Solitary Pulmonary Nodule – Developing A Malignancy Probability Calculation Model

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Abstract: - Since solitary nodules are often malignant and because five-year survival following resection is better when a patient is diagnosed at a very early stage of disease, rapid diagnosis and early resection of all malignant nodules is an important objective. The authors tried and also succeded to achive the goal of the study: to create a malignancy probability calculation model using a batch of 87 patients admitted to Thoracic Surgery Ward, Marius Nasta Pneumology National Institute between January 2001 and September 2006 with utmost smaller or equal to 3 cm solitary pulmonary nodules at plain chest radiograph. Using ***t*** test method, χ^2 Pearson test and logistic regression were selected a few parameters to obtain a model that describes a very good relation between independent variable and the dependent variable, malignancy feature by obtaining a malignancy probability resulting a model, SPN Bucharest statistical model which was validated by appling to the SPN Bucharest batch the Swensen model. The values obtained using SPN Bucharest statistical model are more representative for the etiologic type that it represents, being more close to 0% for the benign feature and more close to 100% for the malign feature of the SPN than ones resulted from applying Swensen model to SPN Bucharest batch.

Key-Words: - pulmonary solitary nodules, malignancy probability calculation, Swensen model, parameters

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in both men and women in industrialized countries. The overall mortality rate for lung cancer is high, and early diagnosis provides the best chance for survival. Diagnostic tests guide lung cancer management decisions, and diagnostic imaging is increasingly being used in an effort to improve the clinical management of patients with lung cancer. Solitary pulmonary nodule (SPN) is typically defined as an intraparenchymal focal, round or oval area of increased opacity <3 cm in diameter. (3, 4) Nearly 1 in every 500 chest radiographs taken reveals a newly diagnosed SPN. More than 150,000 SPNs are detected annually in the United States alone. (1, 2, 5) This estimate is mainly based on chest radiographs. Now, with increasing use of computed tomography (CT) of the chest for screening of lung cancer and chest CT angiography (CTA) for diagnosing pulmonary embolus and for cardiac evaluation, this number is rapidly increasing. The finding of a solitary pulmonary nodule (SPN) on a chest radiograph (CXR) or computed tomography (CT) scan remains a challenge for physicians, despite being one of the most common radiologic findings encountered in clinical practice. Older studies demonstrated that SPNs are seen in approximately 1 of 500 CXRs. (7, 11, 12) In addition, the increasingly widespread use of CT has lead to a tremendous increase in incidentally identified lung nodules. Patients with an SPN rarely have symptoms attributable to the nodule, and so the detection of the SPN is usually serendipitous. The plain chest radiograph usually defines the presence and appearance of the SPN, unless it was discovered on CT or other radiographic imaging performed for another purpose. (6, 8) The lesion must be singular, surrounded by normal lung tissue, and not be involved with obstructive atelectasis or hilar enlargement. There are many benign and malignant processes that may present as a solitary pulmonary nodule (SPN) on a chest radiograph

2. Problem Formulation

The purpouse of this study is to create a calculation model of SPN malignancy probability by using some CT morphologic criteria associated to clinical or biological conditions.

SPN Bucharest batch;

Available population: patients with respiratory symptoms, utmost smaller or equal to 3 cm solitary pulmonary nodules at plain chest radiography. The patients were admitted to Thoracic Surgery Ward, Marius Nasta Pneumology National Institute between January 2001 and September 2006, to establish the etiology of the identified lesion through surgical resection.

Inclusion criteria:

1. Patients with respiratory symptoms and utmost smaller or equal to 3 cm solitary pulmonary nodule image at plain chest radiography acknowledged by CT.
2. Patients without respiratory symptoms and utmost smaller or equal to 3 cm solitary pulmonary nodule image at plain chest radiography randomly discovered during TB contacts screening, employee screening or recurrent examination connected to life insurance.
3. Patients without respiratory symptoms, with malignancy history and utmost smaller or equal to 3 cm solitary pulmonary nodule image at plain chest radiography discovered at oncological follow-up check or during metastasis screening CT recurrent examination.
4. The selection of this study started off the radiological definition of the solitary pulmonary nodule integrated to certain CT features. Were included patients with smaller or equal to 3 cm solitary pulmonary nodule image at plain chest radiography without pulmonary or mediastinal adenopathy or parenchyma lesions, being excluded anything above 3 cm.
5. Patients who met above criteria signed an informed consent before that all the deontological scientific, disclosure criteria were explained to the patients and patients filed in study memorandum slip.
6. All selected patients passed through one CT examination, SPN diameter variation and increase or decrease rate could not be studied because of lack of recurrent CT examination.
7. Persons who have had a certain anatomopathological criteria achieved through subsequent surgery.

Exclusion criteria:

1. Patients being diagnosed as having satellite nodules or micronododular bilaterally pulmonary lesions at CT examination.
2. Patients who haven't met SPN definition criteria after CT examination.
3. Granulomatous diseases with diffuse interstitial involovement being diagnosed revealed by personal history or being suspected by a CT exam performed to a patient with an apparently solitary pulmonary nodule.
4. Patients with TB parenchymatous lesions regardless of the grade of activity which one had ascertained the appearance of one nodule.
5. Patients with an apparently solitary pulmonary nodule which have had metastasis to other organs revealed by CT exam.

Initial batch of patiens consisted in 495 CT examinated cases from Imagistic Ward, Marius Nasta Pneumology National Institute between January 2001 and September 2006 from which were selected 87 cases in SPN Bucharest batch. The patients with or without respiratory symptoms and utmost smaller or equal to 3 cm solitary pulmonary nodule image at plain chest radiography passed to the next stage, CT exam, being included only those with solitary pulmonary nodule image at plain chest radiography acknowledged by CT. The selection of the patients was made through the radiological classical definition of SPN accommodated to CT exam: a solitary pulmonary lesion, variable shape (generally round or egg-shaped but sometimes not being able to distinguish a geometric form), a diameter utmost smaller or equal to 3 cm measured through lung window section, without association of adenopathy (coalescence or not regardless of its location) or other pulmonary parenchyma lesions or pleural. Study inclusion was made only after signing an informed consent.

All patients were diagnosed and the stage of the disease established through anamnesis, prior and current medical history, lifestyle, personal habits, phisycal examination, complete blood tests (CBC, ESR, CRP), spontaneously produced sputum (citopathology report), chest radiography (PA, lateral), bronchoscopy with bronchial material drawing samples (bronchial aspiration, bronchoalveolar microlavage, bronchial mucosa biopsy), CT of lungs, mediastinum, brain pan, abdomen (with contrast).

All patients data were colected and inserted into a table containing clinical data, smoking status, personal history of tuberculosis and neoplasia, the presence of Koch's bacillus in sputum, histopathologic exam, citology adding to those a few CT image description criteria of the solitary pulmonary nodule. These image descriptive criteria led to presumptious CT diagnosis and that was compared to the histopathologic diagnosis.

CT SPN diagnosis criteria are:

1. density (intensity): solid, liquid, mixed, negative.
2. general structure of the nodule throughout densitometric bearingness: homogeneous or unhomogeneous structure, mentioning the causes.
3. eventual excavation of the unhomogeneous structure nodules mentioning the type of the cavern and the aspect of the walls.
4. the possibility of calcification of those with homogeneous structure and the type of calcification.
5. CT dignifing of the unexpressed clinical, radiological or laboratory metastasis.
6. outline: infiltrative or well outlined.
7. the edge: irregular, round, lobulate.
8. localization: central, peripheral, lobar, segmentary.
9. the relationship with pleura of the peripheric solitary pulmonary nodule: infiltration or pleural retraction.
10. the relationship with one or more bronchi the peripherial ones: at air bronchogram the existence of stenosis, amputated, dilatated or filled with foreign bodies bronchi.
11. convergence vessels sign.
12. haloe's sign.
13. nodule's diameter.

The CT examination was performened using a General Electric Medical Systems Sytec Sinergy+ device, performing 7 mm spiral sections, with a pitch of 1 regarding the lung and superior abdomen as a high initial sequency; hereinafter the solitary pulmonary nodule was examined separately onto sectorial enhanced sections, of 1 mm thickness with 1 mm spacing, with high resolution algorithm. These were followed by 3 mm spiral section 1 mm pitch, with i.v. contrast through automatic seringe sections that begun at the aortic arch and ended to the inferior level of hilus to track possible adenopathy, followed by a new 7 mm sequence and a pitch of 1 for the screening of hepatic and suprarenal metastasis. The final sequence consists in 5 mm sections with 5 mm spacing as cerebral screening.

Spiral aquisition technique used in the study which concures with the general aquisition technique lately used.

Spiral CT allows a more accurate SPN diameter measuring and its volume, thus making possible an exact evaluation of its size at recurrent examinations.The study of the nodule throughout its localisation using a spiral protocol, was made with high resolution algorithm images and very enhanced 1 mm continuous sections. This protocol highlights very well anatomic details almost as a histopathological section (especial analizing the small lipidic tissue inclusions or calcifications and its types). This protocol lays a high dose of irradiation of the patient which is overcompensated by the diagnostic value.

Brain i.v. contrast CT exam was rutinely performed to all patients considering the malignancy potential of anykind of this image type.

3. Problem Solution

SPN Bucharest batch with 87 patients was divided into two groups depending on malignancy profile: first group – 29 patients (33.33 %) as having malignant SPN and a second group – 58 patients (66.66 %), as having benign SPN. Statistic analisys used ***t*** test method made for observing the parameter's average value variation which were chosen depending on malignancy profile. There were significant statistic differences between average values of the following parameters: age and the number of year-pack of smoked cigars.

Table 1. Average value of considered parameters related to malignancy profile

Parameter	Malignat tumor (29 patients)		Benign tumor (58 patients)		p
	average	std dev.	average	std dev.	
Age [years]	57.97	10.74	44.28	13.99	*0.000*
Weight [kg]	66.90	8.23	66.34	10.56	0.806
BMI [kg/m2]	23.62	2.39	23.80	2.72	0.763
Year-Pack	20.52	29.119	6	12.087	*0.001*
Trombocyte [Giga/l]	214.06	55.60	217.12	55.61	0.810
CRP [mg/l]	4.52	2.34	5.27	2.67	0.204
Fibrinogen [g/l]	3.29	1.20	3.28	1.48	0.966
Hgb [g/l]	134.17	14.92	134.95	15.11	0.821
Nodule's diameter [cm]	2.49	0.57	2.26	0.68	0.138

In our study one may observe that malignant SPN has a significant statistic higher diagnosis average age and development age towards benign SPN [59.97 years towards 44.28 years, p= 0.000]. This sugests that a 50 years aged patient SPN diagnosed has a higher probability of being malignant while a 40 years aged patient SPN diagnosed has a higher

probability of being benign. Pack-year (no. of daily smoked cigars multiplied by no. of smoking years) parameter has a significant higher average value among malignant SPN patients than benign SPN patients (20.52 towards 6, p=0.001).

Table 2. Qualitative parameters related to malignancy profile

Parameter	Class	Malignancy		P
		Benign	Malign	
Sex	M	27	14	0.879
	F	31	15	
PPH	Present	4	9	*0.003*
	Absent	54	20	
lobe localisation	SL	34	15	0.541
	ML sau IL	24	14	
density	Solid	22	26	*0.000*
	Mixed	36	3	
bronchi relationship	1.air bronchi	3	6	*0.000*
	2.stenosis	7	9	
	3.amputated	2	0	
	4.dilated	4	11	
	5.trajectory deviation	2	1	
	6.in bronchi	2	0	
	7.without	38	2	
structure	Homogeneous	21	21	*0.001*
	Unhomogeneos	37	8	
outline	Spiculi	8	26	*0.000*
	well outlined	50	3	
edge	Irregular	19	24	*0.000*
	Lobulate	2	3	
	Round shaped	37	2	
pleural relationship	Infiltration	7	3	*0.000*
	Retraction	6	23	
	Without	45	3	
Calcification	Present	13	18	*0.000*
	Absent	45	11	
Convergence sign	Present	3	18	*0.000*
Haloe's sign	Absent	55	11	*0.000*
	Present	4	16	
	Absent	54	13	

We used χ^2 Pearson test to select statistic significant qualitative parameters like: personal pathological history such as the presence of a tumor, density, bronchi relationship, structure, the presence of spiculi, edge, pleura relationship, calcifications, convergence vessels sign, haloe's sign as it follows in the above table. Selected parameters were associated using logistic regression to obtain a model that describes a very good relation between independent variable and the dependent variable, malignancy feature by obtaining a malignancy probability. The independent variables influencing malignancy feature are shown below in the table.

Table 3.

Variable	Malignancy odds ratio	95% CI
Age	1.0669	0.9641 to 1.1807
Neoplasia history	21.1489	0.5703 to 784.2350
Density	18.0959	1.2127 to 270.0379
Bronchi involve.	13.2427	0.8065 to 217.4535
Spiculi presence	81.3700	4.3077 to1537.0194
Pleural involve.	18.0875	1.2395 to 263.9495

Malignancy odds ratio expresses the rate of developing a malignant pulmonary lesion among patients who have this features towards those don't have it. This statistic model offers a good case division, by having a 96.55% diagnostic correctness for benign tumors and 89.66% diagnostic correctness for malignant tumors. 94.25% of the cases are correct classified. χ^2 which is a statistic parameter that quantifies how good independent variables characterises malignancy, was 88.7 with a $p<0.0001$. According to Swensen model which includes 6 parameters: age, smoking status, extrathoracic malignancy history in the past 5 years, nodule's size, spiculi presence and the superior lobe site, malignancy odds ratio for each parameter are shown below.

Table 4. Swensen model and its parametres

Variable	Malignancy odds ratio	95% CI
Age	1.1215	1.0237 to 1.2288
Smoking status	0.6031	0.1177 to 3.0914
Neoplasia history	5.6773	0.7771 to 41.4763
Nodule's size	1.5217	0.4552 to 5.0872
Spiculi presence	64.0479	9.9023 to 414.2609
Superior lobe site	0.5920	0.1177 to 2.9776

This statistic model offers a good case division, by having a 91.38 % diagnostic correctness for benign tumors and 86.21 % diagnostic

correctness for malignant tumors. 94.25% of the cases are correct classified. χ^2 was 64.33 with a $p<0.0001$.

We also calculated a modified Swensen model by replacing smoking status with pack-year:

Table 5. Modified Swensen model and its parameters

Variable	Malignancy odds ratio	95% CI
Age	1.1113	1.0177 to 1.2136
Pack-year	1.0114	0.9694 to 1.0551
Neoplasia history	5.3015	0.7487 to 37.5417
Nodule's size	1.5857	0.4697 to 5.3537
Spiculi presence	54.9376	8.7917 to 343.2931
Superior lobe site	0.6200	0.1248 to 3.0808

This statistic model offers a good case division, by having a 91.38 % diagnostic correctness for benign tumors and 86.21 % diagnostic correctness for malignant tumors. 89.66 % of the cases are correct classified. χ^2 was 64.23 with a $p<0.0001$.

Using Bland şi Altman method we compared the original Swensen model with SPN Bucharest model and one can confirm that there are no significant differences between these models. By calculating the area under curve (AUC) for the 3 methods were obtained very good amounts for Swensen model (0.950) and Swensen-PY (0.948) and excellent amouts for SPN Bucharest model (0.989), which were applied to the SPN Bucharest batch.

Table 6. AUC amounts of the studied 3 models

	AUC	SE	95% CI
Swensen model	0.950	0.0292	0.881 to 0.985
Swensen-PY	0.948	0.0298	0.878 to 0.984
SPN Bucharest	0.989	0.014	0.938 to 0.998

Comparing the 3 AUC one may observe that there are no significant differences and certifies the validity of the 3 models of malignancy probability for the cases of SPN Bucharest batch.

Using the above certified model we calculated the probability of malignancy of a SPN histopathological confirmed as being benign respectively non specific inflamatory fibrogranuloma and a malign SPN, respectively an adenocarcinoma and we noticed that the probability value of the benign SPN was 0.92 % concording to histopathologic result and the probability value of the malign SPN was 98.58 %, concording to histopathologic result.

Table 7. AUC value amounts of the studied 3 models

Swensen model ~ Swensen-PY	
Area difference	0.00208
Standard error	0.00547
95% CI	-0.00864 to 0.0128
Level of significance	P = 0.704
Swensen model ~ SPN Bucharest	
Area difference	0.0389
Standard error	0.0257
95% CI	-0.0115 to 0.0894
Level of significance	P = 0.130
Swensen-PY ~ SPN Bucharest	
Area difference	0.041
Standard error	0.026
95% CI	-0.010 to 0.092
Level of significance	P = 0.115

Table 8. Benign/Malign probability estimation of a SPN using SPN Bucharest applied to SPN Bucharest batch

Benign/Malign probability estimation of a SPN using SPN Bucharest applied to SPN Bucharest batch		
Data		
SPN evaluation? (Y or N)	Y/Y	
Age - years	29/54	29/54
Was the cancer diagnosis more than 5 yrs ago? (Y sau N)	N/N	0/0
Rx density? (S-solidă, O-other)	S/S	1/1
Bronchi involve? (N-without, Y-with)	Y/Y	1/1
Spiculi presence? (Y sau N)	N/Y	0/1
Pleural involve? (Y sau N)	N/Y	0/1
Calculation	**Result**	
Complete data?	Yes/Yes	
Adequate evaluation?	Yes/Yes	
X value	4.6741/-4.2401	
Malignancy probability	0.0092/0.9858 **0.92%/98.58%**	

SPN Bucharest batch containing the following parameters: age, smoking status, personal

malignancy history, nodule's size, spiculi presence and the superior lobe site, offers a good division of the cases into benign and malign This statistic model offers a good case division, by having a 96.55% diagnostic correctness for benign tumors and 89.66% diagnostic correctness for malignant tumors. 94.25% of the cases are correct classified. χ^2 was 88.7 with a $p<0.0001$. We compared this model to the preexistent literature Swensen model discovered and certified on american population. (7, 9, 10)

The Swensen model which includes 6 parameters: age, smoking status, extrathoracic malignancy history in the past 5 years, nodule's size, spiculi presence and the superior lobe site offers a 91.38 % diagnostic correctness for benign tumors and 86.21 % diagnostic correctness for malignant tumors. 94.25% of the cases are correct classified. χ^2 was 64.33 with a $p<0.0001$. the validation of this model was made by calculating the area under curve (AUC) for the 3 methods were obtained very good amounts for Swensen model (0.950) and Swensen-PY (0.948) and excellent amouts for SPN Bucharest model (0.989), which were applied to the SPN Bucharest batch.

From these values one may observe, again, that obtained probabilities values using SPN Bucharest statistical model are more representative for the etiologic type that it represents, being more close to 0% for the benign feature and more close to 100% for the malign feature of the SPN than ones resulted from aplling Swensen model to SPN Bucharest batch.

4. Conclusions

1. The appereance of a SPN arround 50 years of age pleades for malignancy, especially to the great smokers, while a SPN diagnosis under 40 years of age pleades for a benign appereance.
2. SPN Bucharest statistical model containing the following parameters: age, smoking status, personal malignancy history, nodule's size, spiculi presence and the superior lobe site, offers a good division of the cases into benign and malign superior to Swensen model.
3. Creating and also continuous improvement of a statistical model for calculation of the benign or malign feature of a case, particullary SPN is not only important for establishing the type of its feature but also for the course of action following initial diagnosis as well as a screening procedure for the type of SPN, a non invasive screening procedure which is well tollerated by the patient in its initial approach.

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