

Fate of Patients Undergoing Pulmonary Metastasectomy for Metastatic Urothelial Carcinoma

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Abstract

Purpose: Systemic chemotherapy remains the standard treatment in metastatic urothelial carcinoma (mUC). Surgery has become a treatment of choice to achieve cure in selected patients with pulmonary metastasis from various types of malignant tumors. Here we retrospectively investigated surgical outcomes and determined a rationale for surgical treatment of lung metastasis in UC patients.

Materials and Methods: We analyzed 19 patients with UC who underwent pulmonary metastasectomy with a curative intent at our institutions. The number of lung metastasis in individual patient ranged from one to 9. The follow-up after pulmonary metastasectomy ranged from 18 to 168 months (median 72 months).

Results: The diameter of metastatic lung tumors ranged from 8mm to 38mm (median 15mm). Five and 10-year overall (OS) and cancer specific (CSS) survival after urothelial cancer lung metastases resection was 95, 69 and 95, 83 percent, respectively.

Shorter OS and CSS after UC lung metastases resection significantly correlated with the presence of local recurrence ($p < 0.001$). OS and CSS of the patient's after UC lung metastases resection with pN0 primary tumor was significantly better compared to pN1 patients ($p < 0.05$).

Conclusions: Surgical resection of chemo-resistant metastatic lung tumors in UC patients can be curative in cases of isolated pulmonary metastasis. It can result in durable oncological control in appropriately selected patients. Local recurrences in urothelial tract resulted in shorter OS and CSS after lung metastasectomy. Meticulous follow up of both metastatic site and urinary tract is necessary in these patients.

Keywords: Urothelial Cancer; Lung Metastasis; Metastatectomy

Introduction

Prognosis of metastatic urothelial carcinoma (mUC) is unfavorable with 5-year survival being less than 15% and systemic chemotherapy remains the standard treatment [1-3]. Although initial response rates to modern cisplatin-based combination regimens have been reported to be around 50–70% [4,5], incomplete remission with residual metastatic lesions or disease progression with de novo appearance of metastasis is not a rare event. The salvage strategy in these patients has yet to be fully established. To achieve surgical consolidation metastasectomy for visceral metastasis could be performed in selected patients. Resection of musculoskeletal metastasis [6], various solid organs metastasis [7] of renal cell carcinoma or liver metastasectomy of colorectal cancer [8]. Surgery has become a treatment of choice to achieve cure in selected patients with pulmonary metastasis from various types of malignant tumors including colorectal cancer [9], gastric cancer [10], and renal cell carcinoma [11]. Recent evidence suggests that solitary small lung metastases could be good

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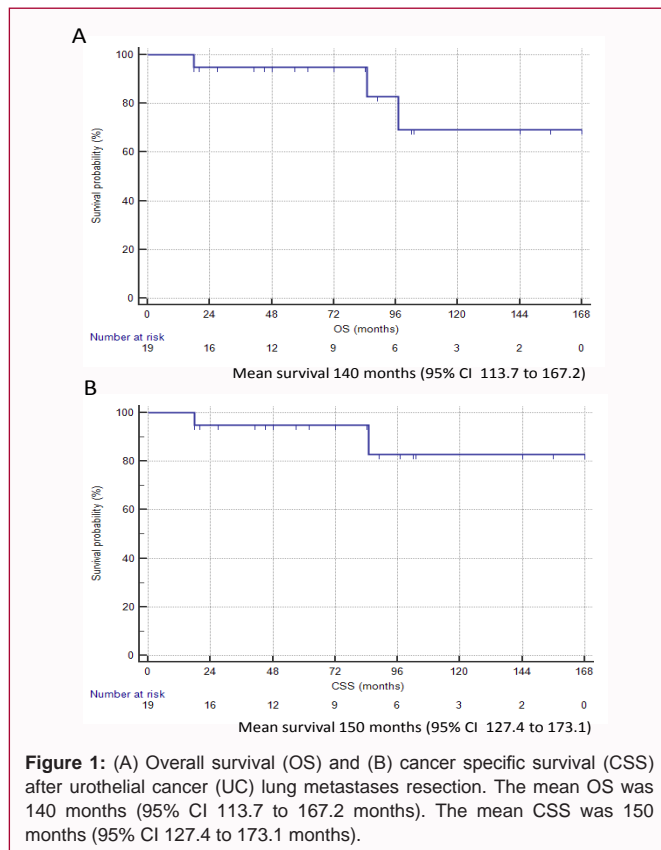
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Table 1: Metastasectomy for lung metastasis. Comparison of the data from literature and the present data.

	Number of Cases	Chemotherapy	5-year OS
Kanzaki (2010)	18	44% (8/18)	47%
Matsuguma (2011)	32	50% (16/32)	50%
Han (2012)	16	89% (14/16)	65%
Present Series	19	47% (9/19)	95%



candidates for surgical resection [12]. However, there are limited reports on surgical resection of pulmonary metastasis in UC. Cowles first reported surgical outcomes in patients with lung metastasis of urothelial carcinoma [13]. Recent insight into this controversial issue is reviewed by Abe et al [14]. The authors stated that patients with limited nodal or pulmonary disease could be good candidate for surgical consolidation. The objectives of this study were to investigate surgical outcomes and to determine a rationale for surgical treatment of lung metastasis in UC patients. Here we report on 19 patients with UC who underwent pulmonary metastasectomy with a curative intent at our institutions.

Patients and Methods

From 2001 to 2015, 19 patients with UC underwent pulmonary metastasectomy with a curative intent at our institutions. There were 9 men and 10 women. Age at the lung metastasectomy (or at the first metastasectomy in patients with multiple operations) ranged from 34 to 82 years (median 65 years). Fourteen patients had solitary metastasis and the remaining 5 patients had 2 to 9 multiple lung metastasis. There were 5(26%) open thoracotomies and 14(74%) VATS. Nine patients (47%) received chemotherapy in the pre-metastasectomy period and 7 patients (37%) received chemotherapy in the post-

metastasectomy period. Primary tumor location was renal pelvis and/or ureter in 12(63%) and bladder in 7(37%) patients. The age at lung tumor resection ranged from 34 to 82 years (median 65 years). The follow-up after pulmonary metastasectomy was 18 to 168 months (median 72 months). All patients gave written informed consent on publication of the clinical data. The data were analyzed retrospectively. Statistical analysis was performed using MedCalc statistical software package (Ostend, Belgium). Statistical comparisons between two groups were made using the Mann-Whitney U-test. Survival curves were generated using the Kaplan-Meier method and the differences between curves evaluated using the log-rank test. All tests were two-sided, and $P < 0.05$ was considered significant.

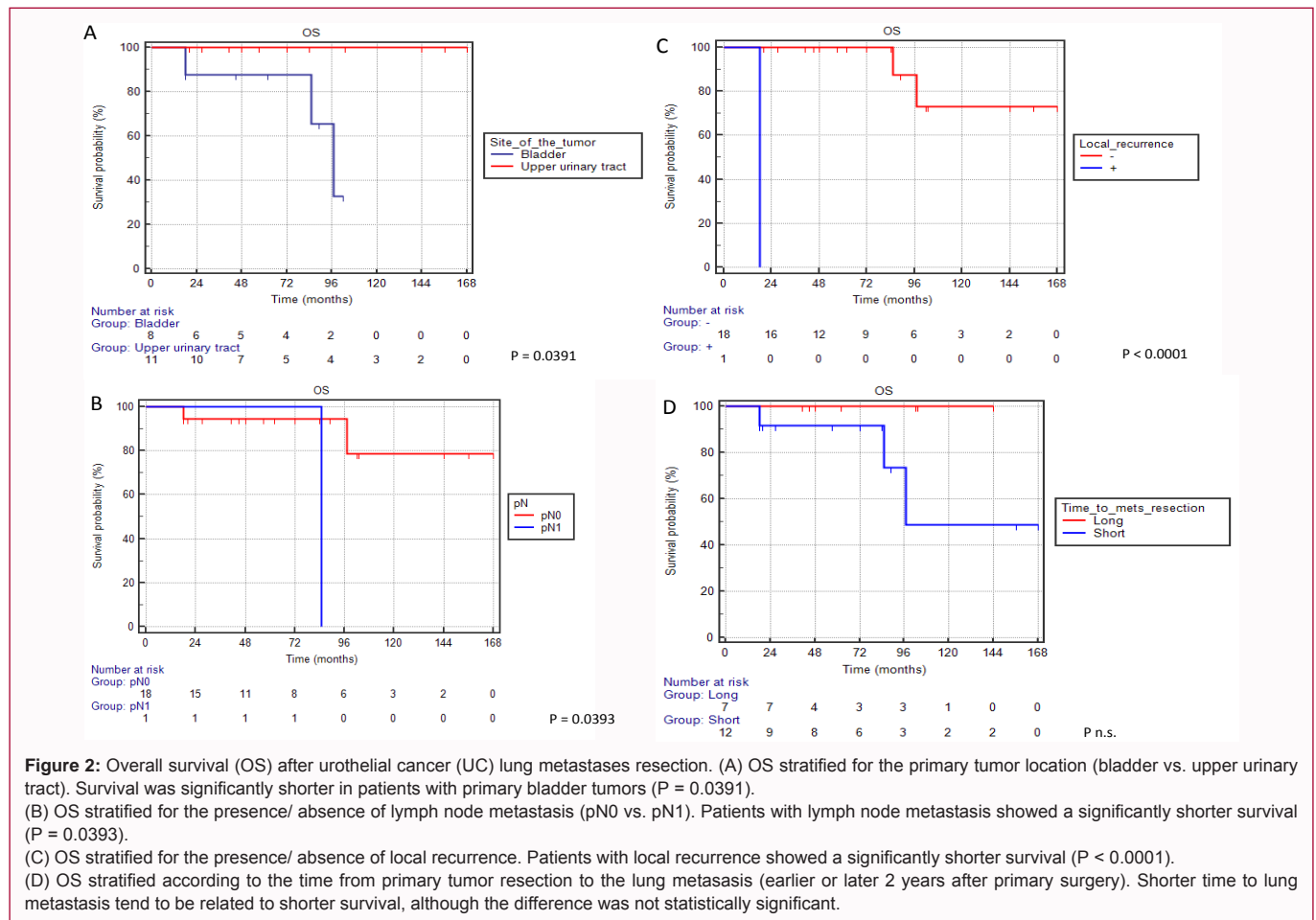
Results

The diameter of metastatic lung tumors ranged from 8mm to 38mm (median 15mm). Sixteen patients had NED during follow up period and 3 patients had recurrent lung disease. Ten patients (53%) survived without recurrence for more than 5 years including 2 patients who had lung metastasis larger than 30mm (38mm and 38mm). One bladder cancer patient had regional lymph node metastasis and one bladder cancer patient had recurrence in vaginal stump. Five upper urinary tract tumor patients had recurrent bladder cancer, which was successfully treated with TURBT.

Mean OS and CSS was 140 (95% CI 113.7 to 167.2) and 150 months (95% CI 127.4 to 173.1), respectively. Five and 10-year overall (OS) and cancer specific (CSS) survival after urothelial cancer lung metastases resection was 95, 69 and 95, 83 percent, respectively (Figure 1). We tried to look for survival predicting factors. Primary upper urinary tract cancers demonstrated significantly longer survival after lung metastases resection than bladder cancers ($p=0.0391$, Figure 2A). pN0 tumors demonstrated significantly better OS and CSS compared to pN1 ($p=0.0393$, Figure 2B). OS and CSS after lung metastases resection significantly dependent on the presence or absence of local recurrence ($p < 0.001$, Figure 2C). Shorter time to metastasis resection after primary surgery (earlier or equal or later than 2 years) had a trend to worse OS, although the difference was not significant (Figure 2D). There was no significant difference in OS and CSS between patients with solitary vs. multiple lung metastasis and patients who underwent chemotherapy vs. those without chemotherapy. This could be explained by the small number of cases and relatively short follow up in the present series. Also, due to the heterogeneity and small number of the patients in the study group, multivariate analysis was not feasible.

One patient had 9 bilateral pulmonary metastatic foci resected after 3 courses of GC chemotherapy. One recurrent pulmonary tumor (25mm) was treated with irradiation and 13 courses of chemotherapy including 3 courses of bronchial arterial infusion chemotherapy after which the patient is now tumor free for 57 months. One patient had no recurrence of UC for 8 years but then the patient was diagnosed with primary pancreatic cancer, which led to the patient's death 6 months later. In one female patient 2 liver metastases were found, which were treated with liver resection and radio frequency ablation followed by a diagnosis of low stage colon cancer, which was resected. The patient is disease free for 42 months. In one female patient, mediastinal lymph node adenopathy was treated with 44Gy irradiation and she is now NED for 43 months.

In one patient who had had underwent sigmoid neo-bladder reconstruction, left terminal ureteral tumor was found 5 years



after resection of lung tumor and the patient was treated with left nephroureterectomy and is now disease free for 24 months.

Case Presentation

Case 1

Sixty-five year-old male underwent left nephro-ureterectomy + bladder cuff resection for upper urinary tract cancer in July 2010, pathology was UC, pT3. He underwent adjuvant Gem-Carbo chemotherapy. Lung metastasis was found during follow up, and he underwent resection of 3 right lung tumors (Figure 3A) in July 2011. In September 2011, he underwent resection of 6 left lung tumors (Figure 3B). In March 2012, he underwent TURBT for bladder cancer. In May 2012, Gem-Carbo chemotherapy was administered followed by proton beam irradiation of recurrent S6 right lung tumor. In October 2012 Gem-Carbo chemotherapy was repeated. In May 2013, right bronchial artery intraarterial chemotherapy was done 4 times for S3 right lung recurrence. In February 2018 he was free from disease.

Case 2

Sixty-five year-old female underwent radical cystectomy for bladder cancer in September 2008. Pathology was UC, pT2b, v+ (Figure 3C). In August 2011 and January 2015 she underwent lung tumor resection for lung metastases (metastatic lung tumors comprised of viable cells (Figure 3D). In February 2013 she underwent liver metastasis resection followed by RFA of liver metastasis.

Case 3

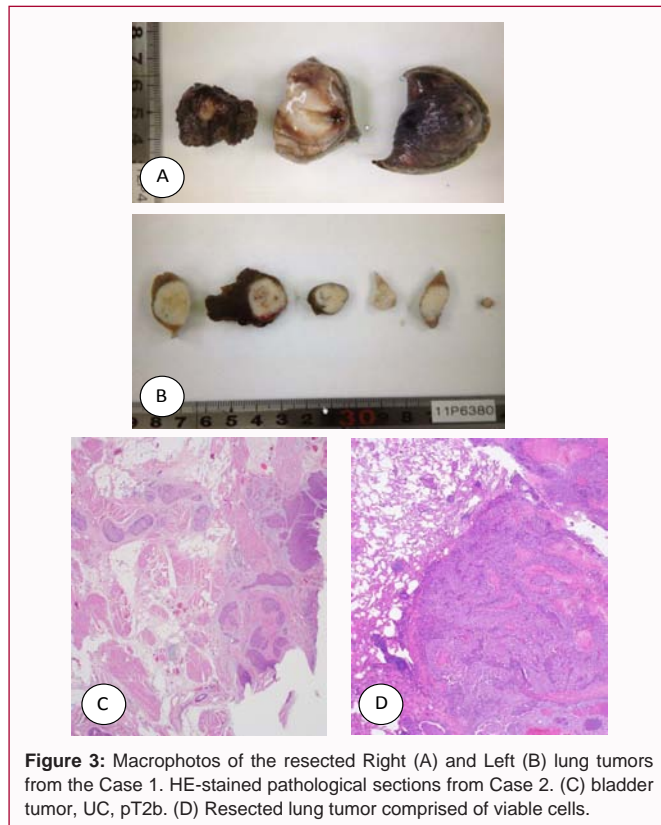
61 year-old female patient. In January 2002, Left nephron ureterectomy was performed for upper urinary tract cancer. In October 2004, 38mm solitary lung metastasis (left S1-2) was resected followed by a radical cystectomy and right ureterocutaneostomy for invasive bladder cancer in February 2005. In November 2005, right lung lobectomy was done for newly appeared another solitary lung metastasis 37mm in diameter. The patient is NED for 150 months now.

Case 4

57 year-old male patient underwent total cystectomy for muscle invasive bladder cancer. During the follow up the 38mm large left lung lower lobe tumor was detected which was successfully resected and the patient had NED for 97 months. However, he died of pancreas cancer.

Case 5

60 year-old female patient underwent total cystectomy which was followed by 3 consecutive lung metastatectomies (2011/8, 2015/1, 2016/8), one time liver metastatectomy (2013/1) (S3) and RFA (radiofrequency ablation) for liver metastasis (S5). At the present time she has lung recurrence with pleural effusion and recurrence of liver metastasis. She is undergoing chemotherapy resulting in shrinkage of metastasis and pleural effusion decrease with 5 cycle s of G Carbo (Gemcitabien 1000mg/body and Carboplatin 150mg/body).



Discussion

Currently, the role of metastasectomy has not yet been firmly determined and there are no strict criteria regarding the indications for resection of urothelial carcinoma metastasis. There are several reports on surgical resection of various site UC metastases [12-14]. A few reports concentrate on surgical resection of UC lung metastasis [15-19]. Although, criteria for surgical resection differ in various reports, however, they have many things in common. Good PS and strong personal motivation for aggressive surgical treatment is compulsory in the patients undergoing this non-standard therapy. Systemic chemotherapy should precede surgical consolidation. Usually, metastasectomy is considered when the patients demonstrate a good response to systemic chemotherapy and have a stable disease without rapid progression. Unfavorable prognosis after metastasis resection in patients refractory to the MVAC regimen has been reported [20]. Thus, salvage metastasectomy for disease refractory to systemic chemotherapy has no survival advantage. Surgery is only indicated to improved performance status of symptomatic patients. In our cases only 47% were received chemotherapy, Nephrectomy was done in 11 patients, so the patients were unfit for platinum based regimens due to impaired kidney function.

Matsuguma et al. reported that a pulmonary metastasis greater than 3cm was a significantly poor prognostic factor in a multivariate analysis [18]. In a series of 18 patients reported by Kannzaki et al. metastatic tumor size was not a significant prognostic factor [16]. In the present series, 2 patients (cases 3 and 4) who had lung metastasis larger than 30mm survived longer than 5 years, alongside with 8 patients having smaller lung tumors.

Based on the present data, patients with lymph node metastasis (pT1) and those with local recurrence should be carefully considered

as candidates for metastatic lung tumors resection due to shorter survival (Figure 2). Lung metastasis stable during long follow up or appearing later after resection of the primary tumor indicates slow overall progression and such patients are best candidates to surgical consolidation (Figure 2).

Due to recent advance in endoscopic surgery (VATS), the increasing number of tumors is resected using this minimum invasive technique. In the report of Matsuguma et al. [18], 34% of the surgeries were VATS. Among our patients VATS was applies in 74%.

Solitary metastasis or metastasis in a single organ, which could be resected with negative surgical margins, is a necessary condition for patient selection. It has been reported that patients with solitary lung metastasis had a significantly longer progression-free survival [17] and overall survival [16,18] than those with multiple lung lesions. Multiple metastases in a single organ or metastases involving several organs make surgical consolidation difficult or even impossible. Residual lesions after surgical resection will result in no survival advantage, and the physical burden of the surgery on a patient might even worsen the survival. One patient in the present series (case 1) had 9 bilateral pulmonary metastatic foci, which were resected surgically or treated by bronchial arterial infusion. Surgery in combination with EBRT is also feasible. However, we were unable to identify the significance of the number of pulmonary metastases because most of our data were based on solitary metastasis. Repeated resections are also feasible. Yokokawa et al. reported a case of 4 consecutive lung metastasectomies, and the patient was alive 33 months after last metastasectomy [21].

Matsuguma et al [18] introduced modified approach to analyze survival in patients with repeated pulmonary resections. When the disease-free status had continued for longer than two years after repeated pulmonary metastasectomy at the last follow-up, the first pulmonary recurrence after the first metastasectomy was not considered an event. They considered modified PFS suitable for evaluating the outcome of treatment in repeated resection. Their result of the 5-year modified PFS was 40%. In our cases, 5-year survival rate is high compared to other reports (Figure 3, Table 1). This can be explained by meticulous follow up and aggressive treatment of new recurrences, both in the urinary tract and outside it. In the present patients' cohort, bladder recurrences of upper urinary tract cancers were frequently seen and in 5 patients TURBT were done. In one patient who had had underwent sigmoid neo-bladder reconstruction, left terminal ureteral tumor was found 5 years after resection of lung tumor and the patient was treated with left nephron ureterectomy and is now disease free for 24 months. Urinary tract recurrent tumor occurred even after metastatic tumor is successfully treated. Thus, meticulous lifelong whole-body follow-up is an important factor for long-term outcome in these patients.

Limitations of this study are limited number of patients and retrospective analysis. Prospective studies including larger patient's cohorts are necessary to determine the role of metastasectomy in metastatic UC.

Conclusions

Surgical resection of chemo-resistant metastatic lung tumors in UC patients can be curative in cases of isolated pulmonary metastasis. It can result in durable oncological control in appropriately selected patients. Urinary tract recurrent tumor occurred even after metastatic tumor is successfully treated. Local recurrences in urothelial tract

resulted in shorter OS and CSS after lung metastasectomy. Meticulous follow up of both metastatic site and urinary tract is necessary in these patients.

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