Title

Pulmonary Metastasectomy – Analysis of survival and prognostic factors in 243 patients.

Running Head

Cheung et al. Pulmonary metastasectomy.

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3 Tables and 2 Figures

ABSTRACT

Introduction

Pulmonary metastases are a sign of advanced malignant disease. Interdisciplinary management of metastatic cancer mandates the consideration of all treatment options, and in select patients pulmonary metastasectomy can be performed with curative intent. This study aims to analyse the prognostic factors associated with survival and optimise the selection of surgical candidates. The sarcoma subset analysis aims to examine the role of multiple repeat resections for pulmonary metastatic recurrence.

Methods

A total of 243 patients were analysed in this retrospective cohort study. Overall survival was estimated using Kaplan-Meier analysis. Univariate analyses with log-rank tests and multivariate analysis with Cox proportional hazards model were undertaken to determine the independent prognostic factors for survival.

Results

Multivariate analyses identified germ cell cancer ($p = 0.01$) and a disease free interval of > 36 months ($p = 0.006$) as significant independent prognostic factors for improved survival, whilst synchronous metastases ($p = 0.04$), multiple metastases ($p = 0.005$) and incomplete resection ($p < 0.001$) were identified as significantly poor prognostic factors. Subset analyses identified ≥ 2 repeat resections within the sarcoma cohort was associated with an increased median survival of 63.5 months ($p = 0.04$).

Discussion

In select patients, pulmonary metastasectomy can be performed with curative intent and have associated long term survival benefits. Patients presenting with recurrent sarcoma pulmonary metastases should be considered for repeat metastasectomy.

Word count: 2067 words

INTRODUCTION

The lungs are the most common site of metastatic disease in many primary malignancies, with colorectal cancer, osteogenic and soft tissue sarcoma, head and neck cancer, malignant melanoma, germ cell tumours and renal cell carcinoma exhibiting the highest incidence of pulmonary metastatic spread [1-8]. Metastatic spread is acknowledged as a sign of advanced malignant disease and confers much higher morbidity and mortality rates. However in select patients, complete surgical excision of pulmonary metastases can be performed with low perioperative morbidity and mortality [1,3,4,6,9]. The criteria for selecting patients for pulmonary metastasectomy has been gradually expanding since first proposed by Thomford and colleagues in 1965 [10]. Pulmonary metastasectomy is now considered suitable for patients with:

1. Control or complete eradication of primary disease,
2. Absence of widely disseminated or uncontrollable extrapulmonary disease,
3. Completely resectable lung metastases,
4. Sufficient cardiopulmonary reserve to tolerate surgery,
5. Lack of a better alternative systemic therapy [6,7,11-15].

Primary tumour type, disease free interval (DFI), completeness of resection, surgical approach, number and laterality of lung metastases, and lymph node metastases are also prognostic factors that play a dynamic role in determining survival outcomes, but do not constitute absolute selection criteria. With the rapid evolution of systemic therapy and advances in diagnostic imaging there is a definite need to continue reviewing these prognosticators to identify those patients who will benefit most from pulmonary metastasectomy and those who should avoid unnecessary surgery. The objective of this study is therefore to analyse the prognostic factors associated with overall survival and to optimise the selection process. Our sarcoma subset analysis aims to examine the role of multiple repeat pulmonary metastasectomy for metastatic recurrence.

METHODS

A retrospective analysis of 243 patients undergoing pulmonary metastasectomy over a 10 year period from 1st January, 2005 to 31st December, 2014 was conducted. Patients were identified on an existing thoracic surgery database. Medical records, both electronic and paper records, were comprehensively reviewed for each patient to collect information on patient demographics and surgery characteristics. All patients underwent computed tomography (CT) of the chest prior to surgery to determine resectability of metastases and the majority of patients underwent positron emission tomography (PET) to exclude widely disseminated extrapulmonary disease. Patients with bilateral pulmonary metastases underwent planned two stage pulmonary metastasectomies, performed approximately 4 weeks apart. Following discharge from hospital, all patients were then followed up with clinical and radiological evaluation (chest X-ray and CT scan) at 3 to 6 monthly intervals depending on tumour histopathology.

Statistical Analysis

Overall survival was calculated from the date of pulmonary metastasectomy until the date of death or date of last follow up. Disease free interval (DFI) was defined as the time between the completion date of primary cancer treatment to the date of diagnosis of secondary metastases. Time to resection was calculated from the date of diagnosis of pulmonary metastases to the date of first pulmonary metastasectomy. For patients undergoing planned two stage pulmonary metastasectomies for bilateral nodules the date of first pulmonary metastasectomy was used to calculate time to resection and date of second pulmonary metastasectomy used to calculate time to follow up or overall survival. Patients were risk stratified into the four groups defined in the International Registry of Lung Metastases (IRLM) for further analysis, Group I: resectable, no risk factors (DFI > 36 months, and single metastases); Group II: resectable, one risk factor (DFI < 36 months or multiple metastases); Group III: resectable, two risk factors (DFI < 36 months and multiple metastases); Group IV: unresectable [6]. The years of life lost due to cancer was calculated by directly comparing each deceased individual's age at death, and the expected life years remaining at the age of primary cancer diagnosis according to the Australian Bureau of Statistics (ABS) life expectancy tables, adjusted for year, state and sex [16].

Statistical analyses were performed using R Studio ® (version 0.99.902, RStudio Inc., Boston, MA). Overall survival was estimated using the Kaplan-Meier method. Comparison groups for univariate and multivariate analyses were pre-determined. Univariate analyses to evaluate differences in overall survival between comparison groups were performed using log-rank tests. Multivariate analyses to determine the independent prognostic factors for overall survival were performed using the Cox proportional hazards model. Prognostic factors were analysed in the multivariate model if the univariate *p*-value was < 0.10 or if considered a clinically significant variable. A *p*-value < 0.05 was considered statistically significant and a *p*-value < 0.001 was considered highly statistically significant.

RESULTS

Study Population and Surgery Characteristics

The follow up period was until death or to a median follow up of 55.8 months (range = 7.4 to 131.1 months). Sarcoma metastases, including soft tissue and osteogenic, represented the predominant primary cancer type (Table 1). The median time to resection was 91 days (range = 0.2 to 107.6 months) and the majority of patients (83%) underwent a video assisted thorascopic surgery (VATS) approach (Table 2). Complete (R₀) resection was achieved in 236 patients (97%), but 7 patients (3%) were found intraoperatively to have unresectable disease and consequently had incomplete (R₁/R₂) resections. These 7 patients were found to have diaphragmatic tumour invasion (3 patients), extensive major vessel vascular invasion (2 patients) and innumerable parenchymal and/or chest wall metastases (2 patients). Metastatic recurrence was

diagnosed upon follow up surveillance in 147 patients (60%), with 86 patients exhibiting recurrence within the lungs and 61 patients exhibiting extrapulmonary recurrence. Repeat pulmonary metastasectomy was subsequently performed on 53 patients (22%). The 4 patients that underwent 5 repeat resections had been diagnosed with metastatic sarcoma (3 patients) and thyroid cancer (1 patient). The sarcoma subset exhibited the highest rate of recurrence. Metastatic recurrence was detected in 62 of 92 sarcoma patients (67%), with 42 exhibiting pulmonary recurrence and 32 of these patients underwent repeat metastasectomy.

Survival & Prognostic Factors

Overall median survival was 57.5 months (95% CI = 42.0 to 78.2 months). Estimated 3-year, 5-year and 10-year survival rates were 60.9%, 46.9% and 30.0%, respectively. At the time of final analyses, 117 patients (48.1%) were alive and 93 patients (38.3%) were alive without evidence of disease. The 126 deceased patients (52%) exhibited a median years of life lost due to cancer of 21.6 years. Germ cell cancer did not reach median survival and exhibited the highest estimated 5-year survival of 92.3%. Melanoma was shown to hold the worst overall survival with a median survival of 22.4 months.

Univariate analyses identified colorectal cancer ($p = 0.01$) and germ cell cancer ($p = 0.02$), alongside a DFI of > 36 months ($p = 0.04$) as factors associated with improved overall survival (Table 3). A less favourable prognosis was identified in patients with multiple resected metastases ($p = 0.001$) and incomplete (R_1/R_2) resection ($p < 0.001$). Patients risk stratified within the IRLM Group III ($p = 0.002$) and Group IV ($p < 0.001$) also demonstrated an associated poor prognosis.

Multivariate analyses identified germ cell cancer ($p = 0.01$) and a DFI of > 36 months ($p = 0.006$) as significant independent prognostic factors for improved overall survival, whilst synchronous metastases ($p = 0.04$), multiple metastases ($p = 0.005$) and incomplete (R_1/R_2) resection ($p < 0.001$) were identified as significant poor prognostic factors for overall survival (Figure 1). No significant difference in overall survival between open thoracotomy and VATS surgical approaches was found. Post-operative complications were reported in 20 patients (8.2%) and post-operative mortality occurred in 1 patient (0.4%) following the development of Acute Respiratory Distress Syndrome (ARDS) and respiratory failure.

Sarcoma Subset

Univariate analyses of sarcoma patients exhibiting pulmonary metastatic recurrence identified ≥ 2 repeat metastasectomies was associated with a significantly higher median survival of 63.5 months and estimated 5-year survival of 63.6% ($p = 0.04$), when compared with no repeat metastasectomy (median survival 22.7 months and estimated 5-year survival 20.0%) following pulmonary recurrence (Figure 2). There was no significant associated survival benefit for patients undergoing 1 repeat metastasectomy (median survival of 33.7 months and estimated 5-year survival 37.4%) compared with no repeat resections.

DISCUSSION

Pulmonary metastasectomy remains an integral treatment option within the interdisciplinary management of metastatic cancer. In the selection of surgical candidates DFI provides a clinical impression of the either indolent or aggressive nature of a malignancy and is consistently shown to have a significant association with long term survival outcomes [1,3,6,11,13,17-21].

Within our study cohort, DFI was defined as the period of time between the completion date of treatment for the primary malignancy and the date of diagnosis of metastatic spread to any location. While this can provide a clinical reflection of tumour biology and natural history, it is dependent on symptoms of relapse and the degree of post-operative radiological surveillance. A DFI of > 36 months was found to hold significantly

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better overall survival ($p = 0.006$) in our study cohort, with a median survival of 101.5 months compared to a median survival of 50.9 months for those patients presenting with a DFI of ≤ 36 months.

In 2006, Rena and colleagues compared DFI periods of 0 – 36 months and > 36 months in 202 patients diagnosed with pulmonary metastases from a variety of primary epithelial tumours. A DFI of > 36 months was demonstrated to hold significantly improved prognosis, with 5-year and 10-year actuarial survivals of 52% and 17%, respectively [20]. Our results similarly demonstrate more optimistic 5-year and 10-year survival outcomes of 57% and 33%, respectively, for patients exhibiting a DFI of > 36 months. These results have corroborated Pastorino and colleagues' findings in the International Registry of Lung Metastases, which first outlined that a DFI of > 36 months is associated with improved 5-year and 10-year survival rates of 45% and 29%, respectively, when compared with a DFI of 12 – 35 months (31% 5-year and 22% 10-year survival) or < 12 months (33% 5-year and 27% 10-year survival) [6].

During follow up, 45.7% of patients within our sarcoma subset developed recurrent pulmonary metastases and 76.2% of these patients underwent repeat metastasectomy. Soft tissue sarcomas and osteosarcomas not only exhibit a natural proclivity to metastasise to the lungs, but a high recurrence rate following complete pulmonary resection ranging from 48.3% to 66.0% [3,22]. Within our cohort, patients undergoing ≥ 2 repeat resections exhibited a significantly higher median survival of 63.5 months ($p = 0.04$). This associated survival benefit undoubtedly reflects many dynamic factors, primarily the selection of patients with less aggressive tumour biology. Without prospective or randomised controlled data any survival benefit cannot be directly attributed to surgical intervention, but the results demonstrate the value of a second, third, fourth, even up to a fifth repeat pulmonary metastasectomy in enabling control of isolated metastatic disease for long periods in select patients.

In 2005, Briccoli and colleagues examined the long term outcomes of 94 patients undergoing repeat pulmonary metastasectomy for recurrent osteosarcoma metastases, concluding that these patients with resectable disease should be considered for reoperation a second, third or even fourth time [23]. As per initial pulmonary metastasectomy selection guidelines, patients should be considered for repeat resection of recurrent sarcoma metastases if they have completely resectable disease without significant compromise of respiratory function, no primary recurrence and no uncontrolled extrapulmonary metastases [18,23-25]. Judicious preoperative screening will identify patients who will benefit most from repeat metastasectomy and those who should avoid unnecessary ongoing loss of lung parenchyma. Weiser and colleagues specifically found that significant independent prognostic factors for poor outcomes were high grade primary tumour histology, ≥ 3 recurrent lung nodules and largest metastases $> 2\text{cm}$ [25]. Whilst definitive guidelines cannot be made without more robust data, the current evidence suggest that multiple repeat resections do not represent worsening prognosis and in fact have associated survival benefits, which reflects the appropriate selection of patients with more favourable tumour biology. And ultimately an aggressive approach to repeat resection for isolated metastatic sarcoma recurrence, even on multiple occasions, may be warranted.

The limitations of this retrospective cohort study stem from the inherent retrospective study design, selection bias within the surgical cohort and restricted analyses of neo adjuvant or adjuvant therapies. The current evidence base and the results from our retrospective cohort study demonstrate that pulmonary metastasectomy and repeat pulmonary resection can have associated long term survival benefits. Patients presenting with recurrent pulmonary sarcoma metastases should be considered for repeat metastasectomy, even on multiple occasions, as an option to enable control of metastatic disease for long periods. Ultimately, future prospective data will further develop more specific and robust guidelines to optimise the process of selecting surgical candidates for pulmonary metastasectomy.

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Figure Legends

1. Figure 1. Survival plots for prognostic factors with multivariate $P < 0.05$ showing (a) disease free interval (DFI); (b) presentation of metastases; (c) number of metastases; (d) completeness of resection.
2. Figure 2. Survival plot of sarcoma subset undergoing repeat pulmonary metastasectomy (PM) following pulmonary recurrence.

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