We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Malignant Pulmonary Solitary Nodules: High Resolution Computed Tomography Morphologic and Ancillary Features in the Differentiation of Histotypes

Michele Scialpi, Teresa Pusiol, Irene Piscioli, Alberto Rebonato, Lucio Cagini, Lucio Bellantonio, Marina Mustica, Francesco Puma, Luca Brunese and Antonio Rotondo

Additional information is available at the end of the chapter

1. Introduction

Solitary pulmonary nodule (SPN) or "coin lesion" is a rounded lesion that does not exceed 3 cm in diameter, completely surrounded by normal lung parenchyma without other concomitant anomalies (not associated with atelectasis or adenopathy), and often asymptomatic. Lesions bigger than 3 cm are more properly called masses and are often malignant [1,2].

SPNs can be found randomly in the course of imaging exams conducted at the level of the neck, upper limbs, chest, abdomen, and are described in approximately 0.9-2% of all chest X-rays [3].

Since the early 80's the advent of computed tomography (CT) has resulted in a large increase in the frequency of detection of SPN. In the clinical practice it is important to determine the radiological and pathological features of benign and malignant tumors for an accurate management [4-13].

According to the literature the overall prevalence of SPNs ranged between 8% and 51% [14,15]. The American College of Chest Physicians (ACCP) does not recommend the implementation of screening for lung cancer in the general population because the implementation of these tests is not so far proved able to achieve a reduction of mortality rates [16].

Because the diagnosis and treatment of early stage lung cancer allows more favourable results, a close monitoring for identified lesions is recommended [17].

A SPN can be attributed to various causes. The first step in the clinical evaluation of these lesions is to define the benignity or malignancy. The most common benign etiologies include infectious granulomas and hamartomas, while the most frequent malignant etiologies include primary lung cancer and lung metastases [2].

The clinical relevance of accurately subtyping lung cancers was initially challenged by the advent of novel therapeutic options (targeted therapies, such as erlotinib/gefitinib and bevacizumab, or third-generation chemotherapeutic agents, such as pemetrexed), which are effective in specific lung cancer subtypes, and needed for a more detailed histological definition of non-small-cell lung cancer (NSCLC), separating at least squamous-cell carcinoma (SQC) from non-SQC. This event led pathologists to concentrate their efforts on the accurate diagnosis of small cell lung carcinoma (SCLC), because further subtyping of NSCLC was an optional and clinically unimportant diagnostic exercise. The generic diagnosis of NSCLC gained popularity originally for cytological samples and later for small biopsies. Currently, on cytological or small biopsy samples, most pathologists are able to correctly distinguish SCLC from NSCLC, and within the NSCLC group to identify well-differentiated or moderately differentiated SQC or adenocarcinoma (ADC). [18,19]

However, a high percentage of cases continues to be simply diagnosed as NSCLC, especially when lacking clear-cut morphologic signs of differentiation. From a practical standpoint, the call back to histological categorization of NSCLC raises several types of questions. Although NSCLC subtyping may be relatively easy and feasible on surgical specimens, there are objective difficulties in examining small biopsies and cytology samples. These techniques often are the only ones for the final diagnosis of lung cancer, as most patients are not candidates for radical surgery. When dealing with these small samples, pathologists may be faced with a higher degree of uncertainty because of the frequent lung tumor heterogeneity and the higher prevalence of poorly differentiated NSCLC among clinically advanced and unresectable cases[18,19]. A useful tool to identify squamous or glandular differentiation and to characterize poorly differentiated NSCLC may be to incorporate ancillary techniques, such as immunohistochemistry. This approach seems the most promising one, although the accuracy, sensitivity, and specificity of the diverse immunohistochemical markers remain to be further defined. Thyroid transcription factor (TTF-1) and/or cytocheratin 7 (CK7) for ADC and p63 and high-molecular weight cytokeratins (HMWCKs) for SQC are the most specific and currently validated immunohistochemical markers that may be suitable for refining most diagnoses even when dealing with quantitatively limited material, such as cytological samples or small-sized biopsies [20,21]. When the pathologist is not able to perform a precise histotype diagnosis, the high-resolution computed tomography (HRCT) may be proposed as further diagnostic approach for determining the lung histotype maligancies with single polmonary nodule presentation [21].

The aim of our study is to assess whether morphological characteristics of a SPN and ancillary signs allow to differentiate between the following lung malignancies: bronchioloalveolar carcinoma (BAC) classified in according to the new criteria, variants of ADC and SCLC.

2. Materials and methods

2.1. Patients

From January 2007 to June 2011 we retrospectively reviewed the HRCT examinations of 33 patients (14 females and 19 males) with SPN presentation and histologic diagnosis of SCLC (n = 5), invasive lepidic ADCs (formerly diagnosed nommucinous BAC with > 5 mm invasion) (n=7), invasive mucinous ADCs (formerly diagnosed mucinous BAC)(n=2) and other variants invasive ADCs (acinar, papillary, solid predominant with mucin production, colloid and enteric variants) (n= 19). SQC, large cell carcinoma, adenosquamous carcinoma and sarcomatoid carcinoma cases were excluded.

The mean age in the three type of SPNs (SCLC, BACs and ADCs) were: 60 years ± 6 (SCLC), 67,2 years ±8,2 (BACs) and 71, 3 years ± 8,5 (ADCs) respectively.

2.2. Histological analysis

The histological diagnosis was performed in accordance with the examination of lobectomy in all cases of ADCs and transbronchial biopsy in 5 SCLC. The classification of ADCs tumors was performed in accordance with the criteria of International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Mutlidisciplinary Classification of Lung Adenocarcinoma [22]. The following immunostaining analysis were performed in all cases of ADCs: TTF1, CK7, P63 and HMWCKs. The immunostaining of synaptophysin and CD56 was performed in all cases of SCLC.

2.3. HRCT technique

The examinations were performed with three different CT scanners: 16-slices CT (Light Speed Pro 16, GE, Milwaukee, USA), 16-slices CT (Toshiba Aquilion, Japan) and 64-slices CT (Philips *Medical Systems, Best, the* Netherlands) by direct volumetric acquisition with high spatial resolution CT (HRCT) in a single inspiratory breath with the patient in a supine position. The technical parameters expected to acquire volumetric reconstruction, are the following: collimation: 1.0-1.25mm, kV: 135, mA: 300, scan time: 0.7 sec / rotation, table speed of 17.85 mm / sec. High-*spatial*-frequency *(bone)* reconstruction algorithm was used. Using the axial images the multiplanar reconstructions (MPRs) with high diagnostic quality were obtained.

2.4. Image analysis

All HRCT images of each SNP were read in consensus by two experienced radiologists (M.S., A.R.) in chest CT with respect to morphology and ancillary signs. Size , margins/countours, calcifications, central necrosis or cavitation and air bronchogram were evaluated for the morphologic assessment [23]. Furthermore, in association with the morphological study the following ancillary signs were assessed: pleural connecting striae and ground glass opacity (GGO).

The percentage of ancillary signs and the morphologic appearance were evaluated for the differential diagnosis.

3. Results

Lesion size ranging from 8 mm to 25 mm (mean 20 mm ±10,4 SD) for SCLC, 15 mm to 30 mm (mean 22,5 ± 5,7 SD) for BACs , 10 mm to 29mm (mean 21,2 ± 5,9 SD) for ADCs.

In the table are reported the data related to the morphologic features and to the ancillary signs with relatives percentages of the three histotype malignant nodules.

Morfologic features: calcifications within the SPN were absent in all case of SCLC and BACs and found in 1/19 (5,2%) cases of ADCs variants; cavitation was observed in 1/5 (20%) cases of SCLC; margins/countours (irregular or spiculated, multilobulated, frayed) were revealed in SCLC, BACs and variants of ADC in 4/5 (80%) 9/9 (100%) 15/19 (79%) and air bronchogram was revealed in SCLC, BACs and variants of ADC in 2/5 (40%) 5/9 (60%) 8/19 (42%) respectively.

Ancillary signs: air bronchogram and pleural connecting striae were found in SCLC, BACs and variants of ADC in 2/5 (40%), 5/9 (60%), 8/19 (42%) and 3/5 (80%), 9/9 (100%) 17/19 (89%) respectively.

The representative HRTC features for the three type of SPNs for SCLC, BACs and variants of ADC are reported in figures 1,2, figures 3-5 and figures 6-9 respectively.
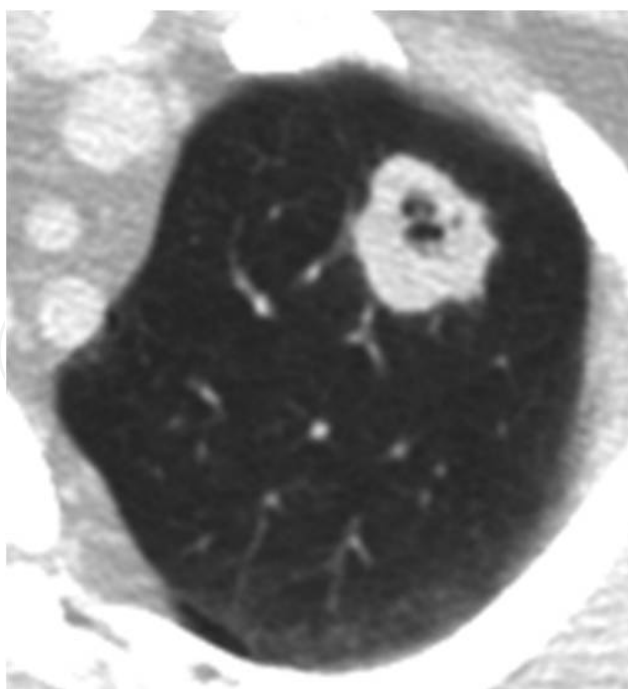

Figure 1. Small cell lung carcinoma in a 59 year-old man. HRCT shows spiculated and lobulated nodule with cavitations in the upper left lobe.

Figure 2.   Small cell lung carcinoma in a 69 year-old man.
HRCT shows spiculated nodule with pleural connecting striae in the ventral segment of the upper right lobe.

HRCT features	SCLC (size ranging from 8 mm to 25 mm (mean 20 mm ±10,4 SD) (n=5)	BAC (size ranging , 15 mm to 30 mm (mean 22,5 ± 5,7 SD) (n=9)	ADCs size ranging 10 mm to 29mm (mean 21,2 ± 5,9 SD) (n=19)
Calcifications	0/5 (0%)	0/9 (0%)	1/19 (5,2%)
Cavitations	1/5 (20%)	0/9 (0%)	0/19 (0%)
Margins (irregular or spiculated, multilobulated)	4/5 (80%)	9/9 (100%)	15/19 (79%)
Air bronchogram	2/5 (40%)	5/9 (60%)	8/19 (42%)
Pleural connecting striae	3/5 (80%)	9/9 (100%)	17/19 (89%)
Ground-glass opacity	1/5 (20%)	9/10 (90%)*	5/19 (26,3%)

*In 1 case of invasive mucinous adenocarcinoma (formerly diagnosed mucinous bronchiolo-alveolar carcinomas) the GGO appearance was not revealed.

Table 1. HRCT morphologic and ancillary of 5 small cell lung carcinomas (SLCL), 7 invasive lepidic adenocarcinomas (formely diagnosed bronchiolo-alveolar carcinomas pattern, with > 5 mm invasion), 2 invasive mucinous adenocarcinomas (formerly diagnosed mucinous bronchiolo-alveolar carcinomas) and 19 other variants invasive ADCs (acinar, papillary, solid predominant with mucin production, colloid and enteric variants).
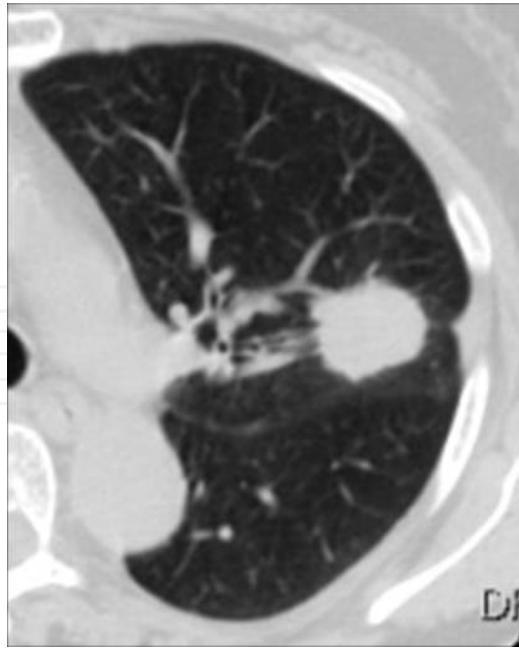
Figure 3. Invasive mucinous adenocarcinoma (formerly diagnosed mucinous bronchiolo-alveolar carcinoma) in a 74 year-old female.
HRCT shows spiculated nodule with pleural connecting striae in the dorsal segment of the left upper lobe.
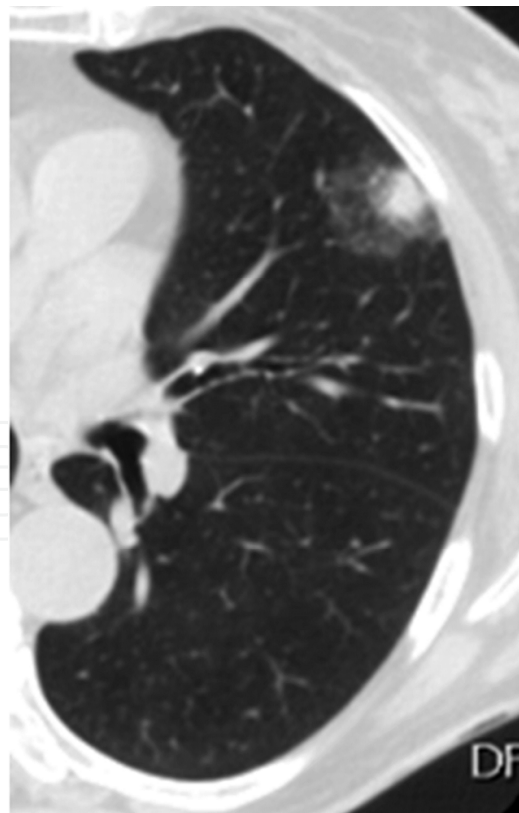

Figure 4. Invasive lepidic adenocarcinoma (formely diagnosed bronchiolo-alveolar carcinoma pattern, with > 5 mm   invasion) in a 75 year-old female. HRCT shows nodule with irregular contours and GGO in the ventral segment of the left upper lobe .
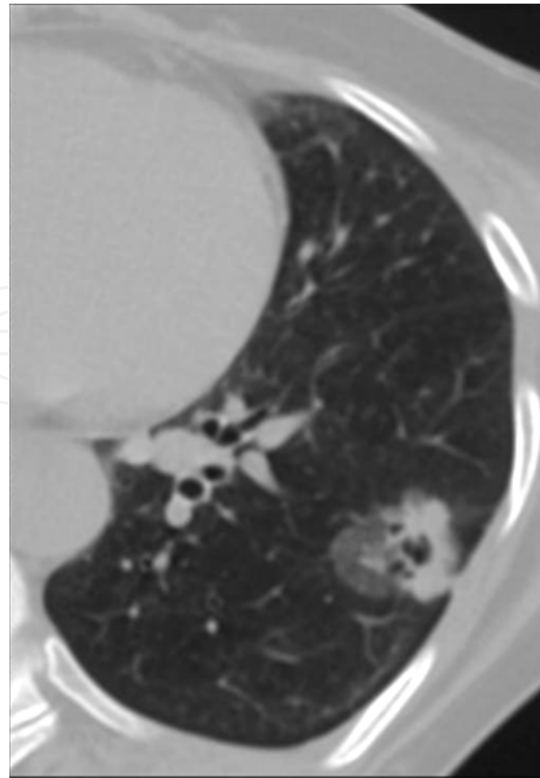
Figure 5. Invasive lepidic adenocarcinoma (formely diagnosed bronchiolo-alveolar carcinoma pattern, with > 5 mm invasion) in a 75 year-old female. HRCT shows lobulated nodule with air bronchogram and GGO in the left lower lobe.

Figure 6. Invasive variant enteric adenocarcinoma in a 76 year-old man. HRCT shows spiculated nodule with pleural connecting irregular striae in the dorsal upper right lobe.

Figure 7. Invasive variant enteric adenocarcinoma in a 79 year-old man.
HRCT shows spiculated nodule with pleural connecting striae and GGO in the ventral upper righ lobe.

Figure 8. Invasive variant colloid adenocarcinoma in a 64 year-old man.
HRCT shows lobulated spiculated nodule with pleural connecting striae and GGO in the left lower lobe.

Figure 9. Invasive variant enteric high grade-fetal adenocarcinoma in a 64 year-old man.
HRCT shows spiculated nodule with pleural connecting striae and GGO in the dorsal upper right lobe.

4. Discussion

Adenocarcinoma is the most common histologic subtype of lung cancer in most countries, accounting for almost half of all lung cancers [24]. A widely divergent clinical, radiologic, molecular, and pathologic spectrum exists within lung adenocarcinoma. As a result, confusion exists, and studies are difficult to compare. Despite remarkable advances in understanding of this tumor in the past decade, remains a need for universally accepted criteria for adenocarcinoma subtypes, in particular tumors formerly classified as BAC [18,19].

As the SPN may be the expression of multiple pathologic entities, the incidental finding of SPN by CT raises the issue of differential diagnosis between benign and malignant nodules. Moreover the importance of differential diagnosis between malignant histotypes can affect the prognosis and management of these patients.

A number of terms have been used to describe lung ADC by CT imaging. In particular, for tumors that present as small nodules, the terms used have reflected the various ground

glass (nonsolid), solid, or part-solid appearances that can occur. Largely based on the Fleischner Society glossary of terms [21] and the recently suggested guidelines by Godoy and Naidich [25] for subsolid nodules, we propose the following definitions: (1) a pure ground-glass nodule (GGN) (synonym: nonsolid nodule) as a focal area of increased lung attenuation within which the margins of any normal structures, e.g., vessels, remain outlined, (2) a solid nodule as a focal area of increased attenuation of such density that any normal structures, e.g., vessels, are completely obscured, and (3) part solid nodule (synonym: semisolid nodule) as a focal nodular opacity containing both solid and ground-glass components [21,25]. The Fleischner Society glossary of terms for thoracic imaging defines a nodule on a CT scan as "a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in greatest diameter" in any plane [21]. If the opacity is greater than 3 cm, it is referred to as a mass [21]. The 3 cm cut-off is in keeping with our concept of the maximum accepted size for the pathologic diagnosis of AIS and MIA. The term subsolid nodule has also entered common radiologic usage, referring to both part-solid nodules and a pure GGN [25]. Optimal evaluation of subsolid nodules requires thin-section CT scans (<3 mm thickness) to assess the solid versus ground-glass components [20,21].

The aim of our study is to assess the morphologic and ancillary HRCT features of the histotypes of malignant SPNs considering that often histological and/or cytological material may be unsatisfactory and immunoistochemical techniques may be not performed.

In our study the calcifications within the SPN were absent in all cases of SCLC and BACs and found in one case of ADCs.

The margins were irregular or spiculated, multilobulated in 4/5 (80%) of SCLC, in 9/9 (100%) of cases previously diagnosed as BACs, and in 15/19 (79%) of other variants of ADCs.

The opacity-like bullous, a sign of the presence of air bronchogram, does not help us in making any differential diagnosis, being present in 40% (2/5) of SCLC in 42% (8/19) of variants of ADCs and in 60% (5/9) of formerly diagnosed BACs. The occurrence of cavitations, expression of the speed of growth of the tumor cell and indicative of the presence of necrosis [26,27], was detected only in one aggressive forms of SCLC (20%). In all cases of all variants of ADCs and in cases previously diagnosed as BACs the cavitations were absent.

The SPN may be connected to the pleura by striae or streaks defined as linear density that extends to the pleura and were the result of a fibrosis in the pulmonary peripheral lung. The striae connecting pleura or pleural effusion tags are found with high frequency in the three tumor subtypes, ranking as a sign that directs us to a differential diagnosis of malignancy without giving specific indications about the histotype tumor (80% SCLC, 89% variants of ADCs, 100% formerly diagnosed BACs).

The ground glass perinodular opacity were areas of increased attenuation of hazy lung with preservation of bronchial and vascular margins [29] and intranodular air bronchogram

were the result of asymptomatic growth with the larger bronchi free of malignancies. The ground glass opacity (GGO) instead is significantly more present in the lesions slower growing and less invasive locoregional (26,3 % variants of ADCs and 90% formerly diagnosed BACs) than lesions infiltrative rapidly (only 20% of SCLC).

In conclusion, ancillary signs (pleural striae and GGO) in association with air bronchogram are suggestive of diagnosis of the invasive lepidic ADCs (formerly diagnosed nommucinous BAC with > 5 mm invasion) and can be considered in the differential diagnosis of malignat SNPs histotypes (SCLC and ADCs)

Author details

Michele Scialpi, Alberto Rebonato, Lucio Bellantonio and Marina Mustica
*Department of Surgical, Radiologic, and Odontostomatologic Sciences, Complex Structure of
Radiology 2, University of Perugia, S. Maria della Misericordia Hospital, S. Andrea delle Fratte,
Perugia, Italy*

Teresa Pusiol
Institute of Anatomic Pathology, S. Maria del Carmine Hospital, Rovereto (Trento), Italy

Irene Piscioli
Institute of Radiology, Budrio Hospital, Bologna, Italy

Lucio Cagini and Francesco Puma
*Department of Surgical, Radiologic, and Odontostomatologic Sciences, Thoracic Surgery
Unit, University of Perugia, S. Maria della Misericordia Hospital, S. Andrea delle Fratte,
Perugia, Italy*

Luca Brunese
Department of Health Science, University of Molise, Campobasso, Italy

Antonio Rotondo
*Department of Clinical and Experimental Medicine and Surgery "F. Magrassi," University of
Naples, Naples, Italy*

5. References

[1] Tuddenham Wj: Glossary of terms for thoracic radiology: recommendations of Nomenclature Committee of Fleischner Society - *AJR* 1984; 143(3):509-517.

[2] Ross H. Albert, John J. Russell: La valutazione di un nodulo solitario del polmone - *Minuti* Sett. 2010 Anno XXXIV - n.8.

[3] Holin S.N., Dwork R.E., Glaser S., et al.: Solitary pulmonary nodules found in a community-wide chest roentgenographic survey - *Am Tuberc Pulm Dis.* 1959; 79:427-439.

[4] Bartolotta TV, Midiri M, Scialpi M, Sciarrino E, Galia M, Lagalla R. Focal nodular hyperplasia in normal and fatty liver: a qualitative and quantitative evaluation with contrast-enhanced ultrasound. Eur Radiol. 2004 Apr;14(4):583-91.

[5] Scialpi M, Pierotti L, Piscioli I, Brunese L, Rotondo A, Yoon SH, Lee JM. Detection of small (<=20 mm) pancreatic adenocarcinoma: histologic grading and CT enhancement features. *Radiology.* 2012;262(3):1044.

[6] Brancato B, Crocetti E, Bianchi S, Catarzi S, Risso GG, Bulgaresi P, Piscioli F, Scialpi M, Ciatto S, Houssami N. Accuracy of needle biopsy of breast lesions visible on ultrasound: audit of fine needle versus core needle biopsy in 3233 consecutive samplings with ascertained outcomes. *Breast.* 2012;21(4):449-54.

[7] Tranfaglia C, Cardinali L, Gattucci M, Scialpi M, Ferolla P, Sinzinger H, Palumbo B (111)in-pentetreotide spet/ct in carcinoid tumours: is the role of hybrid systems advantageous in abdominal or thoracic lesions? *Hell J Nucl Med.* 2011;14(3):274-7.

[8] Pusiol T, Zorzi MG, Morichetti D, Piscioli I, Scialpi M. Uselessness of radiological differentiation of oncocytoma and renal cell carcinoma in management of small renal masses. *World J Urol.* 2011 May 21.

[9] Brancato B, Scialpi M, Pusiol T, Zorzi MG, Morichetti D, Piscioli F. Needle core biopsy should replace fine needle aspiration cytology in ultrasound-guided sampling of breast lesions. *Pathologica.* 2011;103(2):52.

[10] Pusiol T, Zorzi MG, Morichetti D, Piscioli I, Scialpi M. Uselessness of percutaneous core needle renal biopsy in the management of small renal masses. *Urol Int.* 2011;87(1):125-6.

[11] Pusiol T, Zorzi MG, Morichetti D, Piscioli I, Scialpi M. Uselessness of percutaneous core needle renal biopsy in the management of small renal masses. *Urol Int.* 2011;87(1):125-6.

[12] Pusiol T, Zorzi MG, Morichetti G, Piscioli I, Scialpi M. Synchronous nonfunctional duodenal carcinoid and high risk gastrointestinal stromal tumour (GIST) of the stomach. Eur Rev Med *Pharmacol Sci.* 2011;15(5):583-5.

[13] Pusiol T, Franceschetti I, Scialpi M, Piscioli I, Sassi C, Parolari AM. Incidental Necrotizing Paratubal Granuloma Associated with Multiple Neoplasms. *J. Gynecol Surg.* 2011, 27(1): 29-32.

[14] Gohagan J., Marcus P., Fagerstrom R., et al.: Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of National Cancer Institute - *Chest.* 2004;126(1):114-121.

[15] Swensen S.J., Jett J.R., Hartman T.E., Midthun DE, Sloan JA, Sykes AM, Aughenbaugh GL, Clemens MA: Lung cancer screening with CT: Mayo Clinic experience - *Radiology.* 2003; 226(3):756-761.

[16] Bach P.B., Silvestri G.A., Hanger M, Jett JR., for the American College of Chest Physicians: Screening for lung cancer: ACCP evidence-based clinical practice guidelines - 2nd ed. *Chest* 2007; 132(3 suppl):69S-77S.

[17] Steele J.D.: The solitary pulmonary nodule. Report of a cooperative study of resected asymptomatic solitary pulmonary nodules in male - *J Thorac Cardiovasc Surg.* 1963;46:21-39.

[18] World Health Organisation Classification of Tumours, Pathology & Genetics, Tumours of the Lung, Pleura, Thymus and Heart. Edited by Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. Lyon, France: IARC Press, 2004.

[19] Travis WD, Colby TV, Corrin B, et al. Histological Typing of Lung and Pleural Tumors. Berlin: Springer, 1999.

[20] Lee HY, Goo JM, Lee HJ, et al. Usefulness of concurrent reading using thin-section and thick-section CT images in subcentimetre solitary pulmonary nodules. *Clin Radiol* 2009;64:127–132.

[21] Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008;246:697–722.

[22] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE, Garg K, Austin JH, Asamura H, Rusch VW, Hirsch FR, Scagliotti G, Mitsudomi T, Huber RM, Ishikawa Y, Jett J, Sanchez-Cespedes M, Sculier JP, Takahashi T, Tsuboi M, Vansteenkiste J, Wistuba I, Yang PC, Aberle D, Brambilla C, Flieder D, Franklin W, Gazdar A, Gould M, Hasleton P, Henderson D, Johnson B, Johnson D, Kerr K, Kuriyama K, Lee JS, Miller VA, Petersen I, Roggli V, Rosell R, Saijo N, Thunnissen E, Tsao M, Yankelewitz D. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. *J Thorac Oncol.* 2011;6(2):244-85.

[23] Travis WD, Linnoila RI, Tsokos MG, Hitchcock CL, Cutler GB Jr, Nieman L, Chrousos G, Pass H, Doppman J, Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol.* 1991;15(6):529-53.

[24] Curado MP, Edwards B, Shin HR, et al. Cancer Incidence in Five Continents, Vol. IX. Lyon: IARC Scientific Publications, 2007.

[25] Godoy MC, Naidich DP. Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. *Radiology* 2009;253:606– 622.

[26] Pentheroudakis G, Kostadima L, Fountzilas G, Kalogera-Fountzila A, Klouvas G, Kalofonos C, Pavlidis N. Cavitating squamous cell lung carcinoma-distinct entity or not? Analysis of radiologic, histologic, and clinical features. *Lung Cancer* 2004;45:349–355.

[27] Onn A, Choe DH, Herbst RS, Correa AM, Munden RF, Truong MT, Vaporciyan AA, Isobe T, Gilcrease MZ, Marom EM. Tumor cavitation in stage I non-small cell lung cancer: epidermal growth factor receptor expression and prediction of poor outcome. *Radiology* 2005;237:342–347.

[28] Travis WD, Garg K, Franklin WA, Wistuba II, et al. Evolving concepts in the pathology and computed tomography imaging of the lung adenocarcinoma and bronchioloalveolar carcinoma. *J Clin Oncol* 2005; 23: 3279-87.