ROLE OF MEDIASTINAL NODAL STATUS IN THE SELECTION OF PATIENTS WITH NON-SMALL CELL LUNG CANCER AND ISOLATED ADRENAL METASTASES FOR RADICAL SURGICAL TREATMENT

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Abstract

The treatment of patients with isolated adrenal metastases remains controversial. Metastases from NSCLC suggest that these patients could have improved survival. The role of N2 status as independent predictor of poor survival is still unclear and under discussion. The aim of this study was to evaluate the role of mediastinal nodal status in patients with isolated adrenal metastases form Non Small Cell Lung Cancer (NSCLC) treated with surgery. A total of eight patients with NSCLC and isolated adrenal lesions were operated on for a period of ten years. They were divided into two groups depending on the morphology of the adrenal lesion. Group I includes 4 patients with adrenal metastases which underwent lobectomy and Retroperitoneal Endoscopic Adrenalectomy (REA). The loco regional stage was pI in 3 patients and pIIA in one. The mean size of the metastases was 24.5 mm, without capsular invasion and all of them were metachronous. The other four patients were proven to be with adenomas of the adrenal gland. All of the patients underwent lobectomy with locoregional stage pIIIA (3) and pIIA. One stage operation was performed in two cases – left lower lobectomy and adrenalectomy via frenotomy. REA was performed in two of the patients. No major postoperative complications were observed. The median survival is 34.75 months in Group I and 18.6 months in Group II. Two of the patients from Group I are still alive at the end of the study.

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- 57 and 34 months after the initial surgery. The mediastinal nodal status is significant and independent prognostic factor for survival in surgical patients with NSCLC and isolated adrenal metastasis.

**Key words:** lung cancer, adrenal metastases, surgery

**Introduction.** In the last century, the incidence of lung cancer increased, and from a rare disease it became the leading cause of cancer mortality. It is the second most common cancer in both sexes, after prostate cancer in men and breast cancer in women. Newly registered cases in the US for 2018 were 234,030 [1]. According to WHO data, the incidence of lung cancer in Bulgaria in 2018 amounts to 4250 newly registered cases. It ranks second in men after prostate cancer and fifth in women after breast, colon, uterine and uterine cervix cancers [2].

Despite the large number of methods and screening programmes for early diagnosis of lung cancer, at the time of diagnosis, a large proportion of patients are in the IV clinical stage. In the past, metastatic non-small cell lung carcinoma (NSCLC) was considered to be an incurable disease in most cases. From this point of view, only palliative resection of isolated brain metastases in selected patients with controlled primary focus was considered the standard for surgical treatment [3].

Adrenal metastases are one of the most common forms of extrathoracic involvement, but the incidence of isolated metastases at initial staging is low. There are mainly non-randomized retrospective studies in the literature with a small number of surgically treated patients with NSCLC and isolated adrenal metastases. Different authors analyze various prognostic factors, surprisingly, the N2 status has not been sufficiently studied, although it is an independent factor of poor prognosis in operated patients with NSCLC.

The aim of this study was to evaluate the prognostic role of mediastinal nodal status in surgically treated patients with NSCLC and isolated adrenal metastases.

**Materials and methods.** A total of eight patients undergoing radical surgery for NSCLC and isolated adrenal lesions are included in this retrospective study. They were 5 men and 3 women with an average age of 56 (44–61) years.

Patients were treated for a period of ten years, which is a determinant of their heterogeneity with respect to the diagnostic methods – some patients were diagnosed prior to the use of Positron Emission Tomography (PET/CT). Bronchoscopy and Computed Tomography (CT) with venous contrast were used in all patients. Integrated PET/CT was used for five of them. Morphological verification of the process in three patients was achieved with transthoracic true-cut biopsy under ultrasound control. Adrenal glands were examined by magnetic resonance imaging (MRI) in two patients.
The patients were retrospectively divided into two groups depending on the morphology of the isolated adrenal lesion.

Group I included four patients with a median age of 54.8 (44–61) years in whom metastasis was definitely verified after adrenalectomy. The morphology of the lung tumour is squamous cell carcinoma in three patients and adenocarcinoma in one. Lobectomy with systemic mediastinal lymph dissection was performed in all patients with uneventful postoperative period. The pathoanatomical locoregional stage is pI in three patients and pII in one. Adrenal metastases in this group are metachronous with an average disease-free interval of 36.8 months. Three of them are ipsilateral and one is contralateral. The four patients underwent retroperitoneal endoscopic adrenalectomy (REA), and the removed lesions had an average diameter of 24.5 mm and no capsular invasion. In one patient, at the same time as metachronous adrenal metastasis was detected, 12 months after pulmonary resection, a contralateral pulmonary metastasis was detected. REA and right pyramidectomy were performed at 4 week interval. Platinum-based adjuvant chemotherapy was prescribed in all patients.

Group II also included four patients with a median age of 58 (56–60) years, in whom adenoma was verified after adrenalectomy. The morphology of the lung tumour is squamous cell carcinoma in two patients, adenocarcinoma in one patient and large cell carcinoma in one. Lobectomy with systemic mediastinal lymph dissection was performed in all patients with uneventful postoperative period. Three of the patients are in the pathoanatomical loco-regional pIIIA stage, and one is in the pIIIA stage. All benign lesions are synchronous and ipsilateral with an average diameter of 25.3 cm. Two of the patients in this group underwent a one-stage operation – left lower lobectomy and adrenalectomy with transdiaphragmatic approach. The other two patients underwent REA, in interval one month after the lobectomy.

The median follow-up period was 44 months, all patients were followed until their death or the end of the study. The Kaplan–Meier method was used to analyze the survival. Comparison of median survival in both groups was performed using the Log Rank test (Mantel–Cox).

**Results.** No serious early postoperative complications and 30-day postoperative mortality were observed. The average hospital stay is 7 days.

Two of the patients in Group I had died at the end of the study due to disease progression. After 12 months of disease free interval, brain metastases were detected in a patient with consecutive metachronous adrenal and pulmonary metastases. They were initially treated with radiosurgery and after 2 months with open metastasectomy for a residual lesion, followed by chemotherapy. After 8 months, due to a new recurrence of brain metastases, radiosurgery and chemotherapy were performed. At the time of the end of the study, the patient had controlled brain metastases, moderately debilitated brain symptoms, and had undergone chemotherapy and symptomatic treatment 29 months after
initial pulmonary resection. In the last patient in the same group, 30 months after pulmonary resection, recurrence was observed in the ipsilateral mediastinal lymph node and malignant pericardial effusion. The patient underwent pericardial fenestration with subxyphoid access, immunotherapy and radiosurgery of the mediastinal lesion. An excellent response was reported and at the end of the study the patient had no PET/CT progression data and was in good general condition 42 months after the first surgery.

Three patients in Group II died at the end of the study. The latter operated on in this group is alive 20 months after surgery and is clinically healthy. The reported median survival showed statistically significant difference – in Group I it was 34.75 months and in Group II it was 18.60 months ($p = 0.040$). Figure 1 shows the survival curves of the two groups.

Discussion. The concept of oligometastases was introduced in 1995 by Hellman and Weichselbaum [17] and is based on the understanding of the cascading nature of the development of oncological diseases as an intermediate stage between locoregional and systemic progression. Its essence is that local cancer treatment methods can be curative in some patients with isolated metastases. This understanding is embedded in a treatment strategy that in these cases is aggressive and may include surgical resection, stereotactic radiotherapy, radiofrequency ablation, cryoablation and others, alone or more often in combination with systemic chemotherapy. Therefore, oligometastases were differentiated as a new subgroup of M1b in the M component at the last 8th revision of the TNM classification in lung cancer [5].

Despite the growing interest in oligometastases, their definition is not fully understood. They are divided into two groups. Oligometastases or synchronous metastases are defined as a condition with 1 to 5 metastatic lesions in the active
primary focus. Metachronous are defined as those with an appearance six or more months after the primary outbreak, and their appearance after radical treatment of the primary tumour is also referred to as isolated recurrence of the disease.

The adrenal glands represent one of the most common locations for extrathoracic metastases in lung cancer. In autopsy studies, adrenal metastases were found in 25.2% and 43% of patients who died of lung cancer [6]. On the other hand, the reported incidence of isolated adrenal metastases (2.4%) at initial staging is low [7]. According to a study by Unek et al. [8] the incidence of adrenal lesions in patients with NSCLC varies from 4 to 18% and about 60% of them are benign.

For the first time in 1982, Twomey et al. [9] reported a very good long-term outcome after surgical treatment in two people with NSCLC and isolated adrenal metastases. Since then, there have been numerous reports of this problem in the literature, but they mainly cover small, retrospective series of cases or single cases. Unek et al. [8] analyzed a total of 119 published cases and found a median survival of 24 months and a 5-year survival of 32%.

The clinical risk factors for disease recurrence in operated patients with NSCLC and adrenalectomy for isolated metastasis are still debatable. Various variants are discussed in the literature: mediastinal nodal status of the primary tumour, time interval between the onset of the primary lesion and metastasis (synchronous versus metachronous), effect of the metastasis side, on the primary lesion (ipsilateral versus contralateral; bilateral), localization of the primary lung tumour and histologic variant.

Mediastinal nodal status is a major and widely commented determinant of survival after radical surgical treatment of NSCLC, but there is still no consensus on its role in the group with isolated adrenal metastases. For this reason, extensive indications for invasive staging were introduced in the 2014 ESTS Guideline for Preoperative Staging of Mediastinal Lymph Nodes from 2014, excluding only patients with peripheral tumours less than 3 cm in size, and no data for hilar or mediastinal involvement at the same time [10].

Johnson et al. [11] presented a group of patients comparing the survival rates of radically operated patients with oligometastases without involvement of mediastinal lymph nodes and those with N2 disease who were treated non-surgically for palliation. All metastases in this group are synchronous. Five-year survival in the first group was 58% and median survival was not reached, while in the second group, median survival was 18.2 months, with all patients dying within 39 months (58% vs 0%, \( p = 0.028 \)).

In the study of Raz et al. [12] no patients with N2 disease survive after 5 years, compared with a 52% 5-year survival rate in patients without involvement of mediastinal lymph nodes. At the same time, in the results reported by Porte et al. [13] and Mercier et al. [14], mediastinal nodal status was not considered at all as an independent predictor and its effect on survival was not reported.

Poor results in patients with N2 disease suggest that this group should be
identified and excluded from the indications for aggressive surgical treatment in oligometstatic NSCLC. This question remains debatable, because, despite their worse prognosis, in some series, radically operated patients with N2 disease have better survival rates than non-surgically treated. In the future, it is likely that this problem will also be explored from the point of view of heterogeneity within the group with mediastinal lymph node involvement.

The time interval between the diagnosis of primary lung tumour and adrenal metastasis is another well-studied factor. Mercier et al. [14] demonstrated that a disease-free interval of more than 6 months between primary tumour and the diagnosis of adrenal metastasis is a significant predictor of improved survival. In contrast, Raz et al. [12] consider that there is no statistically significant difference.

The influence of the location of the metastasis relative to the primary tumour has been widely discussed. There is a greater likelihood of ipsilateral involvement (72% vs 28%) in patients with solitary adrenal metastases (n = 43, p < 0.01) [15]. Raz et al. [12] found approximately 83% 5-year survival in patients with ipsilateral metastases, while 5-year survival was not observed in contralateral ones. Other authors reported the existence of direct retroperitoneal lymphatic channels connecting the chest to the adrenal glands [15], whereby ipsilateral adrenal metastases can be considered locoregional progression of the disease [16].

The results from our own experience and the increased survival in the M1b group seem paradoxical at first, and their interpretation is difficult due to the small number of patients and the retrospective type of study. Patients with isolated adrenal metastases had a more favourable locoregional status (no involvement of mediastinal lymph nodes), whereas N2 disease was present in three of the patients with adrenal adenomas. According to the literature, the absence of capsular invasion, as well as the long disease-free interval, are favourable factors in the metastasis group.

Conclusion. Mediastinal nodal status is a significant independent prognostic factor of survival in radically operated patients with NSCLC and isolated adrenal metastases.

REFERENCES


