

*Review***DIAGNOSTICS OF INTRAPULMONARY METASTASES FROM COLORECTAL CANCER (LITERATURE SURVEY)****E. Obretenov<sup>1\*</sup>, N. Georgieva<sup>2</sup>**<sup>1</sup>Clinic of Thoracic Surgery UMBAL „Prof. d-r S. Kirkovich”, Stara Zagora, Bulgaria<sup>2</sup>Department of Physics, Biophysics, Roentgenology and Radiology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria**ABSTRACT**

The colon cancer is on the first place as etiologic cause for performing pulmonary resection due to pulmonary metastases. The low effectiveness of chemotherapy in case of metastatic progression from colorectal carcinoma is established. Accordingly, the surgical resection is commonly accepted as the only potential therapeutic option. In favour of the good results from surgical treatment is the trend of earlier finding of pulmonary metastases. The metastases diagnostics has important meaning for differentiation from other lung diseases and for the choice of the therapeutic method. The benefits and disadvantages of non-invasive (chest X-ray, CT, lung perfusion scintigraphy, PET and PET/CT, tumor markers) and invasive (bronchoscopy, mediastinoscopy, VATS (video-assisted thoracic surgery, TTNB (trans-thoracic needle biopsy)) methods for diagnosis of intrapulmonary metastases are analyzed.

**Key words:** colorectal cancer, pulmonary metastases

There are different reports in the scientific literature about the incidence of colorectal carcinoma. According to some authors it is the third most often diagnosed cancer in the world (1-4). The data from P. J Villeneuve and R. S. Sundaresan (5) show that over one million new patients get sick from this insidious disease every year. H. Meulendeld et al. (6) report that 40% of the patients with colorectal carcinoma in Europe are over 75 years of age at the moment of first diagnosis and there are expectations that this number would significantly increase in the next two decades.

The colorectal carcinoma in Bulgaria according to the data from 2012 for prevalence is on third place in men and on second place in women and represents 8.6% from all malignant diseases totally for both sexes. The registered new cases are 2772, and 52,7% of them in men. The diagnosis in 42,4% of the patients is set in advanced III and IV stages. The relative 5 – year survival in Bulgaria is 45,0% for men, 45,3% for women and 45,2% totally for both sexes. It is lower than the average for Europe– 55,6%. (7). According to summed statistics A.

Sach, S. Alberts and R. Adam (8) report that colon carcinoma is the fourth most distributed cancer and it is second most frequent cause for mortality of the patients with oncologic diseases. Approximately 35% from the diagnosed patients are in stage IV and 20% to 50% of the patients in stage II and III reach stage IV despite the treatment (8).

The frequency of the isolated pulmonary metastases is in the range 1,7% to 11,4% (9-14). This is explained by the fact that the venous drainage of medium and lower third of the rectum is through lower and medium rectal veins, avoiding the venous system of v.portae and respectively, the liver which is the first filter (13,15,16). N. Rama et al. (17) registered that the lung metastases predominate when the localization is in lower and medium third of the rectum, in 36% and 39% respectively versus the rest 25% of the patients with localization in the upper third of the rectum. W. Takahashi et al. (1) report that after total removal and treatment of the patients with colorectal carcinoma pulmonary progression is registered approximately in 10%.

The diagnosis is often set according to the clinical symptoms, but usually the pulmonary metastases are asymptomatic (18-20). Clinically they stay undeveloped for long time and barely express in the advanced stages. The

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early establishment of the pulmonary progression is of significant importance for the treatment outcome.

### DIAGNOSTICS

S. Jegatheeswaran et al. (21) report that almost in all patients (99%) with colorectal carcinoma, to exclude metastatic progression or relapse a chest computer tomography (CT) is performed; in 70% of the patients a CT of the liver is needed and additionally CT of the pelvis in 51% of the patients is applied. Positron emission tomography (PET) is used in 86% of the diseased (21).

The diagnostic process of pulmonary metastases from colorectal carcinoma includes several main stages:

**Chest X-ray** – C. Gielen et al. (22) claim that the X-ray of the lungs has low percentage of finding of the pulmonary metastases and insignificant influence on the treatment of the patient. Their data indicate 0,86% finding ability of the pulmonary neoplastic lesions with confidence interval 0,3-1,4 %. In accordance with numerous examinations, the authors do not support the routine usage of the conventional X-ray of the thorax in patients with colorectal cancer (22). Other publications report that this method for establishing of pulmonary metastases is effective in 33% to 40% of the cases (10, 23, 24). Based on a literature analysis of the problem I.Grossmann et al. (10) establish that by X-ray the pulmonary metastases could be visualized in up to 55% of the patients. Similar are the data of J. H. Lee et al. (23), who report based on summed statistics that in 67% of the cases there is benefit of the conventional X-ray for diagnosis of the pulmonary metastatic progression in patients with colorectal cancer.

The early X-rays register formation of network drawing, over which are projected separate small-spotted shadows – the future nodes. The most often X-ray findings according to the different authors are solitary or multiple nodes in consolidation (23, 25, 26). The X-ray image is characterized with differently large round or oval shadow, with significant X-ray intensity, uniform structure, with sharp and smooth, sometimes polycyclic outlines. Rarely a cavity lightening in the tumor core is found. The endobronchial development of the tumor is shown by findings of atelectasis area. The advance of the tumor process is characterized by bronchia compression, expansion in neighbouring lobes and germination in the pleura and the chest wall. The X-ray image often resembles focal pneumonia and is characterized with the presence of thick

spotted shadows, showing a tendency for quick growing and confluence. According to the data from J.H. Kim et al. (25) the X-ray in endobronchial metastases shows obstructive atelectasis and diffuse infiltration of pulmonary parenchyma. The signs of obturative pneumonia are frequent. C. Fournel et al. (26) report that the most frequent X-ray finding in endobronchial metastases is atelectasis in 58% of the cases, followed by pulmonary node in 25%, pulmonary infiltration in 8,3%, pleural collections in 4,2%, hilar formations in 12,5% and mediastinal lymphadenomegaly in 8,3% of patients.

The differential diagnosis of tumor metastases by X-ray is complex. In isolated lesions the benign tumors come into consideration, echinococcosis cyst, tuberculoma and in multiple metastases – disseminated tuberculosis, sarcoidosis, pneumoconiosis, focal pneumonia and etc. Decisive for the diagnosis is the detection and establishment of the primary tumor process.

**Computed tomography of the thorax** – The computed tomography of the chest (CT) has become an important additional tool for the doctor, which is usually used for finding of a tumor disease, evaluation of the therapeutic response and the appearance of relapse (27). Performing a literature analysis about the effectiveness in diagnosis of pulmonary metastases through conventional X-ray and CT of the thorax M.W. Christoffersen et al. (24) report a low sensitivity of the first around 33%, in comparison with CT which reaches sensitivity of 73%. In the recent years computed tomography has become a main method for finding pulmonary metastases (1, 28-33). A. Nordholm-Carstensen et al. (28) advise its performing as a part of the routine care for the oncology patient in the first two years, because the analyses indicate that 84% of the malignant pulmonary lesions develop in this period. (28). T. Kawaguchi et al. (34) describe CT changes in pulmonary metastases like tumor formations with smooth and sharp borders in 42 % or formations with indistinct borders and shape in 56% of the patients. Registered frequently are also spiculative growth aside with pulling of the pleura. Cavity shadows could be observed in them, entirely empty or partially filled with necrotic materia in 26% and existing calcification in 18% of the cases. Except of the pulmonary finding CT could be useful for evaluation of the hilar and mediastinal lymph nodes. Size over 1,0 cm is determined as positive for lymphadenopathy (15).

In spite of all advantages of CT we should note that it has lower specificity for registered undefined lesions of the lung. Their origin remains a serious problem, because they are a frequent finding in 20% to 30% of the cases. According to some of the authors these are malignant in 10%-20% (10), but according to other publications the detected node in the lungs in 65% is a metastasis, and in the rest 35% - benign lesion (35). According to Y. Varol et al. (27) as a suspicious, undefined pulmonary node is defined one or more formations in the pulmonary parenchyma with size less than 1,5cm in diameter.

P. Jess et al. (32) report that by literature data 4 to 42% of the patients with colorectal carcinoma have pulmonary formations found by CT. In their study this percentage has been 20%. In 8,5% they turned to be pulmonary metastases, diagnosed 9 months after operation of colorectal carcinoma. In 4,3% has been established that another neoplastic disease is concerned, in 2,1% it is tuberculosis and in 5,4% for pulmonary metastases developed 16 months after the operation for colorectal cancer and normal CT scan before the operation. Despite that the number of unidentified pulmonary lesions which turn to be malignant is relatively small, it is recommended to use PET/CT scan in the subsequent actions for finding the pulmonary metastases at earliest possible in order to improve the prognosis. The ascertained results oblige us to look hard the histologic verification of the undefined lesions. By the same reason all of the patients with colorectal carcinoma should be examined by CT of the thorax in the following 6-12 months after the operation (32, 36). The metastases appear at average 2-3 years after removal of the primary tumor (18). Based on the data from A. Nordholm-Carstensen et al. (37), after the routine examination with pre-operative CT of the thorax in 9% undefined pulmonary nodes have been found. From them 10,8% turned to be metastases from colorectal cancer and because of this fact a conclusion is driven that only 1 from 100 patients (1%) with colorectal carcinoma undergoing pre-operative scan would have undefined pulmonary lesion which could be detected as metastasis from the main disease. The subsequent low risk suggests that unclear pulmonary finding should not cause additional changes in pre-operative diagnostics and routine schemes of therapeutic management.

In 65,5% of the patients the lesions are localized peripherally and described as sub-pleural. In the rest 34,5%, the findings have been disseminated in the lungs and are recognized as parenchymal. In 16,4% of the

patients calcifications in the nodes are found. The characteristics of the lesions belong to two categories – with round (84%) and irregular (16%) form. During the follow-up 31% of the patients have had progression. Metastases are established in 47% of them (27). In 35% of the patients has been determined that metastases' process has occurred during the follow-up period. Half of these metastases have been demonstrated by increased size or number and the other half has been established histologically. In most of the patients with rectal carcinoma the registered nodes are over 1cm. This fact is explained by the way of vascularization of the rectum (27). The smooth borders and sub-pleural localization are more frequently related to benign lesions (27). Based on his study Y. Varol et al. (27) come to the conclusion that undefined multiple pulmonary nodes with irregular form and border, localized in parenchyma are more probable to be a metastatic disease. A. Brent et al. (38) report that 10% of the patients have had undefined changes in the lungs. Half of them have had dissemination in the regional lymph nodes (N1 and N2) at the time of removal of the primary tumor (38).

J. Nakajima et al. (39) recommend realization of spiral CT of the thorax with thickness of the slice 5mm contrasted before the eventual pulmonary metastase-ectomy operation. The number, size and localization of pulmonary metastases are followed-up. Pulmonary solid node, sometimes with cavity in it, with 5 mm diameter or more, without calcification or occurrence of new nodes, even if their diameter is below 5 mm suggest that these are pulmonary metastases. Patients have been controlled on every 3-6 months by CT and test for carcinoembryonic antigen (CEA) until the finding of relapse of the colorectal carcinoma (24, 39).

Patients with colorectal cancer presenting with four or more undefined pulmonary nodes in pre-operative staging by CT, even with lack of metastases in another location, have a big probability for pulmonary progression of the disease (40). The final diagnosis of the pulmonary formations is based on the images from CT (characteristics and growth rate), PET/CT scanning or the histologic verification. The undefined pulmonary lesions are accepted as benign, when there are no signs registered for malignant growth on the second chest scanning (CT) and lacks increase of CEA at least for a year during the follow-up (10). The lesions most often become evidently malignant in the beginning of the second year after the operation (24).

The small nodes are often seen at CT of the thorax and they usually are benign. The difficulty with these lesions is that they are usually too small (between 0,5 and 1 cm) for assessment of their density and their form. The assessment of the nature of these changes is very difficult. PET has the same disadvantage for small formations. Percutaneous needle biopsy could be technically difficult and predisposes towards diagnostic mistakes. When the histologic result does not show malignancy, the metastases could not be excluded with certainty. Complications, like implantation and dissemination of tumor cells, pneumothorax and hemorrhage could be present after this invasive procedure (10). We share the standpoint of other authors that small lesions on CT (<1cm) should be regarded with limited clinical meaning and to be neglected in the choice of initial treatment (10). D. Gomez et al. (41) report based on summed statistics that unidentified pulmonary nodes are found in 25% (varying from 11 to 35%) from all patients with colorectal carcinoma after CT of the thorax (10). These patients represent a diagnostic problem. The solution is PET/CT or histologic verification by TTNB (transthoracic needle biopsy) or VATS (video-assisted thoracic surgery) if they are localized peripherally. It should be considered that by PET could not be succeeded to distinguish the metastatic disease from benign inflammatory process, because of the small size of the node (41). As a whole in 50% of the patients with unidentified pulmonary nodes a metastatic pulmonary disease is found after a mean period of 10 months (41). Despite of all, it is reported that with conventional computer tomographs 50% of the metastatic pulmonary nodes are missed and they are found during the surgical intervention. In a prospective randomized study Collie et al. establish that this mistake is reduced 2 times by spiral scanning - up to 25% more lesions are found and confirmed during the surgical resection (42).

C. Marron Fernandez et al. (43) report that there is discrepancy between the diagnosed by CT and surgically found and resected pulmonary metastases in 22% of the patients. Their analysis has shown that the discrepancy is more probable in patients with advanced (III, IV) stage of colorectal carcinoma, in nodes with smaller mean size, in diagnosed hepatic metastases, in bilateral (left and right) involvement and in existing multiple nodes on CT (43). Comparing the found metastatic nodes during the CT with these resected during operation, it is established accuracy of the methodology in 85,3% of the patients. In cases with single metastasis it has been 89,8% and in cases with multiple metastasis - 65,8% (33).

Based on the results cited by J. Zabaleta et al. (33), in the international register of pulmonary metastases, the accuracy of CT in terms of finding the exact number of the pulmonary nodes is 61%. Around 30-40% of the additionally imaged lesions with CT and resected during the operative treatment have been benign (33). The sensitivity of CT in patients with single metastasis of colorectal carcinoma has been 95% (33). The pace of discovery of pulmonary metastases by CT with high resolution is 78-84% (24,44).

P. J. Villeneuve and R. S. Sundersan (5) recommend CT of the thorax with high resolution as a choice and test of first line for diagnostics of the pulmonary lesions, especially after contrasting. This technology gives opportunity for acquiring image of the whole chest with 1mm thickness of the slice during one of the phases of inspiration or expiration. The older generation of apparatus are 100% sensitive for nodes >6mm. For the smaller parenchymal lesions the exact sensitivity is achieved in 66% of the cases. The assessment of the pleural nodes is rather more difficult, as accuracy is achieved only in 17% for findings with diameter lower or equal to 6mm. The increased sensitivity to 98% could be achieved with the help of venous contrast.

PET is a method of choice for discovering occult metastases (patients with increased level of CEA, in whom there is no evidence for the disease), in unsuspected pulmonary or hilar lymph-adenomegaly and for assessment of extra-thoracic burden of the disease (5). In some cases the authors recommend pre-operative diagnosis of the pulmonary nodes with TTNB, because this facilitates the operative planning (5). The positive immunohistochemical coloring for TTF1 proves the origin from the lungs or the thyroid gland (91% sensitive, 98% specific), and CDX2 coloring excludes the colorectal origin (83% sensitive, 96% specific). This differentiation is from essential importance, because the treatment, the setting and the volume of the surgical resection of the primary cancer of the lung differs significantly from this for metastases of colorectal carcinoma. It should be taken into consideration that this method is hindered by the small size of the undefined node and may obtain falsely negative results (5).

R. Schneider et al. (13) report that after spiral CT in around 14% of the cases metastases are missed, and after surgery intervention they are confirmed. Approximately 44% of these metastases are less or equal to 2 mm, 30% are less or equal to 4 mm and 26% are bigger than

4 mm. The overall sensitivity of the spiral CT is 86% (13). Based on the data of J. Nakajima et al. (39), more than 40% of the pulmonary nodes with dimensions equal or lower than 5 mm in diameter, which are found by CT with suspicion of pulmonary metastases, are not confirmed from the histology test.

**Lung perfusion scintigraphy** – The nuclear medicine examination with  $^{99m}\text{Tc}$  – MAA. Solitary metastases of the lungs induce predominantly rounded area of impaired perfusion. In our examinations the single metastases in the lung provoke perfusion alterations which are observed in peripheral lung tumor. When the metastasis is situated in the hilum, a perfusion defect in the whole lobe may be observed. In single solitary metastases in the right lung and in bilateral metastases the perfusion indices are most often around the normal ratios right – left. The involvement of one, or both hili and distant mediastinum are indirect sign for advanced metastatic process or presence of multiple metastases. The metastases in the left lung more often induce larger changes in perfusion indices (45). The examination is almost completely displaced by the perfusion CT and PET/CT.

**Positron-emission tomography (PET) and PET/CT** – Positron-emission tomography (PET) is a radionuclide method, which is used for non-invasive finding and quantitative determination of cellular and biochemical processes (46). This is a method for functional imaging, which could be combined with CT or MRI and by this way to improve the diagnostics of malignant diseases based on the pathologic changes in the tissues (47). PET/CT is with a high sensitivity and specificity in diagnosis and treatment of the colorectal cancer in comparison with other diagnostic methods and it is expected in near future it would play main role in this area (1, 31, 46, 47).

Despite of that the method should be used economically effectively because of the high price. It is useful for diagnostics of the tumor formation, for assessment of the dissemination of the process e.g. staging, it gives prognosis for the development of the disease, for plan of the treatment, for assessment of the therapeutic response and for establishment of the possible development of relapse (48). In a prospective trial is reported that the approach in the treatment of patients with colorectal cancer could be changed in 56% of the cases in result of PET, because this method diagnoses additional lesions in comparison with conventional imaging which worsens the prognosis (49). These data clearly show the

powerful prognostic ability of PET accurately to identify the patients who are believed to be with localized form of the disease in comparison with conventional imaging diagnostics (49). Despite the diagnostics of the colorectal cancer, PET/CT does not provide assessment of the tumor invasion, but provides better information for the status of the distant lymph nodes and the metastases in them (1, 31, 50).

#### $^{18}\text{F}$ -2-fluorine-2-desoxy-D-glucose

(FDG) is the most frequently used radio-pharmaceutical in oncology at the moment. The semi-quantitative analysis of FDG-PET images is performed by calculation of the value of the standard uptake value (SUV). Falsely positive results could be obtained in existing chronic inflammation and after operation or radiotherapy, due to secondary increased uptake of FDG in neutrophils, granulation tissue and macrophages (46). Commonly accepted is the role of FDG-PET in the assessment of the therapeutic effect after radiotherapy, chemotherapy and after usage of ablative technics (46, 51). The examination could be performed 4 weeks after termination of chemotherapy, one month after operation and 3 months after radiation, because of the possibility for incorrect positive results in inflammatory or regenerative processes. When it is performed in appropriate time after treatment it has potential to offer information for the vitality of the residual tumor mass, to differentiate tumor from fibrosis and to help in prognosis for survival. The method represents the strongest evidence at the moment in assessment of the possibility for relapse and in the selection of patients for metastasis-ectomy. FDG-PET clearly shows the response of the patient to the treatment, especially by finding the metastatic or possibly relapsing process (1,46,48). The diagnostic value for malignant disease from PET is accepted definitely in solid pulmonary nodes > 1 cm in diameter and SUV > 3. Despite that this diagnostic method could not define if the lesion is primary or secondary (27). In nodes less from 1cm in diameter the identification of metastatic nodes by PET is with low sensitivity around 30% (33, 27). Regarding the pulmonary nodes with dimensions in the range 5 to 10mm, the increased uptake of the isotope increases the probability to register metastatic disease despite that the negative result from PET does not exclude it definitely. In patients with small pulmonary nodes, in which uptake has not been established or it has been minimal on PET images, metastases are found in 20% (41). In these cases only the histologic examination could give definite answer or the CT follow-up

of the lesion (41). Biopsy is not recommended because of the particularly high risk for complications after TTNB and eventual possibility for dissemination (27, 41).

Based on data from A. Vioni and J. Kim (47) in up to 50% from unidentified pulmonary nodes at the end are established to be metastases. In these cases PET/CT has sensitivity and specificity 96% and 83% respectively. PPV and NPV have been 84% and 96%, respectively (47). The authors recommend the usage of PET/CT in non-invasive diagnostics of unidentified pulmonary lesions and focus on the fact that NPV is significantly higher over 90%, which could significantly reduce the need of invasive diagnostic procedures in part of the patients (47). The sensitivity and specificity of PET/CT in diagnostics of colorectal carcinoma is respectively between 89-95% and 83-92% (47). According to another study the sensitivity, specificity and accuracy in finding of unexpected damages from the method are 100%, 97,9% and 98,3% respectively (52). The data from S. Hahn et al. (53), the sensitivity for automatic finding by PET/CT of colorectal hepatic metastases is 96% (86-99%) and 90% (70-99%) for pulmonary lesions. PPV is 80% for the hepatic and 68% for pulmonary lesions with median values of SUVmax 8,8 for the first and 9,3 for the second, respectively.

PET improves capacity of the computed tomography in diagnosing and assessment of pulmonary metastases (42). In retrospective analysis, performed by Reinherdt et al. about sensitivity of PET for lesions with dimensions from 11 to 29 mm, is established that it reaches the highest values to 94% and is around 78% for metastases with dimensions between 8 and 10 mm. Despite that for alterations with size from 5 to 7 mm in the biggest diameter, the sensitivity is only 41%, which shows the limitations of the method for findings with these or smaller dimensions (42). The simultaneous usage of the abilities of PET/CT could offer better accuracy of almost 99% for the bigger nodes (42).

Performing a literature survey about the abilities of PET/CT in comparison with PET, C.D. Collins (48) reports that the accuracy in defining the diagnosis in the different malignant diseases is from 90% to 98% with reduction of 50% in the unclear cases. In suspicion of oncology disease, the image of PET/CT offers additional information in 49% of the cases. The method demonstrates reduction of the level of uncertainty from 15,3% to 3,4% (48). FDG-PET helps to be

specified the CT findings in the lymph nodes with unclear origin (48).

The diagnostic abilities of FDG-PET and PET/CT in patients with colorectal cancer are indisputable for the distribution of the oncology disease (staging) and the appearance of local in the liver or in the lungs relapses after operative treatment (48). In cases of inflammatory diseases is possible increased uptake of FDG in the tissues. Despite the reported high sensitivity, lesion <0.7 cm could not be established accurately. That is why PET/CT is not recommended for routine diagnosis because it is nor efficient nor profitable. If the main tumor mass is bulky, small neighbouring lymph nodes could not be detected as separate structures on the PET image, which is a special advantage of the CT, despite that it is also not able of identifying micro-metastases. MRI is the recommended method for imaging of meso-rectal infiltration (48). Based on literature data comparing the abilities of CT with additional contrasting and PET/CT, the conclusion is that there is little difference in the sensitivity of the two methods - 95% and 91%, respectively. In other scientific reports for patients with preceding hepatic surgery this difference is significant - 100% versus 50% in favor of PET/CT. This method has accuracy of 88% in diagnosis of relapsing colorectal cancer in comparison with 71% for PET. In additional study PET/CT demonstrates sensitivity 89%, specificity 92% and accuracy of 90% for locally relapsing colorectal cancer, the liver and the extra-abdominal localizations. The method has also high sensitivity in finding of extra-hepatic distribution of 89% in comparison with 64% for CT and leads to change in therapeutic strategy in 21% of the cases (48).

PET provides information for inclusion of the mediastinal lymph nodes and for finding of extra-pulmonary progression of the disease (33). But according to other studies the sensitivity of PET/CT for finding metastases in mediastinal lymph collectors is only 35% (54). According to the data by K.M. Musallam et al. (4), <sup>18</sup>F-DG-PET scanning is proved superior to the morphologic imaging diagnostics in the assessment of the participation of lymph node based on data for functional assessment of the tumor metabolism. The analysis of the contemporary scientific literature establish that the change of therapeutic plan based on 18-FDG PET scan of the patients with metastatic colorectal cancer is found in 31.6% of the cases (4). Despite that small malignant lesions could not show increased uptake of radioactive isotope because the present PET – detectors

offer spatial resolution ability of only 5mm. This limitation is strongest in the chest, where finding of lesions with PET is additionally compromised from the breathing moves. Additionally, extensive fibrosis of mediastinal lymph nodes could lead to decrease of uptake of 18F-FDG during the initial PET scanning. Exceptional results are reported about the tumor staging when using PET/CT (4). Numerous studies show that FDG-PET has high sensitivity and high specificity for finding of tumor relapse in patients with colorectal carcinoma and increasing levels of CEA, in which there are no unidentified suspicious findings by the standard imaging techniques. The combination PET/CT outweighs CT and MRI for finding of local relapses and metastatic progression in the liver and other distant places. Despite that the current systems for scanning have some limitations:

1. One of the most important is its low sensitivity for finding of small lesions between 5 and 10mm.
2. The difficult assessment about the invasion of the local tumor in the surrounding tissues.
3. 18F-FDG is limited from the fact that it is not specific for tumors but the uptake of the radio-pharmaceutical could happen in benign tissues like for example infection or inflammation (55).

In conclusion we can state that FDG-PET and PET/CT play significant role for defining the accurate diagnosis of the main disease, the staging and finding of relapse occurrence after treatment. There is more and more evidence that these methods could contribute significantly for assessment of the response from the therapy and for the planning of the treatment (56, 57).

**Bronchoscopy** – The endobronchial metastases from colorectal cancer are rare (58). These could be suspected when they appear after the fifth year (58) and often they are related with increase of the CEA levels without other focal manifestations. Bronchoscopy is not usually in the armory of the colorectal surgeon, but in the conditions of lobar atelectasis it is especially useful method for direct view and histologic verification (14, 26, 59, 60). While 95% of the pulmonary metastases are detectable on CT, only 55% of the endobronchial lesions are defined by this method. (26). The damages are registered in segment bronchia in 56%, in lobar bronchia in 33%, in main bronchia in 6%, and in 5% of the cases they are found in different places (25). In nearly 72% of the patients the metastases have been localized in the right part of the bronchial

tree (25). The bronchoscopy is important to prove the origin of the tumor formation (endobronchial metastasis or primary cancer of the lung) (59).

According to S. Tanaka et al. (61), despite the distinctive signs of the metastatic colorectal adenocarcinoma from primary adenocarcinoma of the lungs, often the distinction is difficult, but identification is very important for the surgery treatment, because the dimensions of the resection for every diagnosis differ significantly. The examination of CDX2 gene is specific marker for defining the probability of development of colorectal cancer as all of the samples should undergo immunohistochemical coloring for CDX2, cytokeratine (CK)7, CK20 and thyroid transcription factor (TTF -1). Positive CDX2 coloring represents a highly sensitive and specific marker of the metastatic colorectal carcinoma, in comparison with the other tests which have lower diagnostic value (61). In some patients TTNB under echography control before the metastase-ectomy is indicated for exclusion of metastases in the mediastinal lymph nodes. Their proving makes the surgical treatment pointless because of the bad prognosis (62).

**Mediastinoscopy** – This method is used when suspecting and for proving of metastases in mediastinal lymph nodes, because in 14% to 42% of the patients these are established (14,63). Sensitivity of CT in these cases is only 73% (63).

**Videothoracoscopy (VATS)** – for identification of lymph metastases in defined group mediastinal lymph nodes and superficial suspicious nodes in the lungs.

**Trans-thoracic needle biopsy (TTNB)** – for wall-attached unidentified pulmonary findings, but with diameter bigger than 3cm.

**Tumor markers – CARCINOEMBRYONIC ANTIGEN (CEA)** – The level of CEA in serum before thoracotomy is one of the most significant prognostic factors in univariate and multivariate analysis for survival after resection of metastatic tumors of the lungs (15, 17, 50, 64, 65). As a whole the increased serum level of CEA is related with the biologic functions of the colorectal carcinoma because its increased expression correlates with bad prognosis not only with organ localization but with its metastatic progression in the lungs (50, 64). The size of the tumor, the number of the pulmonary lesions and the metastases in the lymph nodes represent the extent of metastatic pulmonary disease and they appear as prognostic factors similar to these included in TNM classifications (15, 66). In support of the

latter thesis are the data of the 5 year survival rate of patients with normal or increased levels of CEA, respectively 51,9% for the first versus 38,3% for the second group of patients (29). This difference is significant in the publication of P.J.Villeneuve and R. S. Sundaresan (5), where it is 60% for the first indicator versus 18% for the second group of patients with increase of CEA over 10ng/ml. Similar are the data cited by R. Maeda et al. (67) based on the same criteria but with significantly higher values 91,7% versus 42,6% respectively. T. Treasure et al. (68) report that they have established increased levels of CEA over 5 ng/ml in 3%, 25%, 45% and 65% of the patients in accordance with the stages they have been classified by Dukes A, B, C and D, respectively. After radical resection the serum concentration of CEA drops. According to numerous publications increase of CEA is related with bad outcome after pulmonary metastases-ectomy of the patients and it could be accepted as a contraindication for pulmonary resection (52, 68, 69, 70). On the contrary, J.H. Kim et al. (71) support the standpoint that increased serum levels of CEA should not be taken as contraindication for surgical treatment because the survival after pulmonary metastases-ectomy in patients with normal and high levels are almost the same. Similar is the opinion of S. Limmer et al. (72), who consider that the increased level of CEA and the number of lesions could influence over survival but are not absolute contraindication for surgical resection.

It is supposed that the high values of CEA could be one of the most important indicators for progression of colorectal adenocarcinoma (17). The serum concentration of the antigen is usually considered as an indicator for the volume of the tumor (57). It is well-known that CEA participates in the cell structure and encourages the adhesion of the tumor cells to the normal of the organism. Consequently, its level could be a reflection of the malignancy of the tumor (73). According to R. Koga et al. (73), the time needed for the occurrence of metastases and the level of carcinoembryonic antigen before the thoracotomy could have decisive meaning for the prognosis of the surgical treatment. T. Irvine, M. Scott and C. Clark (74), report that increase of CEA with 1 ng/ml correlates with relapse of the metastases. In 33% of the patients with these changes in the final analysis a relapse of the disease is established. Increase of CEA with 1 unit has predictive value of 74% for relapse or metastases (sensitivity 80%, specificity 86%). Previous studies point the role of the significant increase in the serum levels of CEA

at the occurrence of relapse, but this shows that small changes in CEA could be significant even if these levels are in the range of "normal" limits (74).

According to P.C. Lin et al. (75), the high level of CA19-9 remains independent prognostic factor for patients with normal levels of CEA. The patients with high level of CA19-9 also show more frequent metastases in the lungs in comparison with these with normal levels, 23,1% versus 7,2% respectively (75).

## CONCLUSION

The colorectal cancer keeps first place as an etiologic reason for performance of pulmonary metastases resection (76, 77). It is established the low effectiveness of the chemotherapy in metastatic progress of the colorectal carcinoma. Subsequently the surgical resection aiming the removal of pulmonary metastases is commonly accepted as the only healing therapeutic approach. In favor of the operative treatment is the trend of earlier finding of the pulmonary metastases. The accurate diagnostics contributes for this.

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