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CLINICAL STUDY

Surgical therapy of pulmonary metastases – 10-year results

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Abstract: *Introduction:* The surgical therapy of selected secondary pulmonary tumors, including both solitary and multiple or bilateral tumours, is currently a generally accepted therapeutic procedure demonstrably extending the long term survival of these patients.
Purpose: The purpose of the present study is a ten-year retrospective analysis of a group of patients who underwent surgery due to pulmonary metastases of various primary tumors.
Methods: In 2000–2009, 87 patients (of which 44 were male with a median age of 64 years) with secondary pulmonary tumors underwent surgery at the departments of the authors of this study. Solitary metastases were found in 60 patients, multiple metastases in the remaining patients, while 13 patients had bilateral metastases. The median disease-free period from surgery of the primary tumor was 31 months.
Results: In total, 74 unilateral and 13 bilateral surgeries were performed in one or two periods. The most common type of surgery included anatomical pulmonary resections (32 procedures), wedge resections (29 procedures) and laser excisions (24 procedures). In total, the radical resection was performed in 156 metastases. Post-operative morbidity was 17.2 % with zero mortality. A proportion of 50.6 % of operated patients survived after resection of metastases with median survival of 39 months. The overall three-year and five-year survivals in the group were 57 % and 38 %, respectively. A proportion of 35.6 % of patients live after resection of metastases without disease progression, and the median is 15 months.
Conclusion: The achieved results confirm the positive role of pulmonary metastasectomy in the therapy of disseminated cancer disease *(Tab. 1, Fig. 5, Ref. 34)*. Full Text in PDF *www.elis.sk*.
Key words: pulmonary metastasis, surgical therapy, laser.

Hematogeneous pulmonary metastases are generally considered as a sign of advanced generalization of malignant disease. Up to one third of malignant tumors have pulmonary metastases, and in most of them the lungs are even the first site of dissemination. Nevertheless, in a significant number of patients, the pulmonary affliction is stopped or eliminated during the dissemination of metastases, and these patients may benefit from radical resection of metastases (1, 2). Surgical therapy of the selected secondary pulmonary tumors, not only solitary but also multiple or bilateral, is today generally the accepted therapeutic procedure which demonstrably extends long term survival of these patients with acceptable peri-operative morbidity and mortality. The purpose of the following study is a retrospective analysis of a group of patients who underwent surgery due to pulmonary metastases of various primary tumors over a period of ten years.

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Material and methods

In 2000–2009 we performed surgery on 87 patients with secondary pulmonary tumors. Only patients who had undergone a radical resection of the primary tumor, were free from other extrapulmonary metastases, their pulmonary metastases appeared to be radically removable according to the pre-operative examinations as for the number and location, and the benefit of surgery had exceeded its risks were indicated for the surgery. In multiple metastases we primarily did not determine the maximum possible number of removable metastases but our decision was made case-by-case. Sixty-five patients (74.7 %) had undergone adjuvant oncological therapy of the radically surgically treated primary tumor before resection of the metastases.

The group included 44 males (50.6 %) and 43 females (49.4 %) with the mean age of 60.8 years, ranging from 27 to 77 years (median 64 years). In the groups of males and females, the mean values of age were 61 years (median 64, interval 27–77), and 60.7 years (median 64, interval 31–76), respectively.

Solitary metastases were found in 60 patients (68.9 %), multiple metastases in the remaining number of patients, and 13 patients (14.9 %) had bilateral metastases. Table 1 shows the percentage of single primary malignant tumors with pulmonary metastases. A pre-operative histological or cytological verification of the metastatic lesions was not strictly required. Standard ex-

Tab. 1 Primary malignant tumors with pulmonary metastases.

Primary tumor	Amount	%
Colorectal cancer	39	44.8
Renal cancer	13	14.9
Breast cancer	10	11.4
Bronchial cancer	8	9.2
Gynecological cancers and sarcomas	5	5.7
Malignant melanoma	3	3.5
Malignant fibrous histiocytoma	3	3.5
Other	6	7.0
Total	87	100

amination methods for surgical pulmonary diseases, i.e. computer tomography (CT) alone or in combination with positron emission tomography (PET/CT), fibrobronchoscopy, etc. were used for the diagnosis of metastases.

The surgical approach was either posterolateral thoracotomy or videothoracoscopy. The extent of surgery was based primarily on the location and number of metastases to be resected. With regard to oncological radicality, the removal of metastasis with a safety resection edge of 5 mm of healthy tissue around the focus was considered sufficient. In case of open surgeries, the particular types of the performed procedures included anatomical pulmonary resections which involved segmentectomy, lobectomy, bilobectomy and pneumonectomy, and furthermore non-anatomical pulmonary resections, i.e. wedge or limited and precise laser excisions using the Nd:YAG laser MY 40 1.3 with laser beam wave length of 1318 nm. During the mini-invasive surgeries we removed the metastatic lesions using the wedge resection by means of the endoscopic staplers. The lesions which could not be removed using the radical surgery were treated with radio-frequency ablation (RFA) transcutaneously under the CT control.

In this group of patients we monitored mainly the overall survival, or disease-free interval (DFI) both from primary surgery and after removal of metastases and their relation to the size and histological type of metastases, and type of surgery. Statistical analysis was performed using the STATISTICA 9.0 software.

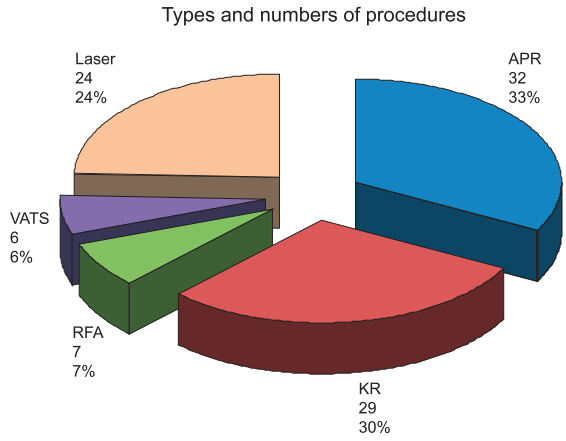

Fig. 1. Types and numbers of procedures. APR – anatomical pulmonary resection, KR – wedge pulmonary resection, Laser – precise laser excision, RFA – radio-frequency ablation, VATS – videothoracoscopic and video-assisted resection.

Basic statistical data were calculated for the measured parameters in the whole group and in the single groups. The effects of single variables on survival time, or DFI were investigated using the Kaplan-Meier method of estimation of distribution survival function, or DFI. The differences in overall survival and DFI between the investigated groups were tested using the so called Log-rank test and Cox regression model.

Results

The median disease-free interval from surgery of the primary tumor regardless of its type was 31 months in the group. The factor of histological type of the primary tumor was statistically significant in this parameter for a short period but not long-term (Log-Rank test: p-value = 0.0880; Wilcoxon test: p-value = 0.0357).

All patients in the group underwent surgical therapy of pulmonary metastases. Seventy-four unilateral (85.1 %) and 13 bilateral

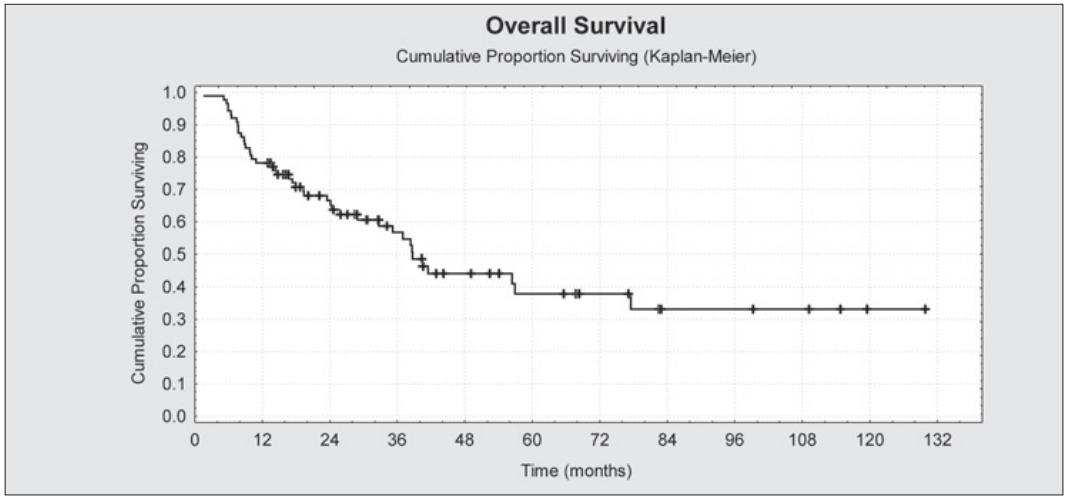

Fig. 2. Overall survival after resection of metastases.

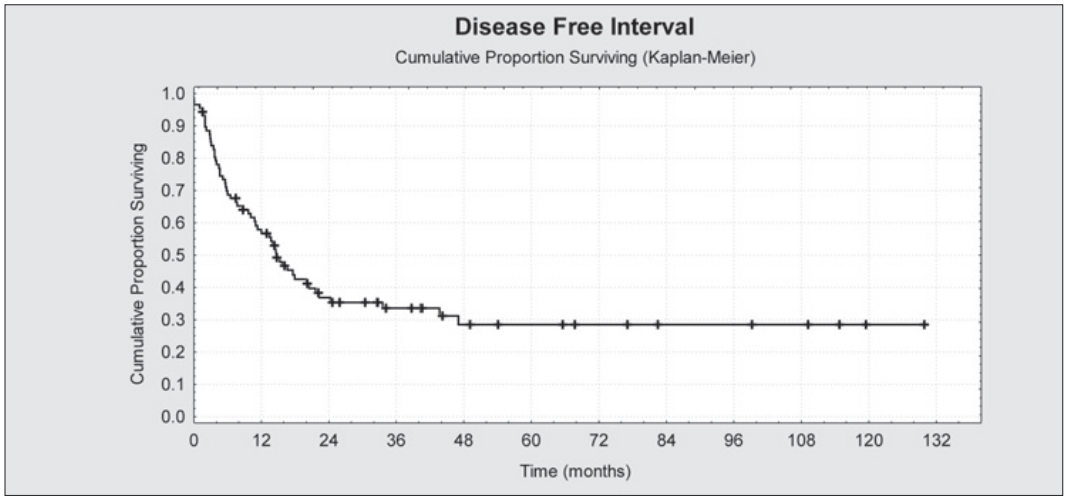

Fig. 3. Disease free interval after resection of metastases.

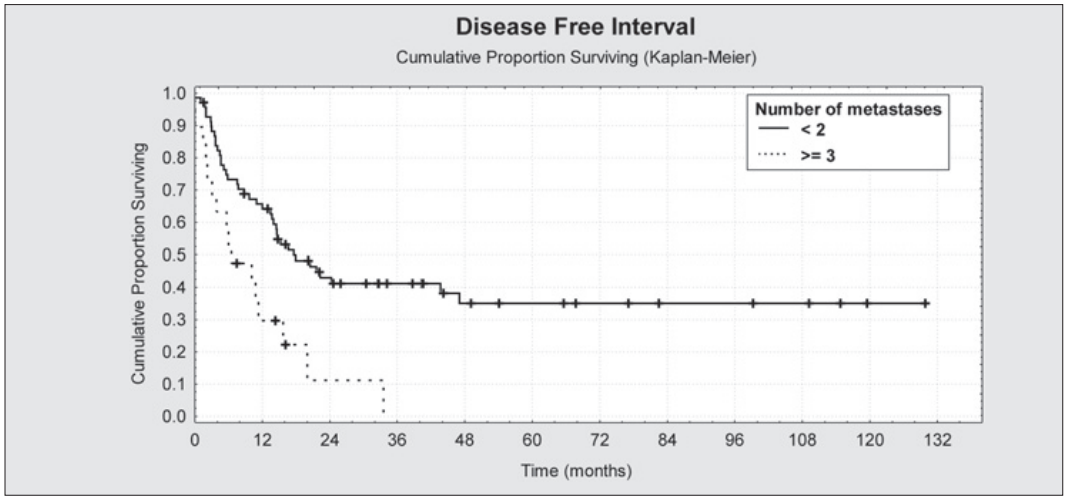

Fig. 4. Dependence of DFI after resection of metastases on a number of metastases regardless a type of tumor.

surgeries (14.9 %) were carried out. Both surgeries were performed on 2 patients (2.3 %) at one time and on 11 patients two times (12.6 %). Thus 98 surgeries were performed on 87 patients in total. Surgical procedures included 6 (6.1%) videothoracoscopies, 85 (86.8 %) posterolateral thoracotomies and 7 (7.1 %) transparietal RFAs. Figure 1 shows particular types and numbers of surgeries. The anatomical pulmonary resections included 2 segmentectomies, 25 lobectomies, 3 bilobectomies and 2 pneumonectomies. In total, the radical resection was performed in 156 metastases, and the remaining 9 metastases were treated with radio-frequency ablation. The highest number of lesions removed in one patient was thirteen while the latter case involved endometroid cancer metastases. The size of metastases ranged from 2–120 mm, with median of 22 mm, and 77 % of removed metastases were above 35 mm in size, 63 % were less than 30 mm in size and 55 % were less than 25 mm in size. The definitive post-operative histology confirmed the pre-operative assumption that all removed metastases were of the same type as the primary malignant tumor.

Fifty-two surgeries (53.1 %) required a removal of hilar and mediastinal lymphatic nodes, in 42 cases performed by means of sampling, and in 10 patients by means of ipsilatral systematic mediastinal lymphadenectomy (SMLA). In eight cases (15.4 % of performed collections) metastases of the same histological type as in the pulmonary lesions were found in the lymphatic nodes out of which five were found in hilar and three in mediastinal lymphatic nodes. An affliction of hilar lymphatic nodes was detected in two patients with solitary metastases of colorectal cancer, one female-patient with multiple metastases of the same tumor, one patient with solitary metastasis of cervical cancer, and one patient with multiple metastases of malignant fibrous histiocytoma. Only one female-patient with solitary metastasis of non-differentiated ductal breast cancer, one male with solitary metastasis of papilocarcinoma of the urinary bladder, and one patient with multiple metastases of malignant fibrous histiocytoma had their mediastinal lymphatic nodes affected by the tumor.

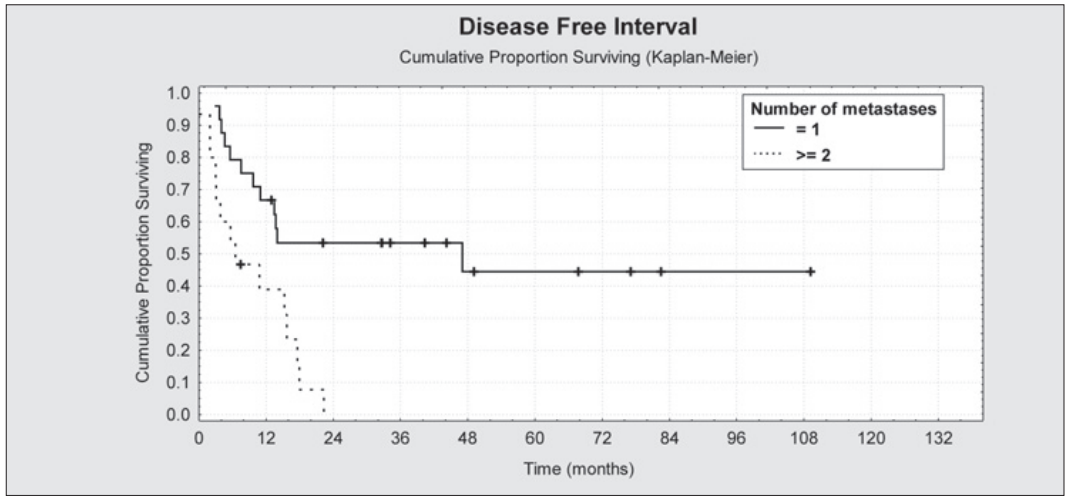

Fig. 5. Dependence of DFI after resection of metastases on a number of colorectal cancer metastases.

We had no peroperative adverse event. The post-operative morbidity was 17.2 % (15 patients), while the most common adverse events were pneumothorax (i.e. post-operative failure of the lung to expand completely) and inflammatory pulmonary complications. We had to solve these adverse events six times (6.9 %) by means of repeated surgery which always included drainage of the respective pleural cavity. None of the patients died in association with surgery within thirty days. The mean duration of post-operative hospitalization was 7.3 days. Sixty-one patients (70.1 %) underwent further oncological therapy following the resection of metastases.

The monitoring of the group of patients for statistical purposes was finished on December 31, 2010, with a median duration of 26 months (2–130). Forty-four patients who underwent surgery (50.6 %) survived up to this date with medial survival time of 39 months (29–77). The underlying malignant disease caused death in 3 of 43 deceased patients. Two patients with colorectal cancer metastases and one with dissemination of the malignant fibrous histiocytoma died out of five patients with dissemination of the metastatic focus into the hilar lymphatic nodes, while one female-patient with non-differentiated ductal breast cancer died out of three operated patients with affliction of ipsilateral mediastinal lymphatic nodes. Cumulative three-year and five-year survivals were 57 % and 38 %, respectively (Fig. 2), while in the colorectal cancer group they were 52 % and 41 %, and in the renal cancer group 66 % and 53 %. No statistically significant factor possibly influencing the overall survival was found in the whole group.

Thirty-one patients (35.6 %) live without progression of the disease after resection of metastases, and the median DFI is 15 months (11–22). In total, 34 % and 28 % of patients survived without any signs of relapse or progression of the disease for three years and 5 years, respectively (Fig. 3). Out of 56 patients who died or live with progression of the disease, 31 patients had a relapse of pulmonary metastases and 25 had dissemination to other organs. The relation between DFI and a patient's age was significant for a short period of time when the patients older than 60 years had a longer DFI but this difference is reduced over a longer period of time (Log-Rank test: p-value = 0.0882; Wilcoxon test: p-value = 0.0158). The risk of progression of the disease in patients with three and more metastases of any primary tumor is 2.5 times higher (statistically significant; Log-Rank test: p-value = 0.0015) (Fig. 4). The relation between DFI after resection of metastases in the group of colorectal cancer and the type of surgery is statistically significant. The lowest DFI was provided by radio-frequency ablation and other types of procedures showed quite similar DFI (Log-Rank test: p-value = 0.0257). The risk of disease progression in patients with two and more metastases of colorectal cancer is 3.4 times higher (statistically significant; Log-Rank test: p-value = 0.0016) (Fig. 5), and the risk of progression of the disease in those with 3 and more metastases is 3.9 times higher (statistically significant; Log-Rank test: p-value = 0.0017).

Discussion

Currently, the radical surgery of secondary pulmonary tumors is indicated in patients whose primary cancer has been radically removed or is under control, no other extrapulmonary metastases are present, number and location of metastases enables their radical resection, and the benefit for patient overweighs the risk of surgery (3, 4). However, recently this model has undergone some changes. For example, even more patients presenting pulmonary and liver metastases of colorectal cancer undergo surgery with quite favorable results (5, 6, 7, 8). Surgery of pulmonary metastases should be indicated as a result of consultations of all involved specialists (thoracic surgeon, oncologist, chest physician, anesthesiologist, radiologist) based on individual review of each single case. The response to previous oncological therapy, i.e. most commonly to chemotherapy, plays a significant role in the decision-making process. If the disease progresses despite any oncologic treatment in terms of increasing the number and size of pulmonary lesions, surgery should not be indicated because the prognosis of these patients is poor. According to the opinion of most respondents of the questionnaire prepared by the European Society of Thoracic

Surgeons, patients with preoperatively documented affliction of the hilar and mediastinal lymphatic nodes should not be surgically treated (9). In some types of cancers (e.g. malignant melanoma, esophageal cancer, breast cancer, etc.) the authors actually do not arrive at consensus because some of them do not recommend metastasectomies of multiple metastases of these tumors due to poor prognosis, especially with short DFI from the surgery of primary tumor, while the other part of authors prefer a more radical approach of indicating surgery regardless of DFI and number of metastases (10, 11, 12, 13, 14). The cases which include metastasectomies of synchronous metastases and elevation of oncological markers are considered as arguable by some authors because of a quite poor prognosis (14, 15). We agree with the more radical views, whereby we put an emphasis on the individual evaluation of each single case.

The principal requirement should always include the achievement of R0 resection while incomplete resections have worse prognoses and should not be performed (16, 17, 18). In case of pulmonary metastases, the removal of the focus at least with a safety resection edge of 5 mm of the surrounding healthy tissue is sufficient. The extent of necessary resection of the pulmonary parenchyma is determined by the number and location of metastases. When possible, we try to perform limited non-anatomical resections (wedge resections) and we try to save the maximum of healthy pulmonary tissue. More extensive procedures such as lobectomies or pneumonectomies do not provide a better long-term survival and they are even worse with regard to morbidity (19). In addition, such extensive resections limit the possible re-operations in case of new metastases because of insufficient residue of functional pulmonary capacity. Nevertheless, anatomical pulmonary resections have their place in surgical therapy of pulmonary metastases albeit in central or multiple lesions when a smaller surgery is technically not feasible or does not guarantee the needed radical character of oncologic outcome. With regard to the aforesaid they should be carefully considered. A modern alternative which significantly saves healthy pulmonary parenchyma and ensures a sufficiently radical oncologic outcome is that of precise laser excision using the Nd:YAG laser MY 40 1.3 that has been particularly developed for the needs of pulmonary oncologic surgery. This type of laser enables an ideal excision of a metastasis together with the necessary resection edge also in cases where it is more deeply located in the pulmonary parenchyma, and furthermore it enables resection of metastases without the need for anatomical pulmonary resection or bilateral surgeries (20). The saving of maximum pulmonary parenchyma does not limit the possibly recommended re-operations in case of recurrence of the disease (21, 22). The number of removed lesions is not primarily limited. The radical character and risks of procedure are decisive. If a radical resection of a metastatic focus cannot be performed for various reasons, it can be treated, as in case of e.g. liver metastases, i.e. by radio-frequency ablation during which we prefer transparietal access under CT control (23). However, its results are apparently worse, as also documented by our experience, and it is a palliative method which means the "last choice" method.

In case of bilateral pulmonary metastases it is not clear whether they should be treated in one or two periods. For various reasons, some authors incline to the first option, some to the other (24, 25). In our opinion, especially two factors should be considered, namely the patient's general condition and the number of removed lesions. In elderly patients with a higher surgical risk and with more metastases, we prefer a two-period surgery, while in younger patients with less metastases we are free to perform a bilateral surgery at one time. The choice of surgery is similarly controversial. A significant section of authors always recommend classical open thoracotomy, or sternotomy in case of a bilateral surgery while referring to the need for thorough palpation of pulmonary tissue in order to avoid overseeing any possible unidentified pathological foci (16, 25, 26). For example, Loeche found in his study other metastases in almost 17 % of performed surgeries (27). The advocates of mini-invasive procedures (videothoracoscopy, video-assisted procedures) oppose by way of high sensitivity of up-to-date CT devices which are able to detect lesions of just 1 mm and by the fact that oncological results are comparable with open surgeries (28, 29). In our group, we found perioperatively a higher number of metastases than expected during the preoperative examination only in 3 cases (3.4 %). All three cases included patients with multiple disease and short DFI from the primary tumor surgery (up to 12 months). Mutsaerts found in his study peroperatively other metastases in almost 30 % of surgically treated patients, more often in multiple lesions which corresponds to our findings (26). Therefore, in our opinion, the mini-invasive procedure can be accepted only in selected individuals with solitary metachromous peripheral metastases with a DFI of years after the primary tumor surgery (14, 16).

The frequency of affliction of hilar and mediastinal lymphatic nodes by dissemination of cancer is described within a range of 8 to 33 % in pulmonary metastases with a demonstrably worse survival (27, 30, 31, 32). The benefit of SMLA in pulmonary metastasectomy is currently under investigation, nevertheless it is largely recommended. It is mainly because of the improvement in staging and choice of adjuvant oncological therapy (30, 32). According to some studies an improvement in long-term survival is also possible, e.g. in patients with preoperatively unidentified affliction of mediastinal lymphatic nodes which may be up to 14% according to Loehe (3, 16, 27, 32). In our group, the tumor infiltration in regional lymphatic nodes was not preoperatively expected in any of our 8 patients (9.2 % of the whole group, 15.4 % of the performed collections). The effect of secondary cancer affliction of hilar and mediastinal lymphatic nodes, or that of their removal, on long-term survival of our patients cannot be evaluated due to a small number of patients. We have been engaged also in SMLA issue in the last two years as being part of a multicentric study investigating its importance in pulmonary metastasectomy. The study is running in co-operation with three departments in the Czech Republic (30).

Five-year survival in patients who underwent metastasectomy varies according to different sources and ranges between tens of percents, with the mean level between 30 and 50 %. However some studies present up to 85 % survival (18, 19, 21, 30, 33, 34).

Our data practically accurately match the commonly determined interval, in case of both whole group and two largest groups, i.e. in colorectal and renal cancers. Numerous studies found in literature describe a number of more or less statistically significant factors which positively or negatively affect the long-term survival after radical surgical therapy of pulmonary metastases. Although the results of these observations vary in certain details, it is possible to logically generalize it to some extent because the basic outputs are similar for all these studies. Thus, the more aggressive and advanced the disease at the time of pulmonary surgery, the worse prognosis can be expected and vice-versa. Long-term survival after pulmonary metastasectomias can therefore be expected in solid, well differentiated tumors of an early stage according to TNM classification, and small solitary metachromous unilateral metastases with long DFI from the surgery of primary tumor, absence of affliction of lymphatic nodes and R0 resection, and normal values of oncological markers, etc (18, 21, 30, 33, 34). Better results are also achieved if metastasectomy is combined with adjuvant oncological therapy (17). This, at least partly, corresponds to our findings when the monitored group of patients with more metastases of any type is at higher risk of recurrence of the disease whereby this association is more marked in colorectal cancer. Therefore, the stated trends should be taken into account in both indication of subsequent oncology therapy after metastasectomy and surgery itself.

Conclusion

The positive effect of pulmonary metastasectomy in long-term survival is doubtless. A precondition includes an accurate selection of patients who will benefit from this procedure and this selection should be performed by a broader team of relevant specialists with individual assessment of each single case. Indication of metastasectomy in multiple and bilateral disease, synchronous metastases or short symptom-free period when worse results maybe expected should be considered especially carefully. Despite the administered chemotherapy or biological therapy, the patients with progression of the disease should not be indicated for surgical therapy. A complete resection of the pathological focus with maximum effort focused on saving the healthy pulmonary tissue in order to enable re-operation in case of recurrence of the disease is mostly recommended and essential. For optimal therapy results, the patients with secondary pulmonary metastases should be referred to specialized centers providing complex oncological care.

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