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Lung cancer with metastatic lung lesions: treatment outcome

Relevance. *Lung cancer (LC) is one of the most unfavorable forms of tumors in terms of timely diagnostics and treatment outcome. Therefore, early detection of LC remains the main organizational medical measure to improve resectability and treatment outcome.*

Purpose of this study – *to increase the treatment efficiency in potentially resectable LC with metastatic lung lesions.*

Results. *103 cases of histologically proven LC with multiple pulmonary nodules detected by computer tomography and regarded as multiple metastases were studied. Video-assisted thoracoscopy has revealed metastases in contralateral lung in 64 (62.1%) patients, of them, 4 (3.9%) had a second extra-pulmonary tumor. 39 (37.9%) patients had non-neoplastic disseminates: fibrosis – 22, anthracosis – 13, tuberculosis and sarcoidosis – 4. 9.3%, 10.3%, and 20.6% of the patients had LC stage I, II and III, respectively. 32 patients underwent surgery: lobectomy – 20, segmentectomy – 2, pneumonectomy – 10. 3 (9.3%) patients had postoperative complications. Nosocomial mortality – 1 (3.1%). 5-year post-surgery survival – 44.1%, with neoplastic metastatic lung lesions – 0% (p<0.0001).*

Conclusions. *Potentially resectable LC with metastatic lung lesions requires a biopsy of pulmonary nodules as a significant number of patients have non-neoplastic lesions. The developed modality using video-assisted thoracoscopy improves the survival rates due to the increase in the number of operable patients.*

Keywords: *metastatic lung lesions, lung cancer, lung biopsy, thoracoscopy.*

Introduction. Lung cancer (LC) is one of the most adverse forms of tumors in terms of timely diagnosis and treatment outcomes. Surgical treatment remains the only radical method that provides satisfactory long-term results of treatment. Only 10–20% of initially registered patients can undergo radical surgery [1]. Therefore, early detection of LC remains the main organizational measure of practical healthcare to increase resectability and improve treatment outcomes [2].

One of the ways to increase resectability is the improvement of differential diagnostics of associated diseases (syndromes) that can mimic an advanced tumor process. One of such syndromes is the disseminated pulmonary disease (DPD) that can manifest not only a metastatic lesion but also a competing non-neoplastic disease — tuberculosis, sarcoidosis, etc. According to M.M. Ilkovich, this syndrome accounts for up to 20% of respiratory diseases and can occur in more than 100 different non-neoplastic diseases [3]. Still, the medical literature lacks data on the incidence, structure, and survival of patients with LC and non-neoplastic DPD.

The purpose of this study is to improve diagnostics and increase the survival rate of patients with X-ray detected LC in combination with DPD.

Materials and methods. The study included retrospective analysis of case histories of 103 patients examined and treated at N.N. Alexandrov National Cancer Center from January, 2001 to December, 2015. The average age was 59.7±8 (35-78) years. 80 of 103 patients were men (78.7%), 23 were women (21.3%). All patients had a morphologically verified LC and CT-detected DPD treated as multiple metastases. 17 patients were diagnosed with primary multiple cancer at admission.

All patients underwent video-assisted thoracoscopy (VATS) with a lung biopsy according to standard methods in order to clarify the prevalence of the tumor process [4]. It was mandatory to receive a preliminary urgent intraoperative morphological conclusion on the sufficient amount and quality of the biopsy material. At detection of Non-neoplastic DPD, a part of the biopsy material was sent for bacteriological examination. Enlarged mediastinal lymph nodes were subject to biopsy.

The patients with proven metastatic nature of dissemination received chemotherapy or symptomatic treatment. The patients with Non-neoplastic DPD underwent radical surgery for LC followed by transfer to pulmonology (TB) hospital.

The overall patient survival was estimated according to the data of the Cancer Register of the Republic of Belarus and was calculated by Kaplan-Meier method using the log-rank test (SPSS Statistics v. 20).

Results.

Table 1 shows the main parameters and efficiency indicators of VATS with lung biopsy.

Table 1 – Indicators of video-assisted thoracoscopy (VATS) efficiency in disseminated pulmonary disease (DPD)

Indicator	Value
Duration of surgery (min)	60±31* (10-180)
Duration of drainage (day)	2,0±1.6 (0-10)
Need for opioids (patients, %)	4 (3,9%)
Complications	4 (3,9%)
Hospital mortality	1 (0,9%)
Duration of hospital stay (days)	7.5±2.6 (1-14)
Diagnostic efficiency	100%

According to Table 1, most of the patients could be discharged two days after VATS (after removal of drainage). The duration of hospital stay encounters future treatment (surgery, chemotherapy).

4 (3.9%) patients had postoperative complications. Unstable aerostasis was observed in 3 patients and resolved

independently after 5–10 days. One patient developed ischemic stroke, and he subsequently died of swelling and dislocation of the brain.

The diagnosis was morphologically verified in all patients. VATS with lung biopsy showed a 100% diagnostic efficacy in DPD.

CT has revealed metastatic lung lesions in all patients. However, the histological examination of biopsy material disproved malignant lung injury in 37.9% of patients. Adenocarcinoma and squamous cell carcinoma prevailed in the structure of Neoplastic DPD (Table 2).

Table 2 – Histological forms of Neoplastic DPD

Histological form of DPD	n (%)
Adenocarcinoma	39 (37.9)
Squamous cell carcinoma	14 (13.6)
Small cell cancer	4 (3.9)
Glandular squamous cancer	2 (1.9)
Large cell carcinoma	2 (1.9)
Leiomyosarcoma	1 (0.97)
Malignant neurolemma	1 (0.97)
Renal cell carcinoma	1 (0,97)
Total	64 (62.1)

In 3 patients, the histological form of disseminates was not characteristic of LC (leiomyosarcoma, renal cell carci-noma, neurolemma), and in 1 patient it was different from the primary tumor. Further examination resulted in finding a second tumor in those 4 (3.9%) patients, and they were prescribed an adequate chemotherapy.

Focal pneumofibrosis and anthracosis of the lungs prevailed in the structure of Non-neoplastic DPD. Tu-berculosis and pulmonary sarcoidosis were less common (Table 3).

Thus, the preoperative CT diagnoses and postoperative morphological diagnoses coincided in 64 (62.1%) patients, with 37.9% of diagnostic errors. After VATS, the treatment plan was changed for 43 (41.8%) patients.

19 (18.4%) patients with Non-neoplastic DPD had intrathoracic (intrapulmonary and/or mediastinal) metastatic lymph nodes.

Table 3 – Histological forms of Non-neoplastic DPD

Histological form	n (%)
Pulmonary fibrosis	22 (21.4)
Pneumoconiosis	13 (12.7)
Sarcoidosis	2 (1.9)
Tuberculosis	2 (1.9)
Total	39 (37.9)

Treatment of patients with Non-neoplastic DPD. 39 patients with LC with DPD NTG had the following tumor staging according to VATS: Ia – 4, Ib – 5, IIa – 4, IIb – 6, IIIa – 14, IIIb – 6. 32 patients underwent radical surgery (Table 4), 20 patients underwent lobectomy with systematic mediastinal lymphadenectomy, and 10 underwent pneumonectomy. In two patients, the intervention volume was limited to segmentectomy due to low spare capacity of lungs (FEV1<30%).

Table 4 – Immediate results of surgical treatment

Indicator	Value
Duration of drainage (day)	2.0±1.6 (0-10)
Duration of the operation (min)	138.8±72 (110-300)
Complications	3 (9.3%)
Hospital mortality	1 (3.1%)

Seven patients were denied surgery due to the local prevalence of the process or functional intolerance. They received chemotherapy.

3 (9.3%) patients had postoperative complications (2 – coagulated haemothorax, 1 – myocardial infarction). One of these patients died of pulmonary embolism.

The median survival of all 39 patients with LC and Non-neoplastic DPD after special antitumor treatment was 22±9 months (95% CI 4.2-39.7). In the presence of Neoplastic DPD, the median survival was 11±1.2 months (95% CI 8.5–13.4). The overall 1-, 3-, and 5-year survival was 75.4±7.1%, 44.5±8.7%, and 36.4±8.8%, vs. 42±6.3%, 8.8±4.5% and 0%, respectively, in the presence of Neoplastic DPD (p<0.0001) (Figure 1).

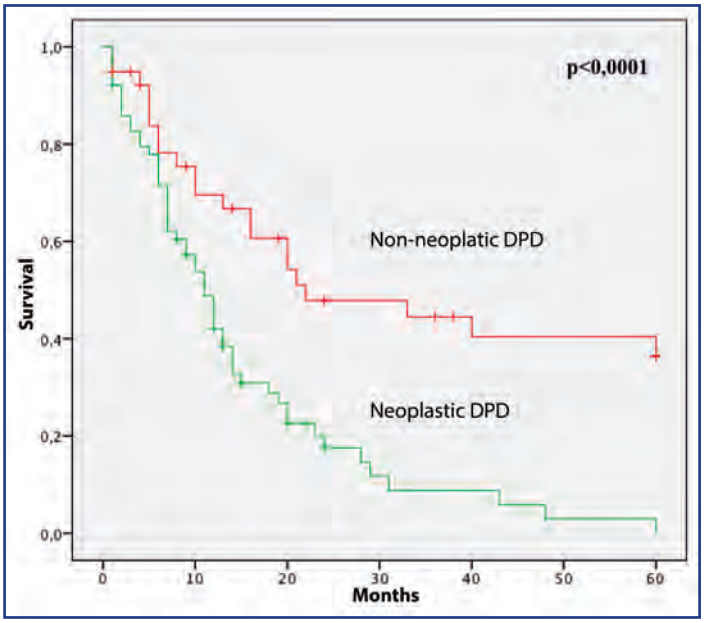

Figure 1 – Survival with lung cancer and neoplastic and non-neoplastic DPD

1-, 3- and 5-year survival of 32 patients after surgical treatment was 80.1±7.3%, 53.9±9.5% and 44.1±10%, p<0.0001 (Figure 2). The median was 40±28 months (95% CI 0-95).

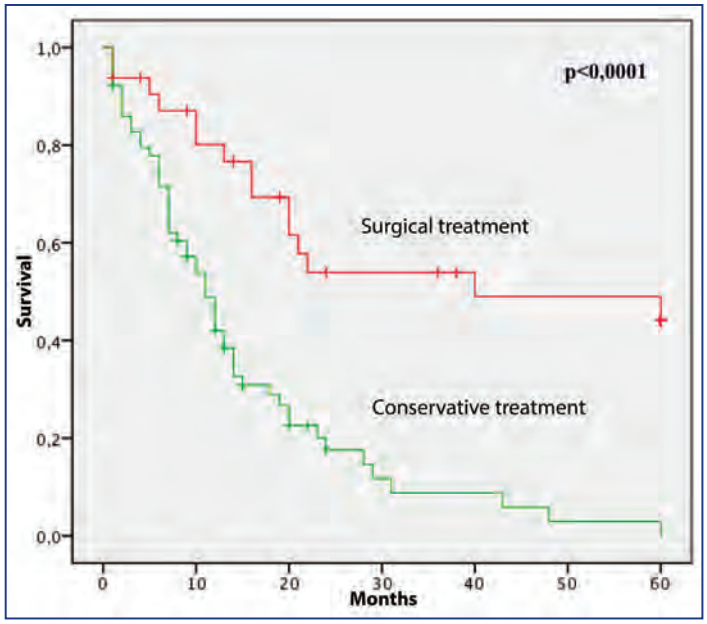

Figure 2 – Survival with lung cancer with DPD after surgical and conservative treatment

Discussion. The generally accepted approach based on US studies [8, 9] does not recommend morphological verification of seeds in patients with histologically confirmed LC in case of CT-detection in the parenchyma of multiple foci more than 5 mm in diameter [5-7]. Therefore, this category of patients is automatically prescribed chemotherapy or symptomatic treatment. There are papers on etiological differences in single (solitary) pulmonary nodes among the population of Asia and North America which are attributed to the epidemiological situation on TB and fungal infections in a particular country [10]. We believe a similar situation is typical for DPD.

Our results confirm the need for morphological verification of seeds in LC. After VATS, the staging was reduced from the 4th to the lower in 38% of patients, and they could receive radical treatment. Diagnostic error frequency was comparable to the frequency in patients with DPD without oncopathologies [3].

A large number of primary-multiple tumors and the detection of seeds of the second (not previously detected) tumor during VATS convince us to go beyond morphological verification of the primary tumor found during bronchoscopy. We found even more inappropriate to perform transthoracic lung biopsy (TTLB) for only peripheral cancer because it does not give an answer to the nature of dissemination but delays the diagnostic search when followed by VATS.

The use of TTLB has limitations in interstitial lung diseases due to low efficiency with a high incidence of complications: intrapleural bleeding – in up to 14–30% of cases, pneumothorax – in up to 35–40% [11–15]. Yaffe D. et al. (2015) and Rotolo N. et al. (2015) report a diagnostic accuracy of more than 90% when conducting TTLB of single nodules under CT control. However, the authors note that the average formation size exceeded 2 cm [16, 17].

Clinical guidelines of the British Thoracic Society for interstitial lung diseases recommend taking pulmonary samples of more than 4 cm in the largest dimension in the inflated state and 3 to 5 cm deep from the pleural surface to obtain a sufficient amount of biopsy material [18]. That being said, the recommendations to use TTLB and EBUS in the initial stages cause perplexity since they provide little material for morphological research. In the end, it delays the examination, increases costs and the risk of complications.

In our study, 18% of patients had Non-neoplastic DPD in combination with metastases in peribronchial or paratracheal lymph nodes (which were a substrate for biopsy in EBUS). In case of EBUS, they would be denied radical treatment as DPD would be automatically interpreted as metastatic.

Thus, planning of adequate treatment requires verification of the diagnosis for each descriptor – T, N, and M what is consistent with the principles of evidence-based medicine.

Immediately after surgery, the frequency of postoperative complications and mortality were comparable to patients without DPD. Still, some researchers have noted a higher incidence of postoperative complications (up to 9.3%) and mortality (up to 4.1%) in patients with LC in the setting of fibrosing alveolitis or other forms of pulmonary fibrosis and a decrease in survival by half vs. the control groups [19-21]. This may be due to the differences in the structure and stage of interstitial lung diseases and in the accounting of complications.

Although non-neoplastic DPD can worsen the results of surgical treatment of lung cancer, it remains the only chance for these patients to cure.

Conclusions. VATS with lung biopsy is the optimal method for obtaining material for histological examination in LC with DPD (diagnostic efficiency – 100%).

1. Seed biopsy is required in the presence of morphological verification of the primary tumor and intrathoracic lymph nodes, since non-neoplastic DPD is detected in 37.9% of patients, who can therefor receive radical surgical treatment.

2. The developed diagnostic and treatment algorithm helps improving the survival of patients with LC and DPD by increasing the number of resectable cases.

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