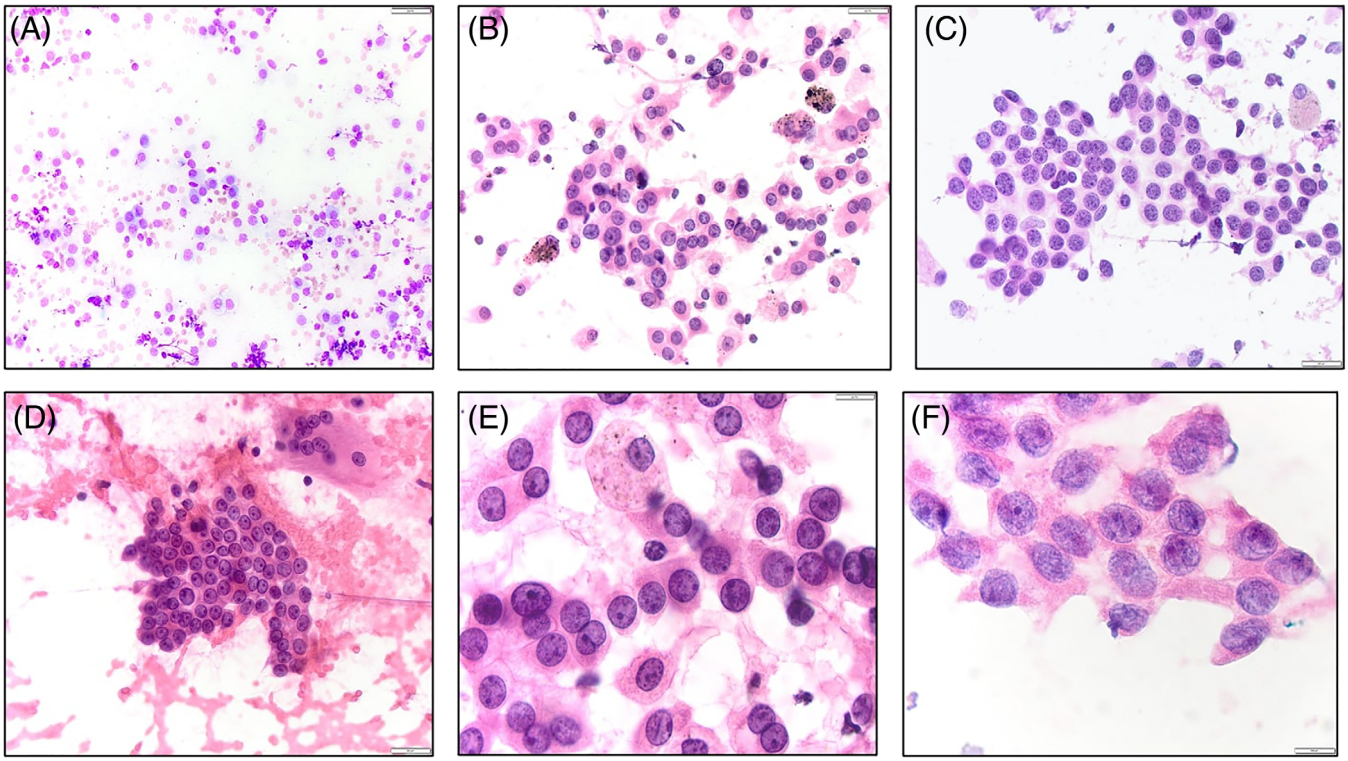

FIGURE 2 Examples of the cytologic features contributing to the Group-1 (Mild atypical features). (A) Hypocellular smear with small uniform neoplastic cells, 100× (diff-quick). This case was reported as a minimally invasive adenocarcinoma with a 0.4 cm invasive part. (B) Flat sheet and single cells of bland neoplastic epithelium with round nuclei and small nucleoli. Rare macrophages are seen among neoplastic cells, 400×. This case was reported as a predominantly lepidic invasive adenocarcinoma. (C) Oval to round uniform nuclei with small nuclei arranged in branching flat sheets, 400×. This case was reported as a minimally invasive adenocarcinoma with a 0.2 cm invasive part. (D) Flat sheets of small bland appearance neoplastic cells with round nuclei and small nucleoli 400×. This case was reported as a predominantly lepidic invasive adenocarcinoma. (E) High magnification appearance of the neoplastic cells. The nuclei of tumor cells are slightly larger than the nuclei of macrophages, which are rarely seen around tumor cells. The neoplastic cells are having round nuclei and fine granular chromatin, 1000×. (F) High magnification appearance of the neoplastic cells. The slightly irregular distributed neoplastic cells have fine granular chromatin and small nucleoli 1000×. This case was reported as a minimally invasive adenocarcinoma with a 0.48 cm invasive part [Color figure can be viewed at wileyonlinelibrary.com]

as well as the ones showing pleomorphism and forming 3D cell clusters. These criteria were selected among the statistically significant results of several studies focusing on lung adenocarcinoma through cytologic specimens.[14–16] The relationship between cytological groups and radiological solid size was also investigated to find a solid size cut-off value that distinguishes mild and severely atypical cytological groups.

Cytological groups are combined with radiological solid size measurements. Four categories are designed to be potentially used intraoperatively to predict the degree of invasion.

2.5 | Step-by-step intraoperative approach proposal for the subsolid lung nodules

(I) Radiological orientation to the resected SLN and measurement of its greatest solid and total sizes via images. (II) Gross examination of the resection specimen in the light of radiological findings, detection of the SLN lesion by cutting the resection material into thin slices, and once detected measuring of the distance of the lesion to the surgical margin. (III) Preparation of cytological smears by scraping the lesion, and microscopic examination to categorize the lesion as Group-1 versus Group-2 according to the cytological features (IV) Giving an IO diagnosis/approach by combining the cytological groups with the radiological sizes. Intraoperative approach categories (IOA) are explained in the following paragraph. (V) If IO diagnosis is critical for surgical management and will cause a major change in the extent of surgery, or if the result of the radiological-cytological approach is not convincing and suspicious for the pathologist, it would be appropriate to obtain a complementary frozen section to increase the accuracy of IO diagnosis. However, since this is a retrospective analysis, the additional value of the frozen section could not be evaluated in this study.

Intraoperative approach (IOA) categories:

1. Favor NN: Cytologic smear lacks neoplastic features (absence of malignancy / any significant cellular atypia / hypocellular smear) regardless of radiological findings or suggests the benign neoplastic formations or reactive processes at most.
2. Favor AIS: Cytologic smear exhibits Group-1 features; the lesion is radiologically smaller than 3 cm and incorporates P-GGN features.

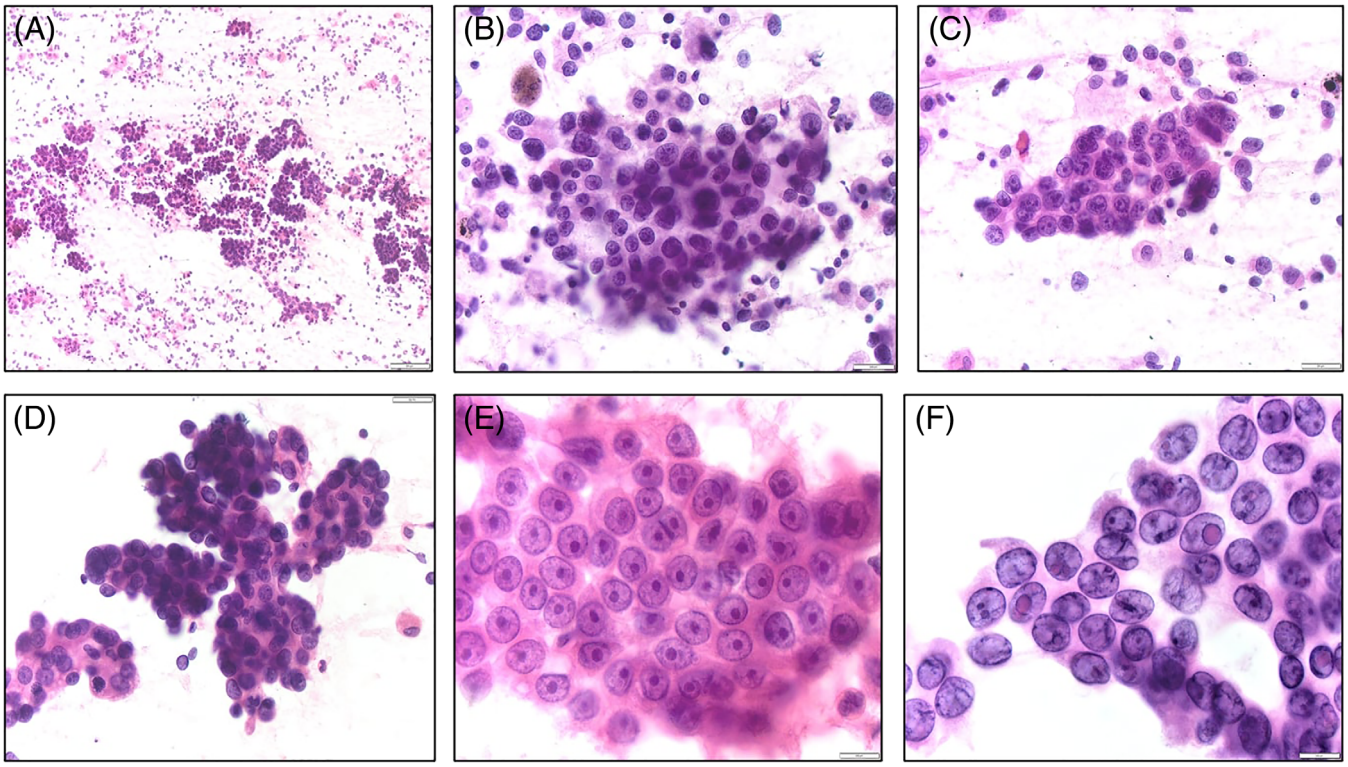

FIGURE 3 Examples of the cytologic features contributing to the Group-2 (severe atypical features/unequivocally carcinoma). (A) Hypercellular smear consisting of numerous cohesive epithelial cells through the low power magnification, 100×. (B) Crowded and overlapping nuclei are seen in scrape cytology. The tumor cells share medium to large-sized nuclei with a moderately pleomorphic nature, 400×. (C) 3D configurated neoplastic clusters consist of mildly pleomorphic cells and the nuclei of the cells have coarse, granular chromatin, 400×. (D) 3D configurated neoplastic epithelial cluster of cells with coarse nuclear chromatin 400×. (E) Flat sheets of medium-sized round neoplastic cells with pronounced macronucleoli, 1000×. (F) Round to oval large neoplastic epithelial cells with intranuclear grooves and a few intranuclear inclusions, 1000× [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Descriptive cytologic properties that constitute the groups

	Group-1	Group-2
Cellularity	Poor/moderate	Moderate/high
Shape of cluster	Sheet-like appearance (2D)	Irregular overlapping (3D)
Size of cells	Small to medium	Medium to large
Size of nucleus	Small to medium & uniform size	Medium to large & pleomorphic
Chromatin pattern	Thick to sparse and fine, granular chromatin with regular or slightly irregular distribution	Fine to coarse, granular chromatin with irregular distribution

Abbreviations: Group-1, mild atypical features; Group-2, severe atypical features/unequivocally carcinoma.

3. Favor MIA: Cytologic smear exhibits Group-1 features; the lesion radiologically shows a PS-GGN appearance with a solid component smaller than 0.5 cm (<0.5 cm).
4. Favor IA: Cytologic smear exhibits Group-2 features regardless of the radiologic solid component size or shows the Group-1 cytologic features with the radiologic solid component size larger than 0.5 cm (≥0.5 cm).

The reliability and applicability of the IOA categories for the management of SLN were investigated by correlating the groups with the final pathological diagnoses provided in accordance with the WHO 2021 classification of lung tumors.[17] The FS slides of the cases which were originally evaluated also by this method were reviewed to determine the issues caused by the FS technique only, which means that their diagnostic value was not analyzed in this study.

2.6 | Statistical methods

By using SPSS19.0 software, the chi-square test was performed to compare the cytological groups and the IOA categories with the final histopathological diagnosis. By using the cytological groups, a receiver operating curve (ROC) was performed to detect the critical value of the radiological solid size. Youden's index was used to maximize the sum of sensitivity and specificity for all the possible values of the cut-off value. A *p*-value of less than .05 was considered statistically significant.

TABLE 2 Characterization of the patients with SLN

	Final pathologic diagnosis: *n* (%)						
	NN	BN	AIS	MIA	IA	Met	All cases
Histologic types	4 (5.88)	2 (2.94)	8 (11.76)	14 (20.59)	39 (57.35)	1 (1.47)	68 (100)
Age							
Mean (range)	64 (58–71)	77 (71–83)	65 (51–78)	64 (39–74)	63 (33–83)	58 (58)	63 (33–83)
Sex							
Male	0 (0)	1 (50)	5 (62)	7 (50)	15 (38)	1 (100)	29 (42)
Female	4 (100)	1 (50)	3 (38)	7 (50)	24 (62)	0 (0)	39 (58)
Total size (cm)							
Mean (range)	0.97 (0.9–1)	0.55 (0.5–0.6)	0.92 (0.5–1)	1.1 (0.4–2.2)	1.6 (0.5–3.4)	0.8 (0.8)	1.32 (0.4–3.4)
Invasive size (cm)							
Mean (range)	–	–	0 (0)	0.35 (0.1–0.5)	0.9 (0.4–2.3)	0.8 (0.8)	0.75 (0.1–2.3)
Radiologic solid size							
<0.5/0 cm	2 (50)/0	2 (100)/1	8 (100)/8	10 (71)/0	9 (22.5)/0	0/0	31 (45.5)/9
≥0.5 cm	2 (50)	0	0	4 (29)	30 (75)	1 (2.5)	37 (54.5)
Surgical procedure							
Wedge	3 (75)	2 (100)	5 (62)	5 (36)	6 (15)	1 (100)	22 (32)
Segmentectomy	1 (25)	0 (0)	3 (38)	3 (21)	10 (26)	0 (0)	17 (25)
Lobectomy	0 (0)	0 (0)	0 (0)	6 (43)	23 (59)	0 (0)	29 (43)
IO management procedure							
SC only	1 (25)	2 (100)	5 (62.5)	8 (57)	17 (44)	0 (0)	33 (49)
SC and FS	3 (75)	0 (0)	3 (37.5)	6 (43)	22 (56)	1 (100)	35 (51)

Abbreviations: AIS, adenocarcinoma in-situ; BN, benign neoplasia; FS, frozen section; IA, invasive adenocarcinoma; Met, metastasis; MIA, minimally invasive adenocarcinoma; NN, non-neoplastic; P-GGN, pure ground glass nodule; SC, scrape cytology.

3 | RESULTS

3.1 | Study cohort; clinicopathological data

A total of 68 resected SLNs were included in the study. Procedures included 22 (32%) wedge resections, 17 (25%) segmentectomies, and 29 (43%) lobectomies. Out of the total cases, 39 (58%) were females, and 29 (42%) were males. The age of patients ranged from 33 years to 83 years (mean = 63). Total tumor size ranged from 0.4 cm to 3.4 cm (mean = 1.32 cm). SC smears were ready for assessment for each case (100%) and contained sufficient amounts of cells representing the lesion. According to the radiologic assessment, 13% of the cases were classified as P-GGN ($n = 9$), while 87% of the cases were classified as PS-GGN ($n = 59$). According to the WHO 2021 classification, the cases included 8 AIS (11.76%), 14 MIA (20.59%), 39 IA (57.35%), and 1 pancreatic adenocarcinoma metastasis (1.47%). Non-neoplastic lesions or benign neoplasms represented 8.82% (6) of the entire study cohort. Three of them were organizing pneumonia (4.4%), 1 radiotherapy (RT)-related fibrotic change (1.5%) (provoked by breast cancer treatment), and 2 bronchiolar adenomas (3%). Most of the IA cases (77.5%) had a radiologic solid part larger than 0.5 cm, yet the remaining (22.5%) cases dealt with a radiologic solid component smaller than 0.5 cm. Similarly, 21% of the MIA cases had a radiologic solid component that was larger than 0.5 cm. All AIS cases were sharing P-GGN appearance radiologically.

Table 2 summarizes these patients' clinicopathological features as well as IO management procedures by their final pathologic diagnosis.

3.2 | Concordance between cytologic features and final pathologic diagnosis

All AIS lesions [8/8 (100%)] demonstrated Group-1 features typically incorporating more hypocellular smears than others. Except for one case demonstrating Group-2 features, all MIA cases [13/14 (93%)] exhibited Group-1 features. More than half of the IA cases (27/40, 67.5%) could be easily identified due to their highly atypical cytological features (Group-2) regardless of their radiologic solid size. However, 32.5% of the IA cases (13/40) displayed Group-1 features that could not be differentiated confidently from the preinvasive or minimally invasive lesions only via their cytologic features only. The concordance between the final pathological diagnosis and the cytologic groups was found statistically significant ($p < .001$) (Table 3).

Except for one bronchiolar adenoma evaluated as "favor AIS," all NN cases [5/6 (83%)] have been correctly distinguished from the

TABLE 3 Comparing the cytologic groups according to their final pathologic diagnosis

		Cytologic groups			
		Group-0 (%)	Group-1 (%)	Group-2 (%)	*p*
Final pathologic diagnosis	NN	5 (83)	1 (17)	0	<.001
	AIS	0 (0)	8 (100)	0 (0)	
	MIA	0 (0)	13 (93)	1(7)	
	IA	0 (0)	13 (32.5)	27 (67.5)	
	Total	5 (7)	35 (52)	28 (41)	

Abbreviations: AIS, adenocarcinoma in-situ; Group-1, mild atypical features; Group-2, severe atypical features/unequivocally carcinoma; IA, invasive adenocarcinoma; MIA, minimally invasive adenocarcinoma; NN, non-neoplastic.

TABLE 4 The relationship between the solid part's radiologic size and the final pathological results

	Final pathologic diagnosis		
Radiologic solid size	AIS: *n* (%)	MIA: *n* (%)	IA: *n* (%)
<0.5 cm	Group-1: 8 (100)	Group-1: 10 (71)	Group-1: 6 (15)
			Group-2: 1 (2.5)
≥0.5 cm	–	Group-1: 3 (22)	Group-1: 7 (17.5)
		Group-2: 1 (7)	Group-2: 26 (65)

Abbreviations: AIS, adenocarcinoma in-situ; IA: invasive adenocarcinoma; MIA, minimally invasive adenocarcinoma.

TABLE 5 Correlation between representative IO and final pathological diagnoses of SLNs

	Final pathologic diagnoses *n* (%)							
IOA	NN	BN	AIS	MIA	IA	Sensitivity	Specificity	Accuracy
Favor AIS	0 (0)	1 (11)	8 (89)	0 (0)	0 (0)	100	98.3	98.5
Favor MIA	0 (0)	0 (0)	0 (0)	10 (62)	6 (38)	77.8	90	87.2
Favor IA	0 (0)	0 (0)	0 (0)	4 (10)	34 (90)	85	88.2	86.5
Favor NN	4 (80)	1 (20)	0 (0)	0 (0)	0 (0)	83.3	100	98.5

Abbreviations: AIS, adenocarcinoma in-situ; BN, benign neoplasia; IA, invasive adenocarcinoma; IOA, Intraoperative approach; MIA, minimally invasive adenocarcinoma; NN, non-neoplastic.

neoplastic SLNs. The accuracy rate of IOA categories for NN lesions was 98.5%.

One of the cases in this series had a history of pancreatic adenocarcinoma. This case was categorized cytologically as Group-2 cytologically on blind review and showed radiological features of PS-GGN, thus being evaluated among the "favor IA" categories in this study. It has been diagnosed as "consistent with pancreatic adenocarcinoma metastasis" in the original IO evaluation using the clinical history files.

3.3 | Combination of radiologic solid size and cytologic features; compatibility of IO and permanent diagnoses

Table 4 shows the distribution of cytological groups by their final pathologic diagnosis based on the radiological solid size (whether greater than 0.5 cm). Table 5 indicates the relation between the IOA categories and the final pathological diagnosis.

All AIS cases (100%) were correctly classified as 'favor AIS' since they had a P-GGN on radiological evaluation as well as Group-1 features. The specificity and sensitivity rates for AIS lesions were 98.3% and 100%, respectively. All MIA cases incorporated a PS-GGN appearance on radiologic images. Ten MIA cases (71%) were correctly diagnosed as 'favor MIA' since their radiological solid sizes were smaller than 0.5 cm and they manifested Group-1 features. However, the remaining four cases (29%) were evaluated as 'favor IA' due to their radiological solid sizes being greater than 0.5 cm. W–hile three of these cases had Group-1 features, one was exceptional in demonstrating Group-2 features. In this case, even though the invasive tumor size measured from permanent sections was 0.2 cm, the solid size measured radiologically was 0.5 cm. The specificity and sensitivity rates for MIA lesions were 90% and 77.8%, respectively.

Thirty-four (34) of the IA cases (85%) were correctly diagnosed as "favor IA." Within this group, 7 cases (20%) had Group-1 features with radiologic solid sizes greater than 0.5 cm, and 27 cases (80%) showed Group-2 features. The remaining 6 cases (15%) were

misclassified as 'favor MIA' because radiologic solid sizes were smaller than 0.5 cm demonstrating Group-1 features. Consequently, the IO predicting rate for IAs has increased to 85% (34/40) from 67.5% (27/40) following the radiologic solid size correlation. The specificity and sensitivity rates for "favor IA" were 88.2% and 85%, respectively. As a result, the accuracy rates of IOA categories, according to their permanent diagnoses, were respectively as follows respectively: favor AIS—98.5%, favor MIA—87.2%, favor IA—86.5 and favor NN—98.5%.

3.4 | Analysis of the ROC curves of the radiologic solid size

The ROC curves of the groups with "mild atypical features/Group-1" and "severe atypical features/unequivocally carcinoma/Group-2" were plotted with the radiologic solid size as predictors (Graphic 1). The results revealed that the AUC was 0.855, the sensitivity was 0.892, the specificity was 0.725, and the Youden index was 0.618. The results indicated that the radiologic solid size of 0.57 cm was of good predictive significance for distinguishing between the cytologic groups ($p < .0001$). According to our results, SLNs with a radiologic solid size over 0.57 cm were associated with Group-2 features. In this context, Group-2 cytologic features were attributed to the IA diagnosis demonstrating 96% of accuracy. In other words, SLNs with solid parts greater than 0.57 cm were much more likely to be associated with IA.

3.5 | Frozen section-related errors

As mentioned above, the FS technique was applied in 35 cases (51%) in addition to SC. Artifactual problems, which might have caused difficulties in histologic evaluation, were not present in 23 cases (66%) on the permanent sections. However, the remaining 12 cases (34%) had certain technical issues. Thus, determining the size of the invasive focus in the permanent section was difficult in seven (7) cases (20%) due to freezing artifacts, fibrosis, and/or inflammation of the background. Total tumor size was identified as reduced in the permanent sections in two (2) cases (5.5%) due to over-trimming. Fortunately, one of them had enough remaining tumors to ensure the performance of any extra test required; however, the other tumor disappeared almost entirely. For this case, we would have used either SC smears or FS slides if tissue was required for molecular testing. In one (1) case (3%), the tumor's invasive size in the FS was smaller than the permanent section size (0.5 cm versus 1 cm) since the invasive part's largest area had not been sampled during the FS analysis. The remaining two (2) cases (5.5%) also had freezing artifacts, yet their evaluation was completed anyway.

4 | DISCUSSION

With the increasing rate of SLNs in clinical practice, the frequency of IO examinations to clarify their nature has been also increasing. It is well known that not all SLNs are neoplastic; however, nearly all that undergo surgery are. Accurate intraoperative diagnosis and correct estimation of the invasive size of neoplastic SLNs are important since the extent of surgical procedures may change accordingly. Lobectomy remains the standard of care for invasive neoplasms larger than 2 cm. However, segmentectomy is the preferentially recommended surgical procedure for smaller neoplasms.[18,19] Wedge resection is also an option for neoplasms less than 1 cm in size, especially for the preinvasive lesions.[19] Since most of the SLNs sent for intraoperative examination are small lesions, one might question whether it is really important to differentiate in-situ vs minimally invasive vs invasive adenocarcinomas from each other during the IO examination if the suspected lesion is smaller than 2 cm. However, this distinction might still be necessary even for small lesions, at least to stay at wedge resection or extend a wedge resection to segmentectomy, and to include lymph node dissection in the surgical procedure.

The decision for surgical excision of SLNs is not given by instant radiological findings, but thoroughly considered and supported by the follow-up, persistence, and progression of the lesion.[20] Many criteria are used to predict the nature of SLN, such as shape, margin, lobulation, spiculation, pleural indentation, air bronchogram, vacuole, and vessel type, along with the lesion's size and volume.[21–23] Among these criteria, solid size measurement is a reliable and practical parameter and can be applied also by pathologists when needed.

The cytological characteristics of pulmonary adenocarcinomas are thoroughly described, and cytology is a well-accepted diagnostic method for lung adenocarcinomas.[24,25] Tanaka et al.[26] investigated the correlation between the cytomorphological and radiological aspects of lung adenocarcinoma patterns (solid vs. non-solid lesions). Despite the small number of cases in their study, it was discovered that cytologic features might provide information regarding the tumor's pathological invasiveness or biological malignancy. They also concluded that this data might be beneficial in making treatment decisions, such as lobectomy versus sublobar resection.[26] In our study, the role of cytological findings in IO management was expanded with the radiological solid size measurement and the reliability and applicability of this method were questioned.

The majority of adenocarcinomas have a distinctive architectural pattern on cytologic specimens as 3D arranged clusters, or acini formations containing columnar, cuboidal, or polygonal cells with fine vacuolated cytoplasm, variably sized round to oval and often eccentric nuclei, finely granular chromatin, and variably prominent central cherry red nucleoli.[27,28] These are common findings regarding invasive adenocarcinomas for any reviewer. In this study, the cases with these findings were categorized as Group-2 (severe atypical features/unequivocally carcinoma). They all were confirmed to be invasive adenocarcinomas on permanent sections, except for one case finally diagnosed as MIA. However, most of the neoplastic SLNs tend to have milder atypical features than classical invasive adenocarcinomas due to the presence of lepidic components in varying amounts, thus displaying low-grade adenocarcinoma features.[26,29] Therefore, making a reliable distinction between preinvasive, minimally invasive, or

invasive adenocarcinoma based on the cytological features alone does not seem to be clinically reasonable or realizable.

Lepidic pattern cytologically mostly consists of uniform single cells or layers with bland nuclei on a clean background.[14,30] It may be difficult to distinguish them from reactive alveolar epithelium, but easier to differentiate from bronchial cells since they do not contain cilia formation. Some cases exhibit nuclear grooves and intranuclear inclusions, as they tend to have slightly increased nuclear size compared to bronchial and alveolar epithelial cells.[16,27,28,31–33] In this study, we gathered all the cases without overt invasive adenocarcinoma features under the title of Group-1. As expected, some were rather hypocellular and consisted of cells with very low nuclear atypia, others were reminiscent of standard adenocarcinoma and standing just one step behind Group-2 features. Thus, the cases in Group-1 were more heterogeneous compared to counterparts in Group-2 in terms of their cytological features.

FS and imprint cytology are traditional IO assessment methods. SC is a modification of imprint cytology obtained by gently scraping or brushing cells from the freshly cut surface of surgically excised specimens. The diagnostic accuracy of IO FS analysis for small pulmonary nodules has been explored in several publications. The overall concordance rate between FS and final pathology diagnosis exceeds 80% for the lung adenocarcinomas.[10,34,35] However, distinguishing AIS from MIA, or MIA from IA in the FS is complicated due to depending on several conditions. In this study, the overall concordance rate of the cytologic groups and radiologic solid size correlation method in relation to SLN lesions reached 84% (57/68) being compatible with FS results in the recent literature. According to Zhu et al.[36] the reasons for underestimating the IA diagnosis during FS are mostly related to sampling (63%), and interpretation (29%) errors, or rarely to poor quality of the sections (8%). Walts et al.[35] presented their root cause analysis for the discrepancies in FS examination between AIS, MIA, and IA. Their study showed that the most common reasons for FS errors and deferrals originated from either the presence or extent of invasion and sampling issues. The distinction between minimally invasive and invasive lesions in IO examination by FS becomes more difficult as the lesion size gets smaller. Thus, FS errors and deferrals were twice as frequent in lesions smaller than a 1 cm.[35] Since the mean size of the SLNs in our series was 1.32 cm, it may be assumed that they reflect the group in which FS errors and deferrals are more frequently found in the literature.

In their study, He et al.[10] found the concordance rate for AIS or MIA diagnoses between frozen and permanent sections as 63.24%. According to the study by Yeh et al.[37] the overdiagnosis rate of MIA in the FS analysis was 52%. In our results, the overdiagnosis rate of MIA in the IO analysis was 29%, whereas the underdiagnosis rate for IA was 15%. Based on these data, it appears that FS analysis is not a perfect method for determining the degree of SLN invasion. On the other hand, correlating cytological features with radiologic solid size may give even more reliable or at least compatible results with the FS technique for SLNs.

The main issue in the IO approach to these lesions is the tissue's protection, since distinguishing AIS, MIA and lepidic predominant IA also becomes quite controversial in relation to permanent sections. Well-preserved tissue is mandatory to be able to evaluate the invasive focus precisely. Invasion is described basically as the loss of lepidic pattern, either a shift in growth pattern from lepidic pattern to others such as acinar and papillary patterns, or the presence of desmoplastic stroma invaded by groups of tumor cells.[17]

The cytologic and radiologic solid size correlation technique has been found very useful, especially for deciding if the targeted P-GGN lesion is surgically removed. Because P-GGN lesions may be quite vague on palpation and macroscopic examination making their identification challenging to surgeons and pathologists, they are usually removed by their anatomic location with the least possible amount of lung parenchyma. All AIS lesions could be recognized as low-grade neoplastic lesions by cytology. Informing the surgeon about the lesion being removed and lacking severe atypia is an adequate answer during IO consultation, even if the diagnosis eventually turns out to be a benign lesion similar to the bronchiolar adenoma case in our series.

We managed to create a separate group (Group-0) to define benign or non-neoplastic conditions that may be encountered, upon reviewing all the cases. However, we failed to create criteria to identify this group of lesions. As known, non-neoplastic lesions are mostly hypocellular compared to neoplastic ones. Scattered inflammatory cells and alveolar macrophages could be dominated in the inflammatory conditions. Benign pulmonary lesions with radiologic SLN appearance are unlikely expected to share atypical nuclear features. Moreover, cilia formation is very helpful for distinction from neoplastic lesions. Some bizarre, atypical cells may be observed in particular cases, perhaps due to the treatment effect or reactive processes. Obtaining and looking through the clinical history is important for the differentiation of these cases.

Bronchiolar adenomas are benign pulmonary neoplasms that may have different sizes of solid or subsolid radiologic features. This entity includes the classical ciliated muconodular papillary tumor (CMPT) (Proximal type) and the non-classical CMPT (Distal type).[38] Our series included two (2) bronchiolar adenomas, with none of them being identified appropriately based on their cytologic features only. In one case, the smears were hypocellular with scattered ciliated cells and mucus in the background, hence it was interpreted as "favor NN" (Proximal type). The other was classified as "favor AIS" having moderate cellular smears with mild atypical features and no cilia formation in the epithelial cells (Distal type). It is assumed that FS analysis would also be inefficient in recognizing this lesion because the presence of ciliated cells is potentially the best clue for the correct interpretation. The problem is that bronchiolar adenomas of distal type do not manifest ciliated cells, as they are generally diagnosed by highlighting the two-cell layer lining on the tubular/alveolar spaces through immunohistochemistry. In the histopathologic examination, they also tend to mimic AIS or MIA. The other potential challenge for the IO examination was the recognition of organizing pneumonia and other non-neoplastic diseases. There were only three (3) non-neoplastic cases in our series, all of them being diagnosed as 'favor NN'. However, they may pose a diagnostic difficulty if they contain more prominent atypia for some

reason. "non-neoplastic/benign condition" diagnosis for a GGN lesion is usually sufficient for most thoracic surgeons during IO evaluation. Their cytologic properties guarantee their formal isolation from malignant tumors. They had more hypocellular smears than neoplastic ones.

Group-2 cases were statistically separated from Group-1 cases by a radiologic 0.57 cm solid size threshold. Since nearly all the Group-2 cases were diagnosed as invasive adenocarcinomas at the end, the surgery team might expect to receive a "favor IA" categorization intraoperatively for SLNs with a solid component larger than 0.57 cm according to the study findings. At the same time, this finding is important in terms of repeating the reliability of the radiological solid diameter to predict IA.

In addition, this study has emphasized some other important concerns that may be encountered depending on the FS process. The most critical aspect is the possibility of complete loss or reduction of the invasive focus due to severe shaving. In some cases, FS artifacts cause difficulties in the evaluation of permanent sections. This problem can be even more important if the lesion is sampled in a single paraffin block. Therefore, the pathologists' simultaneous examination of radiological images is crucial before IO management. Also, the surgery team should be aware of the potential risks related to FS. The potentially reasonable approach is to avoid cutting small lesions in the IO examination and leave the diagnosis to permanent sections with further use of intraoperative SC to ensure a more reliable approach to SLNs. On the other hand, if the lesion is categorized as "favor IA" and the surgeons decide to extend the resection from sublobar to lobectomy following this diagnosis, then the pathologist might add the FS technique to validate the "favor IA" diagnosis that is given by cytological/radiological correlation.

As stated, additional frozen sections were also made from some cases in this series, but the intraoperative accuracy rates of these frozen sections were not compared with the results of cytology/radiology-based diagnosis. For sure, evaluating frozen sections together with the radiological solid size measurements will also increase the accuracy of intraoperative diagnosis in early-stage lung adenocarcinomas. Since we did not make a comparison in this direction, we are unable to say which of these two approaches is better than the other. Nevertheless, it should not be disregarded that the cytological scraping method protects the tissue in contrast to frozen sections.

The main limitations of this study are the low number of cases in some subtypes of lesions as well as its retrospective design. However, this might be the first study in English literature that focused on combining cytological and radiological features for the IO examination of SLNs. While constructing this study, we aimed to find a practical cytological approach to be applied by any pathologist interested in pulmonary pathology. Radiological solid size measurement is the simplest and most accessible approach among radiological parameters which has the potential to clarify the nature of SLNs. We believe that combining cytological features of the lesions with the radiological solid part measurements provides a reliable construct for the IO management of SLNs. This approach should be tested prospectively in much larger series and contexts. In addition, the method's interobserver variability should also be investigated, since all the cytological assessments are performed by the same pathologists in this study.

5 | CONCLUSION

The radiologic SLN terminology does not refer to a specific lesion, but it is critical to identify its potential neoplastic origins that would further define the treatment plan and the surgical procedure applied. The cytological features of SLNs provide valuable information easily obtained via the IO examination. However, it cannot ensure the reliable output on the tumor's invasiveness alone, except for the cases having severely atypical cytological features consistent with clear-cut adenocarcinoma (Group-2). Therefore, we managed to combine the cytological features with the solid size in radiology, which is one of the most reliable parameters in the radiological evaluation of SLNs. It became possible to learn whether the cases with mild atypical cytological features (Group-1) were representing preinvasive or invasive tumors with much higher accuracy. Although CT findings can aid in identifying the malignant characteristics of GGNs, our data revealed that accuracy rates increase when the lesions are cytologically shown to be neoplastic. In addition, if an SLN undoubtedly shows severe cytological atypia compatible with adenocarcinoma, regardless of the solid size on CT, it is most likely a case of invasive adenocarcinoma. We concluded that combining cytological and radiological findings intraoperatively allows the identification of the nature of SLNs with at least equal or even higher accuracy than the traditional FS method which also preserves tissue for detailed analysis and precise categorization of these lesions in permanent sections.

Subsolid lung nodules are unique lesions and thus should be handled with care and caution at every stage of the examination, since the diagnosis and the scope of the surgical procedure applied varies by the millimeter of the invasive focus. It is expected that subsolid lung nodules and the frequency of their intraoperative examination will increase over time.

AUTHOR CONTRIBUTIONS

Pınar Bulutay, **Pınar Fırat**, and **Serhan Tanju**: Involved in the concept and designation of the study. **Pınar Bulutay**: Performed the literature search, analyzed the results and wrote the manuscript. **Pınar Fırat**: Analyzed the cytologic groups' definitive criteria and reviewed the manuscript thoroughly. **Çetin Atasoy**: Measured the solid and total sizes of the cases and was involved in the manuscript review from a radiologist's perspective. **Şükrü Dilege**, **Suat Erus**, and **Serhan Tanju**: Involved in the manuscript review from the perspective of a thoracic surgeon.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare relevant to this article's content.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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