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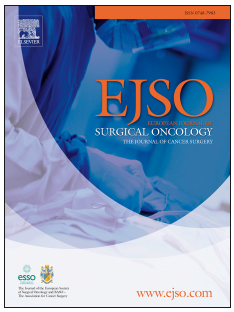

Optimal timing of pulmonary metastasectomy – is a delayed operation beneficial or counterproductive?

M. Krüger, J.D. Schmitto, B. Wiegmannn, T.K. Rajab, A. Haverich

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

Krüger M. [1,*], Schmitto J.D. [1], Wiegmannn B.[1], Rajab T.K. [2], Haverich A. [1]

1. Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany

2. Department of Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Corresponding author*:

Marcus Krueger, M.D.
Division of Cardiothoracic, Transplantation and Vascular Surgery
Hannover Medical School
Carl-Neuberg-Strasse 1
30625 Hannover, Germany
Phone: +49 511 532 -6591
Fax: +49 511 532- 8396
E-mail: Krueger.Marcus@mh-hannover.de

Abstract

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. 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. 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. 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.

Words: 200

Keywords: timing, metastasectomy, pulmonary metastases

Abstract

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. 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 and for delayed metastasectomy. The majority of epidemiological and experimental data, clonal relationship investigations and gene expression investigations taken together support the hypothesis that metastases are not capable of metastasizing to a clinically significant extent. For metastases of renal cell cancer and colorectal cancer an additional effect of neoadjuvant systemic therapy could not be proven in case of complete metastasectomy. 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. 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.

Words: 248

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, 2, 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 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, 10, 11, 12]. Other colleagues prefer a diagnostic interval of three months after the initial diagnosis of pulmonary metastases, either routinely in all patients [13, 14, 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 analysed.

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.

1. 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 Veronesi et al. [22]. After a follow up of 30 years in a randomized setting there was no survival advantage for female patients with breast cancer who had an additional parasternal lymphadenectomy, although positive lymph nodes were diagnosed in 20.5% of these patients. Also, based on data of breast cancer patients, Hölzel et al. [23] formed the hypothesis, that true lymph node and distant metastases do not metastasize. They analysed spatial and temporal metastatic distribution according to the clinical records of 33000 patients registered since 1988. The results clearly speak against a cascade-like metastatic process.

One major argument in favor of the metastatic potential of metastases is the involvement of regional lymph nodes around the target organ of the metastastatic process [11], which might be locally far away from the primary tumor. According to an autopsy analysis, the involvement of mediastinal lymphnodes in patients with lung metastases is about 33% [24]. The data of Pfannschmidt et al. inidicate the percentage of noncontiguous mediastinal lymph nodes (49% in sarcomas, 22.9% in renal cell cancer and 20.3% in colorecatal cancer) [25]. The authors note that pulmonary and hilar lymph node metastases are “believed” to originate from lung metastases. However, pulmonary and hilar lymphnodes are frequently observed without lung metastases in the expected lung segments. Beside the explanation that distant metastases are the origin of lymph node metastases there are other hypotheses that can explain this finding. Sleeman for instance assumes that cells initially metastasize to lymph nodes and later spread to the lung or other organs [26]. Migrating tumor cells are capable of traversing the interstitial space and invading lymphatic vessels. Therefore these metastases represent distant metastases rather than regional lymph node metastases. Furthermore, investigations of clonal relationships suggest that all metastases are based on one subclone of the primary tumor, rather than being based on a subclone of a metastasis [27, 28]. Gene expression analysis supports these results suggesting a continued evolution based on a common parental clone [29].

2. Is the tumor growth of metastases of certain primary tumors predictable?

Spratt and Spratt [30] investigated the natural growth rate of 118 untreated pulmonary metastases. Based on the measurement of the lesion´s diameters on thoracic roentgenograms the authors calculated the tumor doubling time (TDT) for pulmonary metastases. Whereas metastases from colorectal cancers had a mean TDT of 109 days, the

TDT for sarcomas and very young patients regardless of the primary tumor type, were significantly shorter (42 and 37 days respectively).

In a recent study dealing with patients (n=42) who had both hepatic and pulmonary metastases from colorectal cancers the TDT of the pulmonary lesions was as short as 70 days [31].

Chojniak and Younes [32] assessed the TDT using computer tomography. They analysed 408 pulmonary nodules in 22 patients and found a considerably different behavior of lesions in the same patient. The median TDT was 118 days and, like other publications, a wide range of the TDT (22 – 930 days) could be appreciated.

3. Is there an interval between the detection of pulmonary metastases and the resection that reliably predicts metastatic progression?

Maniwa et al. [13] performed a retrospective analysis to investigate the correlation between the interval form diagnosis of metastases to metastasectomy and the probability of an early relapse and reduced survival. They found a significantly longer survival for patients (n=33) with an interval longer than 3 months between the diagnosis of metastases and the resection compared to patients (n=35) with a interval shorter than 3 months. Their retrospective analysis of 68 patients with pulmonary metastases from different primary tumors confirmed better survival for patients with an interval longer than three months between detection and resection of the metastases. However the 5-year-survival of patients with the shorter interval was around 55% and it remains unclear what therapy option should be offered to these patients. Moreover, with 2.9 versus 7.1 months there was a big difference between both groups concerning the average interval.

In contrast, Mountain et al. [33] in 1984 could not prove a correlation between the interval from diagnosis to metastasectomy and the overall survival. This was true for both sarcomatous and carcinomatous primary tumors. An adverse effect of a delayed operation was found in a retrospective study of 38 patients with metastatic colorectal cancer (table 2, van Halteren [6]). The group of patients with delayed metastasectomy was quite small (n=16) and in two patients the interval was remarkably long (15 and 51 months). Moreover, the delayed operation negatively affected only the disease-free survival and had no impact on the overall survival.

Elias et al. [34] argue that the classical approach of waiting 3 to 6 months before the resection of synchronous liver metastases from colorectal cancer is illogical. This opinion is based on a comprehensive review of tumor doubling time (TDT) indicating only a 5% to 10% chance of detecting new metastases within this time frame.

Ueno et al. [35] compared 52 patients, who had a resection of liver metastases from colorectal cancer immediately after the detection of the lesions with 27 prospectively scheduled patients who underwent resection of metastases following radiologic re-evaluation after a 3 month interval. Only two of the 27 patients were excluded from surgery due to progressive disease. Since the 3 years survival rate was slightly lower, although not significant, in the delayed group, no clinical benefit from delayed resection could be proved.

4. Timing of chemotherapy within a multimodal approach

Pulmonary metastasectomy is most often performed for metastases of colorectal cancer and renal cell cancer. In particular regarding these primary tumors there is no consensus among oncologists about the timing of chemotherapy for either synchronous or metachronous metastastic disease. Chemotherapy is administered on discovery of metastases, following local therapy, or not at all in case of complete resection of metastases [36]. This is true for different primary malignancies depending on the efficiency of the respective chemotherapeutic drugs.

Scartozzi et al. [37] achieved a significantly longer median survival time for patients with metastatic colorectal cancer, if the resection of liver metastases was performed within 2 months following the discovery of the metastases, meaning without neoadjuvant chemotherapy (48 months vs. 31 months; p=0,0358). They conclude that metastasectomy should be the initial treatment and neoadjuvant chemotherapy should only be considered for the downsizing the tumors to obtain resectability.

In a retrospective analysis of patients operated on lung metastases between 1983 and 2006, Le Pimpec Barthes et. al [38] ascertained a significantly better survival for patients treated after 1998. Neoadjuvant chemotherapy was supposed to be one of the reasons for this improvement.

Daliani et al. [39] recommend systemic therapy after nephrectomy for patients with renal cell cancer and synchronous metastases. Based on a prospective study including 38 patients, 34 of whom had received an adjuvant treatment over 4 months, they concluded, that regressive or stable disease after that period represents a good predictor for long term survival. The median OS was 4.7 years. However, the benefit of the added systemic therapy remains unclear. Other publications could not prove a benefit for patients with complete resection of metastases related to renal cell cancer [40]. For sarcomatous metastases routine administration of additional chemotherapy in case of complete resection does not seem to improve survival rates [41]. Absent progression of the disease under neoadjuvant

chemotherapy, even for patients with multiple metastases, promises the chance of long time survival (49% at 3 years and 32% at 5 years [41]). Therefore, neoadjuvant chemotherapy might be a tool to detect patients who are suitable for metastasectomy despite having multiple and synchronous lesions and possibly even extrathoracic manifestations.

Several publications reviewing the outcome of pulmonary metastasectomy in patients with different primary tumors fail to prove an advantage of pre- or postoperative chemotherapy [40, 42]. However, chemotherapy is administered in a non-systematic way in those retrospective reviews and according to other publications chemotherapy may improve the survival rates significantly [38].

5. Are repeated operations for intraoperatively missed very small metastases associated with worse improved survival?

Pulmonary nodules as small as 2mm can be detected using modern helical CT scanners with small axial slices. Thus it can be assumed that most palpable malignant lung lesions can be diagnosed preoperatively. By means of a computer-aided detection (CAD) system the preoperative diagnostic yield might be further improved [43].

The size of non-imaged metastases detectable by intraoperative palpation is between 0.4 and 0.8cm [44]. However, under certain circumstances it can be difficult to palpate very small lesions. The palpation can be aggravated due to an incomplete collapse of the non-ventilated lung, central location of the metastasis, or in case of redo operations. Consequently, a delayed metastasectomy could be considered, with the intention of resecting the tiny metastases that might have been overlooked at initial diagnosis.

According to several recent studies, repeated surgical procedures for pulmonary metastases do not influence the survival rate negatively. In a retrospective analysis including 137 patients with pulmonary metastases of colorectal cancers, there was no significant difference in the 5-year survival rate between 121 patients having a single metastasectomy and 16 patients with repeated procedures (55.1% vs 59.5%; $p=0.79$)[45]. Park et al. [46] likewise analyzed patients with colorectal cancers and found a 5-year survival of 79% after the second operation and 78% after the third metastasectomy. In a review including patients with different primary tumors, Kandioler et al. [47] demonstrated 5- and 10-year survival rates for patients (n=35) with repeated metastasectomies of 48% and 28%, respectively.

Discussion:

Several recent publications summarize the rationale and the practical approach to pulmonary metastasectomy [48, 49, 50]. In summary, pulmonary metastasectomy is a widely accepted therapeutic option for metastases of various solid malignant tumors [2, 3, 5, 51, 52]. However, it should be noted that the effectiveness of metastasectomy has not been proven in randomized trials to date [31, 53]. Due to the lack of randomized data, a distinct variability among thoracic surgeons regarding the approach to pulmonary metastasectomy is evident [48]. Of note, this is true for the technique of pulmonary resection, the integration of other treatments and the extent of lymphadenectomy. About 15 to 20% of patients with pulmonary metastases show mediastinal or hilar lymph node involvement [49]. In the majority of series lymph node involvement was an adverse prognostic factor [10, 49]. In contrast, there are publications not showing statistically relevant influence of hilar or mediastinal lymph node metastases on long term survival [52]. Undoubtedly complete surgical resection, disease free interval (DFI), metastases to other organs and the histology of the primary tumor are independent prognostic factors [50, 52, 53].

As stated above, histology of the primary tumor is one of the crucial predictors for outcome after pulmonary metastasectomy. The authors of the International Registry of Lung Metastsaectomy (ILRM) decided to present the data of 5206 cases in four groups: epithelial tumors, soft tissue and bone sarcomas, germ cell tumors and melanoma [2]. Primarily cocncerning metastases of germ cell tumors and osteosarcomas, surgery aims only to resect residual disease while chemotherapy is the critical therapy modality [50, 54]. Based on the resected lesions further therapy can be adapted. Pulmonary metastasectomy for pulmonary metastases of melanomas should be reserved for highly selected patients and should be combined with systemic therapy [48, 50]. About 50% of pulmonary metastasectomies are performed for metastases of colorectal cancers and sarcomas. However, for several other

epithelial tumors feasibility of pulmonary metastasectomy was approved, such as for renal cell cancer, head and neck tumors [50], gastric cancer [55], breast cancer [56] and thyroid malignancies [57].

Only a few publications directly analyzing the outcome depending on a diagnostic interval between diagnosis and metastasectomy are available, three of them analyzing pulmonary metastases and two liver metastases. The only papers demonstrating an advantage to delayed operation are published by Tanaka [14] and Maniwa [13]. They recommend an interval of at least three months between the detection of pulmonary metastases and the metastasectomy, referring to a retrospective analysis of 68 patients which shows a significantly better survival for patients with the delayed operation. The second analysis dealing with pulmonary metastases found an adverse effect on disease-free survival but no difference in the overall survival. The review by Mountain et al. [33] could not prove a correlation between the interval and overall outcome. The two papers dealing with liver metastases found a lower survival rate in the group with the delayed operation. Based on analysis of the tumor doubling time, the chance to detect new metastases is around 5 to 10 % within 3 months. Corresponding with the systematic review of Detterbeck et al. [5] an advantage of a diagnostic delay period prior metastasectomy cannot be proven based on the available data. Bearing in mind the data of Tanaka [14] and Maniwa [13] along with several reports about an early multifocal relapse, further investigations, especially for patients with more advanced disease, are justified.

The risk of metastastic spread originating from both distant and lymph node metastases, is controversially discussed in surgical literature [5, 9]. It is claimed, that this assumption is based on animal experiments and autopsy data [1]. Saito et al. [58] propose a metastatic cascade corresponding to the development of lymph node metastases originating from pulmonary metastases. This assumption is based upon autopsy reports of the 1970-ies [59]. The authors themselves emphasize, that the results should be interpreted with caution.

The decision-making process would be crucially influenced by the assumption of metastases being able to metastasize [1]. Particularly the decision for a metastasectomy within a narrow time frame should be influenced by the answer to this question.
From a present-day perspective the only experimental proof (Hoover and Ketcham 1975 [16]), that metastases themselves metastasize, has lost its convincing character. The alternative source for the metastatic spread in this parabiosis experiment are the circulating tumor cells of the primary tumor.

Hölzel et al. [23] conclude, after the analysis of a considerable amount of data from breast cancer patients, that a complete resection of the primary cancer would prevent further metastases. According to the authors opinion these data clearly show that true metastases, neither distant nor lymph node metastases, spawn new metastases. Moreover, investigations of clonal relationships and gene expression analysis suggest that all metastases are based on a common parental clone of the primary tumor undergoing a continued evolution [27, 28, 29].

No general recommendations concerning the timing of chemotherapy within a multimodal therapy concept can be given. Review of the literature failed to prove an advantage of adding chemotherapy in case of complete resection of all detectable tumor manifestations for metastases of renal cell cancer and colorectal cancer. Bearing in mind the decreasing long time survival of patients with multiple metastases, aggressive histology of the primary tumor or additional lymph node or extra pulmonal metastases, the necessity of close cooperation with specialized oncologists becomes apparent [50]. Neoadjuvant regimens could be a tool to get further information about the malignant behavior of the disease, and progression under chemotherapy might be an argument against aggressive surgical approaches in advanced disease [41].

Repeated metastasectomies are not per se a negative predictor for the overall survival. Therefore, it seems unjustified to delay the metastasectomy in order to prevent overlooking very small metastases. This is particularly true, since the tumor doubling time can strongly vary, as mentioned above. Therefore it is not possible to specify a sensible time interval. Thus, the treatment of metastatic disease requires a multidisciplinary approach. The indication for chemotherapy has to be discussed with respect to the specific tumor for every individual patient.

The majority of data evaluated in this review are based on metastectomies for metastases of colorectal cancer, soft tissue sarcoma and renal cell carcinoma. Together these represent more than 50% of the performed metastasectomies. The results are applicable to metastases of most epithelial tumors. However, for each primary tumor specific therapy options have to be considered and a close co-operation with onclogists is mandatory. Primarily concerning metastases of germ cell tumors and osteosarcomas, surgery aims mainly to resect residual disease, while chemotherapy is the critical therapy modality. For other tumor entities, such as melanoma and renal cell cancer, new promising systemic therapy options have recently become available. For primary tumors with unfavorable

prognosis, such as melanoma or pancreatic cancer, a delayed metastasectomy seems appropriate.

Randomized data regarding metastasectomy, and pulmonary metastasectomy in particular, are not available to date. These data are needed to clarify on the one hand the effectiveness of metastasectomy at all and on the other hand several questions concerning practical issues of this therapy. To get these randomized data will be fraught with difficulties, but nevertheless best efforts should be made to provide these data. One trial, dealing with metastases of colorectal carcinomas, is in progress [53]. The results of this study will hopefully contribute to answer some of the crucial questions.

Based on the data available to date we conclude the following concerning the optimal timing of pulmonary metastasectomy: On the one hand, the majority of data support that metastases cannot metastasize themselves. Therefore, there is no necessity to expedite the timing of metastasectomy in order to prevent further metastastatic spread. On the other hand no advantage of a routinely delayed operation, such as a re-staging following an interval of 3 months, could be proven.

In summary 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. It seems justified to perform a delayed operation, if the indication for resection is questionable due to a high risk of early multilocal relapse.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence this work.

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Arguments for prompt operation	Question to be answered
- 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 pneumonectomy 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?

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

Author / year	primary tumor / metastases	Short interval*	Long interval*
Tanaka 2008 [14]	different primary tumors / lung metastases	35 pts. within 3 months 5-year-survival ~**55%**	33 pts. beyond 3 months 5-year-survival ~**95%**
Van Halteren 1995 [6]	colorectal cancer	<1 month (n=22) **longer** disease-free survival	>1month up to 51 months (n=16) **shorter** disease-free survival
Scartozzi 2011 [37]	colorectal cancer / **liver metastases**	44 pts. within 2 months without neoadj. CT median survival **48 month**	60 pts. beyond 2 months with neoadj. CT median survival **31 month**
Ueno 2011 [35]	colorectal cancer / **liver metastases**	52 pts. within 3 months 3 years survival rate **57,1%**	25 pts. beyond 3 months (2 pts. were excluded) 3 years survival rate **52,2%**

Table 2: Timing of metastasectomy. *interval between detection of metastases and metastasectomy; CT – chemotherapy