

# Diagnostic Approach to Solitary Pulmonary Nodules Discussed in Multidisciplinary Lung Cancer Council

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## ABSTRACT

**Objective:** The primary goal in solitary pulmonary nodule (SPN) management is to distinguish malignant lesions from benign ones. In our study, we aimed to evaluate the follow-up results, malignancy rates, and risk factors for malignancy of SPNs, which were discussed in our multidisciplinary lung cancer council (MLCC) with suspicion of malignancy and decided for surgical treatment.

**Methods:** Cases that were decided for surgical diagnosis and treatment after evaluation in the council were included in our study, which was planned prospectively. Demographic features, nodulsize, radiological features, location, Positron Emission Tomography (PET) findings, whether bronchoscopy and endobronchial ultrasonography were performed and their results, duration of follow-up before surgery, interventions and their results made for diagnosis, surgical method performed, and the final diagnosis were recorded. Chi-square and Mann–Whitney U tests were used in statistical analysis.

**Results:** Of the 33 cases in our study, 10 (30.3%) were female and 23 (69.7%) were male; the average age was  $60.2 \pm 7.9$  (min:42;max:77) years. The average diameter of SPN was measured as  $16.5 \pm 6.3$  (min:7; max:30) mm. When looking at their locations, it was seen that 72.7% were located in the upper lobes. 75.8% of the nodules were solid in character, 39.4% had spiculated contours, and 33.3% had lobulated contours. There was no calcification in 87.9% of the nodules. In the PET computed tomography examination, the average SUVmax value of nodules was measured as  $6.05 \pm 6.01$  (min:0; max:22), and there was no FDG uptake in the mediastinal lymph nodes of 21 (63.6%) cases. Surgical intervention was decided in 27 (81.8%) cases without a diagnosis. The final diagnosis was malignancy in 69.7% of cases. A statistically significant correlation was found between the final diagnosis and the edge features of the nodule and the SUVmax value ( $p=0.021$ ,  $p=0.048$ , respectively).

**Conclusion:** Since SPN can represent early-stage primary lung cancer, risk factors and radiological features for each patient in SPN management should be individually assessed, and decisions should be made with a multidisciplinary approach. The aim is to minimize the outcomes of over-investigation, including patient anxiety and cumulative radiation exposure, while identifying nodules representing early malignancy.

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## INTRODUCTION

Solitary Pulmonary Nodule (SPN) etiology includes both benign and malignant diseases. Granulomatous lesions and hamartomas are among the most common benign diseases, while primary lung cancer and metastases are the most common malignant diseases. Also, inflammatory diseases, vascular lesions, and congenital diseases can cause SPN.<sup>[1]</sup> The approach to SPN is of critical importance due to SPN being the precursor lesion of lung cancer and lung

cancer being among the most common cancers.<sup>[2]</sup> In the USA, 150,000 SPN cases are reported annually, and the prevalence of SPN in screenings of individuals with high risk for lung cancer is determined to be 8–51%.<sup>[2,3]</sup> In another study, the prevalence of malignancy in patients with SPN was shown to vary between 2% and 23%.<sup>[4]</sup>

Various guidelines have established management algorithms for SPNs. Our primary goal is to differentiate malignant nodules from benign ones. Several patient characteristics have been defined as risk factors for pulmonary

malignancy. These include advanced age, female gender, history of smoking, family history of lung cancer, the patient's own history of previous cancer, and exposure to asbestos and radon.<sup>[5]</sup> To best assess the patient in SPN, a comprehensive history along with the patient's radiological features should be evaluated together.

When evaluating a SPN radiologically, some clues have been identified to assist in risk stratification. These include edge characteristics, nodule size, doubling time of the volume, location, density, and calcification. Typically, benign nodules have smooth-bordered edges, while malignant nodules have irregular, lobulated, spiculated contours.<sup>[6]</sup> The size of the nodule is positively associated with the risk of malignancy. Fleischner's advice on nodule size is to take the average of the long and short axis diameters.<sup>[7]</sup> While malignant nodules typically have a growth rate between 30 and 400 days, the doubling time of volume for lung cancer has been reported as an average of 139 days.<sup>[8]</sup> In terms of location, although the site of the SPN is not used as a criterion for malignancy on its own, the upper lobe location is associated with an increased risk of malignancy.<sup>[5]</sup> The probability of malignancy increases as the ground-glass content in SPN increases, but the likelihood of malignancy is lower for nodules with pure ground-glass opacity compared to semi-solid nodules.<sup>[5]</sup> Calcification patterns of nodules in radiological imaging can be helpful in determining whether the nodules are benign. While benign nodules typically show diffuse, central, layered, and popcorn calcification, malignant nodules more commonly show punctate and eccentric calcification.<sup>[9]</sup>

When patient and nodule characteristics in SPN are evaluated as a whole, it can be easier to estimate the risk of malignancy in the nodule. Clinicians can classify this risk qualitatively or use quantitative models. There are various risk analysis calculators, including the American College of Chest Physicians (ACCP), Mayo Clinic, Bayesian, Veteran Affairs, Brock University, and Herder models.<sup>[5]</sup> In these models, the likelihood of the nodule being malignant can be calculated as a percentage using the characteristics of the patient and the nodule. As a result of these calculations, treatment and follow-up plans can be made according to risk groups. The ACCP risk model is recommended in the Fleischner guide.<sup>[10]</sup> For patients in the low-risk group, tomographic follow-up is recommended at varying frequencies, depending on the structure and size of the nodule.<sup>[11]</sup> For patients in the high-risk group, if the patient is suitable for surgery, it is recommended to perform wedge resection primarily with video-assisted thoracoscopic surgery.<sup>[12]</sup>

A SPN can be a benign lesion that does not require surgical intervention, or it can be a primary lung cancer that achieves high survival rates with surgical treatment. Therefore, it is critically important to evaluate SPN cases in multidisciplinary lung councils with clinical, radiological, and risk factors on a patient basis. In our study, we aimed to evaluate the follow-up results, malignancy rates, and risk factors for malignancy of patients we discussed in the multidisciplinary lung council due to the risk of malignancy.

## MATERIALS AND METHODS

Of the 33 patients who were diagnosed with SPN, discussed in the multi-disciplinary lung council due to the risk of malignancy, for whom we decided on surgical diagnosis and treatment, and who accepted to participate in the study, they were included in our study from December 2019 to December 2020. Our study is prospectively planned research. Based on the data obtained from literature reviews, the demographic characteristics of the cases, the size of the nodule, its radiological characteristics, its location, PET computed tomography (PET-CT) findings, whether bronchoscopy and EBUS were performed and their results, the preoperative follow-up period, the interventions performed for preoperative diagnosis and their results, the surgical method used, and the final diagnosis were recorded. Statistical analyzes were performed using the SPSS

19.0 (IBM Corporation, Armonk, NY, USA) package program. Chi-square and Mann-Whitney U tests were used. The study (No. 2023/514/254/22; Date: July 19, 2023) was approved by the ethics committee, and an informed consent form was obtained. It was conducted in accordance with the Declaration of Helsinki.

## RESULTS

Of the 33 cases included in our study, 10 (30.3%) were female 23 (69.7%) were male; the average age was  $60.2 \pm 7.9$  (min:42; max:77) years. When patients were evaluated according to inclusion and exclusion criteria, patients with primary tumors were not included in the study. When we evaluated the characteristics of the nodule radiologically, the average diameter of the SPN was measured as  $16.5 \pm 6.3$  (min:7; max:30)mm. It was seen that the nodule diameter of 27 (81.8%) patients was 2 cm or less. When their locations were examined, it was found that 42.4% were in the right upper lobe, 30.3% were in the left upper lobe, and 72.7% were located in the upper lobes (Figure 1). When the nodules were evaluated according to their edge characteristics, 39.4% had spiculated contours, and 33.3% had lobulated contours. While 25 (75.8%) of the nodules had a solid component, 8 (24.2%) were semi-solid

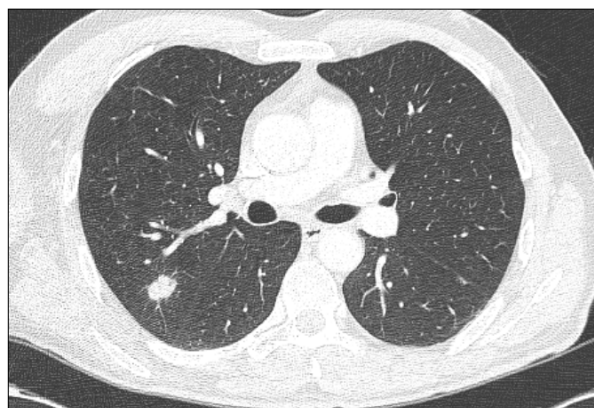


Figure 1. Right lung upper lobe posterior segment solid nodule.

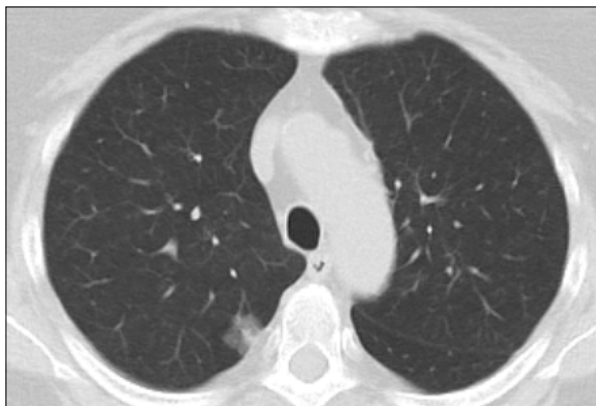


Figure 2. Right lung upper lobe posterior segment semisolid nodule.

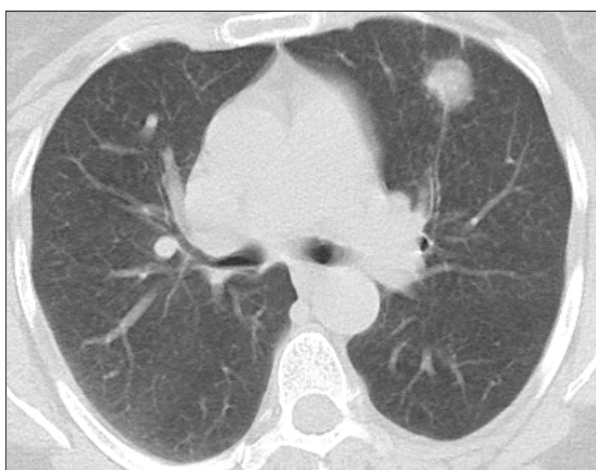


Figure 3. Left lung upper lobe lingular segment ground glass nodule.

(Figures 2 and 3). When evaluated according to whether they contained calcification, 89.9% of the nodules had no calcification. When looking at the follow-up periods from the initial diagnosis to surgical treatment of the nodules, it was calculated as an average of  $1.52 \pm 3.6$  (min:0; max:15) months. In the PET-CT examination, the average SUVmax value of the nodules was measured as  $6.05 \pm 6.01$  (min:0; max: 22), and there was no FDG uptake in the mediastinal lymph nodes in 21 (63.6%) cases. When the diagnostic tests performed on the patients were examined, 24 patients underwent video bronchoscopy, and 6 patients underwent transthoracic needle aspiration biopsy. EBUS was performed for diagnostic and staging purposes in patients with mediastinal lymph node involvement and in need of staging. Thus, malignant patients were staged along with their diagnosis. A surgical decision was made for 27 cases evaluated in our multidisciplinary lung council without diagnosis. While the final diagnosis was malignancy in 69.7% of the cases, it was benign in 30.3%. When the nodule characteristics of patients with malignant outcomes were examined, a statistically significant relationship was found between the edge of the nodule and malignancy ( $p=0.021$ ). All nodules with spiculated contours and 81.8% of nodules

with lobulated contours were malignant. At the same time, 56.5% of the malignant nodules had spiculated contours, 39.1% had lobulated contours, and 13.0% had smooth contours. There was also a statistically significant relationship between the SUVmax value of the nodule and the final diagnosis ( $p=0.048$ ). The average SUVmax value of malignant nodules was 8.61, and the average SUVmax value of benign nodules was 3.5. No relationship was found between age, gender, nodule localization, presence of calcification, and structure of the nodule and the final diagnosis.

## DISCUSSION

In our study, the final diagnosis was found to be malignancy in 23 (69.7%) of the 33 patients who were diagnosed with SPN, discussed in the multidisciplinary lung council with the suspicion of malignancy, and received a histopathological diagnosis. When the radiological characteristics of SPN were examined, a statistically significant relationship was found between the edge of the nodule and malignancy. There was also a statistically significant relationship between the SUVmax value of the nodule and the final diagnosis.

When literature data for cancer prevalence in SPN were examined, in a study conducted by Li et al.<sup>[13]</sup> at Wuhan Central Hospital in China involving 496 patients with histopathological diagnosis, it was found that 425 patients were diagnosed with malignant tumors and 71 patients were diagnosed with other non- malignant lung diseases. In a study involving 244 patients in the United Kingdom, it was shown that 99 (40.6%) patients had malignant nodules.<sup>[14]</sup> In a study conducted by Sim et al.,<sup>[15]</sup> 85% of 186 patients with pathologically confirmed diagnosis were reported to be malignant, and 15% had benign pathology. In a study by Schultz et al.<sup>[16]</sup> involving 151 patients, the prevalence of malignancy was 44%. In a study conducted in the Netherlands involving 106 patients, it was shown that 61 patients (57%) had malignant nodules.<sup>[17]</sup> When the data of our country are examined, in a study conducted by Caylak et al.<sup>[18]</sup> involving 110 patients, 35% of the nodules were observed as malignant, and 65% were benign. There are different rates related to SPN malignancy prevalence in the literature. In our study, it was found that 69.7% (23 patient) of 33 patients with histopathologically confirmed SPN diagnosis had malignant nodules.

Evaluating the edge features of a nodule morphologically when assessing an SPN in risk classification is an important clue. In radiological imaging, a spiculated edge is a finding supporting malignancy.<sup>[19]</sup> The positive predictive value for malignancy is between 88 and 94%.<sup>[20]</sup> In the literature, nodules with spiculated edges are almost always defined as an indicator of malignancy in most of all studies.<sup>[19-23]</sup> The lobulated edge has also been shown to be the ultimate precursor of SPN malignancy in some studies.<sup>[6,23]</sup> Consistent with the literature data, our study found a statistically significant relationship between the edge characteristics of the nodule and malignancy.

Because cancer cells have high metabolic activity, positron emission tomography (PET-CT) is used in functional imaging to differentiate between benign and malignant diseases. PET-CT is recommended for nodules 8–10 mm and larger in diameter, and the possibility of malignancy increases in nodules with PET-CT uptake and a SUVmax value above 2.5.<sup>[24]</sup> In a retrospective study involving SPN patients, the sensitivity of PET-CT was evaluated at 97% and the specificity at 85%.<sup>[25]</sup> In a study by Yilmaz et al.<sup>[26]</sup> involving 241 patients, when average SUVmax values were compared according to nodule diameter, the average SUVmax value of the patients was found to be significantly higher in patients with nodule diameter  $\geq 1$  cm, and the average SUVmax value of malignant nodules was significantly higher. In our study, a statistically significant relationship was found between the SUVmax value of the nodule and malignancy. The average SUVmax value of the nodules was measured as  $6.05 \pm 6.01$  (min:0; max:22). When mediastinal lymph nodes were evaluated with PET-CT, there was no FDG uptake in the mediastinal lymph nodes of 21 (63.6%) cases.

In SPN, the risk of malignancy increases as the nodule size increases. Nodule size is an independent indicator of malignancy risk. More than 80% of benign nodules have a diameter  $< 2$  cm. However, 15% of malignant nodules have a diameter  $< 1$  cm, and 42% have a diameter  $< 2$  cm.<sup>[27]</sup> Numerous studies have shown that as nodule size increases, the risk of malignancy increases.<sup>[5,7,21–23]</sup> In our study, the average diameter of the nodules was measured as  $16.5 \pm 6.3$  (min:7; max:30) mm, and no significant relationship was shown between nodule size and malignancy. When the nodule sizes of the patients were examined, it was seen that the nodule diameter of 27 (81.8%) patients was 2 cm or below. Twenty of these patients had a malignant diagnosis. At the same time, 69.7% of all patients in our study had histopathological malignancies. This situation shows us the importance of diagnostic biopsy for smaller-sized SPNs as well.

According to the Fleischner guide, the upper lobe location of the nodule and suspicious morphology increase the risk of malignancy.<sup>[7]</sup> In a study conducted by McWilliams et al.,<sup>[5]</sup> the upper lobe location of the nodule was shown to be associated with an increased risk of malignancy. In a study conducted by Swensen et al.,<sup>[21]</sup> the upper lobe location was determined as an independent determinant of malignancy. In our study, when the locations were examined, 42.4% were in the right upper lobe, 30.3% were in the left upper lobe, and 72.7% were located in the upper lobes, but no significant relationship was found between localization and malignancy. Regarding the density of the nodule, according to the Fleischner guide, the malignancy rate of semisolid nodules is higher than that of solid nodules. The studies conducted also support this situation.<sup>[5]</sup> However, in our study, no significant relationship was shown between malignancy and nodule structure.

In SPN, the presence and pattern of calcification are parameters evaluated in the differentiation of benign and malignant diseases.<sup>[9]</sup> In a study conducted by Toomeset al.,<sup>[28]</sup>

92% of calcified SPNs were benign. In a study conducted by Yilmaz et al.,<sup>[26]</sup> similar to these data, it was shown that the average SUVmax value in calcified SPN was lower than non-calcified ones. In our study, however, 89.9% of the nodules had no calcification, and no significant relationship was found between malignancy and calcification.

Several guidelines have been developed for SPN follow-up. The Fleischner Society guideline suggests a CT follow-up after 3 months, a PET-CT scan, and/or biopsy for solid nodules larger than 8 mm in high-risk patients. For ground-glass nodules larger than 6 mm, they recommend a CT follow-up every 6–12 months, followed by a CT follow-up every 2 years up to 5 years. For semisolid nodules larger than 6 mm, they recommend a CT follow-up every 3–6 months, followed by an annual CT follow-up up to 5 years.<sup>[7]</sup> The ACCP 2013 guideline suggests tissue diagnosis if growth is observed during the follow-up of a nodule smaller than one centimeter and a candidate for surgery.<sup>[28]</sup> In our study, when we looked at the follow-up periods from the initial diagnosis of the nodules to the surgical procedure, it was determined to be an average of  $1.52 \pm 3.6$  (min:0; max:15) months. We see that the follow-up time in our study is shorter than the guidelines' recommendations. When we look at the histopathological diagnoses of the nodules, the fact that a high rate like 69.7% is of malignant character suggests that a definitive judgment cannot be made without a tissue diagnosis, even though important approaches are obtained with various models to determine the risk of malignancy of the nodule. In a study conducted among pulmonologists, chest surgeons, and radiologists in SPN follow-up, a survey study was conducted on the same cases with specialist doctors, and the preferred treatment approach was evaluated. Significant differences were observed in the treatment approach in all three specializations.<sup>[29]</sup> This situation suggests the importance of discussing the cases in multidisciplinary councils attended by pulmonology, chest surgery, radiology, medical oncology, and radiation oncology.

## Conclusion

In conclusion, with this study, the follow-up results of SPNs discussed in the multidisciplinary lung council, malignancy rates, and risk factors for malignancy have been evaluated. The approach to SPN is critically important on one hand due to the possibility of achieving a cure with surgical resection for primary lung cancer and, on the other hand, because of the possibility of a benign nodule being directed to surgery with an aggressive approach. The aim is to minimize the outcomes of over-investigation, including patient anxiety and cumulative radiation exposure, while identifying nodules representing early malignancy. At this stage, the patient's preferences can also guide the decision. The situation can be discussed in detail with the patient, and a joint decision can be made while staying true to medical terminology. For nodules carrying a high risk of malignancy, histopathological verification at this stage can provide a chance for cure in diagnosed lung cancers, while a conservative approach favoring waiting can rob the

patient of their chance for a cure. Although various algorithms are used to determine the risk of malignancy of the nodule, a definitive judgment cannot be made without a tissue diagnosis. In SPN management, risk factors and radiological characteristics for each patient should be evaluated individually, and decisions should be made with a multidisciplinary approach.

### Limitations

The study's limitations include being a single-center study and having a limited sample size. Also, the study being based on a population referred for biopsy or surgery can lead to selection bias.

### Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 19.07.2023, Decision No: 2023/514/254/22).

### Informed Consent

Retrospective study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: S.Ş.C., R.D.; Design: S.Ş.C., R.D.; Supervision: S.Ş.C., R.D.; Fundings: E.E.G., H.Ç.E.; Materials: E.E.G., K.B.Ö.; Data: H.Ç.E., E.E.G.; Analysis: N.K., K.B.Ö.; Literature search: H.Ç.E., N.K.; Writing: H.Ç.E.; Critical revision: H.Ç.E., K.B.Ö., N.K.

### Conflict of Interest

None declared.

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## Multidisipliner Toraks Konseyinde Tartışılan Soliter Pulmoner Nodüllere Tanısal Yaklaşım

**Amaç:** Soliter akciğer nodülü (SPN) yönetiminde ana hedef malign lezyonları benign lezyonlardan ayırabilmektir. Çalışmamızda malignite şüphesiyle multidisipliner akciğer kanseri konseyimizde (MAKK) tartışılan ve cerrahi tedavi kararı verilen SPN'lerin izlem sonuçları, malignite oranları ve malignite için risk faktörlerini değerlendirmeyi amaçladık.

**Gereç ve Yöntem:** Prospektif olarak planlanan çalışmamıza MAKK'ye cerrahi girişim önerisi ile çıkardığımız ve konseyde değerlendirerek cerrahi tanı ve tedavi kararı verdiğimiz olgular dahil edildi. Olguların demografik özellikleri, nodül boyutu, radyolojik özellikleri, yerleşimi, Pozitron Emisyon Tomografisi bulguları, bronkoskopi ve endobronşial ultrasonografi yapıp yapılmadığı ve sonuçları, cerrahi öncesi takip süresi, tanı için yapılan girişimler ve sonuçları, yapılan cerrahi metodu ve final tanı kayıt altına alındı.

**Bulgular:** Çalışmamızdaki 33 olgunun 10'u (%30.3) kadın, 23'ü (%69.7) erkek; yaş ortalamaları  $60.2 \pm 7.9$  (min: 42; maks: 77) yıl idi. SPN'nin ortalama çapı  $16.5 \pm 6.3$  (min: 7; maks: 30) mm ölçüldü. Yerleşimlerine bakıldığında %72.7'sinin üst loblarda yerleştiği görüldü. Nodüllerin %75.8'i solid özellikte olup, %39.4'ü spiküler konturlu, %33.3'ü lobüle konturlu idi. Nodüllerin %87.9'unda kalsifikasyon yoktu. PET-CT incelemesinde nodüllerin ortalama SUVmaks değeri  $6.05 \pm 6.01$  (min: 0; maks: 22) olarak ölçüldü ve 21 (%63.6) olgunun mediastinal lenf bezlerinde FDG tutulumu yoktu. 27 (%81.8) olguya tanısız olarak cerrahi girişim kararı verilmişti. Olguların %69.7'sinde final tanı malignite idi. Final tanı ile nodülün kenar özellikleri ve SUVmaks değeri arasında istatistiksel olarak anlamlı bir ilişki saptandı ( $p=0.021$ ,  $p=0.048$ ).

**Sonuç:** SPN erken evre primer akciğer kanserini temsil edebileceğinden SPN yönetiminde her hasta için risk faktörleri ve radyolojik özellikleri bireysel olarak değerlendirilmeli ve multidisipliner yaklaşımla karar alınmalıdır. Amaç, erken maligniteyi temsil eden nodülleri tespit ederken, hasta kaygısı ve kümülatif radyasyon maruziyeti dahil olmak üzere aşırı incelemenin sonuçlarını en aza indirmektir.

**Anahtar Sözcükler:** Benign; cerrah; malign; soliter pulmoner nodül.