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Influence of Obesity on the Course of Malignant Neoplastic Disease in Patients After Pulmonary Metastasectomy

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Abstract. *Background/Aim: The aim of the study was to determine whether increased body mass index (BMI) in patients operated on for lung metastases influences the course of the disease. Materials and Methods: The retrospective data of 97 patients previously operated on for different malignancies were analyzed. There were 40 obese patients (BMI >30 kg/m^2, mean 33.9±4.5) and 57 non-obese patients (BMI 25.8±2.7 kg/m^2, p<0.001). Disease-free interval (DFI), the overall survival (OS) and survival after pulmonary metastasectomy were analyzed. Results: DFI and OS were longer in obese than in non-obese patients (82.1±83.5 months vs. 43.0±44.4, p<0.01 and 110.7±81.3 months vs. 69.9±52.9 p<0.005, respectively). Survival after pulmonary metastasectomy was 27.2±25.6 months and was longer in obese and overweight patients than in normal weight patients (20.2±18.4 months vs. 29.4±26.5, p<0.05). Conclusion: Being obese or overweight is a favorable prognostic factor in patients after surgical resection of lung metastases of different malignancies.*

With the increasing epidemic of obesity in the world, the incidence of malignancies related to obesity also increases (1). Obesity-related cancers include breast cancer in postmenopausal women, colon cancer, cancer of the lower esophagus, gastric cancer, liver cancer, gall bladder cancer, pancreatic cancer, uterine cancer, ovarian cancer and renal cancer (2). Obesity is also associated with increased risk of metastases, including lung metastases, in some cancers (3).

In the course of some malignancies a paradoxical phenomenon has been observed, indicating that obesity may be an oncogenic factor and – at the same time – may constitute a favorable prognostic factor (4, 5). The dual and opposite influence of obesity on the course of the same disease has been called the obesity paradox and has been described in some chronic diseases, including cardiovascular (6) and cerebrovascular diseases (7). These paradoxical effects of obesity may occur also in patients with metastases, including patients with malignancies not related to obesity. In a recent large-scale study of 4,010 cancer patients in good general condition, with distant metastases, median OS was twice as high in obese patients as in normal weight patients (8). However, there are also reports stating that there is no beneficial effect of obesity on metastatic neoplastic disease (9-11).

The problem of the influence of obesity on the course of metastatic malignancies has not yet been unequivocally explained. Especially, there are no studies on the influence of obesity on survival of patients with operable lung metastases. Therefore, this study was undertaken to evaluate the long-term outcome of surgical treatment of obese and non-obese patients who after resection of primary neoplasm had lung metastases removed.

Materials and Methods

Data from 99 patients who had a resection of lung metastasis from different primary malignancies between 2001 and 2016 were analyzed. The study was retrospective, and the condition for including patients in the study was access to anesthesia documentation containing body weight and height prior to performing pulmonary metastasectomy. Analysis was performed in the groups depending on body mass index (BMI). Underweight was diagnosed when the BMI

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Table I. *The most common coexisting or previously treated diseases in normal weight, overweight and obese patients, who underwent pulmonary metastasectomy.*

	Normal weight patients n=18		Overweight patients n=39		Obese patients n=40	
Cardiovascular diseases	4	22%	15	38%	21	53%
Previously treated other malignancy	2	11%	4	10%	5	13%
Diabetes	2	11%	5	12%	9	23%
Hypothyroidism	1	6%	0	0	5	13%
Respiratory system diseases	0	0	4	10%	2	5%

Table II. *Type of surgery in the normal weight, overweight and obese patients who underwent pulmonary metastasectomy.*

Type of surgery	Normal weight patients n=18		Overweight patients n=39		Obese patients n=40	
Mechanical resection	12	66.7%	25	64.1%	22	55.0%
Anatomical resection	4	22.2%	13	33.3%	11	27.5%
Non-radical resection	2	11.1%	1	2.6%	6	15.0%
Mechanical with partial chest wall resection	0	0	0	0	1	2.5%

was below 18.5 kg/m^2 (1 patient), normal body weight when BMI was in the range of 18.5-24.9 kg/m^2 (18 patients), overweight when the BMI was in the range of 25.0-29.9 kg/m^2 (39 patients), obesity class I-IV when BMI was in the range of 30.0-49.9 kg/m^2 (40 patients), and obesity class V when BMI was > 50.0 kg/m^2 (1 patient). Two patients with extreme body weight – underweight and obesity class V – were excluded from the analysis. In the final analysis the material of the study consisted of 97 patients, including 50 women and 47 men, mean age 62.8±8.7 years, with a mean BMI of 29.2±5.3 kg/m^2.

There were 18 normal weight patients (19%), 39 overweight patients (40%) and 40 patients with obesity class I-IV (41%). Among normal weight patients, there were 9 women and 9 men, aged 61.3±9.1 years, with BMI of 22.5±1.2 kg/m^2. Among the overweight patients there were 18 women and 21 men, aged 61.4±8 years, with a BMI of 27.4±1.1 kg/m^2. Patients with normal weight and overweight were referred to as non-obese patients. The group of obese patients consisted of 23 women and 17 men, aged 64.9±9 years, with mean BMI of 33.9±3.2 kg/m^2. BMI differences between the group of 40 obese patients (41%) and the group of 57 normal weight and overweight patients (59%) were statistically significant (25.8±2.7 kg/m^2 *vs.* 33.9±4.5 kg/m^2, $p<0.001$).

The most common coexisting diseases were cardiovascular diseases (hypertension, coronary heart disease, myocardial infarction, stroke, cardiac arrhythmia), previously treated cancers, diabetes mellitus, hypothyroidism and respiratory diseases such as chronic obstructive pulmonary disease and asthma. The incidence of these diseases according to BMI groups is shown in Table I.

Primary tumors included the following histopathological types: squamous cell carcinoma and adenocarcinoma in 81 patients (18 normal weight, 31 overweight and 33 obese), sarcoma in 11 patients (1 normal weight, 5 overweight and 5 obese) and melanoma in 5 patients (3 overweight and 2 obese). The primary tumor sites were: large intestine (28 patients), kidney (19 patients), breast (9 patients), uterus (7 patients), lung (7 patients), bladder (3 patients), larynx (2 patients) thyroid (2 patients), stomach (1 patient), salivary gland (1 patient), tongue (1 patient), soft palate (1 patient). The location of melanoma was as follows: skin (4 patients) and eye (1 patient). The location of sarcoma was as follows: soft tissue (breast, uterus, small intestine) in 10 patients and bone in 1 patient.

Surgical removal of lung metastases consisted of mechanical resection in 69 patients and of anatomical resection in 28 patients. In 1 patient, mechanical resection was associated with partial resection of the chest wall. In 9 patients, metastatic resection was non-radical, because of multiple small nodules detected during the surgical procedure (Table II).

The following parameters were calculated: the time between primary tumor resection and pulmonary metastasectomy, *i.e.* disease-free interval (DFI); the time between resection of the primary tumor and death or date of the last information about the patient (for all alive patients in mid-November 2016), *i.e.* overall survival (OS); and the time between pulmonary metastasectomy and the death or date of last information about the patient. Information about the date of death was obtained from the Regional Office for Civil Status and the Center for Personalization of Documents of the Ministry of Interior and Administration in Warsaw.

In the statistical analysis of the results the program Statistica 12 (Krakow, Poland) was used. The survival time analysis was based on the Kaplan-Meier curves with Wilcoxon's test according to Gehan for group comparison. When comparing normal distribution data, Student's *t*-test was used, and for non-parametric data the Mann-Whitney *U*-test was used. The value of $p<0.05$ was considered statistically significant.

Results

DFI was 59.2±6.1 months (median: 39 months) for the entire group and was longer in obese than in non-obese patients: 82.1±83.5 *vs.* 43.0±44.4, $p<0.01$. Figure 1 shows Kaplan–Meier

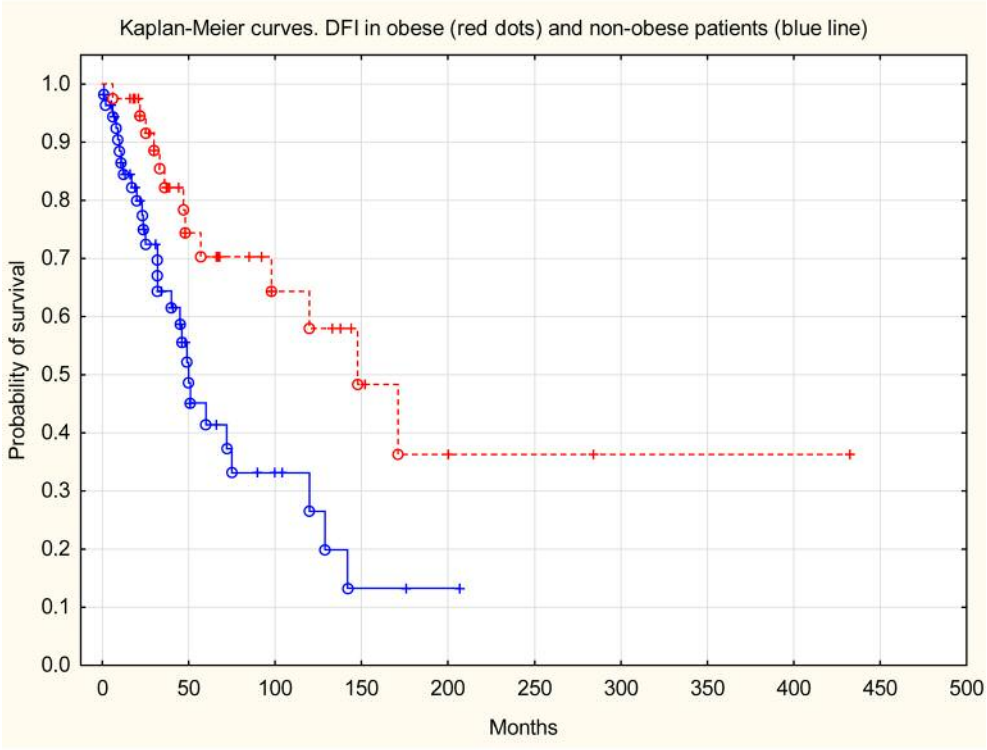

Figure 1. *Time between resection of primary neoplasm and resection of pulmonary metastasis in 40 obese and 57 non-obese patients.*

curves for DFI in the groups of obese and non-obese patients. During the follow-up forty-four patients (45.4%) died in 19.1±15.7 months (median: 33 months) after pulmonary metastasectomy. OS was 86.7±60.6 months (median: 65 months) and was longer for obese than non-obese patients: 110.7±81.3 months *vs*. 69.9±52.9 months $p<0.005$. Figure 2 shows Kaplan–Meier curves for OS in the groups of obese and non-obese patients.

The time from pulmonary metastasectomy to death or until the last observation of the patient was 27.2±25.6 months (median: 23 months). The time from pulmonary metastasectomy to death or until the last observation of the patient in the group of 79 obese and overweight patients was longer than in the group of 18 normal weight patients (20.2±18.4 months *vs*. 29.4±26.5 months, $p<0.05$).

Discussion

In this study, encompassing a group of 97 patients operated on for pulmonary metastases of different histopathological types, including squamous cell carcinoma, adenocarcinoma, melanoma and sarcoma, and of different localization of primary tumors, obesity was found to be a factor indicating longer course of the neoplastic disease – counting both from the surgical removal of the primary tumor to the removal of the lung metastasis and to death or to the last observation. Thus, longer DFI and longer OS in obese as compared with non-obese patients revealed a protective effect of obesity in the course of some neoplastic diseases with pulmonary operable metastases. Moreover, obesity and overweight were found to be favorable prognostic factors, indicating longer survival after pulmonary metastasectomy.

Occurrence of pulmonary metastases is usually a poor prognostic factor, but in selected cases, mainly isolated, peripheral and small (<3 cm) metastatic lesions in patients with good general condition and without contraindications to surgical treatment, their removal is possible (12). In our material pulmonary metastasectomy was performed in patients with various neoplasms – mostly cancer of the large intestine, kidney, breast, uterus and lung, less often malignancies of other organs. Mean DFI was 59.2±6.1 months and was almost twice as long in obese as in non-obese patients indicating that obesity was a factor related to slower progression of neoplastic disease after resection of the primary tumor. Mean OS was 86.7±60.6 months and – similarly as DFI – was longer in obese than in non-obese patients (110.7±81.3 months *vs*. 69.9±52.9 months, $p<0.005$). Moreover, comparison of survival after pulmonary metastasectomy in the group of obese and overweight patients and in the group of normal weight patients revealed

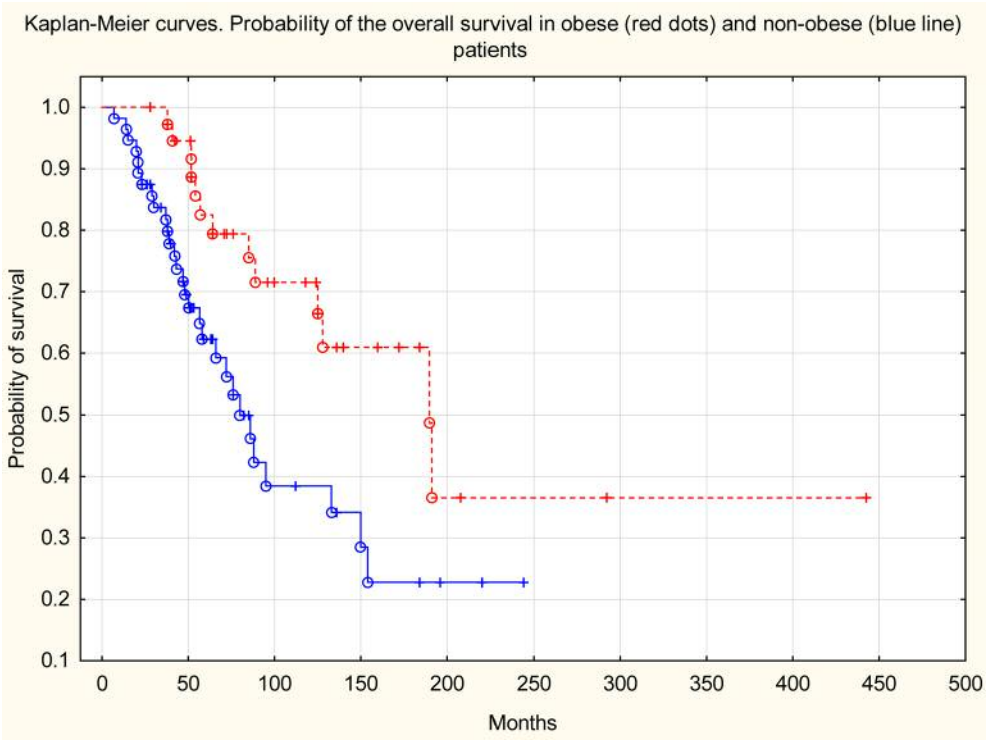

Figure 2. *Probability of overall survival in 40 obese and 57 non-obese patients operated on for primary neoplasm and lung metastasis.*

approximately 9-month longer survival in the former group: 20.2±18.4 months *vs*. 29.4±26.5 months, $p<0.05$.

More than half of our patients, *i.e*. 62 (64%), suffered from a neoplasm belonging to the group of cancers related to obesity, such as colorectal, breast, uterine, ovarian, and kidney cancer. Obesity is a factor associated with the risk of occurrence of multiple malignancies (1, 2, 13-15) and the risk of developing metastases in the course of some malignancies (3, 16). However, a favorable influence of overweight and obesity on the course of some neoplastic diseases have been also observed (17-19). Recently, a few studies have reported a relation between obesity and overweight and better prognosis in some cancer patients (20-22). In patients with locally advanced non-small-cell lung cancer obesity was associated with increased OS (22). In the early stage of colorectal cancer, the risk of death was lowest in the overweight patients (20). In different histopathological types of cancer, the risk of death decreased with increasing subcutaneous fat tissue (21).

Increased OS in obese patients with metastases has been observed in some other studies (8, 23, 24). In patients with remote metastases of nasopharyngeal cancer, obesity and overweight were favorable prognostic factors related to increased OS compared to non-obese patients (24). In patients with colorectal cancer who had surgery because of liver metastases (median follow-up of 39 months), obesity was a factor related to longer OS (23). In patients undergoing radiotherapy due to metastases of neoplasms of various organs, lower all-cause mortality was observed in both obese patients and overweight patients compared to patients with normal weight (8). However, we could not find any published data regarding the influence of obesity at the time of pulmonary metastasectomy on DFI and OS.

In considering the relationship between obesity and the course of neoplastic disease, the impact of such obesity-related factors as adiponectin and impaired glucose metabolism (23) can be taken into account. In patients with non-metastatic kidney cancer a negative correlation between adiponectin and BMI and shorter OS in patients with high serum adiponectin was observed (5). In obese patients surgically treated for liver metastases of colorectal cancer, diabetes had an unfavorable influence on OS, unlike in obese patients without diabetes (23).

The strengths of our study are the large number of patients with operable pulmonary metastases and the long time of observation of the patients. The weak point in our study is that the causes of death of the observed patients were unknown; whether these were cancer-related causes of death or related to cardiovascular or other diseases remains unexplained. The relationship between obesity and survival

may differ depending on the cause of death: for example, obese patients with renal cancer have been shown to have shortened OS, but after taking into account the causes of death, it turned out that survival related only to cancer was longer in obese than in non-obese patients; the authors called this phenomenon a 'paradox within a paradox' (25). The disadvantage of our work is also that we did not have data on BMI at the time of primary tumor surgery or data on the dynamics of BMI changes in the course of the disease.

Conclusion

In patients with operable pulmonary metastases of different malignancies, increased BMI significantly influences the course of the neoplastic disease. Overall survival and disease-free interval are longer in obese than in non-obese patients undergoing pulmonary metastasectomy. Being obese or overweight is a favorable prognostic factor in patients after surgical resection of lung metastases of different malignancies.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this article.

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