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Review

Optimal timing of pulmonary metastasectomy – Is a delayed operation beneficial or counterproductive?

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Abstract

Introduction: Pulmonary metastasectomy represents an established approach in the treatment of lung metastases related to several solid malignant tumors, promising the chance of long term survival. Regarding the proper timing of metastasectomy both operation promptly after diagnosis and delayed operation after an interval of 3 months are common practice.
Materials and methods: A systematic Medline search addressing the optimal timing of metastasectomy was performed. Since the search query "timing of metastasectomy" yields only a limited number of articles, the Medline search was expanded to include the main arguments for prompt metastasectomy ("metastases of metastasis", "growth rate of pulmonary metastases") and for delayed metastasectomy.
Results: Based on the data available to date, there is no necessity to expedite the timing of the operation. On the other hand, there is no evidence that a delayed operation, for example after re-staging following an interval of 3 months, provides a benefit.
Conclusion: Therefore the timing of metastasectomy should only depend on the patient's requirements, such as general state of health and oncologic considerations, such as promising multimodal therapy concepts, extrathoracal tumor manifestations or oncologic type of the primary tumor. A delayed operation seems justified if the indication for resection is questionable due to a high risk of early multilocal recurrence.

Keywords: Timing; Metastasectomy; Pulmonary metastases

Introduction

In general, local control of solid malignant tumors can usually be achieved by modern medicine whereas curative therapy of malignant diseases is limited by distant metastases. The lung, specifically the pulmonal-arterial vascular bed, represents the first filter for hematogenous metastases of many solid malignant tumors. Therefore pulmonary metastases are very frequent and have increasingly become the focus of surgical procedures.

With the aid of laser-technology, the excision of pulmonary nodular lesions is possible with a parenchyma-sparing resection. In addition, retrospective publications have demonstrated significantly increased long term survival after pulmonary metastasectomy.[1–3] *Sternberg and Sonnet*[4] pointed out, that even 125 years after the first metastasectomy, many open questions about the pulmonary metastasectomy exist. Prospective randomized data, which could provide some answers regarding pulmonary metastatic surgery, are not available to date. Ethical aspects and difficulties to compare the data are the main reasons. Thus, pivotal questions, like the limits for indications for surgical treatment, proper access and technique concerning the operation, benefits of intraoperative chemotherapy and systemic lymphadenectomy and especially optimal timing for surgery have to be answered based on personal experience and retrospective observational studies due to missing general standards.

A number of surgeons have recommend to operate as soon as the patient's clinical situation allows it.[5,6] This

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approach is often influenced by the fear that metastases could generate new metastases[5,7] or concern for rapid local tumor progression.[8] The risk of metastastic spread originating from both distant and lymph node metastases, is discussed in the surgical literature.[7,9–12] Other colleagues prefer a diagnostic interval of three months after the initial diagnosis of pulmonary metastases, either routinely in all patients[13–15] or in selected patients.[8]

Materials and methods

The U.S. National Library of Medicine (http://www.ncbi.nlm.nih.gov/) database was queried for search strings related to the related emphases of this review: "metastasis of metastases", "eligible point of time for metastasectomy", "timing of surgery for metastases", with the focus on pulmonary metastases, as well as keywords, which resulted from further studies of the publications. Besides the latest publications, the basic publications to the respective topics were taken into consideration. Due to the small number of publications addressing the questioned issue, articles concerning metastasectomy in other organs were also analyzed.

Since the concrete question "timing of pulmonary metastasectomy" is the subject of very few articles, the Pubmed search was expanded to the main arguments for prompt metastasectomy ("metastases of metastasis", "growth rate of pulmonary metastases") and for delayed metastasectomy ("early relapse after metastasectomy", "chemotherapy and complete metastasectomy", "repeated metastasectomies").

Results

Since no general standards or well-recognized recommendations concerning the eligible point of time for pulmonary metastasectomy exist, it is sensible to investigate the significance of arguments for and against the operation within a narrow time frame after the diagnosis of metastases.

According to the results of the literature there are two main arguments for and at least three arguments against a prompt operation of pulmonary metastases after their diagnosis. These arguments are summarized in Table 1. Below the scientific background for these arguments is presented according to literature researches.

Table 1
Arguments for and against carrying out metastasectomy within a narrow time frame after the diagnosis of metastases.

	Question to be answered
Arguments for prompt operation	
-the risk of metastatic progress in case metastases could create new metastases	(1)Do metastases metastasize?
-the risk of technical unresectability or the need to perform a pneu monectomy due to local growth of central lesions	(2)Is the tumor growth of metastases of certain primary tumors predictable?
Arguments against prompt operation	
-patients with massive progress of the metastastatic disease within the first months can be excluded from futile surgery	(3)Is there a reliable interval between the detection of pulmonary metastases and the resection with respect to the prediction of the metastatic progress?
-application of chemotherapy prior to the metastasectomy	(4)Can neoadjuvant chemotherapy improve the outcome for patients with intended complete resection of pulmonary metastases?
-risk of repeated operations in case very small lesions are overlooked	(5)Are repeated operations associated with worse survival?

Do metastases metastasize?

The risk of metastases creating new metastases would be a striking argument to perform a metastasectomy as soon as the patient's general state of health allows. However are there reliable data supporting the possibility of metastatic spread based on metastatic disease?

In fact an animal experiment, published as early as 1975 by Hoover and Ketcham,[16] suggested that metastases themselves have the capacity to metastasize. After having developed pulmonary metastases, the primary tumor was resected in a mice model. One week after the tumor resection the mouse bearing the metastases was joined at its peritoneal cavity with a syngenic host mouse. The parabiosis was maintained for around 4 weeks. 80% of the guest mice (43/54) had metastases. The conclusion of the authors was that the metastases in the guest mice were generated from the metastases of the host. However, circulating tumor cells in the blood circulation are another potential source of these metastases. Hoover and Ketcham assumed in 1975, that 7 days between the resection of the primary tumor and the parabiosis represent a long period. At that time most publications had documented tumor cells in the circulation for only a period of several hours. However, current evidence indicates that circulating tumor cells are traceable months and even years after complete resection of the primary tumor.[17,18] Moreover, disseminated tumor cells can recirculate from bone marrow, due to so far unknown stimuli.[17]

In another experimental approach Sugarbaker[19] et al. found no evidence that metastases can generate metastasis. Healthy lung tissue was transplanted in mice with pulmonary metastases. Examination of the transplanted tissue revealed no evidence for metastases. Tait et al.[20] summarized all experimental data in a review article. The authors emphasized that the only experimental proof was published by Hoover and Ketcham[16] with the uncertainty about the role of circulating dormant tumor cells.

Epidemiological data suggests that lymph node metastases are not the origin for prognostically relevant additional metastases.[21] This is exemplified by a publication by

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