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UTILITY AND ALGORITHM OF IMAGING MODALITIES IN DIAGNOSIS AND STAGING OF BRONCHOGENIC CARCINOMA

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Abstract

The utility and algorithm of diagnostic and particularly radiological conventional and digital methods in diagnosis and staging of central and peripheral, non-small cell and small cell bronchogenic carcinoma are presented in this paper.

Their sensitivity and specificity in the assessment of malignant mediastinal and hilar adenopathy, pleural and chest wall infiltration and tissue categorisation of the solitary pulmonary nodule are discussed.

It is concluded that digital methods - spiral CT, US and MRI, in spite of quoted limitations, have considerably improved the diagnosis and staging of bronchogenic carcinoma.

Although CT is superior over conventional radiological methods, it should be used in definitive staging complementary with the other imaging modalities, endoscopic and bioptic methods, as well as obligatory histological confirmation of the .diagnosis.

Key words: bronchogenic carcinoma, diagnosis, algorithm, imaging modalities.

Introduction

Although the first announcements regarding bronchogenic carcinoma (BC) have been seen in autopsy reports from 18th century, a hundred years ago BC compared to other types of carcinoma was rare.

Relation between BC and smoking is undisputable since long time ago.

The consumption of cigarettes in US have started to increase significantly around 1915, and twenty years later a parallel increase in number of diseased people and mortality caused by BC was apparent. In

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1935, 4300 people died of it, and in 1957 more than 135 000 people died of the same cause (1).

According to the latest reports from World Health Organization the following has been concluded:

- In spite of thousands of studies which have shown that tobacco in all it's forms kills it's users and smoking of cigarettes kills a non-users as well, people continue to smoke, and the mortality caused by tobacco consumption is still increasing.
- Almost one billion people in the world smoke – about 35% in developed and 50% in developing countries. The trend in both countries shows that the level of smoking among men have reached it's peak and is slowly decreasing, having in mind that this is the habit of poor and less educated men.
- About 250 million women in the world smoke – about 22% in developed and 9% in developing countries. Smoking cigarettes among women is decreasing in many developed countries but not in all – in South, East and Central European countries is even increasing.
- In general, more and more people smoke and smokers consume more and more cigarettes. Tobacco production have reached the proportion of global epidemic. Tobacco industry around the world is producing almost one thousand cigarettes per each man, woman and child on this planet annually.
- The vast majority of smokers start using tobacco in their early youth. Among young people, almost one quarter of smokers start smoking before they reach 10 years-of-age. The sooner they start smoking the bigger the risk of acquiring diseases related to smoking (cancer, heart diseases).

A special emphasis is put on the danger from passive smoking:

- The risk of BC among non-smokers exposed to passive smoking have increased to 20-30%, and the risk of heart disease increased to 23%.
- 40% of world children is exposed to passive smoking in their homes.
- Smoking in pregnancy is dangerous both for the mother and for the fetus, and exposing of pregnant woman to passive smoking can damage fetus as well.

Further on, the following has been emphasized:

- Tobacco is the greatest killer, much greater than all other forms of pollution and greater than AIDS, drugs, car accidents, murders and suicides in total.

- Tobacco is a killer and should not be advertised or financially supported.
- Every cigarette shortens smoker's life for 7 minutes.
- Every 10 seconds in the world one person dies of a smoking-related disease.
- Children are most vulnerable. Girls and women throughout world are targets of expensive and attractive advertisements of smoking as a symbol of freedom, emancipation, enthusiasm and wealth.
- Tobacco companies are responsible for damaging consequences of smoking.
- Practically, all body part are exposed to damaging consequences of the tobacco use (hair, skin, limbs, bones, eyes, teeth, respiratory, cardiovascular, nervous, gastrointestinal, urogenital, haematopoetic and immune system, male and female reproduction etc).
- Smoking is responsible for: 90% of lung cancer, 75% of chronic bronchitis and emphysema, and 25% of ishaemic heart disease.
- Half of smokers die in their middle age – between 35 and 65 years-of-age.
- At the beginning of 21st century about one third of young people in the world, including the increasing number of women, use tobacco.

The results of the researches performed during last 5 years show more and more gloo - my picture caused by the danger of smoking:

- Annual mortality caused by smoking in industrial countries in 1950 was 0,3 million, in 1975 – 1,3 million, in 2002 – 2,1 million, and a prediction for the period between 2025 and 2030 is 3 million people.
- In developing countries annual mortality for 1950 is unknown, in 1975 was 0,2 million, in 2000 – 2,1 million, and a prediction for the period between 2025 and 2030 is 7 million people (2).

Regarding the therapy for BC, as we know, certain progress has been made in the last twenty years (introduction of new cytostatic drugs, their combination, synergism, reduced toxicity, it's combination with radiotherapy etc). But a significant increase in length of survival period have not been achieved yet, unfortunately.

In spite of the mentioned increase in the incidence and mortality from BC, the degree of resectability has not changed significantly, which emphasizes the fact that, still, there are no successful methods for

establishing an early diagnosis. That is why the fight against smoking in order to prevent and stop tobacco addiction, is the only safe way of reducing its incidence.

Diagnostic methods

Bronchogenic carcinoma is a mean disease because its symptoms may lack or are discrete and not typical, especially at the onset of the disease. That is the reason why its diagnosing is complex and difficult. The main goal during the evaluation of the patient with any neoplasm is to reach a correct patohistological diagnosis. The next step is to determine its degree of spread-classification or staging, in order to apply adequate (optimal) therapy as an important assumption for the extension of patient's survival (1,3).

Beside valuable clinical, laboratory and especially endoscopic and biopsy methods, there are digital radiological diagnostic methods with aspiration biopsies that are used in diagnosing BC.

When staging a non- small cell BC the aim is to determine its resectability in order to dissect a tumor with all involved mediastinal lymph nodes of the N_2 patient or in order to apply a pre-operative or post-operative chemotherapy and radiotherapy, which will help increase a 5-year survival of patients (4,5,6,7).

Although CT, MRI, scintigraphy and biopsy can discover occult extrathoracic lesions in brain, liver, suprarenal gland or bones in asymptomatic patients as well, these are not considered a routine methods and are only indicated on the basis of anamnesis, physical examination and laboratory results. There was a warning that there is an increase of incidence of adenocarcinoma with occult metastasis in brain in at least 20% of these patients and there is a possibility of resection of solitary brain metastasis (8).

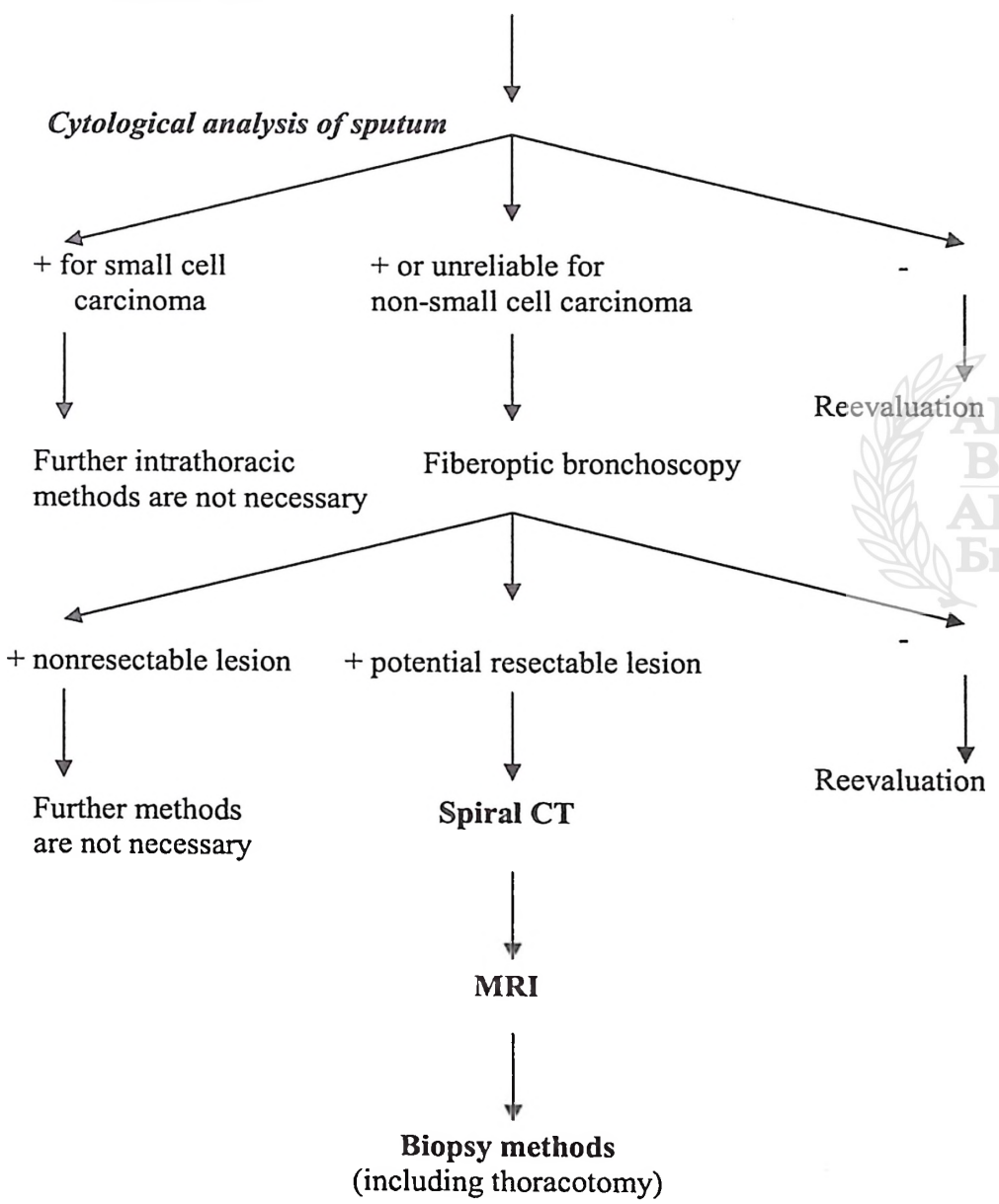
Staging of small cell BC is different compared to a non-small cell BC because of it's high tendency to metastasizing. According to results of huge studies, following percentages of these lesions were found: intracranial lesions – in 10-15%, liver lesions – in 28%, and bone lesions – in 29% of the patients (9). That is why CT, ultrasound, scintigraphy and biopsy were recommended as a routine methods in staging of patients with small cell BC. Unfortunately, when implemented for complete staging, about one third of patients will be in the stage of limited disease and two thirds in the stage of spread disease (1).

Algorithm and discussion

In algorithm of diagnostic methods in patients with central BC after performing a chest radiography of thoracic organs, cytological

analysis of sputum, bronchoscopy, CT and MRI, obligatory are biopsy methods (including thoracotomy) with a sequence interrupted in a case of small cell and nonresectable non-small cell carcinoma. (**Scheme 1.** adjusted to Robert D. Pugatch's Scheme, 1986.).

Scheme 1. *Algorithm of diagnostic methods*
- central bronchogenic carcinoma -



A standard radiography is considered useful in the initial detection and screening of patients with central BC.

False-negative results are seen in the initial phase of metastasizing into lymph nodes and small lesions in bronchial lumen with no obstruction, while false-positive results are seen when vascular structures or fat tissue collections are misdiagnosed as a tumor (10, 11).

Although a classic CT has been considered a standard method in detection of mediastinal abnormalities, it was possible to make an error in estimating invasion of mediastinal structures - pleura or thoracic wall (excluding bone structures), and spiral CT is considered superior in such cases (11, 12, 13, 14).

Earlier percentage of CT sensitivity regarding the involvement of lymph nodes following the criteria of its size was very high (up to 95%), while later it has decreased (down to cca 65%). False-negative results were seen in cases of positive lymph nodes without their enlargement, especially in adenocarcinomas (14, 15, 16, 17, 18).

Specificity, as well, was high (cca 80%) depending on the criteria of the size, and it has decreased (down to cca 65%). False-positive results were seen in cases of enlarged lymph nodes caused by something else (e.g. reactive hyperplasia), and biopsy is necessary (8, 14, 18, 19).

It is believed that MRI has advantages over CT in preoperative staging because it provides us with additional information; it easily differentiate lymph nodes from blood vessels; provides analysis of subcarinal and aortopulmonal region; easily differentiate the confinement of tumor to bronchus or its penetration to tracheal carina. MRI is a method of choice for apical tumors with the involvement of soft tissue structures of the neck (8, 14, 20, 21, 22, 23).

In the algorithm of diagnostic methods in cases of solitary pulmonary nodule (SPN) up to 3 cm in diameter, a chest radiography is performed and after that a CT, in order to determine the presence of calcifications. Nodules with low CT numbers undergo biopsy, and a positive ones or inconclusive ones are indication for the resection using thoracoscopy or thoracotomy (8, 24, 25) (**Scheme 2.** adjusted to Robert D. Pugatch's Scheme, 1986.)

The principle: " Watch and wait" in cases of SLN is not recommended, especially not in high-risk cases, and it is obligatory to reach a definite diagnosis in spite of the lesion's size (8).

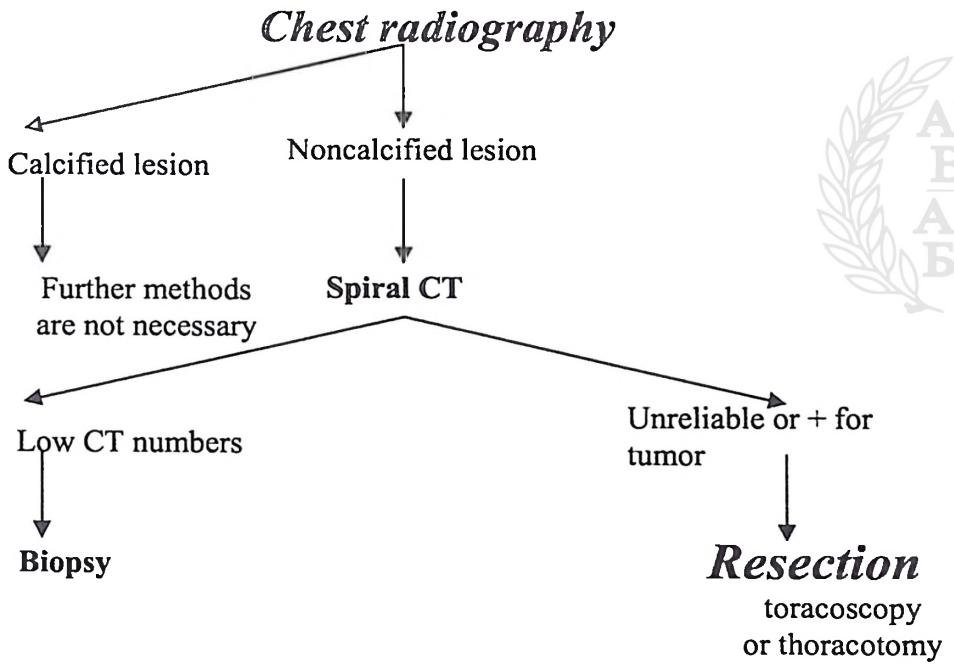
A chest radiography is considered an initial method in detection of all SPNs, and a threshold in detection is lesion's diameter of 1 cm. Lesions that have 1-2 cm in diameter can be overlooked because of the superposition of the bone and vascular structures, especially those that have less than 1 cm in diameter, which is confirmed by a comparison with previous x-rays (8).

The value of CT is in its possibility to confirm the presence of nodule; it is reliable in detecting and characterizing calcifications within a tumor, as well as in detecting enlarged lymph nodes and occult lesions on other sites (24, 25).

Sensitivity of classic CT in a detection of SPNs is high. False-negative results are seen in lesions whose diameter is below a threshold of resolution, in partial volume effect or moving of the lesion due to breathing (25, 26, 27).

Specificity of classic CT is very high in cases of high CT numbers and in cases when calcifications are present, and varies in cases of low CT numbers because such numbers are seen in 50% of benign and in majority of malignant lesions. False-positive results are seen in benign lesions without calcifications or not apparent ones, so the lesion is considered malignant (24, 25, 26, 27, 28).

Scheme 2. Algorithm of diagnostic methods
- peripheral bronchogenic carcinoma (SPN) -



BC show a benefit of using a low-dose CT in screening asymptomatic early BC (eight BCs were discovered in more than 700 heavy smokers; all eight of them were operable) (33).

CT fluoroscopy that provides a continuous CT image and easier visualization, is more and more used in interventional procedures (trans-bronchial biopsy). Its disadvantage is a high exposure to radiation (34).

It is also agreed that CT is useful in estimating a possibility of reaching a positive histological results in samples taken with fiberoptic bronchoscopic biopsy, by using numerous CT indicators (tumor's irregular form and blur contours; if the distance between a tumor and a starting point of the nearest lobar bronchus is less than 4 cm; endobronchial component in the tumor itself; segmental or some bigger air way that leads toward a tumor (35).

Because of a well known limitations (low proton density, artifacts of sensibility due to air – tissue interaction, loss of signal due to breathing and cardiovascular movements), lungs have been neglected in their imaging using MRI. But, thank to numerous technical improvements of the method and application of contrast media, its use has increased both in presentation of lungs as well as in performing lung angiography (characterization of lung nodules; estimation of stages of BC, especially in estimation of thoracic wall's involvement, estimation of inflammatory process in cases of interstitial disease of the lungs, acute lung embolism; chronic thromboembolic lung hyperten-sion; vascularization of malignant neoplasm; vascular abnormalities). Soon, a perfusion images (by using extracellular and intracellular contrast media) will be available, together with a ventilation images (by using inhaling hyperpolarizing gas, paramagnetic oxygen or contrast media in a form of aerosol). It is believed that combination of visualization, morphology and functional evaluation of ventilation and perfusion is better than any other technique (36).

It is also confirmed that ECG-triggered 3D contrast MR angiography has improved the quality of images and possibility of finding hilar and mediastinal invasion of BC (37).

Further on, it was found that a diagnostic potential of virtual bronchoscopy compared to bronchospcopy, axial CT sections, a multiplanar reconstruction (MPR) and minimal intensity projections (MIP), has advantages (passing by stenosis is possible only by using virtual endoscopy). That is why it is believed that virtual endoscopy is a non-invasive method of identification of endoluminal tumors and is comparable with real bronchoscopy (38).

Finally, PET scanning is considered superior to actual "gold standard" – CT scanning in clinical staging of mediastinum in cases of non-small cell BC (39).

Conclusions

Digital radiological diagnostic methods like CT, ultrasound, MRI and especially spiral CT have considerably improved diagnostics of BC. They are superior to classic radiological methods in estimating

its stage according to TNM classification and in planning optimal treatment.

Difficulties exist regarding its sensitivity and specificity in estimating malignant mediastinal and hilar adenopathy, invasion of mediastinal structures, pleura and thoracic wall, as well as in categorizing the nature of SPN.

Beside above mentioned difficulties, chest radiography and spiral CT are considered a valuable standard methods in diagnosis of local and regional spread of BC. But for definitive staging in algorithm of diagnostic methods, these should be used complementary to the other digital methods with obligatory endoscopic and biopsy methods that will provide us with patohistological confirmation of the diagnosis.

Apstrakt

Vrijednost i algoritam dijagnostičkih, a posebno radioloških konvencionalnih i digitalnih metoda u dijagnostici i steidžingu centralnog i perifernog, nemikrocelularnog i mikrocelularnog bronhogenog karcinoma, su prezentirani u ovom radu.

Njihova senzitivnost i specifičnost u procjeni maligne medijastinalne i hilarne adenopatije, infiltracije pleure i torakalnog zida, te karakterizacije prirode solitarnog plućnog nodula, su diskutovane.

Zaključeno je da su digitalne metode - CT, UZ i MRI, a posebno spiralni CT, i pored navedenih ograničenja, znatno unaprijedile dijagnostiku i steidžing bronhogenog karcinoma.

Mada je superioran nad konvencionalnim radiološkim dijagnostičkim metodama, CT u definitivnom staging-u treba koristiti komplementarno s ostalim imidžing, endoskopskim i bioptičkim metodama, uz obaveznu patohistološku potvrdu dijagnoze.

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