ANTICANCER RESEARCH *40*: 7045-7051 (2020)
doi:10.21873/anticanres.14731

Outcomes and Prognostic Factors Following Surgical Treatment of Pulmonary Metastases from Colorectal Carcinoma

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Abstract. *Background/Aim: The lungs are the second most common site of cancer dissemination. The aim of this study was to analyze a cohort of patients operated for pulmonary metastases from colorectal carcinoma over a period of 18 years. Patients and Methods: In a group of 104 patients, relations were sought between overall survival or disease-free survival and preoperative levels of selected biomarkers, number of metastases and the condition of the intrathoracic lymphatic nodes. Median observation period was 63 months. Results: The 5-year survival rate was 54.3%. Risk of disease progression and risk of death increases in case of occurrence of 2 or more metastases, affection of intrathoracic lymph nodes and levels of CA 19-9, TPS or CEA above cut-off value. Conclusion: Prognostic factors that determine overall survival as well as disease-free survival are the number of metastases, the condition of intrathoracic lymphatic nodes and the preoperative levels of biomarkers.*

The lungs are the second most common site of cancer dissemination, with 30-40% of all solid tumors metastasizing in the lungs (1). Following the liver, the lungs are the second most common location for colorectal carcinoma (CRC) organ dissemination, whereby lung metastases are sooner or later diagnosed in approximately 10-25% of patients (2-4). There is a shortage of larger controlled studies; moreover, the studied cohorts are usually heterogeneous and limited by a short follow-up. At present, the surgical treatment of CRC lung metastases is, in the absence of more effective therapeutic procedures with a lower morbidity, a generally accepted therapeutic procedure (5). The aim of this study was to conduct an analysis of a cohort of patients operated on for lung metastases from CRC over a period of 18 years.

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Key Words: Lung cancer, pulmonary metastases, colorectal carcinoma, surgery, biomarker, prognosis.

Patients and Methods

From 1/2000 to 12/2017, we surgically treated 104 patients with lung metastases from CRC. In total, there were 126 interventions performed in 104 patients. Subsequently, 10 patients (9.6%) had to undergo radical surgery again for a relapse of lung metastases. Radical resection was performed on a total of 171 metastases. The median amount of time between the initial surgery on the primary tumor and the metastasectomy was 24 months. The median observation period was 63 months. Characteristics of the patient group and surgical procedures are provided in Table I.

The indication criteria for pulmonary metastasectomy (PM) were the radical removal of the primary malignant tumor and the absence of extrapulmonary metastases other than the resectable hepatic metastases. Other conditions included pulmonary metastases that, were assessed as radically resectable during the preoperative examination in terms of number and location, patients capable of undergoing general anesthesia and the potential benefits from the surgery exceeding the risks. The excluding criteria were the presence of extrapulmonary metastases (except the resectable hepatic metastases) and preoperatively confirmed malignant lymph nodes (LNs).

The extent of intervention was based on the location and number of resected lesions. Resection of the metastasis with a safety margin of 10 mm of healthy tissue around the circumference of the deposit

was considered sufficient in terms of oncological radicality. The specific types of performed interventions were anatomical lung resections, non-anatomical lung resections, *i.e.* wedge resections, and precise laser excisions using the Nd:YAG laser MY 40 1.3 (Gebrüder Martin GmbH & Co. KG, KLS Martin Group, Tuttlingen, Germany) with a laser beam wavelength of 1318 nm. Systematic nodal dissection was performed in accordance with the established procedure of The International Association for the Study of Lung Cancer (IASLC) from 2009 (6).

The preoperative serum levels of the following biomarkers were determined: carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), using the chemiluminescence ACCESS CEA and CA 19-9 assays (Beckman Coulter, Inc., Brea, CA, USA) in the DxI 800 (Beckman Coulter, Inc.), and tissue polypeptide specific antigen (TPS), using the immunoradiometric assay TPS IRMA (IDL Biotech AB, Bromma, Sweden) in the Stratec SR 300 (Stratec SE, Birkenfeld, Germany). The laboratory cut-off values for the individual biomarkers were: CEA 3 μg/l; CA 19-9 28 IU/l; TPS 90 IU/l.

We evaluated the overall survival (OS) and disease-free survival (DFS) after metastasectomy in the presented cohort, and their relationship to the age and gender of the patient, preoperative biomarkers levels, location of the primary tumor, when the metastasis occurred, type of surgical intervention, number and size of the metastases, condition of the intrathoracic lymphatic nodes and the administration of adjuvant oncological therapy after metastasectomy. The approval of the Ethics Committee was not required for this retrospective study.

A statistical analysis was performed using the SAS software (SAS Institute Inc., Cary, NC, USA). The analysis of overall survival and time to disease progression/progression-free survival was calculated using the Kaplan-Meier survival curves and was limited to 5 years from PM. The impact of the individual factors was tested using the Log-rank test and Cox regression model. The statistical significance was set up at alpha=5%.

Table I. *Characteristics of patients in the study.*

Variables	No.	%
Gender		
Male	56	53.8
Female	48	46.2
Median of age (years)	66 (29-81)	
Primary tumor		
Colon	62	59.6
Rectum	42	40.4
Pulmonary metastases		
Metachronous	89	85.6
Synchronous	15	14.4
Solitary	74	71.2
Multiple	30	28.8
Bilateral	12	11.5
↑ preoperative levels of biomarkers		
CEA (cut-off 3 μg/l)	38	36.5
CA 19-9 (cut-off 28 IU/l)	13	12.5
TPS (cut-off 90 IU/l)	43	41.3
Type of operations		
Wedge resections	56	44.4
Precision laser excisions	33	26.2
Segmentectomy	6	4.8
Lobectomy	29	23.0
Bi-lobectomy	1	0.8
Pneumonectomy	1	0.8
Median of size of metastases (mm)	16 (1.5-75)	
Involvement of intrathoracic LNs	7	7.3
N1	4	
N2	2	
N1+N2	1	
Postoperative morbidity	10	9.6
Reoperation	3	2.9
30 days mortality	0	0

CEA: Carcinoembryogenic antigen, CA 19-9: carbohydrate antigen 19-9, TPS: tissue polypeptide specific antigen, LNs: lymph nodes.

Results

Five-year OS and DFS in the cohort were 54.3% and 38.4%, respectively. Patients with 2 or more metastases from CRC had a 2.0-times higher risk of disease progression (p=0.0104; Figure 1) and a 2.1 times higher risk of death (p=0.0202). Patients with intrathoracic LNs affected by tumor dissemination had a 2.6-times higher risk of disease progression (p=0.0378; Figure 2) and a 4.3 times higher risk of death (p=0.0014). TPS levels above the cut-off value of 90 IU/l increase the risk of disease progression by 2.2 (p=0.0148; Figure 3) and the risk of death by 3.9 (p=0.0013). Levels of CA19-9 above the cut-off value of 28 IU/l increase the risk of disease progression by 2.4 (p=0.0112; Figure 4) and the risk of death by 2.7 (p=0.0107). Levels of CEA above the cut-off value of 3 μg/l increase the risk of death by 2.4 (p=0.0170). The patients who did not undergo the repeated PM for a relapse of the metastatic disease had a 4.3 times higher risk of death compared to patients who did (p=0.0090). Using a Cox multivariate stepwise regression, elevated preoperative CEA levels (HR=3.6), CA19-9 (HR=3.4), TPS (HR=3.4) and positive LNs status (HR=3.9) were identified as a statistically significant factors for OS; CEA (HR=2.0), CA19-9 (HR=3.0) and the number of metastases ≥2 (HR=2.5) for DFS.

Discussion

The generally accepted conditions for the indication of PM are: a low chance of possible extrapulmonary dissemination at the site of the primary tumor, a high chance of achieving a complete resection of lung metastases while maintaining sufficient pulmonary reserve, and the absence of alternative therapy with lower morbidity (5, 7). The synchronous or metachronous presence of operable hepatic metastases from CRC are therefore no longer a contraindication for PM because the sequenced surgery of hepatic and pulmonary deposits renders relatively encouraging results (8-11). We achieved a median survival of 73 months and a 5-year survival rate of 60% in these patients.

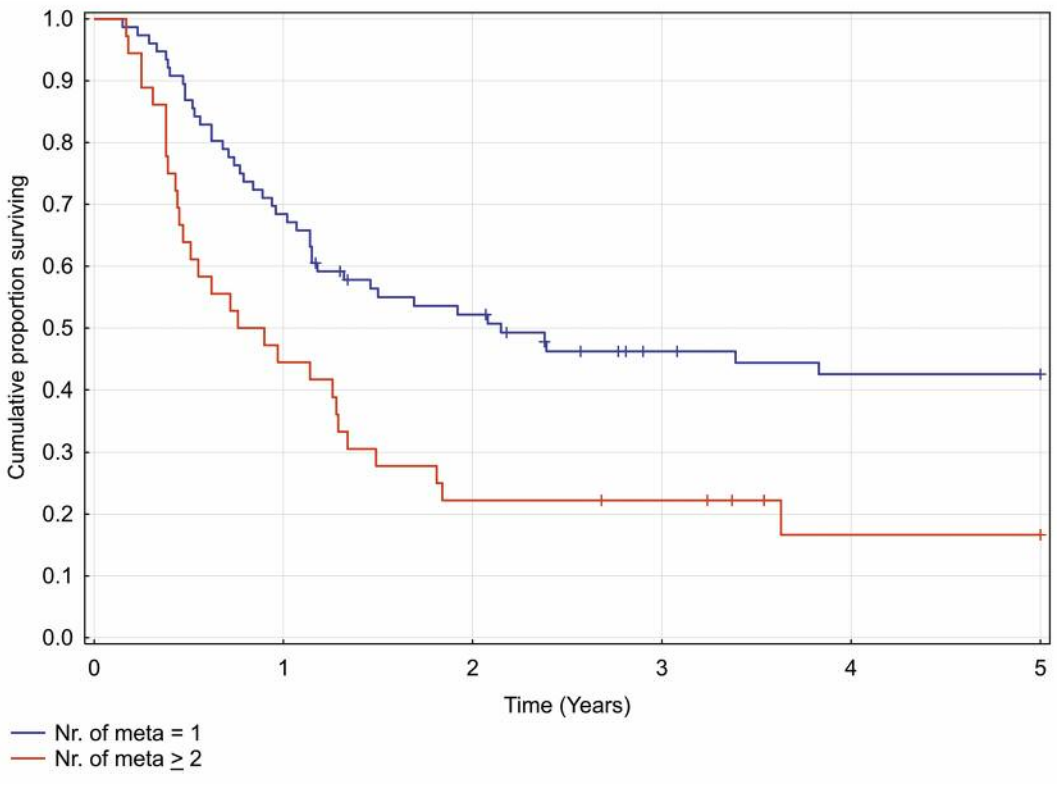

Figure 1. *Relationship between disease-free survival (DFS) after metastasectomy and number of metastases*.

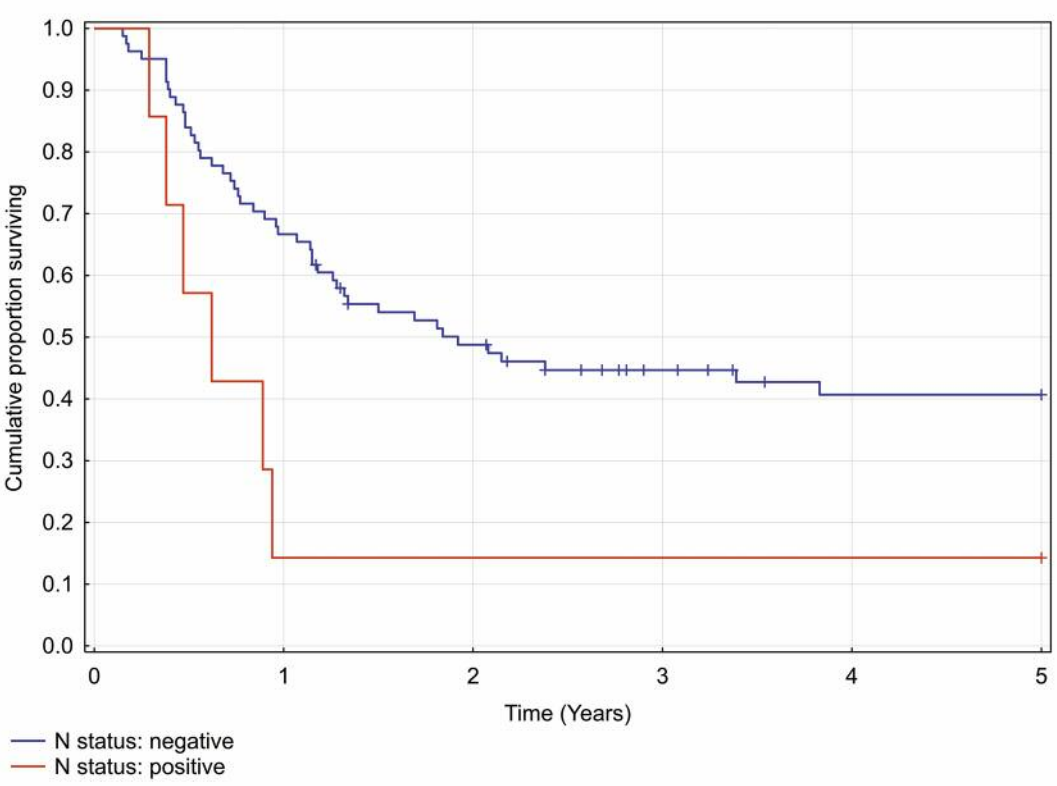

Figure 2. *Relationship between disease-free survival (DFS) after metastasectomy and N-status*.

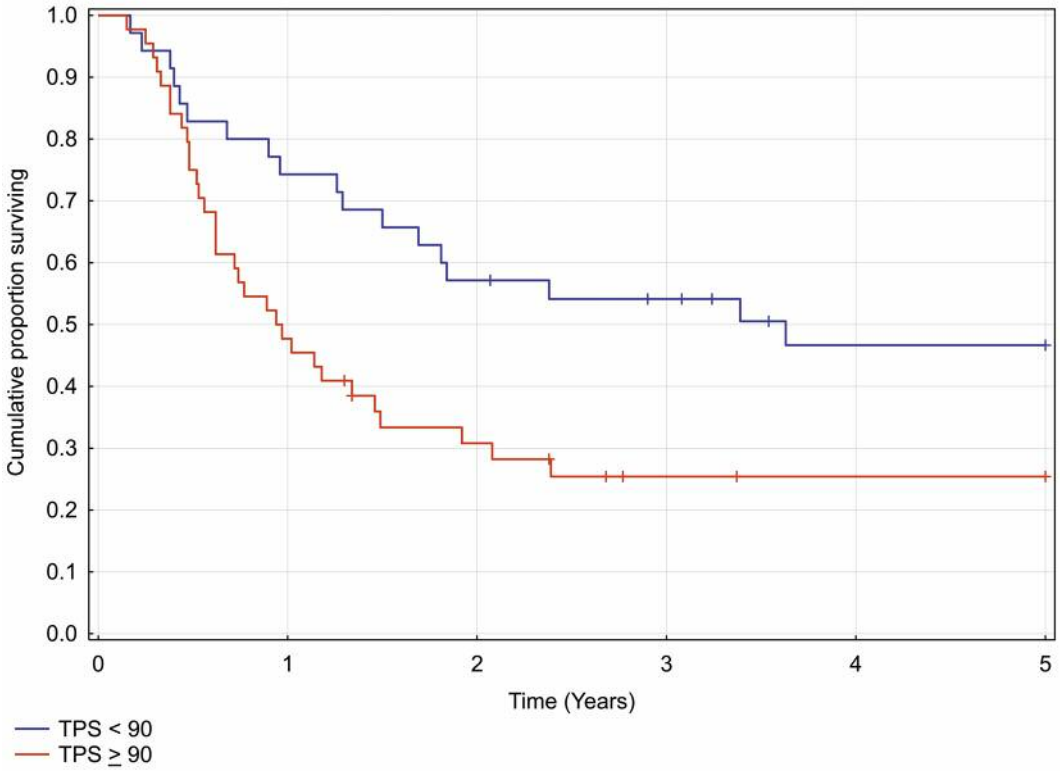

Figure 3. *Relationship between disease-free survival (DFS) after metastasectomy and preoperative serum level of tissue polypeptide specific antigen (TPS).*

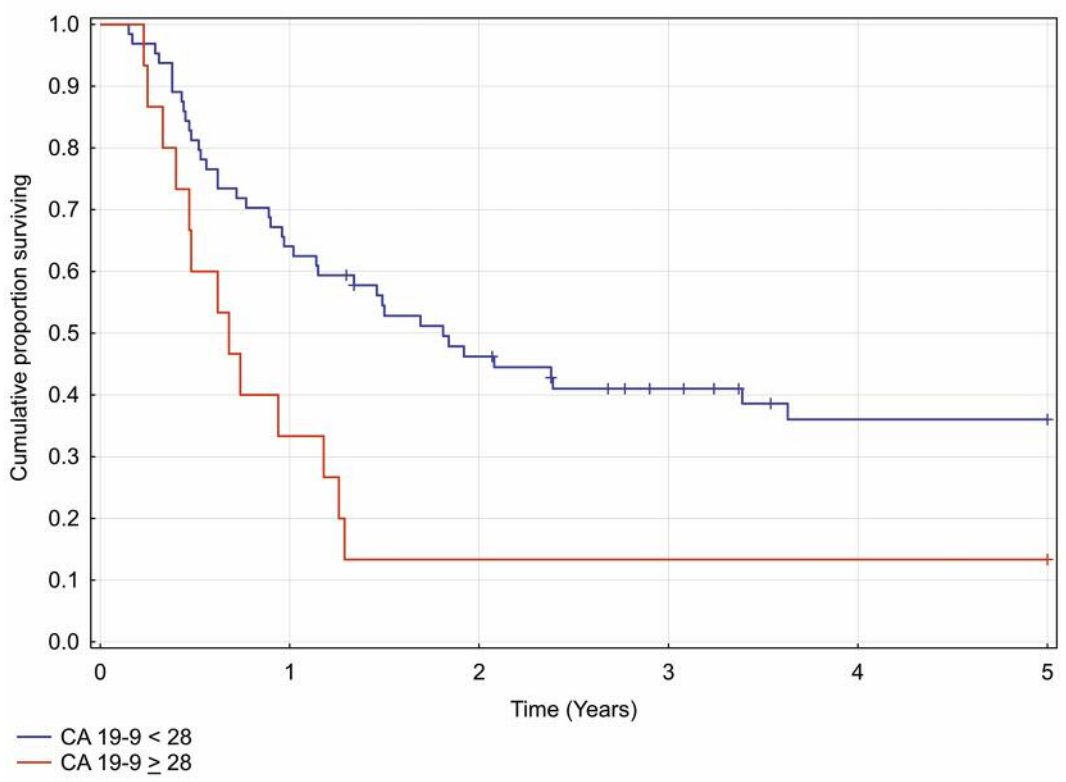

Figure 4. *Relationship between disease-free survival (DFS) after metastasectomy and preoperative serum level of carbohydrate antigen 19-9 (CA 19-9).*

However, when taking into consideration the indications for PM, other factors such as preoperative levels of some of the selected biomarkers also play a relatively important role. A number of authors point out the negative impact of preoperative CEA elevation on the prognosis of patients who underwent PM (5, 12-15), which corresponds with our findings in the case of OS. However, in our cohort, the preoperative elevation of two more biomarkers, TPS and CA 19-9, was shown to be significantly linked to a worse OS and DFS.

The number of diagnosed or resected lung metastases has also been shown to be another significant factor affecting both OS and DFS. Our results show that there is a significant difference in OS and DFS between patients with 1 resected metastasis and patients with 2 or more resected CRC metastases. Although other authors have presented similar findings, they have defined the border between a negative and positive prognosis using a different number of metastases. Tsitsias, *et al*. (12) and Pagès, *et al*. (16), state that the border lies between 1 and 2 metastases, while Cho, *et al*. (17) states that it is between 3 and 4 metastases. Despite the different results, it can be said that in general, the higher number of metastases, the worse the prognosis and *vice versa*, regardless of the definite number of metastases. Indicating a patient with multiple metastases for PM should be evaluated individually and very thoroughly while taking into account other influencing factors. On the other hand, in patients with bilateral lesions, especially where it concerns isolated deposits, PM should not be *a priori* contraindicated.

The involvement of intrathoracic LNs in pulmonary metastases from CRC ranges between 10-20% and very clearly worsens the patient's prognosis (both DFS and OS) (18-20). According to Bölükbasi, *et al*. (19) and Ali, *et al*. (20), the risk of the involvement of intrathoracic LNs increases with the number of metastases; with each additional one increasing the risk by 16%. Nevertheless, it remains unclear to what extent the survival of patients is affected by the involvement of individual levels of LNs (N1, N2), or by the number of affected nodal zones. While the involvement of intrathoracic LNs amongst our cohort was demonstrated in a smaller number of operated patients than that usually reported (7.3%), the prognosis was significantly worse (the risk of disease progression was 2.6 times higher, the risk of death 4.3 times higher). Based on these results, we think that patients with preoperative confirmation of tumor dissemination in the intrathoracic LNs should not be indicated for PM at all. On the other hand, we agree with the recommendations of some authors to perform a systematic nodal dissection of the intrathoracic LNs during PM. This should be done in order to improve the accuracy of the staging or selection of adjuvant oncological therapy, and is especially important given that the sensitivity of preoperative imaging methods in diagnosing LNs cancer is not high (20-23). Whereas the effect of systematic nodal dissection during PM on OS remains unclear, Pagés, *et al*. (16) state that its absence has a significant link to a higher 5-year risk of pulmonary metastases relapse.

Shiono, *et al*. (24) or Hernández, *et al*. (25) have demonstrated that the individual resections exercised yielded no statistically significant difference in OS and DFS. We nevertheless consider microscopically margin-negative resection (R0 resection) to be essential and hold that incomplete resections should not be performed. We agree with and follow the recommendations of Welter, *et al*. (26), according to whom the safety margin of healthy tissue on the circumference of the resected metastasis should increase with the size of the metastasis and should not be smaller than 7 mm.

The 5-year survival rate of 54.3% found in our cohort corresponds with other published results, in which it ranges between 34-75% (13, 15-17, 23, 27-29). The relatively small difference between the 5- and 10-year survival rate in our group (around 7%) shows that patients who survived 5 years following PM have a relatively high chance of real long-term survival. In other words, the probability of pulmonary metastasis relapse after 5 years from PM is rather low. Nevertheless, should pulmonary metastases recur, a repeated attempt should be made. Our results, as well as the experience of other authors, prove that repeated PM demonstrably extends OS compared to other treatment modalities (4, 9, 11, 23, 30, 31). It is relatively surprising that, in contrast to the data published in a wide range of literature, we did not find any significant relationship between OS, or DFS, and the location of CRC (rectum vs. colon), the time of the metastasis creation (synchronous vs. metachronous), the size of metastasis and the administration of chemotherapy after PM (4, 8, 12, 17, 19, 28, 29). Regardless of this, we can say that, in general, the best results in terms of long-term survival can be expected in solitary, metachronous and small size metastases, with a disease-free interval >1 year from the resection of the primary tumor, R0 resection of the metastases, the absence of intrathoracic LNs involvement; as well as in well differentiated tumors or, more precisely, colon carcinoma with normal levels of biomarkers preceding metastasectomy and an absence of hepatic metastases (4, 8, 12-17, 19, 23, 27-29).

The strengths of the presented results are mainly the long follow-up of the patient group and its gender and age balance, examination of selected biomarkers in all patients in the group, unified standard surgical technique and indication criteria, achieving R0 resection and systematic nodal dissection in all metastasectomies. The limitation of the study may be a higher number of patients with metachronous metastases and a smaller total number of patients.

In conclusion, radical PM as a potentially curative method can extend the survival of patients with lung metastases from CRC. Achieving the R0 resection is essential, whereby maximum effort should be made to preserve healthy lung

tissue that can enable the repeated surgical management recommended in the majority of cases of disease relapse. Systematic nodal dissection should be an essential part of every PM. We confirmed the following prognostic factors affecting OS and DFS: number of metastases, the condition of the intrathoracic lymphatic nodes and the preoperative levels of biomarkers.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding the topic, creation and publication of this article.

Authors' Contributions

Conceptualization: JV, RK; Methodology: JV, RK, JF, OT; Investigation: JS, MS, KP, MS, BV; Statistical analyses: SK; Writing – Original Draft Preparation: JV, RK; Writing – Review and Editing: JV, RK, OT, VT.

Acknowledgements

This work was supported by the Charles University Research Fund (Progres Q39); by the grant of Ministry of Health of the Czech Republic – Conceptual Development of Research Organization (University Hospital Pilsen – FNPl, 00669806); BBMRI-CZ: Biobank network – a versatile platform for the research of the etiopathogenesis of diseases (CZ.02.1.01/0.0/0.0/16_013/0001674); Bank of the clinical samples (LM2018125).

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Received September 21, 2020
Revised October 4, 2020
Accepted October 12, 2020