Fast and Effective Diagnosis in Solitary Pulmonary Nodules: Video Assisted Thoracic Surgery

Soliter Pulmoner Nodüllerde Hızlı ve Etkili Tanı: Video-Yardımlı Göğüs Cerrahisi

Erdoğan DADAŞ,[a]
Berker ÖZKAN,[b]
Serhan TANJU,[c]
Alper TOKER,[b]
Şükrü DİLEGE[d]

[a]Department of Thoracic Surgery, Adıyaman University Faculty of Medicine, Adıyaman
[b]Department of Thoracic Surgery, İstanbul University İstanbul Faculty of Medicine,
[c]Clinic of Thoracic Surgery, Vehbi Koç Foundation American Hospital,
[d]Department of Thoracic Surgery, Koç University Faculty of Medicine, İstanbul

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Yazışma Adresi/*Correspondence:*
Erdoğan DADAŞ
Adıyaman University Faculty of Medicine, Department of Thoracic Surgery, Adıyaman, TÜRKİYE/TURKEY
erdogandadas@yahoo.com

ABSTRACT Objective: Despite the developments in imaging techniques, and mostly the determination of solitary pulmonary nodules being detectable, the optimal management of the solitary pulmonary nodules is still controversial. The aim of this study is to evaluate the effectiveness of the diagnostic tests and determine a fast and effective approach to solitary pulmonary nodules. **Material and Methods:** Records of the 82 patients with solitary pulmonary nodule who underwent open resection or video-assisted thoracic surgery for certain diagnosis or treatment between December 2001 and June 2011 were examined retrospectively. The patients were evaluated in terms of age, sex, smoking history, existence of extra-thoracal malignancy, imaging techniques, invasive procedures including bronchoscopy and/or thorax computerized tomography guided transthoracic needle biopsy, surgical processes, morbidity, mortality and histopathologic diagnosis. **Results:** Surgical tissue diagnoses were provided for all patients. Video-assisted thoracic surgery was used to get the tissue diagnoses in 53 patients, and open lung biopsy was used in 26 patients. In 3 cases the tissue diagnoses were obtained by thorax computerized tomography-guided transthoracic needle biopsy. Forty-four of the patients underwent surgical anatomic resection at the same session. Definitive diagnoses consisted of 49 (60%) malignant lesions, and 33 (40%) benign lesions. All patients were evaluated with thorax computerized tomography, 60 of them underwent positron emission tomography and 35 patients had invasive procedures consisting of bronchoscopy and/or thorax computerized tomography-guided transthoracic needle biopsy. The rate of definitive diagnosis by thorax computerized tomography-guided transthoracic needle biopsy was only 14%, while definitive diagnosis could not be obtained by bronchoscopy in any patients. General diagnostic accuracy rates, sensitivity, specifity, negative and positive predictive values between positron emission tomography and thorax computerized tomography were statistically non-significant. **Conclusion:** After radiological evaluation with thorax computerized tomography, we have considered that an option should be advised to the patients, skipping other diagnostic tests, and administering video assisted thoracic surgery to patients to provide a tissue diagnosis. Also if indicated and in proper cases, administering anatomic resection at the same session might be possible.

Key Words: Solitary pulmonary nodule; diagnostic imaging; thoracic surgery, video-assisted

ÖZET Amaç: Görüntüleme tekniklerindeki gelişmelere ve daha çok pulmoner nodülün saptanır olmasına rağmen, soliter pulmoner nodüllere optimal yaklaşım belirsizliğini korumaya devam etmektedir. Bu çalışmanın amacı, tanısal testlerin etkinliğinin değerlendirilerek soliter pulmoner nodüllere hızlı ve etkili bir yaklaşım belirlemektir. **Gereç ve Yöntemler:** 2001 Aralık-2011 Haziran tarihleri arasında, kesin tanı veya tedavi amacı ile açık rezeksiyon veya video-yardımlı göğüs cerrahisi uygulanan 82 soliter pulmoner nodüllü hastanın kayıtları retrospektif olarak incelendi. Hastalar yaş, cinsiyet, sigara hikayesi, toraks dışı malignite varlığı, görüntüleme yöntemleri, bronkoskopi ve toraks bilgisayarlı tomografi eşliğinde transtorakal iğne biyopsiyi içeren girişimsel işlemler, uygulanan cerrahi işlemler, morbidite, mortalite ve histopatolojik sonuçlar açısından değerlendirildi. **Bulgular:** Tüm olgularda cerrahi doku tanısı sağlandı. Elli üç hastada doku tanısı elde etmek için video-yardımlı göğüs cerrahi kullanılırken 26 hastada açık akciğer biyopsisi kullanıldı. Üç olguda ise doku tanısı toraks bilgisayarlı tomografi eşliğinde transtorakal iğne biyopsisi ile elde edildi. Kırk dört olguda aynı seansta cerrahi anatomik rezeksiyon uygulandı. Kesin tanılar, 49 (%60) malign, 33 (%40) benign lezyonlardan oluşmaktaydı. Tüm hastalar toraks bilgisayarlı tomografi ile değerlendirilirken, 60 hastaya pozitron emisyon tomografi, 35 hastaya bronkoskopi ve/veya toraks bilgisayarlı tomografi eşliğinde transtorakal iğne biyopsisinden oluşan girişimsel işlemler uygulandı. Bronkoskopi ile hiç bir hastada kesin tanı elde edilemezken, tomografi eşliğinde transtorakal iğne biyopsi ile kesin tanı oranı sadece %14 idi. Genel tanısal doğruluk oranı, sensitivite, spesivite, negatif ve pozitif prediktif değer açısından toraks bilgisayarlı tomografi ile pozitron emisyon tomografi arasındaki fark istatistiki olarak anlamlı değildi. **Sonuç:** Toraks bilgisayarlı tomografi ile radyolojik değerlendirme sonrası, diğer tanısal testler atlanarak, cerrahi doku tanısı için, hastalara video-yardımlı göğüs cerrahisinin bir seçenek olarak sunulması gerektiğini düşünmekteyiz. Zira endikasyonu olan, uygun olgularda aynı seansta anatomik rezeksiyonun yapılması mümkün olabilecektir.

Anahtar Kelimeler: Soliter pulmoner nodül; tanısal görüntüleme; göğüs cerrahisi, video yardımlı

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In the USA, approximately 150 000 solitary pulmonary nodules (SPN) are diagnosed per year, and more than 90% of them are diagnosed accidentally.[1] The causes of SPNs vary from primary lung cancer and extra-thoracal malignancies, to lung infections, scar formations and other benign lesions. Modern imaging tests and Thorax Computerized Tomography (CT) guided needle biopsy are highly sensitive for identifying a malignant SPN, but the specificity of imaging tests is variable and often poor.[2] On the other hand, the diagnosis of SPNs is a complex algorithm in which doctors follow different approaches. Performed diagnostic tests show variability, and because of this, in many patients, diagnosing process takes longer time or fails to diagnose. The time between the initial thorax CT and the absolute diagnosis of the SPN assumed to take a long time and should be shortened.[3] The aim of this study is to evaluate the effectiveness of the diagnostic tests and determine a fast and effective approach to SPNs.

MATERIAL AND METHODS

Records of the 82 patients with SPN, who underwent Video-Assisted Thoracic Surgery (VATS) or open resection surgery, in Istanbul University, Istanbul Faculty of Medicine, between December 2001 and June 2011 were examined retrospectively. All patients were evaluated primarily by the administered imaging techniques, invasive diagnostic procedures consisting of bronchoscopy and/or thorax CT-guided Transthoracic Needle Biopsy (TTNB) and surgical procedures, secondarily by their age, sex, smoking history, existence of extra-thoracal malignancy, morbidity, mortality and histopathologic results.

Eighteen of the patients had extra-thoracic malignity, and pulmonary nodule was detected in them in thorax CT during the oncological follow-up period. 13 of these patients had Positron Emission Tomography (PET-CT) and 2 patients had invasive tests consisting of bronchoscopy and/or CT guided TTNB. 64 patients (78%) were diagnosed with pulmonologist/chest diseases specialist with thorax CT, 47 of them had PET-CT, and 33 had invasive tests consisting of bronchoscopy and/or thorax CT-guided TTNB. 3 patients were diagnosed exactly by thorax CT-guided TTNB and underwent surgery for treatment of primary lung Carcinoma, and all other patients underwent surgery for certain diagnoses of SPNs.

Patients who had irregular (spiculated or lobulated) nodules on thorax CT admitted as "radiologically malign", and patients who have regular nodules admitted as "radiologically benign". In PET-CT, the standardized uptake value (SUV_{max}) was greater than 2.5 admitted as malignancy criteria and SUV_{max} was smaller than 2.5 admitted as benignancy criteria.

In our clinic, approach to SPNs was as open surgery via mini-thoracotomy until 2006, since then with our growing experience, VATS has been used commonly. VATS was performed at the operating room under general anesthesia by using double-lumen endotracheal tube allowing opposite side lung ventilation, while it was remaining single lumen in apneic period or atelectatic in the same side lung. The patients were positioned in which the upper arm was ensured to be in abduction position for providing superior displacement of the scapula and in the lateral decubitus position. The first incision was always performed through 5^{th} or 6^{th} intercostal space (ICS)-mid axillary line. 10 mm trocar was placed and 30^{o} telescope was inserted through the camera to thorax. Under thoracoscopic control, 2 more trocars were inserted; one was through 4^{th} ICS-anterior axillary line and the other one was inserted through 5^{th} ICS auscultatory triangle. Under thoracoscopic control, by the help of the graspers, pulmonary nodule was located by finger palpation, excised by endoscopic linear stapler (Endo-Cutter 45 mm. Ethicon Corp., Norderstedt, Germany) and sent to histopathologic analysis.

In primary malign cases and in chosen metastatic cases which the primary tumor was under control and did not have extra-thoracal metastases with adequate values of respiratory function tests, VATS or open anatomic resection (segmentectomy, lobectomy or pneumonectomy) with mediastinal lymph node dissection was ad-

ministered. If the lesion was benign, metastatic or inadequate values of respiratory function test as regards the procedure was ended. For open surgical procedures, different kinds of thoracotomies used, such as anterior thoracotomy, lateral thoracotomy or posterolateral thoracotomy.

The patients' data were retrospectively and statistically analyzed in terms of relationship between the dimension of nodules and malignancy, the values of sensitivity, specifity, positive predictive value (PPV), negative predictive value (NPV) and general diagnostic accuracy rates of thorax CT and PET-CT, definitive diagnostic rates of bronchoscopy and thorax CT-guided TTNB. All of the patients were instructed, and gave written consents for the surgical procedure.

STATISTICAL ANALYSIS

Data analysis was performed using the computer software Statistical Package for Social Sciences (SPSS) (Chicago, USA) for Windows version (16.0). Pearson's X^2 test was used to determine whether there was any significant difference between the groups. The X^2 test was replaced by Fisher's exact test if the cell frequencies of any of the 2x2 contingency table went below 5.

RESULTS

Fifty one of the patients were male and 31 were female, the male/female ratio was 1.6/1, the mean age was 52.7 years (25-82 years). 52 of the patients (63%) had smoking history or were still smoking. 18 patients were under control for extra-thoracic malignancy. 4 of these patients had breast cancer, 3 of them had renal cell cancer, 3 of them had colorectal cancer and 3 of them had cancers of the head and neck. 1 patient had uterine leiomyosarcoma, 1 patient had bladder cancer, 1 patient had liver cancer, 1 patient had skin cancer and 1 patient had thymoma. Indications for surgery were; malignancy criteria on CT seen in 32 patients, extrathoracic malignancy in 18 patients, radiologically unidentified nodule in 19 patients and surgery was necessary for tissue diagnosis to exclude malignancy in 13 patients (Table 1).

All patients were evaluated with thorax CT. In their CT reports, 73 patients' nodule dimensions were recorded, but in 9 patients' reports there were no record about the dimensions of the nodule. In 47 cases (64%), nodule dimensions were between 8-20 mm (little nodules) and the mean nodule dimension was 14.75 mm, and in 26 cases (36%) the dimensions were between 21-30 mm (bigger nodules), and the mean nodule dimension was 25.5 mm. 28 of the little nodules (60%), and 17 of the bigger nodules (65%) were malignant. The relationship between the dimensions of the nodule and malignancy were not statistically significant (X^2=0,002, df=1, p>0,05).

Despite every patient in the study had thorax CT, only 51 of them had edge specifications. 37 of them had malignancy criteria, and 14 of them had benign criteria. The sensitivity of the thorax CT was 84%, specifity was 50%, PPV was 76%, NPV was 64% and general correct diagnosis ratio was 72% (Table 2).

Sixty of the patients (73%) were evaluated with PET-CT. In 42 cases (70%), PET-CT showed

TABLE 1: Patients' characteristics.

Patients number	82
Sex (Male/Female)	51/31
Mean (Ranged)	52,7 yrs (25-82 yrs)
Smoking History	52 patients
Cancer History	
Breast Ca	4
Renal cell Ca	3
Colo-rectal Ca	3
Head and neck Ca	3
Uterus LMS	1
Bladder Ca	1
Thymoma	1
Liver Ca	1
Skin Ca	1
Indications	
Malign Characteristics on CT	32 (39%)
Extra-thoracic malignancy history	18 (22%)
Radiologically indetermined nodules	19 (23%)
Rule out malignancy	13 (16%)

Yrs: Years; LMS: Leiomyosarcoma; Ca: Carcinoma.

TABLE 2: Diagnostic efficacy of CT.

	Finding of CT		
	Malignant (n)	Benign (n)	Overall (n)
Diagnostic Accuracy	76% (28)	64% (9)	72% (37)
False Positive	24% (9)		
False Negative		36% (5)	
Sensitivity			84%
Specifity			50%

TABLE 3: Diagnostic efficacy of PET/CT.

	Finding of PET/CT		
	Malignant (n)	Benign (n)	Overall (n)
Diagnostic Accuracy	81%(34)	61%(11)	75%(45)
False Positive	19%(8)		
False Negative		39%(7)	
Sensitivity			83%
Specifity			57%

malignant properties, and in 18 cases (30%) benign properties were seen. The sensitivity of the PET-CT was 83%, specifity was 57%, PPV was 81%, NPV was 61% and general correct diagnosis ratio was 75% (Table 3). The sensitivity, specifity, PPV, NPV and general correct diagnosis ratio between thorax CT and PET-CT wasn't statistically significant (X^2=0.086, df=1, p>0,05).

Thirty five of the patients (43%) had bronchoscopy and/or thorax CT-guided TTNB (Bronchoscopy in 13 patients, TTNB in 14 cases, and both of them in 8 patients). Only 2 (9.5%) of the 21 patients had endobronchial lesions, who had bronchoscopy, one of them was obstructive who had punch biopsy, and the other case showed blunting in carina and had transbronchial needle biopsy (TBNB). In both cases, no tissue diagnosis were acquired. Only 3 (14%) of the 22 patients who had TTNB could be diagnosed by tissue sample.

In all cases surgical tissue diagnoses were acquired. VATS was administered to 54 patients (66%) totally; in 47 patients (89%) VATS wedge resection was enough for tissue diagnosis, but in 6 patients (11%), intense intrapleural adhesions were seen during exploration with VATS, and because of this, anterior mini thoracotomy was administered and nodule excision and tissue diagnosis was acquired under thoracoscopy. One patient who had tissue diagnosis before surgery underwent VATS anatomic resection directly. In 4 cases, after VATS wedge resection, open anatomic resection was administered. In 28 patients (34%) open surgery was administered directly. In 26 patients, tissue diagnosis was acquired by thoracotomy. 2 patients who had tissue diagnosis before surgery, open anatomic resection was administered directly.

Impending 21 VATS, 23 open anatomic resection, in total of 44 cases (54%), had 5 segmentectomies, 37 lobectomies, 1 bilobectomy and 1 pneumonectomy. The process was terminated after wedge resection was performed in 38 patients (46%). No mortality was seen in the series. In 10 (12%) of all patients morbidity was seen (VATS plus open surgery). 50 patients who had only VATS or VATS plus mini thoracotomy (wedge resection, wedge resection plus anatomic resection, anatomic resection), 3 patients (6%) and 32 patients who had open surgery (initially VATS or directly), 7 patients (22%) had complications after surgery. There were borderline significant difference in morbidity between VATS and open surgery (X^2=3,37, df=1, p=0,06). Pneumonia was seen in 3 of the VATS administered patients. In patients who had open surgery, 2 pneumonia, 1 prolonged air leakage, 1 atrial fibrillation, 1 chilothorax, 1 diaphragm elevation and 1 pneumothorax after drain take-out were seen.

The exact diagnoses of our patients were: 37 (45%) primary lung carcinoma, 12 (15%) metastatic lung carcinoma, 33 (40%) benign. In 11 (61%) of the 18 patients who had extra-thoracic malignancy preoperatively, metastatic lesions started, in 4 (22%) of them benign lesions started, and primary lung carcinoma started in 3 (17%) of them. In one patient, no history of extra-thoracal malignancies, and metastasis of colon carcinoma were detected. Adenocarcinoma was the most frequent primary lung carcinoma (n=15), head & neck and colorectal tumors were the most frequent metastatic lung carcinomas. Hamartomas were the most frequent benign tumors (Table 4).

TABLE 4: Histopathologic description of pulmonary nodules resected by VATS and open surgery.

Malignant	49 (60%)
Primary Lung Cancer	37 (45%)
Adenocarcinoma	22
-Bronchoalveolar Ca	7
-Others	15
Squamous cell Ca	5
Carcinoid tm	6
-Typical	4
-Atypical	2
Large cell carcinoma	2
Mix adeno-large cell carcinoma	1
Inflammatory myofibroblastic tm	1
Metastatic Pulmonary Tumors	12 (15%)
Colo-rectal Ca	3
Head and neck Ca	3
Breast Ca	2
Hepatic Ca	1
Renal cell Ca	1
Bladder Ca	1
Uterus LMS	1
Benign	33 (40%)
Hamartoma	11
Tuberculoma	7
Cyst hidatic	3
Organized pneumonia	2
Fibrocalcific nodule	2
Hyalinized granuloma	1
Fibrocazeous nodule	1
Active Tbc infection	1
Inflammatory cystic bronchial formation	1
Necrotizing vasculitis	1
Abscess formation	1
Inflammatory pseudo-tumor	1
Reactive changes	1

LMS: Leiomyosarcom; Tbc: Tuberculosis; Ca: Cancer; tm: Thoracic malignancy.

DISCUSSION

Recently, helical CT has become more important in imaging lung tumors. Small size pulmonary nodules which can not be detected with conventional radiography can be detected with helical CT. There are a lot of choices in the diagnosis and treatment of the SPNs: Following enlargement, biopsy and resection. Appropriateness of each of these choices is related to these factors below: Radiologic properties, dimensions of the tumor, history of the disease and physical examination. Tumors causing distortion in neighboring vessels, spiculated, possessing irregular margins are related to malignancy.[4] Hasegawa et al.[5] stated the tumor doubling time (VDT) of the SPNs having malignant properties: In pure ground-glass opacities 813±375 days, in mixed or partially ground-glass opacities 457±260 days, in solid opacities 149±125 days. In the same study, the nodules smaller than 10mm in diameter VDT found 536±283 days and nodules greater than 20mm in diameter VDT found 299±273 days.

Clinical specifications and radiologic findings can be used to guess the possibility of cancer. But, according to these parameters, it is impossible to get absolute results.[6] It is essential to determine the type of the SPN for the decision of therapy and planning the treatment strategy. Mostly, cytological or histological confirmation is impossible without surgery.[7,8]

Median test types administered to the patients with SPN take 4, and the time elapsed to get the absolute diagnosis is 41.4 days. Therefore, diagnostic tests are mostly drawn a blank. Age, referring by a specialist, smoking history, positive radiologic malign properties and mediastinal extension affect the number of diagnostic tests to be made. Being older than 65 years, patients who have smoking history or are still smoking, patients referred by a specialist, and patients who have spiculated nodules, significantly increases the number of the tests that will be made. In 22.2% of the patients, before reaching the definitive diagnosis, one of the imaging tests will be repeated at least once. In half of the patients approximately, the invasive diagnostic tests are applied (bronchoscopy, TTNB, TBNB, exploratory thoracotomy). Before getting a definitive diagnosis in 13 % of the patients, one invasive test repeats at least once.[3]

Ciriaco et al. stated that, 130 (86 %) of the 151 patients with SPN, could not be diagnosed by thorax CT-guided TTNB, because of the deep localization of nodule or small dimensions.[9] They stated in the same study, barely in 21 (14 %) patients, they

could acquire definitive diagnosis and they stated in the same study that in all patients bronchoscopy was negative. A meta-analysis of Gould et al. in which they evaluated the accuracy ratio of the tests, effectiveness and cost effectivity, they recommended: 1- For patients in whom the probability of malignancy was low, and if the CT findings promoting malignancy, PET-CT could be used selectively.[10] If PET-CT is positive, surgery is either more effective or cost-effective than TTNB. If PET-CT is negative, TTNB is more effective than follow-up. 2- For patients in whom the probability of malignancy is mid-level, a choice should be made between more aggressive and less aggressive methods related to the postoperative complication risks, the success rate expected from TTNB and the choice of patient. For example, TTNB can be preferred for patients risky for surgery. 3- For patients in whom the probability of malignancy is high, and if the CT findings promoting malignancy, surgery is convenient. Even in patients for whom both CT and PET-CT are not promoting malignancy, TTNB is more effective. These authors have stated that in patients with SPN, TTNB or surgical tissue diagnosis is a "must have".

In our study, thorax CT-guided TTNB diagnosis ratio was very low and also no patients were exactly diagnosed by bronchoscopy. Since SPNs are usually located in peripheral lung parenchyma, it is not surprise that the success rate of bronchoscopy is very low. On the other hand, in our study, success rate of thorax CT-guided TTNB was the same with the results of Ciriaco et al.[9] We think that, bronchoscopy and TTNB applications lengthen the diagnosis process and remain without result.

Khandani and Fielding, in nodules greater than 8mm, with highly risky SPN patients, suggest diagnostic PET instead of CT.[11] The authors stated that, if PET is positive, malign SPN probability is higher than 85% and procedures needed for definitive diagnosis must be started immediately. The same authors stated that in case of negative PET imaging, cancer probability is very low, NPV of PET imaging is above 90% and CT imaging can be excluded and more than 3 months sequences of CT follow-ups could be enough. The authors suggest PET imaging instead of CT, and can not exclude tissue diagnosis for follow-up, they leave an open door saying "maybe" for radiologic follow-ups.

Rena et al., state that PET-CT has a sensitivity of 95%, specifity of 77% and PPV of 87% giving a low specifity ratio in their study.[12] In another study, Jeong et al. state in malign SPN cases giving sensitivity values of CT and PET-CT 82% and 88%, specifity values 66% and 77% and general correct diagnose ratio 72% and 81% respectively.[13] In the same study, values are 61% PPV for CT, 72% for PET-CT, 81% NPV for CT, 90% for PET-CT; and these findings show that in terms of specifity, PET-CT is superior than CT. Lesions show benign characteristics in CT, like satellite nodules, benign calcifications, even if they have malign levels of FDG take-up in PET-CT, should be admitted benign and before surgical resection, percutaneous needle biopsy should be tried. Evangelista et al., determined 77% sensitivity, 85% specifity, 89% PPV, 69% NPV and 80% general correct diagnosis ratio in PET-CT for nodules greater than 8 mm.[14]

In miscellaneous studies, there are very different ratios about the sensitivity, specifity, PPV, NPV and general correct diagnosis rates of PET-CT. In some studies specifity, in some of them sensitivity, in some of them PPV and in some of them, the NPV values are higher, and in result, there is a serious standardization problem about this point. All of these problems cause confusions in daily practice, lengthen the diagnosis process and cause loss of the chance of finding a cure. This situation affects the survival time negatively. In our study, there were no significant differences between CT and PET-CT's sensitivity, specifity, PPV, NPV and general correct diagnose rates.

In a study by Cao et al. the average cost of PET-CT was calculated as $1478.[15] Dale et al., calculated the CT-guided TTNB cost as $2913. Sugi et al. calculated the VATS cost as $3190.[16,17] After all these results, we think that in SPNs, PET-CT do not contribute to the diagnosis, after thorax CT. Despite some studies in which the authors stated the definitive diagnosis ratios being high in CT-guided TTNB, we think quite the opposite. Its ef-

fectiveness, costs, and complications as pneumothorax and hemorrhage are quite often. Forasmuch, nowadays CT imaging is preferred as the first test in many SPNs' diagnosis. Gould et al. think the same as we do, and they suggest thorax CT as the initial test for diagnosis of SPNs.[10]

All lung surface, chest wall and mediastinum can be visualized perfectly with VATS, and with VATS there is no need of costa retraction, there are less postoperative pains and pulmonary function recovery is faster. VATS has almost 100% of sensitivity and specifity and give chance to avoid thoracotomy for benign cases.[3] In our study, VATS provided adequate material in all patients for diagnosis. In our series there is no mortality. Morbidity occured in 6% of our patients whom received VATS. Our study showed that VATS is superior to open surgery in terms of morbidity. With VATS, in most of our cases and in the same session, both definitive diagnosis and surgical treatment were provided.

In result, today, in diagnosis of SPN, VATS has almost 100% of sensitivity and specifity. PET-CT imaging, bronchoscopy and CT-guided TTNB tests are not meaningful for SPN diagnosis. Except for the nodules which are radiologically benign, including calcification, or in two year follow-up showed no growth. We think that VATS is better approach for early, correct and cost-effective diagnosis of SPNs which is bigger than 8 mm on thorax CT. However, more studies are needed to determine minimal invasive methods for certain diagnose of the SPNs.

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