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Prognostic analysis of pulmonary metastasectomy

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Abstract
Introduction: Metastasectomy is the most frequent surgical resection undertaken by thoracic surgeons, being the lung is the second common site of metastases. Pulmonary metastasectomy is currently indicated for patients with the following criteria: primary tumor controlled, possibility of complete resection verified by computed tomography (CT) of the chest, pulmonary function and performance status compatible with the proposed lung resection, and lack of another available treatment that would be more effective than the surgical procedure.

Material and Methods: This is a prospective study conducted in the Department of Surgical Oncology at Kidwai Memorial Institute of Oncology from July 2018 to December 2019. all patients who underwent pulmonary metastasectomy were included in this analysis. Individual patient data were obtained from the case records. A total of 60 patient records were obtained, of that only 47 cases were taken analysis. Patients who underwent planned sequential or staged metastasectomies were considered to have single metastasectomy and redo surgery.

Results: A total of 60 patients underwent pulmonary metastasectomy, of which only 47 patient records were taken for analysis. Overall there were 27 males (57.4%), and the mean age was 32 years (median 29 years, range 14-65 years). Sarcomas, both soft tissue and osteogenic constituted 64 % of pulmonary metastasectomies (osteosarcoma – 34%, sarcoma – 30%), and the rest comprised of epithelial tumors (31%, which includes various subsites like breast, parotid, cervix, endometrium, testis and rectum [13 %]) and other sites (2 patients 4%, Giant cell tumor of bone and choriocarcinoma).

Conclusions: Good prognostic variables like increasing DFI (> 1 year), ability to do R0 resection, solitary metastasis, size of the lesion less than 1 cm, and absence of mediastinal nodal positivity showed a trend towards improved survival. Good prognostic group selected on the basis of the risk factors like completely resected lesions, DFI and number of metastases show a difference in survival between good risk and poor risk groups (87% and 64% at 36 months).

Keywords: Pulmonary metastasectomy, metastatic, prognostic analysis

Introduction

Metastasectomy is the most frequent surgical resection undertaken by thoracic surgeons, being the lung is the second common site of metastases. [1] Pulmonary metastasectomy is currently indicated for patients with the following criteria: primary tumor controlled, possibility of complete resection verified by computed tomography (CT) of the chest, pulmonary function and performance status compatible with the proposed lung resection, and lack of another available treatment that would be more effective than the surgical procedure [2, 3].

After the liver, the lung is the second most common site for metastatic involvement in neoplastic disease when all histologies are considered [4]. Consequently, 20–54% of patients with cancer will have pulmonary metastases at some point in the natural history of their disease [5]. In the absence of extrathoracic metastases (approximately 25% of patients with disseminated disease), complete resection is associated with increased survival, regardless of histology. With appropriate patient selection, life expectancy will often be improved with pulmonary metastasectomy. Cures are reported, either with resection alone or in combination with chemotherapy [6].

Even in the context of unresectability, surgical forms of palliation may serve to improve quality of life. For other patients (e.g., nonseminomatous germ cell tumors) surgery may have a more diagnostic role such as defining residual disease potentially amenable to salvage forms of therapy [7].

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Material and Methods
This is a prospective study conducted in the Department of Surgical Oncology at Kidwai Memorial Institute of Oncology from July 2018 to December 2019. all patients who underwent pulmonary metastasectomy were included in this analysis. Individual patient data were obtained from the case records. A total of 53 patient records were obtained, of that only 42 cases were taken analysis. Patients who underwent planned sequential or staged metastasectomies were considered to have single metastasectomy and redo surgery.

Analysis was done using SPSS 25th statistical package. Following variables were tested: DFI, unilateral or bilateral presentation, number of metastases, histological type and site of primary tumor, margin status, size of metastases, mediastinal nodes. Survival was calculated from the time of first metastasectomy to the last date of follow up by means of Kaplan – Meier estimate.

Results
A total of 60 patients underwent pulmonary metastasectomy, of which only 47 patient records were taken for analysis. The rest 13 patients were excluded based on various reasons, benign pathology (5), different histology (3), unresectable disease (3). These 47 patients underwent 50 metastasectomies (3 for recurrent disease). Staged bilateral metastasectomy was considered as single procedure. Survival was calculated from the time of first metastasectomy to the last date of follow up. Average follow up was 28 months (range 4 months to 84 months). 12 patients were lost to follow up after a variable period of follow up ranging from 19 months to 60 months (average – of 32 months).

Overall there were 27 males (57.4%), and the mean age was 32 years (median 29 years, range 14-65 years). Sarcomas, both soft tissue and osteogenic constituted 64 % of pulmonary metastasectomies (osteosarcoma – 34%, sarcoma – 30%), and the rest comprised of epithelial tumors (31%, which includes various subsites like breast, parotid, cervix, endometrium, testis and rectum [13 %]) and other sites (2 patients 4%, Giant cell tumor of bone and choriocarcinoma).

In the whole series the, 25% of patients had DFI of 0 to 10 months, 34% had DFI of 13 to 35 months and 41 % had DFI of > 36 months. The median DFI was 32.4 months. Most common presentation was unilateral (85%). The surgical approach was monolateral thoracotomy in 85 % and bilateral staged thoracotomy in 15 %. For large majority of tumours wedge resections (70%), were the procedure most commonly done, lobectomies (30%) unilobar or bilobar were usually done for large lesions or centrally placed lesions not amenable to wedge resections.

On the basis of pathological analysis 58% of patients had only single metastases, 32% had 2 to 3 metastases and around 10% had > 4 metastases. The resections were complete (R0) in 89% and R1 in 11 %. The maximum numbers of metastases were 23 in one patient with NSGCT of testis.

Majority of the metastases were of size between 2 to 4 cm (70%), lesions less tha 1 cm and more than 4 cm accounted for 9% and 21 % respectively.

Lympnodal dissection was done in 10 cases of the total 13 lobectomies and metastases to these lymph nodes were found in only 3 cases. 7 patients reoccurred of which only two patients underwent redo metastasectomy.

There was no operative mortality in the entire cohort of patients. The overall survival irrespective of the type of primary in this study was 67% at 5 years.

The following variables were tested for assessing the impact on prognosis:

Completeness of resection (R0 Vs R1)
The overall survival was 79% at 36 months for patients with R0 resection. In patients who had R1 resection, none of them survived beyond 45 months, overall survival was only 21% at 36 months. This difference was not found to be significant in both univariate and multivariate analysis using Cox regression analysis.

Disease free interval (DFI)
For patients with a DFI of 0 to 11 months, the overall survival was 71% at 36 months. For patients who had DFI of 12 to 35 months the overall survival was 75 % at 36 months. Patients who had DFI > 36 months the overall survival was 75% at 36months. This was also tested for significance in both univariate and multivariate analysis using Cox regression analysis and was not found to be significant.

Number of proven metastases
Patients with single metastases had survival of 81.3% and 68% at 36 months and 60 months respectively. For the patients who had 2 to 3 metastases the survival was 62% at 36 months, and as no further events occurred beyond this, survival at 60 months could not be calculated. In patients who had > 4 metastases the survival was 74% at both 36 months. This variable also was not found to be significant in both univariate and multivariate analysis.

Histological type of tumor
The overall survival among patients with osteosarcoma was 74.6% at 36 months. In patients with metastatic soft tissue sarcoma was 71.2% at 36 months. The overall survival in patients with metastatic rectal tumors was 67.8% and 63.7% in patients with other epithelial carcinoma at 36 months respectively.

Mediastinal nodes
In patients who had positive mediastinal nodes none of them survived beyond 10 months. While in patients who were node negative 75% survived at 36 months and 25% at 60 months respectively.

Unilateral and bilateral metastases
The survival in patients who had unilateral metastases was 73.5% and 62.9% at 36 months and 60 months respectively, while patients who had bilateral metastases the survival was 64.3 % and 64.8% at 36 months and 60 months respectively this was also not found to be significant in univariate and multivariate analysis.

Size of the metastases
Survival among patients who had lesions less than 1 cm were 74% at 36 months, while larger lesions >4 cm and lesions 1 to 4 cm had survival of 64% and 69% respectively. However in both univariate and multivariate analysis this not found to be significant.

Recurrence
7 patients (14.8%) recurred within a mean period of 20 months (range 2 to 50 months). Only 2 patients underwent redo metastasectomy and all three had a mean survival of 34 months

(range 22 to 50 months) and only one expired, however all patients who did not undergo metastasectomy expired within a mean period of 4 months.

Prognostic grouping
A prognostic group was made based on number of metastases and DFI. They were considerd low risk Group I – Resectable, no risk factors (DFI > 36 months and single metastases), intermediate risk, Group II (DFI < 36 months or multiple metastases), and high risk, Group III (DFI <36 months and multiple metastases). In patients who where in Group III the survival was 64% at 36 months, in Group II there was 74% survival at 36 months and 50 % at 60 months respectively, and in patients with Group I the survival of 87% at 36 months. This was also not found to be significant in both univariate and multivariate analysis.

Post-operative mortality and complications
There was no 30-day post-operative mortality and only 7% morbidity (4 patients, 3 were cardiac events in the form of SVT, and the other was pulmonary which required postoperative mechanical ventilation).

Discussion
The benefit of pulmonary metastasectomy is still questioned by physicians because patients are offered this treatment to a highly select group of patients and on a highly individualized basis depending on the philosophy and policy of the treating physician and the institute. The prognosis of these patients without surgical resection is still fully not known and its unlikely that the benefit of surgical resection compared with supportive care alone could alone be defined in randomized manner prospectively. Marcove *et al*. documented that the natural history of unresected pulmonary metastasis was associated with 50% mortality at 1 year, 87% mortality at 2 years, 94% at 3 years and none survived 5 years [8]. With improved medical and surgical treatments, it has been possible now to attain a 5-year survival of 49% [9].

In this study, the overall survival in the entire cohort of patients was 67% at 5 years which is higher than seen in the literature (34% at 5 years) because of the selection bias and small number of patients [10]. There was a tendency to offer metastasectomy to patients who had longer disease-free interval as can be seen in our frequency of DFI where almost 73% of patients had DFI of greater than 12 months and among them majority had DFI of greater than 36 months (41%). Other problem in this study was about 30 % of the patients were to lost to follow up after an average time of 32 months (range 19 to 60 months), hence information on events beyond this was unavailable so as to give a meaningful survival figures at 5 years. Though the variables like decreasing DFI, increase in no of metastasis, increase in size of lesion, R1 resections, bilateral presentation and mediastinal lymphnode positivity were associated with decreased survival at 3 years, these were not found to be significant in univariate or multivariate analysis using Cox regression analysis.

Epithelial tumours had lower survival at 3 years in comparison with sarcomatous tumours which is also in occurrence with the literature [11]. Patients with osteosarcoma had longer survival than soft tissue sarcoma at 36 months after metastasectomy (75% and 71% respectively). The reasons may be multifactorial, like chemotherapy offered for patients who had synchronous metastases, and probably because of the inherent natural history of the lesion developing after a long DFI. Also, it is a fact that synchronous metastases in osteosarcoma need not represent a more aggressive disease, which is however not true in patients with epithelial cancer.

Our attempt to identify a good prognostic group based on the risk factors like completely resected lesions, DFI and number of metastases was not successful as it failed to show significance in univariate and multivariate analysis, though there was difference in survival between good risk and poor risk groups (87% and 64% at 36 months).

Another observation in this study was in patients who recurred after metastasectomy and could undergo a R0 redo metastasectomy, had an average survival of 34 months (22 to 50 months) in comparison to patients who could not undergo metastasectomy as none of them survived beyond 7 months (mean of 4 months). This was also observed in the International Registry of Lung Metastasis study [12]. This good survival observed in patients who underwent redo metastasectomy can be explained by the inherent biology of the lesion as these patients had an average time to recurrence of 22 months (15 to 41 months).

However, in spite of all these shortcomings it can be confirmed that metastasectomy is a potentially curative treatment that can be done safely with low mortality or morbidity. In our series, there was no 30-day post-operative mortality and only 7% morbidity (4 patients, 3 were cardiac events in the form of SVT, and the other was pulmonary which required postoperative mechanical ventilation).

Conclusions
Good prognostic variables like increasing DFI (> 1 year), ability to do R0 resection, solitary metastasis, size of the lesion less than 1 cm, and absence of mediastinal nodal positivity showed a trend towards improved survival. Good prognostic group selected on the basis of the risk factors like completely resected lesions, DFI and number of metastases show a difference in survival between good risk and poor risk groups (87% and 64% at 36 months). Although these were not found to be significant in univariate or multivariate analysis using Cox regression analysis.

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