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RADIOLOGICAL AND "IMAGING" METHODS IN TNM CLASSIFICATION OF NON-SMALL-CELL LUNG CANCER

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A b s t r a c t: Lung cancer is the most common worldwide malignnant disease according to its incidence and mortality. The aim of our study was to evaluate the diagnostic value of the radiological and imaging methods, according to the TNM classification, compared to postoperative histological diagnosis.

Thirty-seven patients with pulmonary carcinoma were studied prospectively using native chest radiography (PA and LL view), computed tomography (CT) and magnetic resonance imaging (MRI) during ten days before thoracotomy.

Radiological and imaging findings were reviewed separately and results were compared with surgical and pathohistological findings on the basis of the TNM classification. All patients underwent chest x-rays, CT was performed in 36 patients and MRI in 12 of them.

Imaging methods (CT and MRI) showed more accuracy in sensitivity and specificity compared with the native chest radiography in a great percentage. Generally no statistically significant differences were found between the two imaging methods for the evaluation of tumour extent (T) or lymph node metastases (N). MRI was slightly superior to CT in determination of the chest wall extent of the tumour.

In conclusion CT remains the imaging modality of choice both for assessing patients with abnormal chest radiographs suspected of having lung cancer, and in staging patients with histologically proven pulmonary carcinoma.

Key words: CT, MRI, lung cancer staging, TNM classification, NSCLC = non-small-cell lung cancer.

Introduction

Lung cancer is the most common worldwide malignant disease according to its incidence and mortality. A total of 611 new cases were diagnosed and 467 patients died from lung cancer, which was the leading cause of all cancer deaths in R. Macedonia in 2001. The five-year survival of the disease is not more than 10% to 15% [1].

Pathological evaluation for lung cancer diagnosis may be based on several types of biopsy specimen, including bronchoscopic and transthoracic needle biopsies, as well as surgical biopsy procedures such as thoracoscopy, excisional wedge biopsy, and lobectomy – pneumonectomy. Light microscopy is sufficient for diagnosis in virtually all cases of lung cancer.

The international standard for histological classification of lung tumours has been proposed by the World Health Organization (WHO) and the International Association for the Study of Lung Cancer (IASLC). There are four major histological types [2]: 1) adenocarcinoma with its subtype bronchioloalveolar carcinoma; 2) squamous cell carcinoma; 3) small cell carcinoma (SCLC) and 4) large cell carcinoma.

Complete surgical excision of carcinoma remains the most effective form of therapy and the only reasonable hope for a definitive cure of the patient. Thus, it is necessary to accept an adequate staging system which represents the extent of the disease. The main role of staging is to select patients who will benefit from surgical resection and to determine the prognosis of the disease. The responsibility for accurate staging is shared by the pulmologists, radiologists, surgeons and pathologists. All of them should accept a uniform staging system.

The last modification of the Lung Cancer Staging System which was established in 1997 contains two major components [3]:

1. The anatomical extent of the disease (TNM), determined by the extent of primary tumour (T), presence of intrapulmonary, hilar or mediastinal lymph node metastases (N), and extrathoracic metastases (M).

2. The cell type of the tumour. The present Staging System for lung cancer is exclusively related to the non-small-cell type of lung cancer (NSCLC). Patients with small cell lung carcinoma (SCLC) are still staged as with either limited or extensive disease according to the classification of the Veterans Administration Lung Cancer Group.

Different combinations of TNM subsets and stage grouping are presented in Table 1, according to the new revisions of the international system for lung cancer staging [3, 4].

Table 1 – Табела 1

Levels of TNM classification
Сшейени на ТНМ класификацијаша

0	CA *in situ*
IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0
	T3N0M0
IIIA	T3N1M0
	T1N2M0
	T2N2M0
	T3N2M0
IIIB	T4N0M0
	T4N1M0
	T4N2M0
	T1N3M0
	T2N3M0
	T3N3M0
	T4N3M0
IV	any T & N, M1

Methods of staging

A variety of techniques can be used to investigate T, N, and M parameters and to determine the relevant tumour stage.

Native chest radiographs (PA and LL view) – most of them have been already established during the initial diagnostic workup. For example, chest radiographs would reveal the size of circumscribed lung lesion and the degree of associated atelectasis or obstructive pneumonitis in the presence of airway obstruction. The chest radiograph would establish the presence or absence of pleu-

ral effusion, with exception of the situation when atelectasis or obstructive pneumonitis of a lower lobe obscures its presence (Figure 1).

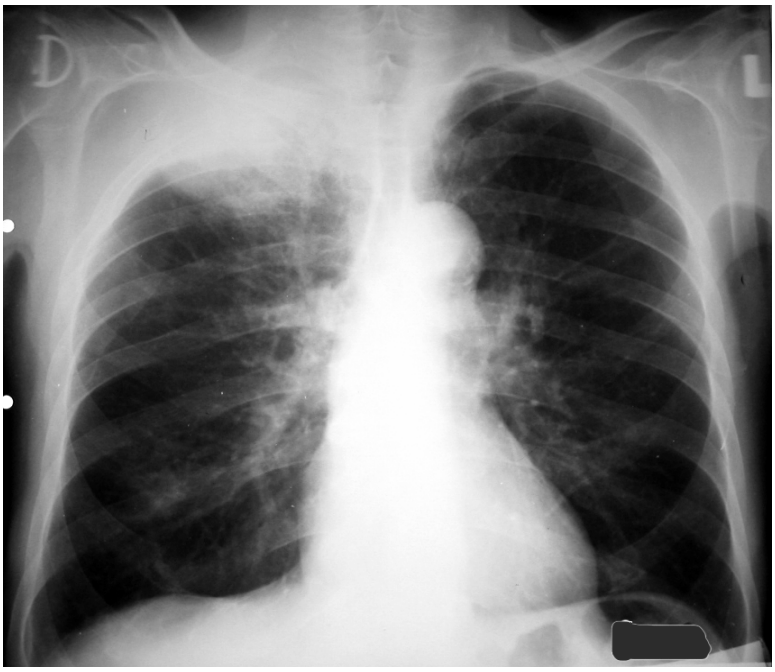

Figure 1 – Native CXR. Tu mass in right apex with rib destruction
Слика 1 – Нативна радиографија.Ту маса десно апикално со ребрена деструкција

In some cases, extrapulmonary spread of the tumour may be evident from only native chest radiographs. Evidence of invasion of the mediastinum may be suggested by marked elevation of hemidiaphragm (paralysis of the phrenical nerve), or by clinical signs of superior vena cava syndrome or laryngeal paralysis.

Hilar (N1), ipsilateral (N2), or contralateral (N3) mediastinal lymph node metastases (according to the American Thoracic Society Classification System) are often present at the time of initial diagnosis of pulmonary carcinoma.

If there are no such signs, it is necessary to resort to *computed tomography (CT)* or *magnetic resonance imaging (MRI)* for adequate evaluation of both tumour extent (T) and lymph node (N) metastases. Patients with evidence of distant metastases (M) are not included in this category, since this group is immediately sent for an oncological and/or irradiation treatment as a first choice.

In some instances, accurate staging and determination of appropriate treatment in patients with lung cancer can be done non-invasively with imaging

modalities alone, although in most instances some degree of mediastinoscopy and surgical staging is also necessary [5].

The majority of studies evaluating CT scan accuracy have used a short axis of > 1cm as a threshold for definition of abnormal mediastinal and hilar lymph nodes. These studies have also demonstrated that, regardless the threshold size, an isolated CT scan finding could not be considered as conclusive evidence that lymph nodes were malignant. In other words, there are many false positive results that are detected by CT [6].

Recently, a new method has aroused attention in tumour staging. This is positron emission tomography (PET), with-18 fluoro 2 deoxy D-glucose which relies on the biochemical difference between normal and neoplastic cells. Unfortunately, we do not have our own experience with this method.

The diagnostic performance of radiological and imaging methods compared with pathohistological diagnosis as a golden standard is the basic aim of this study.

Material and methods

The prospective study carried out during 2003–04 included 37 patients with diagnosis of primary lung cancer during no more than 10 days before thoracotomy, regardless of age or gender. The cohort consisted of 30 males with a mean age of 69.7 ± 7.8 years. The diagnosis of NSCLC was obtained either as a result of the cytology of the sputum or by needle biopsy of a lung nodule-mass, or by a flexible bronchoscopy biopsy specimen for the histopathology.

The most frequent histological type was squamous cell carcinoma in 16 patients, then adenocarcinoma in 14, large cell carcinoma in 4, and mixed forms – pleomorphic carcinoma – in 3 patients. The analyses were obtained from various anatomicalarts of the lungs such as upper lobe / middle lobe – lingula / lower lobe in 22, 3 and 12 of the cases, respectively.

Patients were excluded if the histological diagnosis was other than NSCLC, if there was clinical evidence of tumour dissemination or distant metastases M1, or if they had undergone chemotherapy or irradiation. Patients in whom CT (allergy on i.v. contrast) or MRI imaging was contraindicated were also excluded.

All study subjects underwent posteroanterior and lateral chest radiography followed by an imaging investigation regardless of the plain chest radiographic findings, unless distant metastases were suspected.

CT was performed as the first imaging investigation in 33 patients, in 3 cases after MRI and in 1 patient it was not done. MRI was done on 12 patients, as the first investigation in 3 of them and in 1 patient as the single imaging method.

Statistical analysis:

We used descriptive (frequencies, proportions and percentages) and analytical methods for the statistical analysis of the obtained data. Wilcoxon signed rank test and Spearman's (Ro-Nonparametric) test were used for comparison and correlation of the radiological and imaging techniques between each other as well as with the histological findings. Sensitivity, specificity, negative predictive value and positive predictive value were assessed through the receiver operator curves (ROC) with pathohistological diagnosis taken as a golden standard. Overall statistical analysis was performed by SPSS programme, release 10.

Results

The native chest x-ray could not be matched with the histological diagnosis ($p < 0.01$), demonstrating the existence of lower diagnostic performance for detection of TNM stages. The CT did not differ significantly ($p > 0.05$) from the histological diagnosis, i.e. it appears that CT has comparable diagnostic performance with the golden standard (histology). The same observation was obtained for the comparison of MRI and the histological diagnosis ($p > 0.05$). As expected, CT and MRI showed significantly better diagnostic performance than the native chest x-ray ($p < 0.01$ and $p < 0.05$, respectively). In contrast, there was no statistical difference between the diagnostic performance of CT and MRI ($p > 0.05$) (Figure 2).

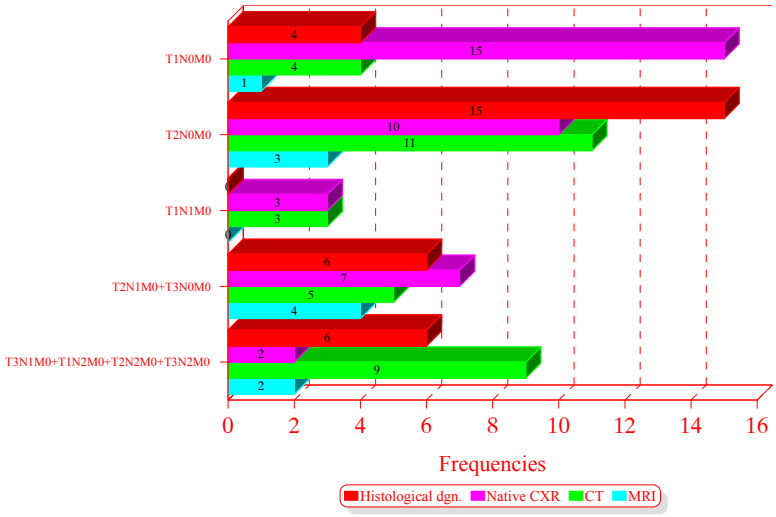

Figure 2 – TNM classification for all diagnostic methods
Слика 2 – ТНМ класификација за сите дијагностички методи

The Spearman's ρ(Ro)-nonparametric correlations are presented in Table 2:

Table 2– Табела 2

Spearman's ρ(Ro) - nonparametric correlation
Нейарамейшриска ρ(Ro) корелација сйоред Сйирман

Correlated methods	ρ coefficient	p value
ch.x-ray vs. hist.dg.	0,450	< 0,01
CT vs. hist.dg.	0,719	< 0,01
MRI vs. hist.dg.	0,644	< 0,05
ch.x-ray vs. CT	0,552	< 0,01
ch.x-ray vs. MRI	0,625	< 0,01
MRI vs. CT	0,990	< 0,01

The diagnostic performance data (ROC) analysis for the CT and MRI in comparison with the golden standard is presented in Figure 3.

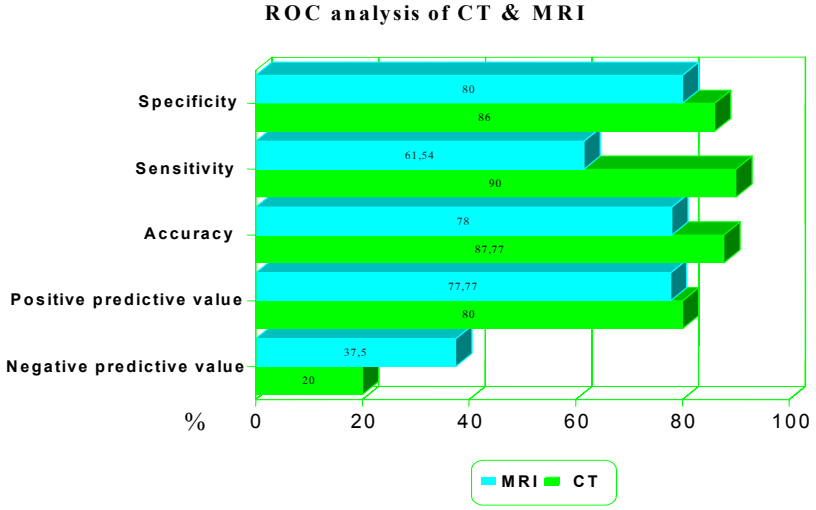

Figure 3 – Receiver operating characteristic (ROC)-analysis
Слика 3 – РОК анализи

In 24 patients a subanalysis was made for the pathohistological changes of lymph nodes with all investigation methods, revealing 46 hilar and mediastinal lymph nodes. The results were interpreted according to the American Thoracic Society (ATS) system for lympho-nodal classification.

Table 3 – Табела 3

Results of lymphonodal classification
Резултати од лимфоноднатa класификација

ATS classification	Ms-changed	Non-changed
1 upper paratracheal	1	5
4 lower paratracheal	3	9
5 aorticopulmonary	1	7
7 subcarinal	3	5
8 paraesophageal	0	2
9 ligg.pulmonary	0	3
10 hilar – peribronchial	2	5
summary	10	36

Discussion

From a technical point of view, MRI shows significant disadvantages compared to CT. It is a costly and time-consuming procedure, and the spatial resolution is less than that achieved by CT. Artifacts and blurring structures related to the respiratory and cardiac motions have been reduced with the use of cardiac gating techniques. Disadvantages of CT are related to the administration of intravenous contrast, ionization and poorer spatial resolution in MP (multiplanar) reconstructions of the sagittal and coronal views [7].

In general, we obtained no statistically significant difference between imaging methods in the determination of T and N. In selected cases, as it will be discussed later, MRI can play a significant complementary role in the evaluation and staging of the lung cancer.

T – characterization

We have confirmed with nearly identical statistical conclusions in sense of sensitivity and specificity of CT and MRI the previous observations of Musset *et a.l*, Martini *et al*. [8, 9]. However, a more detailed analysis of our results has shown that particular attention has to be directed to some specific characteristics of T and N. Hence, we did not confirm the potential advantage of MRI about histological differentiation of tumourous vs. non tumourous tissue in comparison with CT. In addition, we could not detect small peribronchial tumoural involvement or small-granulated pleural carcinosis with both imaging methods that were histologically confirmed thereafter. The utility of T2-WI was mainly assumed in differentiation between tumour vs. atelectasis, and in confirmation of the cystic portion of the tumours.

A significant difference in the diagnostic performance of CT and MRI was found in detection of pathological changes of the bronchial wall, thoracic cage, mediastinum and pleura. The number of patients with these characteristics was 6, 3, 2 and 2, respectively. From 6 patients with invasion of the bronchial wall a combined CT-MRI investigation was performed on 4 of them. In 3 patients a significantly increased accuracy of CT in detection of endobronchial lesions or bronchial narrowing compared to MRI was found.

Additionally, in the three cases with a superior sulcus tumour, rib destruction was detected on native chest radiograph and CT but not on MRI (Figure 4).

Fig. 4 – CT of invasive Tu mass with thoracic cage destruction
Слика 4 – КТ на инвазивна Ту маса со деструкција на торакалниот ѕид

On the other hand, MRI was shown to have superior diagnostic performance in one case with thoracic cage invasion, i.e. invasion of the parietal pleura and surrounding soft tissues. Furthermore, in 2 cases of mediastinal invasion MRI was found as a superior method in delineation of tumour margins and invasion of mediastinal fat (with both T1-WI and T2-WI), as well as in pericardial affection in the second case (Figure 5).

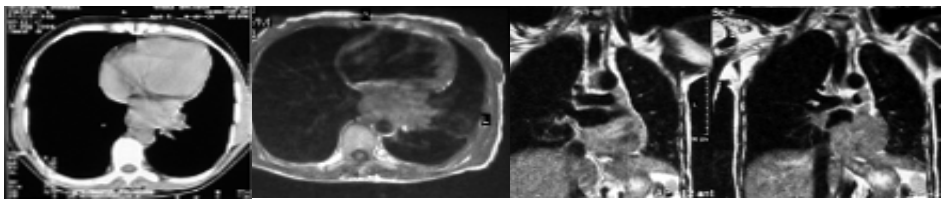

Figure 5 – Combined CT and MRI images of Tu invasion of pericardial and mediastinal fat infiltration.
Слика 5 – КТ и МРИ снимки од Ту инвазија на перикардот и медијастиналната маст

Two patients had pleural manifestation of the disease. MRI could not identify the suspected pleural plaques on CT in one of them. In contrast, MRI could delineate the tumour from the surrounding atelectasis in the other case.

N – characterization

In 24 patients a pathohistologycal lymph node investigation was performed, finding 46 hilar and mediastinal lymph nodes. The results were interpreted according to the American Thoracic Society (ATS) system for lymphonodal classification.

Pathohistological findings confirmed malignancy in only 22% (10/46) of all biopsied lymph nodes. Metastases on only one lymph node level were found in 6 patients, while changes on two or more levels were found in the others.

Hilar adenopathy N1 was confirmed in 8 patients. A false positive determination of hilar lymph nodes with both methods (CT and MRI) was found in 4 patients. Indeed, the lymph nodes were only slightly enlarged but not metastatically changed (only reactive).

We did not confirm the significant difference between T1-WI and T2-WI reported by Webb *et al*. (10), relating to the greater diagnostic performance of T1-WI for metastatically changed nodes in comparison to T2-WI (due to better achieved contrast among the lymph node and high signal intensity from mediastinal fat).

We compared the MRI and CT images in 12 patients: both methods confirmed metastatically changed lymph nodes in 30% while in 38% of cases

the diagnosis was not established by both methods; 17% were visualized with CT and 15% with MRI solely. The rate of sensitivity and specificity was higher in the enlarged lymph nodes (threshold level > 10mm in lower diameter).

Conclusions

CT and MRI have shown greater sensitivity and specificity as to the final pathohistological diagnosis compared to the native chest radiograph. The sensitivity of CT was moderately superior to MRI. MRI on the other hand was superior to CT in estimation of mediastinal and thoracic wall invasion. The difference between the two methods in evaluation of tumour extension or lymph nodal involvement in lung cancer was not statistically significant.

Our opinion is that CT remains the imaging modality of choice for both assessments of patients with abnormal chest native radiographs and suspected lung cancer as well as staging of the patients with previously diagnosed pulmonary carcinoma.

The applicability and high diagnostic performance of the CT in the imaging staging of lung cancer could prevent inappropriate surgical treatment in inoperable patients, and could facilitate surgical approach in operable cases.

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Резиме

РАДИОЛОШКИ И „IMAGING“ МЕТОДИ ВО ТНМ КЛАСИФИКАЦИЈАТА КАЈ НЕСИТНОКЛЕТОЧНИОТ БЕЛОДРОБЕН КАРЦИНОМ

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Според инциденцата и морталитетот белодробниот карцином е најзастапеното малигно заболување ширум светот.

Целта на студијата е да ја евалуираме дијагностичката вредност на радиолошките и „imaging“ методите, во склад со ТНМ класификацијата, споредено со постоперативната патохистолошка дијагноза.

Материјал и методи: 37 пациенти со претходно верифициран белодробен карцином беа вклучени во проспективно дијагностичко испитување со нативна ртг радиографија (ПА и ЛЛ позиција), компјутеризирана томографија (КТ) и магнетна резонанца (МРИ) во текот на десет дена пред торакотомијата. Кај сите пациенти се направи нативна ртг графија, додека кај 36 направивме КТ, а МРИ кај 12 од нив.

Резултати: Радиолошките и „imaging“ наодите беа посебно проценети и добиените резултати споредени со патохистолошкиот наод во склад со ТНМ класификацијата. „Imaging“ методите (КТ и МРИ) покажаа изразено повисоки вредности за сензитивност и специфичност во однос на нативните радиограми. Генерално не забележавме статистички сигнификантна разлика помеѓу двете „imaging“ методи при евалуацијата на тумоурската експанзија (Т) или лимфонодните метастази (Н). МРИ се покажа умерено супериорна при проценка на тумоурската инвазија на градниот кош.

Заклучок: Компјутеризираната томографија останува „imaging“ метод на избор кај пациентите со абнормална градна радиографија за адек-

ватна евалуација на заболувањето, како и кај случаите со веќе дијагностициран неситноклеточен белодробен карцином за одредување на неговиот прецизен стејџинг.

Клучни зборови: КТ, МРИ, стејџинг, ТНМ класификација, НСКБК = неситноклеточен белодробен карцином.

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	T3N0M0
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	T1N2M0
	T2N2M0
	T3N2M0
IIIB	**T4N0M0**
	T4N1M0
	T4N2M0
	T1N3M0
	T2N3M0
	T3N3M0
	T4N3M0
IV	**any T & N, M1**

Table 2. Spearman's ρ(Ro) - nonparametric correlation
Табела 2. Непараметриска ρ(Ro) корелација по Спирман

Correlated methods	ρ coefficient	p value
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Figure 2. TNM classification for all diagnostic methods
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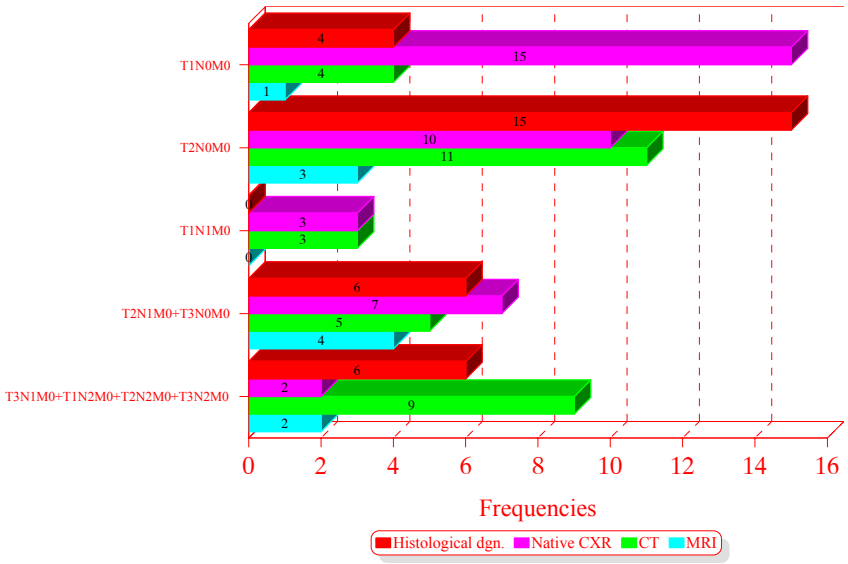

Figure 3. Receiver operating characteristic (ROC)-analysis
Слика 3. РОК анализи

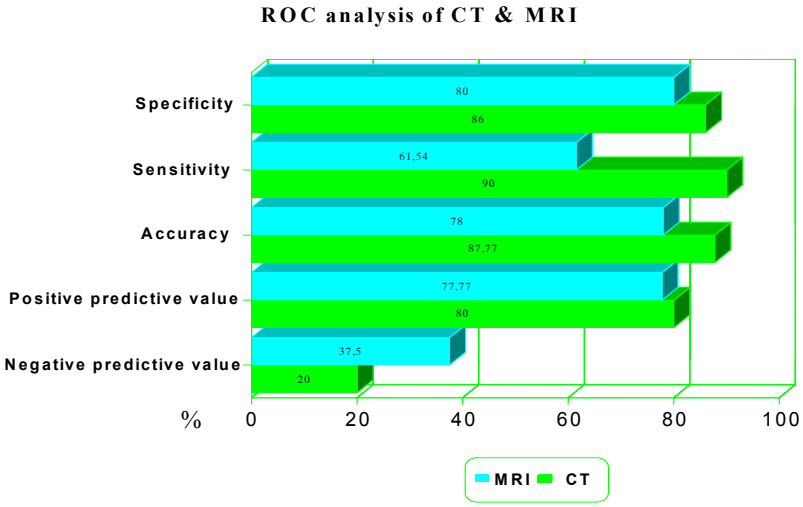

Fig. 4 - CT of invasive Tu mass with thoracic cage destruction
Слика 4 - КТ на инвазивна Ту маса со деструкција на торакалниот зид

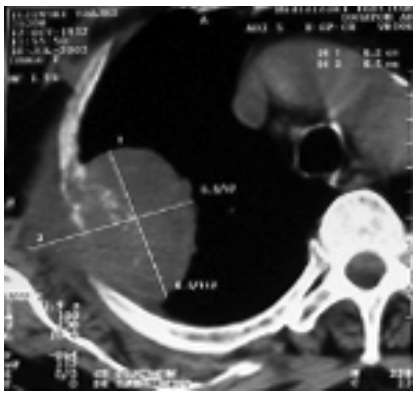

Figure 5. Combined CT and MRI images of Tu invasion of pericardial and mediastinal fat infiltration.
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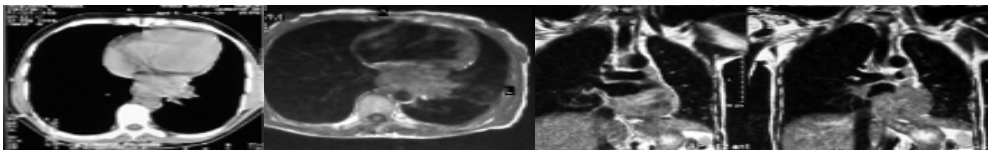

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РАДИОЛОШКИ И "ИМИЏИНГ" МЕТОДИ ВО ТНМ КЛАСИФИКАЦИЈАТА КАЈ НЕСИТНОКЛЕТОЧНИОТ БЕЛОДРОБЕН КАРЦИНОМ

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Според инциденцата и морталитетот белодробниот карцином е најзастапеното малигно заболување ширум целиот свет.

Целта на студијата е да ја евалуираме дијагностичката вредност на радиолошките и "имиџинг" методите, во склад со ТНМ класификацијата, споредено со постоперативната патохистолошка дијагноза.

Материјал и методи: 37 пациенти со претходно верифициран белодробен карцином беа вклучени во проспективно дијагностичко испитување со нативна ртг радиографија (ПА и ЛЛ позиција), компјутеризирана томографија (КТ) и магнетна резонанца (МРИ) во текот на десет дена пред торакотомијата. Кај сите пациенти се направи нативна ртг графија, додека кај 36 направивме КТ, а МРИ кај 12 од нив.

Резултати: Радиолошките и "имиџинг" наодите беа посебно проценети и добиените резултати споредени со патохистолошкиот наод во склад со ТНМ класификацијата. "Имиџинг" методите (КТ и МРИ) покажаа изразено повисоки вредности за сензитивност и специфичност во однос на нативните радиограми. Генерално не забележавме статистички сигнификантна разлика помеѓу двете "имиџинг" методи при евалуацијата на тумоурската експанзија (Т) или

лимфонодните метастази (Н). МРИ се покажа умерено супериорна при проценка на тумоурската инвазија на градниот кош.

Заклучок: Компјутеризираната томографија останува имиџинг метод на избор кај пациентите со абнормална градна радиографија за адекватна евалуација на заболувањето, како и кај случаите со веќе дијагностициран неситноклеточен белодробен карцином за одредување на неговиот прецизен стејџинг.

Клучни зборови: КТ, МРИ, стејџинг, ТНМ класификација, НСКБК = неситноклеточен белодробен карцином