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CROSS BORDER COOPERATION PROGRAMME

LATVIA-LITHUANIA-BELARUS

Project: Improvement of the health service by means of IT technology in dermal and lungs cancer diagnostics (IHSIT-CD, LLB2-242)

Algorithm for lung cancer radiological diagnosis

Task: development of decision making system for automatic diagnostics solutions of lung cancers on the base of IT- analysis of data.

Lung cancer can manifest as a solitary pulmonary nodule, and such cancer is suitable for screening with CT. In this case the algorithm should include:
Patient age,
Smoking history,
working conditions (professional disease),
chronic lung diseases.

Lung nodules are characterized on CT or chest X-ray according:
nodule size,
nodule shape,
nodule density
multiple nodules
nodules localization (supleural or parenchymal lesions)

The other manifestation of lung cancer are signs of central airways obstruction: intrabroncheal lesions, infiltration, atelectasis, etc.
Usually it is difficult to recognize in central bronchi growing cancer on first CT images. So in our opinion we should include these patients in our algorithm as well

cause it could be of a great value for the user while deciding about diagnosis or further diagnostic modalities for the patient.

Lung solitary nodule

Lung nodules are detected very commonly on computed tomographic (CT) scans of the chest, and the ability to detect very small nodules improves with each new generation of CT scanner. In reported studies, up to 51% of smokers aged 50 years or older have pulmonary nodules on CT scans.

Not every focal opacity qualifies as a nodule. A committee of the Fleischner Society on CT nomenclature described the pathologic definition of a nodule as a "small, approximately spherical, circumscribed focus of abnormal tissue" and the radiologic definition as a "round opacity, at least moderately well marginated and no greater than 3 cm in maximum diameter". Therefore, a linear or essentially two-dimensional opacity that does not have an approximately spherical component is not a nodule. In general, purely linear or sheetlike lung opacities are unlikely to represent neoplasms and do not require follow-up, even when the maximum dimension exceeds 8 mm.

Depending on their appearance and radiologic context, certain nodular opacities may be judged sufficiently typical of scarring that follow-up is not warranted.

Management decisions should not be based on nodule size alone. While any calcification in a small nodule favors a benign cause, central, laminar, or dense diffuse patterns of calcification are reliable evidence of benignancy. Fat content suggests a hamartoma or occasionally a lipoid granuloma or lipoma. Solid versus nonsolid appearance, spiculation, or other characteristics influence the likelihood of malignancy and probable growth rate in any given case.

Other features such as clustering of multiple nodules in a single location in the lung tend to favor an infectious process, although a dominant nodule with adjacent small satellite nodules can be seen in primary lung cancer. For a single nodule, upper lobe location increases the likelihood of malignancy, because primary lung cancers are more common in the upper lobes.

On the other hand, small, irregular, benign subpleural opacities, presumably due to scarring, are extremely common in the apical areas in older patients, whereas triangular or ovoid circumscribed nodules 3–9 mm in diameter adjacent to pleural fissures commonly represent intrapulmonary lymph nodes. A history of cancer can

greatly increase the likelihood of a nodule being malignant, depending on the nature and stage of the primary neoplasm.

On the basis of analysis of information from the ongoing Mayo Clinic CT Screening Trial, Midthun et al reported that fewer than 1% of very small (<5-mm) nodules in patients without a history of cancer were malignant. They indicated a likelihood of malignancy of 0.2% for nodules smaller than 3 mm, 0.9% for those 4–7 mm, 18% for those 8–20 mm, and 50% for those larger than 20 mm.

Several large screening programs are continuing, and although the available data are still incomplete, certain tentative conclusions can be drawn at the present:

Approximately half of all smokers over 50 years of age have at least one lung nodule at the time of an initial screening examination. In addition, approximately 10% of screening subjects develop a new nodule during a 1-year period .

The probability that a given nodule is malignant increases according to its size. Even in smokers, the percentage of all nodules smaller than 4 mm that will eventually turn into lethal cancers is very low (<1%), whereas for those in the 8-mm range the percentage is approximately 10%–20% .

Cigarette smokers are at greater risk for lethal cancers, and malignant nodules in smokers grow faster, on average, than do those in nonsmokers. Also, the cancer risk for smokers increases in proportion to the degree and duration of exposure to cigarette smoke.

Certain features of nodules correlate with likelihood of malignancy, cell type, and growth rate. For instance, small purely ground-glass opacity (nonsolid) nodules that have malignant histopathologic features tend to grow very slowly, with a mean volume doubling time on the order of 2 years. Solid cancers, on the other hand, tend to grow more rapidly, with a mean volume doubling time on the order of 6 months. The growth rate of partly solid nodules tends to fall between these extremes, and this particular morphologic pattern is highly predictive of adenocarcinoma.

Increasing patient age generally correlates with increasing likelihood of malignancy. Lung cancer is uncommon in patients younger than 40 years and is rare in those younger than 35 years. At the other end of the age scale, although the likelihood of cancer increases, surgical intervention carries greater risks. Also, the likelihood of a small nodule evolving into a cancer that will cause premature death becomes a lesser concern as comorbidity increases in a person and predicted survival decreases with advancing years.

On CT images nodules according density are classified as ground-glass opacity, as ground-glass opacity with a solid component, or as solid. Solid nodules or with a solid component are more likely to appear malignant ones.

In certain clinical settings, such as a patient presenting with neutropenic fever, the presence of a nodule may indicate active infection, and short-term imaging follow-up or intervention may be appropriate.
Previous CT scans, chest radiographs, and other pertinent imaging studies should be obtained for comparison whenever possible, as they may serve to demonstrate either stability or interval growth of the nodule in question.

Lung cancer verification procedures

Confirmation of the diagnosis with tissue is important in most patients.
Inclusion of verification procedures should be helpful for data base users while selecting the proper method, making the investigation cost-effective.

Cytological examination of sputum has a sub-optimal diagnostic yield unless the tumour is large and centrally located; bronchoscopy is therefore the usual way by which to sample endobronchial lesions. Using a combination of biopsy, bronchial washings and brushings, the diagnostic yield is between 80% and 90% of proximal tumours (Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. Chest 2003;123:115S-28S). Percutaneous fine needle aspiration or biopsy is usually more appropriate in peripheral lung lesions, although a multivariate analysis of 660 lung biopsies found complication risks of pneumothorax (25%), haemothorax (4%) and chest tube placement (1%) (Yeow KM, Su IH, Pan KT, Tsay PK, Lui KW, Cheung YC, et al. Risk factors of pneumothorax and bleeding: multivariate analysis of 660 CT-guided coaxial cutting needle lung biopsies. Chest 2004;126:748-54). Fine needle aspiration can also diagnose and stage lung cancer in those found to have palpable supraclavicular lymph nodes and skin metastasis, in turn indicating that a thorough clinical examination is necessary in all patients.

Some patients are diagnosed with lung cancer following investigation of a unilateral pleural effusion (Maskell NA, Butland RJ. BTS guidelines for the investigation of a unilateral pleural effusion in adults. Thorax 2003;58 Suppl. 2:ii8-17). Pleural fluid analysis has a sensitivity of ~60% for malignancy while performing a concomitant blind biopsy using an Abrams needle can increase the diagnostic yield by up to 10% (Walshe AD, Douglas JG, Kerr KM, McKean ME, Godden DJ. An audit of the clinical investigation of pleural effusion. Thorax 1992;47:734-7). However, CT guided pleural biopsy is now considered a far more reliable diagnostic test in an undiagnosed unilateral pleural effusion and helps overcome some of the problems associated with blind biopsy. (Maskell NA, Gleeson FV, Davies RJ. Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. Lancet 2003;361:1326-30).

Staging procedures

Staging procedures could be included in the algorithm for the purpose to point out for of this data base user the next steps and examinations for staging the disease.

The extent of CT coverage should include the lower neck (defined as the level of the vocal cords) for the detection of supraclavicular nodal metastases. If there are lower abdominal symptoms or signs or a previous history of abdominal malignancy, the pelvis should also be imaged. CT usually gives accurate measurement of T stage, except where there is doubt about mediastinal invasion.

Evaluation of Primary Tumor (the T Factor)

The distinction between T1 and T2 lesions is generally based on size and rarely impacts the choice of therapy. Imaging cannot reliably determine the presence of visceral pleural invasion for peripheral tumors. Confirming T3 or T4 status based on imaging alone, however, can be quite difficult. Features such as discrete bone destruction, rib erosion, or tumor adjacent to a mediastinal structure without an associated fat plane are diagnostic of chest wall or mediastinal invasion. Computed tomography (CT) features of chest wall invasion include >3 cm of contact with the

pleural surface, pleural thickening, absence of fat planes, and an obtuse angle of tumor with the chest wall.

T1 - tumor
Diameter of 3 cm or smaller and surrounded by lung or visceral pleura or endobronchial tumor distal to the lobar bronchus
T1A= T1B= 2 cm - 3 cm

T2 - tumor
Greater than 3 and smaller than 7 cm
T2a= 3 cm - 5 cm
T2b= 5 cm - 7 cm
Invasion of the visceral pleura
Atelectasis or obstructive pneumopathy involving less than the whole lung
Tumor involving the main bronchus 2 cm or more distal to the carina.

T3 – tumor
Tumor with atelectasis or obstructive pneumonitis of the entire lung
Tumor in the main bronchus within 2 cm of the carina but not invading it
Tumor of any size with invasion of non-vital structures such as the chest wall, mediastinal pleura, diaphragm, pericardium.
Separate tumour nodules in the same lobe as the primary tumor.

Chest pain usually indicates chest wall invasion (i.e.T3). A Pancoast tumor is a tumor that involves the superior sulcus and the chest wall is almost always involved in these patients (i.e. T3).

T4 - tumor
Invasion of vital mediastinal structures: fat, heart, trachea, esophagus, great vessels, recurrent laryngeal nerve, carina.
Invasion of vertebral body.
Malignant pleural or pericardial effusion (cytologically proven).
Separate tumour nodule(s) in a different ipsilateral lobe to that of the primary tumor.

Lymph nodes

The size and site of enlarged nodes at CT scanning should be reported in accordance with the International Association for the Study of Lung Cancer (IASLC) nodal map. In addition, CT may be able to detect features of nodal involvement such as a rounded heterogeneous appearance with central necrosis.

A maximal short axis diameter in the transverse plane of >10 mm is widely regarded as the cut-off point to indicate abnormal enlargement. However, it is recognised that lymph node enlargement can occur as a reaction to tumour, distal atelectasis/pneumonia or associated pulmonary disease, and that microscopic tumour involvement may be found in normal sized nodes.

Therefore, unless there is clear involvement of the mediastinal lymph nodes by tumour extension, further evaluation of mediastinal lymph node involvement should be undertaken by mediastinal sampling.

CT may identify sites of metastatic disease but, if there is any doubt, further evaluation is required before excluding patients from radical treatment.

It is rational to include in the algorithm lymph node status according basic lymph node zones such as N1, N2 or N3 for every cancer case. It is optional to decide if there is a need to include lymph node status according lymph nodes stations (1-14). It may be reasonable if taking into account the next step procedures for lymph node morphology status verification:

Supraclavicular zone (1)

1. Low cervical, supraclavicular and sternal notch nodes

Superior Mediastinal Nodes (2-4)

2. Upper Paratracheal: above the aortic arch, but below the clavicles.

3A. Pre-vascular: these nodes are not adjacent to the trachea like the nodes in station 2, but they are either anterior to the vessels.

3P. Pre-vertebral: these nodes are not adjacent to the trachea like the nodes in station 2, but they are behind the esophagus, which is prevertebral (3P).

4. Lower Paratracheal (including Azygos Nodes): below upper margin of aortic arch down to level of main bronchus.

Aortic Nodes (5-6)

5. Subaortic (A-P window): nodes lateral to ligamentum arteriosum. These nodes are not located between the aorta and the pulmonary trunk, but lateral to these vessels.

6. Para-aortic (ascending aorta or phrenic): nodes lying anterior and lateral to the ascending aorta and the aortic arch.

Inferior Mediastinal Nodes (7-9)

7. Subcarinal.

8. Paraesophageal (below carina).

9. Pulmonary Ligament: nodes lying within the pulmonary ligaments.

Hilar, Interlobar, Lobar, Segmental and Subsegmental Nodes (10-14)

N1 - Nodes

N1-nodes are ipsilateral nodes within the lung up to hilar nodes. N1 alters the prognosis but not the management. A T1-tumor without positive nodes within the lung has a 5-y survival of 61%.The same T1-tumor with N1-nodes has a 5-y survival of only 34%.

N2 - Nodes

N2-nodes are resectable, but there is only a subset of patients with N2 disease that benefits from resection. Those are the patients who, after a negative mediastinoscopy, are found to have microscopic metastatic disease at the time of thoracotomy. Those patients have a better prognosis. Patients however with bulky N2-nodes on CT will not undergo surgery. They are treated with neo-adjuvant therapy followed by definitive locoregional treatment, which may consist of either radiotherapy or surgery.

Distant metastases

Staging procedures for distant metastases could be included in this algorithm (optional). Brain MRI and bone marrow biopsy are recommended for small cell lung cancer staging. Bone scintigraphy is indicated in cases of suspected bone metastases.

Other

Blood tests, radioimmune tests or other may be a supportive data in diagnosis management, so it is usefull to include them into the algorithm.

Ecog performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

(Oken et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982)

Such attributes in the algorithm as cancer localization, growing type, lung function tests are available for every patient but may not carry in any valuable data except statistics, so it is optional about these data inclusion.

Table of main parameters (attributes) for the alorithm

No.	Parameter	Number of Values	Values	Remarks
1.	Gender	2	Man Woman	Patient chacacterization attributes
2.	ECOG	5	0,1,2,3,4	
Risk factors				
3.	Age	4	>74y 55-74 50-54 <50	Risk factors are pointed out in Fleishner recommendations concerning lung cancer screening;
4.	Smoking history	6	No Quit smoking <15 y ago >30 pack years 20-30 pack years <20 pack years Secondhand smoking	
5.	Professional exposure: radon, asbestos, silica, chromium	2	Yes No	
6.	Family history on	2	Yes	

	lung cancer		No	
7.	Chronic lung disease	2	Yes No	
8.	Cancer history	2	Yes No	
9.	Previous chest radiation therapy	2	Yes No	
Lung nodule characterization				
10.	Lung nodule size CT	6	<3mm, 4-7mm, 8-10mm, 11-15mm, 16-20mm, >20mm	This section could be of great value creating the data base, but still there is no lung cancer screening in Lithuania and Belarus, so in case of selecting only this part we could face the problem of the lack of patients in our data base
11.	Lung nodule density CT	6	ground glass nodule, ground glass+solid nodule, solid nodule, fat containing, calcified	
12.	Lung nodule shape CT	3	Round Oval Lobulated Irregular	
13.	Lung nodule localization CT	3	Peripheral Subpleural Pleural	
X-ray image (optional)				
14.	Lung nodule size	4	<10mm 10-15mm 15-20mm >20mm	Thinking about different kind of data base users it is rational (but optional) to include chest x-ray examination into the algorithm. Usually it is the first examination for the patient, especially in small hospitals, so it could be of value for the physician.
15.	Lung parenchyma changes	4	Infiltration Atelectasis Both No	
16.	Pleural fluid		Yes No Bilateral	
17.	Mediastinal widening	2	Yes No	
18.	Hilar enlargement	2	Yes No	
Central airways cancer signs				
19.	Intrabroncheal nodule	2	Yes No	Lung cancer usually is diagnosed together with some infectious disease incidentally, cause only then patient observes
20.	Broncheal stenosis	2	Yes No	
21.	Infiltration	6	No Diffuse/multiple Segmental Lobar	

			Lung Bilateral	some symptoms, so it is rational to include patients with central airways disease in the algorithm.
22.	Atelectasis	4	No Segmental Lobar Lung	
23.	Pleural fluid	3	No Unilateral Bilateral	
Lymph nodes evaluation on CT				
24.	N1 l/n >10mm	2	Yes No	Lymph nodes are always evaluated on CT images, so these attributes could be mentioned even if only primary diagnostic (without staging procedures) algorithm will be selected
25.	N2 l/n >10mm	2	Yes No	
26.	N3 l/n >10mm	2	Yes No	
Additional info (optional)				
27.	Blood test leucocytosis	2	Yes No	These attributes are optional. They are usually done in lung cancer treating centers, but less in small hospitals, so this section could be discussed
28.	Blood test trombocytosis	2	Yes No	
29.	Blood test anemia	2	Yes No	
30.	Autofluorescent bronchoscopy	2	Fluorescent No fluorescence	
31.	Lung function test FVC	2	Normal Abnormal	
32.	Lung function test FEV1	2	Normal Abnormal	
33.	CEA	2	Normal Elevated	
34.	CYFRA	2	Normal Elevated	
35.	SCC	2	Normal Elevated	
36.	Sputum cytology cancer cells	2	Yes No	
Cancer characterization and staging				
37.	Hystology	4	Squamous cancer Adenocarcinoma Small cell cancer Other	The data base of patients will be collected after proving the disease by operation, so this data should be
38.	Grade	4	G1 G2	

			G3 Other	collected for the approval of results.
39.	Growing type	3	Peripheral Central Peribroncheal/mediastinal	
40.	Localization	6	L1/ L2/ L3/ /L1 /L2 Other	
41.	Lymph node verification assessment	8	Mediastinoscopy Toracoscopy Endoscopic ultrasound (EUS) Endobroncheal ultrasound (EBUS) US guided biopsy VATS Parasternal mediastinotomy Other	
42.	T TNM classification	6	T1a T1b T2a T2b T3 T4	
43.	N TNM	4	N1 N2 N3 N0	
44.	Nodal stations (N map)(optional)	15	N1-14 N0	It is optional to mention N stations, this section may be removed after discussions
Distant metastases investigation (optional)				
45.	Bone scintigraphy metastases	3	Yes No surveilance	Distant metastases evaluation is optional and not always available. This section could be removed after discussions
46.	Brain MRI/CT	3	Yes No survailance	
47.	Bone marrow aspiration cancer cells	2	Yes No	